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(54) Title: CARBOLINE DERIVATIVES USEFUL IN THE INHIBITION OF ANGIOGENESIS

(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 useful in the inhibition of VEGF production, 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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CARBOLINE DERIVATIVES USEFUL IN THE INHIBITION OF ANGIOGENESIS

Field of the Invention

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

Background of the Invention

Aberrant angiogenesis plays a critical role in the pathogenesis of numerous diseases, including malignant, ischemic, inflammatory and immune disorders (Carmeliet, *Nat. Med.*, **9(6)**:653-60 (2003), Ferrara, *Semin. Oncol.*, **29(6 Suppl 16)**: 10-4 (2002)). 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 (Witmer *et al.*, *Prog. Retin Eye Res.*, **22(1)**:1-29 (2003), Clark *et al.*, *Nat. Rev. Drug Discovery*, **2**:448-459 (2003)). 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 (Ferrara *et al.*, *Nat. Med.*, **5(12)**:1359-64 (1999), Kerbel *et al.*, *Nat. Rev. Cancer*, **2(10)**:727-39 (2002), Rofstad *et al.*, *Cancer Res.*, **60(17)**:4932-8 (2000)). Among these growth factors, Vascular Endothelial Growth Factor (VEGF) plays a central role in angiogenesis (Ferrara, *Semin. Oncol.*, **29(6 Suppl 16)**:10-4 (2002)).

VEGF, also known as VEGF-A, was initially identified for its ability to induce vascular permeability and to promote vascular endothelial cell proliferation (Leung *et al.*, *Science*, **246**:1306-1309 (1989), Plouet *et al.*, *EMBO J.*, **8**:3801-3806 (1989), Connolly *et al.*, *J. Biol Chem.*, **264**:20011-20024 (1989)). VEGF is encoded by a single gene that gives rise to four isoforms by alternative splicing (Tischer *et al.*, *J. Biol. Chem.*, **266**:11947-11954 (1991)). 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 (Ortega *et al.*, *Front. Biosci.*, **4**:D141-52 (1999), Sato *et al.*, *Annals of New York Academy of Science*, *902*:201-207, (2000)). 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 (Shalaby *et al.*, *Nature*, *376*:62-66, (1995)). VEGFR-1 inhibits endothelial cell growth either by acting as a decoy or by suppressing signaling pathways through VEGFR-2 (Fong *et al.*, *Nature*, *376*:66-70 (1995)).

Over 30 years ago, it was proposed that inhibition of tumor angiogenesis could be an effective approach for the treatment of cancer (Folkman, *N. Engl. J. Med.*, *285*(21):1182-6 (1971)). VEGF and its receptor have been demonstrated to have a central role in tumor angiogenesis, especially in the early stages of tumor growth (Hanahan *et al.*, *Cell*, *86*:353-364, 1996)). Indeed, increased levels of VEGF expression have been correlated with microvessel density in primary tumor tissues (Gasparini *et al.*, *J. Natl. Cancer Inst.*, *89*:139-147 (1997)). Moreover, increased levels of the VEGF transcript are found in virtually all of the common solid tumors (Ferrara *et al.*, *Endocr. Rev.*, *18*:4-25, 1997)). 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 (Dirix *et al.*, *Br. J. Cancer*, 76:238-243 (1997)). 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 (Carmeliet *et al.*, *Nature*, *380*:435-439 (1996)). Direct evidence for the involvement of VEGF in tumorgenesis was demonstrated by using specific antibodies against VEGF in human xenografts implanted in nude mice (Kim *et al.*, *Nature*, *362*:841-844 (1993), Hichlin *et al.*, *Drug Discovery Today*, *6*:517-528 (2001)). 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 (Lin *et al.*, *Cell Growth Differ.*, *9*(1):49-58 (1998)), and demonstrated that inactivation of VEGF by specific antibody treatment directly resulted in a nearly complete suppression of tumor-associated neovascularization (Borgstrom *et al.*, *Prostate*, *35*:1-10 (1998), Yuan *et al.*. *Proc. Natl. Acad. Sci. USA*, *93*:14765-14770 (1996)).

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 Witmer *et al.*, *Prog. Retin Eye Res.*, *22*(1):1-29 (2003)). 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 (Funatsu *et al.*., *Am. J. Ophthalmol.*, *133*(4):537-43 (2002), Lip *et al.*, *Ophthalmology*, *108*(4):705-10 (2001)). In addition, studies using transgenic mice demonstrated that overexpression of VEGF in retinal pigment epithelial cells or photoreceptor cells results in choroidal or retinal neovasucularization (Schwesinger *et al., Am. J. Pathol.*, *158*(3):1161-72 (2001), Ohno-Matsui *et al., Am. J. Pathol.*, *160*(2):711-9 (2002)). 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. (Eyetech Study Group, *22*(2):143-52 (2002), Krzystolik *et al., Arch. Ophthalmol.*, *120*(3):338-46 (2002), Shen *et al., Lab Invest.*, *82*(2):167-82 (2002), Honda *et al., Gene Ther.*, *7*(11):978-85 (2000), Saishin *et al., J. Cell Physiol.*, *195*(2):241-8 (2003)).

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 (Maxwell *et al., Nature*, *399*:271-275 (1999), Rak *et al., Cancer Res.*, *60*:490-498 (2000)). 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 (Ikeda *et al., J. Biol. Chem.* *270*:19761-19766 (1995), Stein *et al., Mol. Cell. Biol.* *18*:3112-3119 (1998), Levy *et al., J. Biol. Chem.* *271*:2746-2753 (1996)). 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 (Liu *et al., Circ. Res.*, *77*:638-643 (1995), Semenza, *Annu. Rev. Cell. Dev. Biol.*, *5*:551-578 (1999)). The stability of VEGF mRNA is also greatly enhanced as a consequence of the binding of factors to elements in the 3'-UTR (Goldberg *et al., J. Biol. Cell. J. Biol. Chem.*, *277*(16):13635-40 (2002)). 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 (Kraggerud *et al., Anticancer Res.*, *15*:683-686 (1995)). 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 (Stein *et al., Mol. Cell. Biol.* *18*:3112-3119 (1998), Levy *et al., J. Biol. Chem.* *271*:2746-2753 (1996), Huez *et al., Mol. Cell. Biol.*, *18*:6178-6190 (1998), Akiri *et al., Oncogene*, *17*:227-236 (1998)).

There is a large body of experimental evidence indicating that tumor growth can be inhibited by the prevention of neovascularization (Lin *et al., Cell Growth Differ.*, *9*(1):49-58 (1998), Zhu *et al., Invest. New Drugs*, *17*:195-212 (1999)). Tumor vessels are generally immature and constantly undergo remodeling (Carmeliet, *Nat. Med.*, *9*(6):653-60 (2003), Carmeliet *et al., Nature*, *407*:249-257 (2000)). Active and aberrant angiogenesis is the result of a disruption in the normal balance of proangiogenic 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 (Kim *et al.*, *Nature*, *362*:841-844 (1993), Millauer *et al.*, *Nature*, *367*:576-579 (1994), Fong *et al.*, *Cancer Res.*, *59*:99-106 (1999)). Among many angiogenesis targets, VEGF and its receptor are most attractive (Carmeliet, *Nat. Med.*, *9*(6):653-60 (2003), Ortega *et al.*, *Front. Biosci.*, *4*:D141-52 (1999)). 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 carcinomas, sarcomas and gliomas (Ferrara *et al.*, *Endocr. Rev.*, *18*:4-25, 1997), Kim *et al.*, *Nature*, *362*:841-844 (1993), Millauer *et al.*, *Nature*, *367*:576-579 (1994), Fong *et al.*, *Cancer Res.*, *59*:99-106 (1999), Geng *et al.*, *Cancer Res.*, *61*:2413-2419 (2001)). In addition, inhibition of VEGF by anti-VEGF antibody did not result in significant side effects in fully developed rodents or primates (Ryan *et al*, *Toxicol. Pathol.*, *27*:78-86 (1999), Ferrara *et al.*, *Nat. Med.*, *4*:336-340 (1998)). 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 (Matter, *Drug Discovery Today*, *6*:1005-1024 (2001), Hichlin *et al.*, *Drug Discovery Today*, *6*:517-528 (2001)).

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 (Witmer *et al.*, *Prog. Retin Eye Res.*, *22*(1):1-29 (2003), Holash *et al.*, *Science*, *284*:1994-1998 (1999)). Data from preclinical experiments and clinical trials have demonstrated that blockade of VEGF alone is sufficient to alleviate or stabilize disease progression (Eyetech Study Group, *22*(2):143-52 (2002), Krzystolik *et al.*, *Arch. Ophthalmol.*, *120*(3):338-46 (2002), Shen *et al.*, *Lab Invest.*, *82*(2):167-82 (2002), Honda *et al.*, *Gene Ther.*, *7*(11):978-85 (2000), Saishin *et al.*, *J. Cell Physiol.*, *195*(2):241-8 (2003)). 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 (Ozaki H, Seo MS, Ozaki *et al.*, *Am. J. Pathol.*, *156*(2):697-707 (2000)). 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 (Reich *et al.*, *Mol. Vis. 30*;9:210-6 (2003)). These results indicate that selective inhibition of VEGF expression is achievable and offers validation of this approach for the treatment of ocular neovascular diseases such as exudative macular degeneration and diabetic retinopathy.

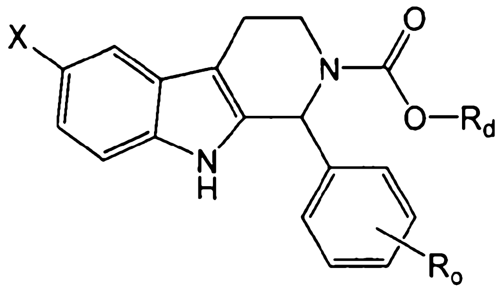
Three approaches have been used to inhibit VEGF activity, including (1) neutralization of VEGF activity by using a specific antibody, soluble VEGF receptor or aptamer oligos against the VEGF/VEGFR interaction (Kim *et al.*, *Nature*, *362*:841-844 (1993), Lin *et al.*, *Cell Growth Differ.*, *9*(1):49-58 (1998), Borgstrom *et al.*, *Prostate*, *35*:1-10 (1998), Zhu *et al.*, *Invest. New Drugs*, *17*:195-212 (1999), Millauer *et al.*, *Nature*, *367*:576-579 (1994), Asano *et al.*, *Jpn. J. Cancer Res.*, *90*(1):93-100 (1999), Brekken *et al.*, *Cancer Res.*, *60*(18):5117-24 (2000)); (2) inhibition of VEGFR mediated signal transduction by specific small molecule tyrosine kinase inhibitors (Fong *et al.*, *Cancer Res.*, *59*:99-106 (1999), Wedge *et al.*, *Cancer Res.*, *60*(4):970-5 (2000), Laird *et al.*, *Cancer Res.*, *60*(15):4152-60 (2000)); and (3) inhibition of VEGF/VEGFR expression by using antisense, siRNA or ribozyme (Reich *et al.*, *Mol. Vis. 30*;9:210-6 (2003), Parry *et al.*, *Nucleic Acids Res.*, *27*:2569-2577 (1999), Ellis *et al.*, *Surgery*, *120*:871-878 (1996), Filleur *et al.*, *Cancer Res.*, *63*(14):3919-22 (2003)). 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 RD many of whom are also hypertensive (Giles *et al.*, *Cancer*, *97*(8):1920-8 (2003), Sugimoto *et al.*, *J. Biol. Chem.*, *278*(15):12605-8 (2003), Bergsland *et al.*, American Society of Clinical Oncology 36th Annual Meeting, 20-23 May, 2000, New Orleans, LA, USA, Abstract 939), DeVore *et al.*, American Society of Clinical Oncology 36th Annual Meeting, 20-23 May, 2000, New Orleans, LA, USA, Abstract 1896).

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.

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

Summary of the Invention

According to a first embodiment of the invention, there is provided a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt, racemate or stereoisomer thereof, wherein,

X is hydrogen; C_1 to C_6 alkyl optionally substituted with one or more halogen; hydroxyl; halogen; or C_1 to C_5 alkoxy optionally substituted with phenyl;

R_0 is halogen; cyano; nitro; sulfonyl substituted with C_1 to C_6 alkyl or morpholinyl; amino optionally substituted with C_1 to C_6 alkyl, -C(O)-R_b, -C(O)O-R_b, alkylsulfonyl, morpholinyl or tetrahydropyranyl; C_1 to C_6 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen or amino; -C(O)-R_n; or -OR_a;

R_a is hydrogen; C_2 to C_8 alkenyl; -C(O)O-R_b; -C(O)-NH-R_b; C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen, C_1 to C_4 alkoxy, C_1 to C_4 alkoxy-C_1 to C_4 alkoxy, amino, alkylamino, dialkylamino, acetamide, -C(O)-R_b, -C(O)O-R_b, aryl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxolan-2-one, oxiranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3-triazole, 1,2,4-triazole, furan, imidazole, isoxazole, isothiazole, oxazole, pyrazole, thiazole, thiophene or tetrazole;

wherein amino is optionally substituted with C_1 to C_4 alkoxycarbonyl, imidazole, isothiazole, pyrazole, pyridine, pyrazine, pyrimidine, pyrrole, thiazole, wherein pyridine and thiazole are each optionally substituted with C_1 to C_4 alkyl;

wherein alkylamino and dialkylamino are each optionally substituted on alkyl with hydroxyl, C_1 to C_4 alkoxy, imidazole, pyrazole, pyrrole or tetrazole; and

wherein morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl and oxiranyl are each optionally substituted with -C(O)-R_n, -C(O)O-R_n or C_1 to C_4 alkyl, wherein C_1 to C_4 alkyl is optionally substituted with hydroxyl;

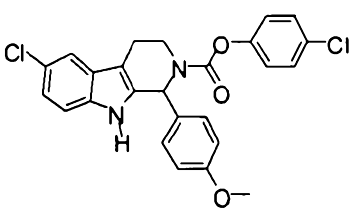
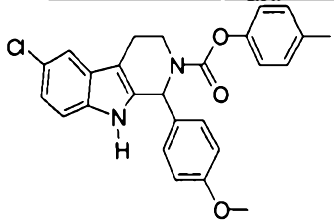
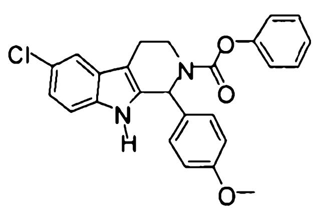
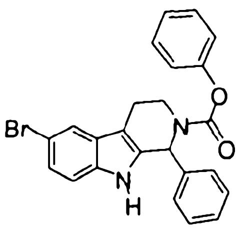
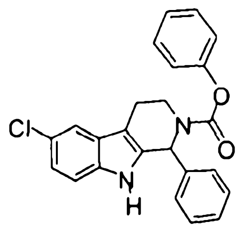
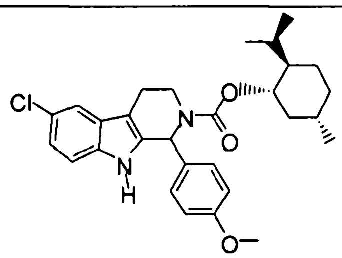
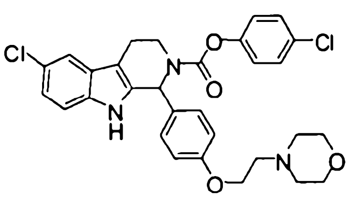
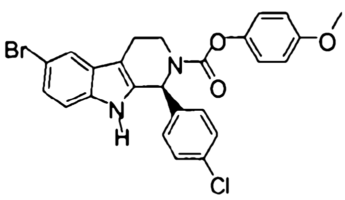
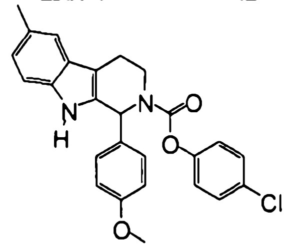
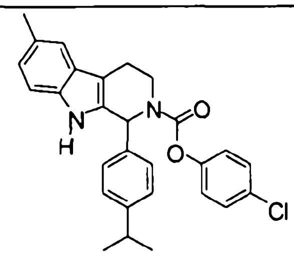
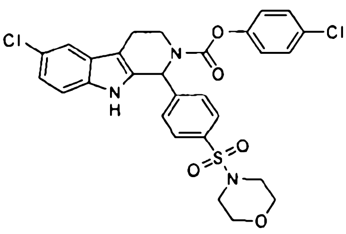
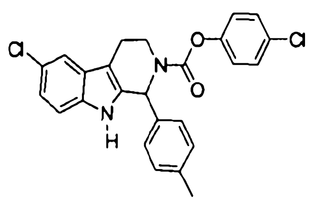
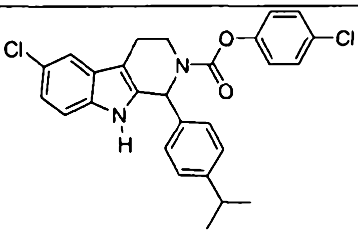
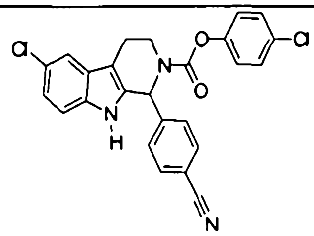
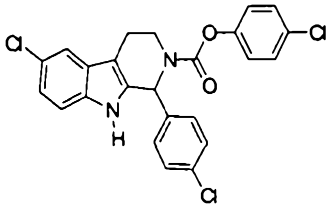
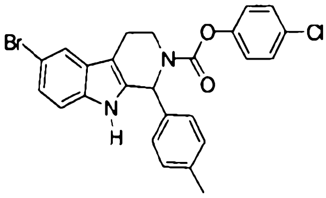
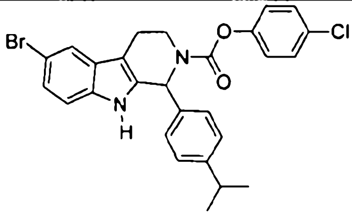
R_b is hydroxyl; amino; alkylamino, optionally substituted on alkyl with hydroxyl, amino, alkylamino or C_1 to C_4 alkoxy; C_1 to C_4 alkoxy; C_2 to C_8 alkenyl; C_2 to C_8 alkynyl; aryl optionally substituted with one or more substituents independently selected from halogen and C_1 to C_4 alkoxy; furan; or C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from C_1 to C_4 alkoxy, aryl, amino, morpholinyl, piperidinyl or piperazinyl;

R_d is phenyl substituted by one or more substituents independently selected from halogen, nitro, C_1 to C_6 alkyl, -C(O)O-R_e, and -OR_e;

R_e is hydrogen; C_1 to C_6 alkyl optionally substituted with one or more substituents independently selected from halogen and alkoxy; or phenyl, wherein phenyl is optionally substituted with one or more substituents independently selected from halogen and alkoxy; and

R_n is hydroxyl, C_1 to C_4 alkoxy, amino or C_1 to C_6 alkyl.

According to a second embodiment of the invention, there is provided a compound, wherein said compound is selected from the group consisting of

 10	 17	 60
 76	 121	 192
 331	 332	 341
 344	 346	 347
 348		 350
 351	 353	 354

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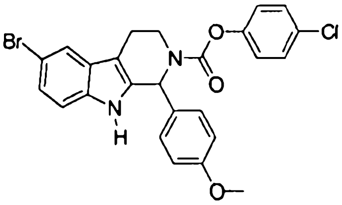
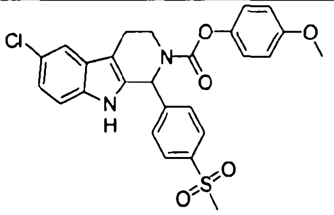
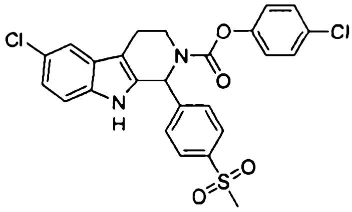
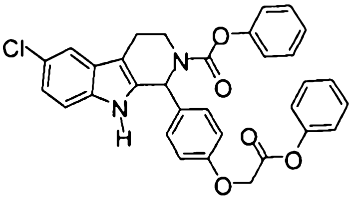
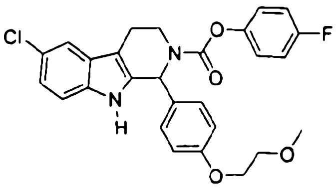
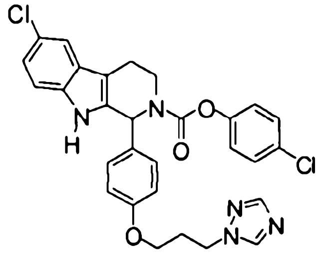
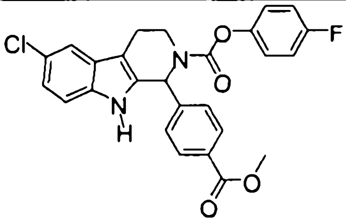
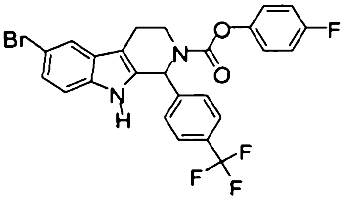
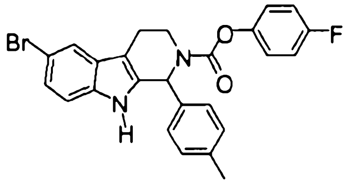
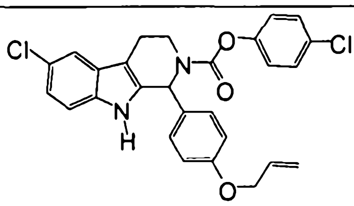
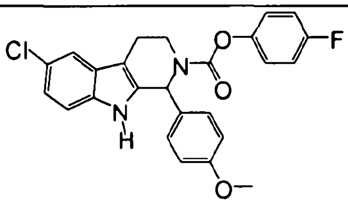
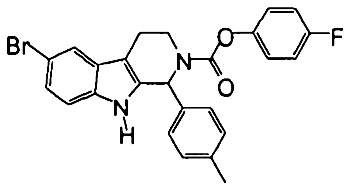
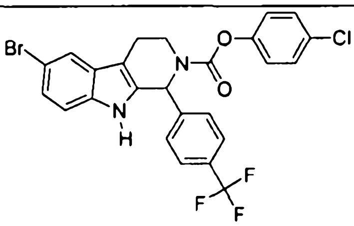
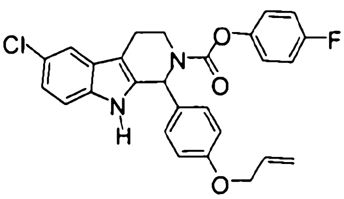
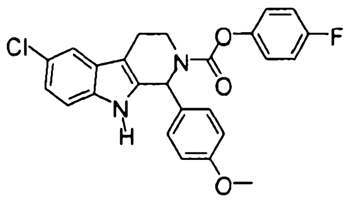
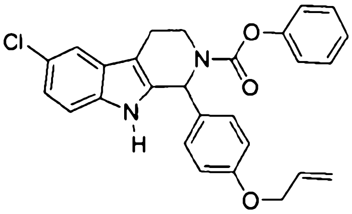
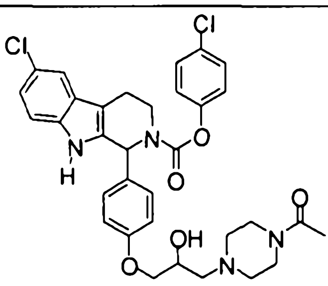
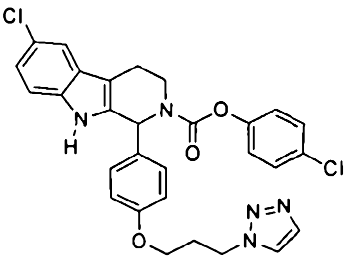
 355	 359	 360
 366	 388	 391
 395	 397	 398
 400	 401	 403
 405	 409	 410
 413	 415	 417

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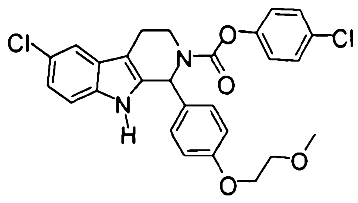
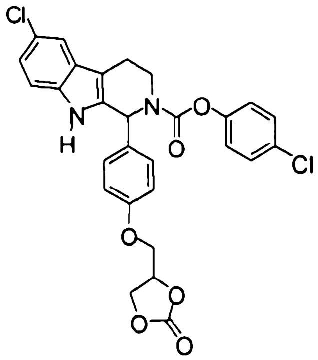
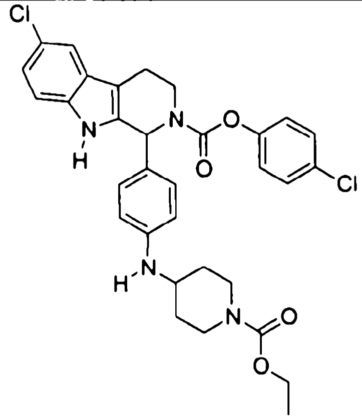
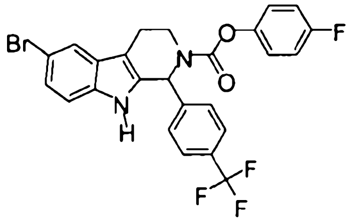
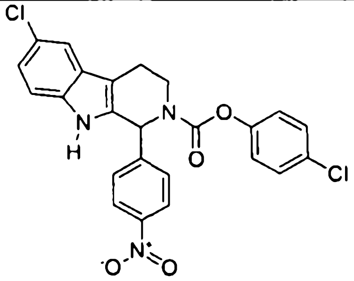
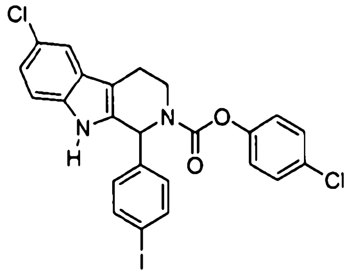
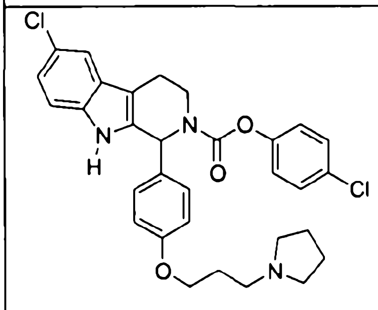
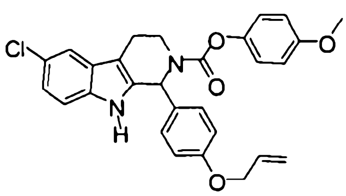
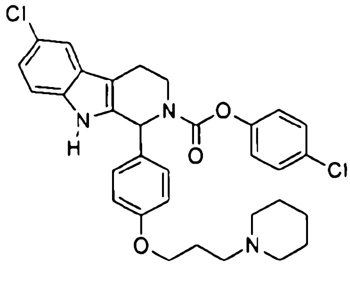
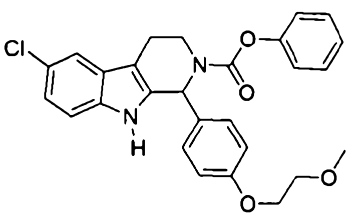
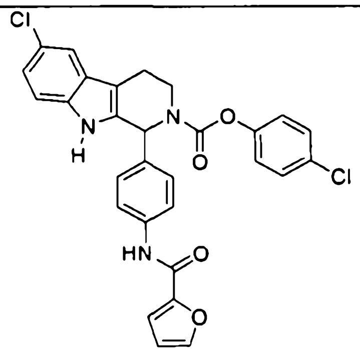
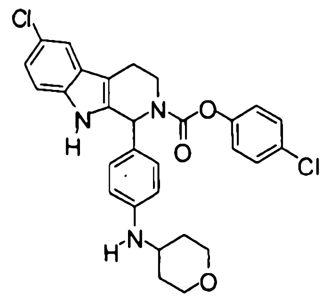
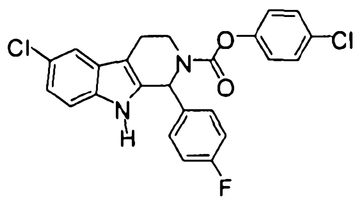
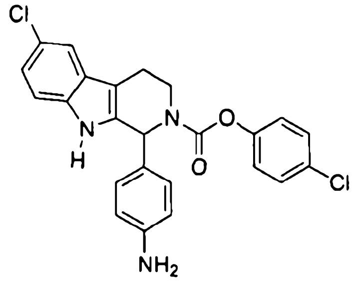
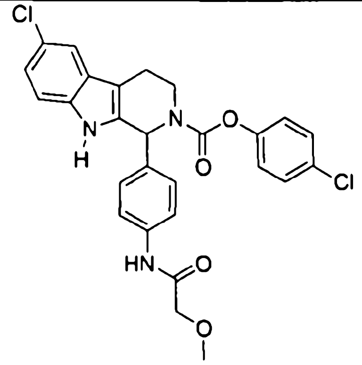
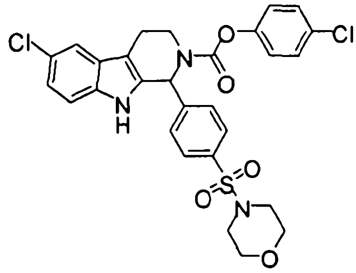
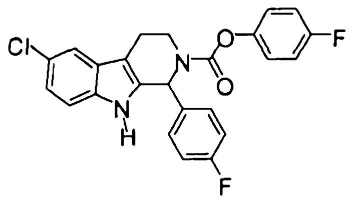
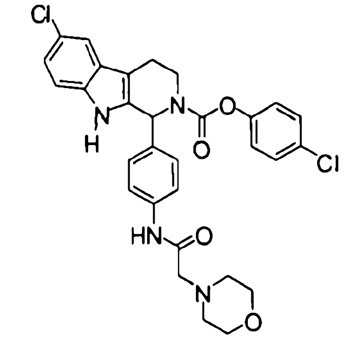
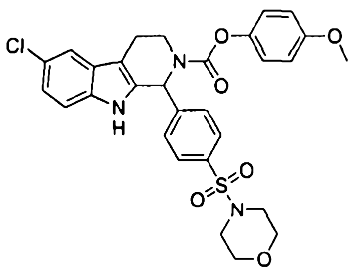
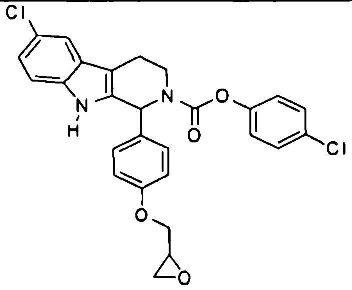
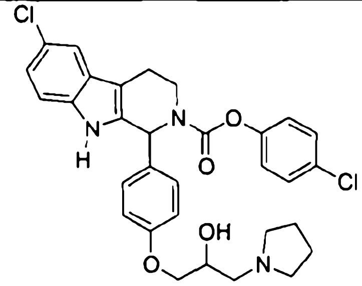
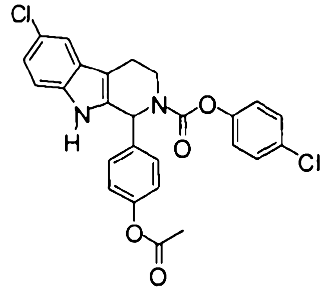
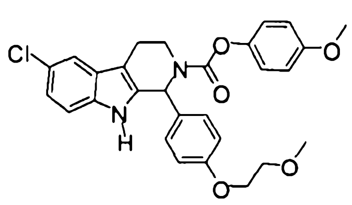
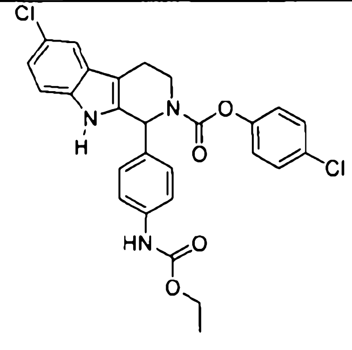
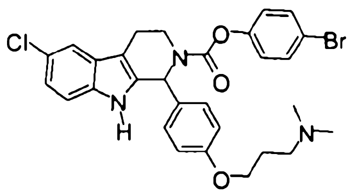
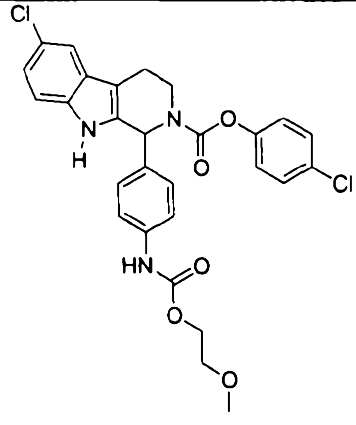
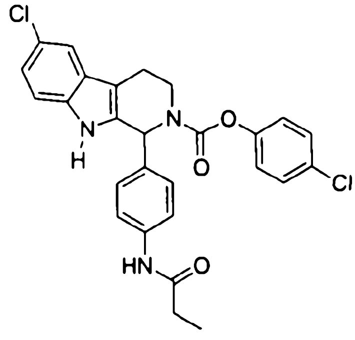
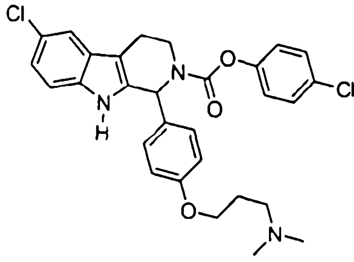
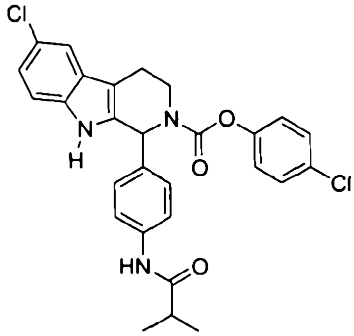
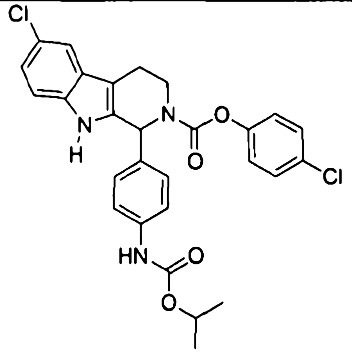
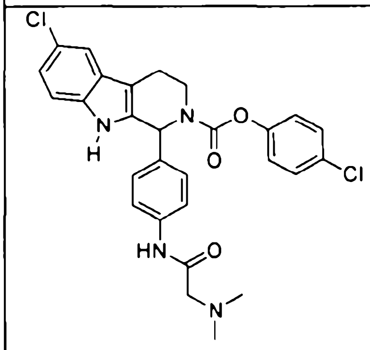
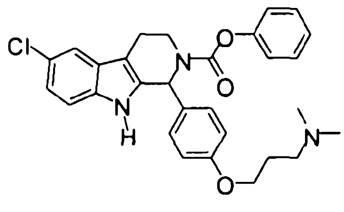
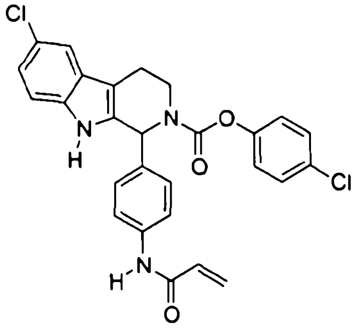
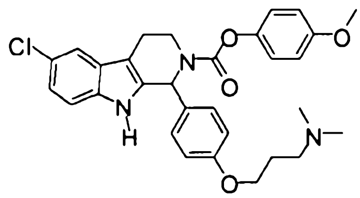
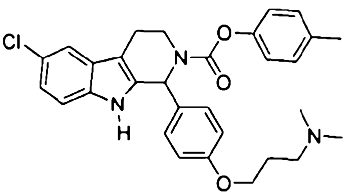
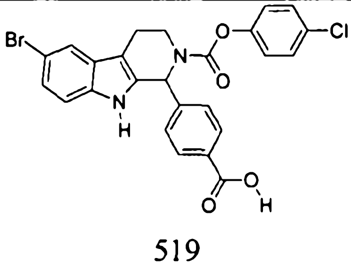
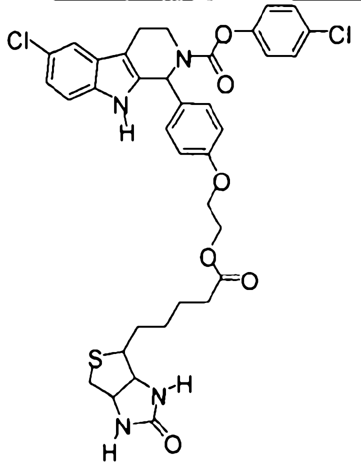
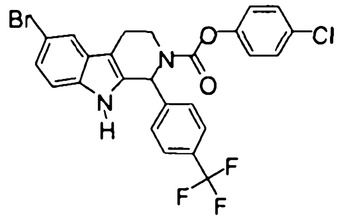
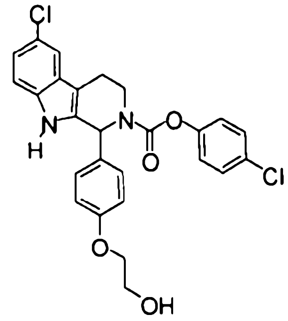
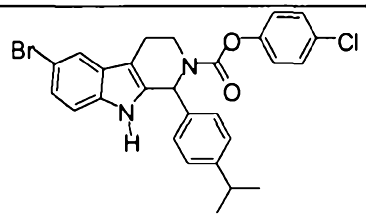
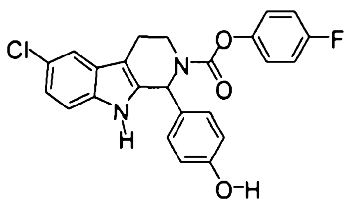
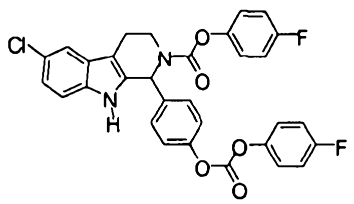
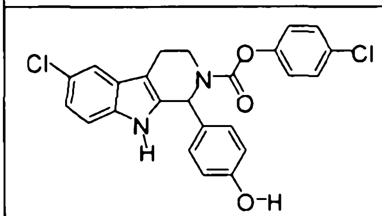
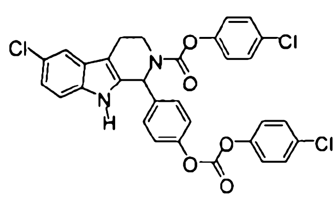
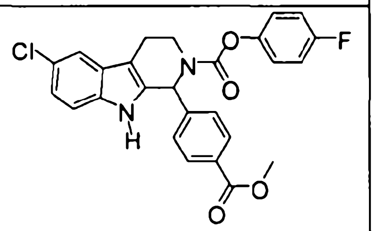
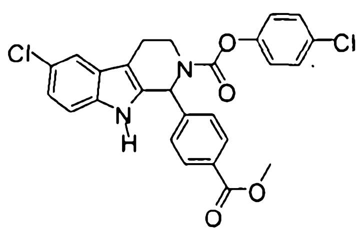
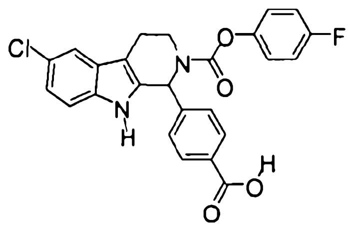
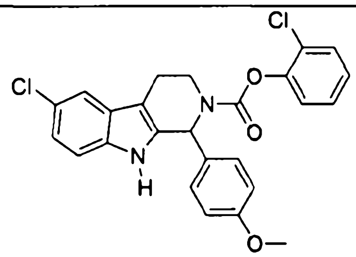
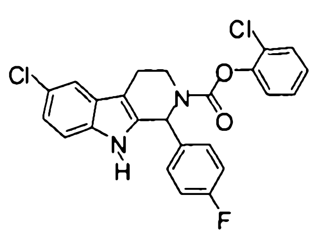
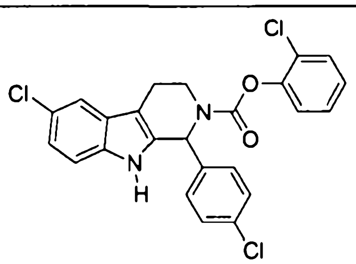
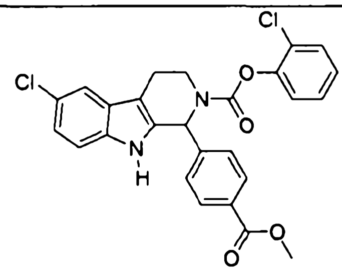
 418	 421	 422
 426	 427	 428
 429	 432	 433
 436	 437	 440

 444	 446	 448
 450	 452	 454
 455	 460	 462
 463	 465	 467

 468	 470	 471
 479	 482	 489
 491	 493	 500
 501	 502	 519

 544	 570	 571
 572	 575	 576
 577	 578	 579
 580	 581	 587
 588	 589	 590

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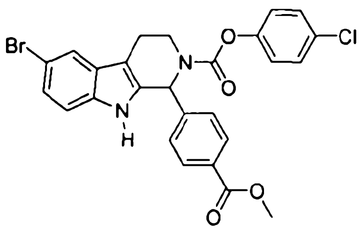
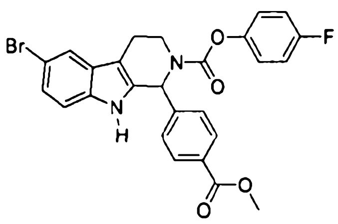
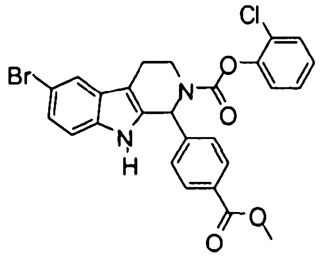
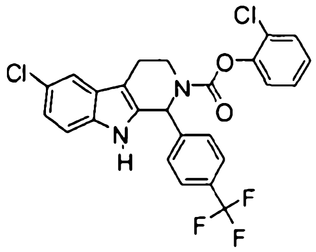
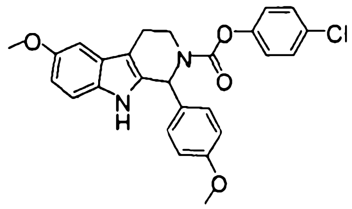
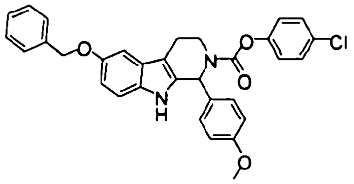
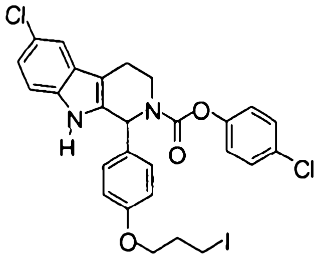
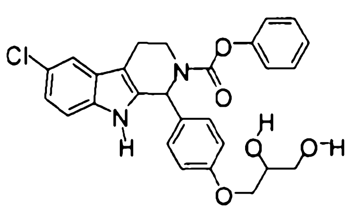
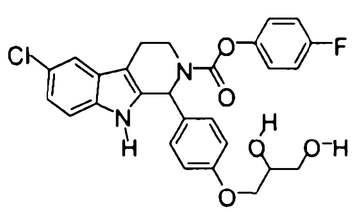
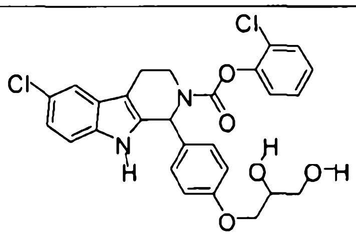
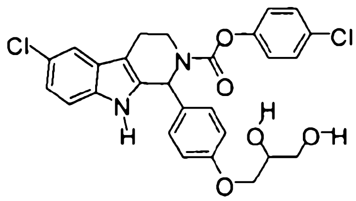
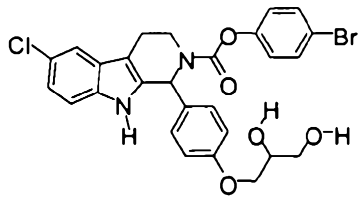
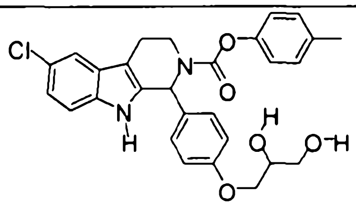
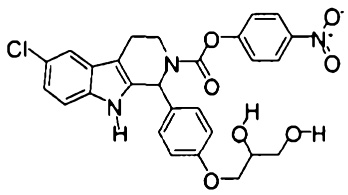
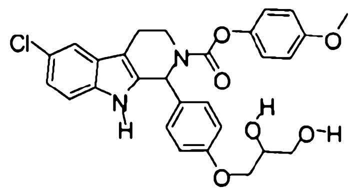
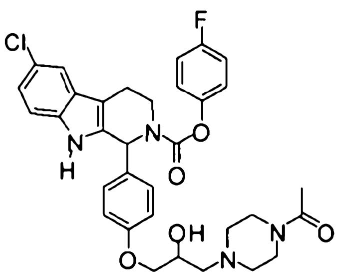
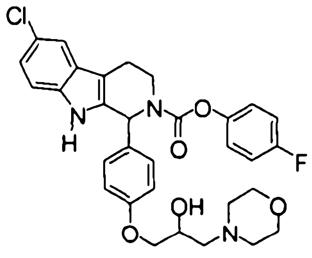
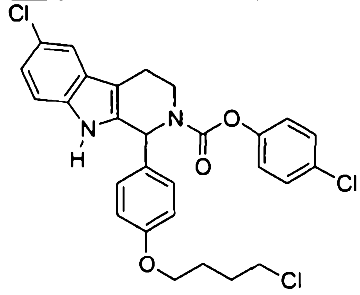
 591	 592	 593
 594	 614	 616
 617	 626	 627
 628	 629	 630
 631	 632	 635
 637	 638	 660

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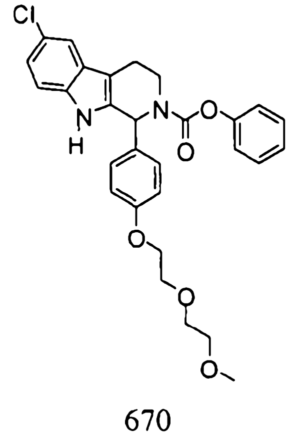
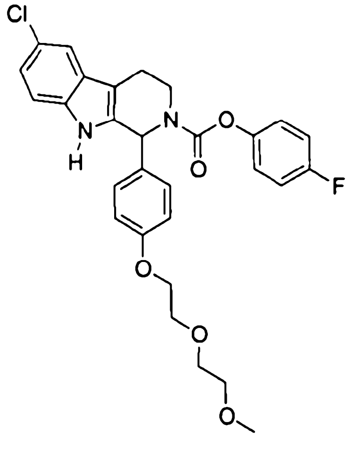
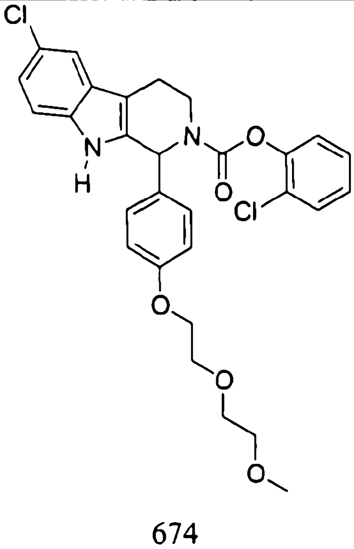
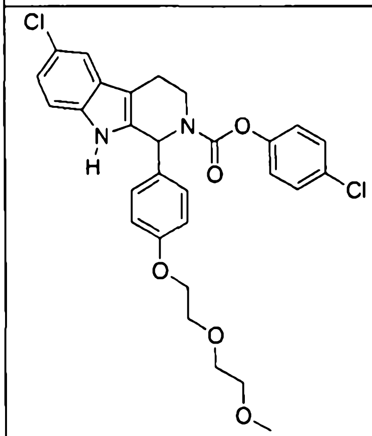
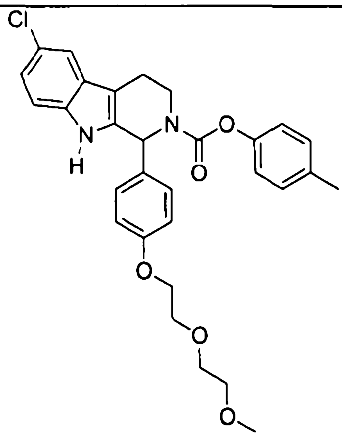
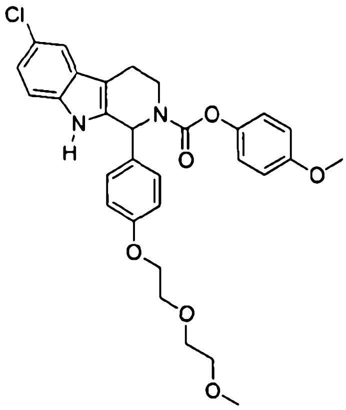
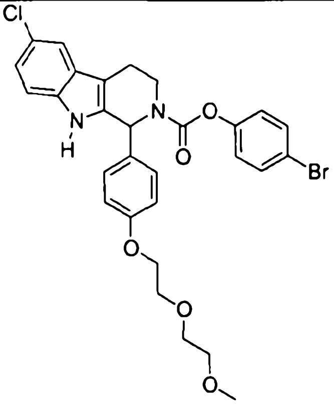
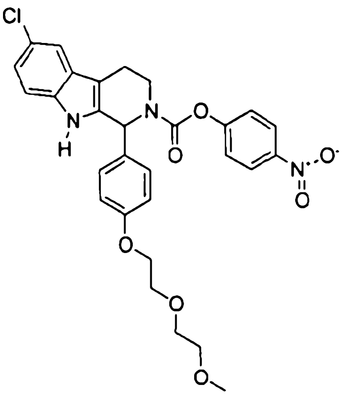
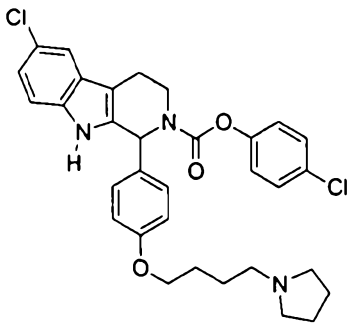
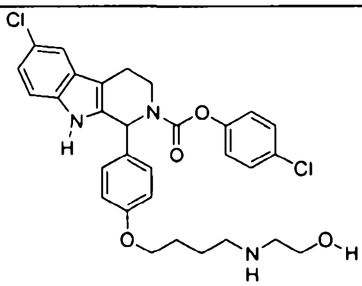
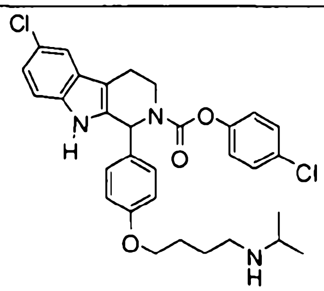
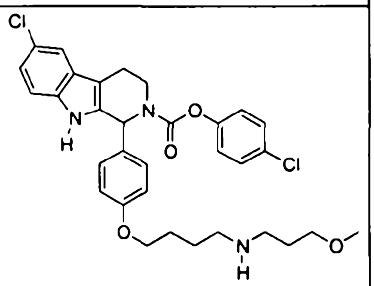
 670	 673	 674
 675	 677	 678
 680	 681	 698
 699	 700	 701

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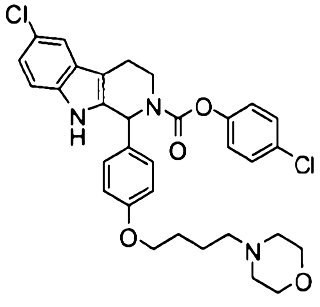
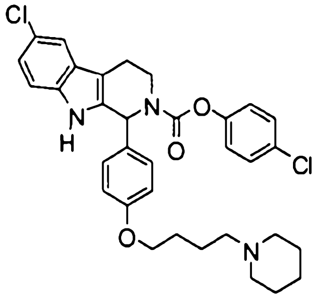
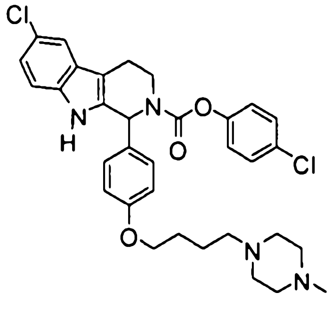
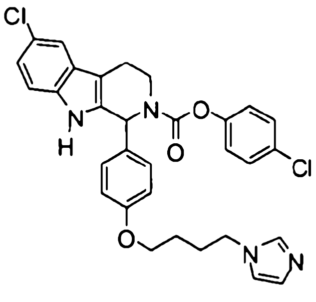
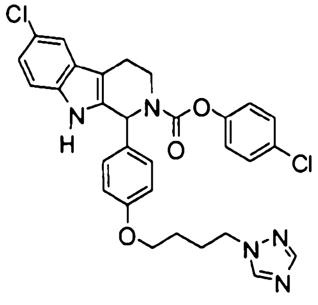
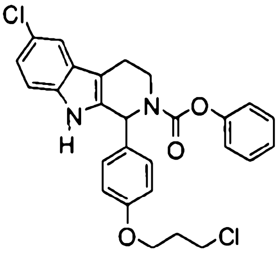
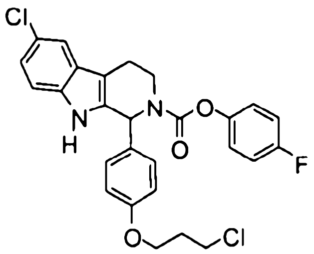
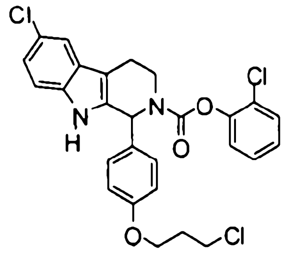
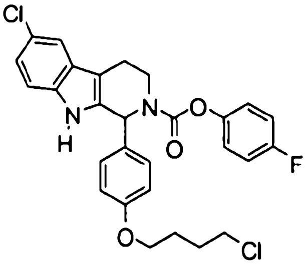
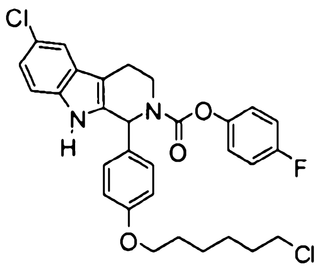
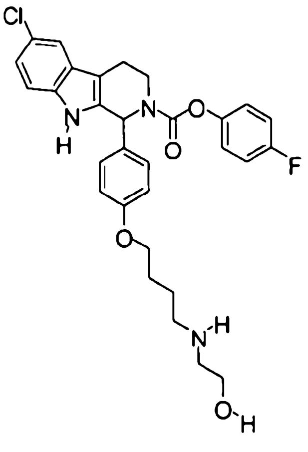
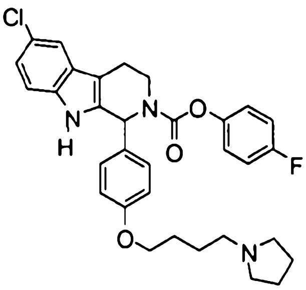
 702	 703	 704
 705	 706	 710
 712	 713	 719
 723	 735	 736

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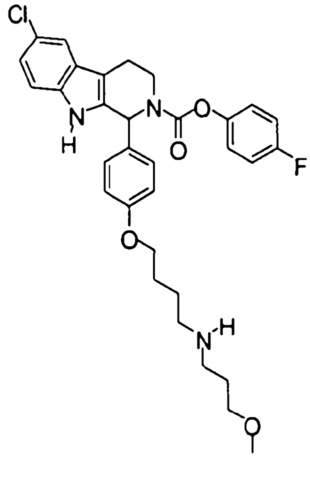
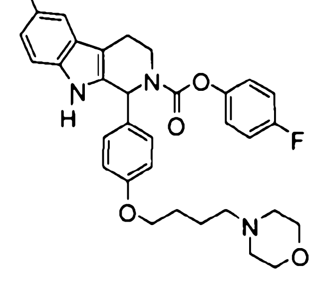
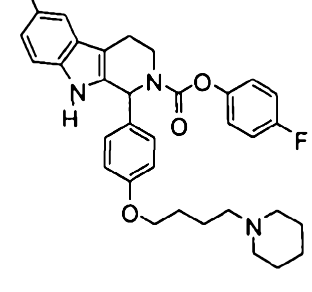
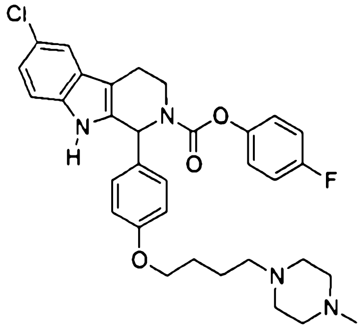
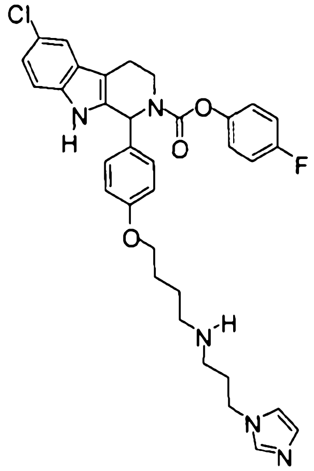
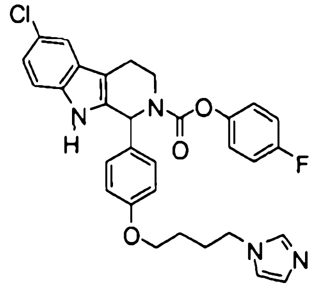
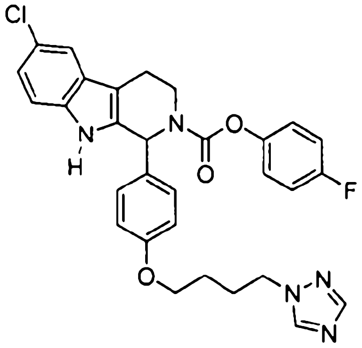
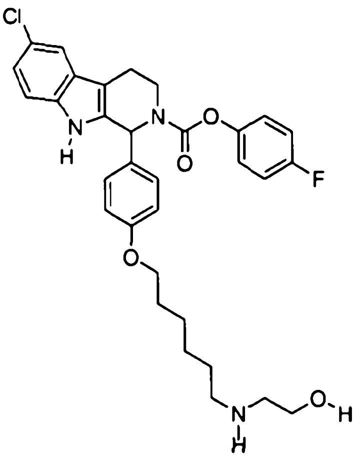
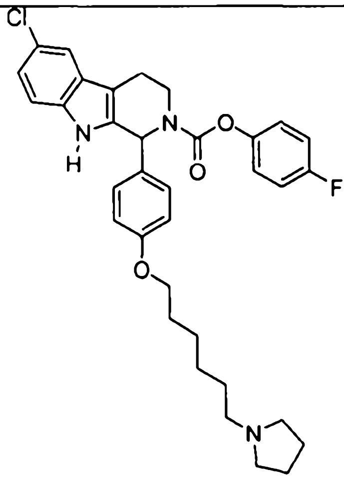
 737	 738	 739
 740	 741	 742
 743	 772	 773

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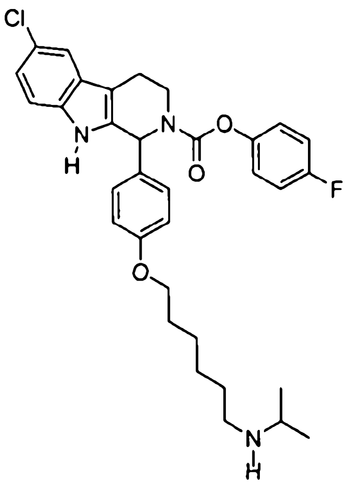

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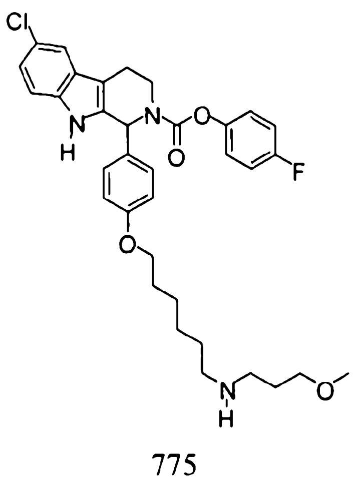

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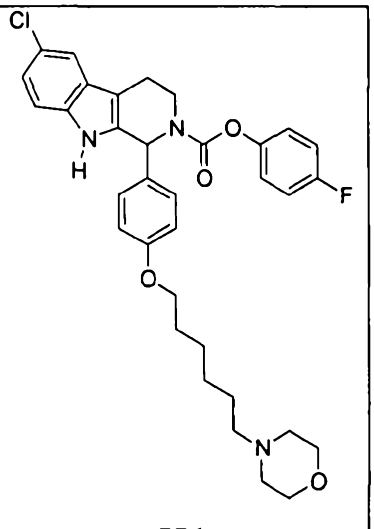

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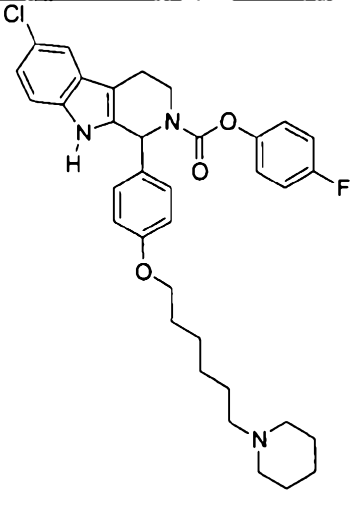

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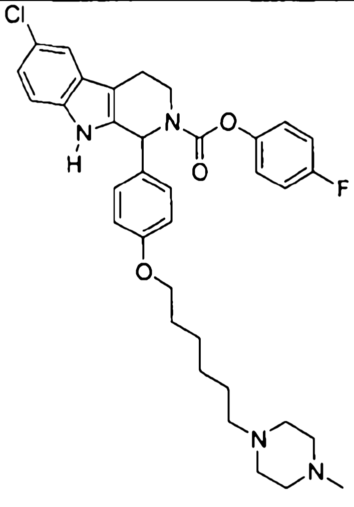

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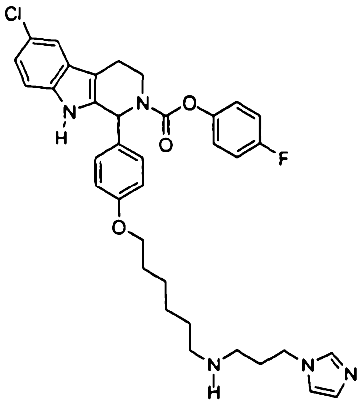

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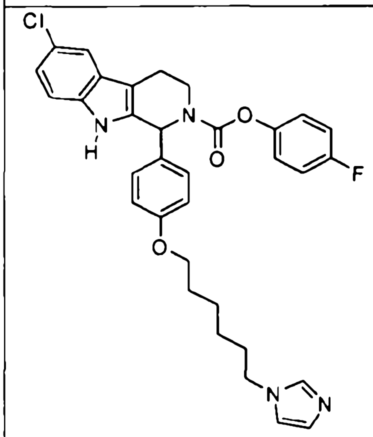

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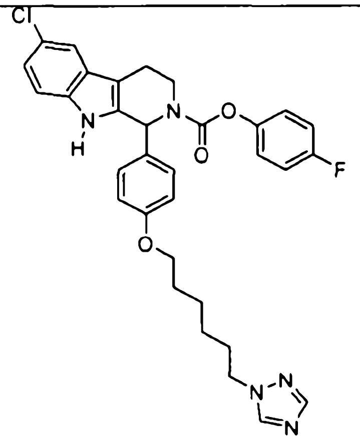

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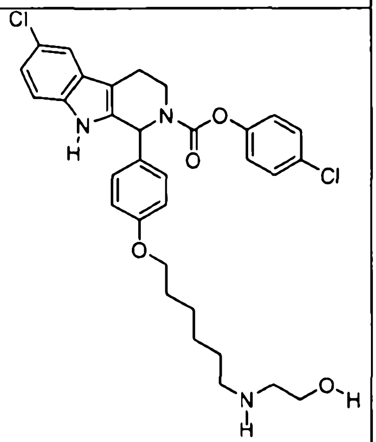

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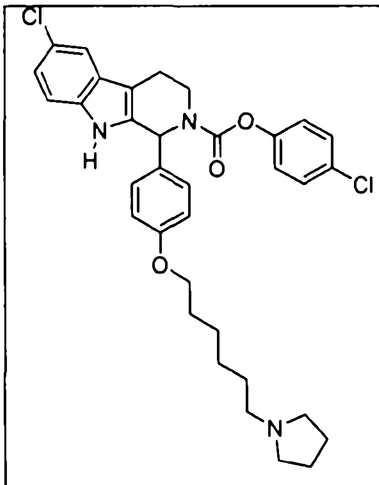
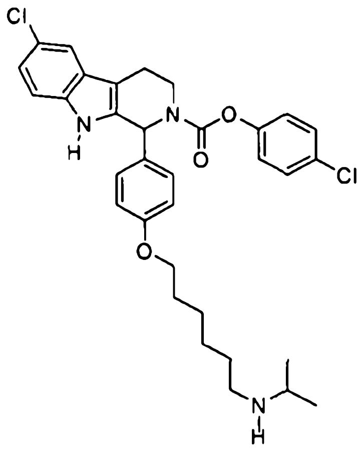
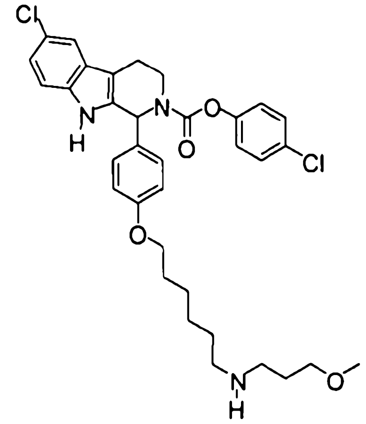
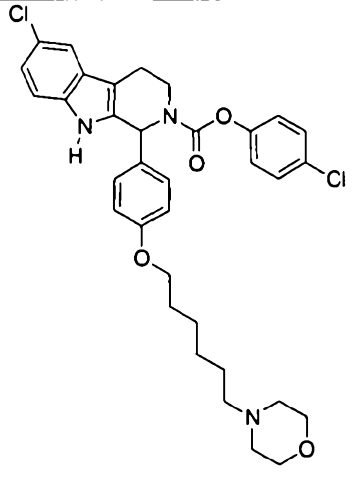
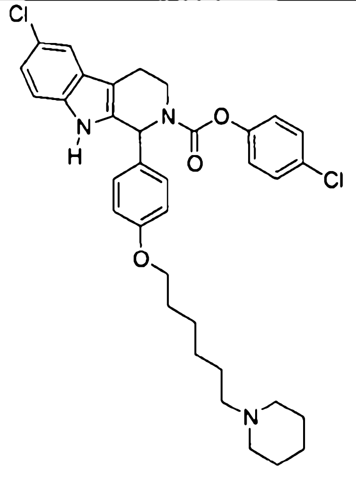
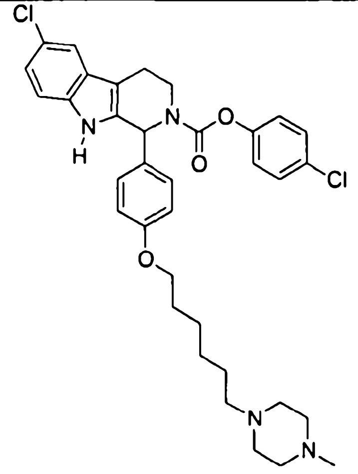
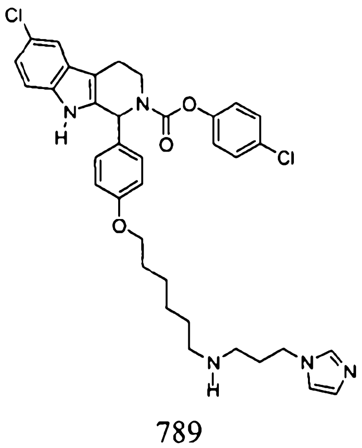
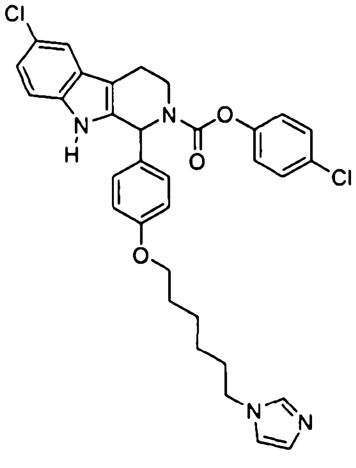
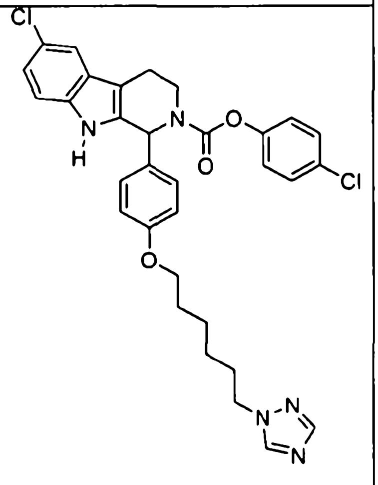
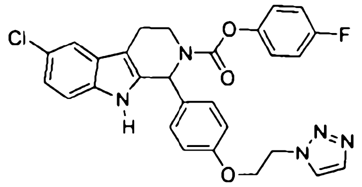
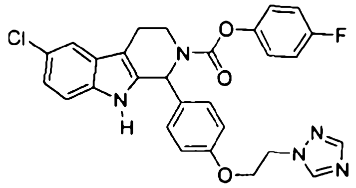
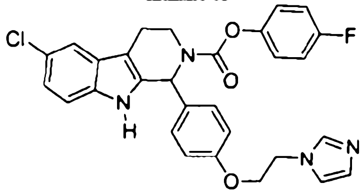
 783	 784	 785
 786	 787	 788
 789	 790	 791
 833	 834	 835

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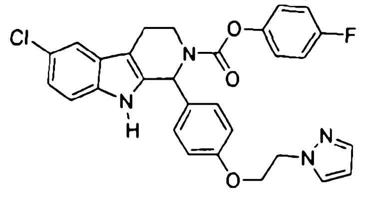
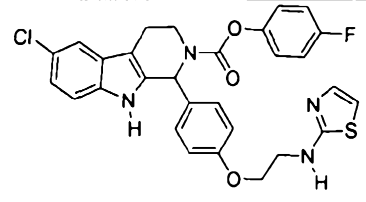
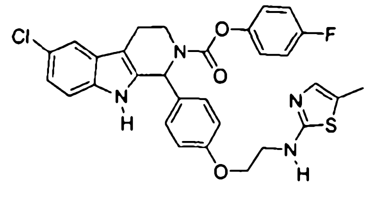
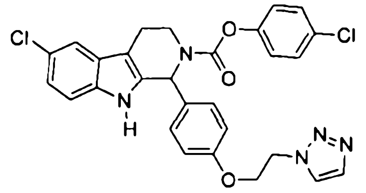
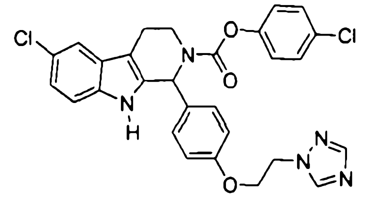
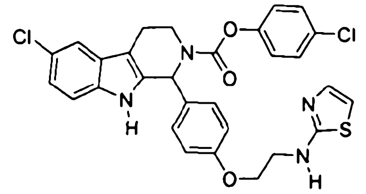
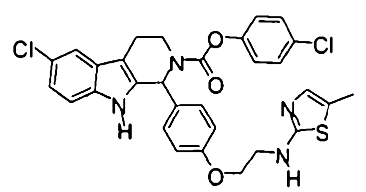
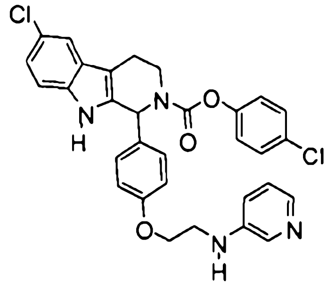
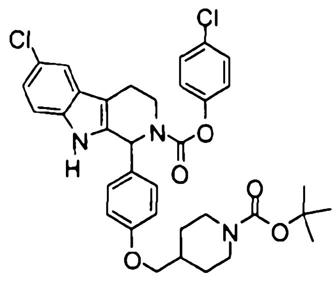
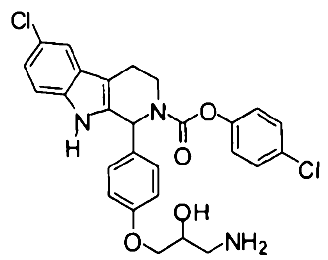
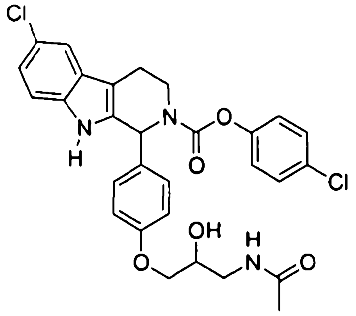
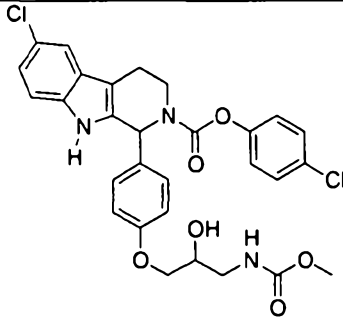
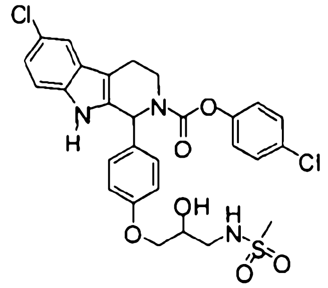
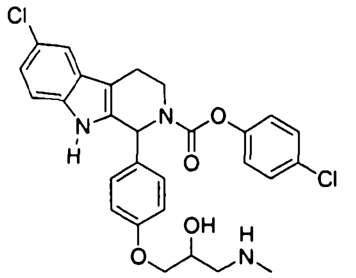
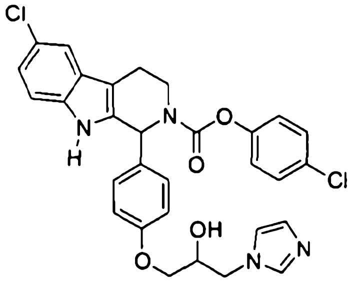
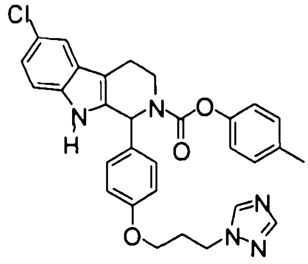
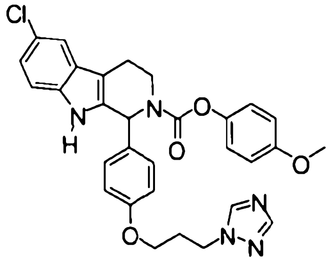
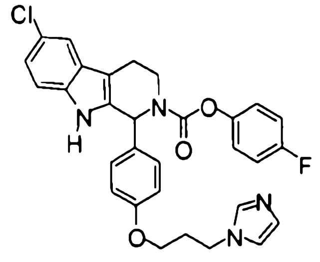
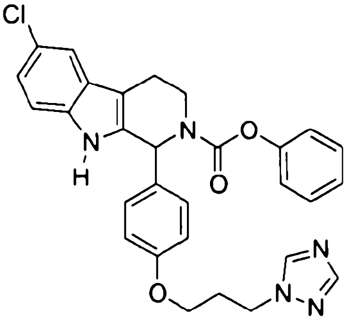
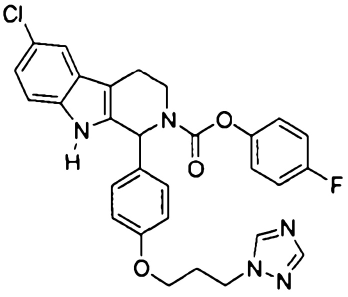
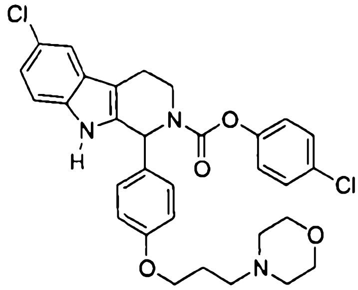
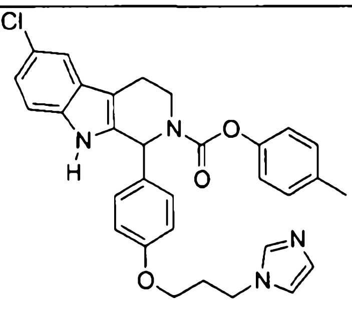
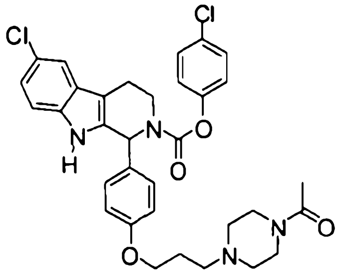
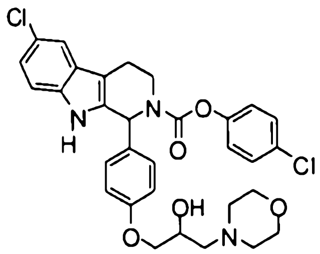
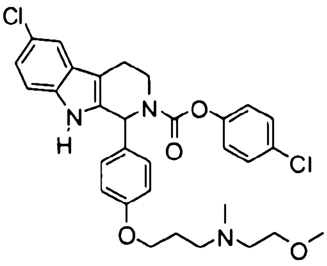
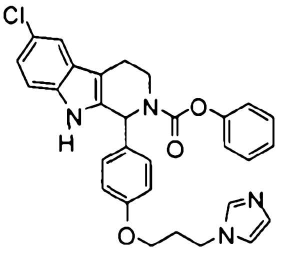
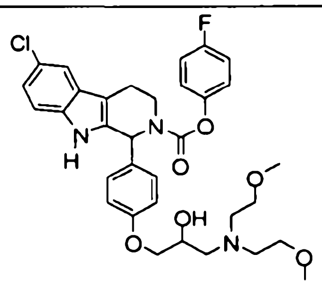
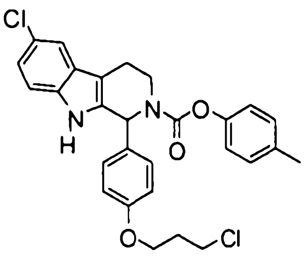
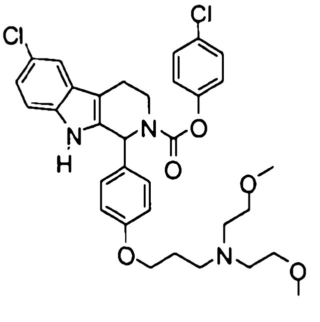
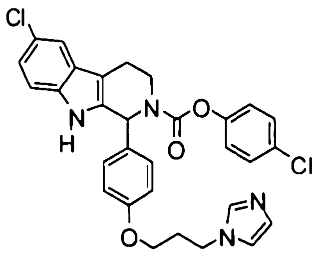
 836	 837	 838
 839	 840	 841
 842	 843	 845
 846	 847	 848
 849	 850	 867

 882	 888	 889
 891	 892	 894
 900	 903	 904
 908	 911	 913
 915	 916	 917

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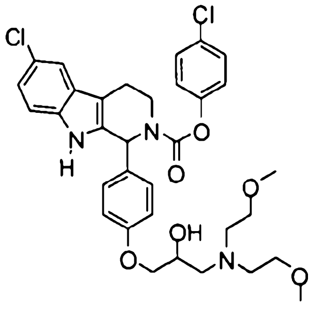
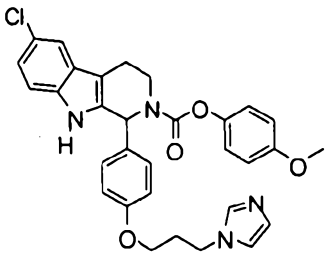
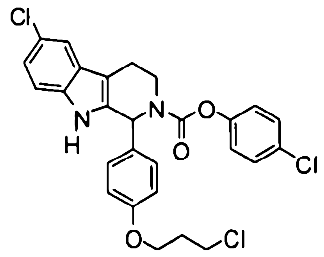
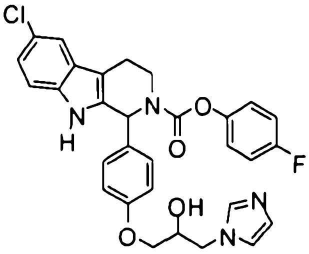
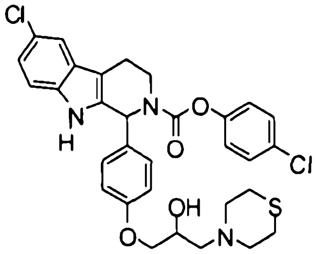
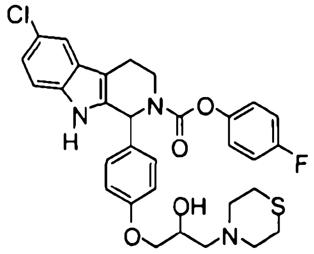
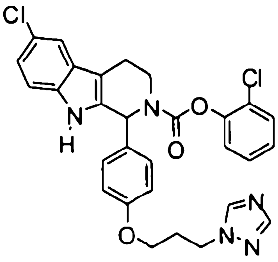
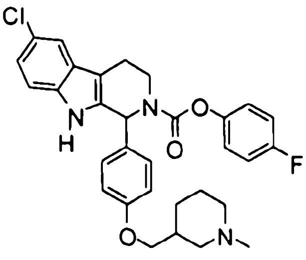
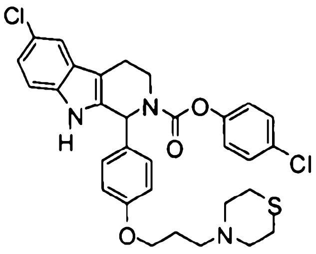
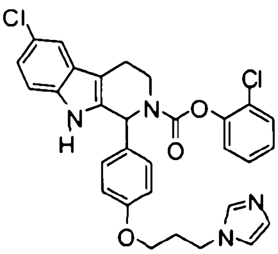
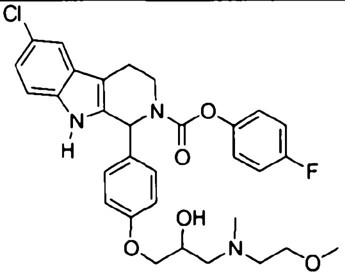
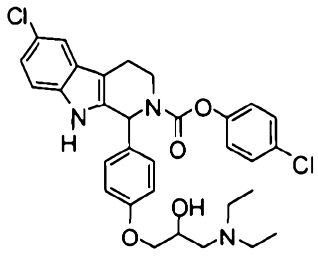
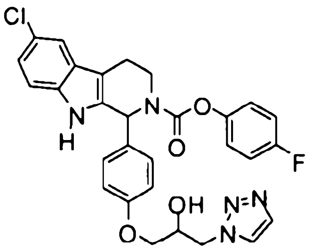
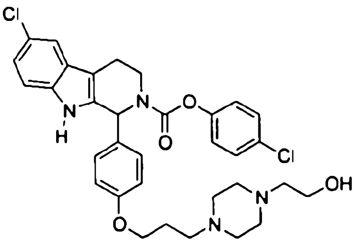
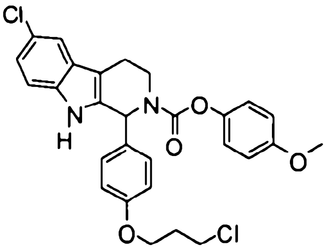
 918	 920	 921
 922	 923	 925
 926	 932	 933
 934	 936	 938
 941	 942	 944

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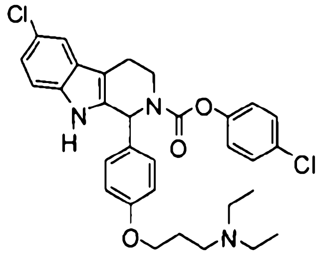
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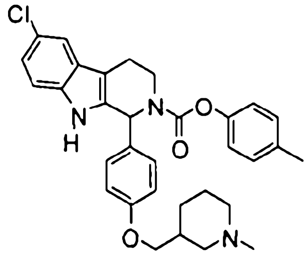
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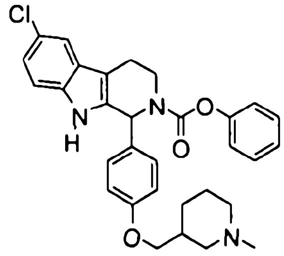
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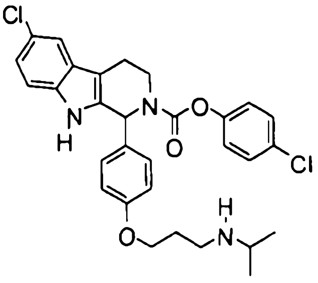
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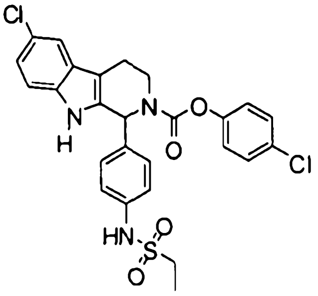
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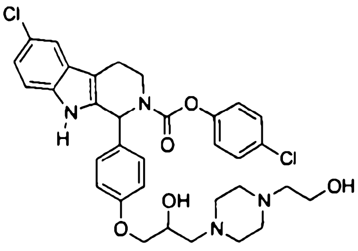
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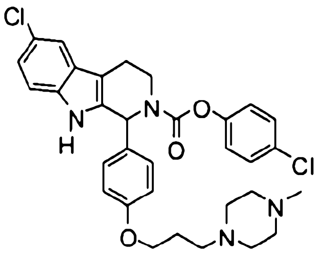
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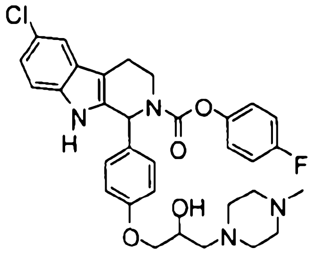
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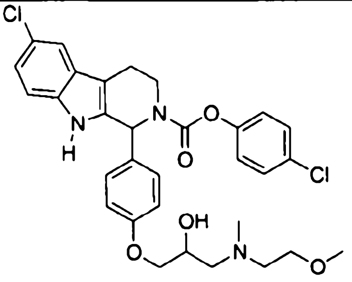
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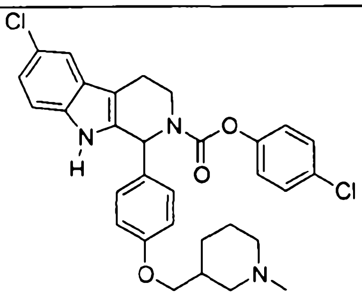
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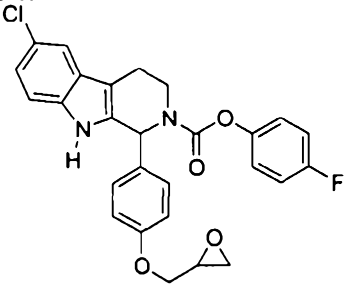
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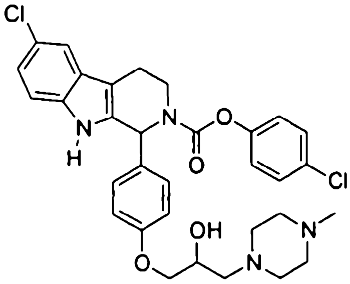
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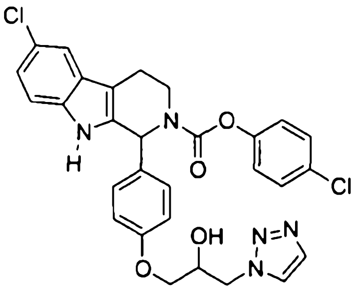
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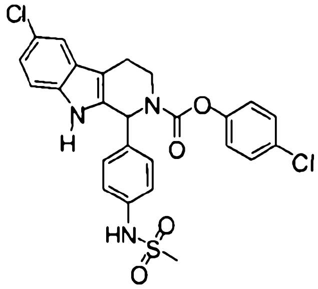
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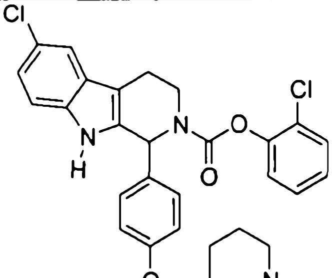
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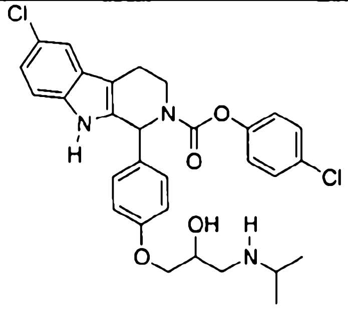
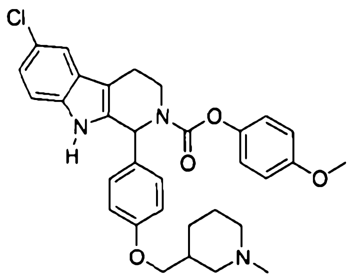
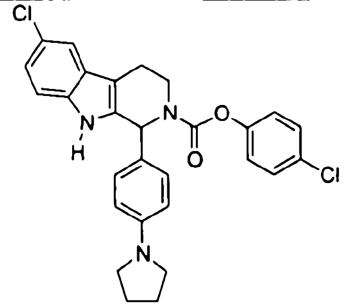
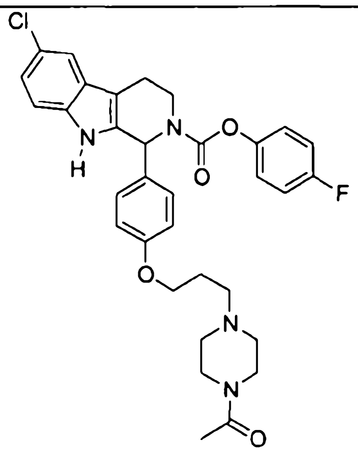
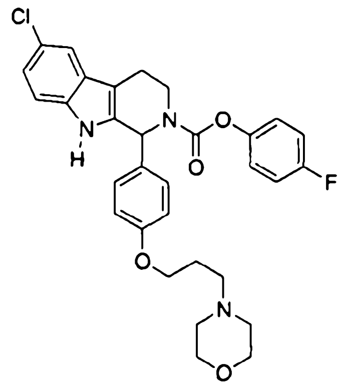
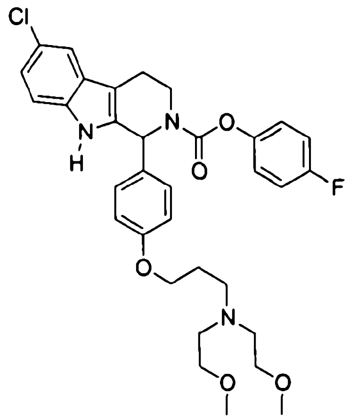
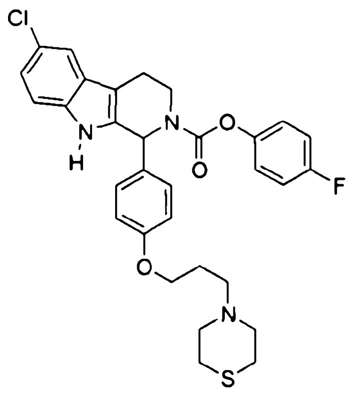
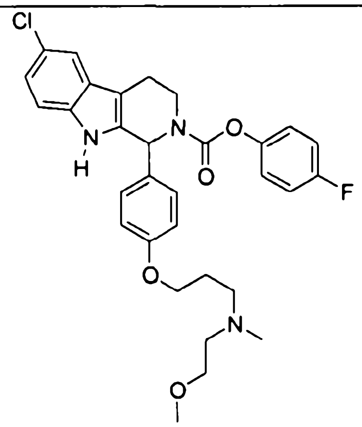
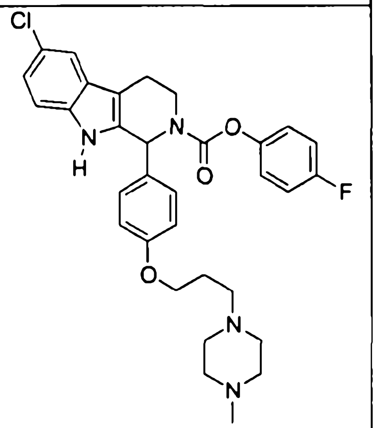
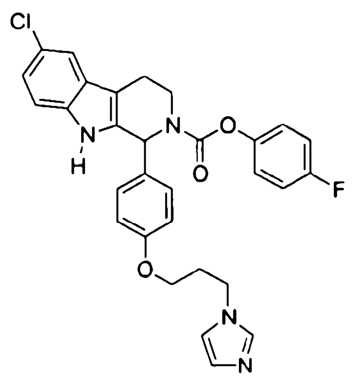
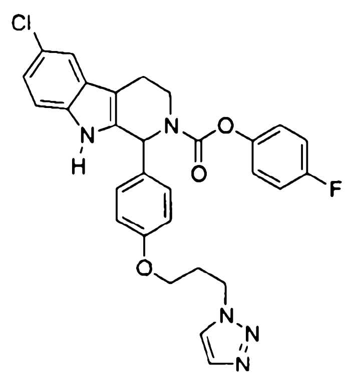
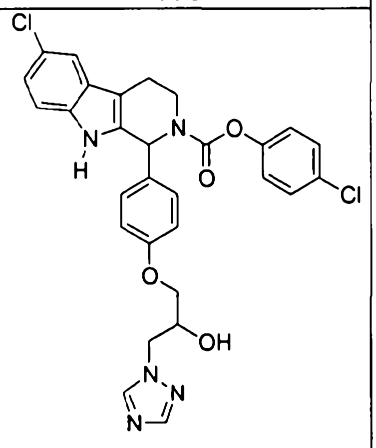
 977	 981	 984
 988	 989	 990
 991	 992	 993
 994	 995	 996

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or a pharmaceutically acceptable salt, racemate or stereoisomer thereof.

According to a third embodiment of the invention, there is provided a pharmaceutical composition comprising a compound in accordance with the first embodiment of the present invention or a pharmaceutically acceptable salt, racemate or stereoisomer thereof and a pharmaceutically acceptable excipient.

According to a fourth embodiment of the invention, there is provided a pharmaceutical composition comprising a compound in accordance with the second embodiment of the present invention or a pharmaceutically acceptable salt, racemate or stereoisomer thereof and a pharmaceutically acceptable excipient.

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), (II) and (III), including Formulas (I-a) to (I-l), 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 or exudative macular degeneration.

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, rheumatoid arthritis, psoriasis, atherosclerosis, chronic inflammation, other chronic inflammation-related diseases and disorders, obesity, or exudative macular degeneration using the compounds described herein.

In one embodiment, the invention is directed to methods for inhibiting VEGF production comprising administering a VEGF-expression 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 yet another embodiment, methods for the treatment of cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, chronic inflammation, other chronic inflammation-related diseases and disorders, obesity, 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.

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

Brief Description of the Drawings

FIG 1. Figure 1 illustrates inhibition of VEGF expression by a certain compound of the invention.

FIG 2. Figure 2 illustrates that the activity of phosphdiesterase 5 (PDE-5) is not effected by certain compounds of the invention.

Detailed Description of the Invention

Aberrant up-regulation of Vascular Endothelial Growth Factor (VEGF), a key factor for angiogenesis, is an important contributor to the pathogenesis of disease states such as cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, chronic inflammation, other chronic inflammation-related diseases and disorders, obesity, or exudative macular degeneration. 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 nanomolar to sub-nanomolar activity for the inhibition of VEGF expression.

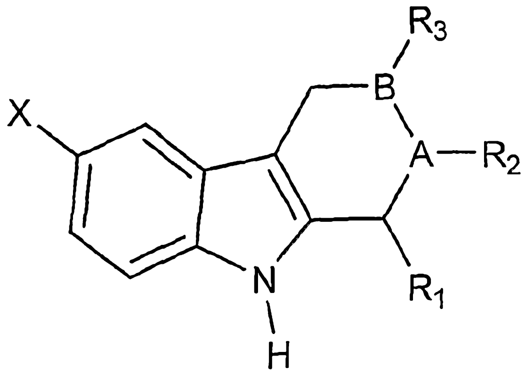
A. Compounds of the Invention

In one aspect of the invention, compounds 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 or exudative macular degeneration. In certain embodiments, the compounds of the invention specifically inhibit VEGF production, while in other embodiments, the compounds of the invention inhibit VEGF expression as well as that of other angiogenesis factors such as FGF-2. In this regard, pan-angiogenic inhibitor may be preferred in methods of inhibiting tumor growth, while VEGF specific inhibitors may be preferred for the treatment of ocular neovascular disorders (Eyetech Study Group, *22*(2):143-52 (2002)).

The compounds of the invention generally include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as enantiomerically pure compositions. The compounds may exist as (*R*) or (*S*) isomers (when one chiral center is present) in enantiomerically pure compositions. In a preferred embodiment, the compounds of the invention are the (*S*) isomers and may exist as enantiomerically pure compositions comprising only the (*S*) isomer. As one of skill will recognize, when more than one chiral center is present, the compounds of the invention may exist as (*R,R*), (*R,S*), (*S,R*), (*S,S*), *etc.* isomer. Preferred compounds included (*S,S*) and (*S,R*) isomers.

As used herein, "enantiomerically pure" refers to compositions consisting substantially of a single isomer, preferably consisting of 90%, 92%, 95%, 98%, 99%, or 100% of a single isomer.

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 C_1 to C_6 alkyl, optionally substituted with one or more halogens; a hydroxyl group; a halogen; a C_1 to C_5 alkoxy, optionally substituted with a C_6 to C_{10} aryl group;

A is C or N;

B is C or N, with the proviso that at least one of A or B is N, and that when A is N, B is C;

R_1 is a hydroxyl group; a C_1 to C_8 alkyl group, optionally substituted with an alkylthio group, a 5 to 10 membered heteroaryl, a C_6 to C_{10} aryl group optionally substituted with at least one independently selected R_o group; a C_2 to C_8 alkyenyl group; a C_2 to C_8 alkynyl group; a 3 to 12 membered heterocycle group, wherein the heterocycle group is optionally substituted with at least one independently selected halogen, oxo, amino, alkylamino, acetamino, thio, or alkylthio group; a 5 to 12 membered heteroaryl group, wherein the heteroaryl group is optionally substituted with at least one independently selected halogen, oxo, amino, alkylamino, acetamino, thio, or alkylthio group; or a C_6 to C_{10} aryl group, optionally substituted with at least one independently selected R_o group;

R_o is a halogen; a cyano; a nitro; a sulfonyl, wherein the sulfonyl is optionally substituted with a C_1 to C_6 alkyl or a 3 to 10 membered heterocycle; an amino group, wherein the amino group is optionally substituted with a C_1 to C_6 alkyl, -C(O)-R_b, -C(O)O-R_b, a sulfonyl, an alkylsulfonyl, a 3 to 10 membered heterocycle group optionally substituted with a -C(O)O-R_n; -C(O)-NH-R_b; a 5 to 6 membered heterocycle; a 5 to 6 membered heteroaryl; a C_1 to C_6 alkyl group, wherein the alkyl group is optionally substituted with at least one independently selected hydroxyl, halogen, amino, or 3 to 12 membered heterocycle group, wherein the amino group and heterocycle group are optionally substituted with at least one independently selected C_1 to C_4 alkyl group, which C_1 to C_4 alkyl group is optionally substituted with at least one independently selected C_1 to C_4 alkoxy group, amino group, alkylamino group, or 5 to 10 membered heterocycle group; a -C(O)-R_n group; or an -OR_a group;

R_a is hydrogen; C_2 to C_8 alkylene; a -C(O)O-R_b group; a -C(O)-NH-R_b; a C_1 to C_8 alkyl, wherein the alkyl group is optionally substituted with at least one independently selected hydroxyl, halogen, C_1 to C_4 alkoxy, amino, alkylamino, acetamide, -C(O)-R_b, -C(O)O-R_b, C_6 to C_{10} aryl, 3 to 12 membered heterocycle, or 5 to 12 heteroaryl group, further wherein the alkylamino is optionally substituted with a hydroxyl, a C_1 to C_4 alkoxy, or a 5 to 12 membered heteroaryl optionally substituted with a C_1 to C_4 alkyl, further wherein the acetamide is optionally substituted with a C_1 to C_4 alkoxy, sulfonyl, or alkylsulfonyl, further wherein and the heterocycle group is optionally substituted with a C_1 to C_4 alkyl optionally substituted with a hydroxyl group, -C(O)-R_n, -C(O)O-R_n, or an oxo group;

R_b is hydroxyl; an amino; an alkylamino, wherein the alkylamino is optionally substituted with a hydroxyl, an amino, an alkylamino, a C_1 to C_4 alkoxy, a 3 to 12 membered heterocycle optionally substituted with at least one independently selected C_1 to C_6 alkyl, oxo, -C(O)O-R_n, or a 5 to 12 membered heteroaryl optionally substituted with a C_1 to C_4 alkyl; a C_1 to C_4 alkoxy; a C_2 to C_8 alkenyl; a C_2 to C_8 alkynyl; a C_6 to C_{10} aryl, wherein the aryl is optionally substituted with at least one independently selected halogen or C_1 to C_4 alkoxy; a 5 to 12 membered heteroaryl; 3 to 12 membered heterocycle group, wherein the heterocycle is optionally substituted with at least one independently selected acetamide, -C(O)O-R_n, 5 to 6 membered heterocycle, or C_1 to C_6 alkyl optionally substituted with a hydroxyl, C_1 to C_4 alkoxy, amino group, or alkylamino group; or a C_1 to C_8 alkyl, wherein the alkyl is optionally substituted with at least one independently selected C_1 to C_4 alkoxy, C_6 to C_{10} aryl, amino, or 3 to 12 membered heterocycle group, wherein the amino and heterocycle groups are optionally substituted with at least one independently selected C_1 to C_6 alkyl, oxo, or -C(O)O-R_n group;

R_2 is a hydrogen; a hydroxyl; a 5 to 10 membered heteroaryl group; a C_1 to C_8 alkyl group, wherein the alkyl group is optionally substituted with a hydroxyl, a C_1 to C_4 alkoxy, a 3 to 10 membered heterocycle, a 5 to 10 membered heteroaryl, or C_6 to C_{10} aryl group; a -C(O)-R_c group; a -C(O)O-R_d group; a -C(O)-N(R_dR_d) group; a -C(S)-N(R_dR_d) group; a -C(S)-O-R_e group; a -S(O_2)-R_e group; a -C(NR_e)-S-R_e group; or a -C(S)-S-R_f group;

R_c is hydrogen; an amino, wherein the amino is optionally substituted with at least one independently selected C_1 to C_6 alkyl or C_6 to C_{10} aryl group; a C_6 to C_{10} aryl, wherein the aryl is optionally substituted with at least one independently selected halogen, haloalkyl, hydroxyl, C_1 to C_4 alkoxy, or C_1 to C_6 alkyl group; -C(O)-R_n; a 5 to 6 membered heterocycle, wherein the heterocycle is optionally substituted with a -C(O)-R_n group; a 5 to 6 membered heteroaryl; a thiazoleamino group; a C_1 to C_8 alkyl group, wherein the alkyl group is optionally substituted with at least one independently selected halogen, a C_1 to C_4 alkoxy, a phenyloxy, a C_6 to C_{10}

aryl, -C(O)-R_n, -O-C(O)-R_n, hydroxyl, or amino group, optionally substituted with a -C(O)O-R_n group;

R_d is independently hydrogen; a C_2 to C_8 alkenyl group; a C_2 to C_8 alkynyl group; a C_6 to C_{10} aryl group, wherein the aryl is optionally substituted with at least one independently selected halogen, nitro, C_1 to C_6 alkyl, -C(O)O-R_e, or -OR_e; or a C_1 to C_8 alkyl group, wherein the alkyl group is optionally substituted with at least one independently selected halogen, C_1 to C_4 alkyl, C_1 to C_4 alkoxy, phenyloxy, C_6 to C_{10} aryl, 5 to 6 membered heteroaryl, -C(O)-R_n, -O-C(O)-R_n, or hydroxyl group, wherein the C_6 to C_{10} aryl group is optionally substituted with at least one independently selected halogen or haloalkyl group;

R_e is a hydrogen; a C_1 to C_6 alkyl group, wherein the alkyl group is optionally substituted with at least one independently selected halogen or alkoxy group; or a C_6 to C_{10} aryl group, wherein the aryl group is optionally substituted with at least one independently selected halogen or alkoxy group;

R_f is a C_1 to C_6 alkyl group, optionally substituted with at least one independently selected halogen, hydroxyl, C_1 to C_4 alkoxy, cyano, C_6 to C_{10} aryl, or -C(O)-R_n group, wherein the alkoxy group may be optionally substituted with at least one C_1 to C_4 alkoxy group and the aryl group may be optionally substituted with at least one independently selected halogen, hydroxyl, C_1 to C_4 alkoxy, cyano, or C_1 to C_6 alkyl group;

R_n is a hydroxyl, C_1 to C_4 alkoxy, amino, or C_1 to C_6 alkyl group;

R_3 is hydrogen or -C(O)-R_g;

R_g is a hydroxyl group;; an amino group, wherein the amino is optionally substituted with a C_6 to C_{10} cycloalkyl group or a 5 to 10 membered heteroaryl group; or a 5 to 10 membered heterocycle group, wherein the heterocycle group is optionally substituted with a-C(O)-R_n group; and

n is 0, 1, 2, or 3.

As will be evident to one of skill in the art, the compounds of Formula (I) comprise at least one stereocenter (*e.g.*, at the R_1 substituent), and may exist as a racemic mixture or as an enantiomerically pure composition. In a preferred embodiment, the compounds of Formula (I) are the (S) isomer, in an enantiomerically pure composition.

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 include C_1 to C_8, C_1 to C_6, or C_1 to C_4 alkyl groups. 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, "alkenyl" generally refers to linear, branched or cyclic alkene radicals having one or more carbon-carbon double bonds, such as C_2 to C_8 and C_2 to C_6 alkenyl groups, including 3-propenyl.

As used herein, "alkynyl" generally refers to linear, branched or cyclic alkyne radicals having one or more carbon-carbon triple bonds, such as C_2 to C_8 and C_2 to C_6 alkynyl groups, including hex-3-yne.

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 napthyl (*i.e.*, napthalene) 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 one or more heteroatoms, 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, dihydro-chromen-4-only, 1,3-diazine, 1,2-diazine, 1,2-diazole, 1,4-diazanaphthalene, furan, furazan, imidazole, indole, isoxazole, isoquinoline, isothiazole, isoindolyl, 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. In certain embodiments, the heteroaryl may be optionally substituted.

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. In some embodiments, the heterocycle groups may be selected from heterocycle groups that contain one or more heteroatoms, two or more heteroatoms, three or more heteroatoms, or four or more heteroatoms. Example of heterocycle 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, "alkanoyl" generally refers to a group with the structure –C(O)-R. In certain embodiments, R may be a hydrogen, an alkyl, an 4-morpholinyl group, or a thiazoleamino group.

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_5 alkyl group.

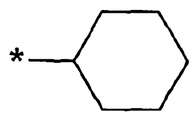
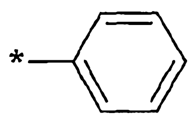
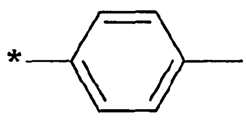
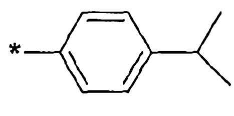
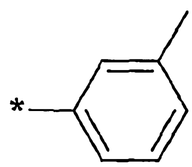
For the purposes of this invention, halo substituents may be independently selected from the halogens such as fluorine, chlorine, bromine, iodine, and astatine.

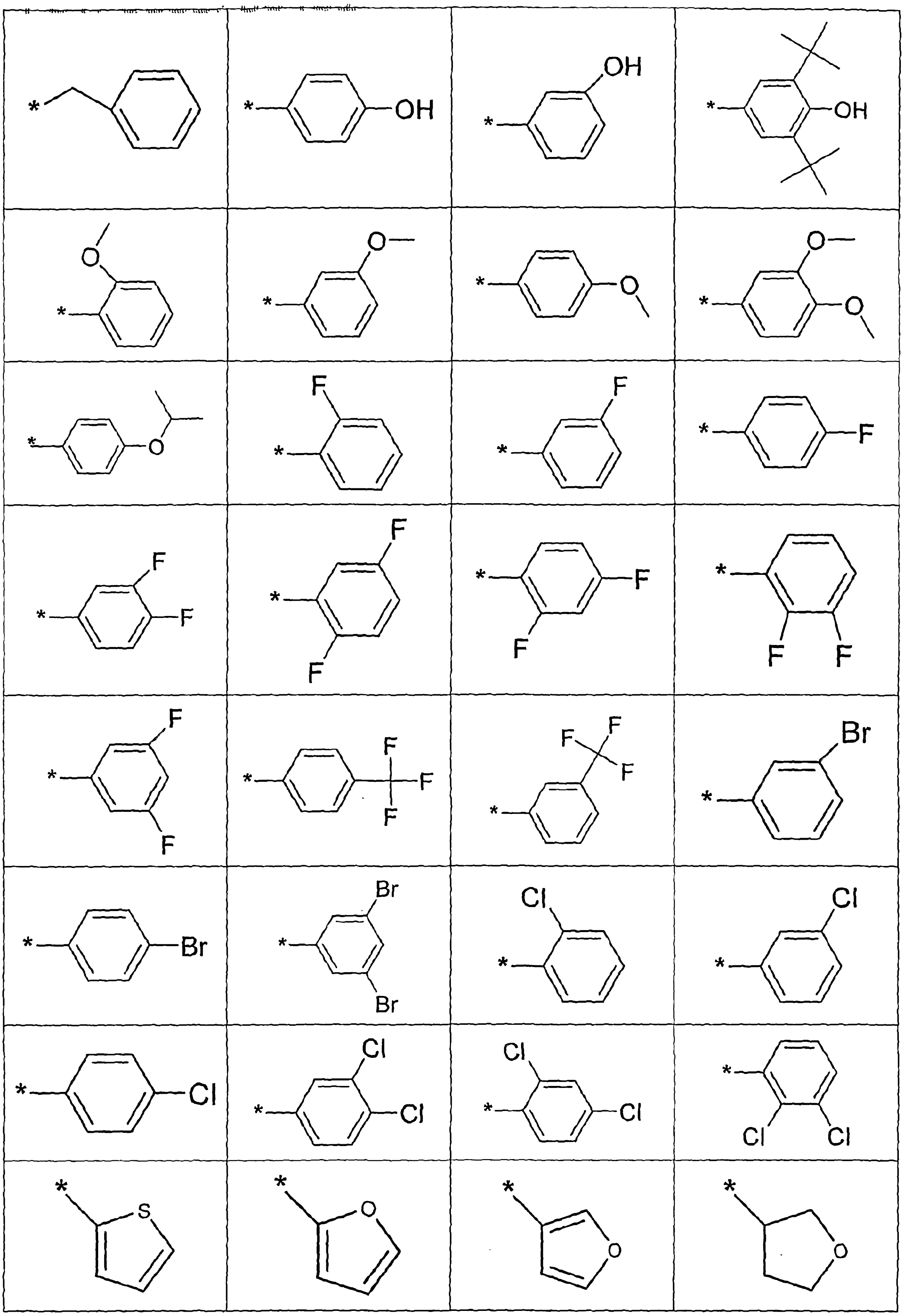
In certain preferred embodiments, X may be hydrogen, methoxy, hydroxyl, benzoxy, or a halogen, preferably bromide or chloride. In other embodiments, X may preferably be a C_1 to C_4 alkyl or a haloalkyl.

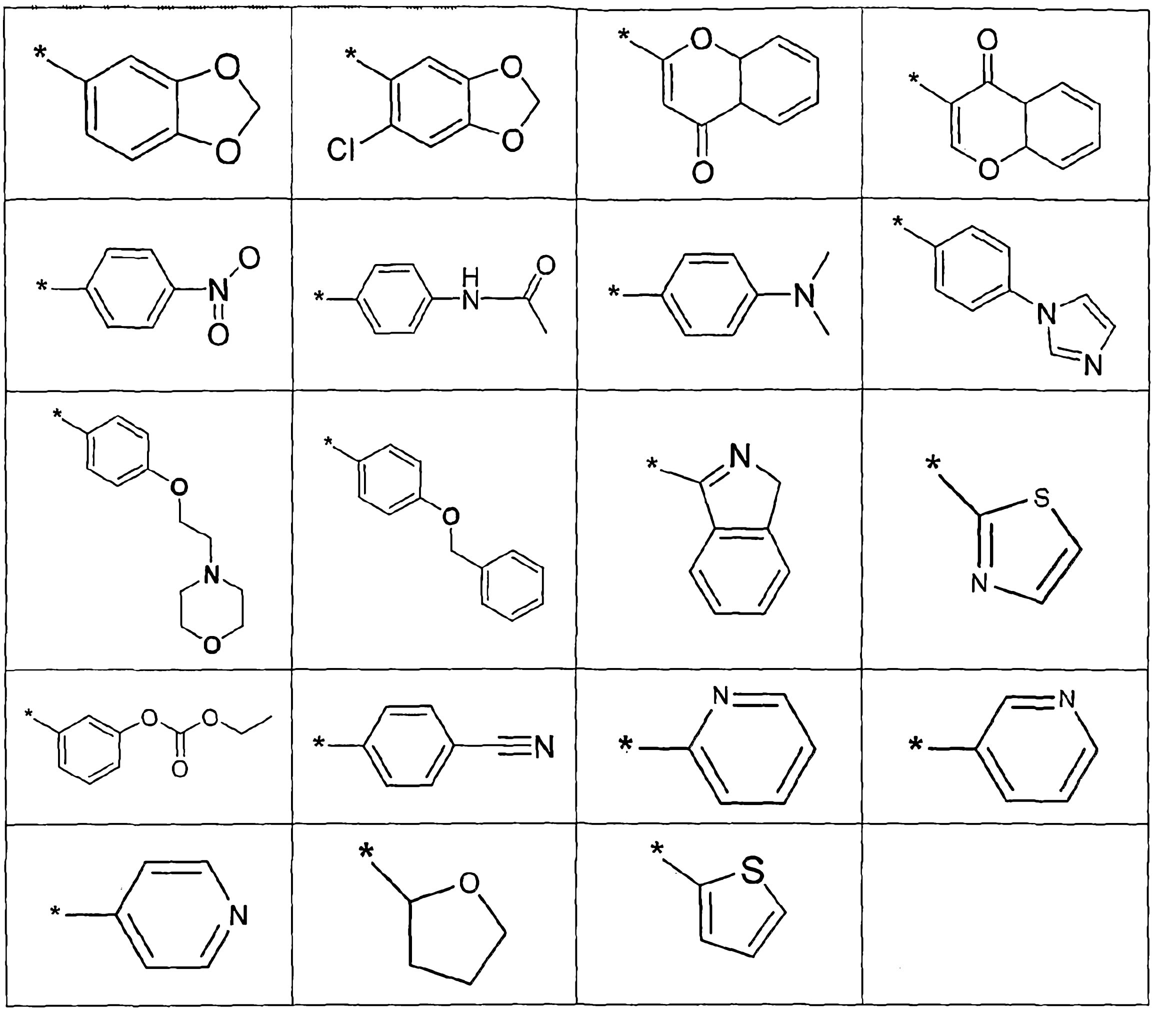
R_1 may preferably be a C_6 to C_8 aryl group, optionally substituted with at least one R_0 group. R_0 may then preferably be methoxy, benzoxy, a C_1 to C_6 alkyl, a 5 to 6 membered heteroaryl (such as furyl or imidazole), cyano, nitro, tri-fluro methyl, or a halogen, more preferably methoxy, benzoxy, iso-butyl or a halogen, and more preferably methoxy, iso-butyl, bromide or chloride. Alternatively, R_1 may be a 5 to 10 membered heteroaryl or 3 to 12 membered heterocycle, such as a pyridinyl group, a thiophene group, a furyl group, a tetrahydro furyl group, and a thiazole group dihydro-chromen-4-onyl group, a 1*H*-isoindolyl group, or a benzodioxole group.

R_2 may preferably be a $-CH_2$-furyl group, a pyrimidyl group, or a –C(O)O-R_d group. R_d may preferably then be a C_1 to C_6 alkyl, optionally substituted with at least one halogen; or a C_5 to C_6 aryl, optionally substituted with at least one methyl, methoxy, or halogen.

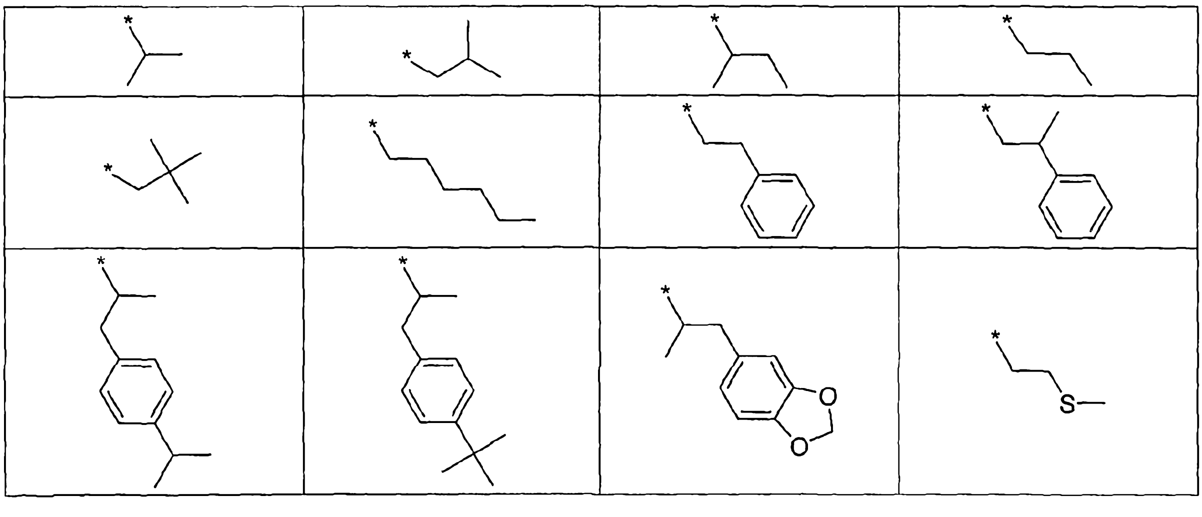
Preferred R_1 substituents also include the following, where the * indicates the bond of attachment to the carboline scaffold molecule.

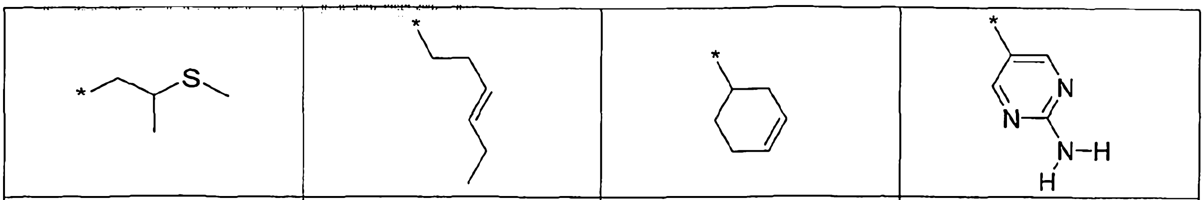
-OH	-ethyl	-pentyl	
			

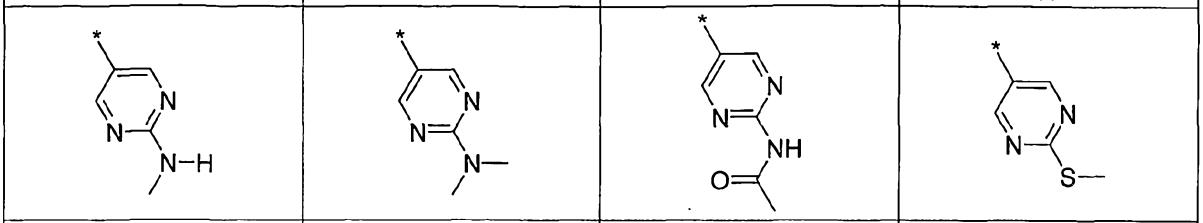


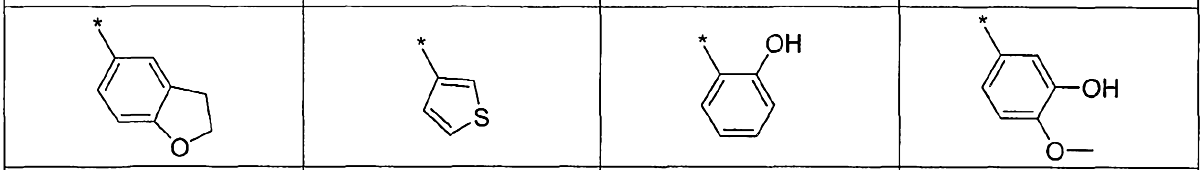


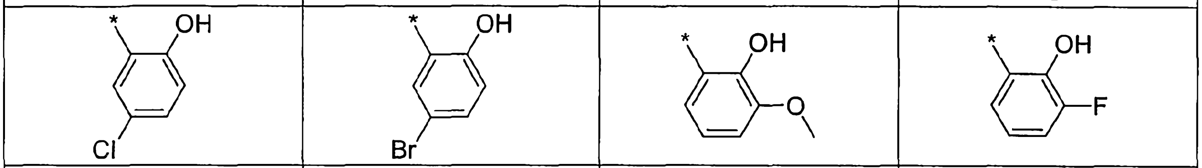
Other preferred R_1 substituents include the following, where the * indicates the bond of attachment to the carboline scaffold molecule.

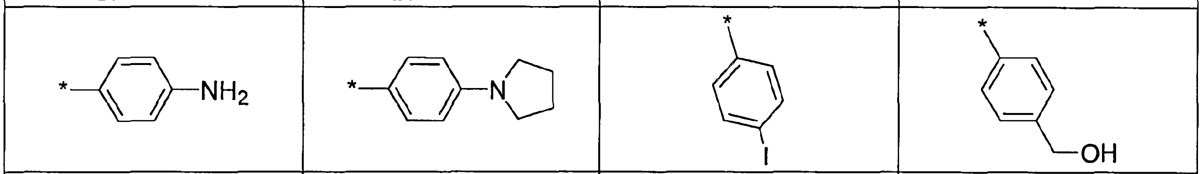


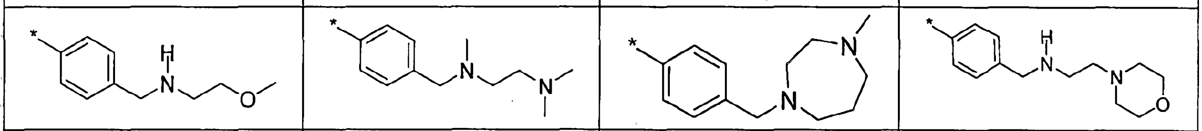


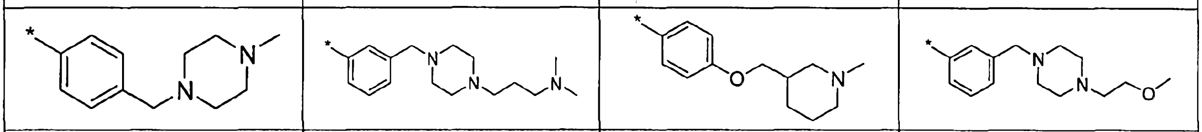


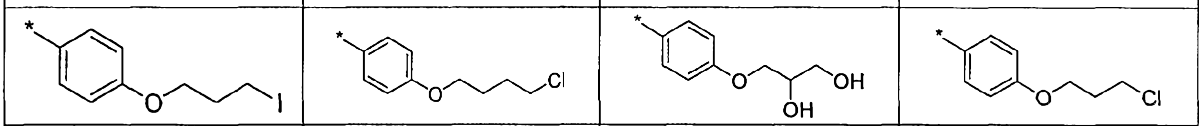


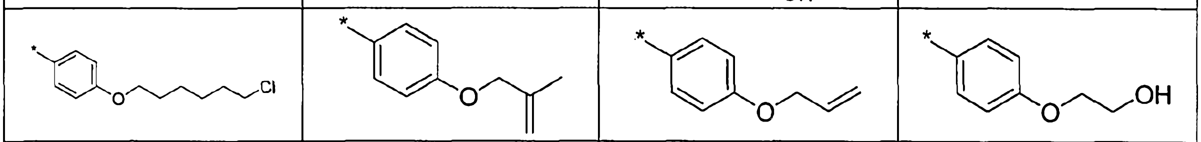


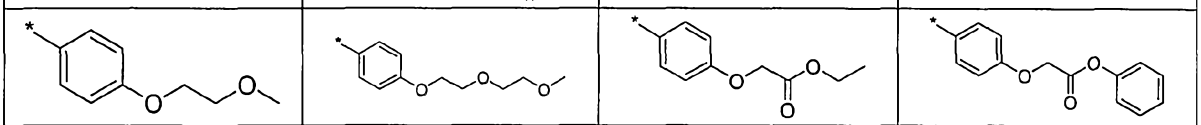


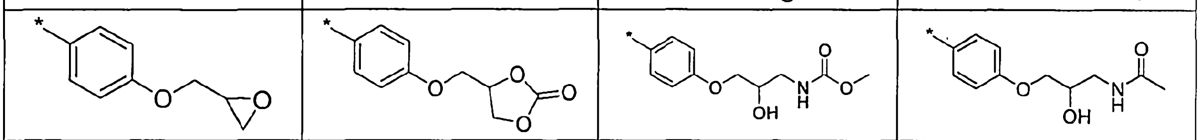


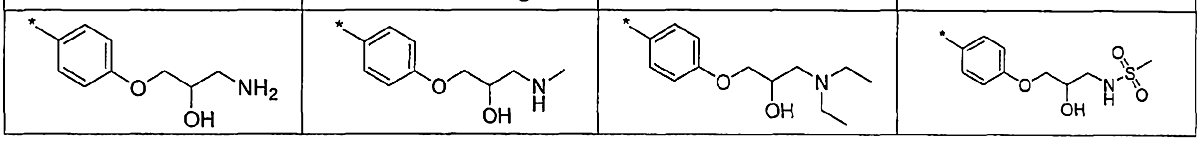


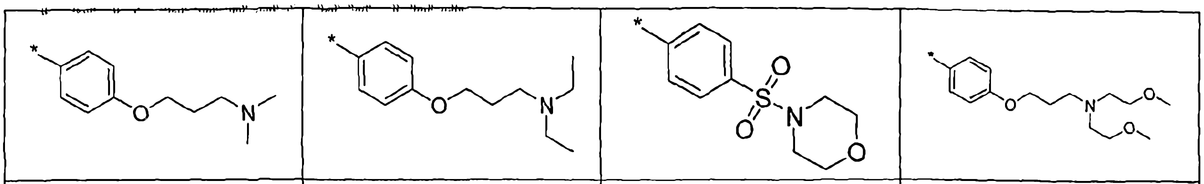


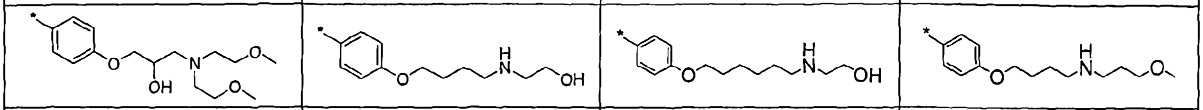


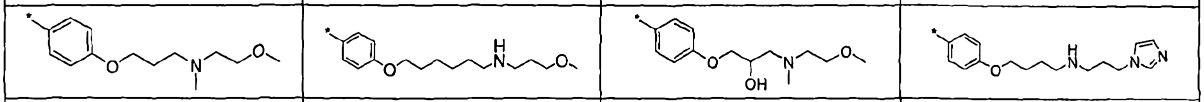


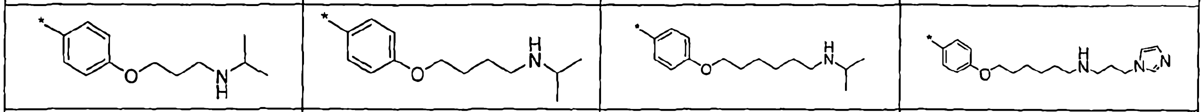


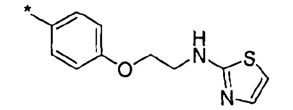
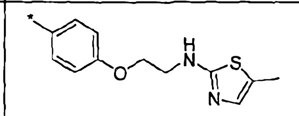
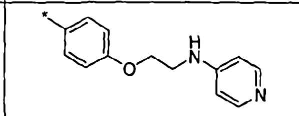
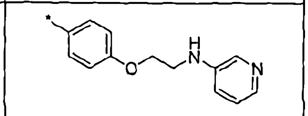


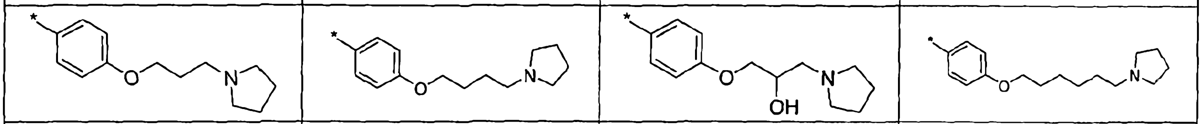


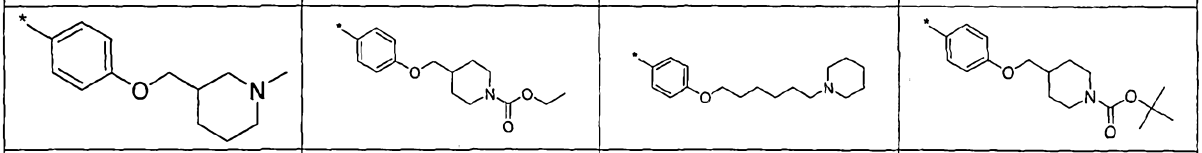


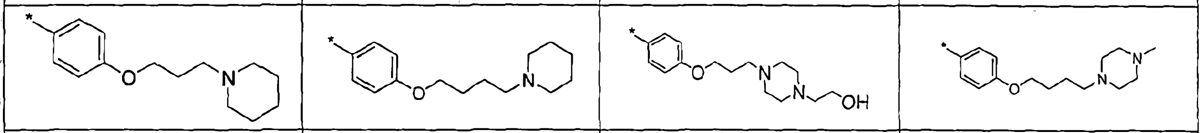


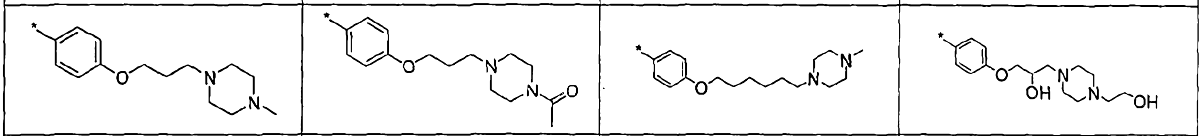


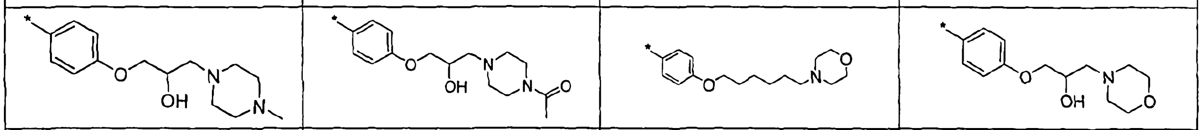
 and regioisomers thereof	 and regioisomers thereof	 and regioisomers thereof	 and regioisomers thereof

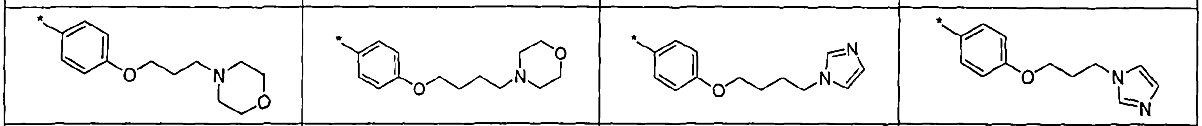


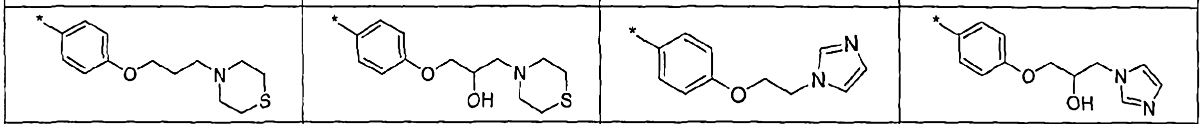


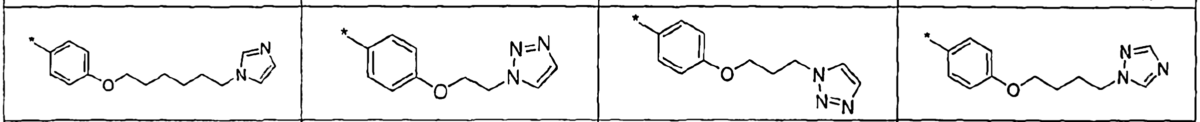


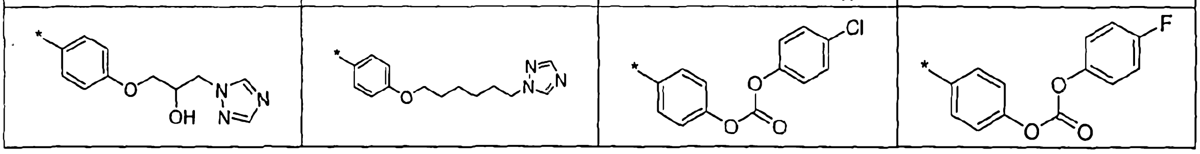


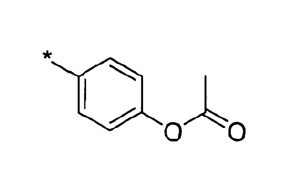
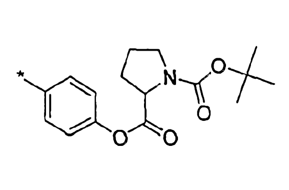
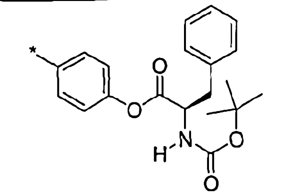
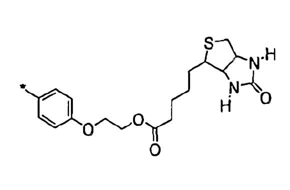
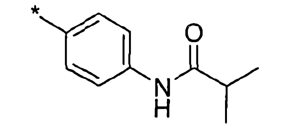
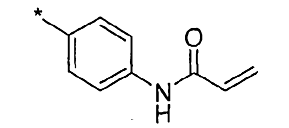
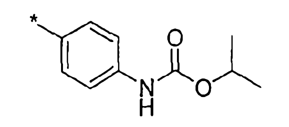
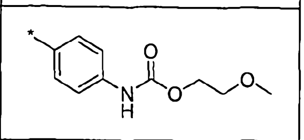
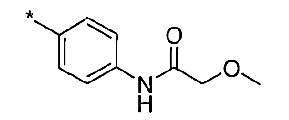
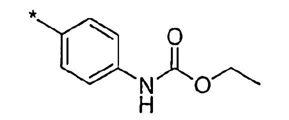
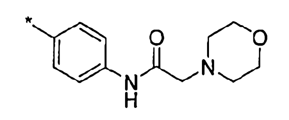
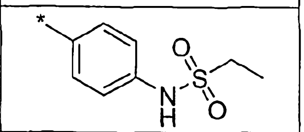
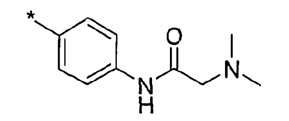
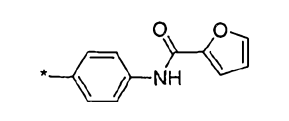
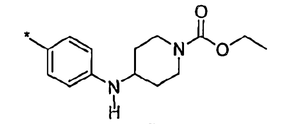
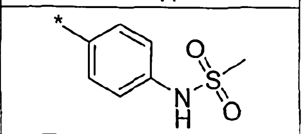
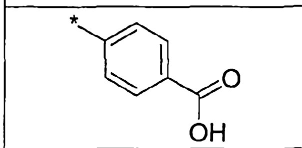
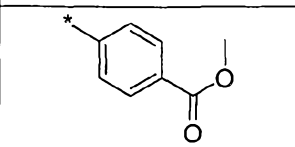
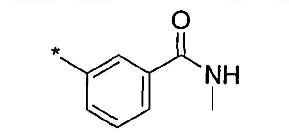
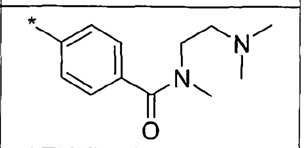
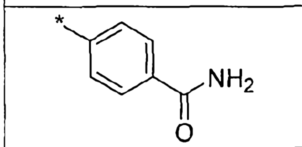
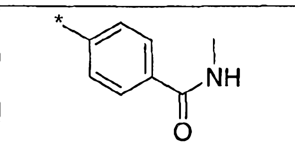
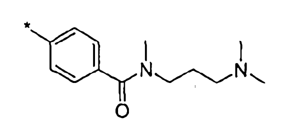
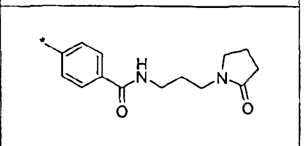
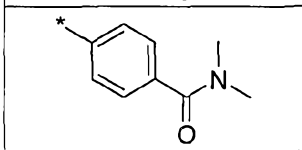
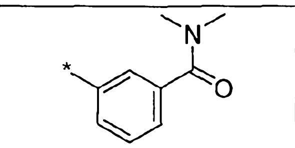
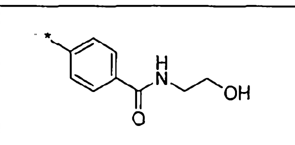
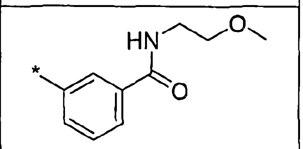
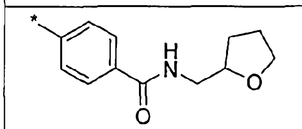
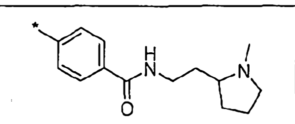
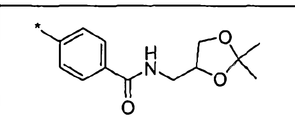
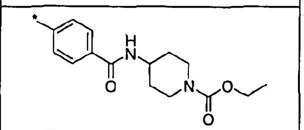
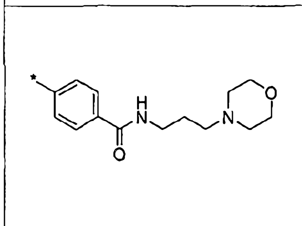
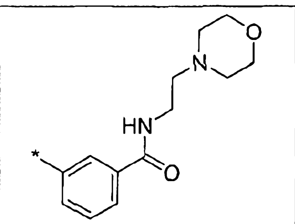
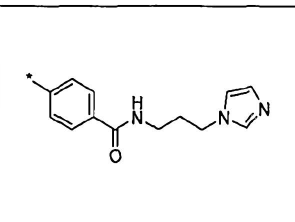
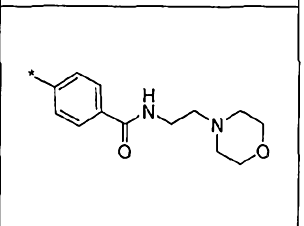
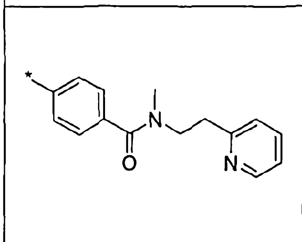
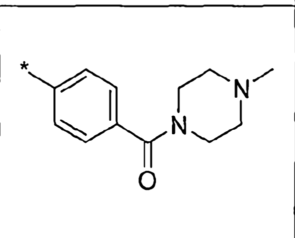
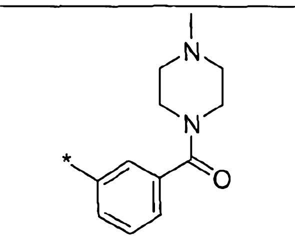
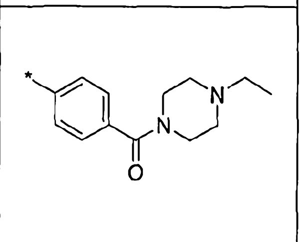


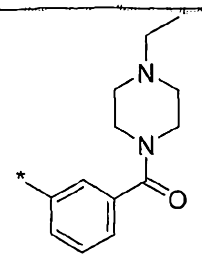
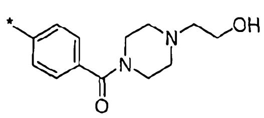
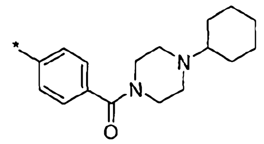
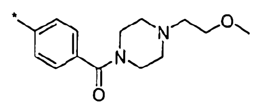
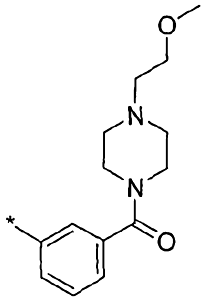
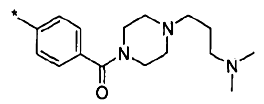
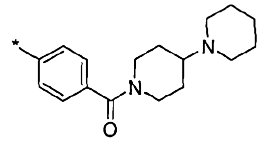
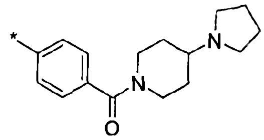
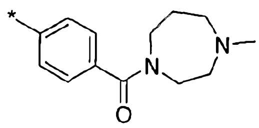
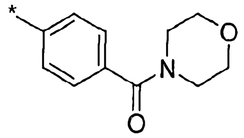
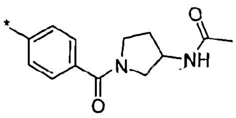
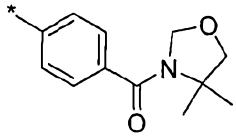
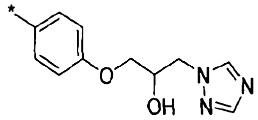
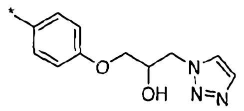
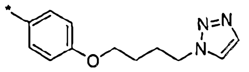
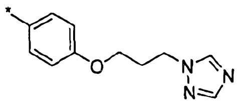
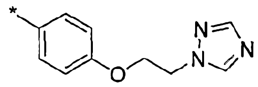




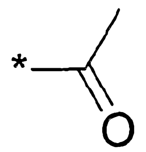
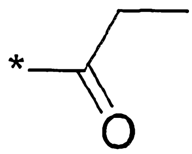
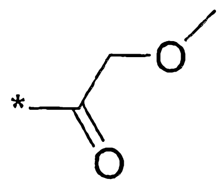
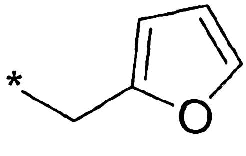
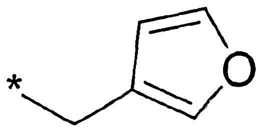
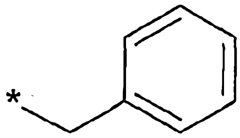
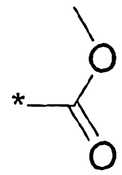
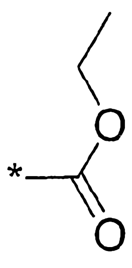
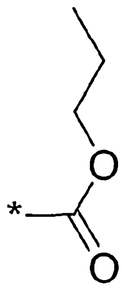
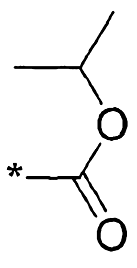
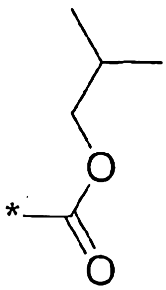


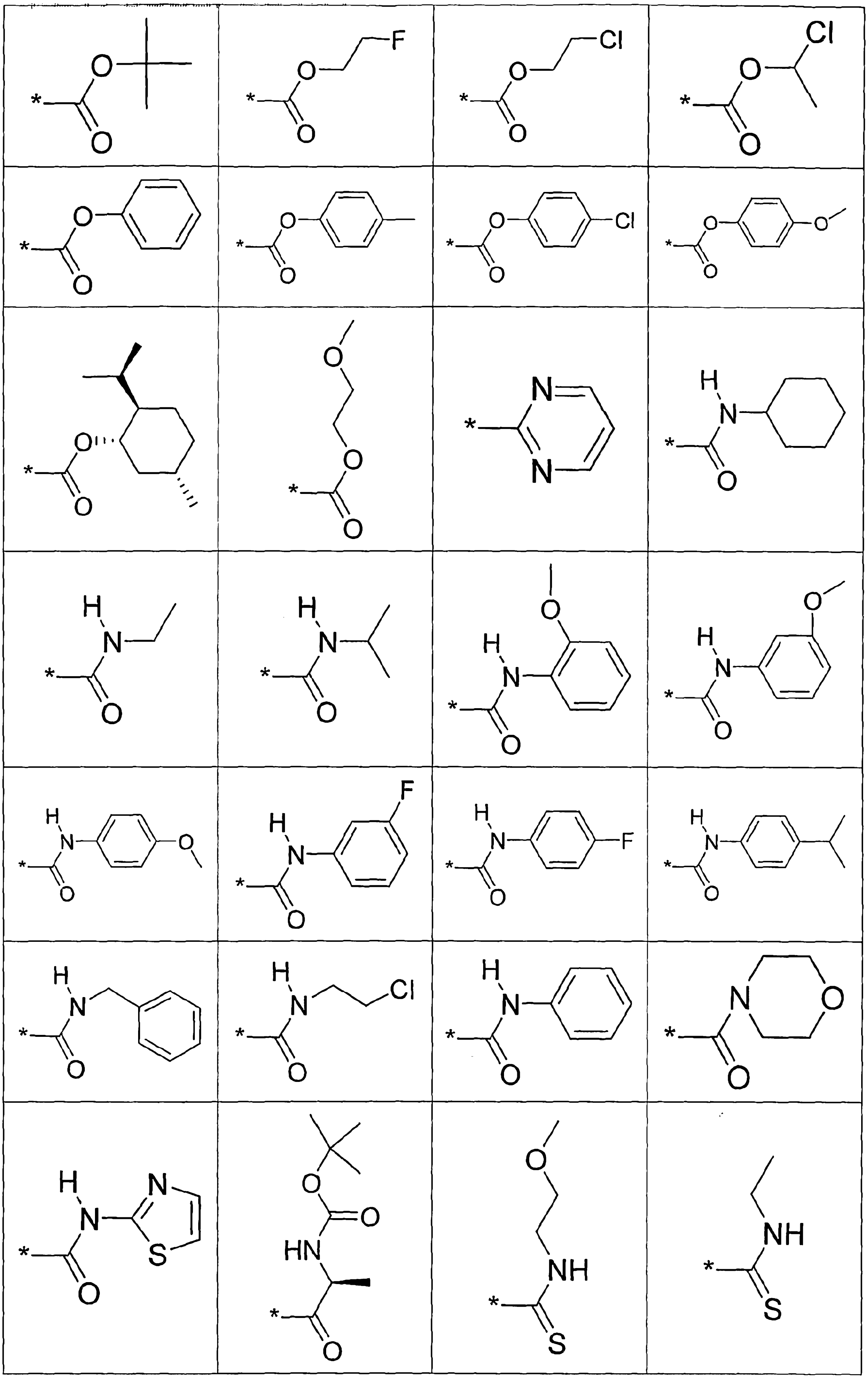


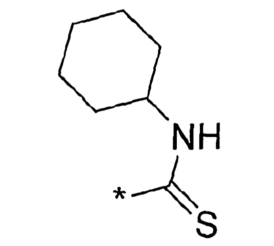
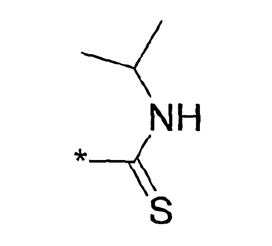
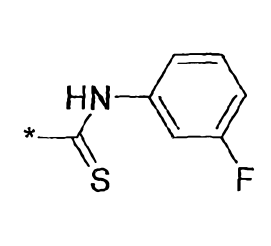
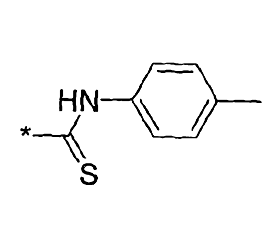
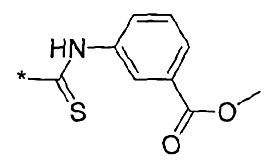
			
			
			
			
			
			
			
			
			
			

Preferred R_2 substituents also include the following, where the * indicates the bond of attachment to the carboline scaffold molecule.

-H -OH			
			
			



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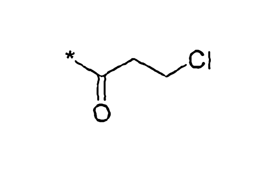
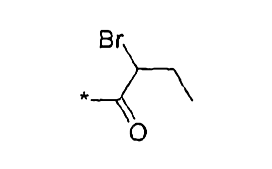
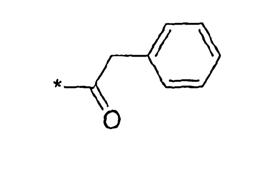
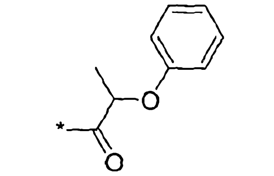
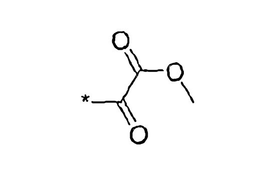
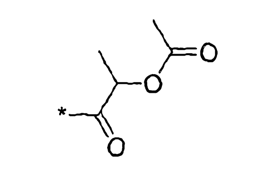
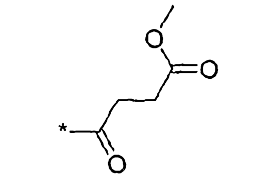
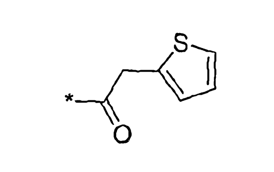
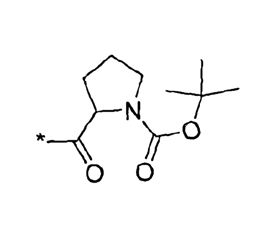
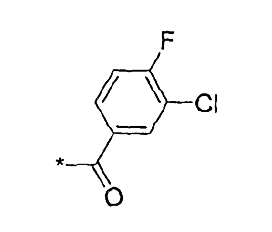
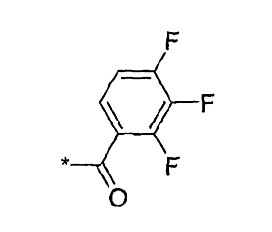
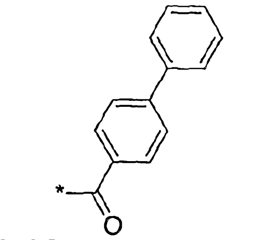
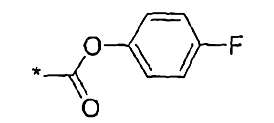
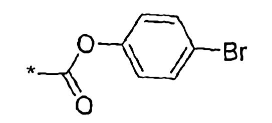
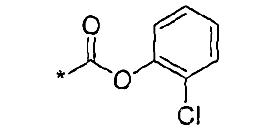
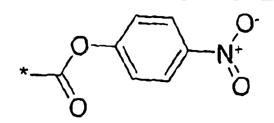
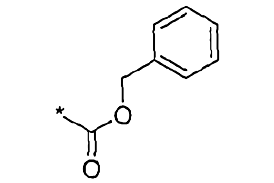
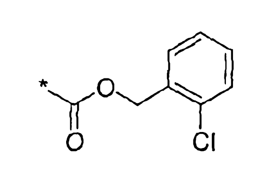
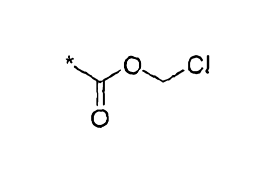
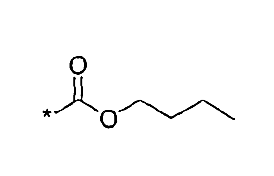
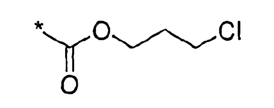
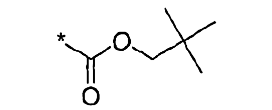
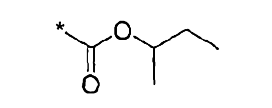
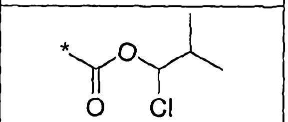
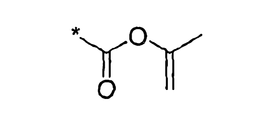
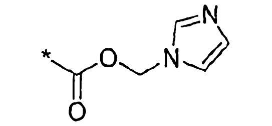
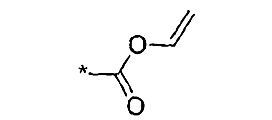
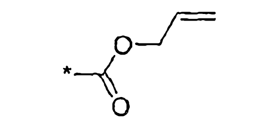
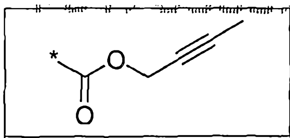
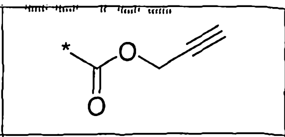
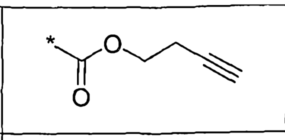
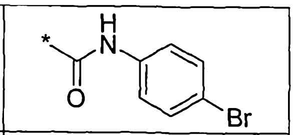
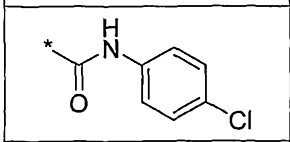
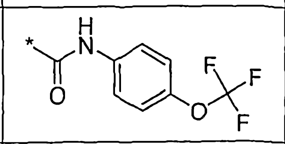
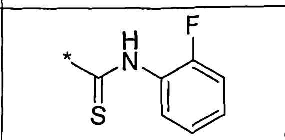
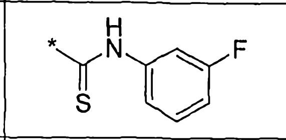
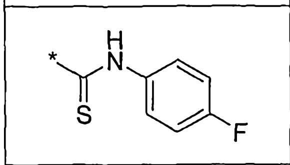
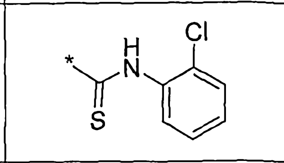
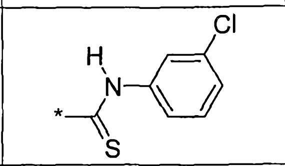
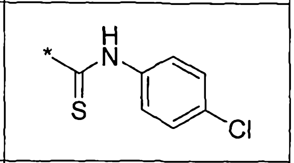
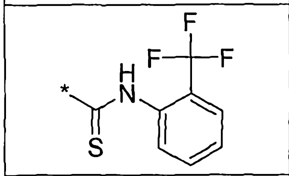
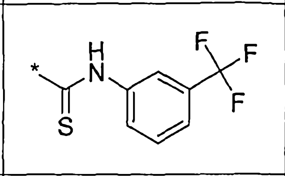
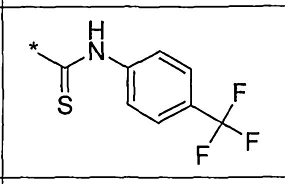
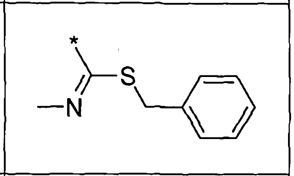
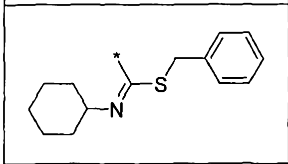
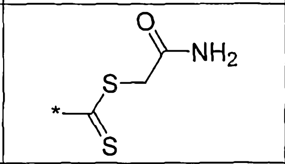
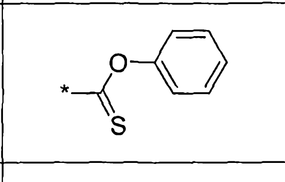
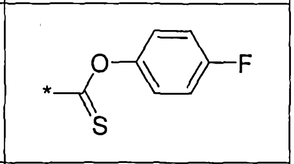
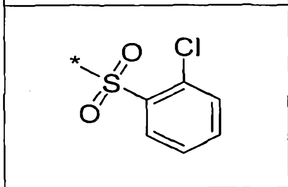
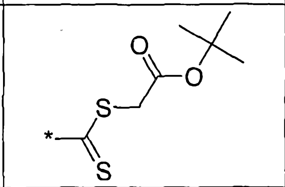
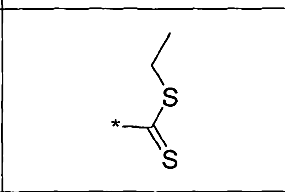
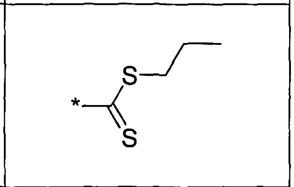
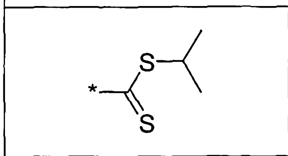
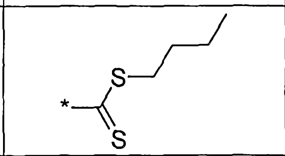
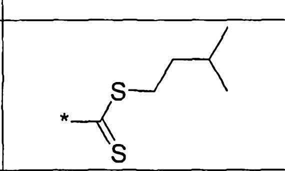
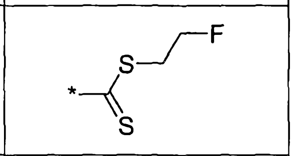
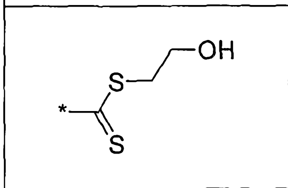
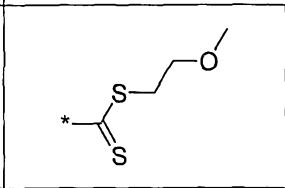
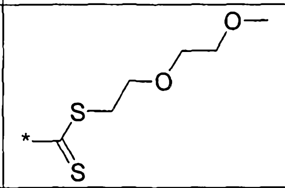
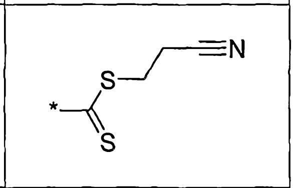
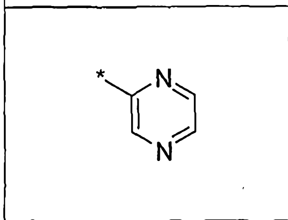
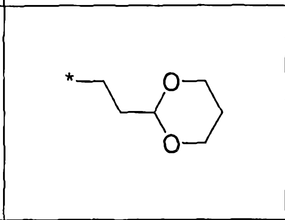
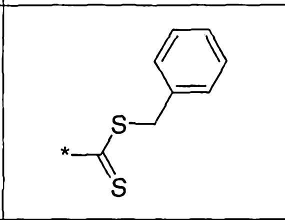
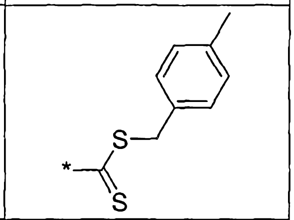
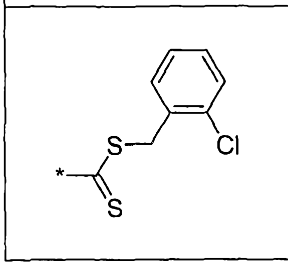
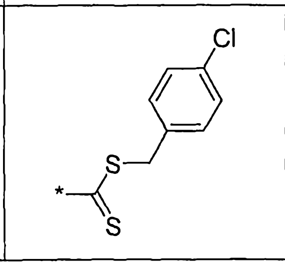
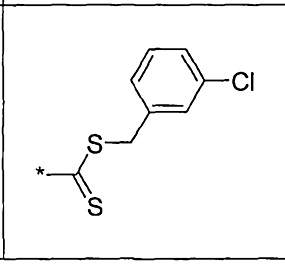
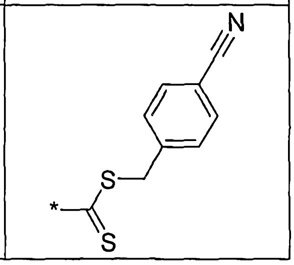
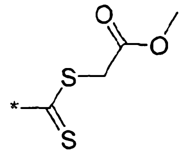
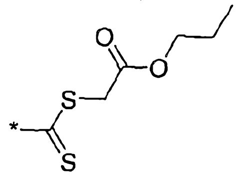
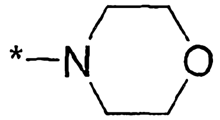
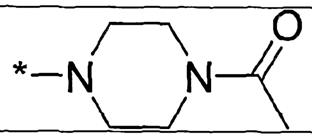
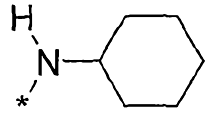
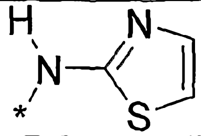
			
			
			
			
			
			
			

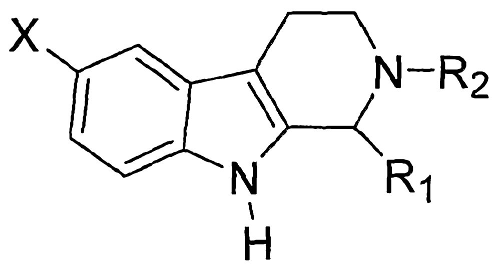
			
			
			
			
			
			
			
			
			
			

Preferred R_3 substituents include the following, where the * indicates the bond of attachment to the carboline scaffold molecule.

*—OH		
		

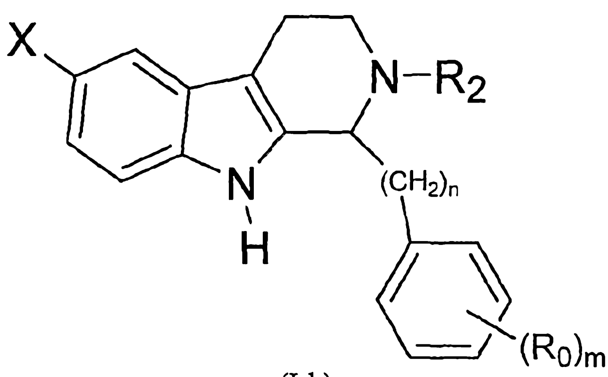
A preferred class of compounds within Formula (I) include those compounds of Formula (I-a) as shown below.



(I-a)

wherein X, R_1 and R_2 are defined as described with regard to Formula (I) and the preferred embodiments described above.

Another preferred class of compounds within Formula (I) include those compounds of Formula (I-b) as shown below.



(I-b)

wherein:

X is a halogen;

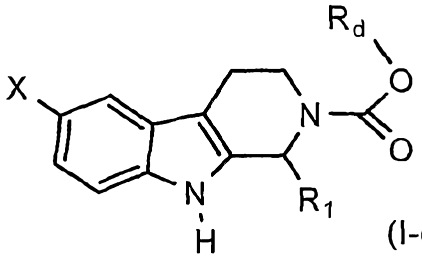
R_2 is as described above with regard to Formula (I);

R_0 is as described above with regard to Formula (I);

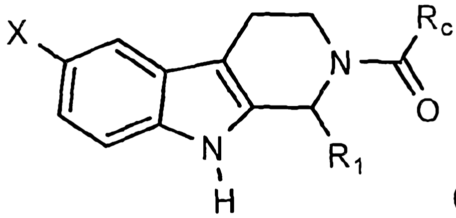
m is 0, 1, 2, or 3; and

n is 0, 1, 2, or 3.

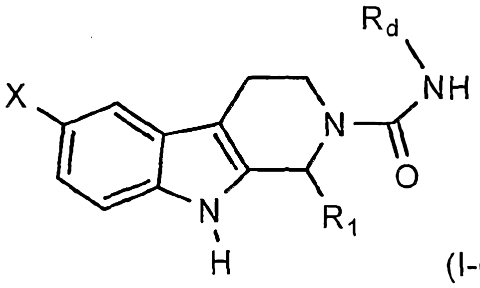
Other preferred classes of compounds within Formula (I) include the following.



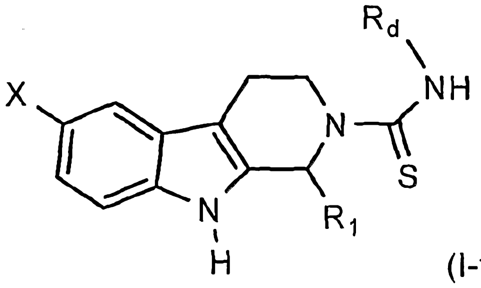
(I-c)



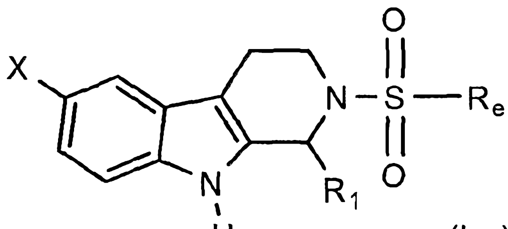
(I-d)



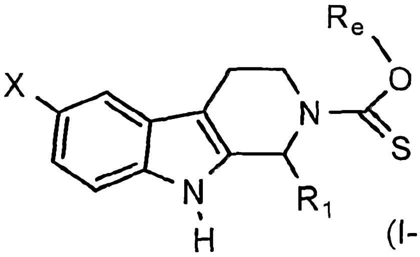
(I-e)



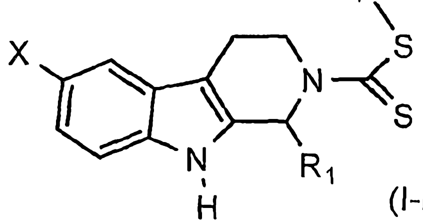
(I-f)



(I-g)



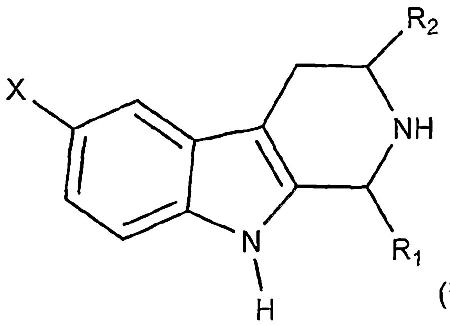
(I-h)



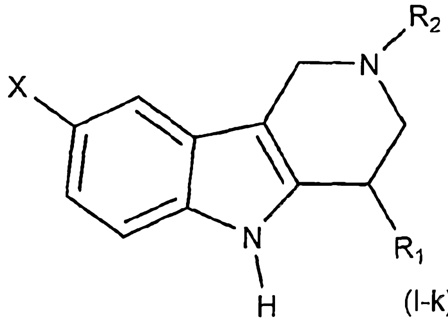
(I-i)

It is understood that substituents X and R_1, R_c, R_d, and R_e of the compounds of Formulas (I-c) to (I-i) are defined as in Formula (I).

In other embodiments, preferred compounds of the present invention useful in the inhibition of VEGF production include those of Formulas (I-i) through (I-l), as shown below. In the embodiments of Formulas (I-j) through (I-l), substituents X, R_1, R_2, R_3, *etc.* are defined as in Formula (I), as well as Formulas (I-a) to (I-i).



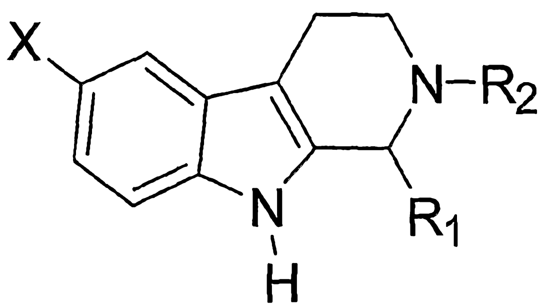
(I-j)



(I-k)

Also included within the scope of the invention are pharmaceutically acceptable salts, hydrates, solvates, calthrates, polymorphs, racemates and stereoisomers of the compounds described herein.

In another aspect of the invention, preferred compounds of the present invention useful in the inhibition of VEGF production include those of Formula (I-l) as shown below.



(I-l)

wherein,

X is hydrogen; a hydroxyl group; a halogen; a C_1-C_4 alkyl; a C_1 to C_5 alkoxy, optionally substituted with a C_6 to C_8 aryl group;

R_1 is a hydroxyl group; a C_1 to C_8 alkyl group, optionally substituted with a C_6 to C_8 aryl group, wherein the C_6 to C_8 aryl group is optionally substituted with at least one R_0 group; a heterocycle group; a heteroaryl group; and a C_6 to C_8 aryl group, optionally substituted with at least one R_0 group;

R_0 is a halogen; a C_1 to C_6 alkyl, optionally substituted with one or more halogen groups; a cyano group; a nitro group; an amino group; an aminoalkyl group; an acetamide group; an imidazole group; or OR_a;

R_a is hydrogen; a C_1 to C_6 alkyl, optionally substituted with a heterocycle group or a C_6 to C_8 aryl group; or a -C(O)O-R_b;

R_b is C_1 to C_4 alkyl group;

R_2 is a hydrogen; a hydroxyl; a heteroaryl group; a C_1 to C_8 alkyl group, optionally substituted with an alkoxy, hydroxyl, heteroaryl, or C_6 to C_8 aryl group; a -C(O)-R_c group; a -C(O)O-R_d group; a -C(O)NH-R_d group; a -C(S)NH-R_d group; a -S(O_2)-R_e group; or (1S)-isopropyl-carbamic acid tert-butyl ester;

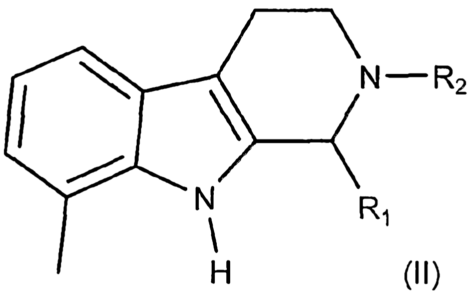
R_c is hydrogen; a 4-morpholinyl group; a thiazoleamino group; a piperazinyl group, optionally substituted with a -C(O)CH_3 group; a C_1 to C_6 alkyl group, optionally substituted with a halogen, an alkoxy, or hydroxyl group;

R_d is hydrogen; a benzyl group; a C_1 to C_8 alkyl group, optionally substituted with a halogen or an alkoxy group; a C_6 to C_8 aryl group, optionally substituted with at least one halogen, C_1 to C_5 alkyl, -C(O)OR_e, or OR_e;

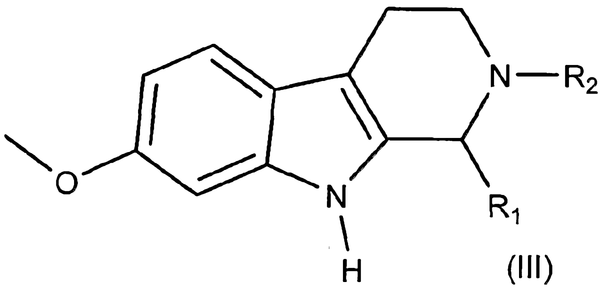
R_e is a hydrogen; a C_1 to C_6 alkyl group, optionally substituted with at least one halogen or alkoxy group; or a C_6 to C_8 aryl group; and

n is 0, 1, 2, or 3.

In another embodiment, compounds of Formulas (II) and (III) are provided.



(II)

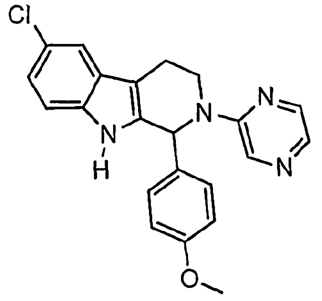
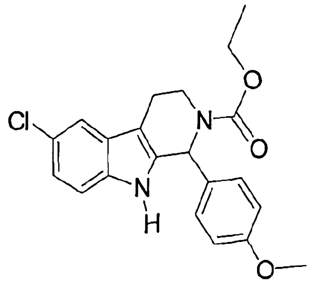
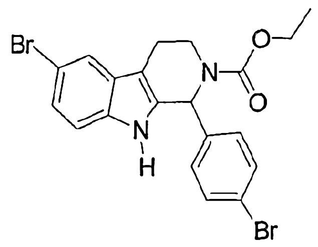
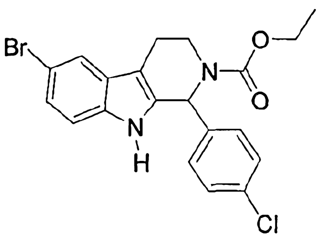
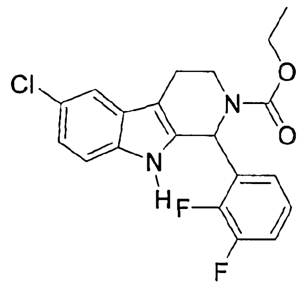
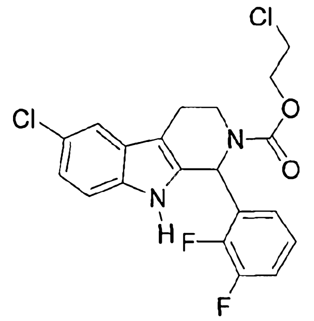
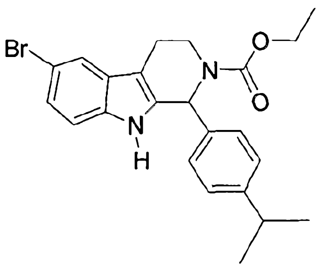
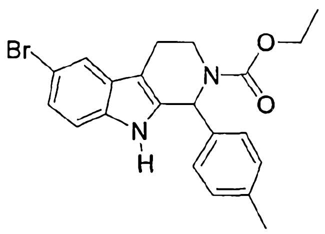
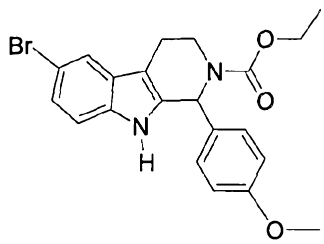
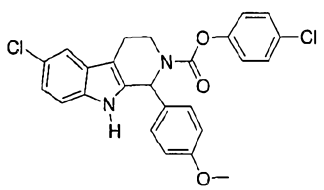
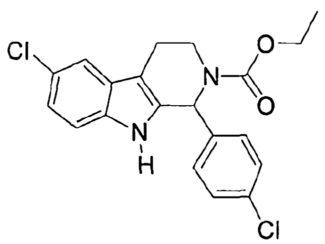
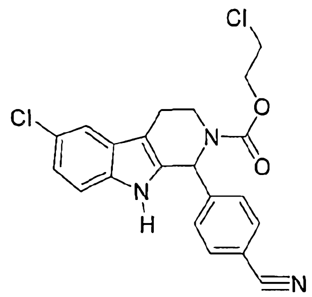


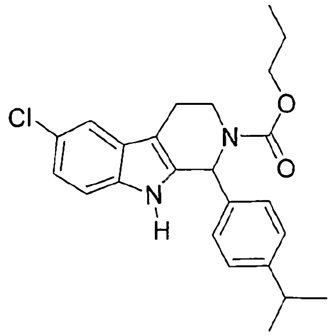
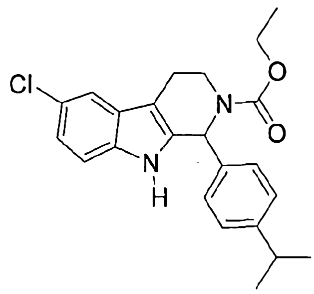
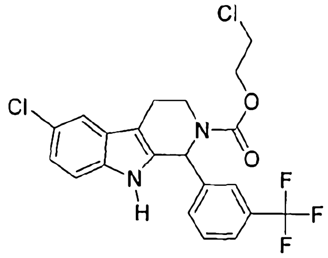
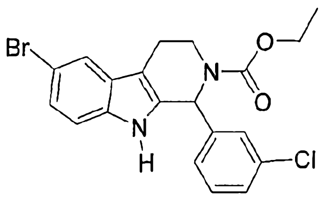
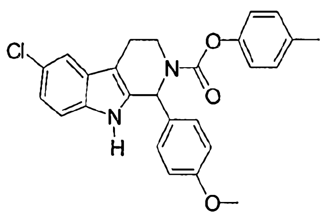
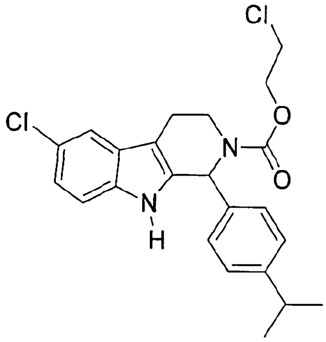
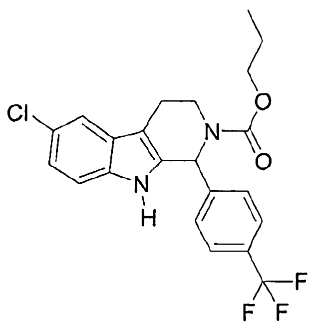
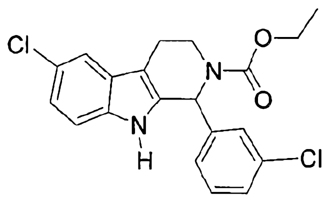
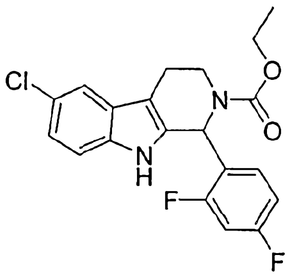
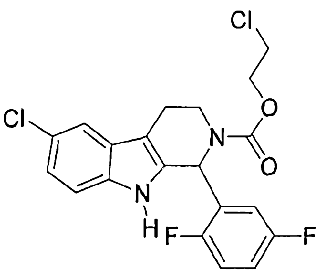
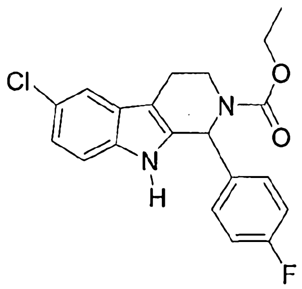
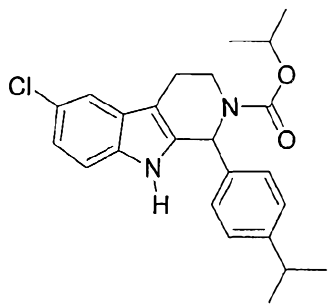
(III)

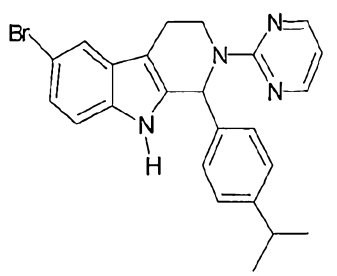
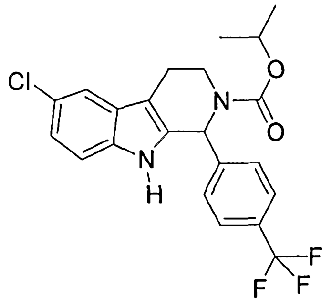
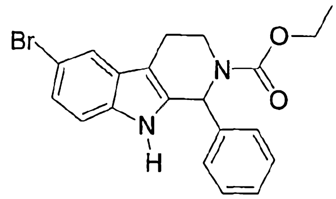
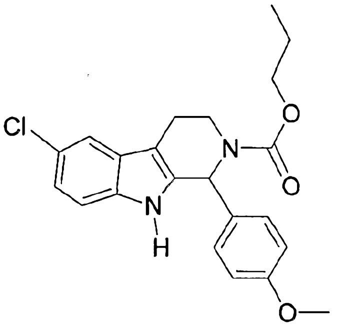
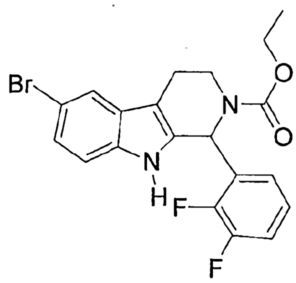
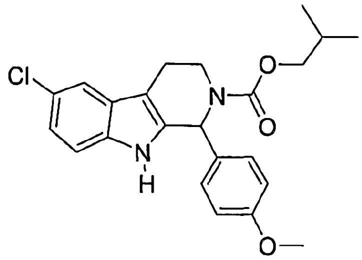
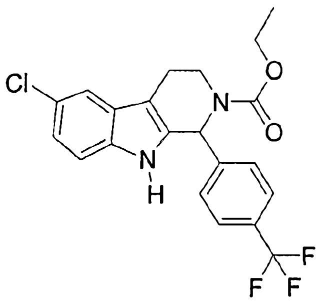
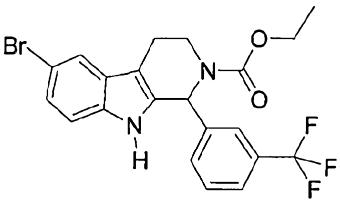
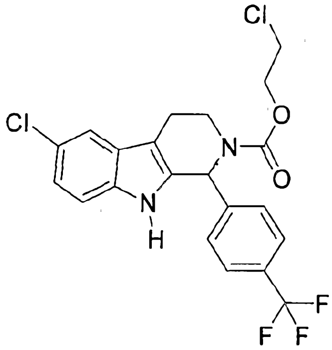
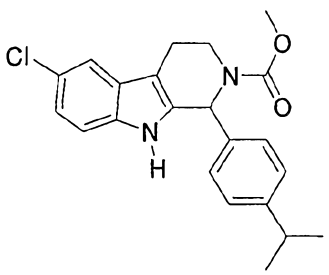
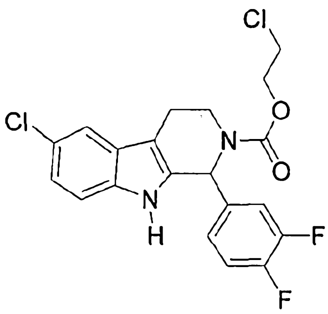
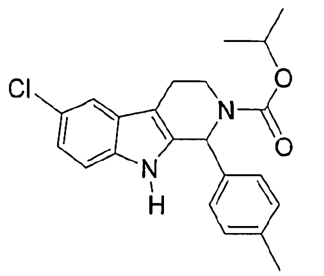
Wherein R_1 and R_2 are defined as described above with regard with Formula (I).

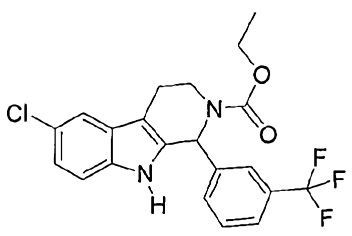
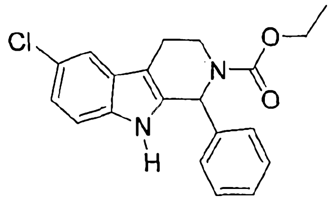
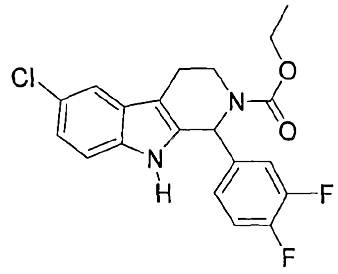
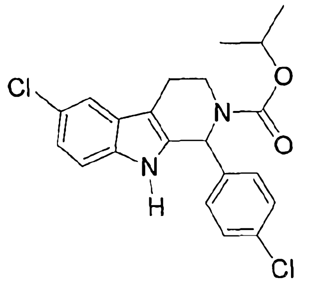
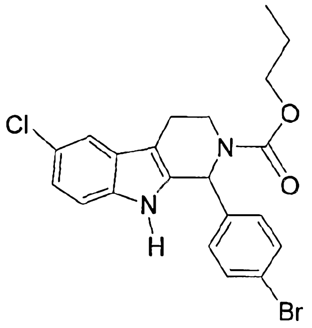
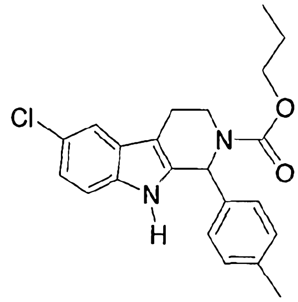
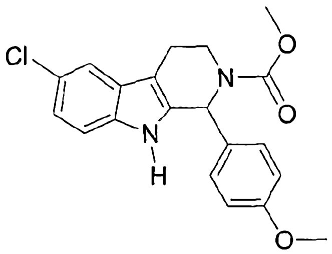
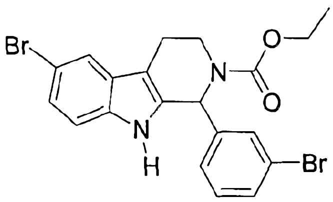
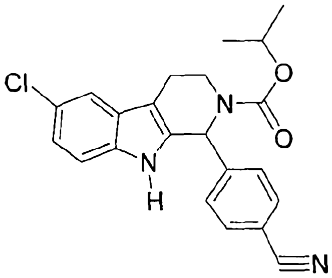
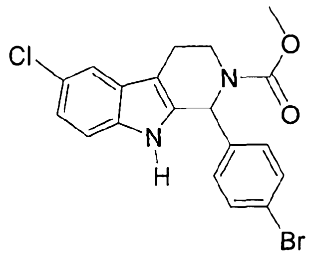
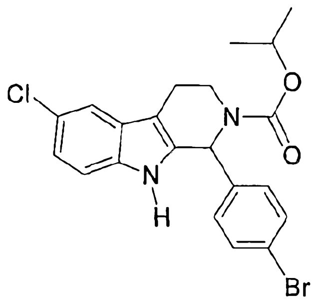
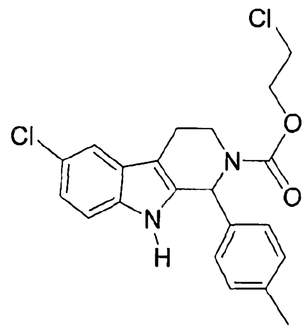
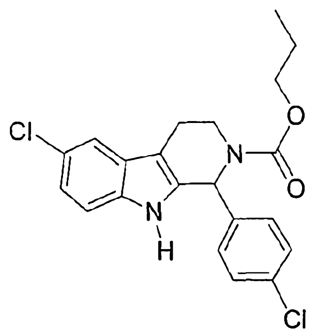
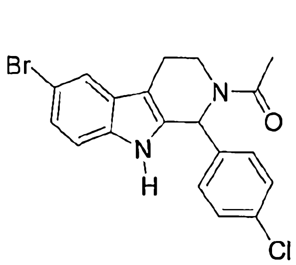
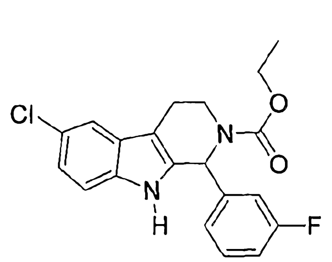
For the purposes of this invention, where one or more functionalities encompassing X R_1, R_2, R_0, R_a, R_b, R_c, R_d, and R_e, are incorporated into a molecule of Formulas (I), (II), and (III), including Formulas (I-a) to (I-k), each of the functionalities appearing at any location within the disclosed 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.

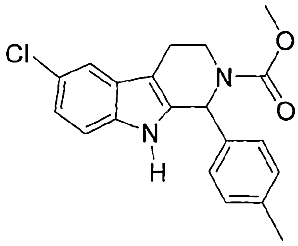
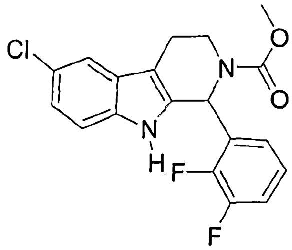
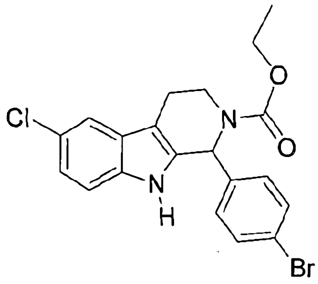
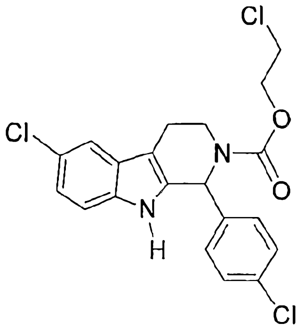
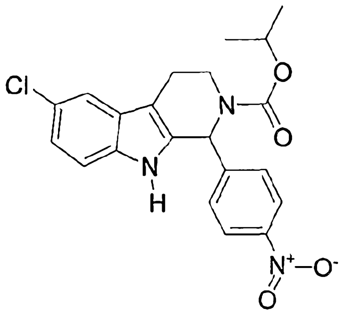
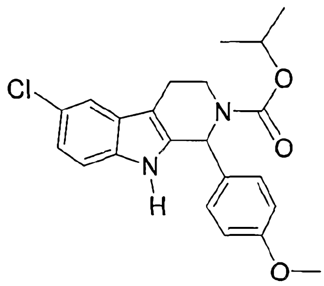
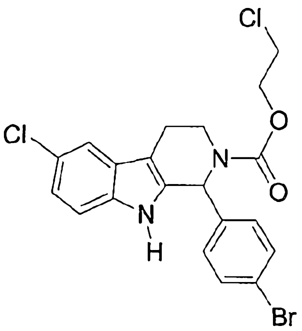
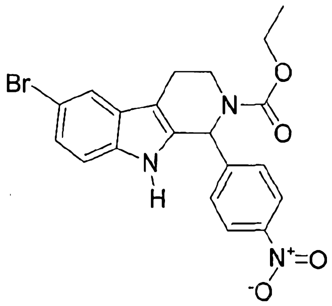
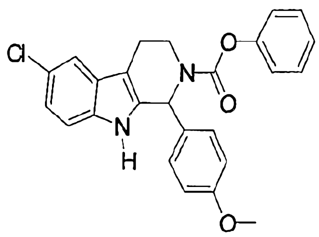
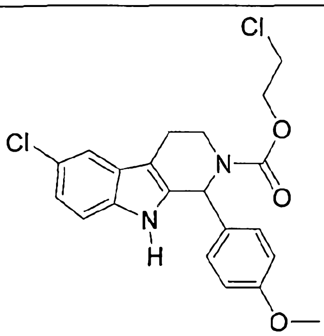
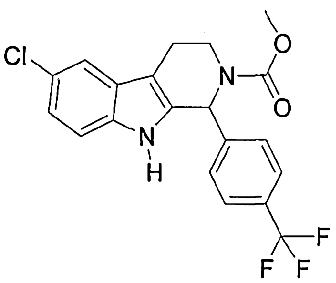
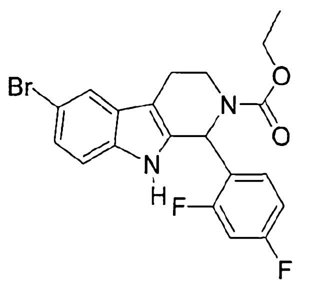
Preferred compounds of the invention include the following.

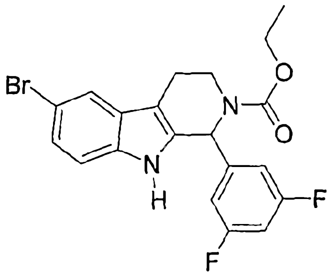
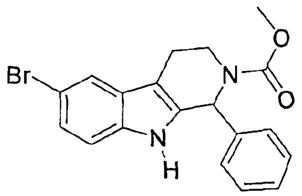
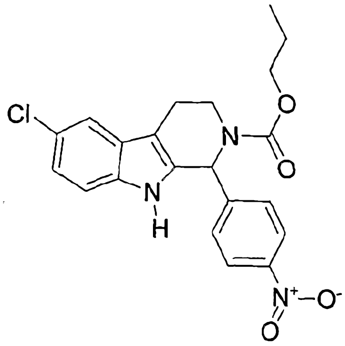
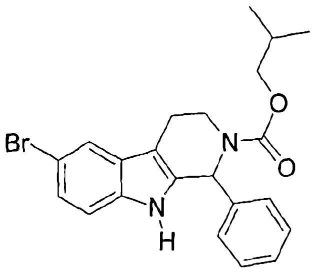
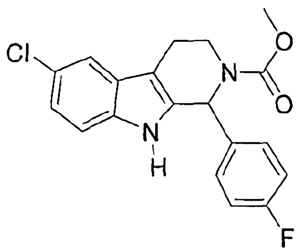
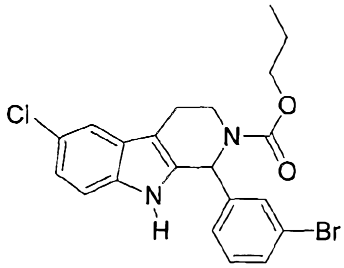
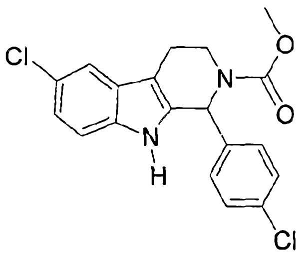
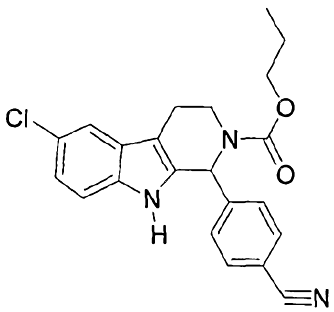
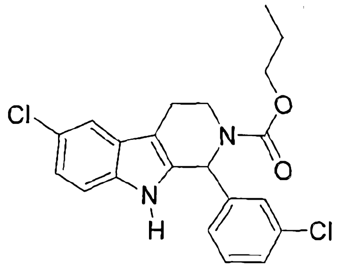
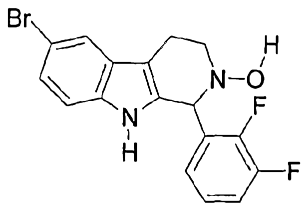
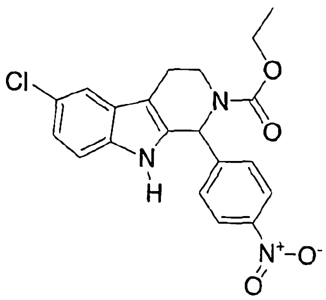
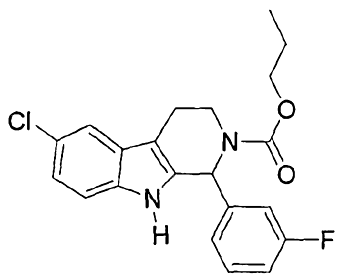
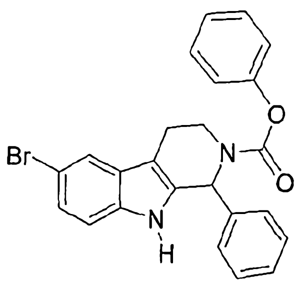
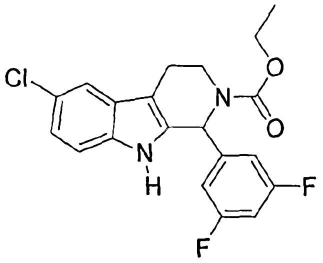
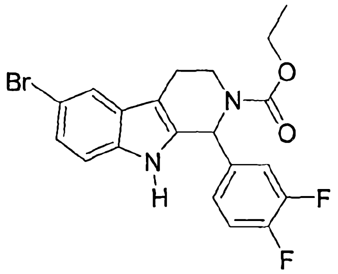
**1**	**2**	**3**
**4**	**5**	**6**
**7**	**8**	**9**
**10**	**11**	**12**

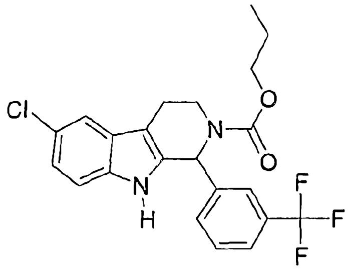
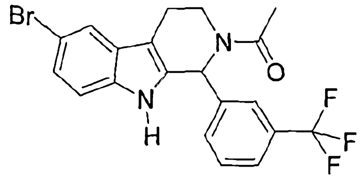
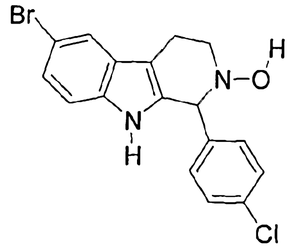
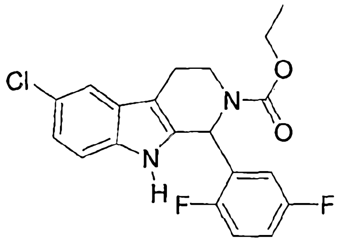
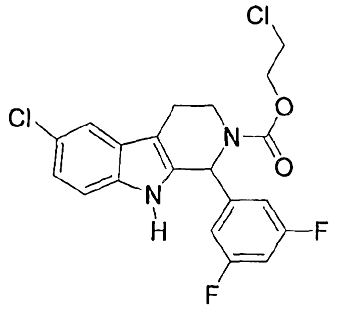
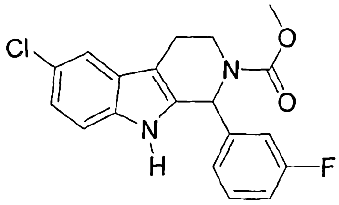
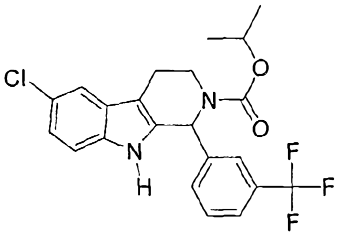
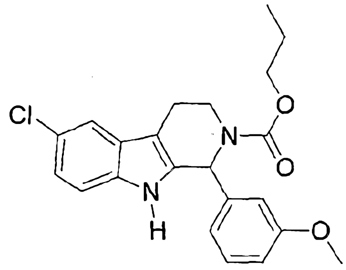
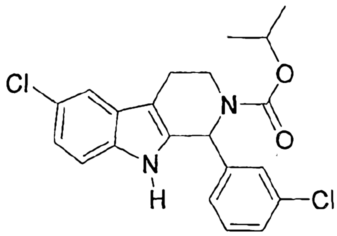
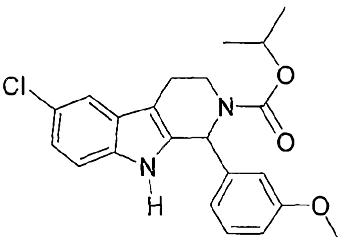
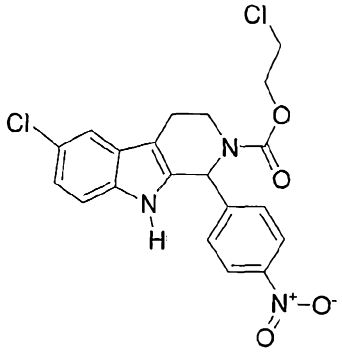
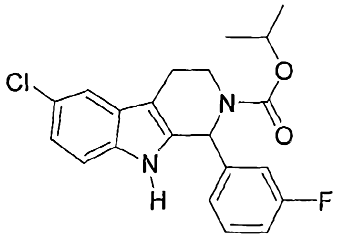
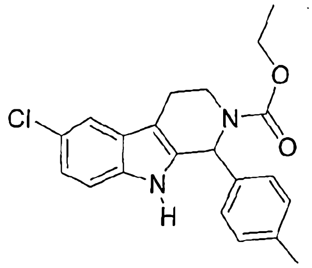
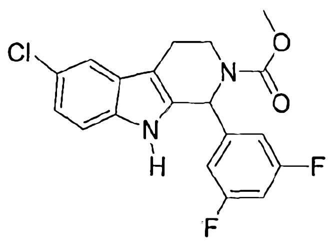
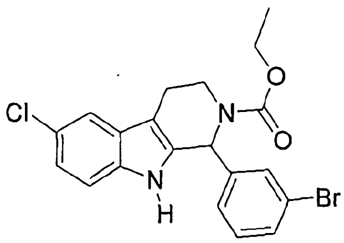
 13	 14	 15
 16	 17	 18
 19	 20	 21
 22	 23	 24

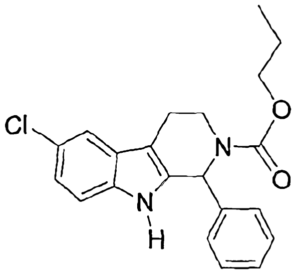
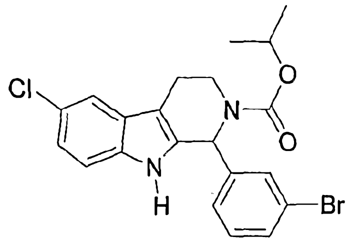
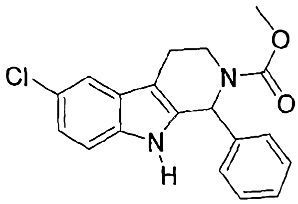
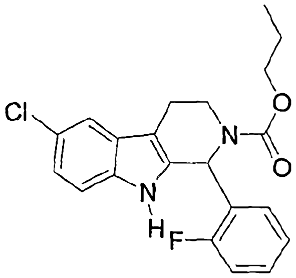
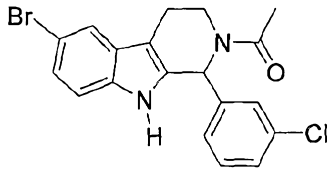
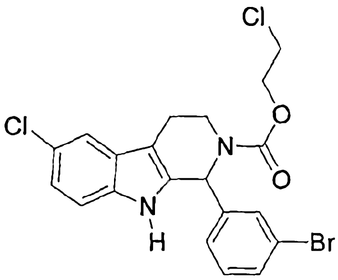
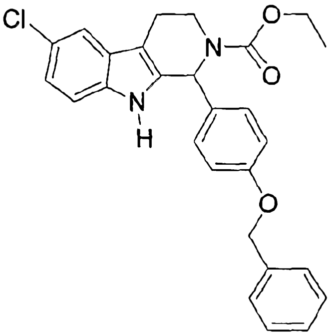
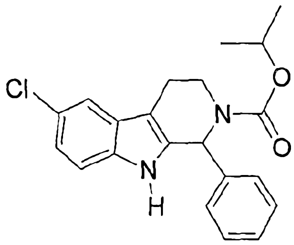
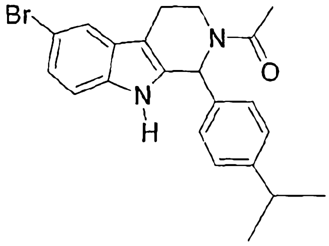
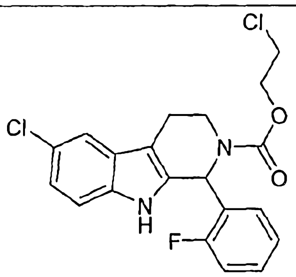
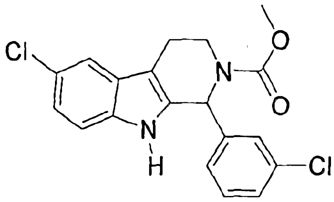
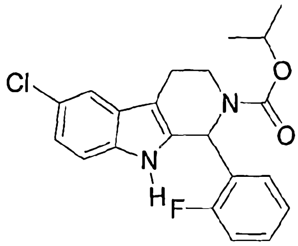
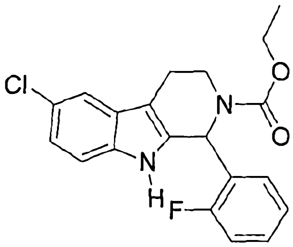
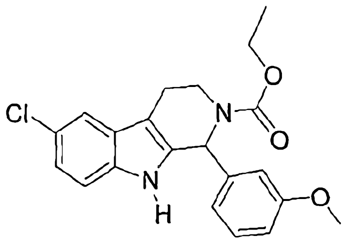
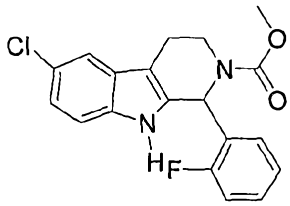
 **25**	 **26**	 **27**
 **28**	 **29**	 **30**
 **31**	 **32**	 **33**
 **34**	 **35**	 **36**

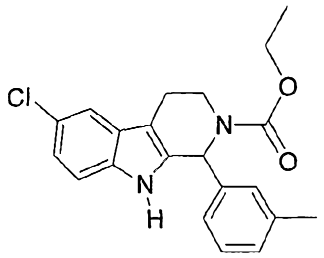
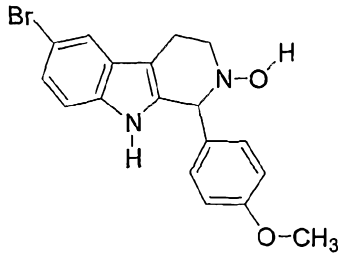
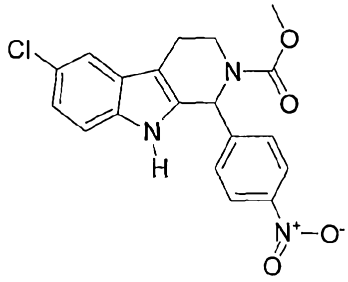
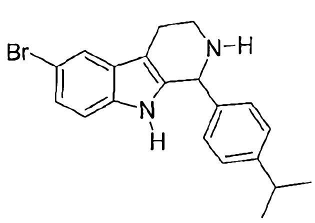
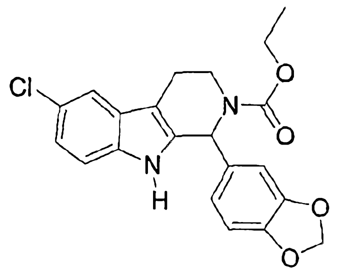
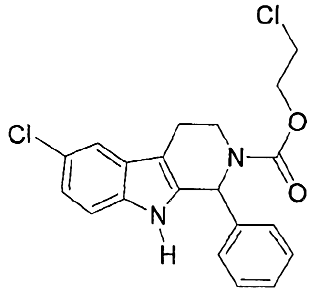
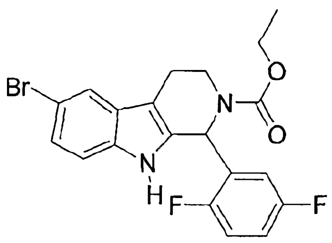
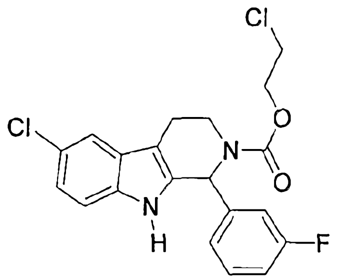
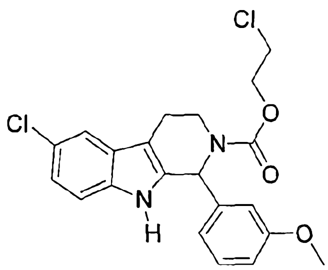
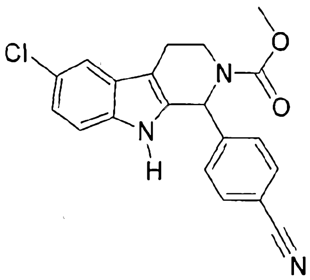
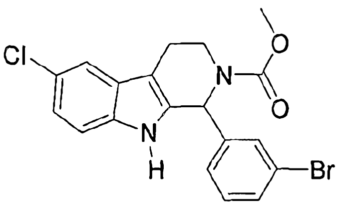
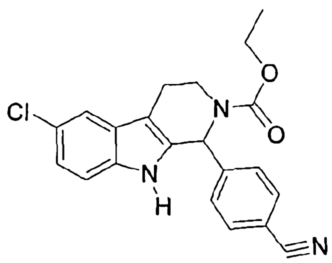
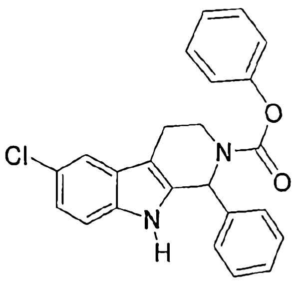
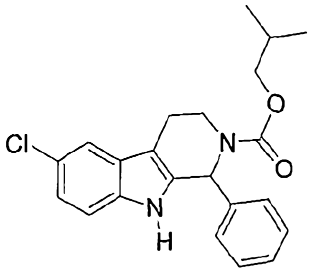
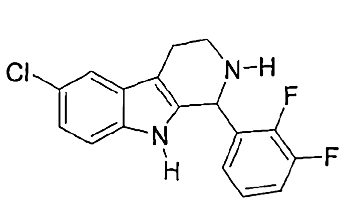
 **37**	 **38**	 **39**
 **40**	 **41**	 **42**
 **43**	 **44**	 **45**
 **46**	 **47**	 **48**
 **49**	 **50**	 **51**

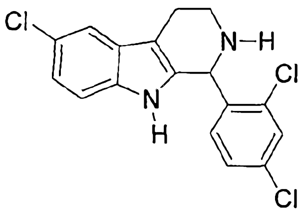
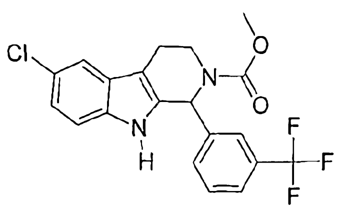
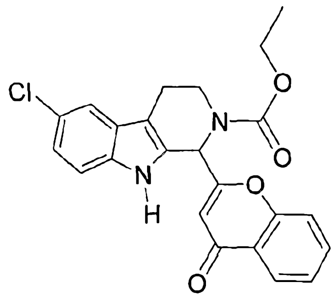
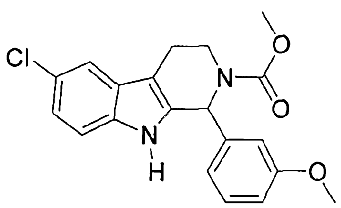
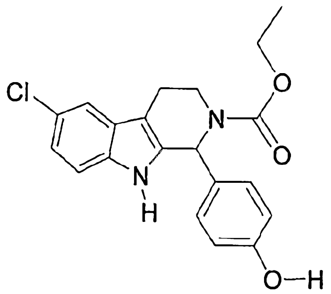
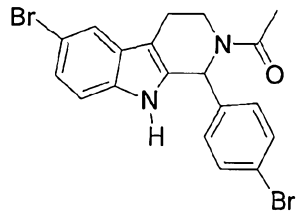
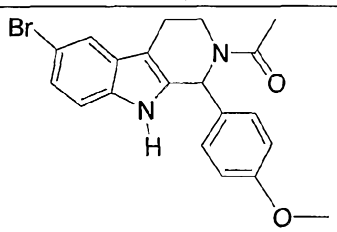
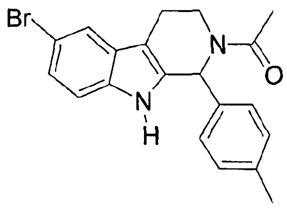
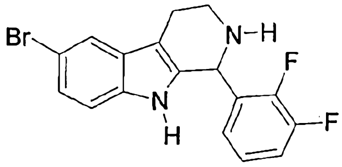
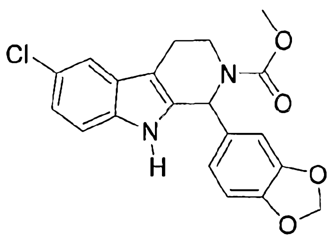
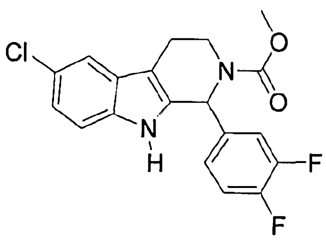
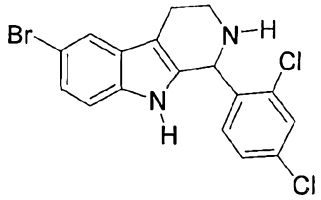
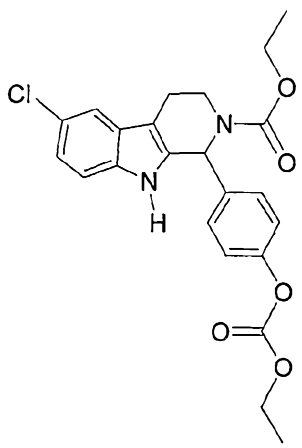
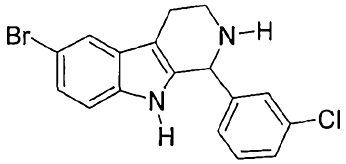
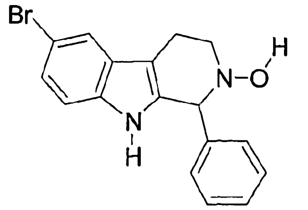
 **52**	 **53**	 **54**
 **55**	 **56**	 **57**
 **58**	 **59**	 **60**
 **61**	 **62**	 **63**

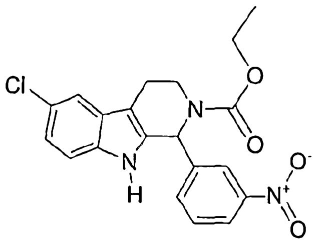
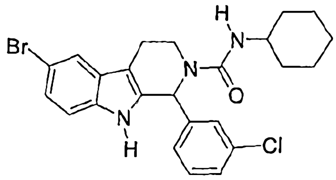
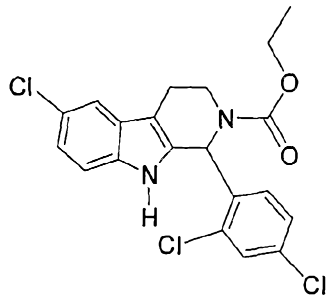
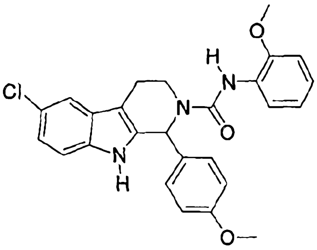
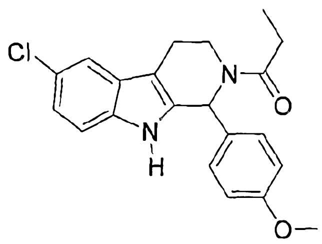
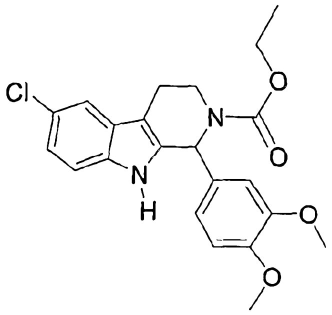
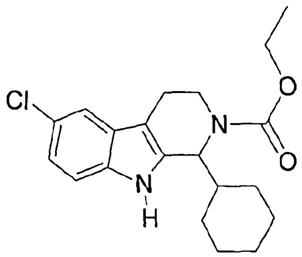
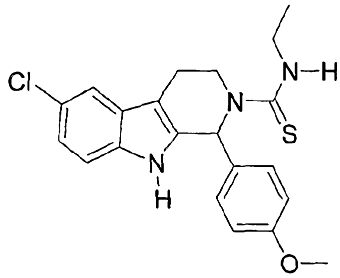
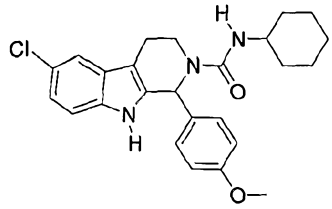
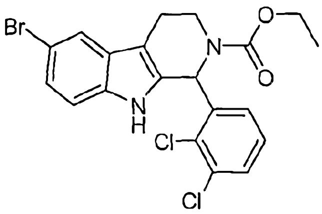
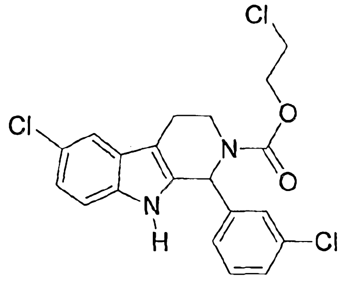
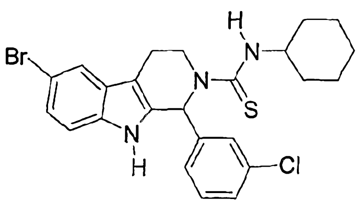
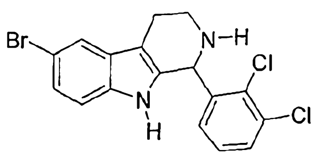
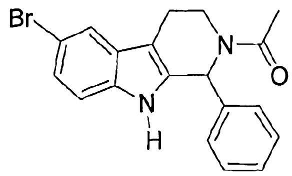
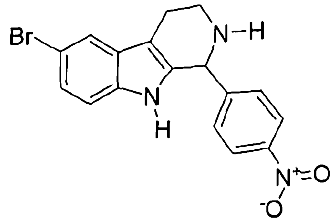
 **64**	 **65**	 **66**
 **67**	 **68**	 **69**
 **70**	 **71**	 **72**
 **73**	 **74**	 **75**
 **76**	 **77**	 **78**

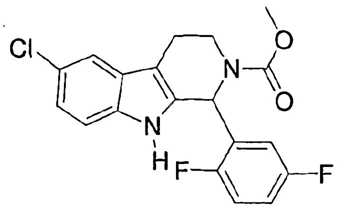
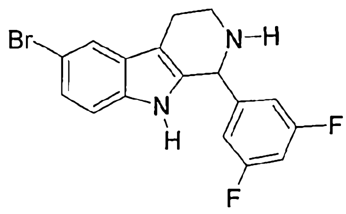
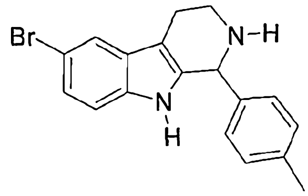
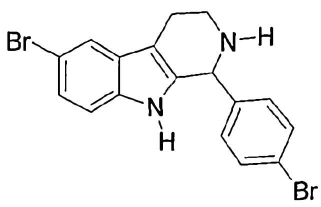
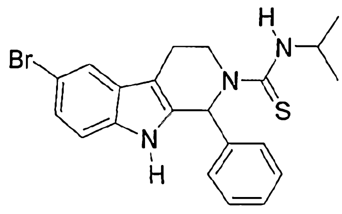
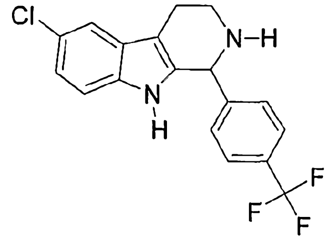
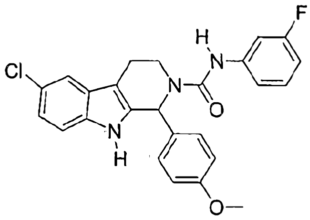
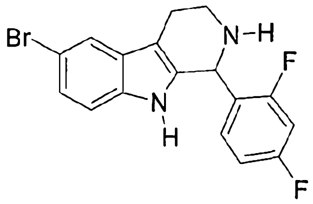
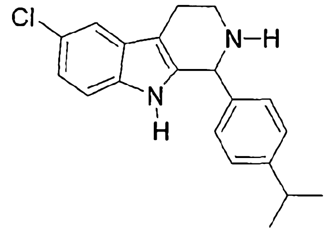
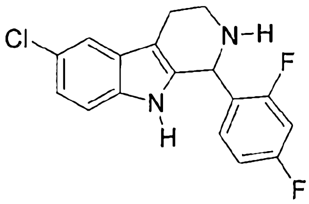
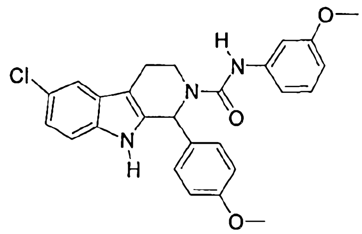
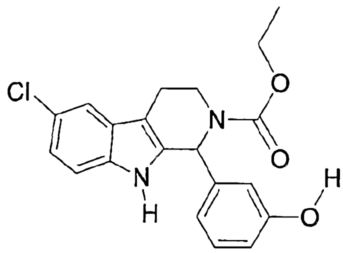
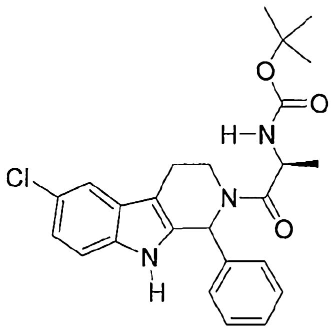
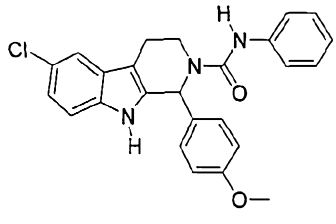
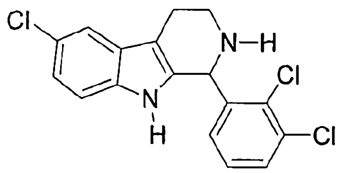
 **79**	 **80**	 **81**
 **82**	 **83**	 **84**
 **85**	 **86**	 **87**
 **88**	 **89**	 **90**
 **91**	 **92**	 **93**

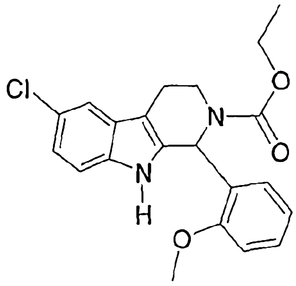
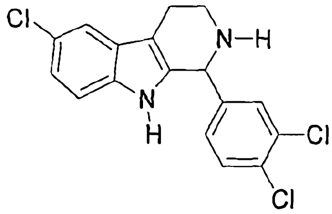
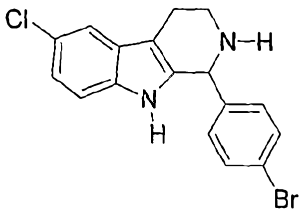
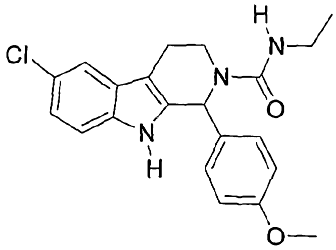
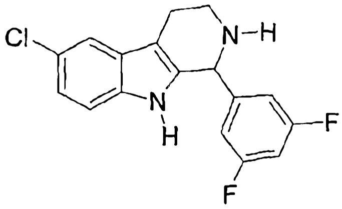
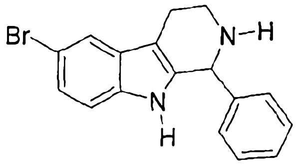
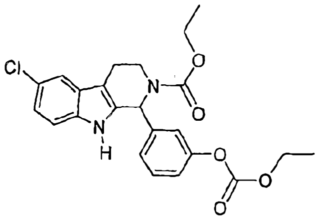
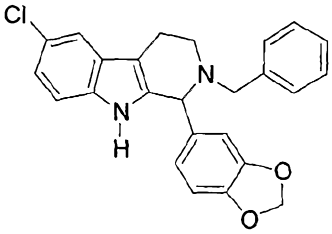
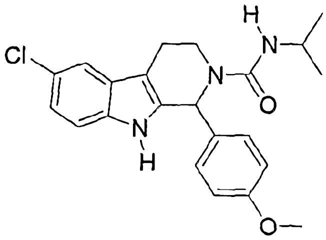
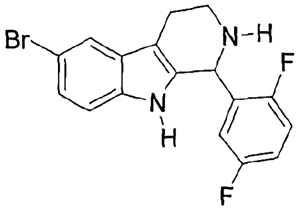
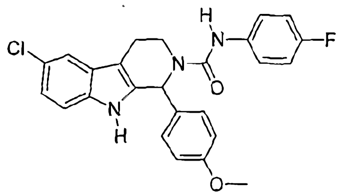
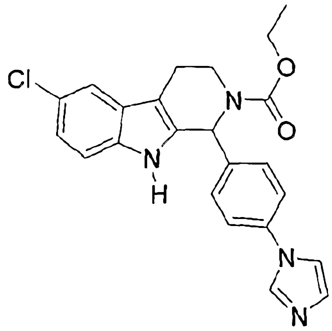
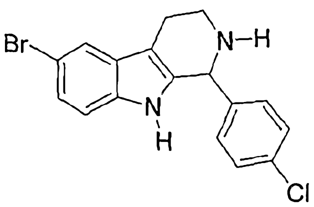
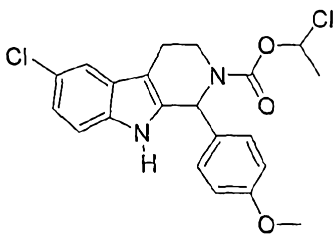
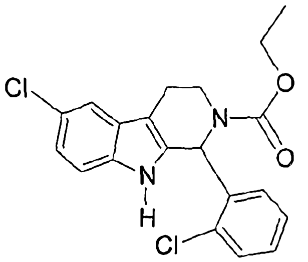
 **94**	 **95**	 **96**
 **97**	 **98**	 **99**
 **100**	 **101**	 **102**
 **103**	 **104**	 **105**
 **106**	 **107**	 **108**

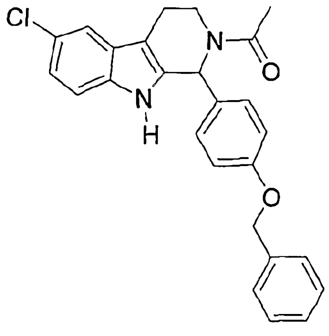
 **109**	 **110**	 **111**
 **112**	 **113**	 **114**
 **115**	 **116**	 **117**
 **118**	 **119**	 **120**
 **121**	 **122**	 **123**

 **124**	 **125**	 **126**
 **127**	 **128**	 **129**
 **130**	 **131**	 **132**
 **133**	 **134**	 **135**
 **136**	 **137**	 **138**

 **139**	 **140**	 **141**
 **142**	 **143**	 **144**
 **145**	 **146**	 **147**
 **148**	 **149**	 **150**
 **151**	 **152**	 **153**

 154	 155	 156
 157	 158	 159
 160	 161	 162
 163	 164	 165
 166	 167	 168

 169	 170	 171
 172	 173	 174
 175	 176	 177
 178	 179	 180
 181	 182	 183



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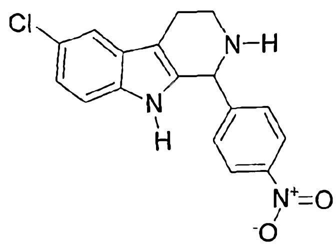

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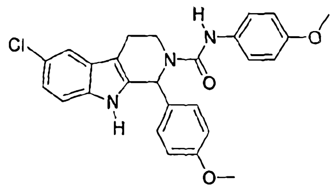

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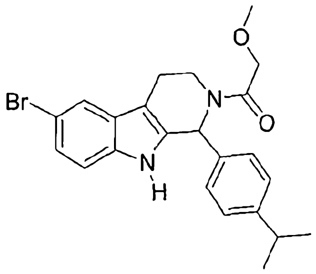

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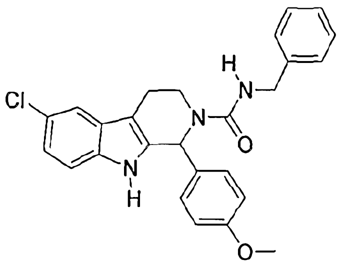

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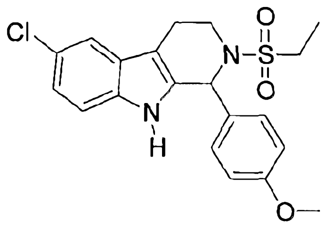

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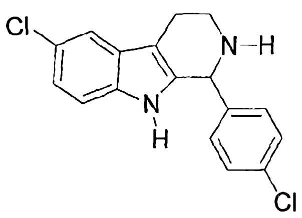

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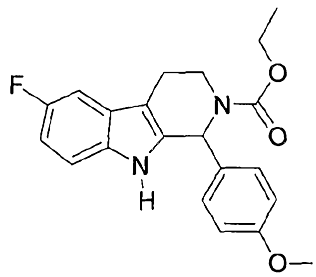

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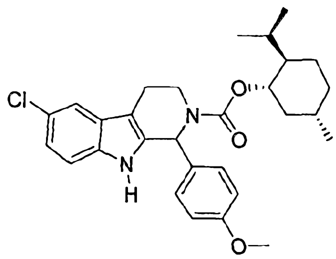

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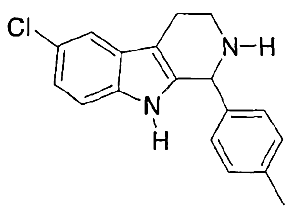

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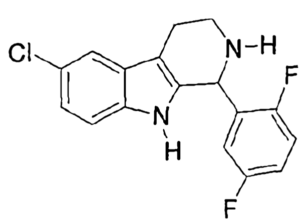

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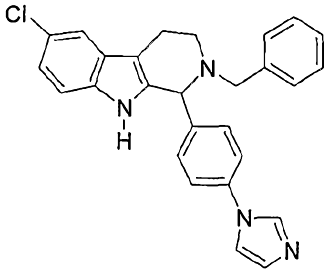

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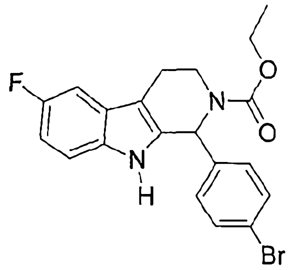

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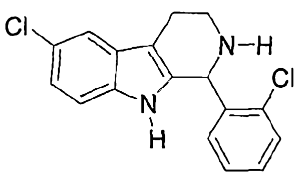

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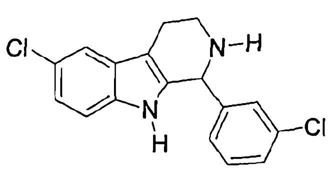

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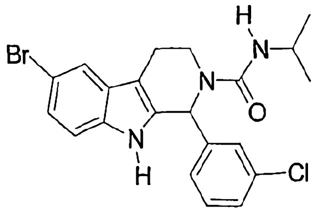
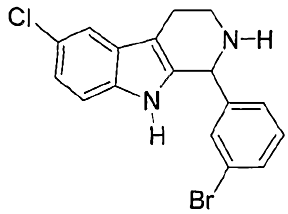
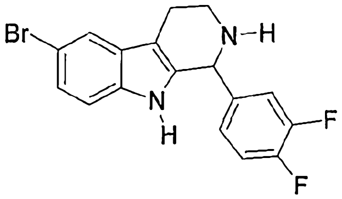
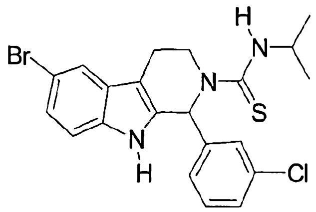
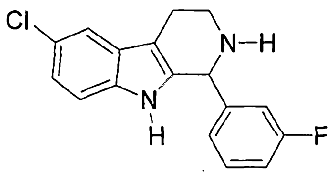
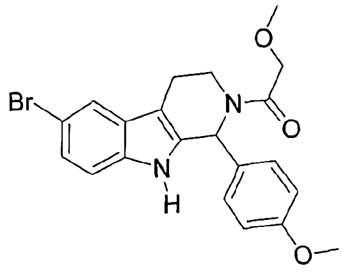
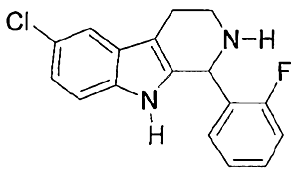
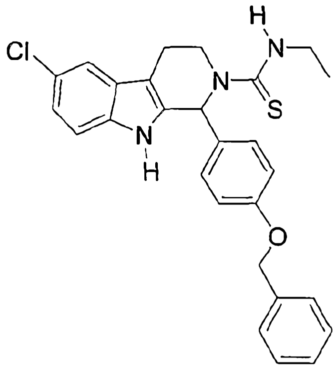
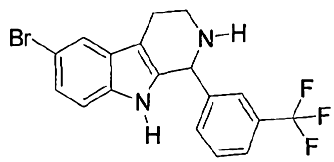
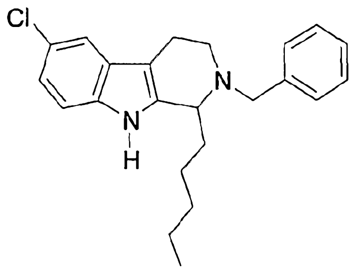
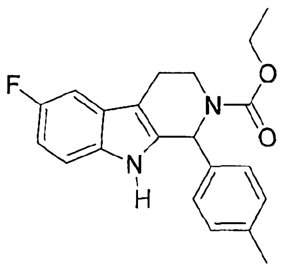
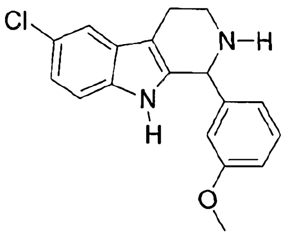
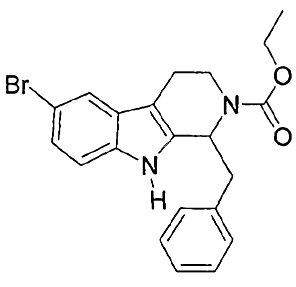
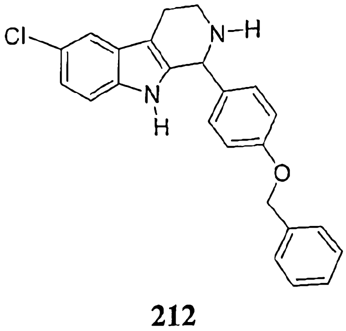
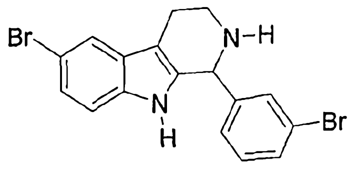
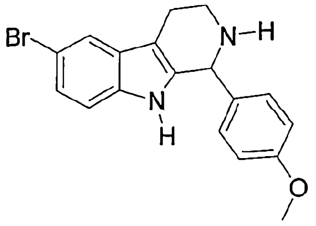
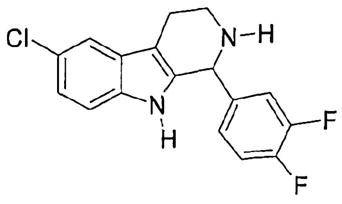
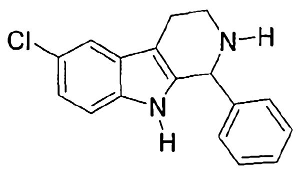
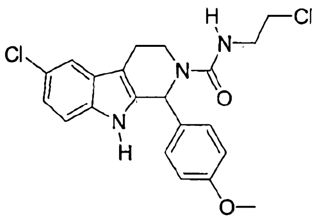
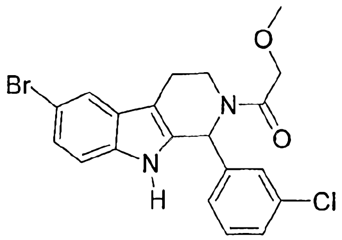
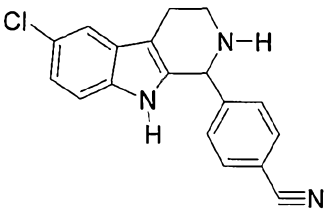
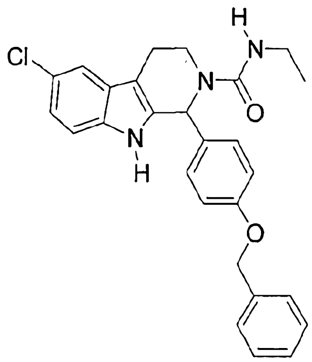
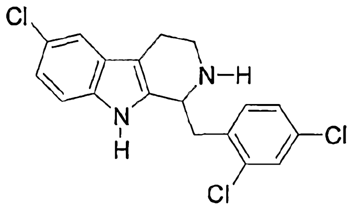
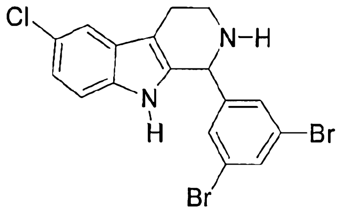
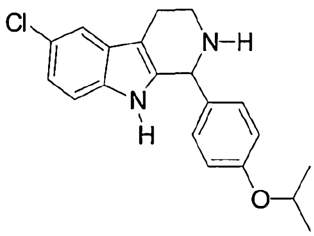
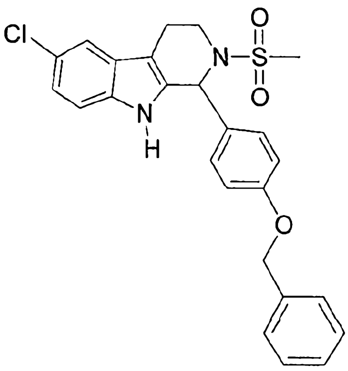
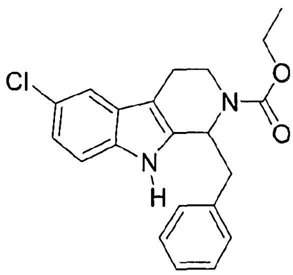
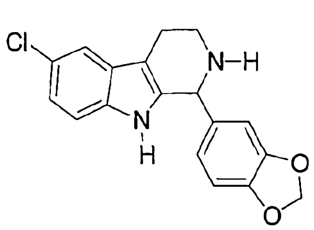
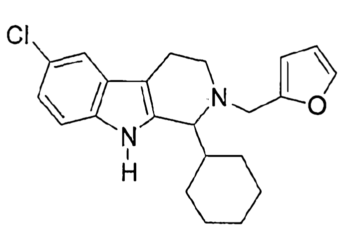
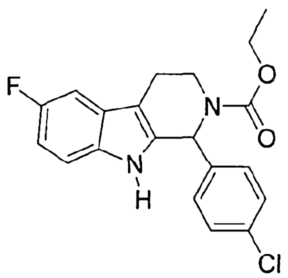
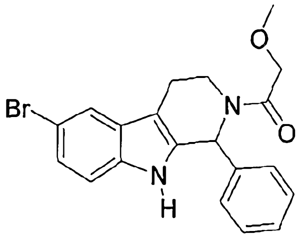
 **199**	 **200**	 **201**
 **202**	 **203**	 **204**
 **205**	 **206**	 **207**
 **208**	 **209**	 **210**
 **211**	 **212**	 **213**

 **214**	 **215**	 **216**
 **217**	 **218**	 **220**
 **221**	 **222**	 **223**
 **224**	 **225**	 **226**
 **227**	 **228**	 **229**



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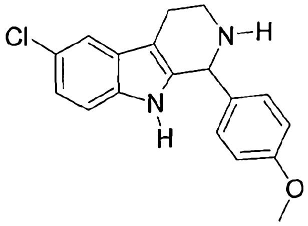

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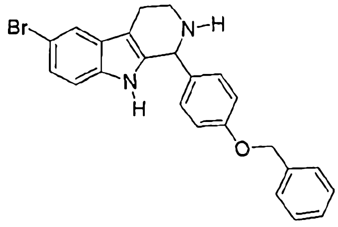

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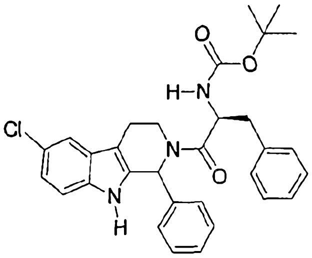

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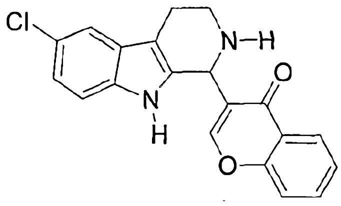

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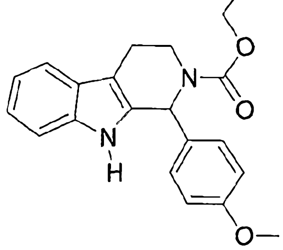

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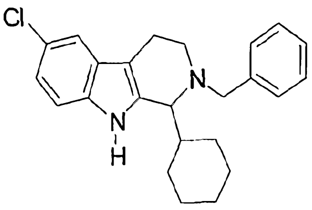

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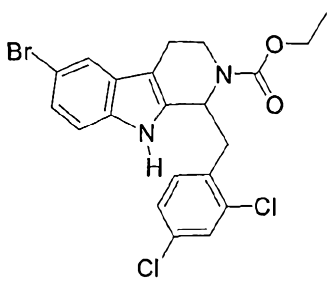

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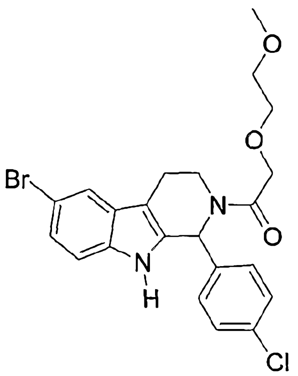

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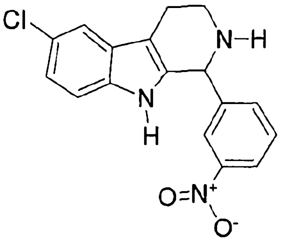

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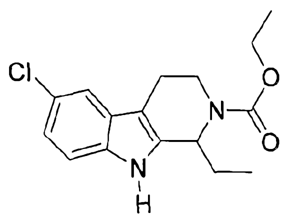

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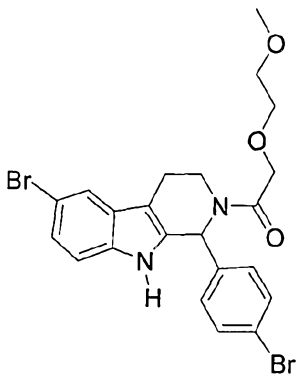

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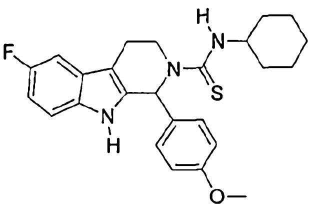

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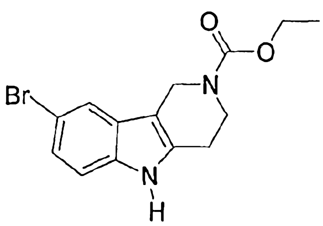

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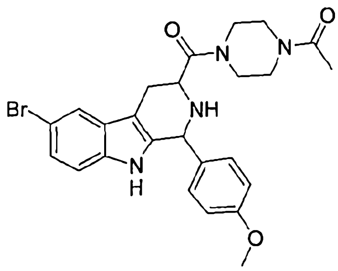

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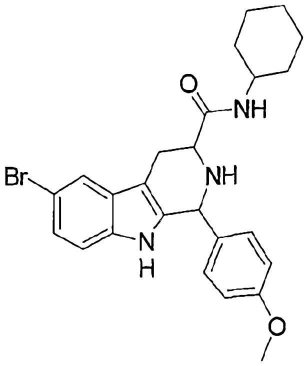
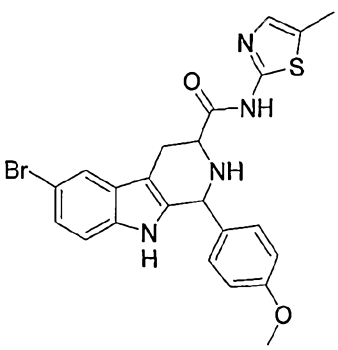
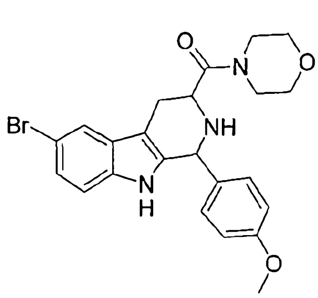
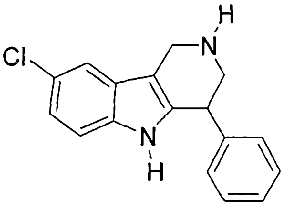
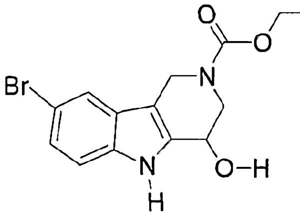
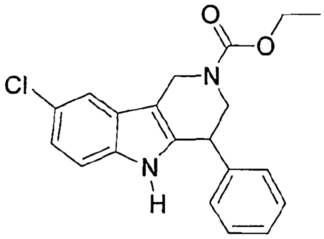
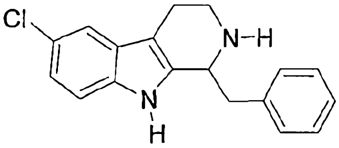
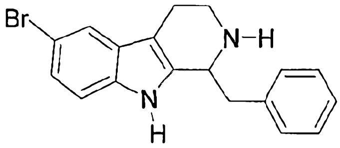
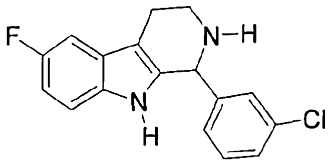
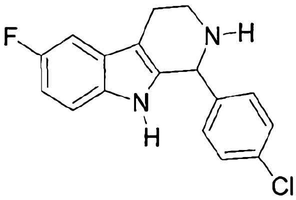
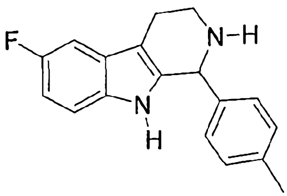
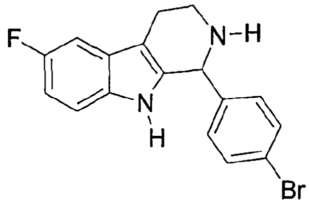
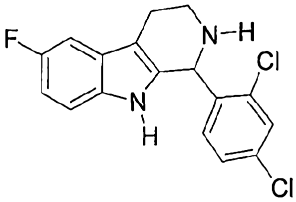
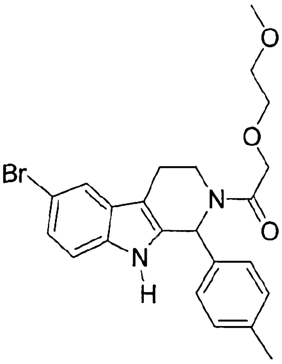
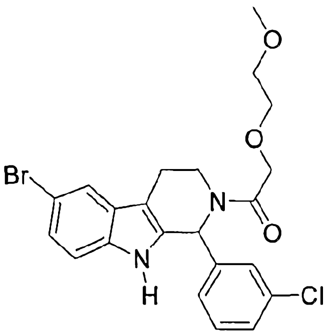
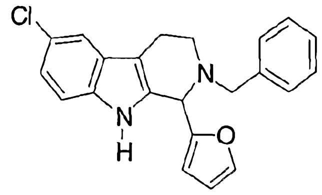
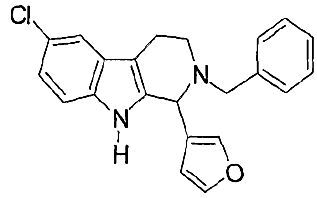
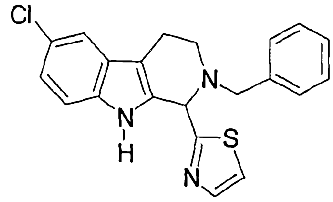
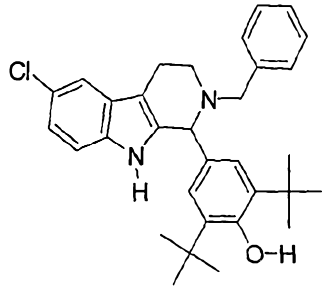
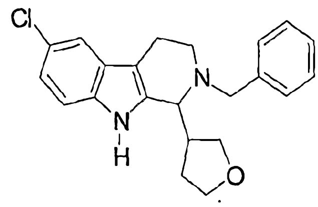
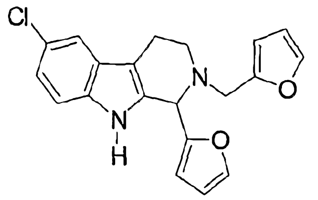
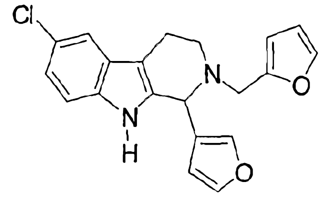
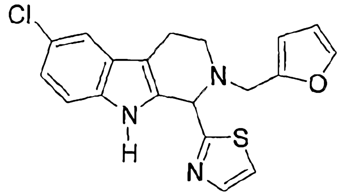
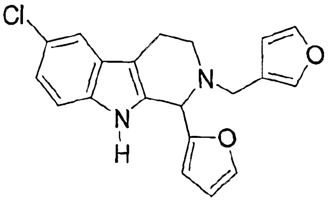
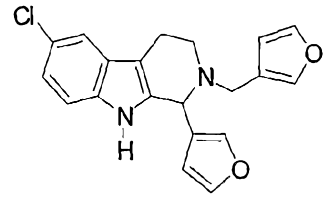
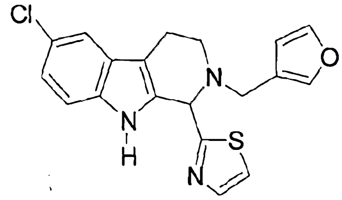
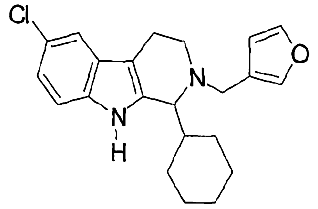
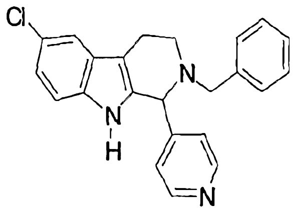
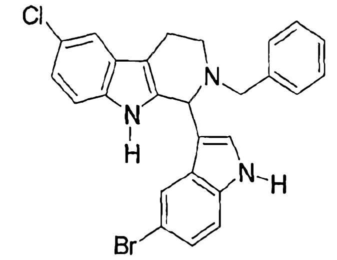
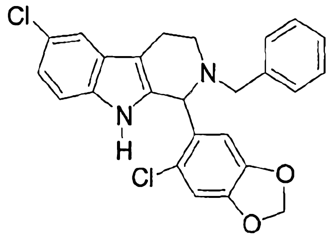
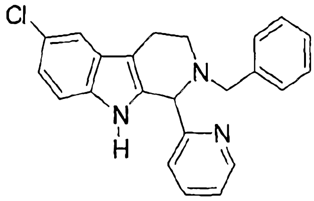
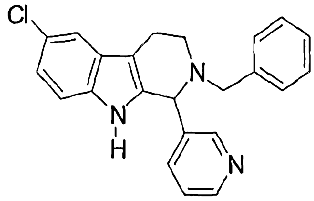
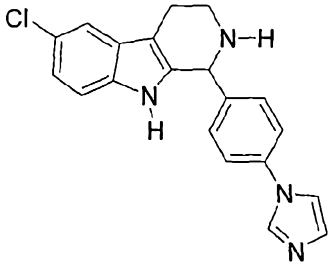
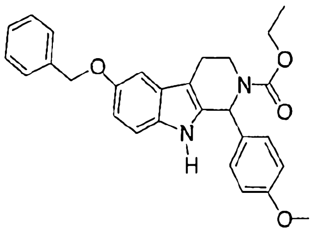
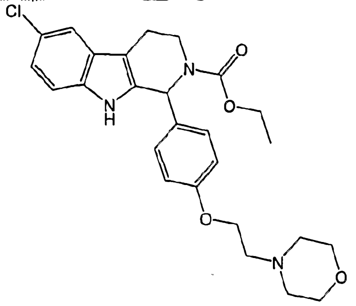
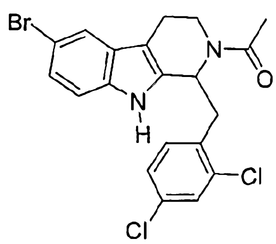
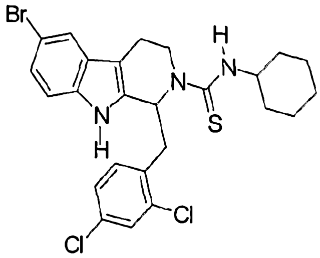
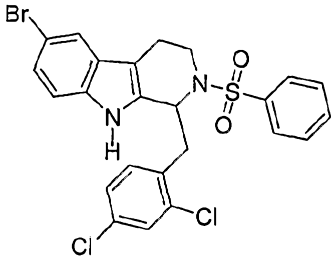
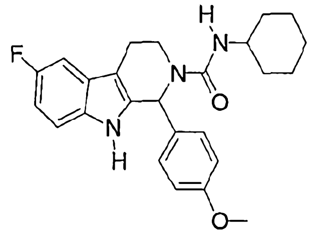
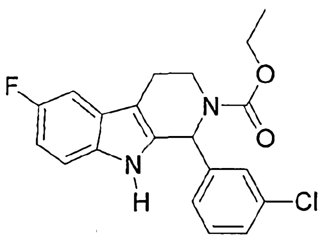
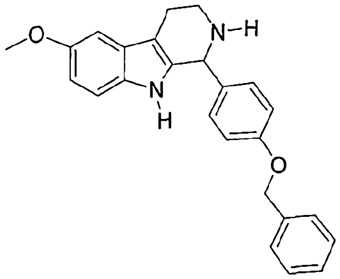
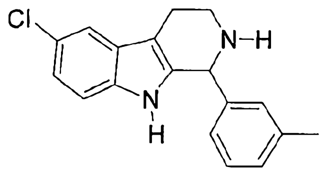
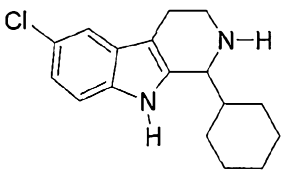
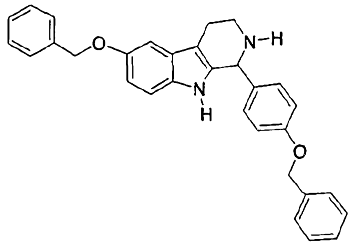
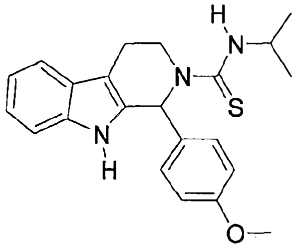
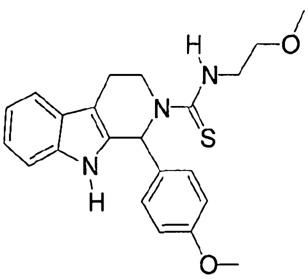
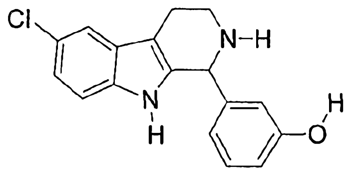
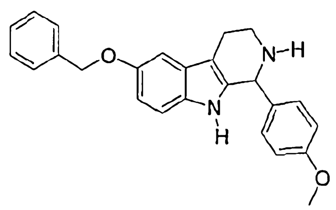
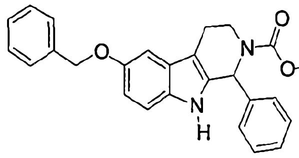
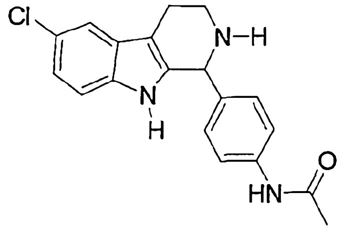
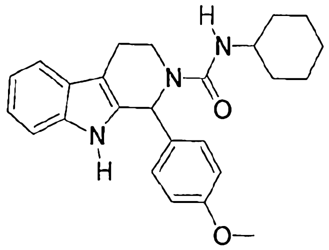
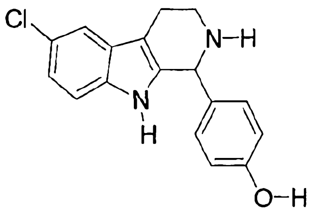
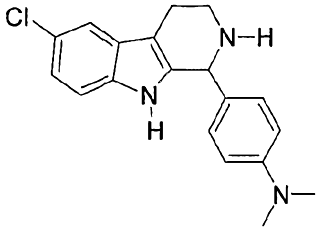
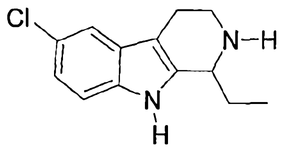
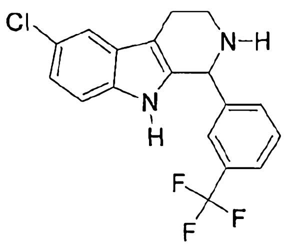
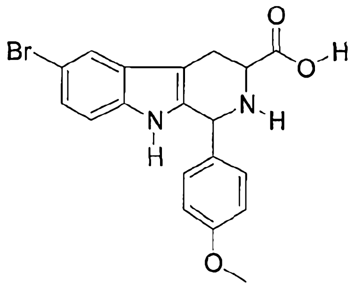
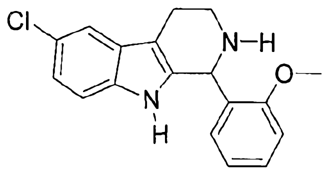
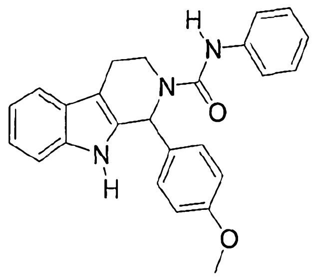
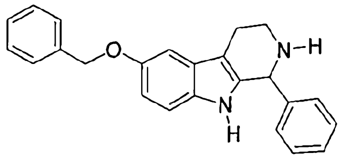
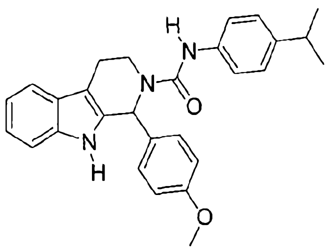
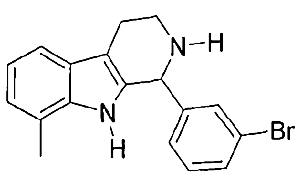
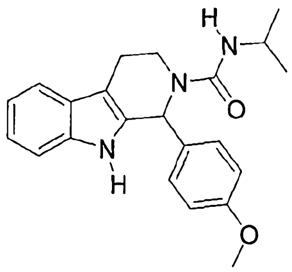
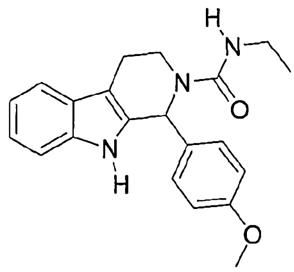
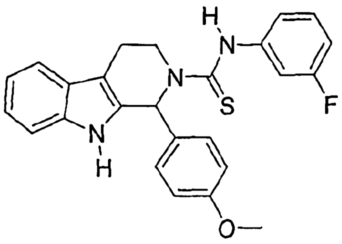
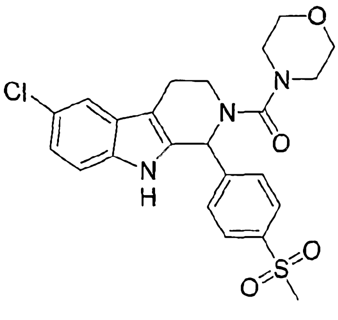
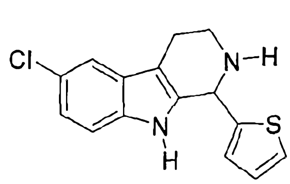
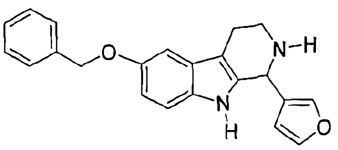
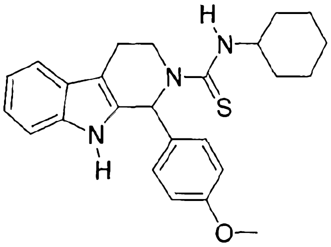
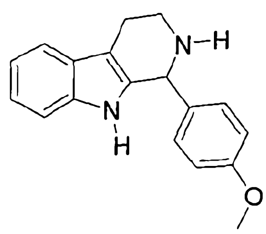
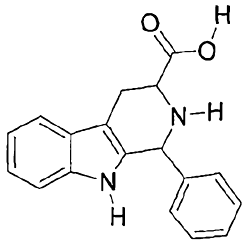
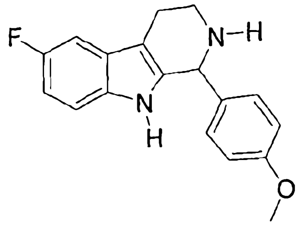
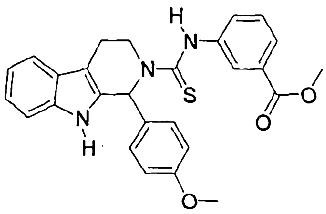
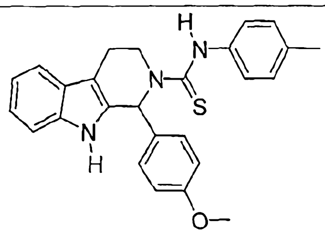
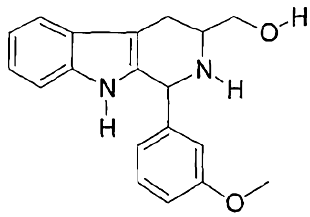
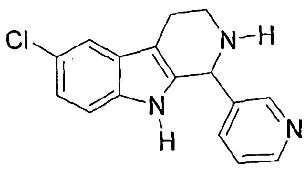
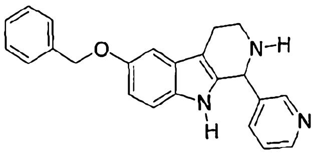
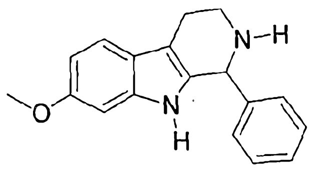
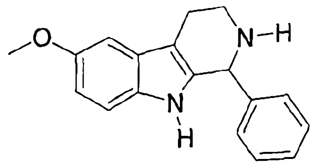
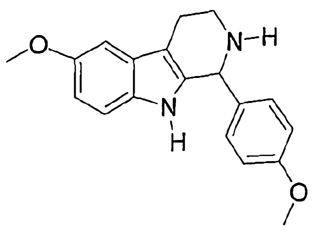
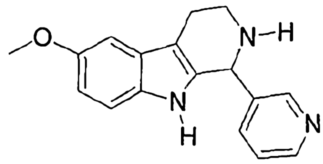
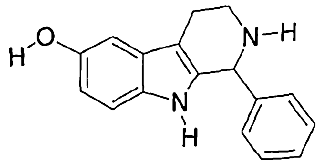
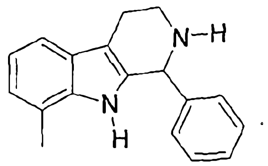
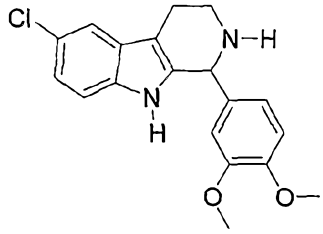
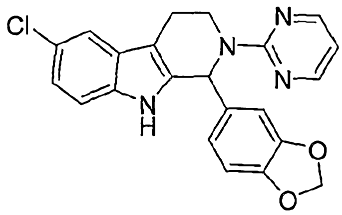
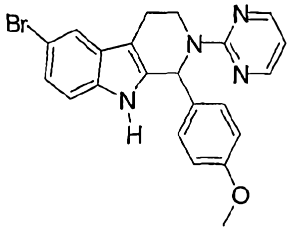
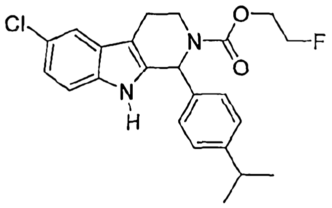
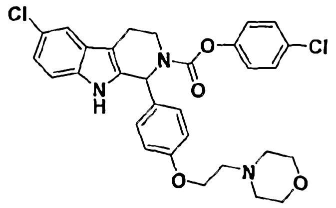
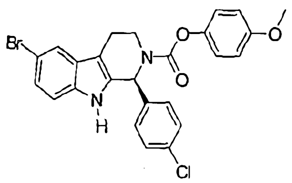
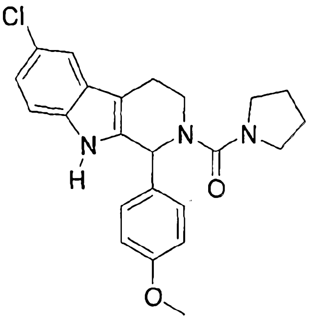
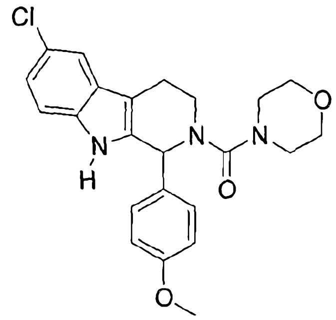
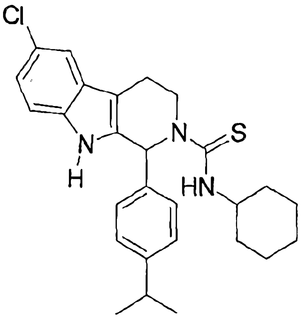
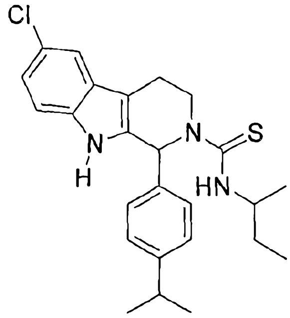
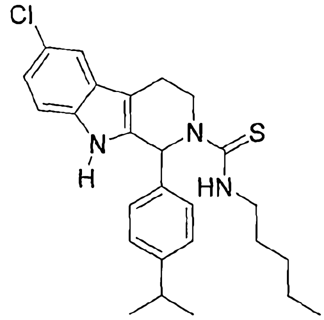
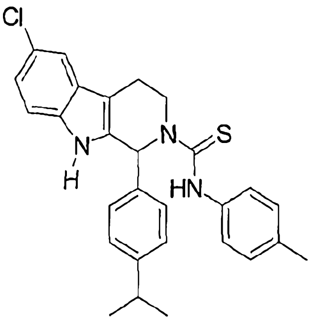
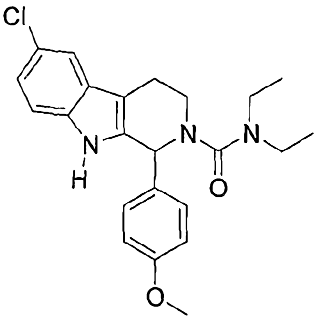
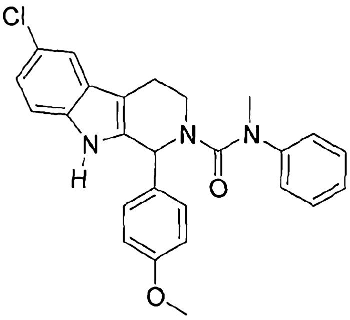
 **245**	 **246**	 **247**
 **248**	 **249**	 **250**
 **251**	 **252**	 **253**
 **254**	 **255**	 **256**
 **257**	 **258**	 **259**

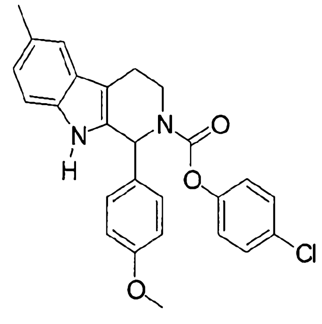
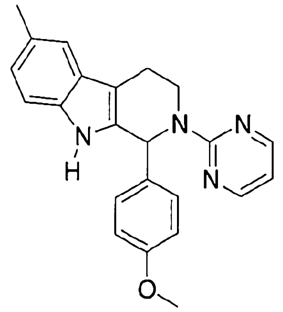
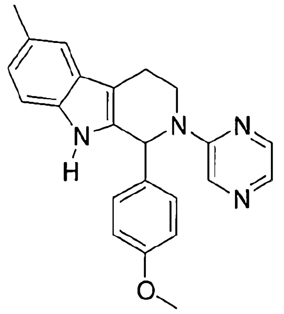
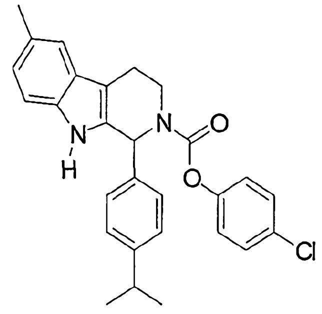
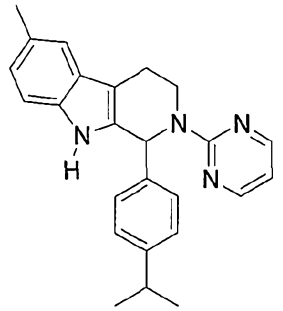
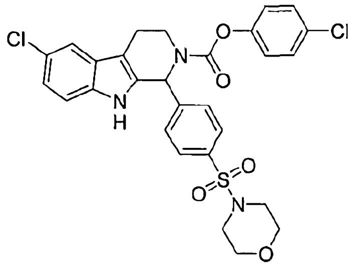
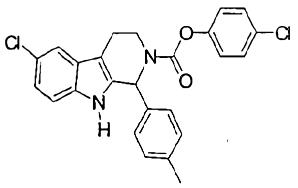
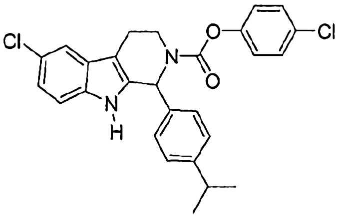
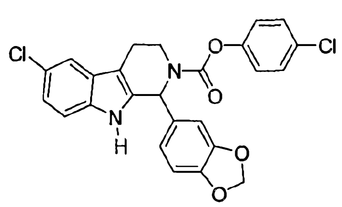
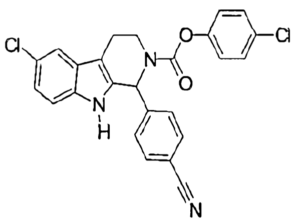
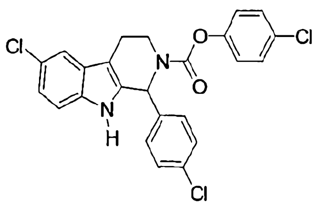
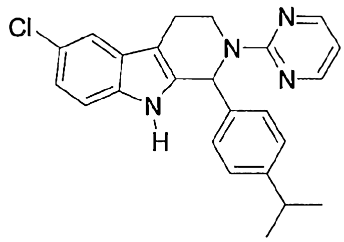
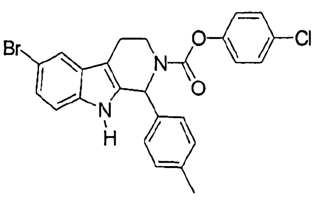
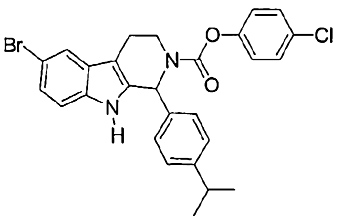
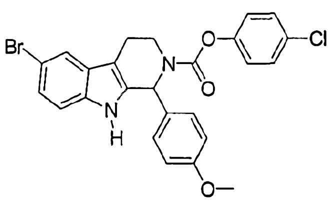
 **260**	 **261**	 **262**
 **263**	 **264**	 **265**
 **266**	 **267**	 **268**
 **269**	 **270**	 **271**
 **272**	 **273**	 **274**
 **275**	 **276**	 **277**

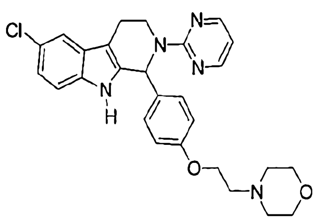
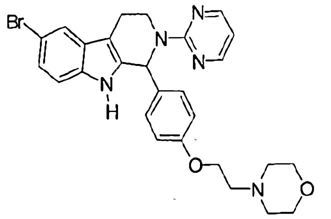
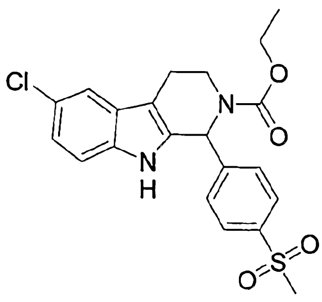
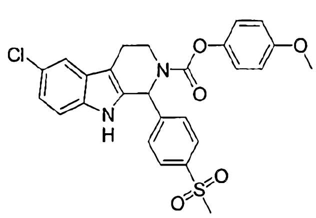
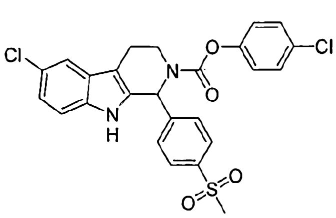
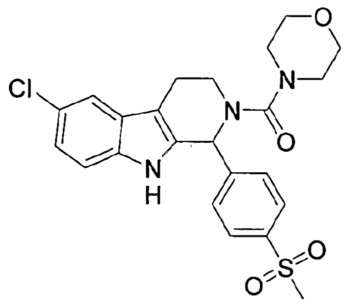
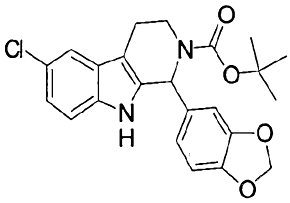
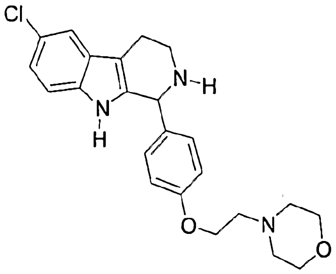
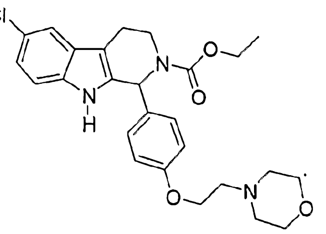
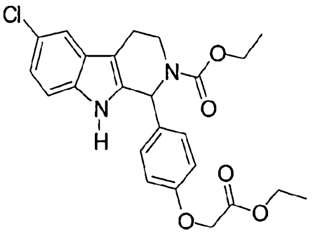
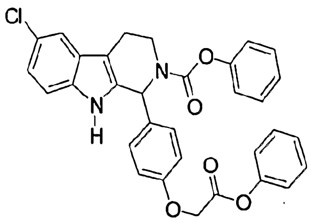
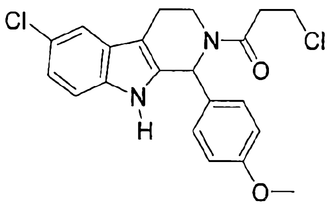
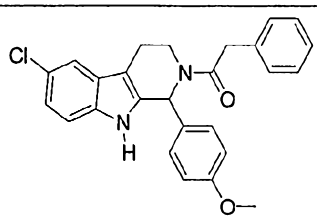
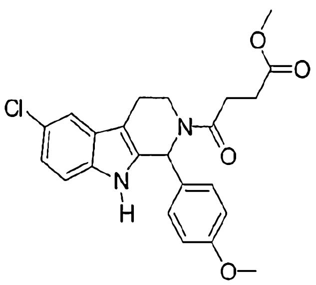
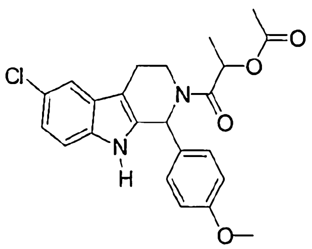
 **278**	 **279**	 **280**
 **281**	 **282**	 **283**
 **284**	 **285**	 **286**
 **287**	 **288**	 **289**
 **290**	 **291**	 **292**

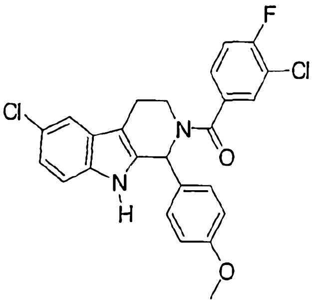
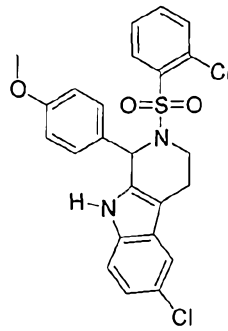
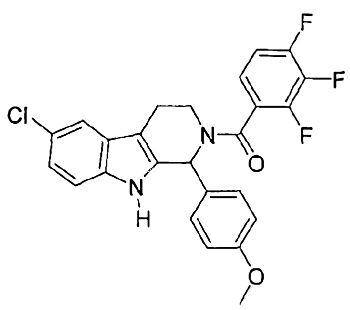
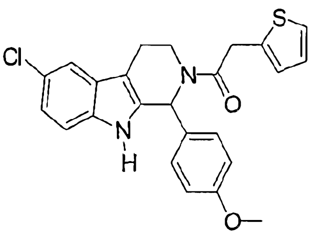
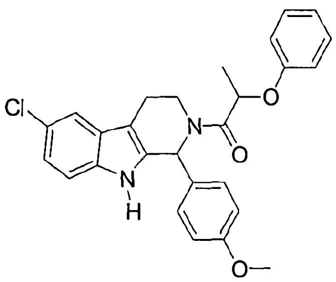
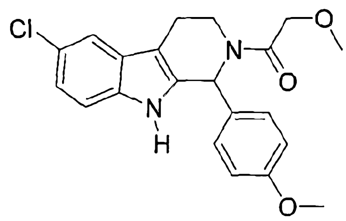
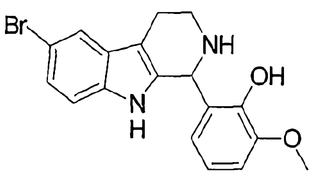
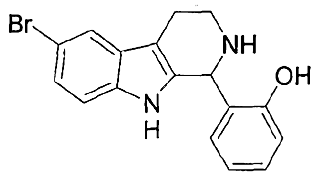
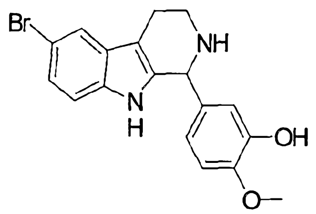
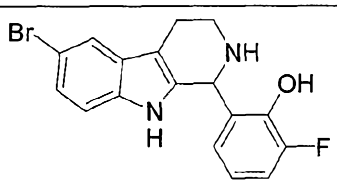
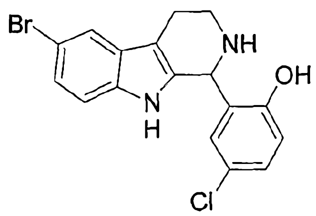
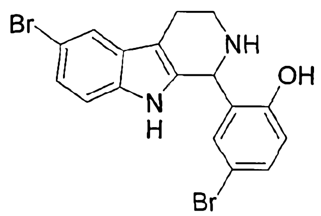
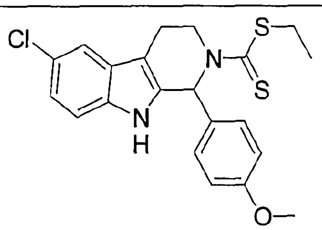
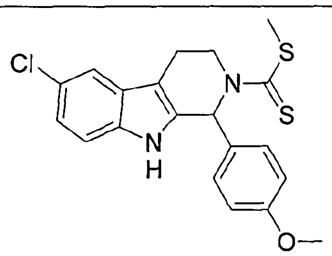
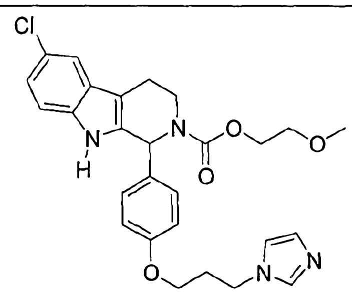
 **293**	 **294**	 **295**
 **296**	 **297**	 **298**
 **299**	 **300**	 **301**
 **302**	 **303**	 **304**
 **305**	 **306**	 **307**

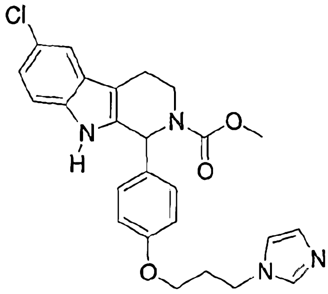
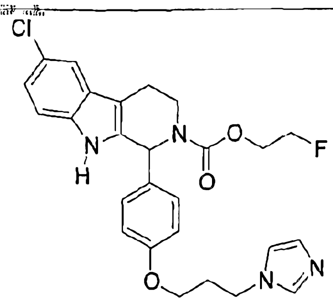
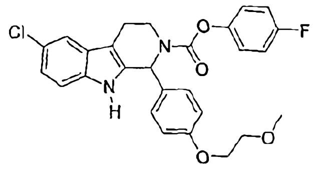
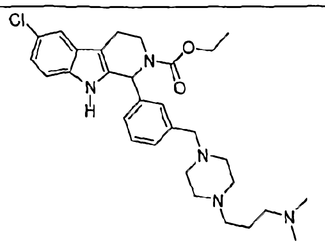
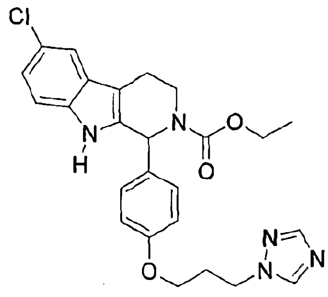
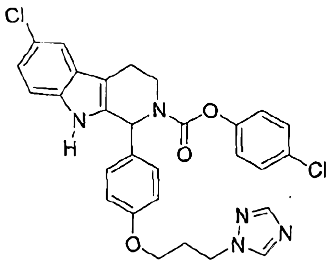
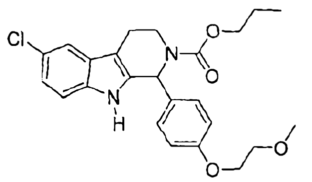
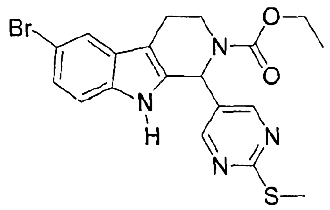
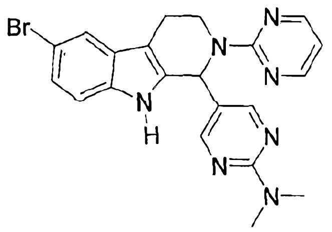
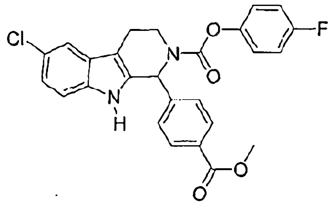
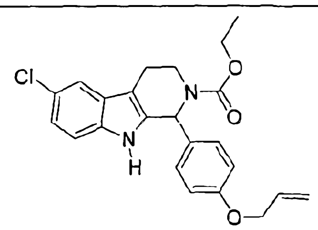
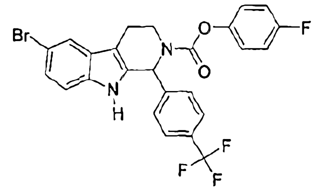
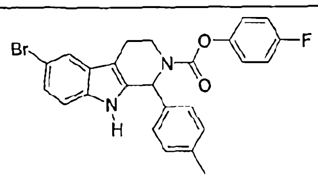
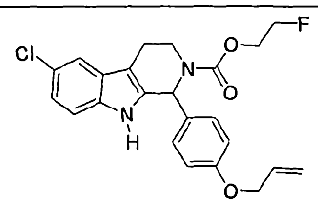
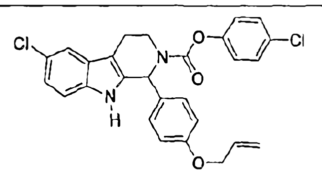
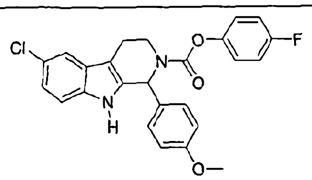
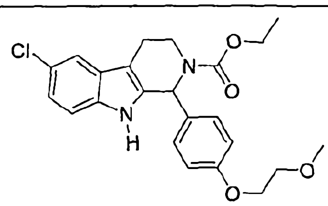
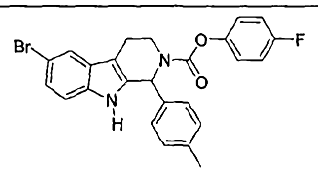
 **308**	 **309**	 **310**
 **311**	 **312**	 **313**
 **314**	 **315**	 **316**
 **317**	 **318**	 **319**
 **320**	 **321**	 **322**
 **323**	 **324**	 **325**

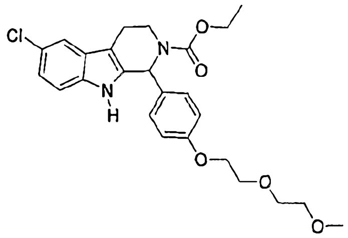
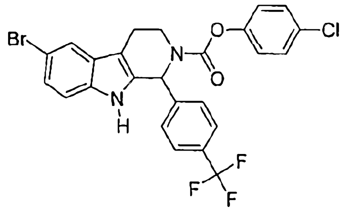
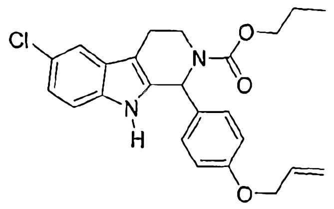
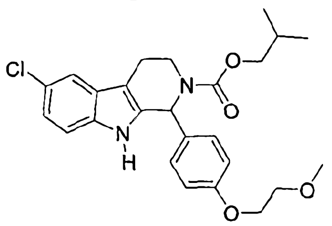
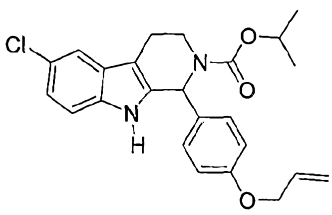
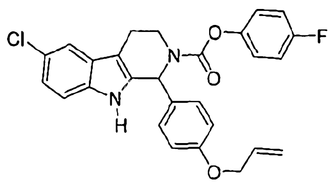
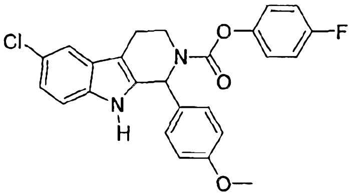
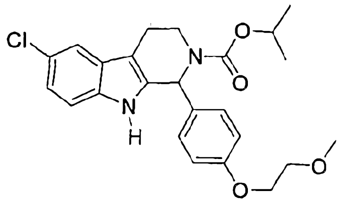
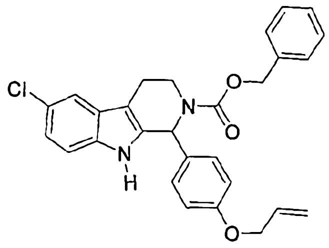
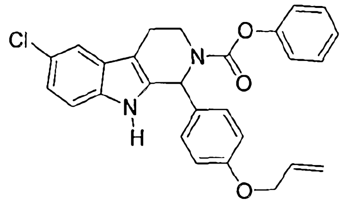
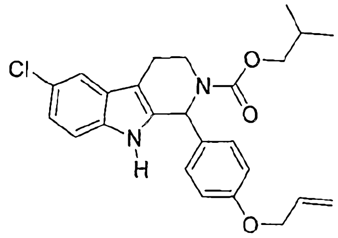
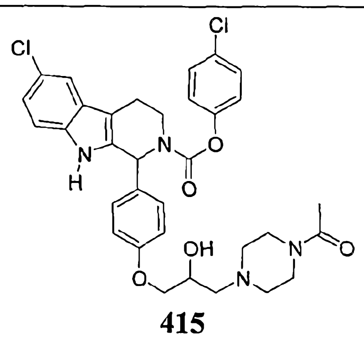
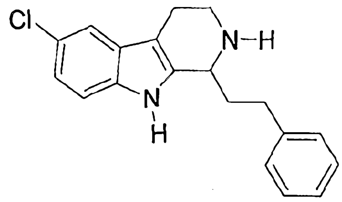
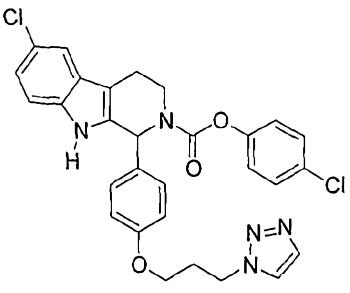
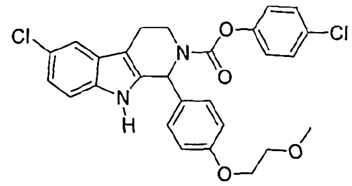
 **326**	 **327**	 **328**
 **329**	 **330**	 **331**
 **332**	 **333**	 **334**
 **335**	 **336**	 **337**
 **338**	 **339**	 **340**

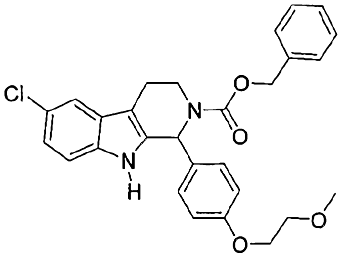
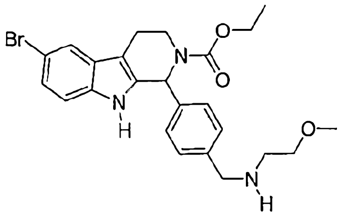
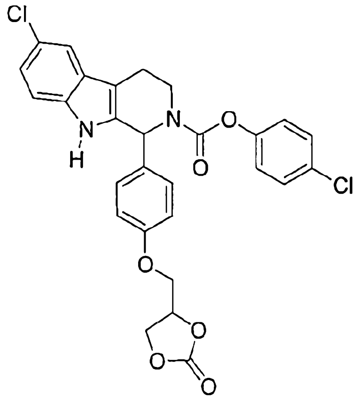
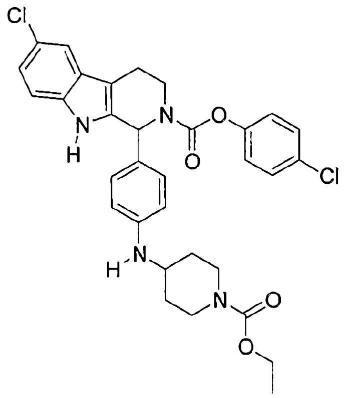
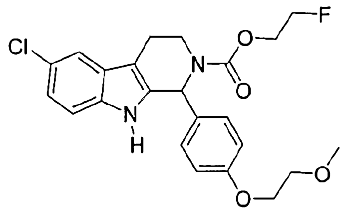
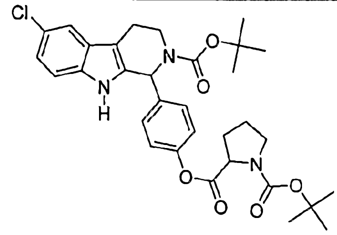
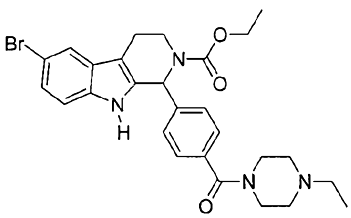
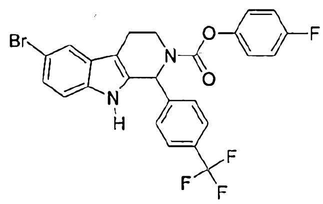
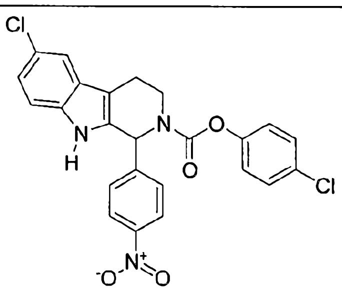
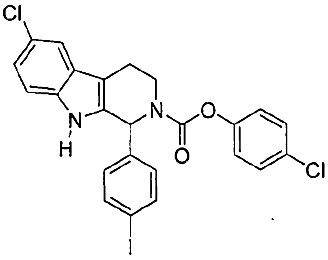
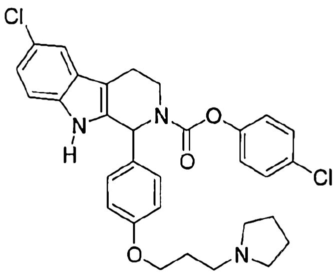
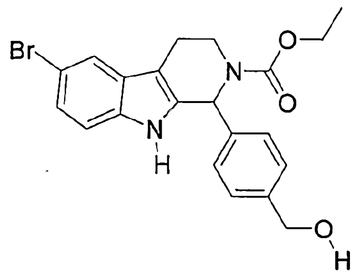
 341	 342	 343
 344	 345	 346
 347	 348	 349
 350	 351	 352
 353	 354	 355

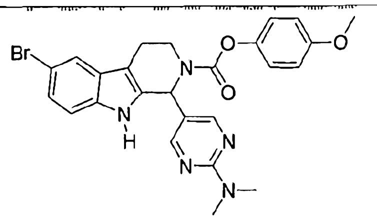
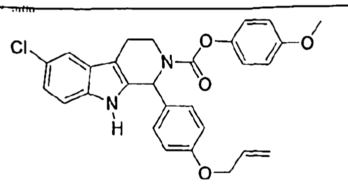
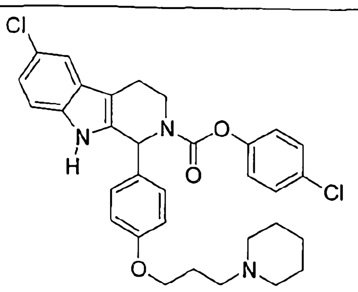
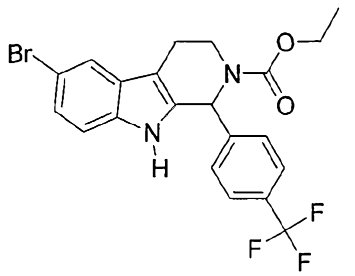
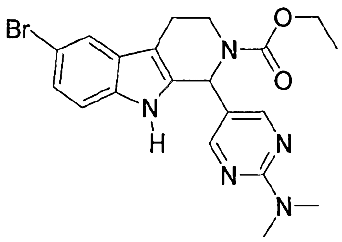
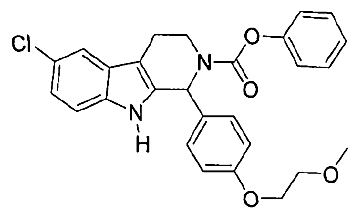
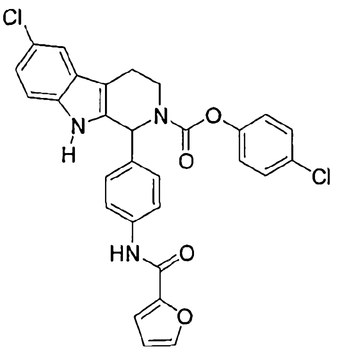
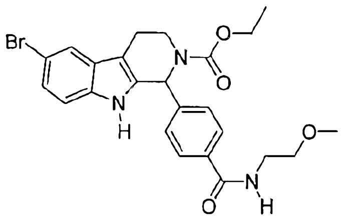
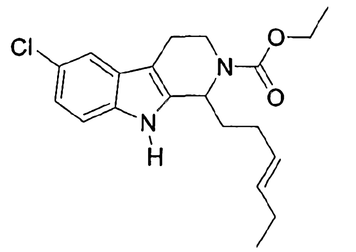
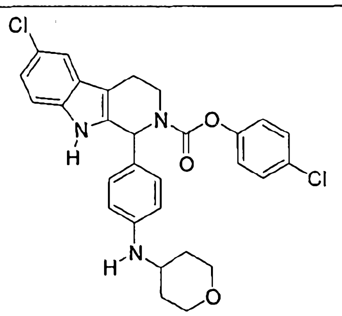
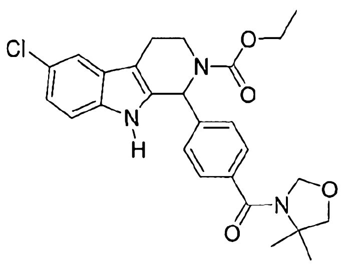
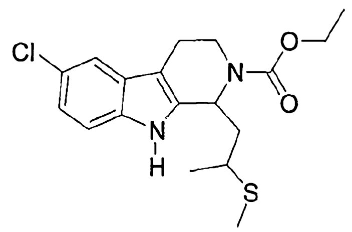
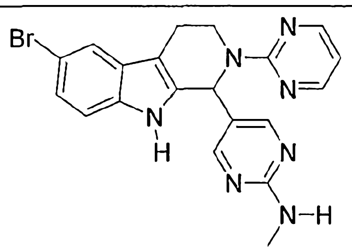
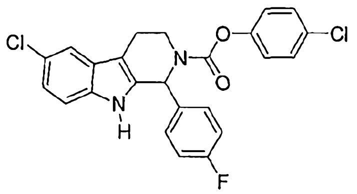
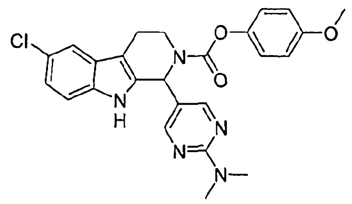
 **356**	 **357**	 **358**
 **359**	 **360**	 **361**
 **362**	 **363**	 **364**
 **365**	 **366**	 **367**
 **368**	 **369**	 **370**

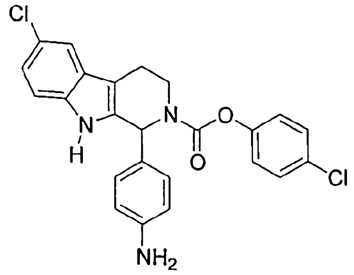
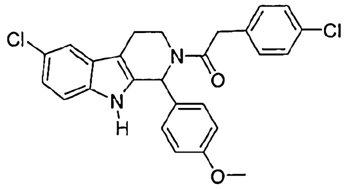
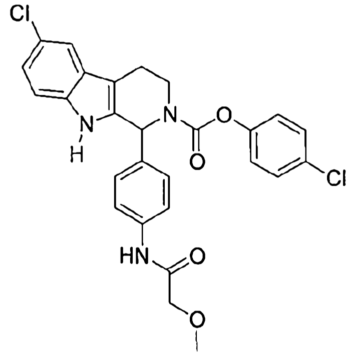
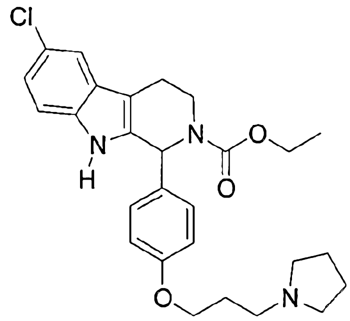
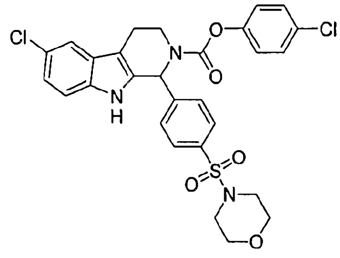
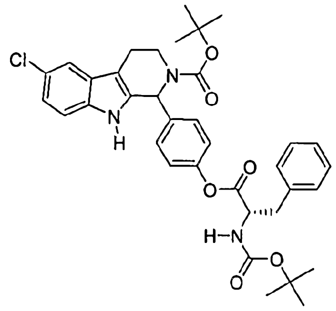
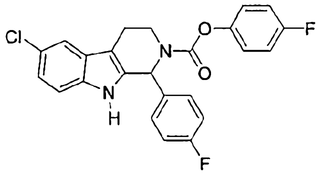
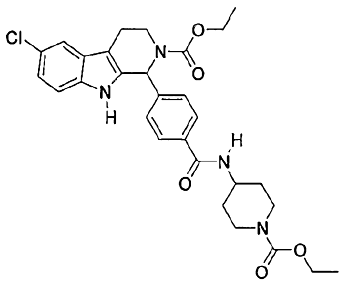
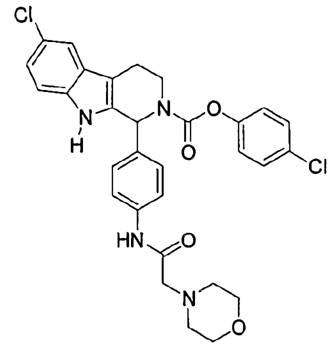
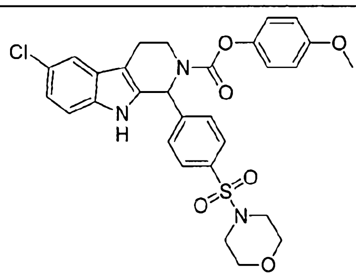
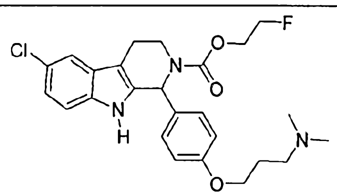
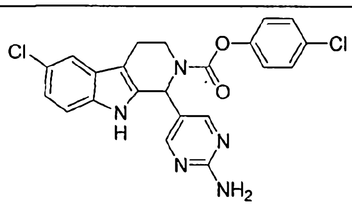
 **371**	 **372**	 **373**
 **374**	 **375**	 **376**
 **377**	 **378**	 **379**
 **380**	 **381**	 **382**
 **383**	 **384**	 **385**

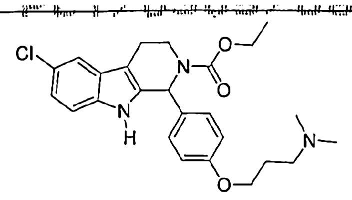
 **386**	 **387**	 **388**
 **389**	 **390**	 **391**
 **392**	 **393**	 **394**
 **395**	 **396**	 **397**
 **398**	 **399**	 **400**
 **401**	 **402**	 **403**

 **404**	 **405**	 **406**
 **407**	 **408**	 **409**
 **410**	 **411**	 **412**
 **413**	 **414**	 **415**
 **416**	 **417**	 **418**

 419	 420	 421
 422	 423	 424
 425	 426	 427
 428	 429	 430

 **431**	 **432**	 **433**
 **434**	 **435**	 **436**
 **437**	 **438**	 **439**
 **440**	 **441**	 **442**
 **443**	 **444**	 **445**

 **446**	 **447**	 **448**
 **449**	 **450**	 **451**
 **452**	 **453**	 **454**
 **455**	 **456**	 **457**



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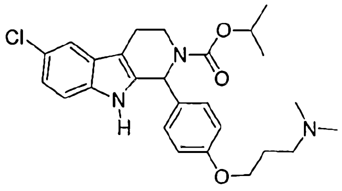

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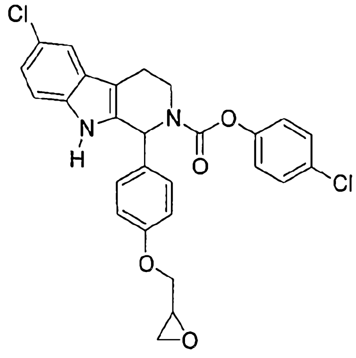

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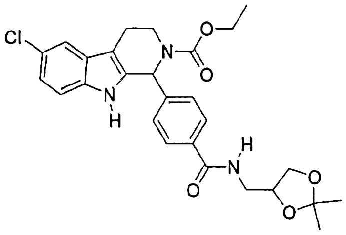

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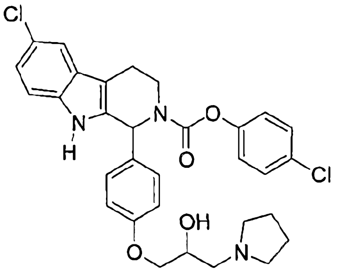

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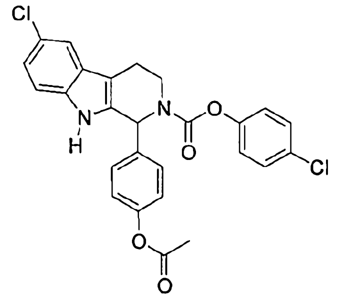

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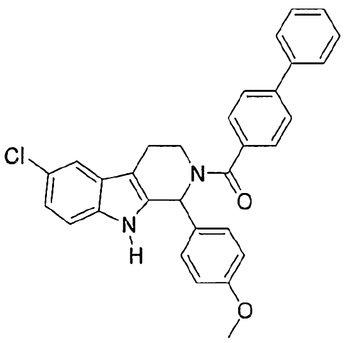

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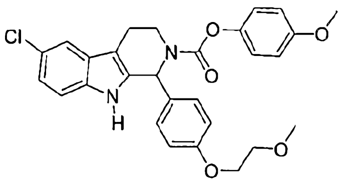

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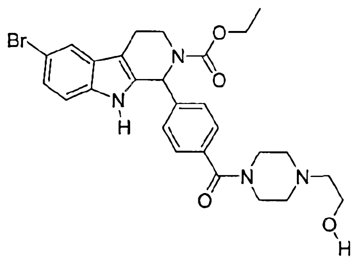

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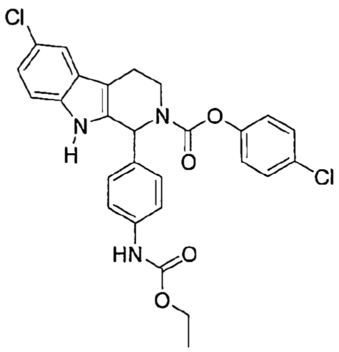

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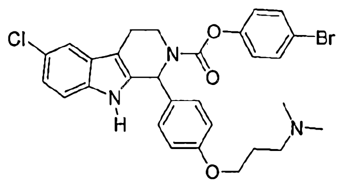

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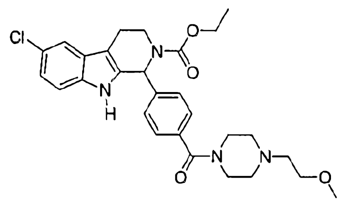

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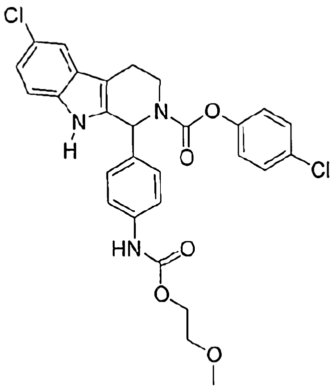
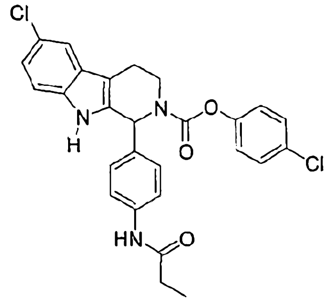
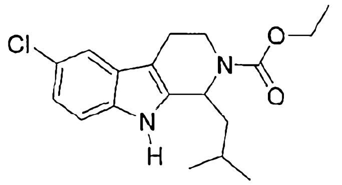
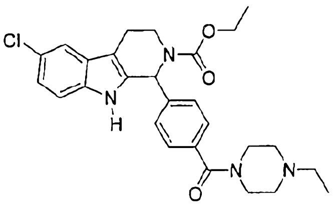
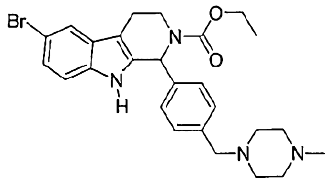
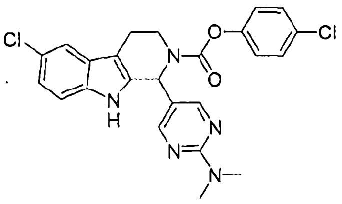
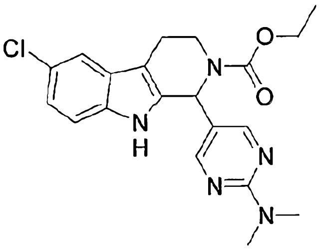
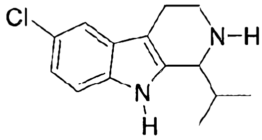
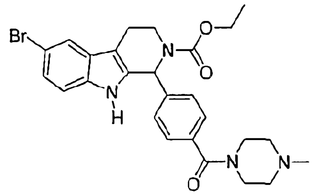
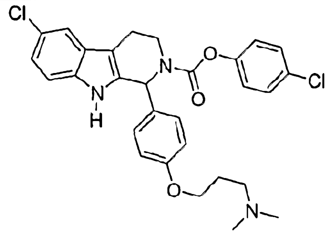
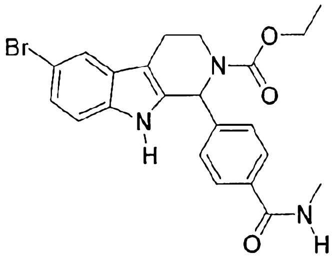
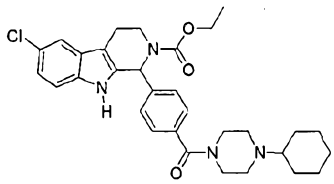
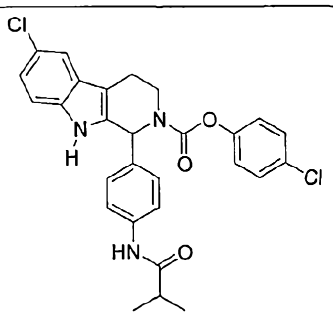
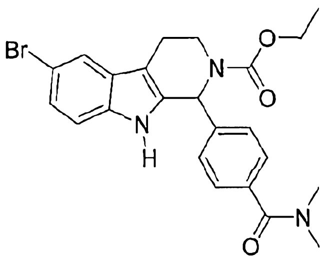
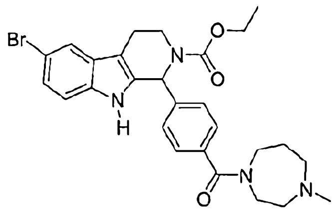
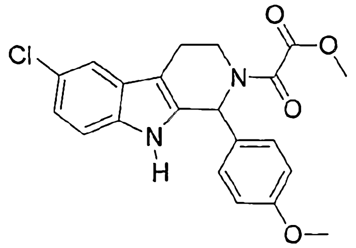
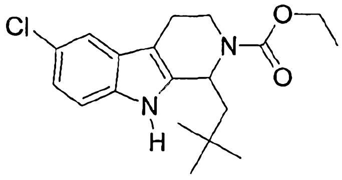
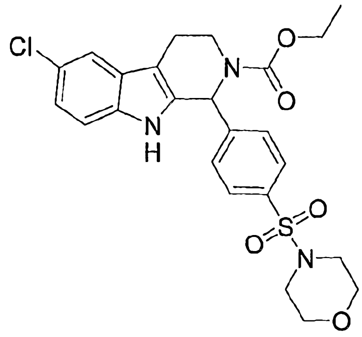
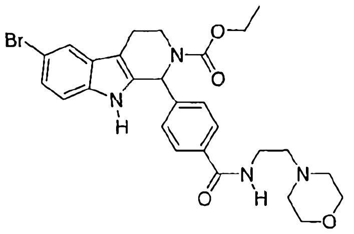
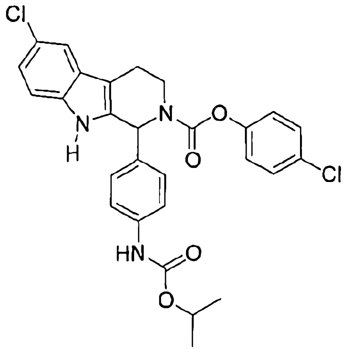
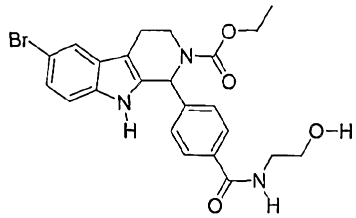
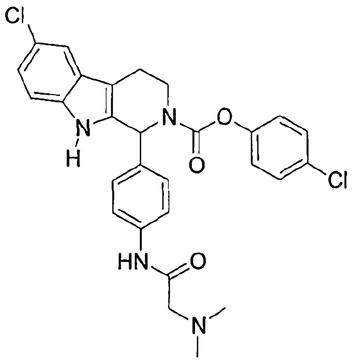
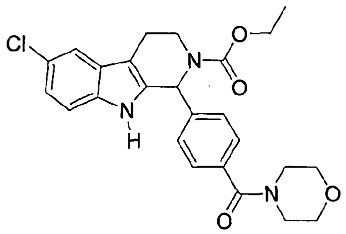
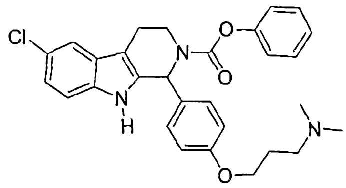
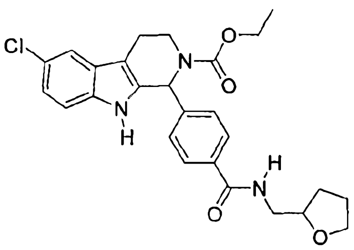
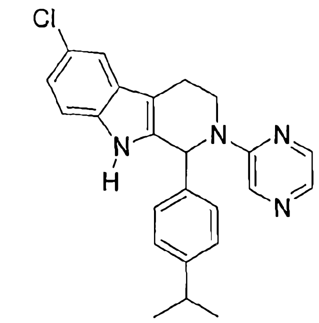
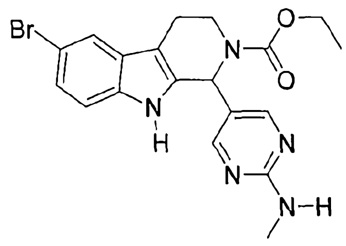
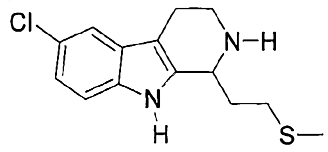
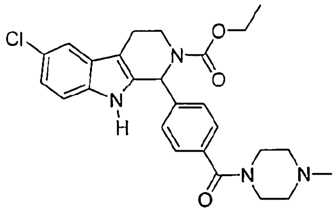
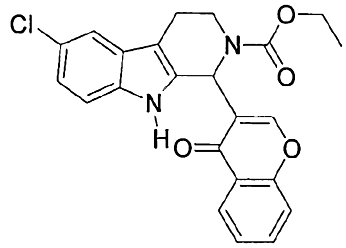
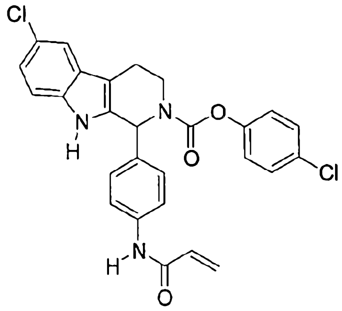
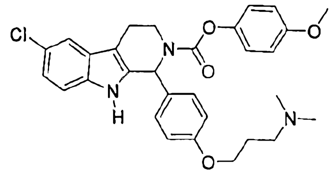
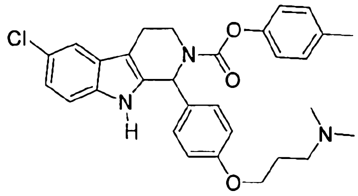
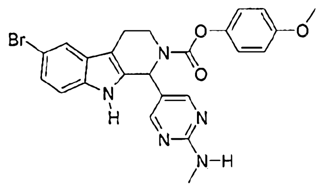
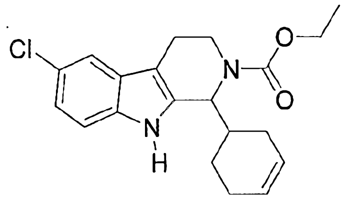
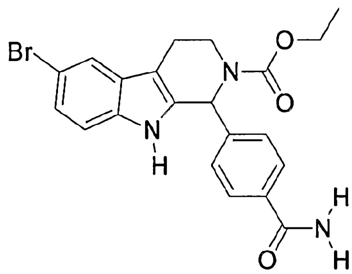
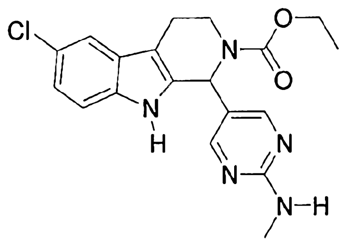
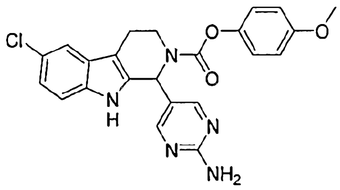
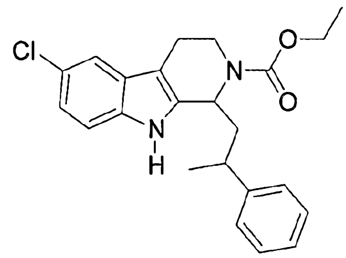
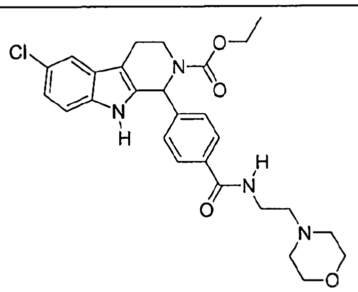
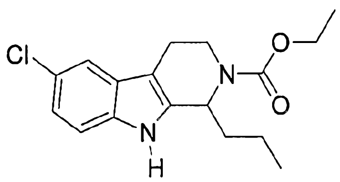
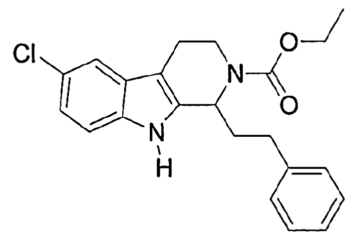
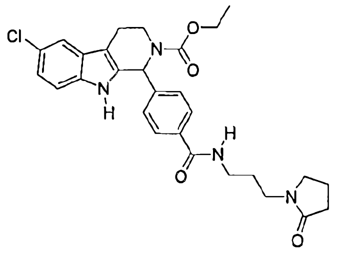
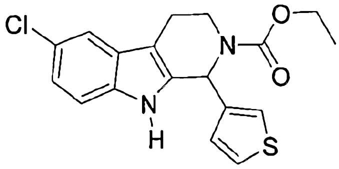
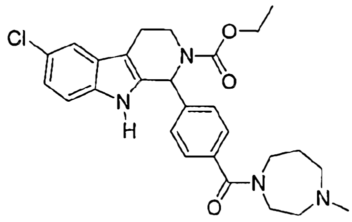
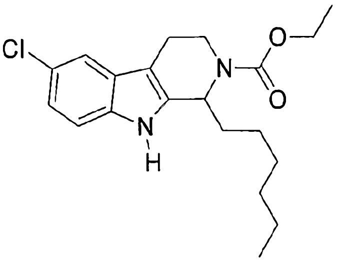
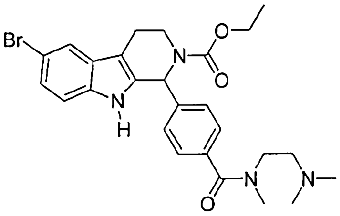
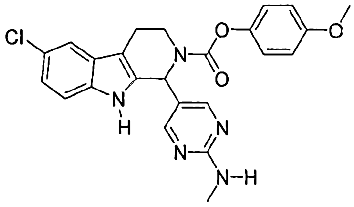
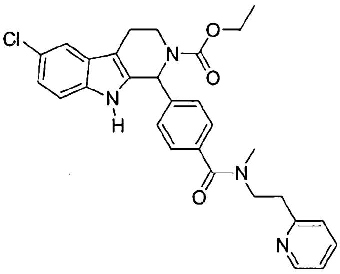
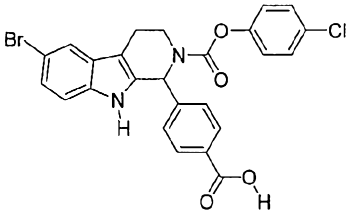
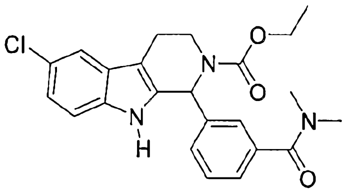
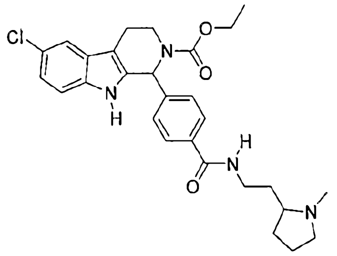
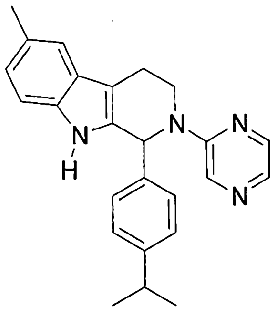
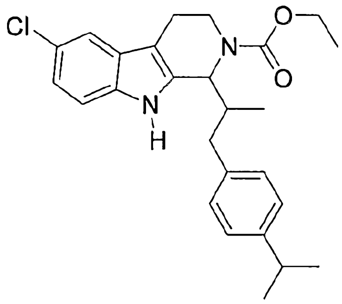
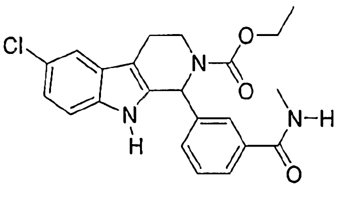
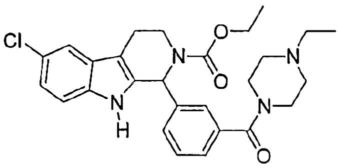
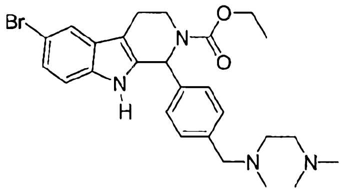
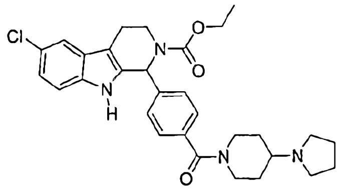
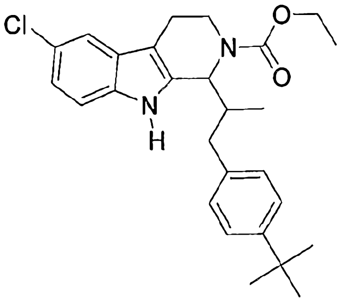
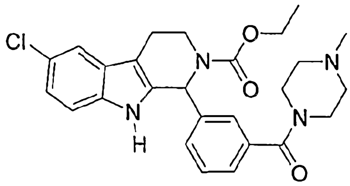
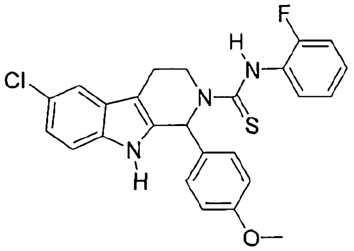
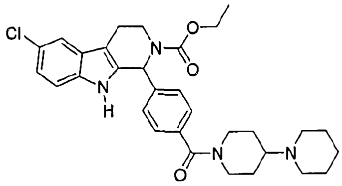
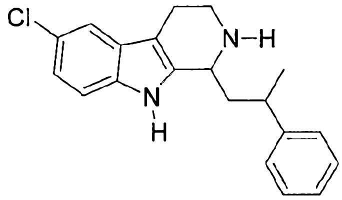
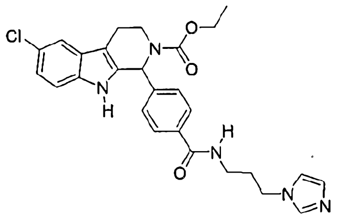
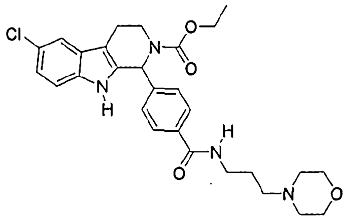
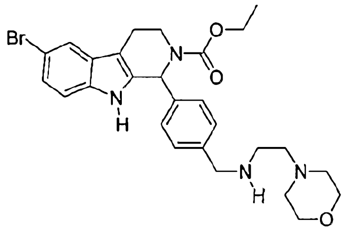
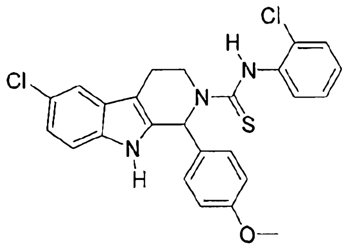
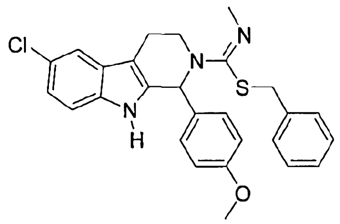
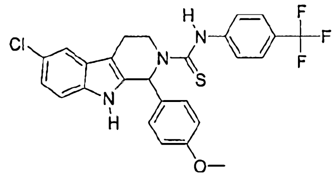
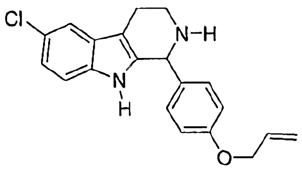
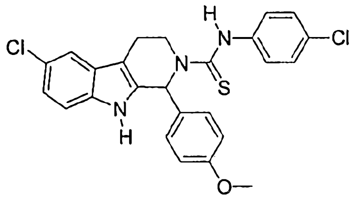
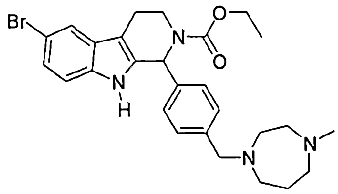
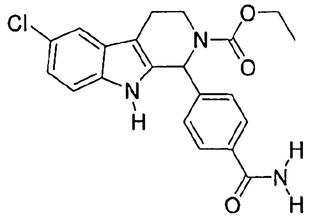
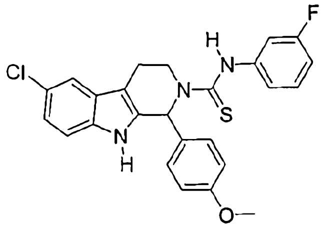
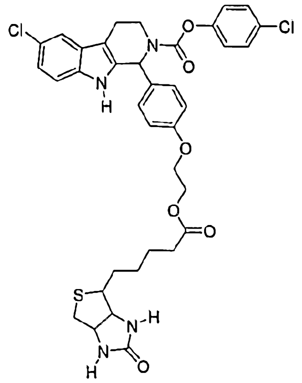
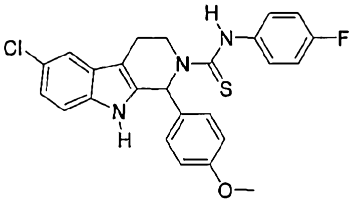
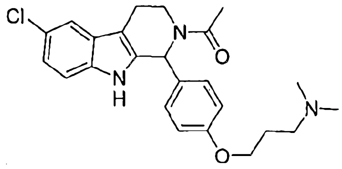
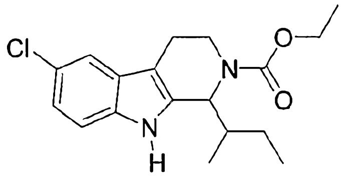
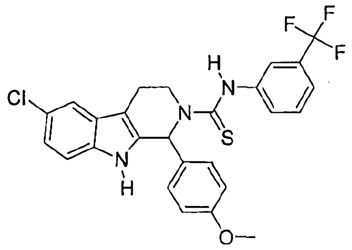
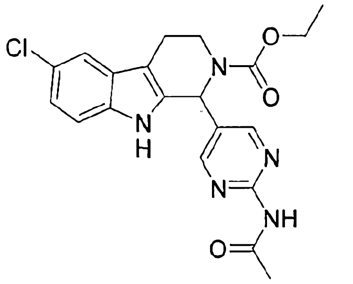
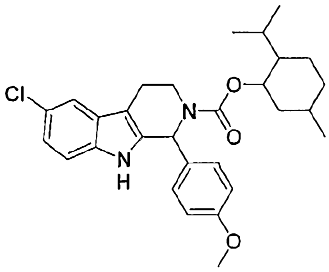
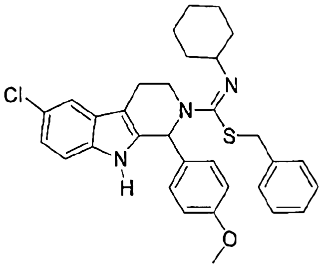
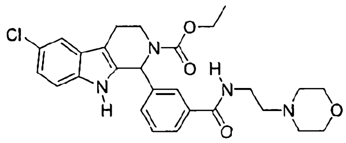
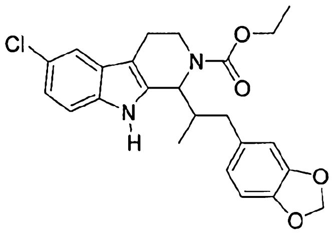
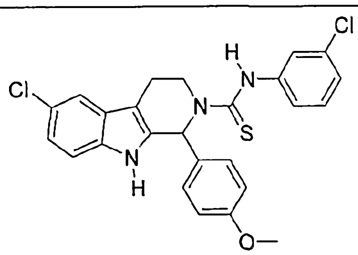
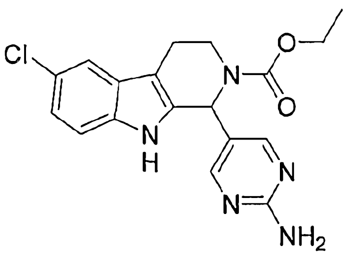
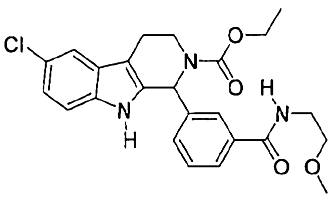
 **470**	 **471**	 **472**
 **473**	 **474**	 **475**
 **476**	 **477**	 **478**
 **479**	 **480**	 **481**
 **482**	 **483**	 **484**

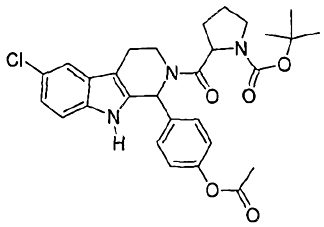
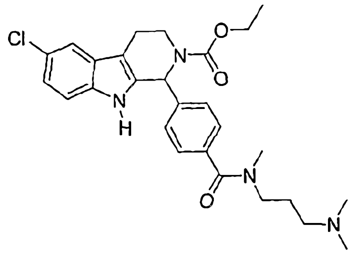
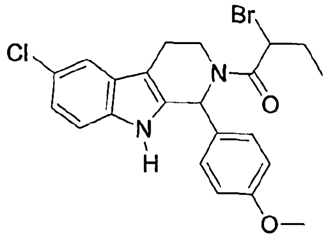
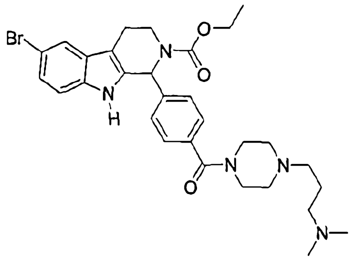
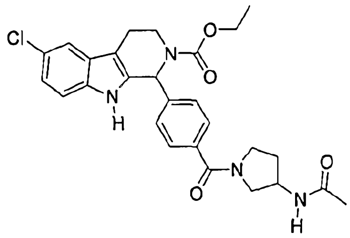
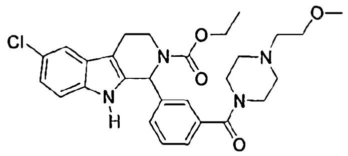
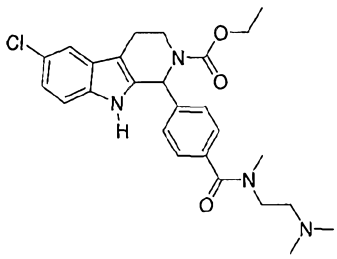
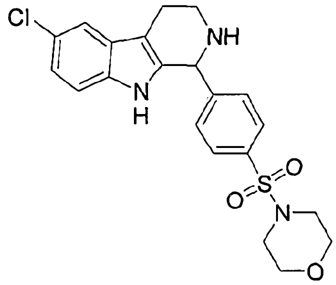
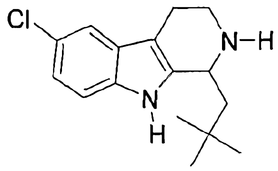
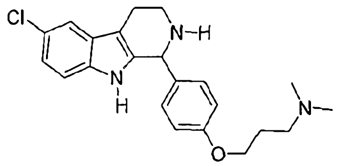
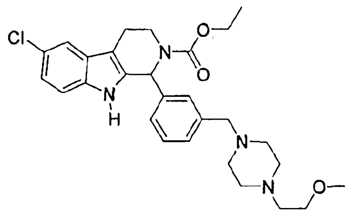
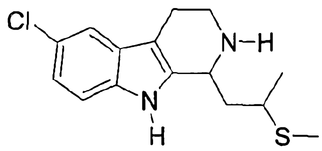
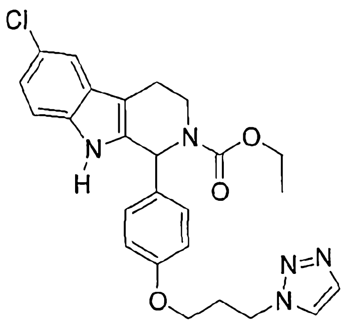
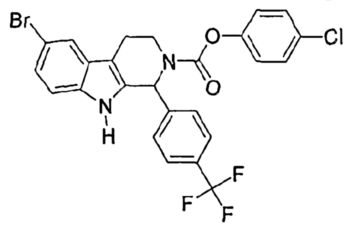
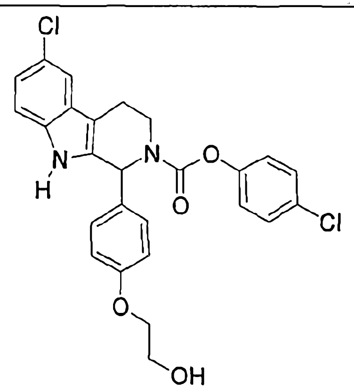
 **485**	 **486**	 **487**
 **488**	 **489**	 **490**
 **491**	 **492**	 **493**
 **494**	 **495**	 **496**

 **497**	 **498**	 **499**
 **500**	 **501**	 **502**
 **503**	 **504**	 **505**
 **506**	 **507**	 **508**
 **509**	 **510**	 **511**

 512	 513	 514
 515	 516	 517
 518	 519	 520
 521	 522	 523
 524	 525	 526

 **527**	 **528**	 **529**
 **530**	 **531**	 **532**
 **533**	 **534**	 **535**
 **536**	 **537**	 **538**
 **539**	 **540**	 **541**

 **542**	 **543**	 **544**
 **545**	 **546**	 **547**
 **548**	 **549**	 **550**
 **551**	 **552**	 **553**
 **554**	 **555**	 **556**

 **557**	 **558**	 **559**
 **560**	 **561**	 **562**
 **563**	 **564**	 **565**
 **566**	 **567**	 **568**
 **569**	 **570**	 **571**

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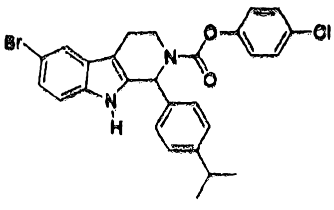
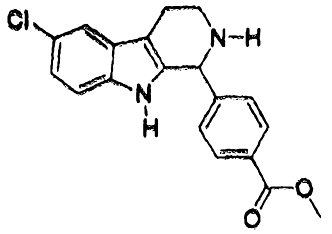
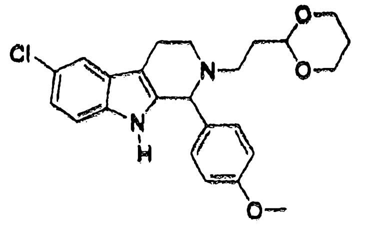
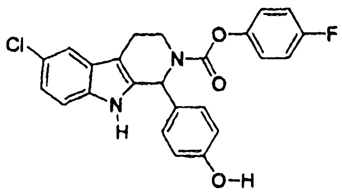
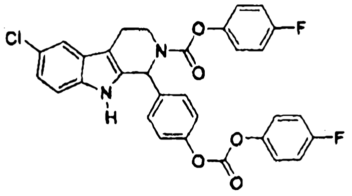
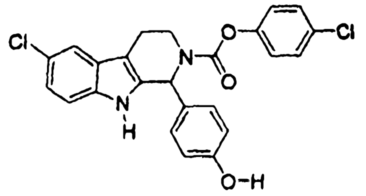
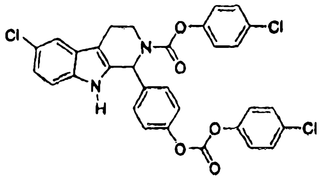
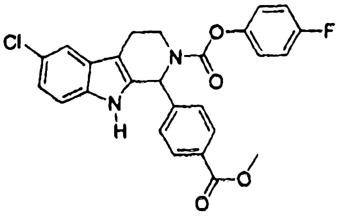
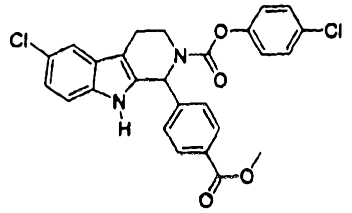
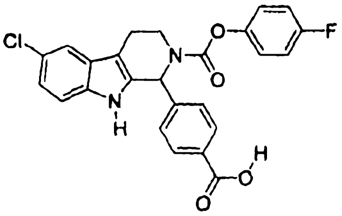
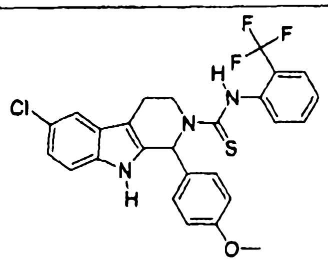
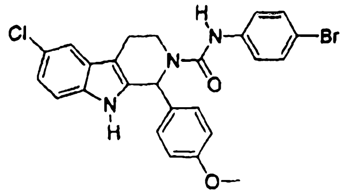
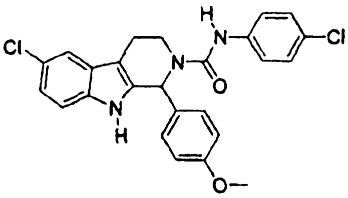
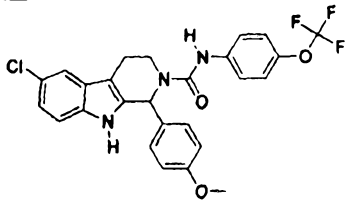
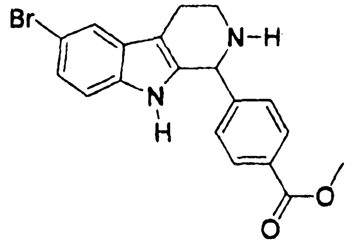
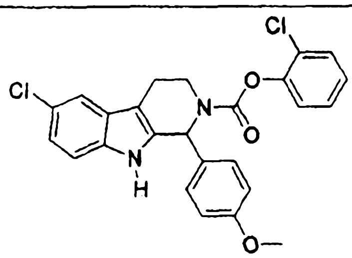
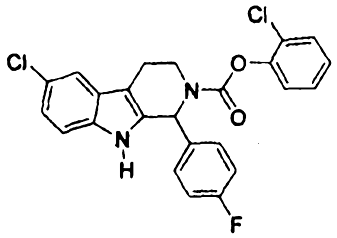
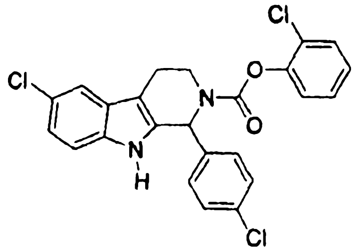
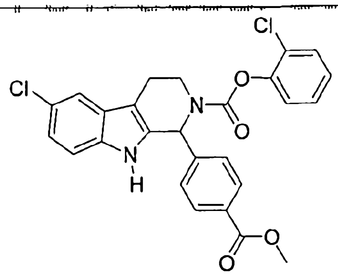
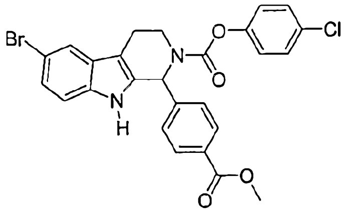
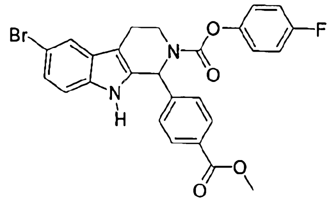
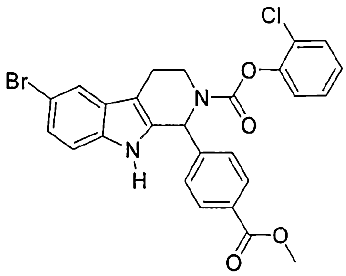
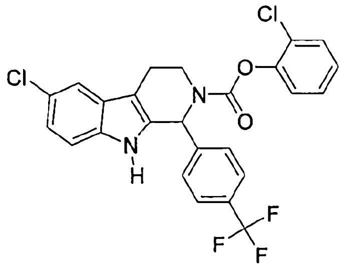
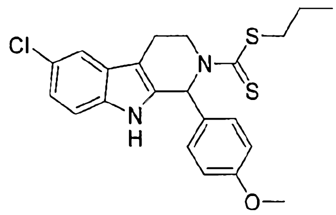
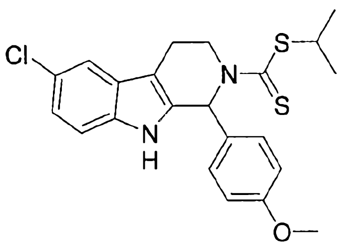
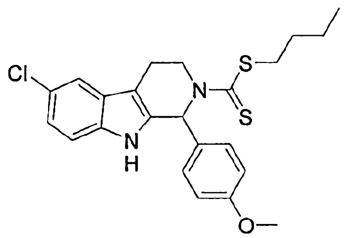
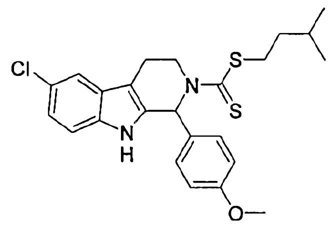
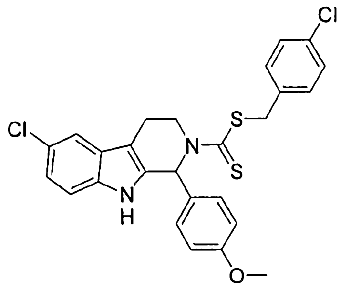
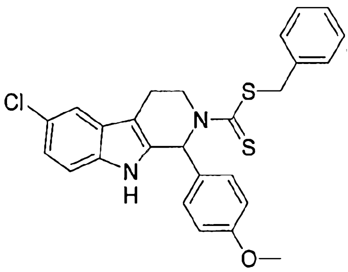
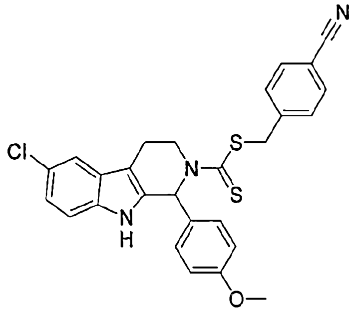
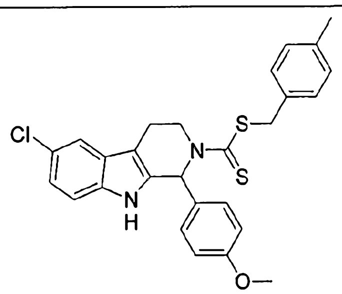
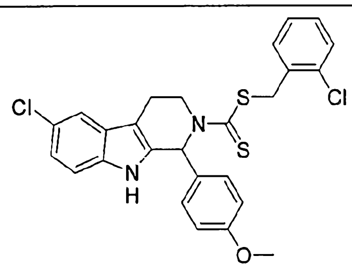
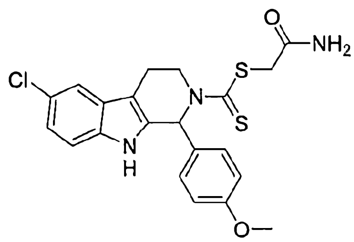
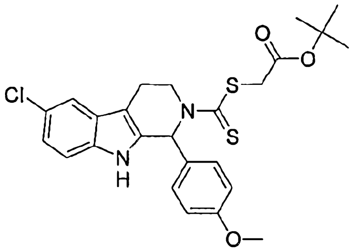
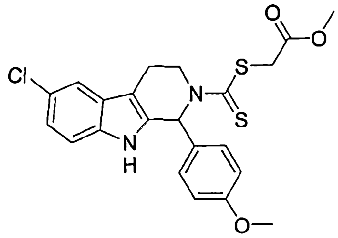
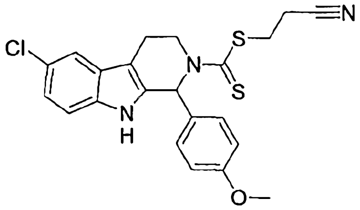
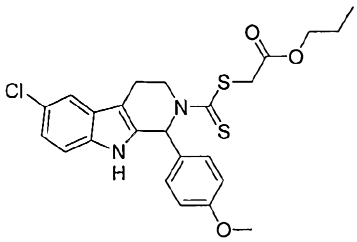
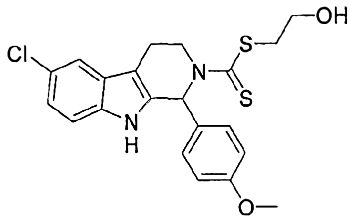
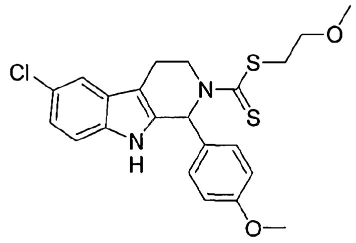
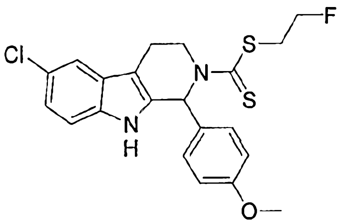
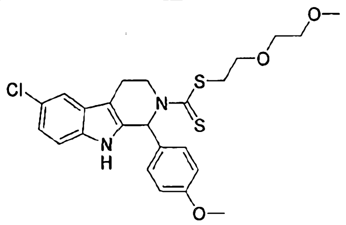
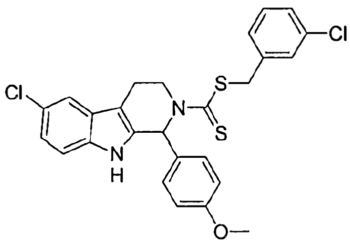
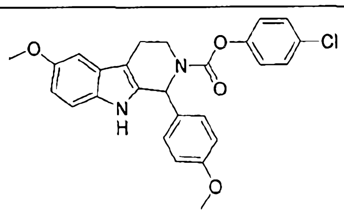
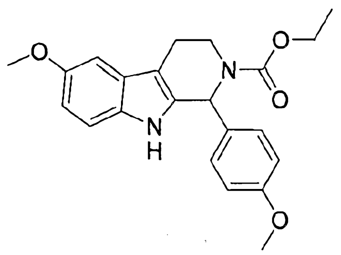
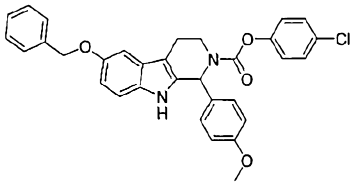
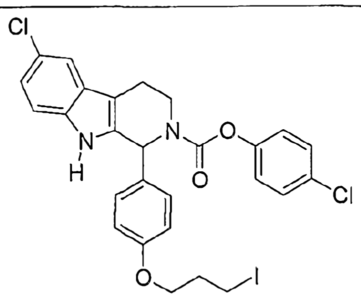
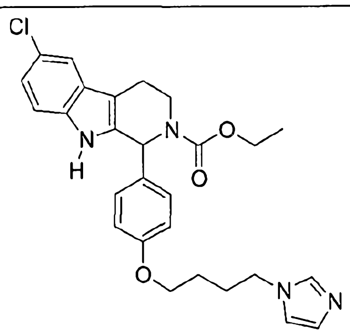
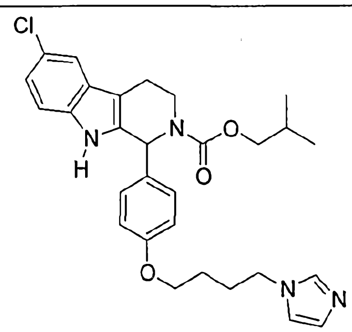
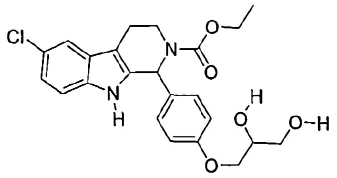
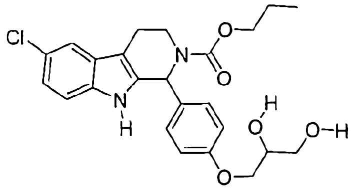
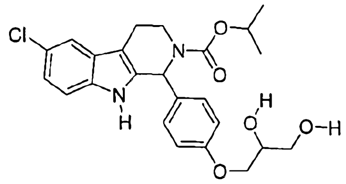
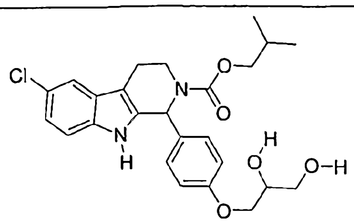
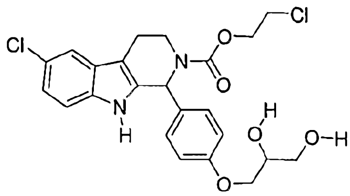
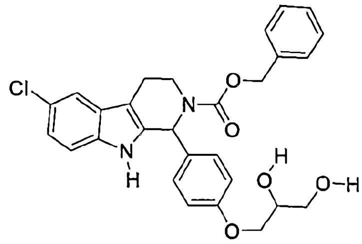
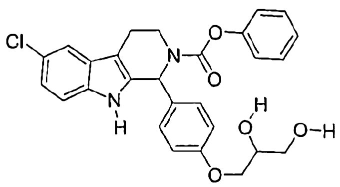
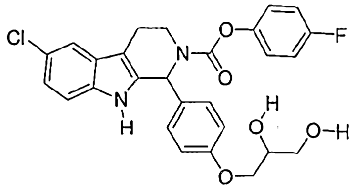
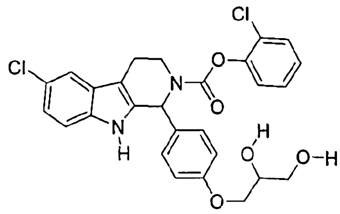
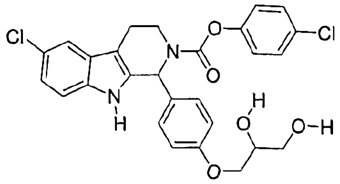
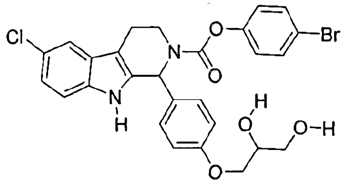
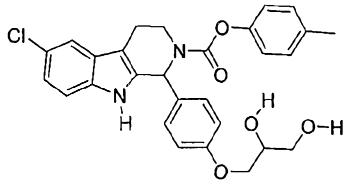
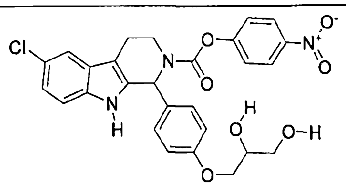
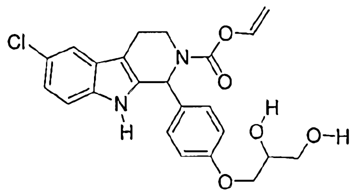
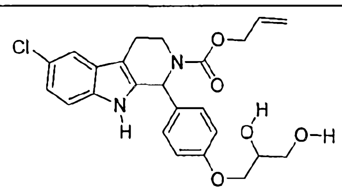
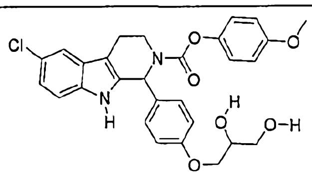
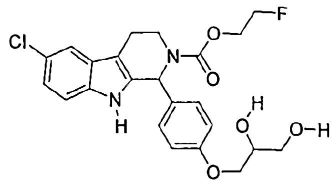
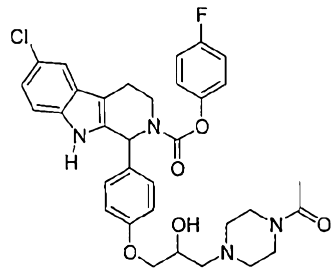
 **572**	 **573**	 **574**
 **575**	 **576**	 **577**
 **578**	 **579**	 **580**
 **581**	 **582**	 **583**
 **584**	 **585**	 **586**
 **587**	 **588**	 **589**

 **590**	 **591**	 **592**
 **593**	 **594**	 **595**
 **596**	 **597**	 **598**
 **599**	 **600**	 **601**
 **602**	 **603**	 **604**

 **605**	 **606**	 **607**
 **608**	 **609**	 **610**
 **611**	 **612**	 **613**
 **614**	 **615**	 **616**
 **617**	 **618**	 **619**

 **620**	 **621**	 **622**
 **623**	 **624**	 **625**
 **626**	 **627**	 **628**
 **629**	 **630**	 **631**
 **632**	 **633**	 **634**
 **635**	 **636**	 **637**

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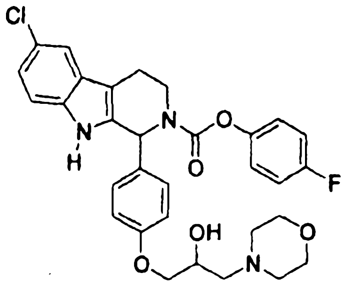
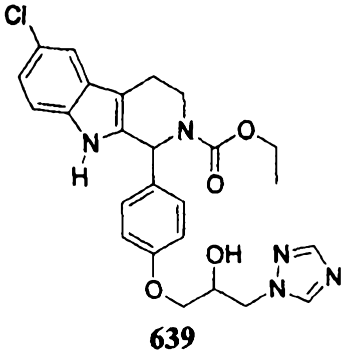
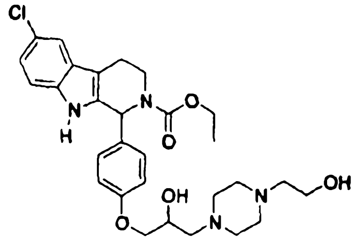
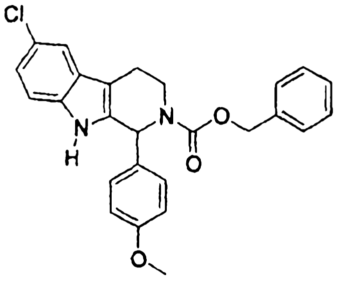
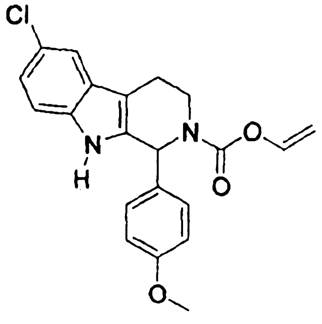
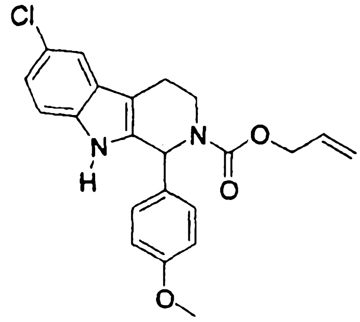
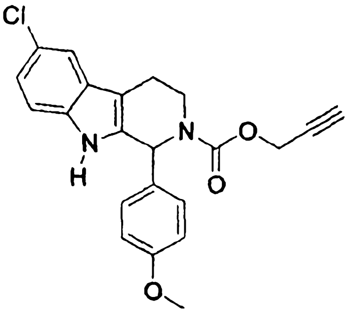
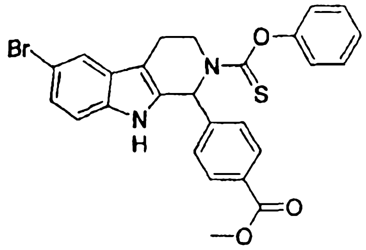
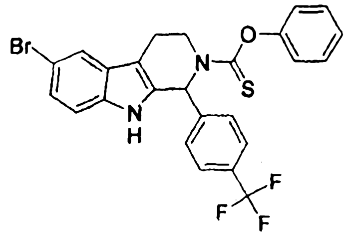
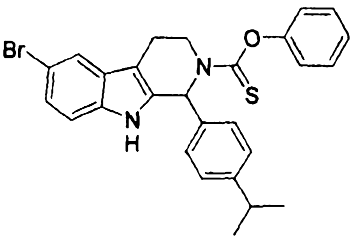
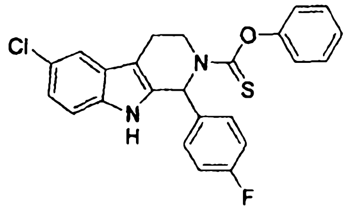
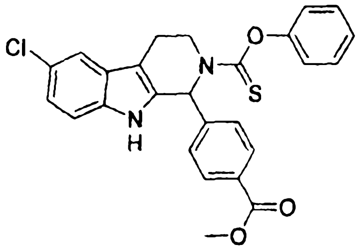
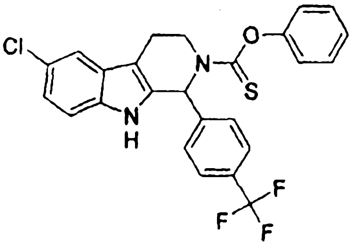
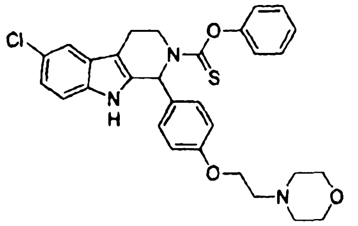
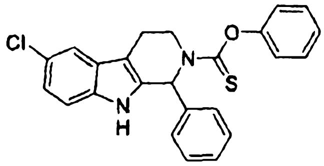
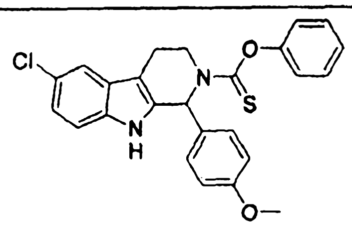
 **638**	 **639**	 **640**
 **641**	 **642**	 **643**
 **644**	 **645**	 **646**
 **647**	 **648**	 **649**
 **650**	 **651**	 **652**



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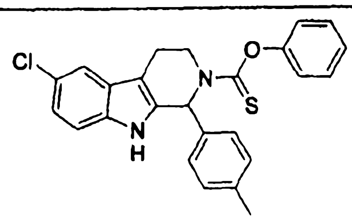

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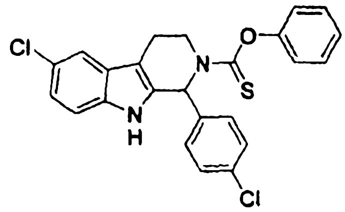

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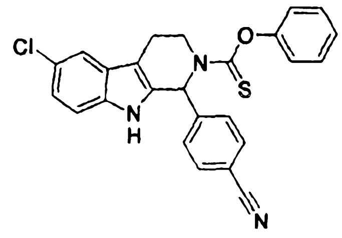

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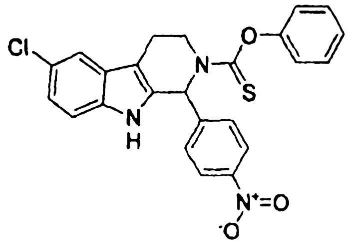

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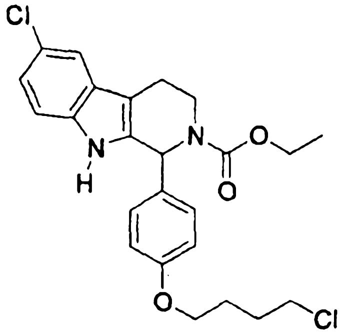

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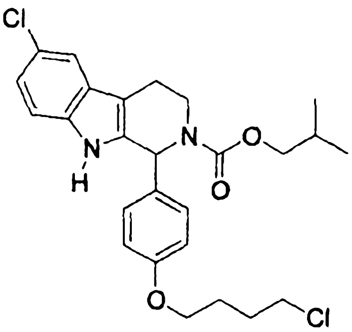

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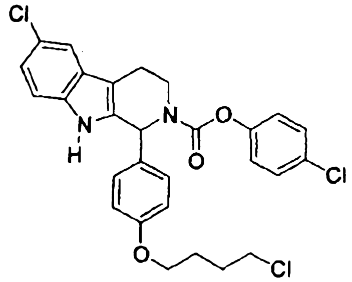

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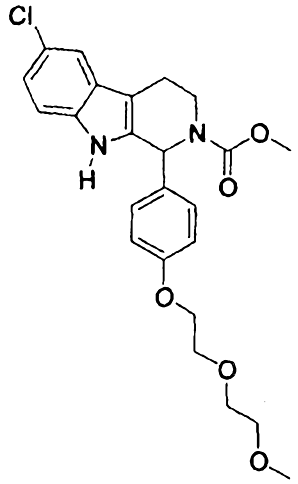

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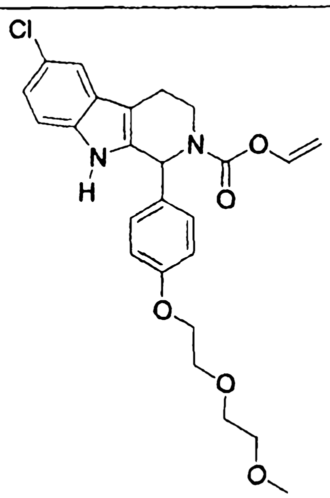

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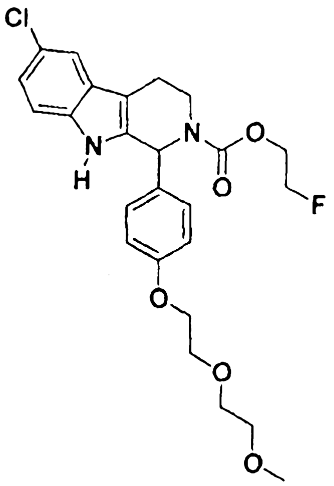

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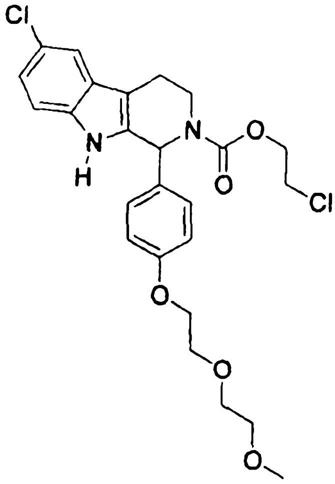

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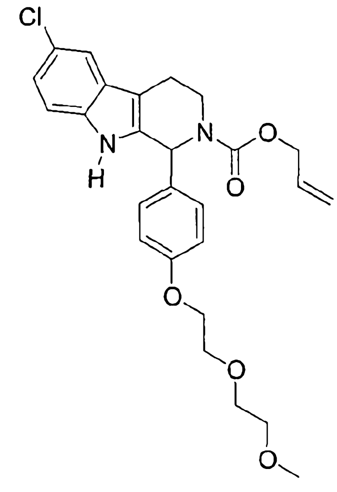
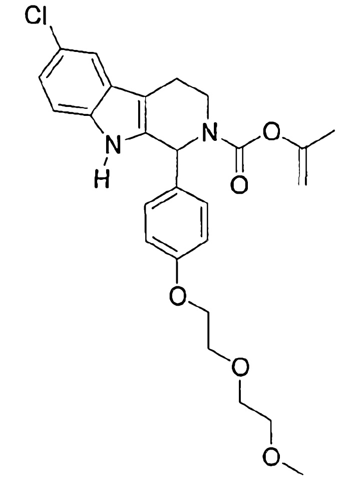
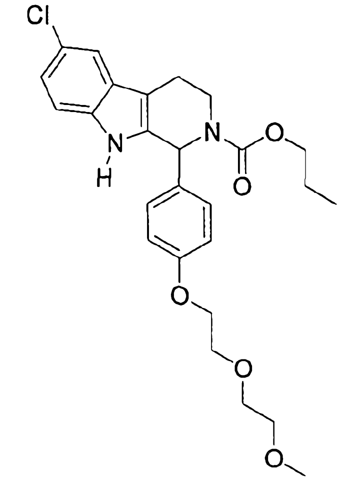
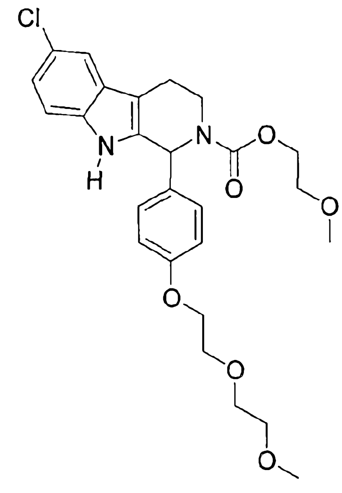
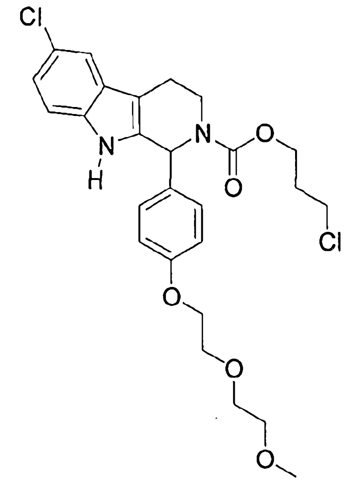
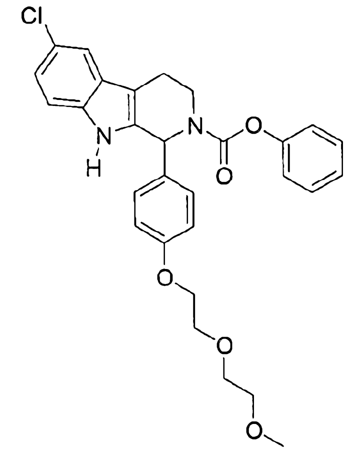
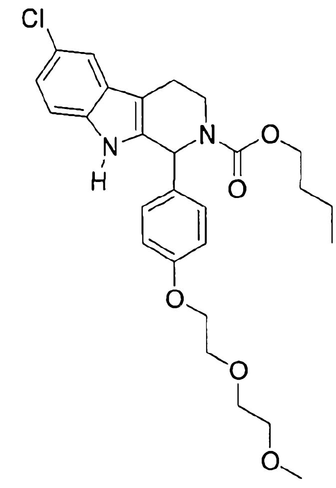
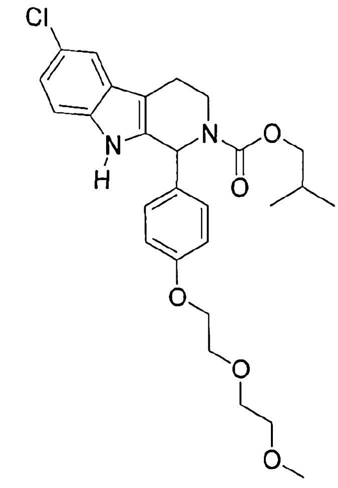
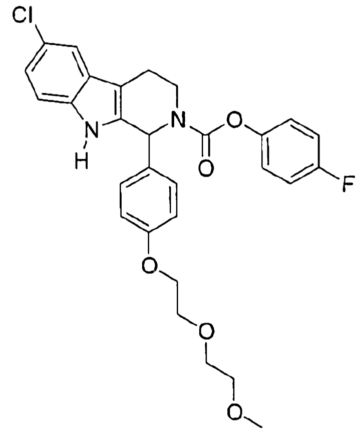
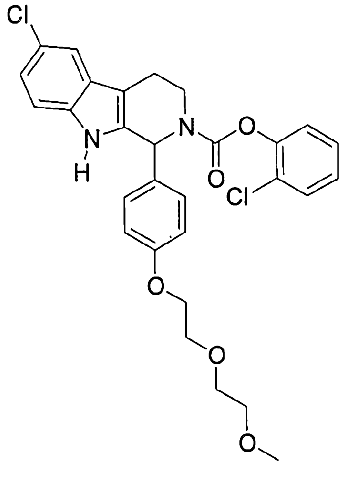
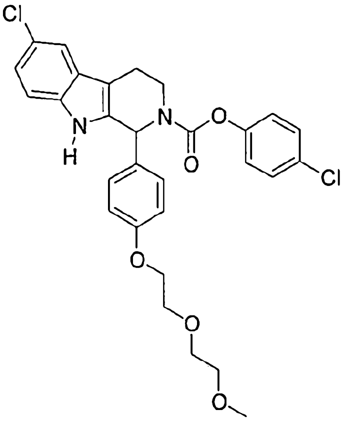
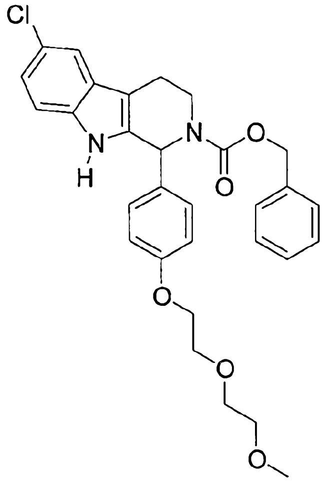
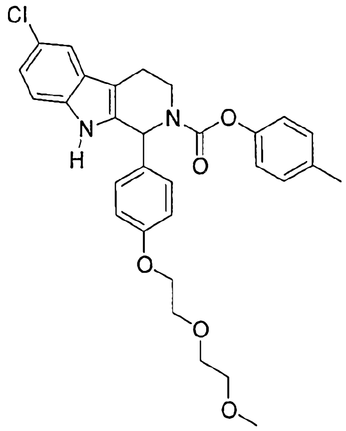
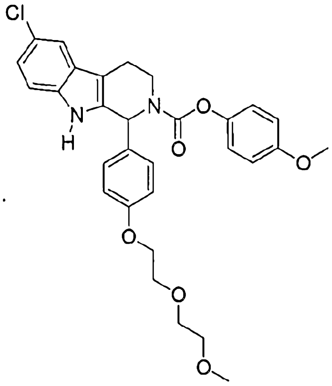
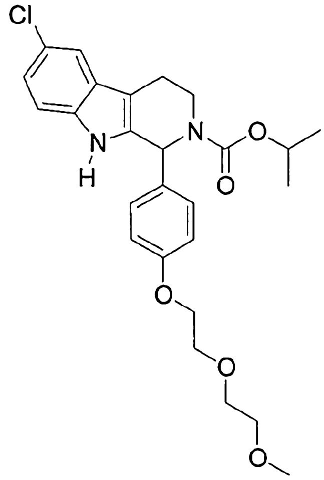
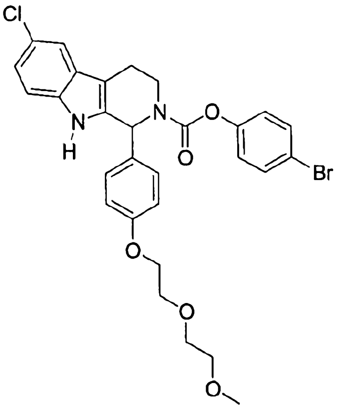
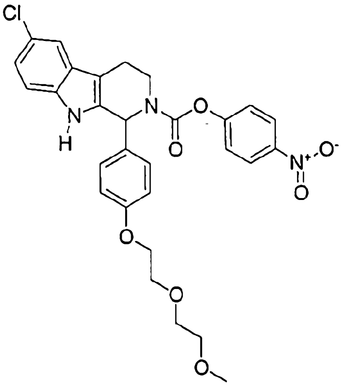
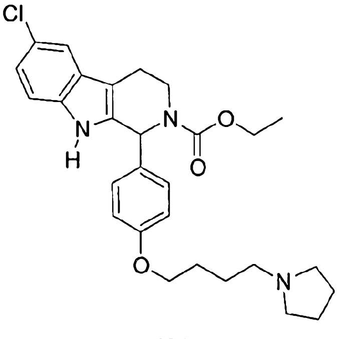
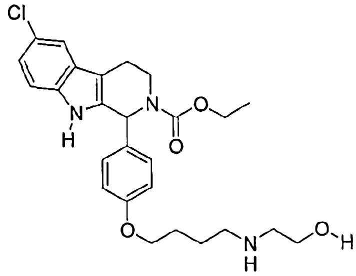
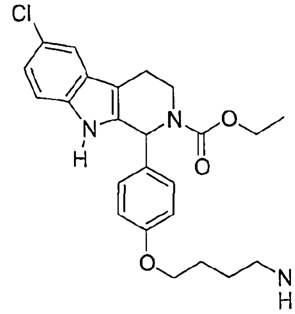
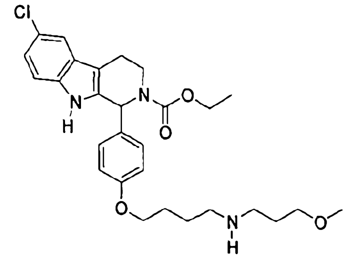
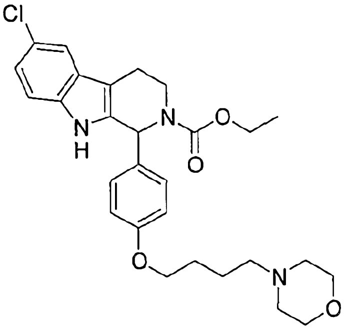
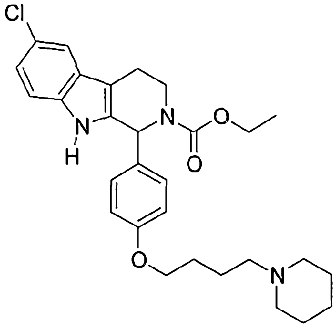
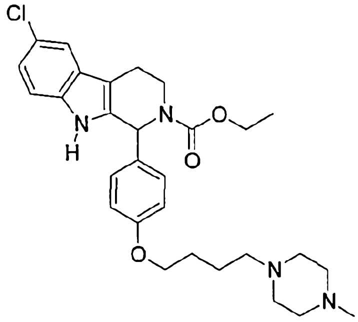
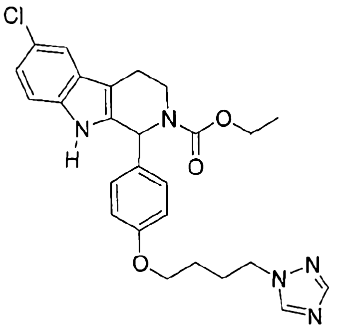
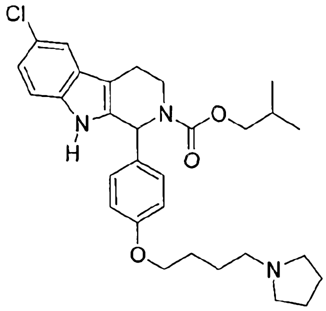
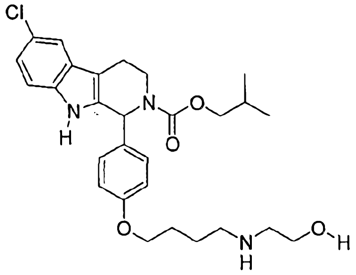
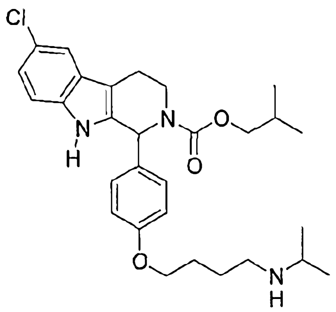
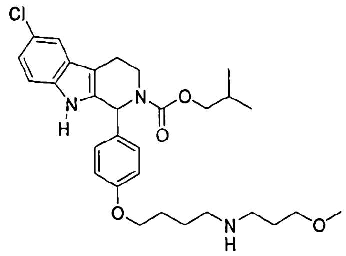
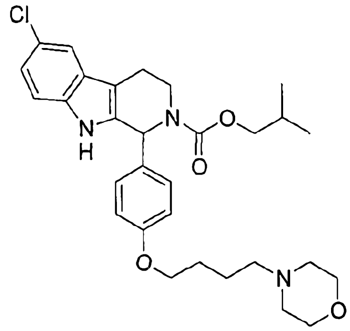
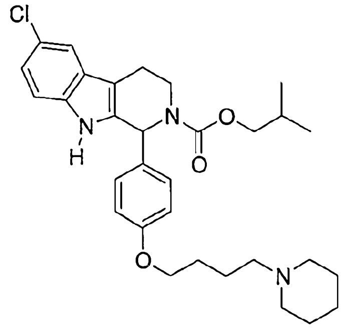
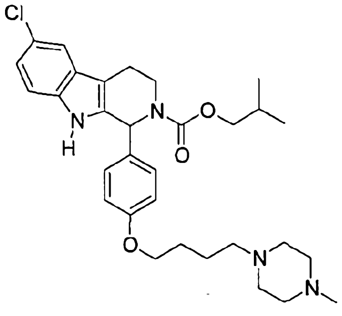
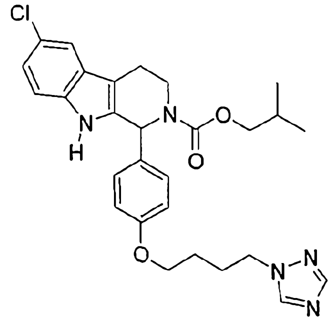
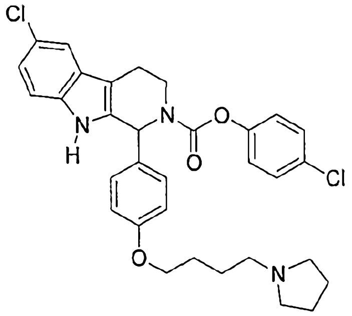
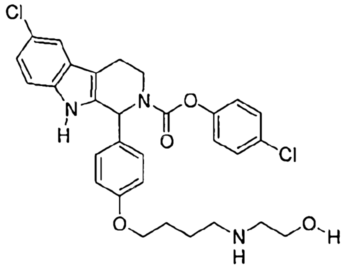
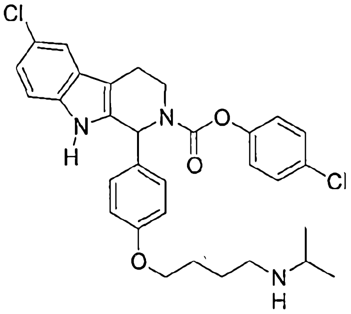
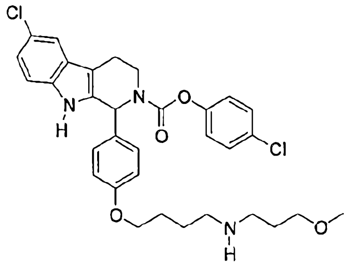
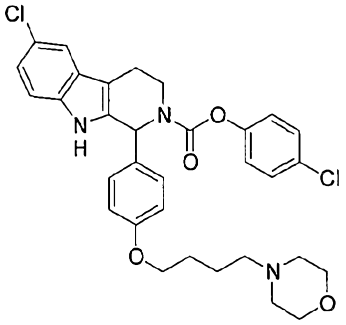
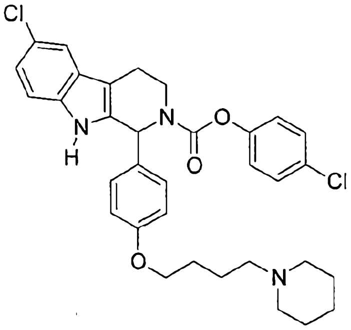
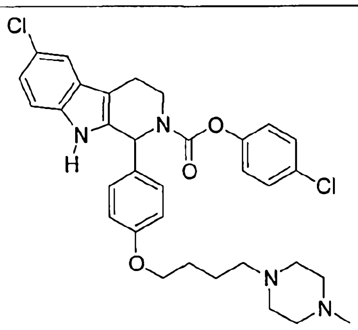
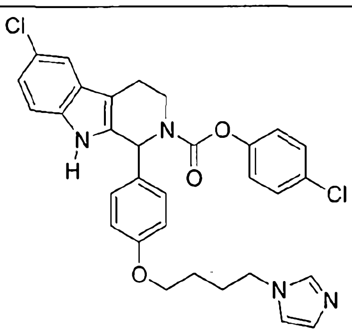
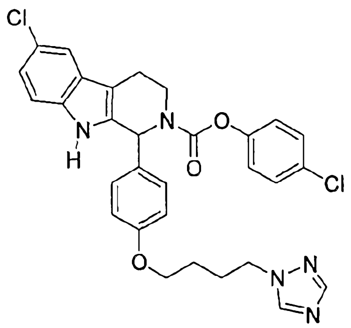
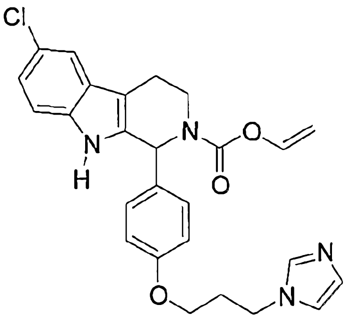
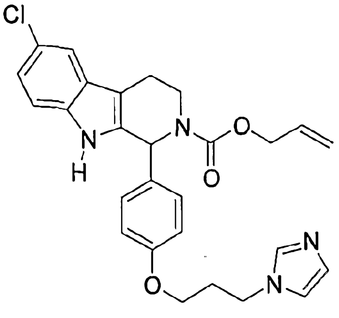
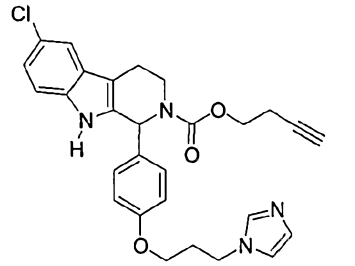
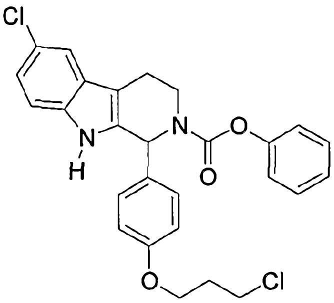
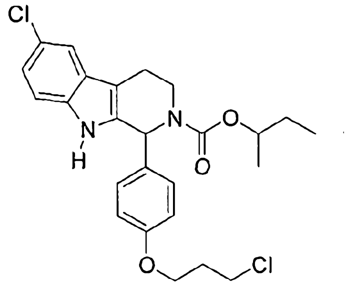
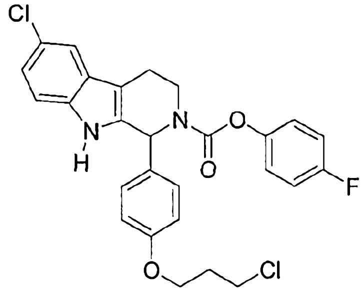
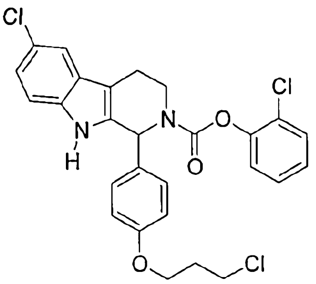
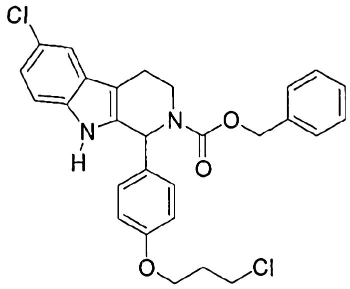
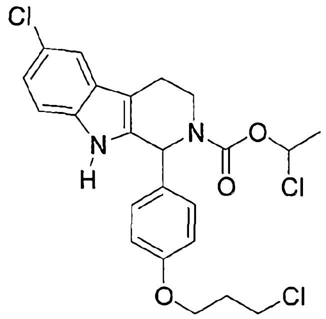
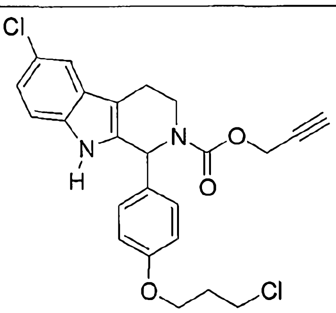
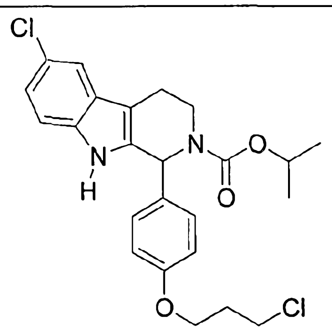
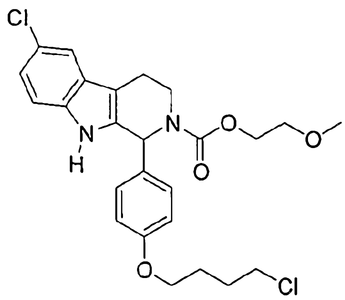
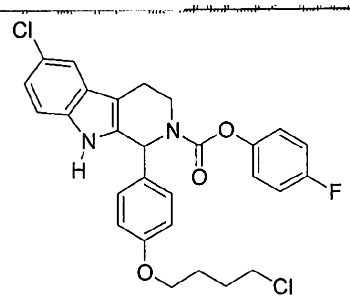
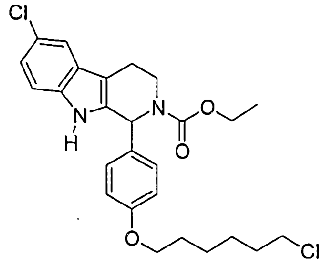
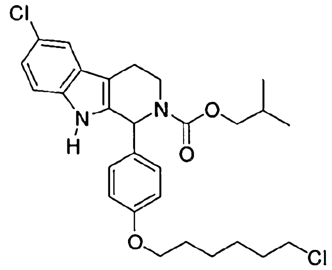
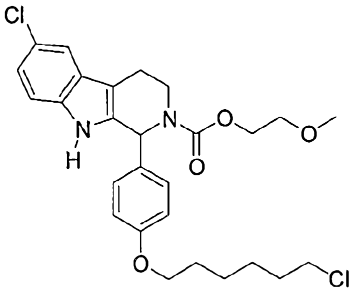
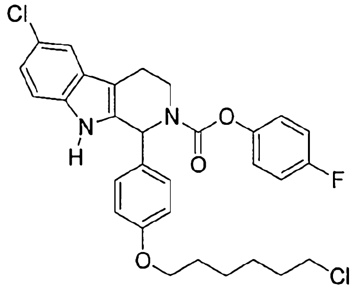
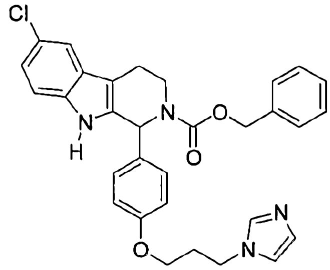
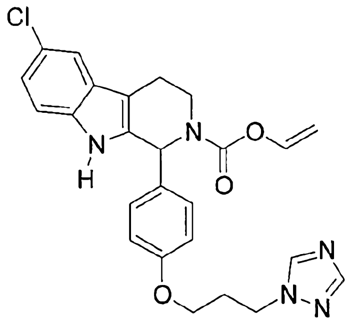
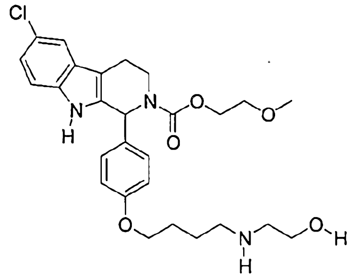
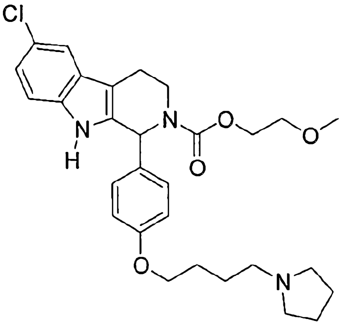
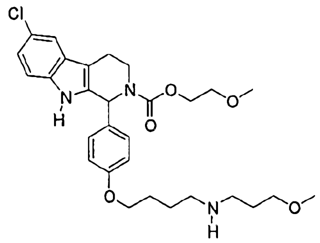
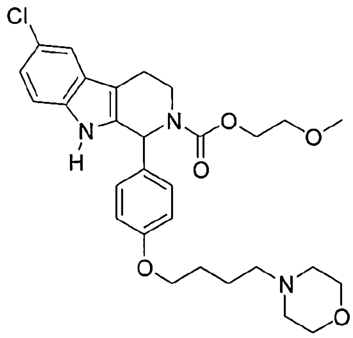
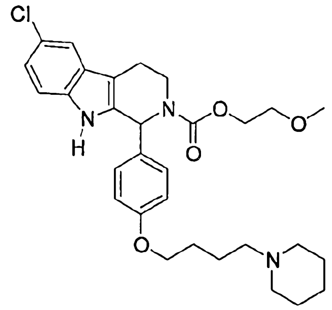
 **665**	 **666**	 **667**
 **668**	 **669**	 **670**
 **671**	 **672**	 **673**

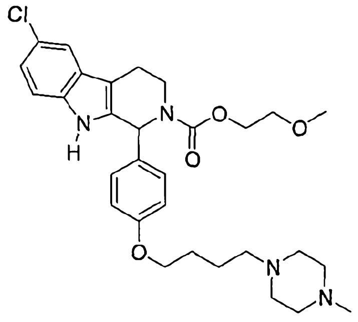
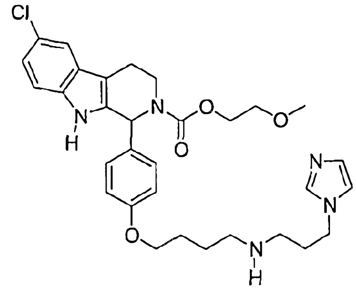
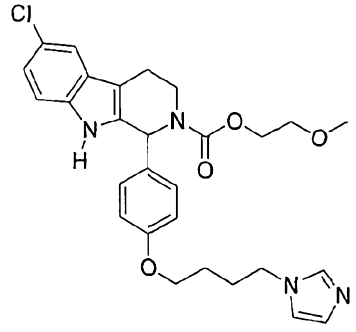
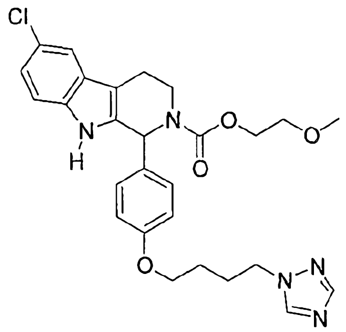
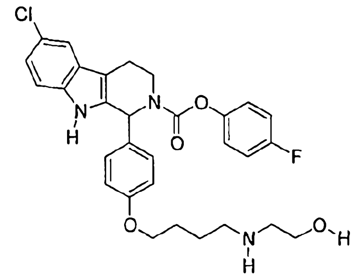
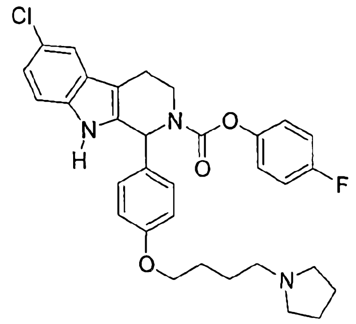
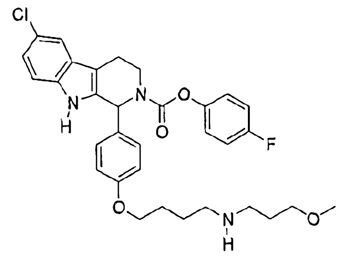
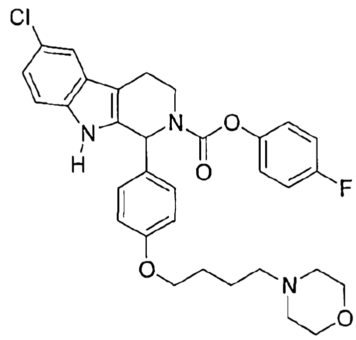
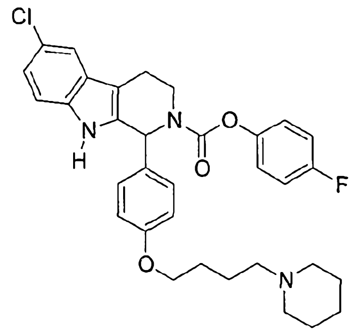
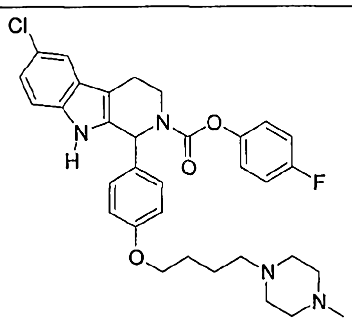
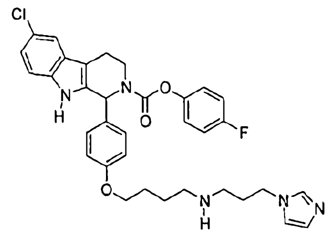
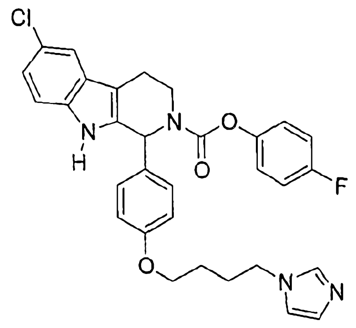
 **674**	 **675**	 **676**
 **677**	 **678**	 **679**
 **680**	 **681**	 **682**

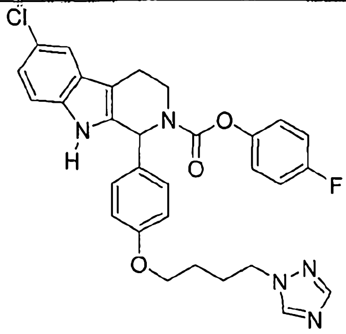
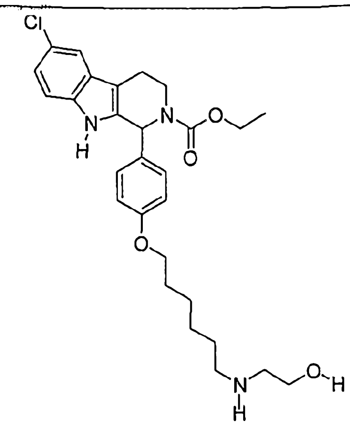
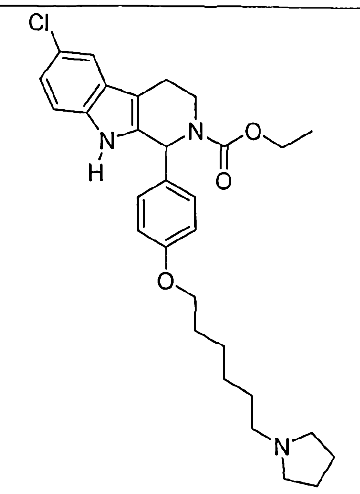
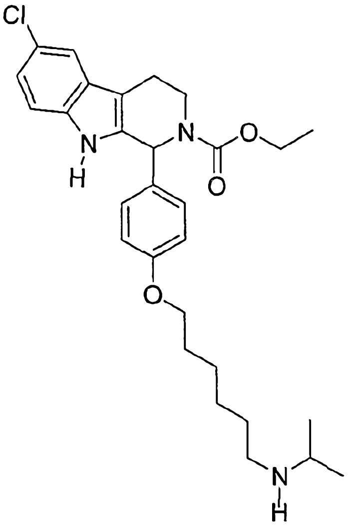
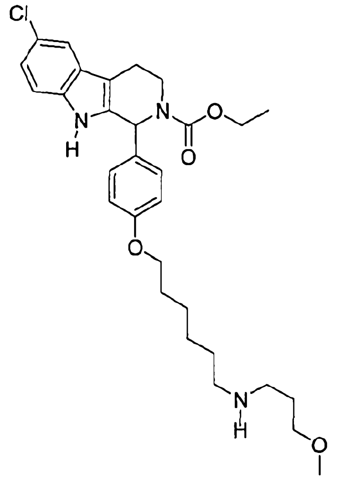
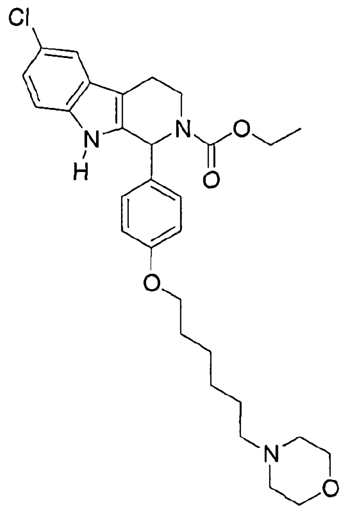
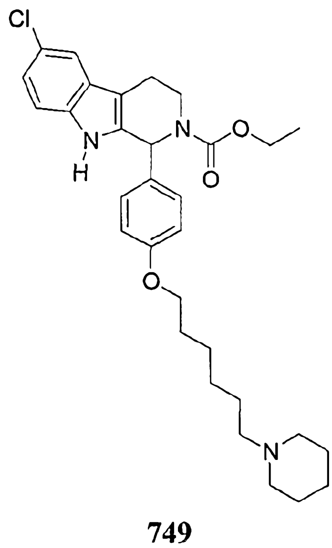
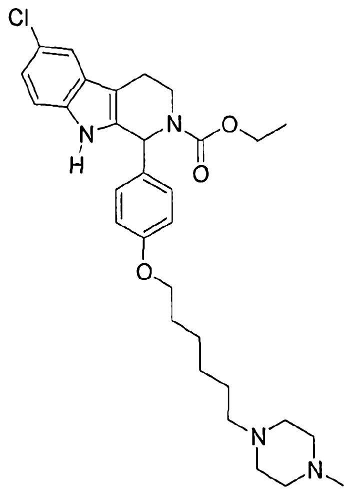
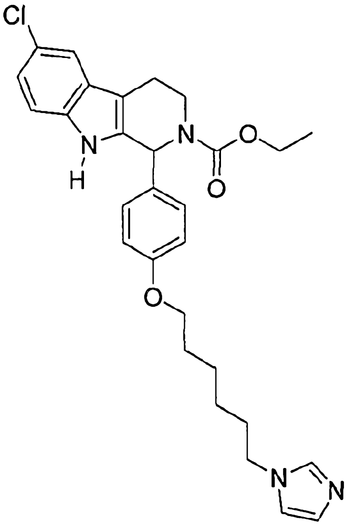
 **683**	 **684**	 **685**
 **686**	 **687**	 **688**
 **689**	 **690**	 **691**
 **692**	 **693**	 **694**

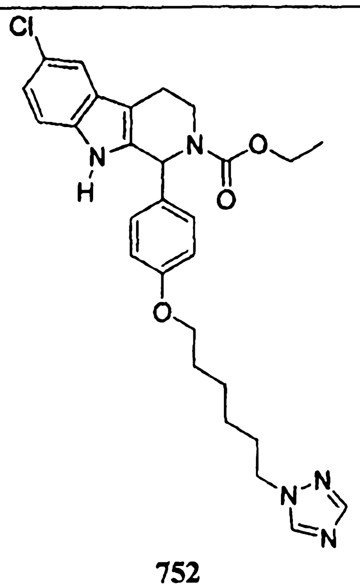
 **695**	 **696**	 **697**
 **698**	 **699**	 **700**
 **701**	 **702**	 **703**
 **704**	 **705**	 **706**

 **707**	 **708**	 **709**
 **710**	 **711**	 **712**
 **713**	 **714**	 **715**
 **716**	 **717**	 **718**

 719	 720	 721
 722	 723	 724
 725	 726	 727
 728	 729	 730

 **731**	 **732**	 **733**
 **734**	 **735**	 **736**
 **737**	 **738**	 **739**
 **740**	 **741**	 **742**

 **743**	 **744**	 **745**
 **746**	 **747**	 **748**
 **749**	 **750**	 **751**



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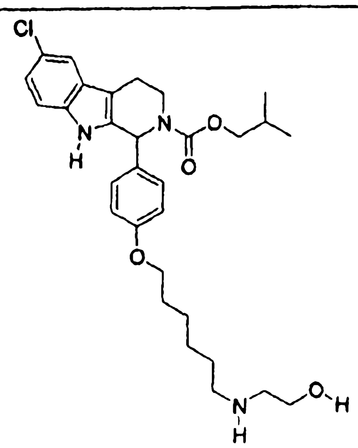

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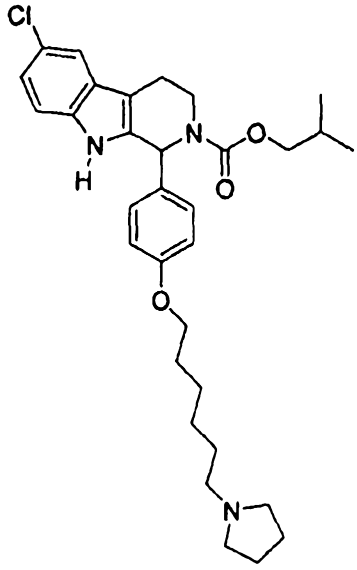

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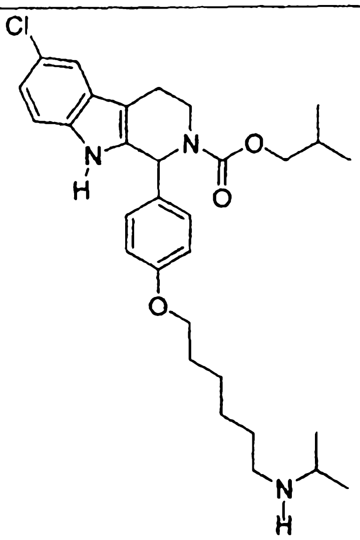

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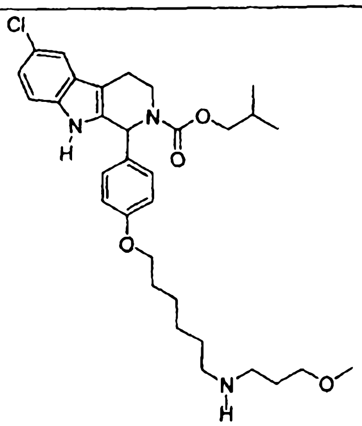

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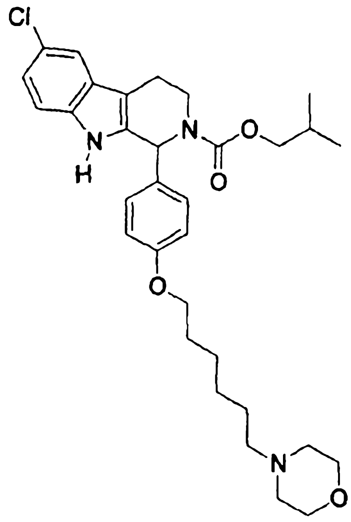

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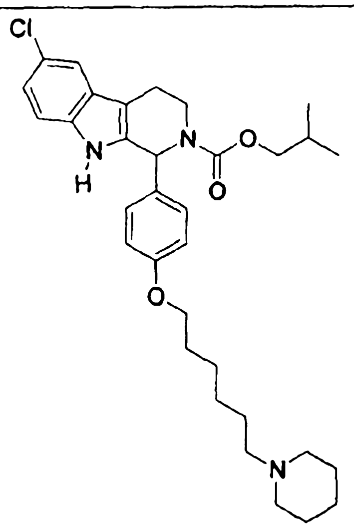

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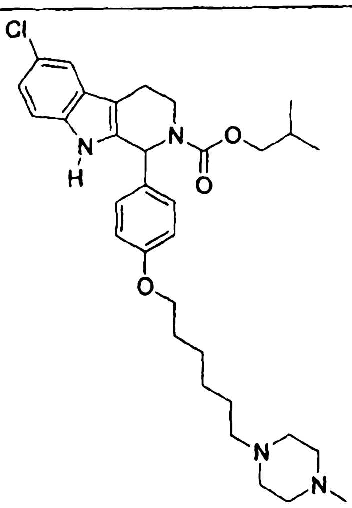

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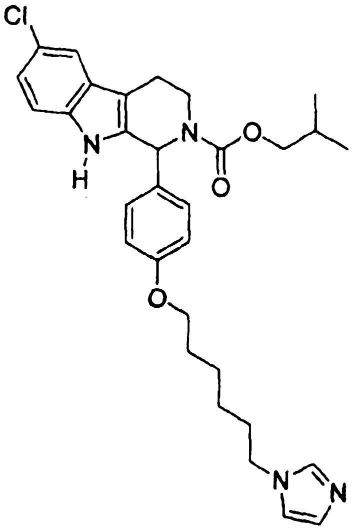

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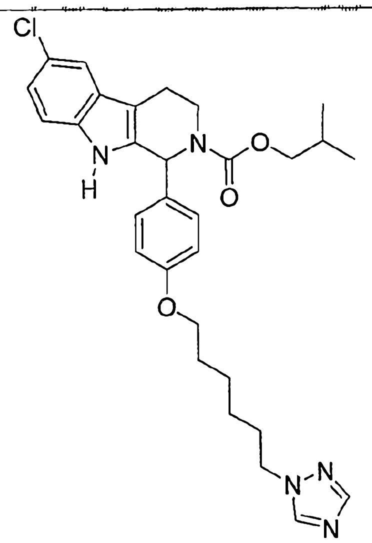

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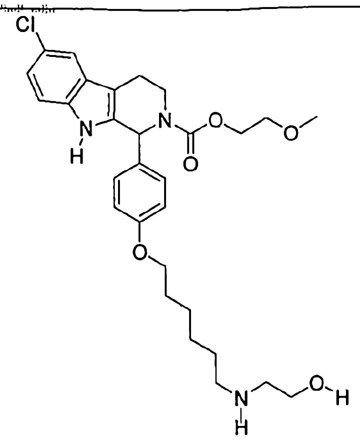

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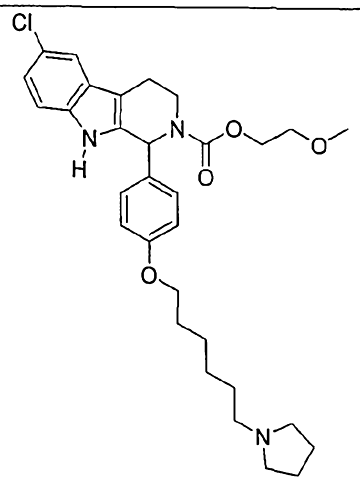

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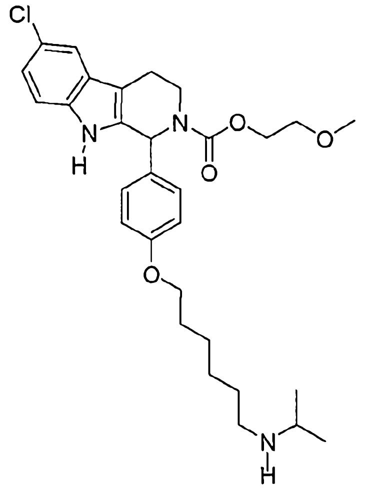

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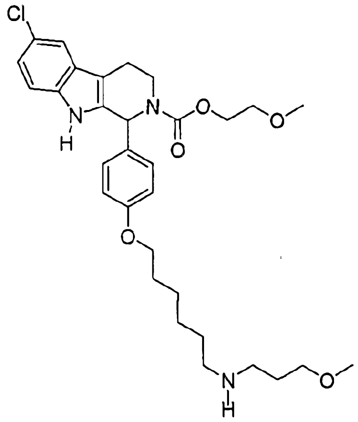

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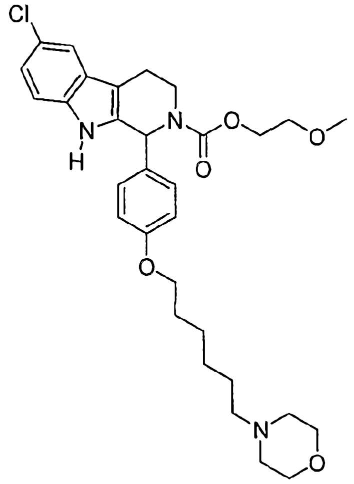

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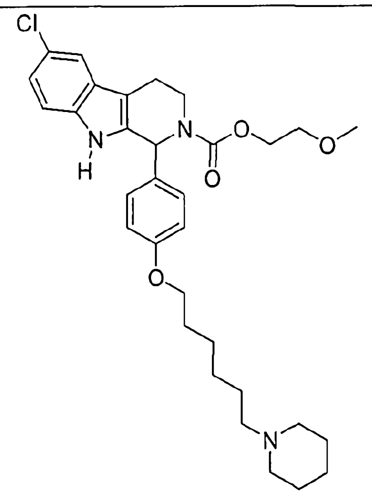

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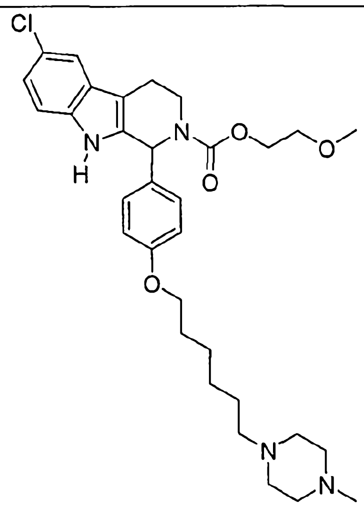

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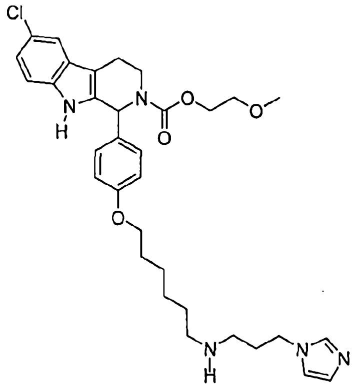

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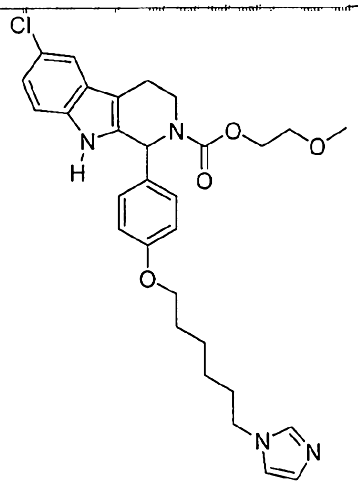

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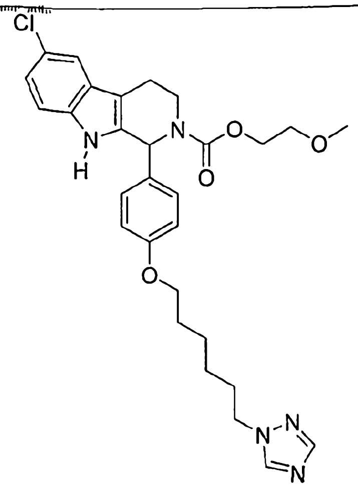

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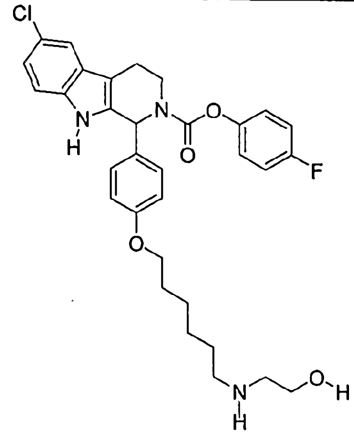

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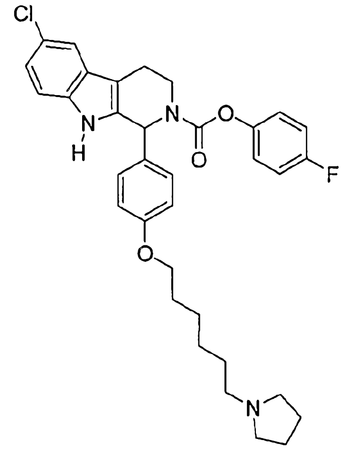

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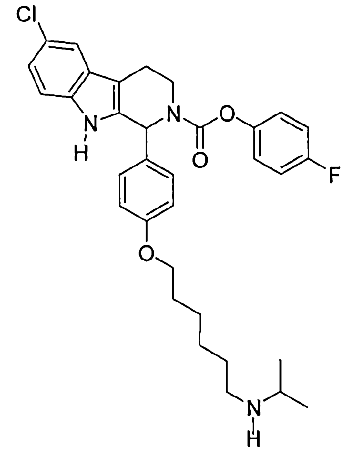

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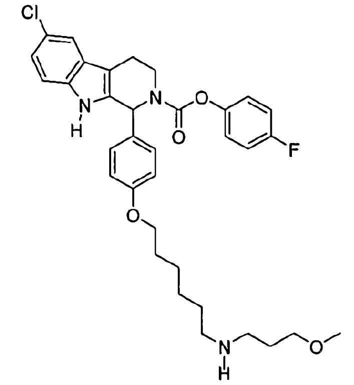

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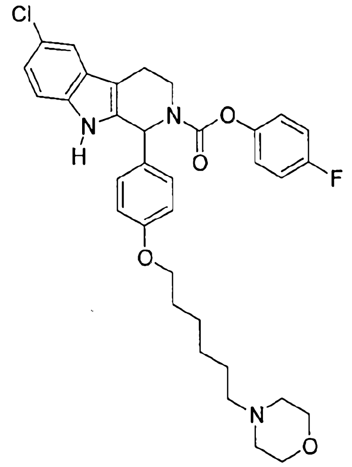

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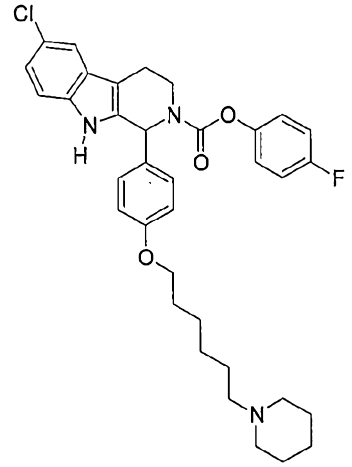

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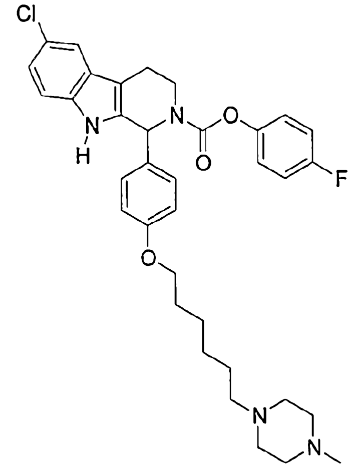

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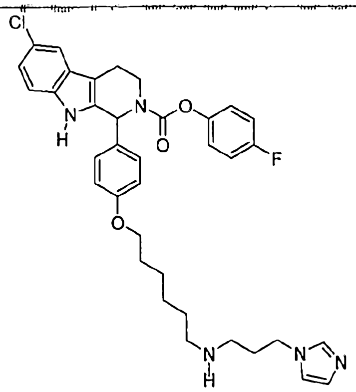

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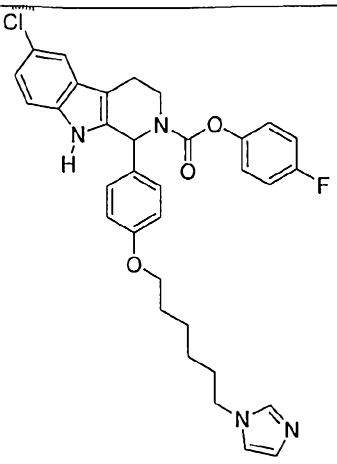

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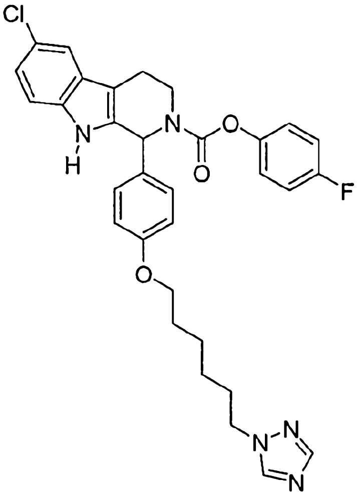

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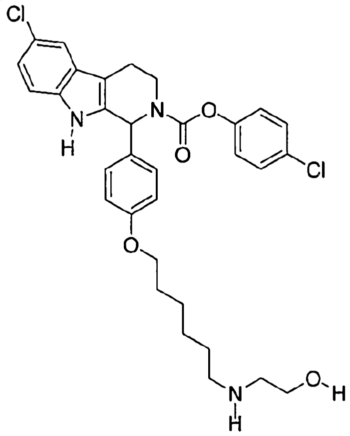

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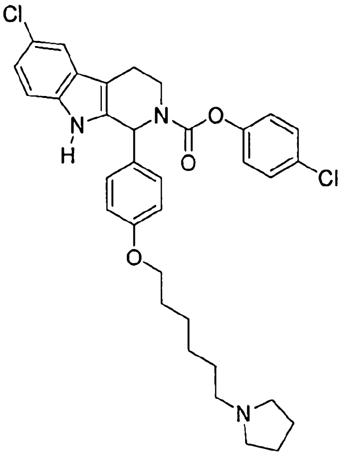

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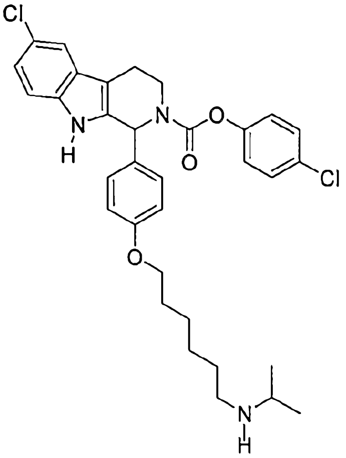

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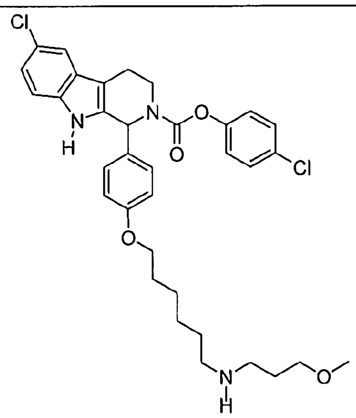

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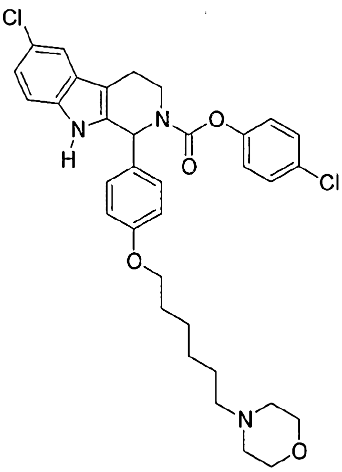

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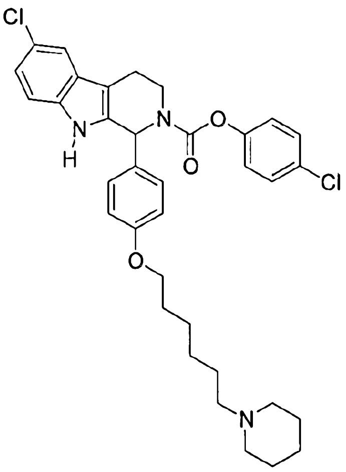

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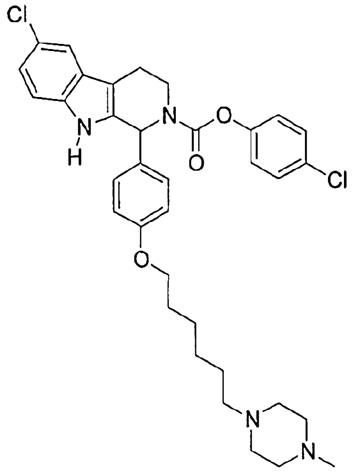

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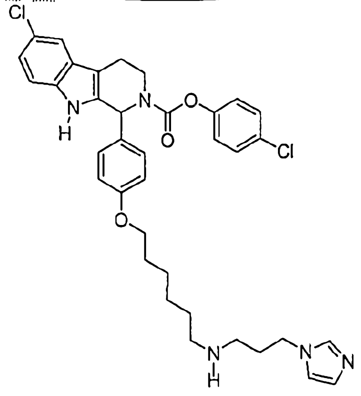

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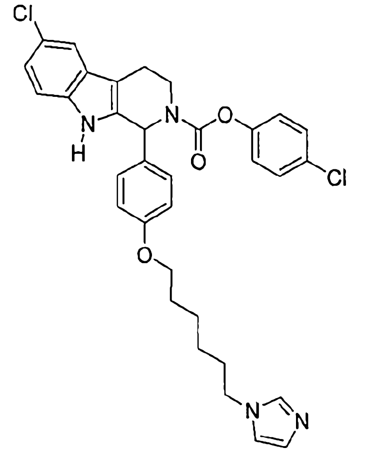

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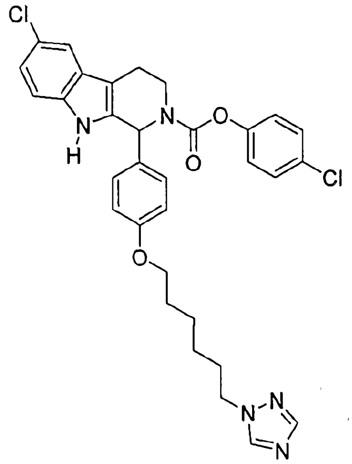

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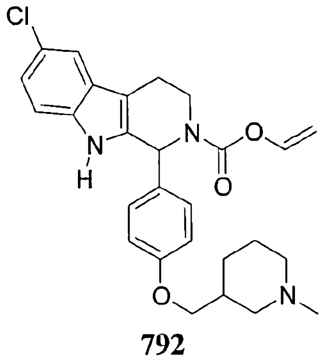

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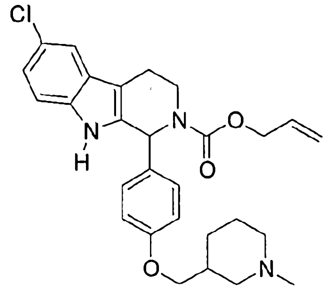

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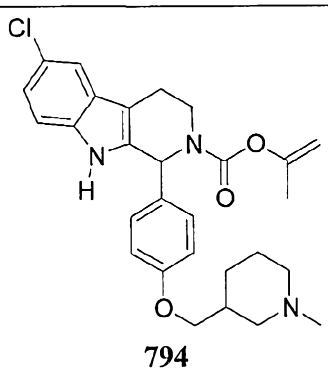

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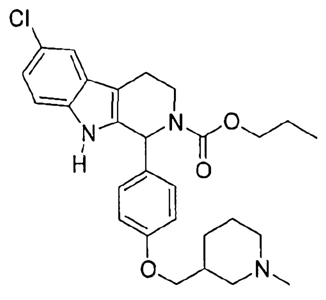

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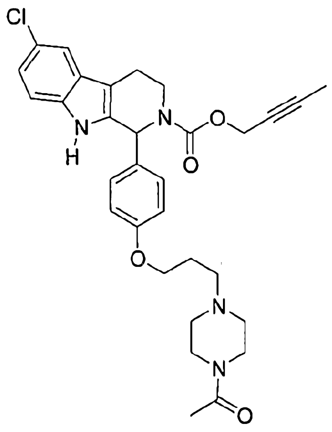

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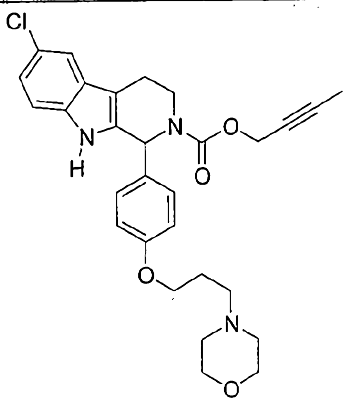
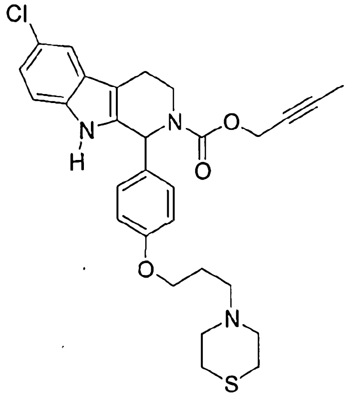
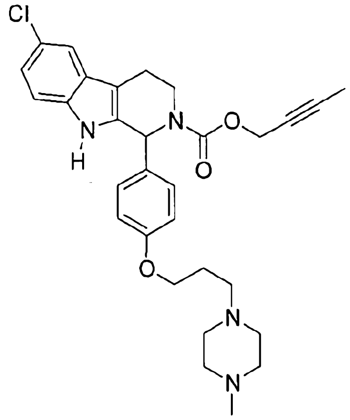
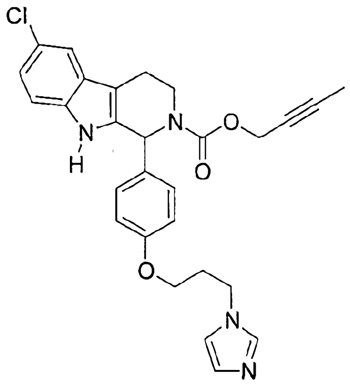
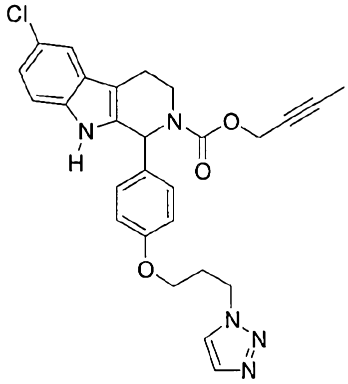
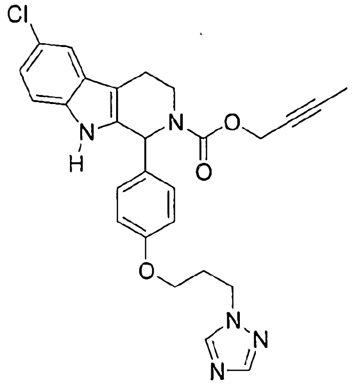
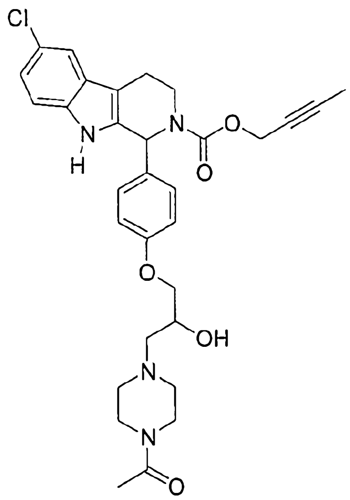
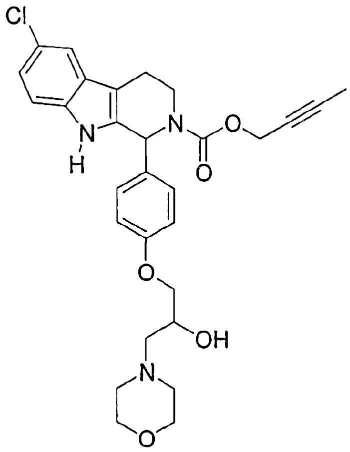
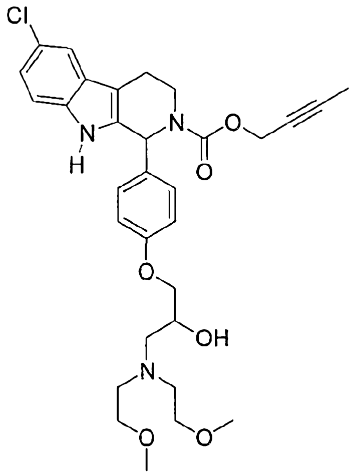
 **797**	 **798**	 **799**
 **800**	 **801**	 **802**
 **803**	 **804**	 **805**

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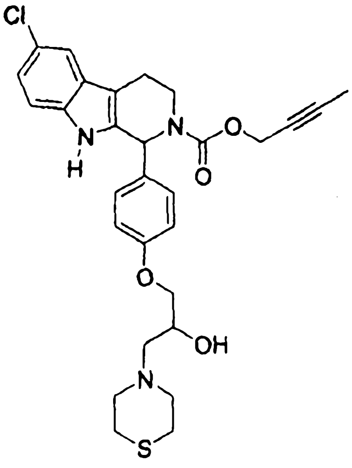
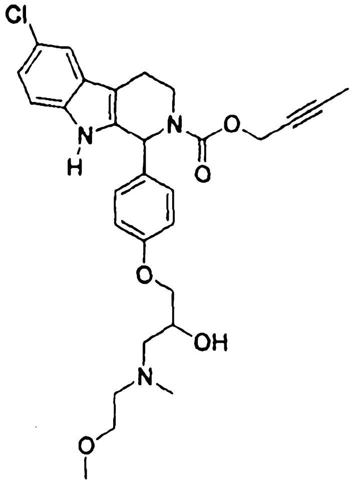
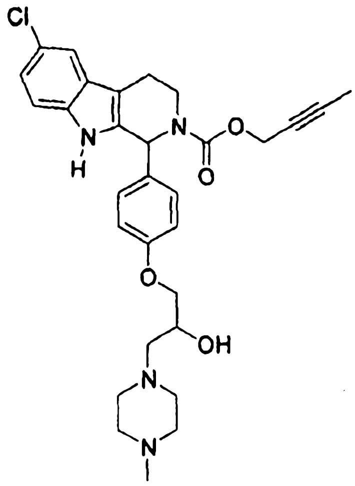
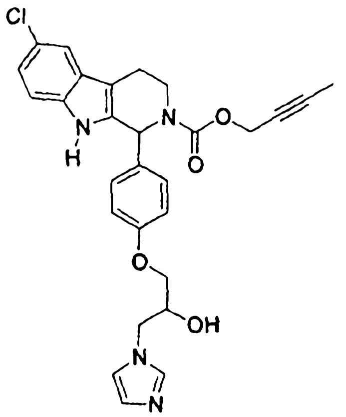
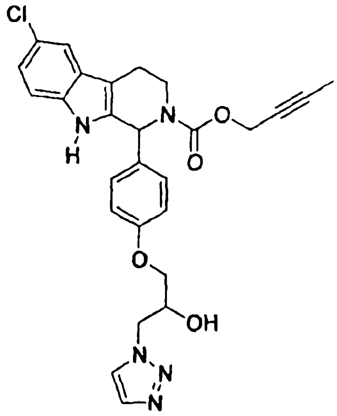
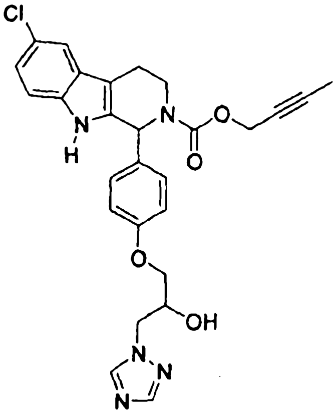
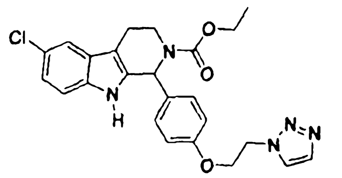
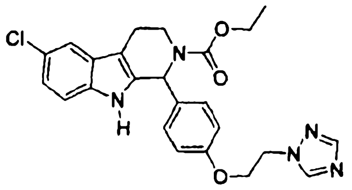
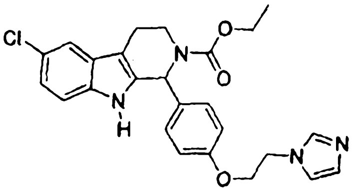
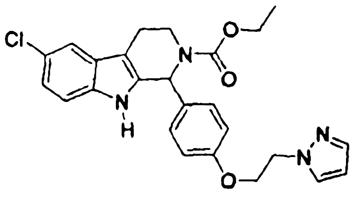
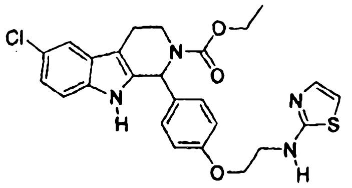
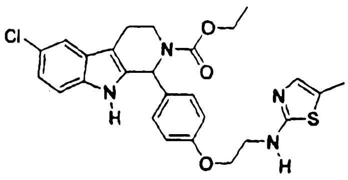
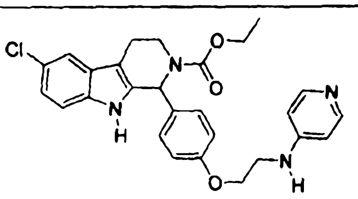
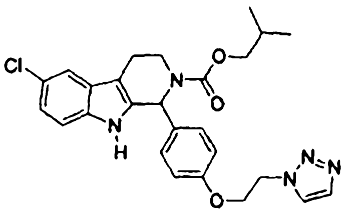
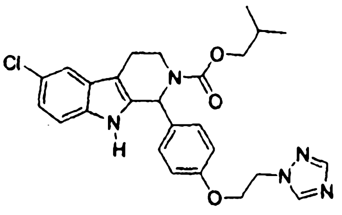
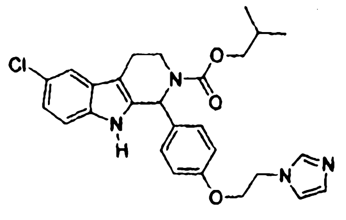
 **806**	 **807**	 **808**
 **809**	 **810**	 **811**
 **812**	 **813**	 **814**
 **815**	 **816**	 **817**
 **818**	 **819**	 **820**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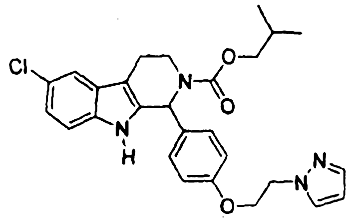
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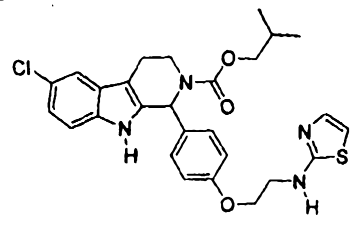
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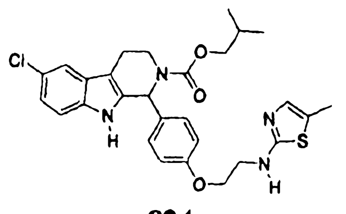
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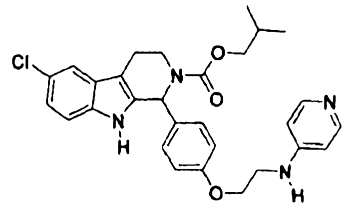
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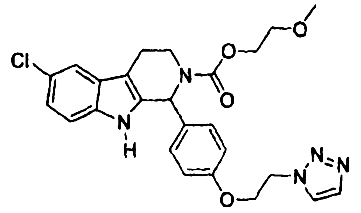
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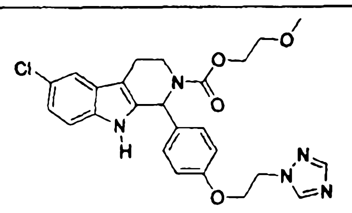
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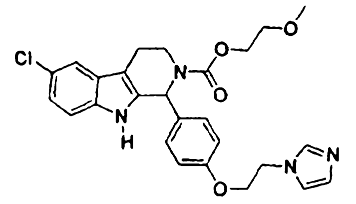
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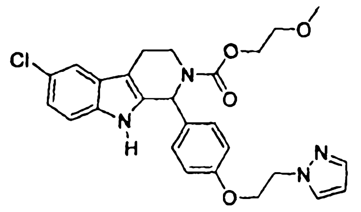
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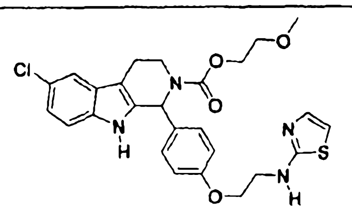
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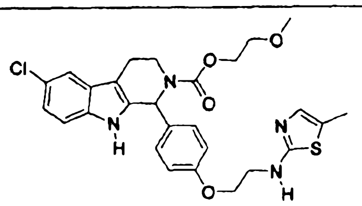
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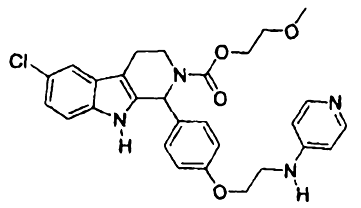
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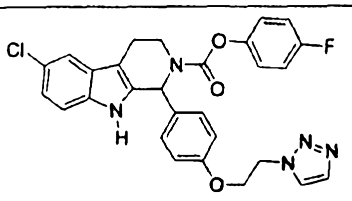
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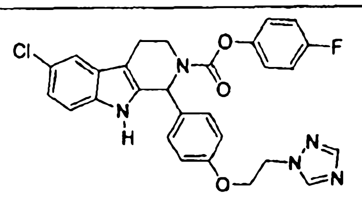
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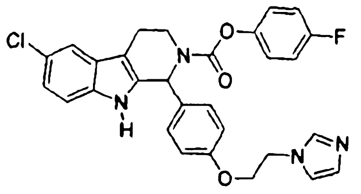
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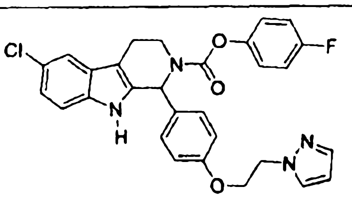
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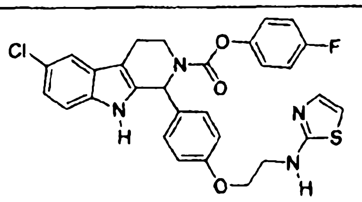
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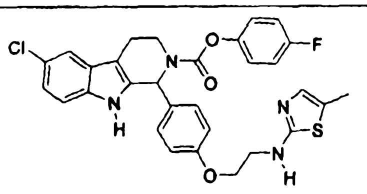
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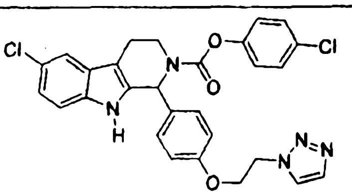
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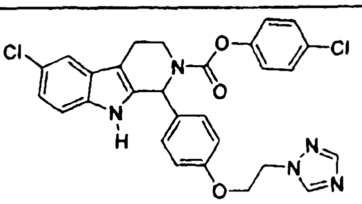
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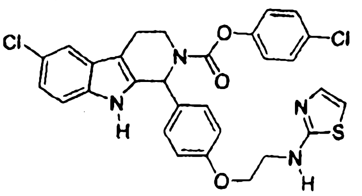
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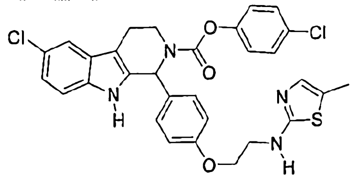
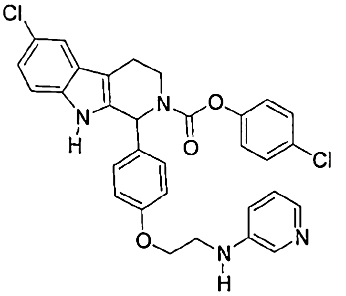
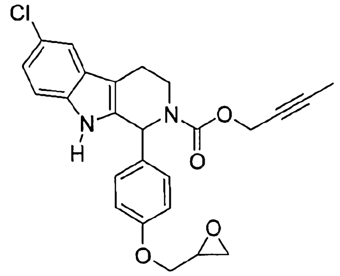
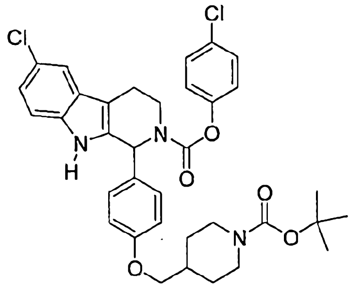
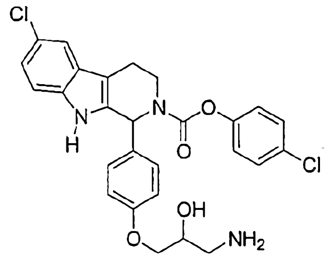
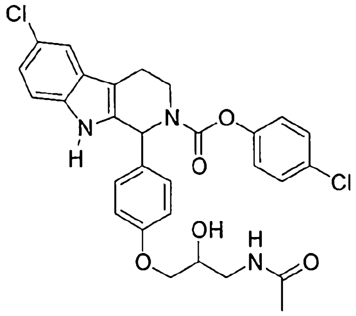
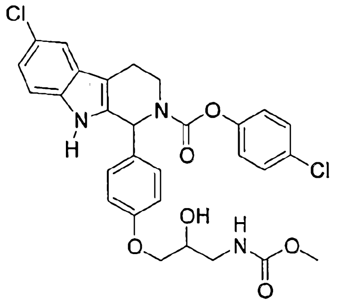
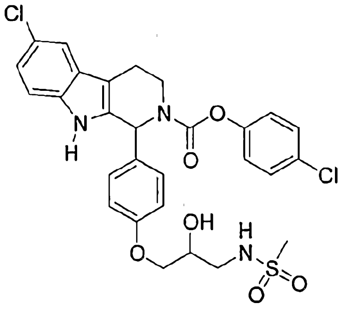
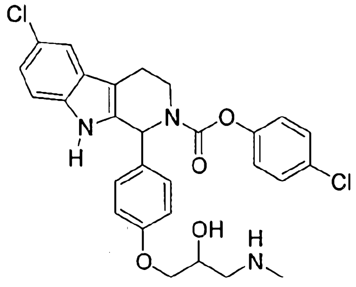
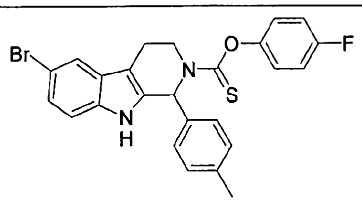
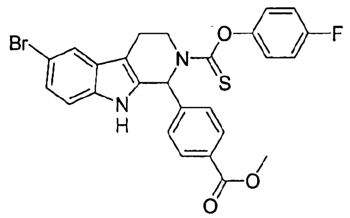
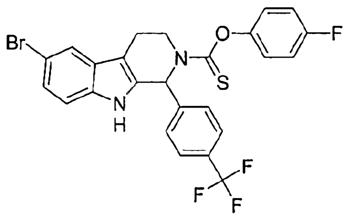
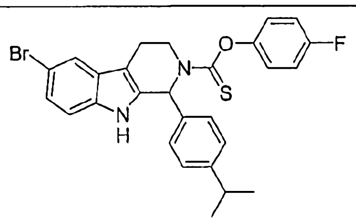
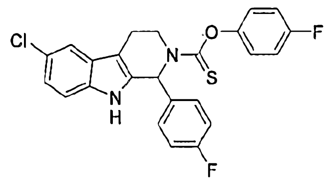
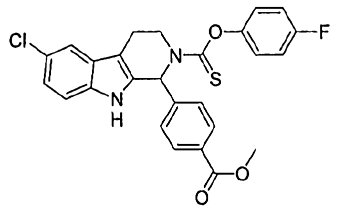
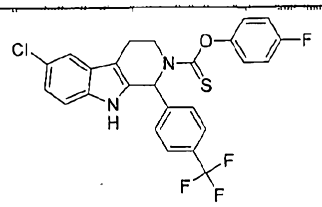
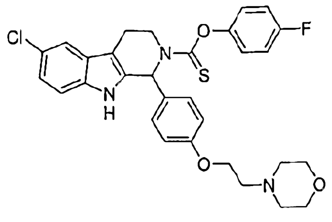
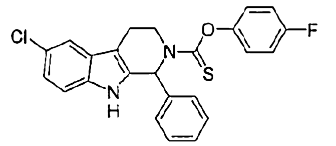
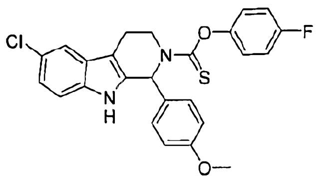
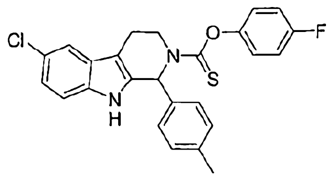
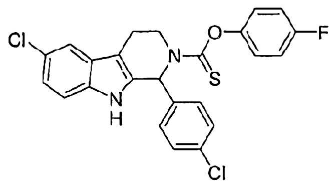
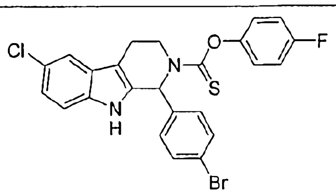
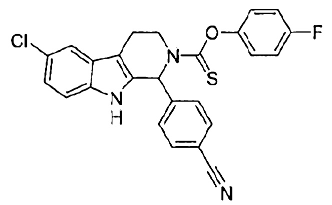
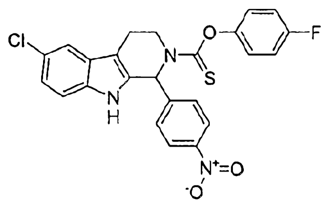
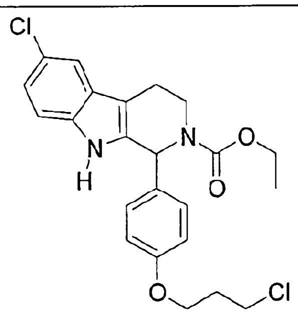
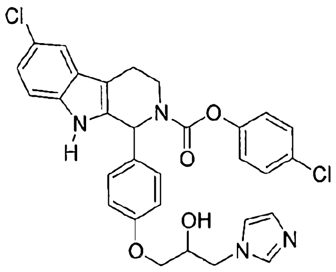
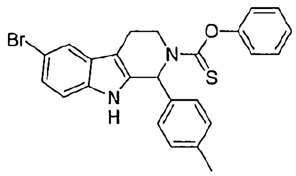
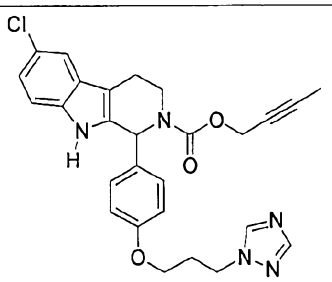
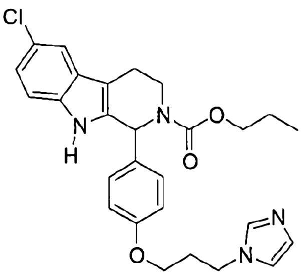
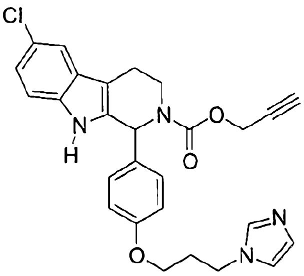
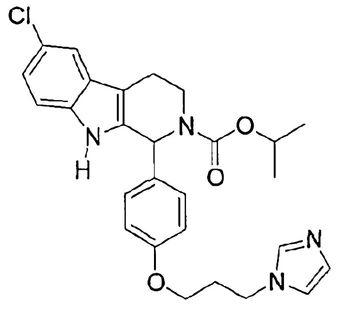
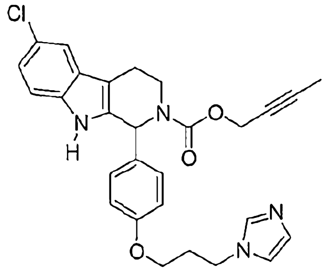
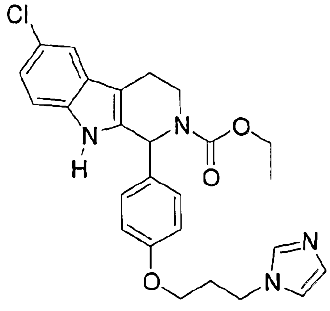
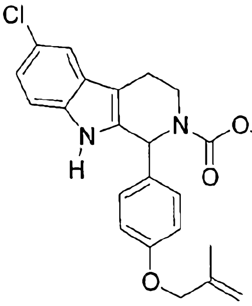
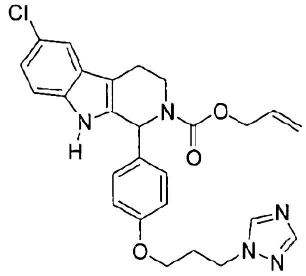
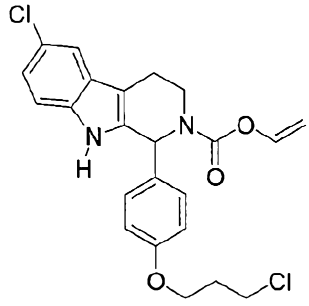
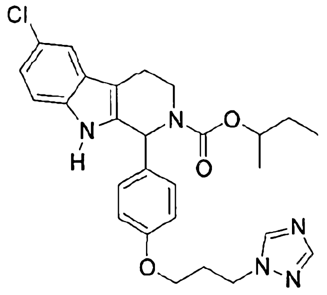
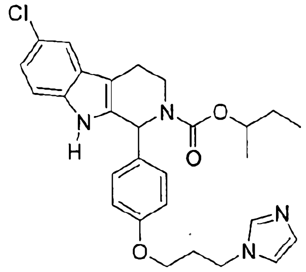
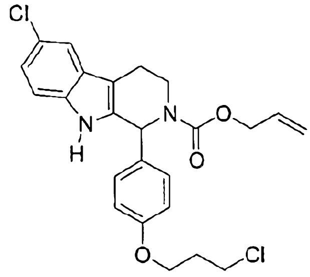
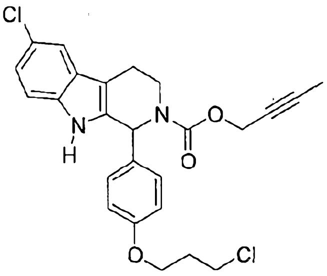
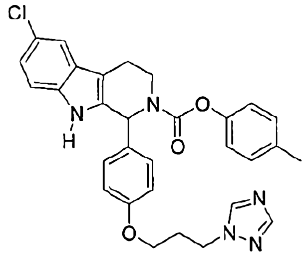
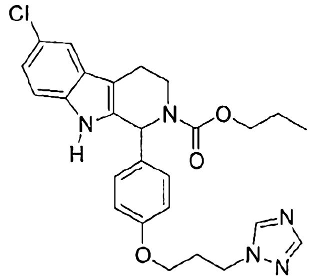
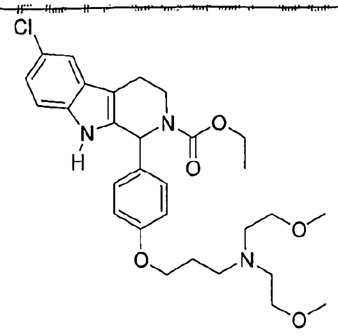
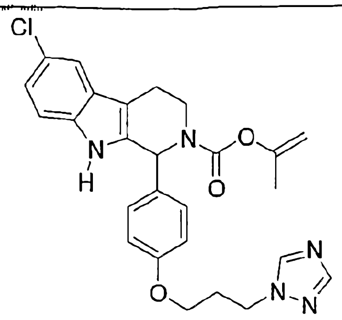
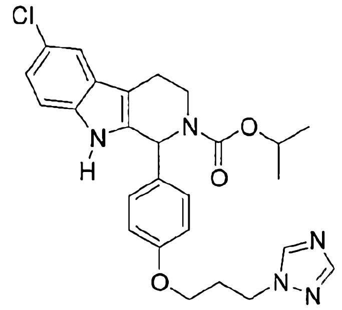
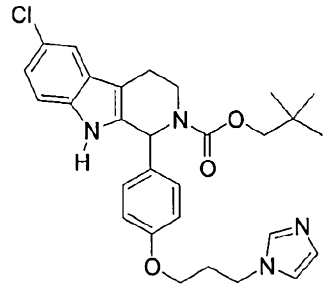
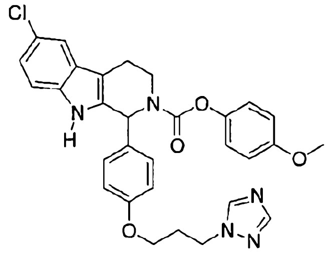
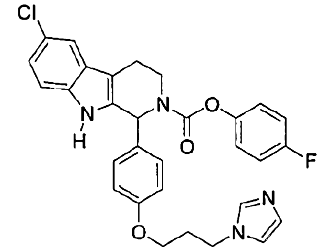
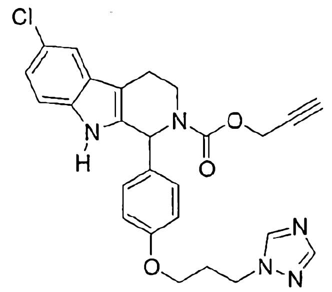
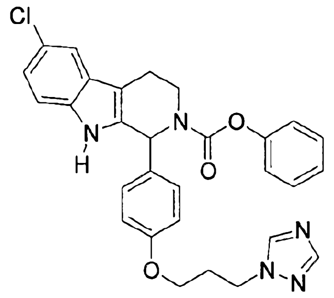
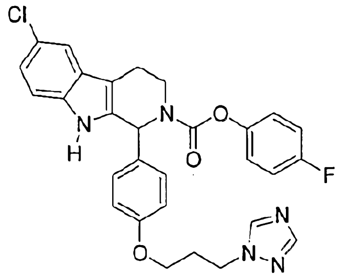
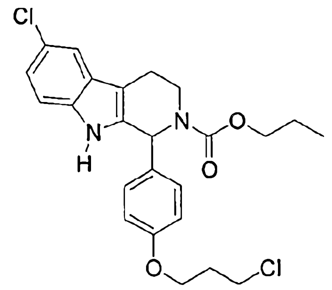
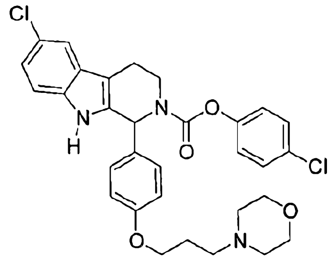
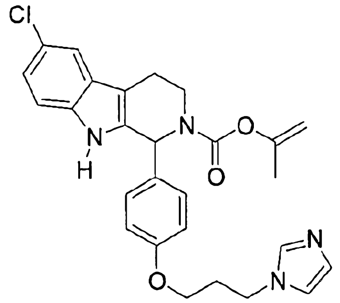
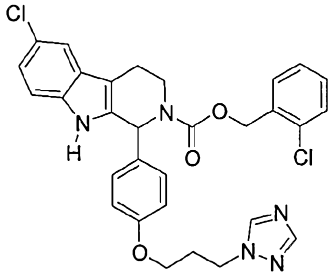
 842	 843	 844
 845	 846	 847
 848	 849	 850
 851	 852	 853
 854	 855	 856

 **857**	 **858**	 **859**
 **860**	 **861**	 **862**
 **863**	 **864**	 **865**
 **866**	 **867**	 **868**
 **869**	 **870**	 **871**

 **872**	 **873**	 **874**
 **875**	 **876**	 **877**
 **878**	 **879**	 **880**
 **881**	 **882**	 **883**

 **884**	 **885**	 **886**
 **887**	 **888**	 **889**
 **890**	 **891**	 **892**
 **893**	 **894**	 **895**



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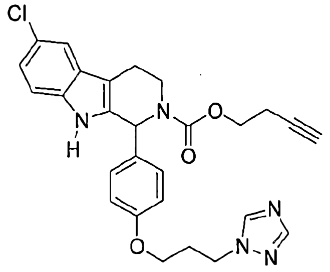

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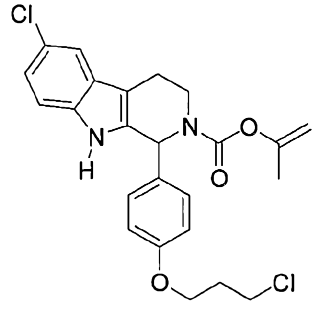

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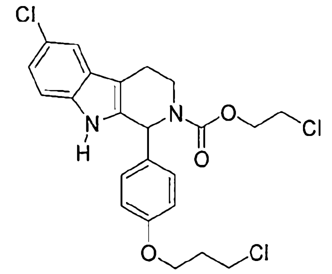

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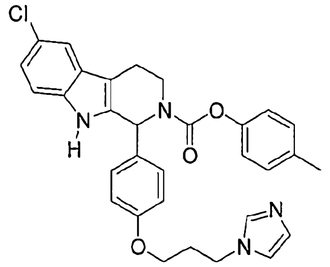

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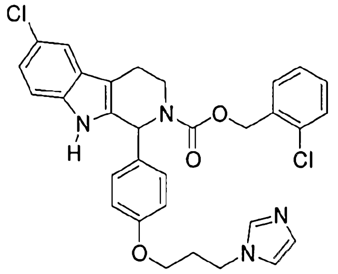

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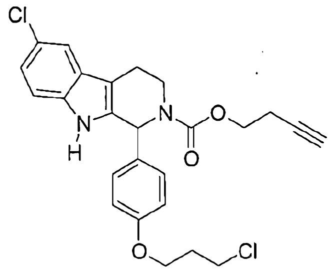

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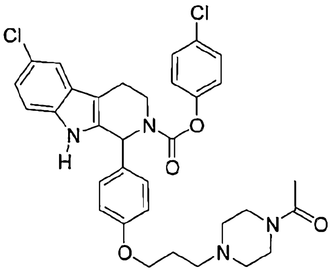

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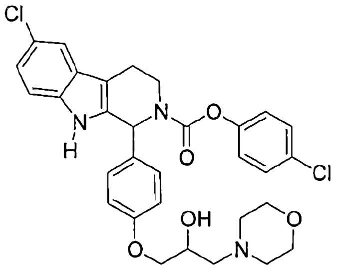

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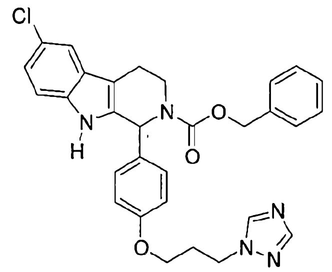

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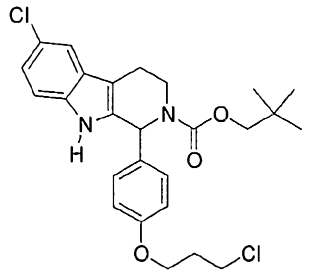

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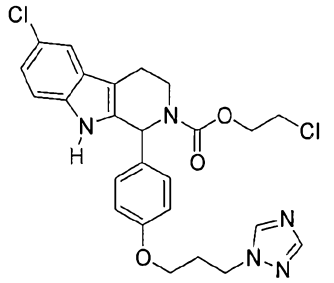

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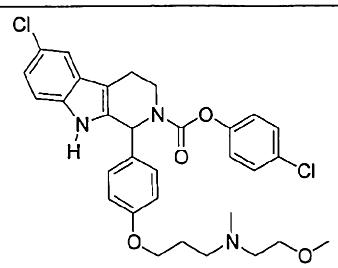

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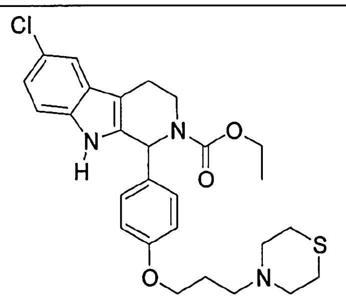

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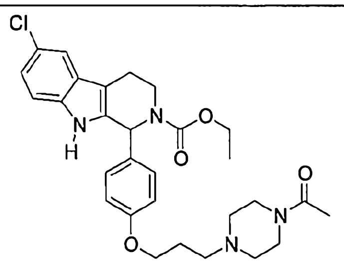

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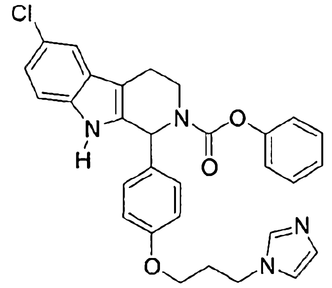
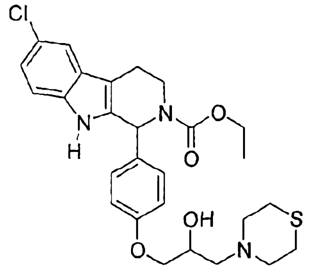
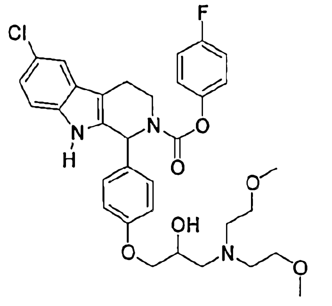
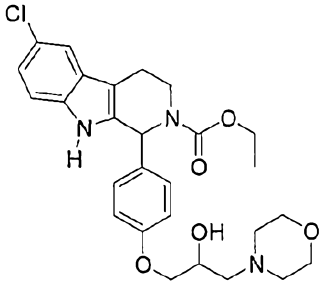
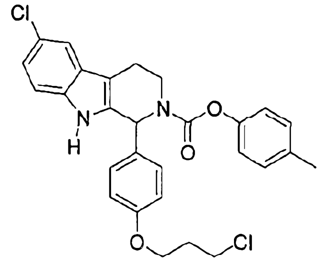
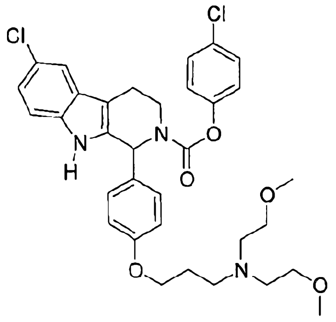
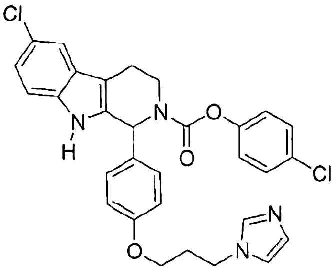
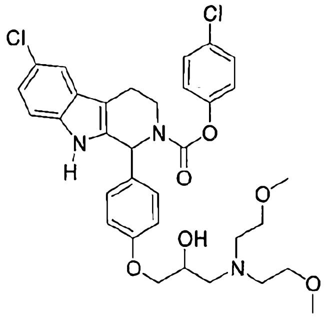
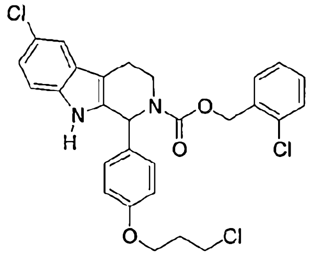
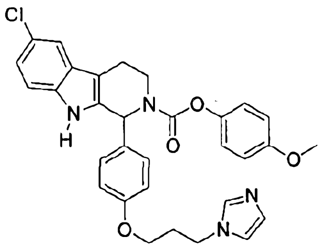
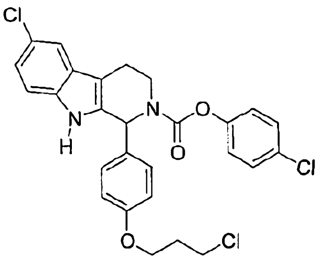
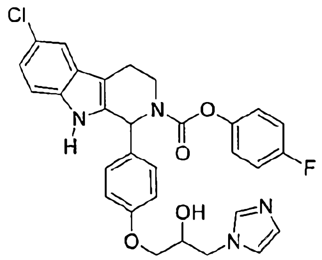
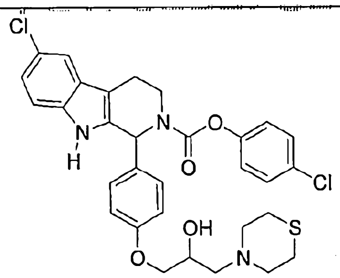
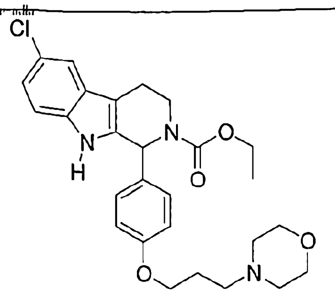
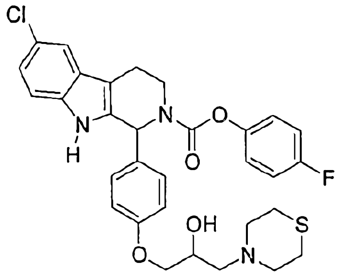
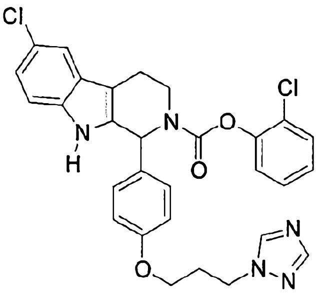
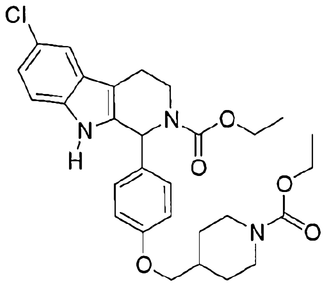
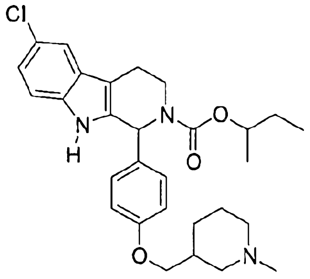
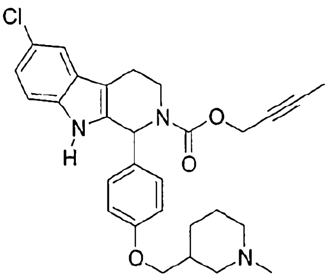
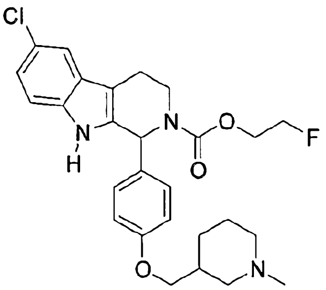
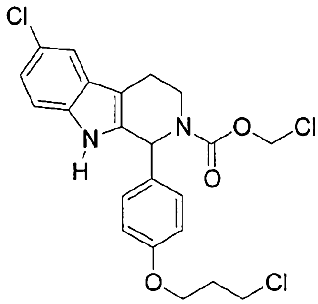
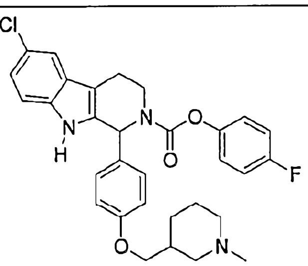
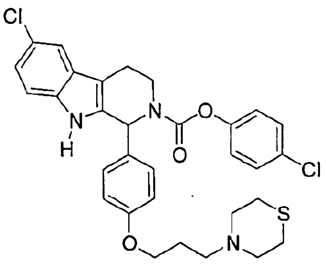
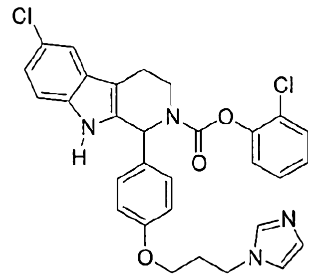
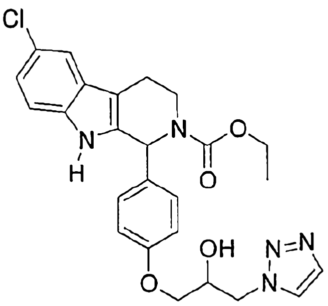
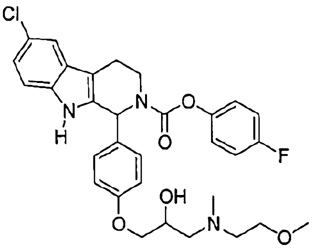
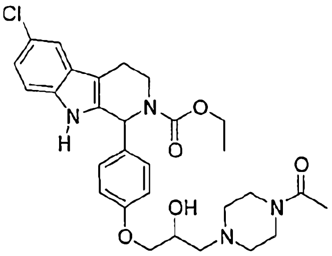
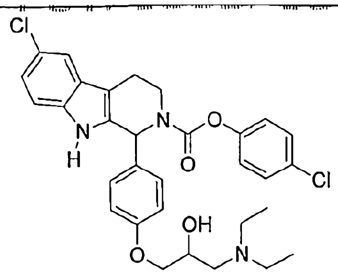
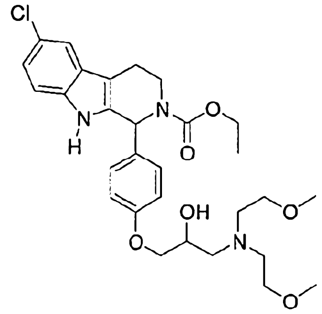
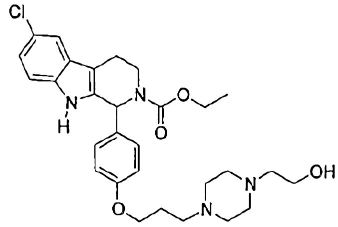
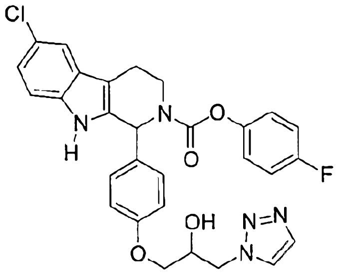
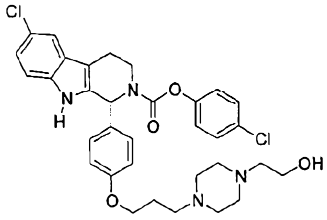
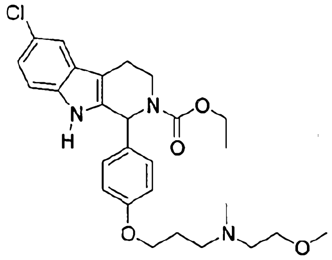
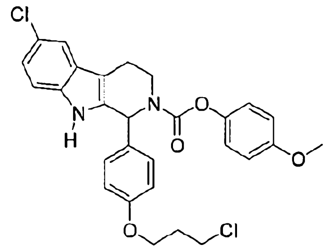
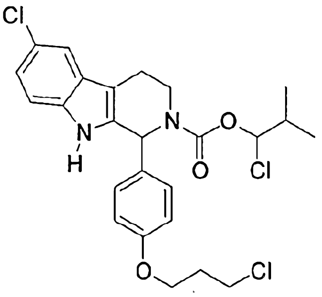
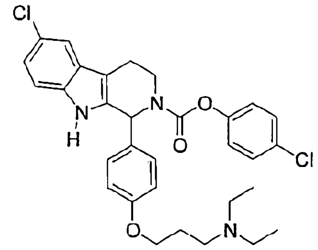
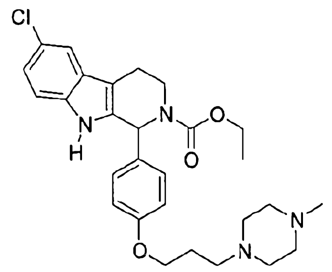
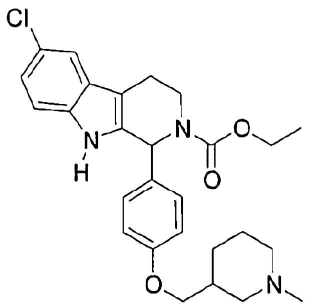
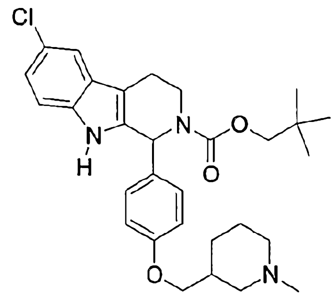
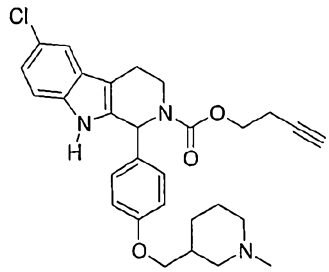
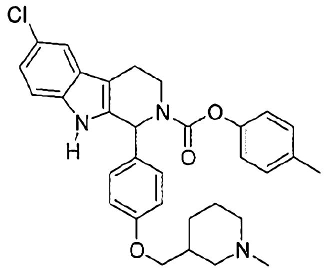
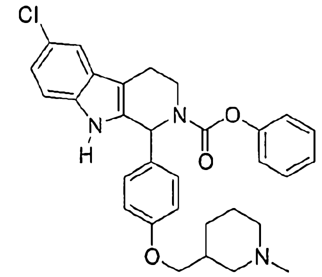
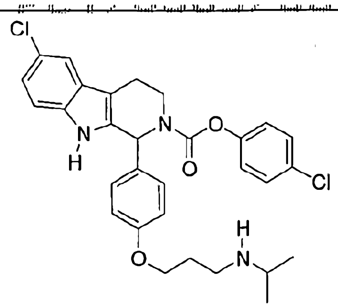
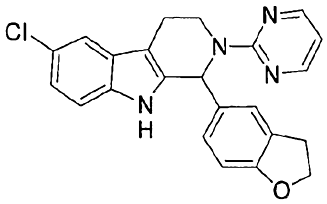
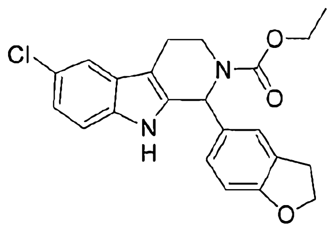
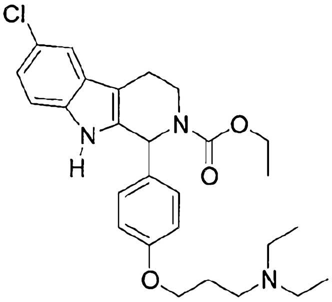
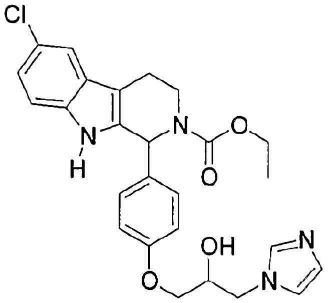
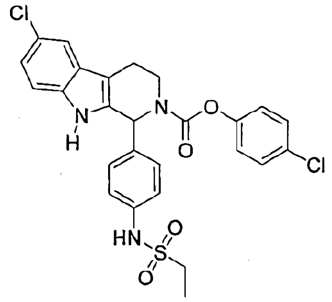
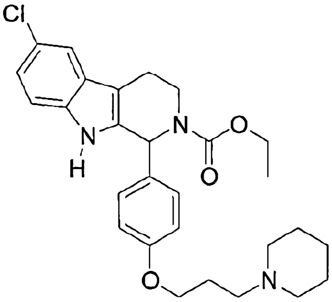
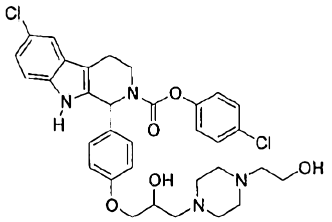
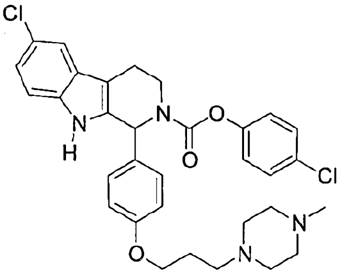
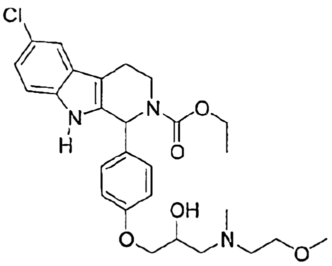
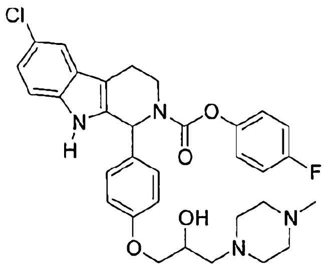
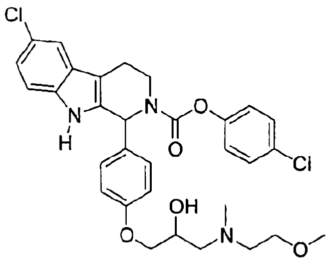
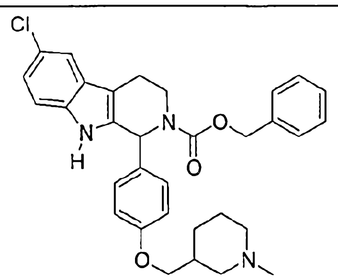
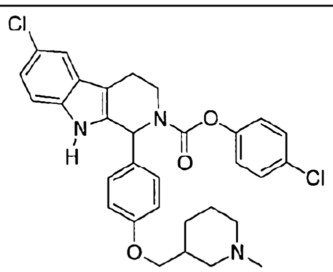
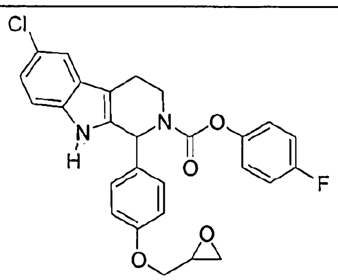
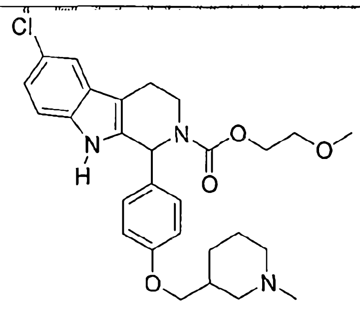
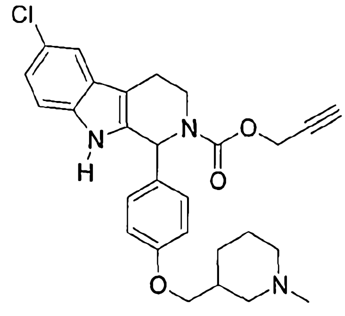
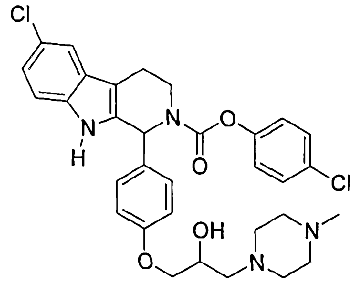
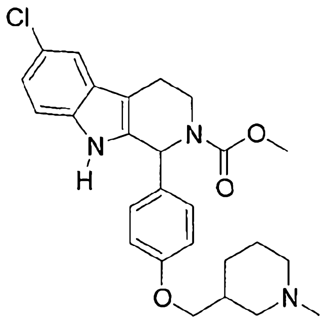
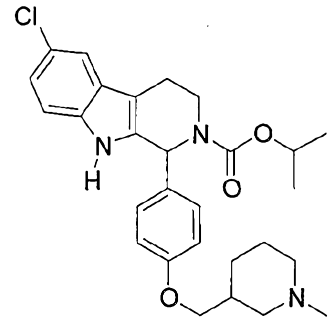
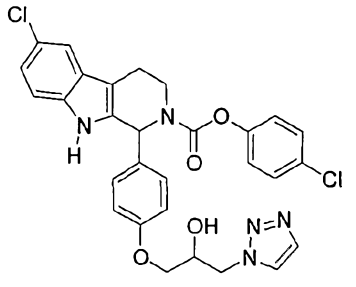
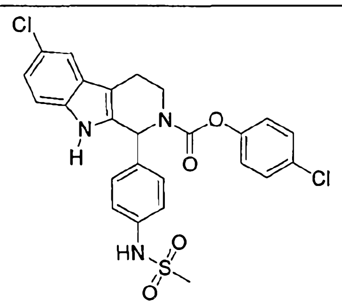
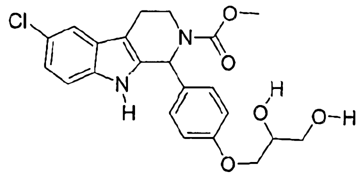
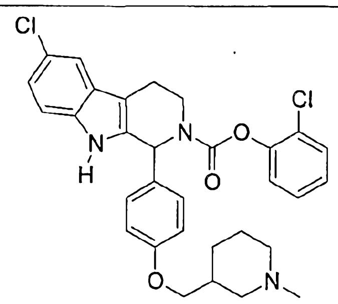
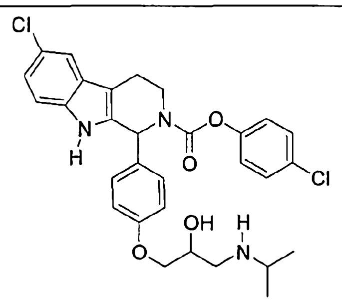
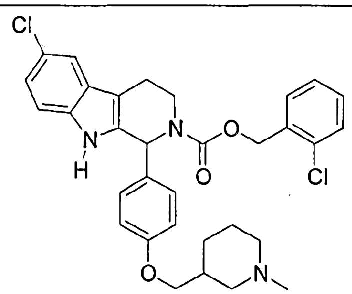
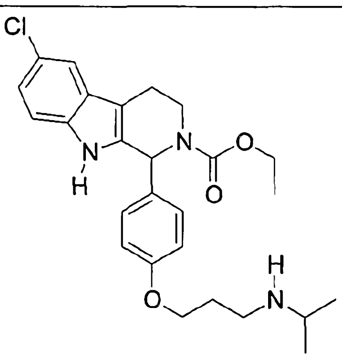
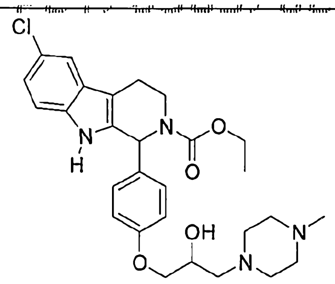
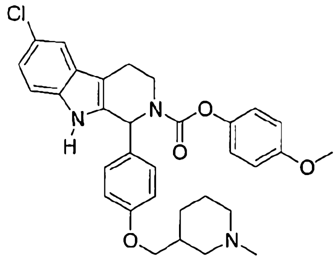
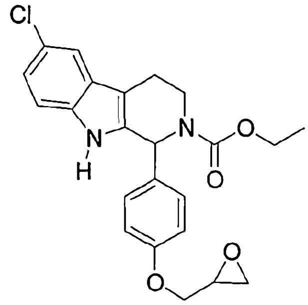
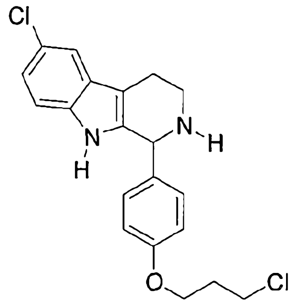
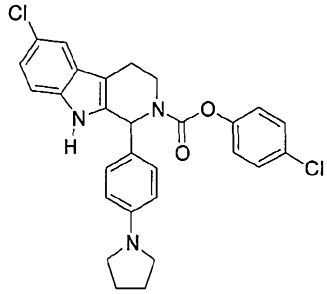
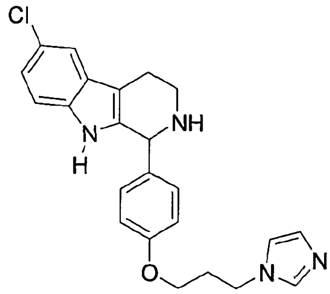
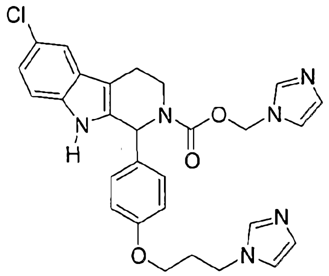
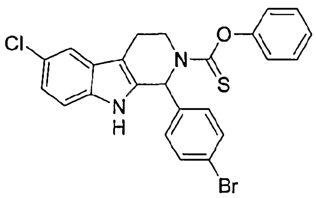
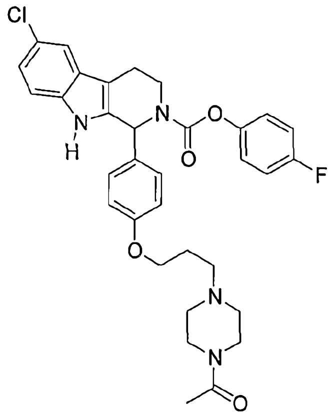
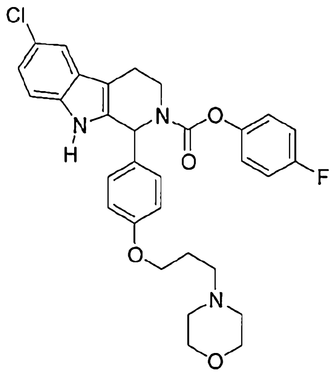
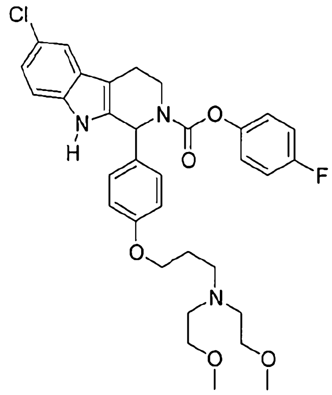
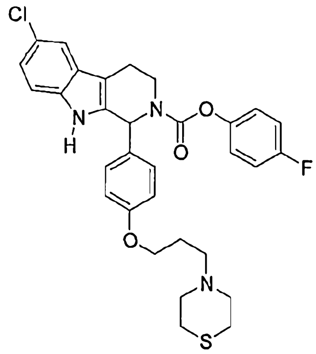
 **911**	 **912**	 **913**
 **914**	 **915**	 **916**
 **917**	 **918**	 **919**
 **920**	 **921**	 **922**

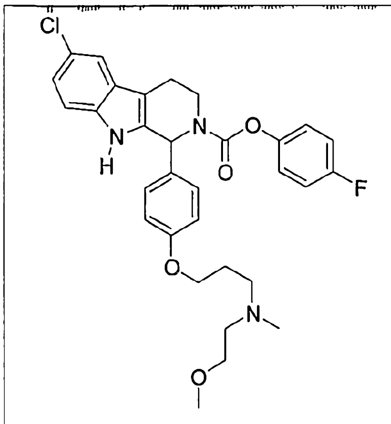
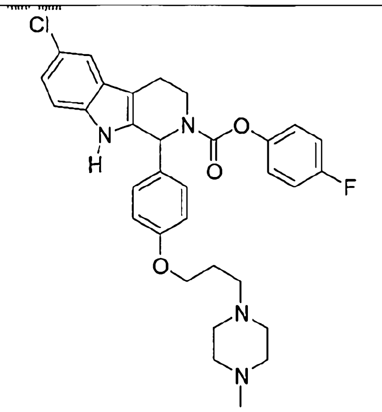
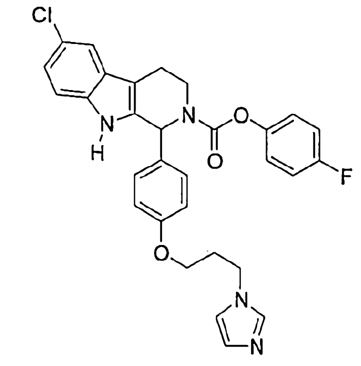
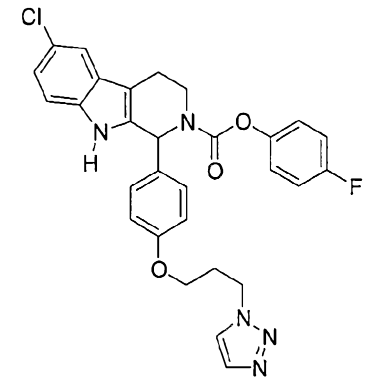
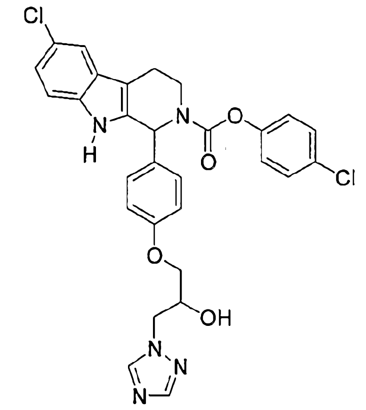
 **923**	 **924**	 **925**
 **926**	 **927**	 **928**
 **929**	 **930**	 **931**
 **932**	 **933**	 **934**
 **935**	 **936**	 **937**

 **938**	 **939**	 **940**
 **941**	 **942**	 **943**
 **944**	 **945**	 **946**
 **947**	 **948**	 **949**
 **950**	 **951**	 **952**

 953	 954	 955
 956	 957	 958
 959	 960	 961
 962	 963	 964
 965	 966	 967

 968	 969	 970
 971	 972	 973
 974	 975	 976
 977	 978	 979

 **980**	 **981**	 **982**
 **983**	 **984**	 **985**
 **986**	 **987**	 **988**
 **989**	 **990**	 **991**

 992	 993	 994
 995	 996	

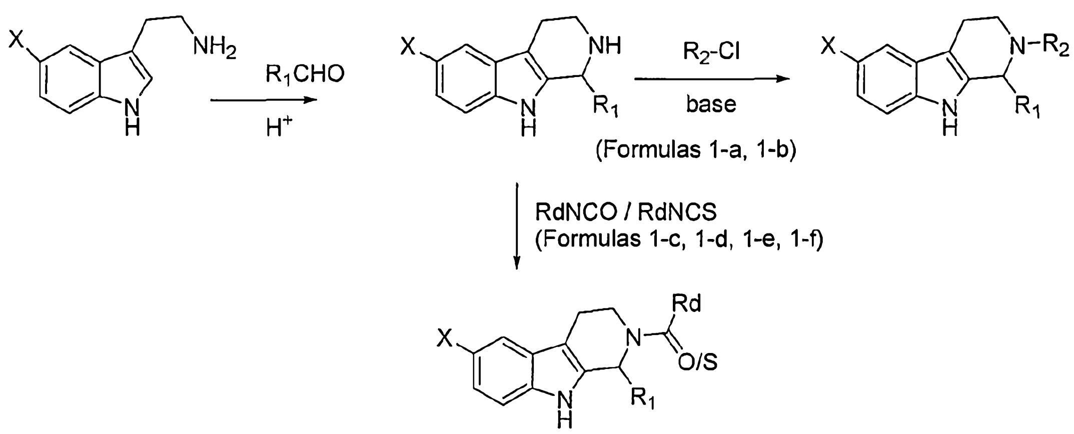
In certain embodiments, preferred compounds include those with an EC_{50} in the VEGF ELISA assay described in Example 2 of less than about 2 uM, more preferably between about 2 uM and about 0.04 uM (200 nM to 40 nM); more preferably from about 0.04 uM to about 0.008 uM to (40 nM to 8 nM); and more preferably less than about 0.008 uM (< 8 nM). Particularly preferred compounds are Compound Nos: 2, 4, 5, 7, 8, 10, 11, 12, 17, 23, 25, 81, 102, 112, 140, 328, 329, 330, 331, 332, 355, 816, 817, 818, 823, 824, 825, 830, 831, 832, 837, 838, 841, 842, 843, and regioisomers thereof. In one embodiment, the preferred compounds of the invention form a racemic mixture, and in another embodiment the compounds of the invention are the (*R*), (*S*), (*R,R*), (*S,S*), (*R,S*), (*S,R*) isomer, in an enantiomerically pure composition. More preferably, the compounds of the invention are the (*S*) isomers, in an enantiomerically pure composition.

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.

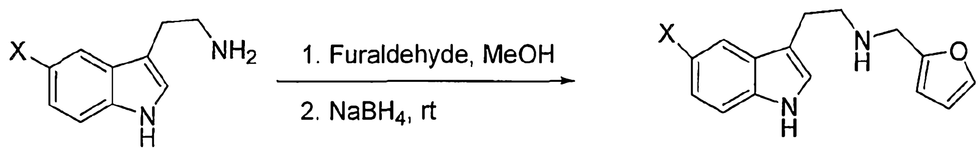
B. Preparation of Compounds of the Invention

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, **Scheme I** may be used to make compounds of Formula I. **Scheme Ia** can be used when in conjunction with **Scheme I** when R_2 is a -CH_2-furanyl group. Alternatively, for asymmetric synthesis when R_2 is hydrogen or hydroxyl , **Scheme Ib** may be used.

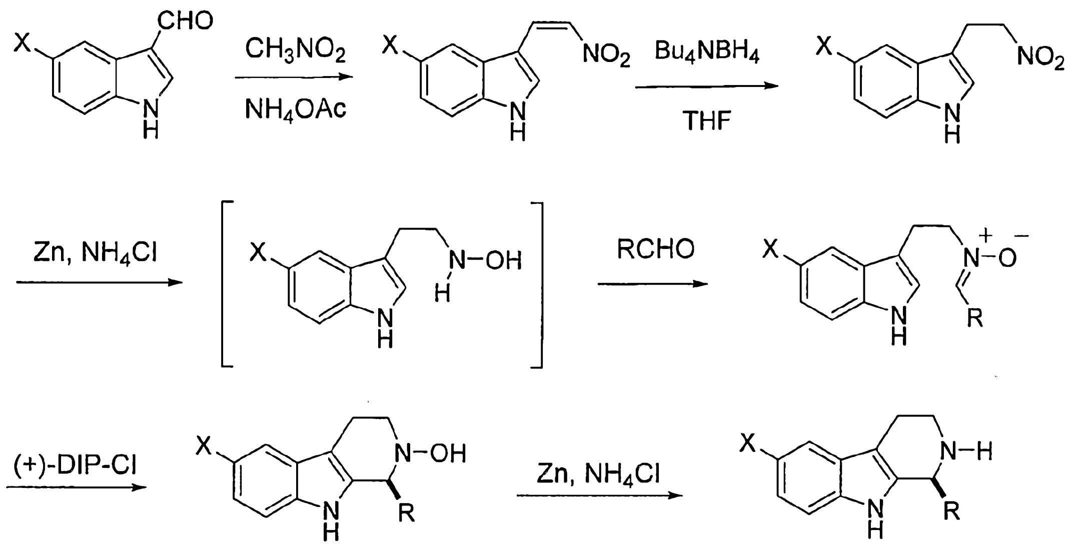
Scheme I



Scheme Ia

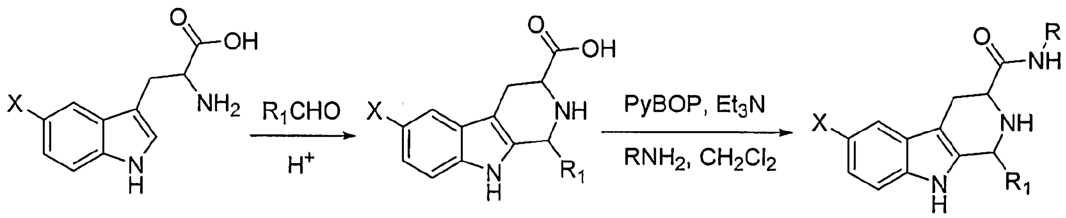


Scheme Ib



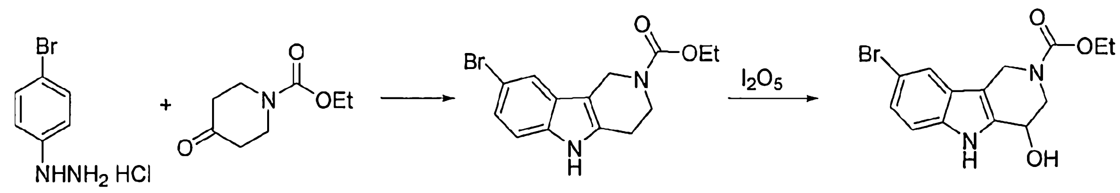
Scheme II can be used to prepare compounds of Formula I-h.

Scheme II



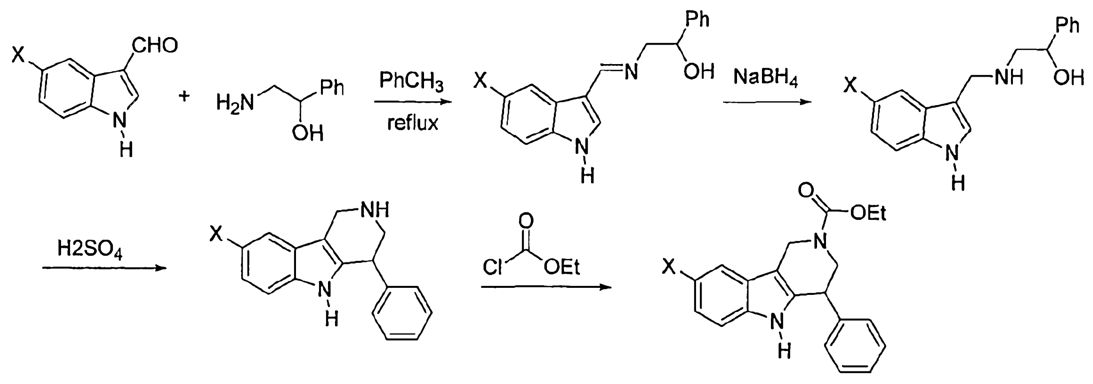
Schemes IIIa or IIIb can be used to prepare compounds of Formula I-i.

Scheme IIIa



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

Scheme IIIb

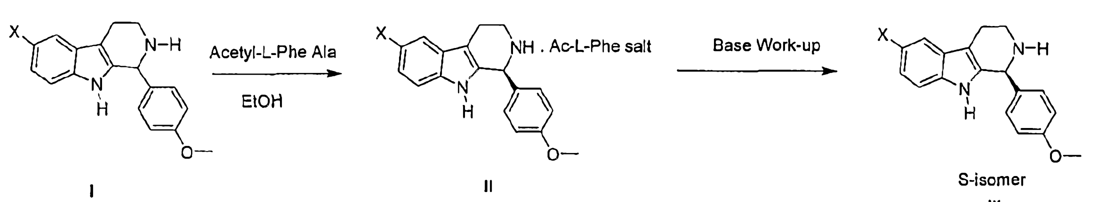


Ref: Magid Abou-Gharbia *et al*, *J. Med. Chem.* 1987, 30, 1818.

In a preferred embodiment, compounds of the invention may be resolved to enantiomerically pure compositions using any method known in art. By way of example, compounds of the invention may be resolved by direct crystallization of enantiomer mixtures, by diastereomer salt formation of enantiomers, by the formation of diasteriomers and separation, or by enzymatic resolution.

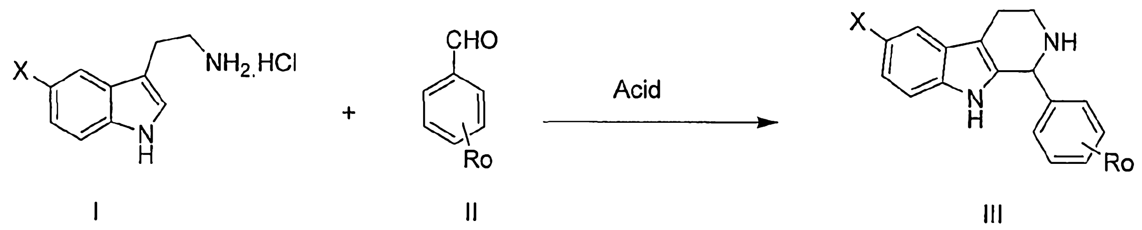
In a preferred embodiment, compounds of the invention may be resolved through crystallization using, *e.g.*, N-acetyl-L-phenylalanine to obtain the (*S*) isomer, or N-acetyl-D-phenylalanine to obtain the (*R*) isomer, in a manner similar to that illustrated in **Scheme IV**.

Scheme IV



In certain embodiments, exemplary methods of **Scheme I** for preparing preferred compounds of Formula I involve the formation of free amine Pictet-Spengler reaction products/intermediates, as described below in Procedure-I.

Procedure-I

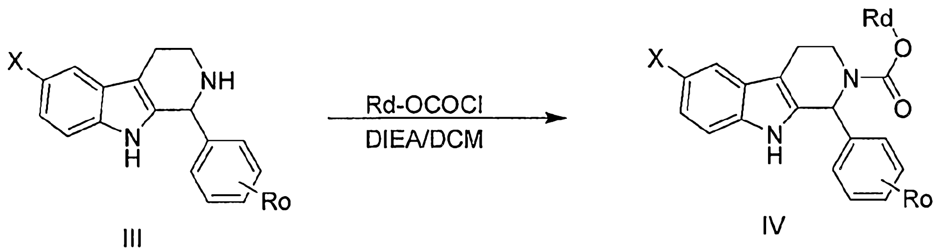


In one embodiment, Procedure-I may involve adding a desired Aldehyde (II) to a suspension of 5-substituted tryptamine. HCl (I) in 0.1N sulfuric acid. The solution may then be stirred at about 110°C - 120°C in a closed reaction vessel until the reaction is sufficient to complete, *e.g.*, for about 15 minutes to about 20 hours. After completion of the reaction, the reaction mixture may be cooled to room temperature and the precipitated salt may be filtered. The filtered residue may then be washed with ether, EtOAc or a mixture of DCM and DMF and dried to give the product (III) as acid salt. Alternatively, a desired Aldehyde (II) may be added to a suspension of 5-substituted tryptamine.HCl (I) in acetic acid and refluxed until the reaction is sufficiently complete, *e.g.*, for about 15 minutes to about 20 hours. After completion of the reaction, the reaction mixture may be cooled to room temperature and the acid salt may be filtered. The filtered residue may then be washed with acetic acid followed by DCM and dried to give the product (III) as acid salt. The free amine (III) may be obtained by extraction with EtOAc and washing with aqueous ammonium hydroxide or 1M aq. sodium hydroxide.

The free amine, or its salt, may then be used to form other preferred compounds of Formula I, such as carbamate analogs (Formula 1-c, Procedure-II), amide analogs, including N-acetyl analogs (Formula I-c, Procedure-IIIa and Procedure-IIIb), urea and thiourea analogs (Formula I-e and I-f, Procedure-IV and Procedure-V respectively), sulfoxide analogs (Formula 1-g, Procedure-VI), and pyrimidine analogs (Procedure-VII).

More particularly, Procedure-II may be used to synthesize carbamate analogs of free amines (III), or their salts.

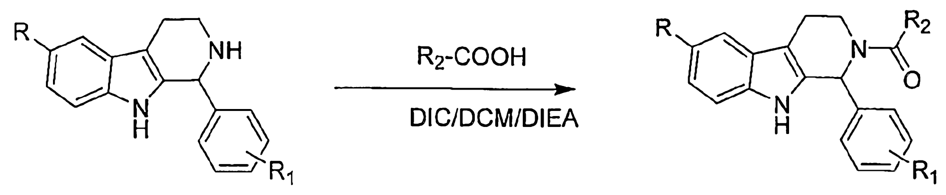
Procedure-II



In accordance with Procedure-II, diisopropylethylamine (DIEA) may be added to the free amine (III), or its acid salt in dichloromethane (DCM), followed by slow addition of substituted chloroformate. The reaction mixture may be stirred at room temperature for about 1 to 20 hours. The solvent may then be evaporated and the crude product may either be purified by HPLC or silica gel column chromatography.

Procedure-IIIa may be used to synthesize amide analogs of free amine (III), or their salts.

Procedure-IIIa

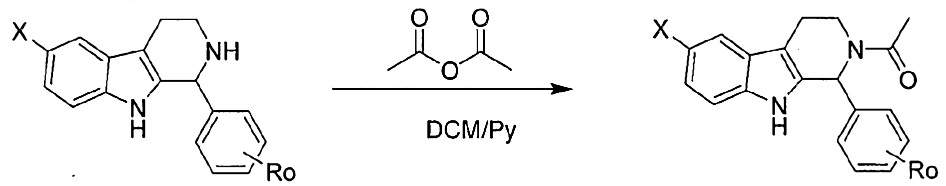


III X

In accordance with Procedure-IIIa, a 15 min pre-stirred mixture of an R_2-acid and diisopropyl carbodiimide (DIC) may be added to the free amine (III), or its acid salt in DCM and DIEA. The reaction mixture may be stirring for about 1 h. The solvents may then be evaporated and the crude product purified by HPLC.

Alternatively, Procedure-IIIb may be used to synthesize N-acetyl analogs of free amines (III), or their salts.

Procedure-IIIb

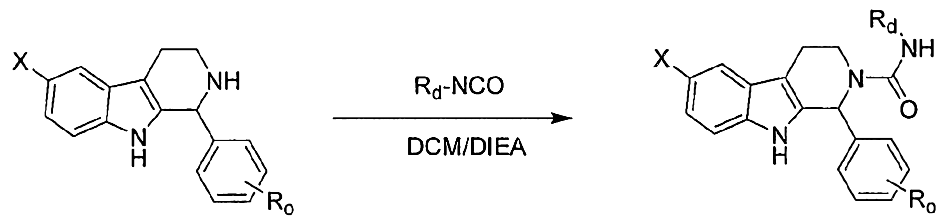


III V

In accordance with Procedure-IIIb, pyridine may be added to the free amine (III), or its acid salt in DCM, followed by acetic anhydride. The reaction mixture may be stirred at room temperature for about 8 to 20 hours. The solvents may then be evaporated and the crude product was purified by HPLC.

Procedure-IV may be used to synthesize urea analogs of free amines (III), or their salts.

Procedure-IV

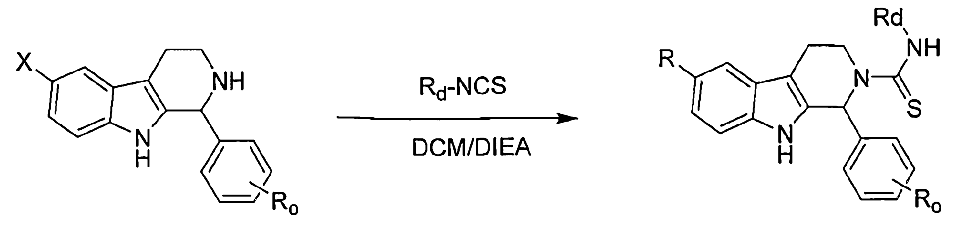


III VI

In accordance with Procedure-IV, DIEA and R_2-isocyanate may be added to the free amine (III), or its acid salt in DCM. The reaction mixture may be refluxed for about 1.5 h. The solvents may then be evaporated and the crude product purified by HPLC.

Procedure-V may be used to synthesize thiourea analogs of free amines (III), or their salts.

Procedure-V

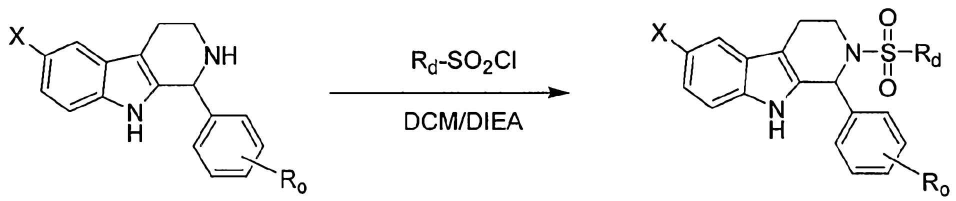


III VIII

In accordance with Procedure-V, DIEA and R_2-isothiocyanate may be added to the free amine (III), or its acid salt in DCM. The reaction mixture may be refluxed for about 12 h. The solvents may then be evaporated and the crude product purified by HPLC.

Procedure-VI may be used to synthesize sulfonyl analogs of free amines (III), or their salts.

Procedure-VI

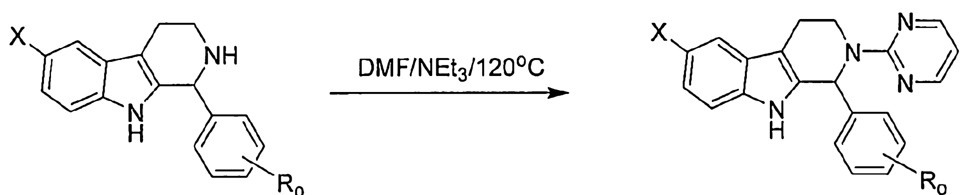


III IX

In accordance with Procedure-VI, DIEA and R_2-sulfonylchloride may be added to the free amine (III), or its acid salt in DCM. The reaction mixture may be stirred at room temperature for about 12 h. The solvents may then be evaporated and the crude product purified by HPLC.

Procedure-VII may be used to synthesize pyrimidine analogs of free amines (III), or their salts.

Procedure VII



III VII

In accordance with Procedure-VII, triethylamine and 2-bromopyrimidine in N,N-dimethylformamide (DMF) may be added to the free amine (III), or its acid salt in DCM. The reaction mixture may be heated to about 120°C for about 12 h. The solvents may then be evaporated and the crude product purified by HPLC.

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.

C. Methods of the Invention

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, rheumatoid arthritis, psoriasis, atherosclerosis, chronic inflammation, other chronic inflammation-related diseases and disorders, obesity, or exudative macular degeneration using the compounds described herein.

In one embodiment, the invention is directed to methods for inhibiting VEGF production comprising administering a VEGF-expression 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 yet another embodiment, methods for treating cancer, diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, chronic inflammation, other chronic inflammation-related diseases and disorders, obesity, 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.

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 preferred embodiments, the methods of the invention comprise administering a therapeutically effective amount of at least one compound of the invention, wherein the compound is an (*S*) isomer.

According to the methods of the invention, the compound(s) may be administered to the subject via any drug delivery route known in the art. Specific exemplary administration routes include oral, ocular, rectal, buccal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous (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, ED_{50}/LD_{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 0.1 μg/mL to approximately 100 μg/mL, preferably from approximately 5 μg/mL to approximately 50 μg/mL , more preferably from approximately 5 μg/mL to approximately 10 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 alternative embodiments, it may be preferred that the pH is adjusted to a range from about pH 5.0 to about pH 8.0.

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.

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 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.

I. 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 appreciated 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

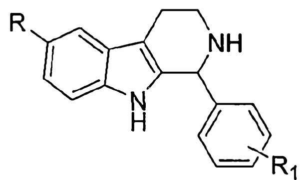
Using the schemes and procedures described above in Section B, one may prepare certain compounds of the invention as follows. Other preferred compounds of the invention, such as those in Table 5 below, may be similarly prepared.

Example 1A – Compounds of Formula I, Scheme I

Certain compounds of Formula I may be prepared according to Scheme I using free amine products/intermediates, or their salts prepared in accordance with Procedure I. By way of example, certain free amines (III), or their salts are prepared using Procedure I. Table 4 illustrates certain free amines (III) or their salts, Intermediates 1-11.

Table 4

Intermediate	R – of Free Amine (III)	R_1 – of Free Amine (III)
1	Cl	4-OMe
2	Cl	2,3-difluoro
3	Cl	4-Cl
4	Cl	4-CN
5	Cl	4-F
6	Cl	4-iPr
7	Br	4-Cl
8	Br	4-Me
9	Br	4-iPr
10	Br	3-Cl
11	Br	4-OMe
12	Cl	4-(2-morpholine-4-yl-ethoxy)



(III)

Intermediate-1:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (5.8 g, 25 mmol), p-anisaldehyde (6.13 mL, 50 mmol) and 0.1N sulfuric acid (60 mL) to give the title compound as an acid salt (6.1 g, 59%). ES-MS: 313 $(M+H)^+$. Alternatively, this intermediate is prepared using Procedure-1B with 5-chlorotryptamine.HCl (20g, 86.5 mmol), p-anisaldehyde (15.9 mL, 130 mmol) and acetic acid (250 mL) to give the title compound as an acid salt (25.8g, 79%). ES-MS: 313 $(M+H)^+$.

Intermediate-2:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (116 mg, 0.5 mmol), 2,3-difluoro benzaldehyde (109 μL, 1 mmol) and 0.1N sulfuric acid (2 mL) to give the title compound as an acid salt (158 mg, 75%). ES-MS: 319 $(M+H)^+$

Intermediate-3:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (462 mg, 2 mmol), 4-chloro benzaldehyde (562 mg, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as an acid salt (825 mg, 99%). ES-MS: 317 $(M+H)^+$

Intermediate-4:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (462 mg, 2 mmol), 4-cyano benzaldehyde (525 mg, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as an acid salt (810 mg, 100%). ES-MS: 308 $(M+H)^+$

Intermediate-5:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (374 mg, 1.5 mmol), 4-fluoro benzaldehyde (322 μL, 3 mmol) and 0.1N sulfuric acid (4 mL) to give the title compound as an acid salt (250 mg, 42%). ES-MS: 301 $(M+H)^+$

Intermediate-6:

This intermediate is prepared using Procedure-I with 5-chlorotryptamine.HCl (1.15 g, 5 mmol), 4-isopropyl benzaldehyde (1.516 mL, 10 mmol) and 0.1N sulfuric acid (12 mL) to give the title compound as an acid salt (628 mg, 30%). ES-MS: 325 $(M+H)^+$

Intermediate-7:

This intermediate is prepared using Procedure-I with 5-bromotryptamine.HCl (551 mg, 2 mmol), 4-chloro benzaldehyde (562 mg, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as an acid salt (330 mg, 36%). ES-MS: 363 $(M+H)^+$

Intermediate-8:

This intermediate is prepared using Procedure-I with 5-bromotryptamine.HCl (551 mg, 2 mmol), p-tolualdehyde (471 μL, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as hydrogen sulfate salt (257 mg, 29%). ES-MS: 341 $(M+H)^+$. Alternatively, this intermediate is prepared using Procedure-1B with 5-bromotryptamine.HCl (10 g , 36.3 mmol), p-tolualdehyde (6.41 mL, 54.5 mmol) and acetic acid (120 mL) to give the title compound as acetate salt (14.5 g, 100%). ES-MS: 341 $(M+H)^+$

Intermediate-9 (Compound 112):

This product/intermediate is prepared using Procedure-I with 5-bromotryptamine.HCl (551 mg, 2 mmol), 4-isopropyl benzaldehyde (606 μL, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as hydrogen sulfate salt (329 mg, 35%). ES-MS: 369 $(M+H)^+$. Alternatively, this intermediate is prepared using Procedure-1B with 5-bromotryptamine.HCl (10 g , 36.3 mmol), 4-isopropyl benzaldehyde (8.24 mL, 54.5 mmol) and acetic acid (120 mL) to give the title compound as acetate salt (13 g, 77%). ES-MS: 369 $(M+H)^+$

Intermediate-10:

This intermediate is prepared using Procedure-I with 5-bromotryptamine.HCl (551 mg, 2 mmol), 3-chloro benzaldehyde (453 μL, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as an acid salt (662 mg, 72%). ES-MS: 361 $(M+H)^+$

Intermediate-11:

This intermediate is prepared using Procedure-I with 5-bromotryptamine.HCl (551 mg, 2 mmol), p-anisaldehyde (491 μL, 4 mmol) and 0.1N sulfuric acid (8 mL) to give the title compound as an acid salt (611 mg, 67%). ES-MS: 357 $(M+H)^+$

Intermediate-12:

The 4-(2-Morpholin-4-yl-ethoxy)-benzaldehyde reaction intermediate is prepared by combining 4-hydroxybenzaldehyde (1.2 g, 10.0 mmol), 4-(2-chloroethyl)-morpholine hydrochloride (2.0 g, 11.0 mmol), potassium carbonate (4.1 g, 30.0 mmol), and potassium iodide (170 mg, 1 mmol) in 100 ml of acetone and heating to reflux with stirring. After all the 4-hydroxybenzaldehyde is consumed (48 hours by LC/MS), the solids are filtered and the solvent is removed *in vacuo*. The yield is 4.1 g.

Then Intermediate 12 is prepared in accordance with Procedure-IB. Thus, 5-Chlorotryptamine hydrochloride (231 mg, 1.0 mmol) is combined with 4-(2-Morpholin-4-yl-ethoxy)-benzaldehyde (565 mg, ~1.2 mmol) in 3 mL of glacial acetic acid. The suspension is heated to about 120°C for 10 minutes with constant cooling and a max power of 300W using the CEM Explorer microwave system. Acetonitrile (2 mL) is added to the cooled reaction mixture, and the solid is filtered and washed with 1 mL of acetonitrile to produce the acetic acid salt of Intermediate 12 (6-Chloro-1-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-2,3,4,9-tetrahydro-1H-β-carboline) (179 mg, 34%).

Intermediates 1-12 may then be used to prepare compounds of the invention according to Procedures II through VII as follows.

Compound 2:

This product is prepared by Procedure-II using the Intermediate-1 (3 g, 9.6 mmol), ethyl chloroformate (1.37 mL, 14.4 mmol) and DIEA (2.5 mL, 14.4 mmol) in dichloromethane (70 mL) to give the title compound as white powder (1.56 g, 42%). ES-MS: 385 $(M+H)^+$.

Compound 4:

This product is prepared by Procedure-II using the Intermediate-7 (72 mg, 0.2 mmol), ethyl chloroformate (29 μL, 0.3 mmol) and DIEA (52 μL, 0.3 mmol) in dichloromethane (2 mL) to give the title compound as white powder (37 mg, 43%). ES-MS: 435 $(M+H)^+$.

Compound 5:

This product is prepared by the Procedure-II using the Intermediate-2 (50 mg, 0.16 mmol), ethyl chloroformate (23 μL, 0.24 mmol) and DIEA (42 μL, 0.24 mmol) in dichloromethane (2 mL) to give the title compound as white powder (25 mg, 41%). ES-MS: 391 $(M+H)^+$.

Compound 7:

This product is prepared by the Procedure-II using the Intermediate-9 (74 mg, 0.2 mmol), ethyl chloroformate (29 μL, 0.3 mmol) and DIEA (52 μL, 0.3 mmol) in dichloromethane (2 mL) to give the title compound as white powder (34 mg, 38%). ES-MS: 441 $(M+H)^+$.

Compound 8:

This product is prepared by the Procedure-II using the Intermediate-8 (72 mg, 0.2 mmol), ethyl chloroformate (29 μL, 0.3 mmol) and DIEA (52 μL, 0.3 mmol) in dichloromethane (2 mL) to give the title compound as white powder (39 mg, 47%). ES-MS: 413 $(M+H)^+$.

Compound 10:

This product is prepared by the Procedure-II using the Intermediate-1 acetate (10.5 g, 28.2 mmol), 4-chlorophenyl chloroformate (4.74 mL, 33.8 mmol) and DIEA (9.8 mL, 56.4 mmol) in dichloromethane (300 mL) to give the title compound as white powder (10.2 g, 78%). ES-MS: 467 $(M+H)^+$.

Compound 11:

This product is prepared by the Procedure-II using the Intermediate-3 (63 mg, 0.2 mmol), ethyl chloroformate (29 μL, 0.3 mmol) and DIEA (52 μL, 0.3 mmol) in dichloromethane (2 mL) to give the title compound as white powder (31 mg, 40%). ES-MS: 389 $(M+H)^+$.

Compound 12:

This product is prepared by the Procedure-II using the Intermediate-4 (31 mg, 0.1 mmol), 2-chloroethyl chloroformate (16 μL, 0.15 mmol) and DIEA (26 μL, 0.15 mmol) in dichloromethane (2 mL) to give the title compound as white powder (22 mg, 53%). ES-MS: 414 $(M+H)^+$.

Compound 17:

This product is prepared by the Procedure-II using the Intermediate-1 (47 mg, 0.15 mmol), 4-methylphenyl chloroformate (33 μL, 0.23 mmol) and DIEA (39 μL, 0.23 mmol) in dichloromethane (2 mL) to give the title compound as white powder (34 mg, 51%). ES-MS: 447 $(M+H)^+$.

Compound 23:

This product is prepared by the Procedure-II using the Intermediate-5 (30 mg, 0.1 mmol), ethyl chloroformate (14 μL, 0.15 mmol) and DIEA (26 μL, 0.15 mmol) in dichloromethane (2 mL) to give the title compound as white powder (21 mg, 56%). ES-MS: 373 $(M+H)^+$.

Compound 25:

This product is prepared by the Procedure-VII using the Intermediate-9 (74 mg, 0.2 mmol), 2-bromopyrimidine (48 mg, 0.3 mmol) and triethylamine (42 μL, 0.3 mmol) in DMF (2 mL) to give the title compound (42 mg, 47%). ES-MS: 447 $(M+H)^+$.

Compound 102:

This product is prepared by the Procedure-IIIb using the Intermediate-9 (74 mg, 0.2 mmol), acetic anhydride (47 μL, 0.5 mmol) and pyridine (41 μL, 0.5 mmol) in dichloromethane (2 mL) to give the title compound as white powder (31 mg, 38%). ES-MS: 411 $(M+H)^+$.

Compound 140:

This product is prepared by the Procedure-IV using the Intermediate-10 (72 mg, 0.2 mmol), cyclohexyl isocyanate (26 μL, 0.2 mmol) and DIEA (37 μL, 0.21 mmol) in dichloromethane (2 mL) to give the title compound as white powder (51 mg, 53%). ES-MS: 486 $(M+H)^+$.

Compound 166:

This product is prepared by the Procedure-IIIa using its free amine intermediate (141 mg, 0.5 mmol), Boc-L-Alanine (105 mg, 0.6 mmol), DIC (94 μL, 0.6 mmol), DIEA (105 μL, 0.6 mmol) and dichloromethane (4 mL) to give the title compound (105 mg, 46%). ES-MS: 420 $(M+H)^+$.

Compound 225:

This product is prepared by the Procedure-VI using its free amine intermediate (78 mg, 0.2 mmol), methyl sulfonylchloride (16 μL, 0.2 mmol) and DIEA (37 μL, 0.21 mmol) and dichloromethane (2 mL) to give the title compound (32 mg, 34%). ES-MS: 461 $(M+H)^+$.

Compound 242:

This product is prepared by the Procedure-V using its free amine intermediate (59 mg, 0.2 mmol), cyclohexyl isothiocyanate (29 μL, 0.2 mmol), DIEA (35 μL, 0.2 mmol) and dichloromethane (4 mL) to give the title compound (52 mg, 60%). ES-MS: 438 $(M+H)^+$.

Compound 279:

This product is prepared by generating Intermediate 12 (6-Chloro-1-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-2,3,4,9-tetrahydro-1H-β-carboline) using Procedure-I. Intermediate 12 is then used to generate Compound 279 (6-Chloro-1-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1,3,4,9-tetrahydro-b-carboline-2-carboxylic acid ethyl ester) using Procedure-II.

In accordance with Procedure-II, Intermediate **12** (82 mg, 0.20 mmol), ethyl chloroformate (24 mg, 21μL, 0.22 mmol), and diisopropylethylamine (175 μL, 1.00 mmol) are dissolved in methylene chloride (2 mL) and stirred at room temperature for 15 minutes to form Compound 279. The solvent is removed under a stream of nitrogen. The crude mixture is purified by preparative reversed phase HPLC on a C-18 column using a gradient of acetonitrile in water buffered with 0.2% trifluoroacetic acid (TFA). The TFA salt of Compound 279 (3.7 mg, 3%) is isolated as a yellow solid. The same procedure may be applied for other carbamate formation reactions according to Procedure-II.

Compound 320:

This product/intermediate is prepared using Procedure-I with 5-benzyloxy tryptamine.HCl (100 mg, 0.33 mmol), pyridine-3-carboxaldehyde (62 μL, 0.66 mmol) and 0.1N sulfuric acid (2 mL) to give the title compound as dihydrogen sulfate salt (64 mg, 55%). ES-MS: 356 $(M+H)^+$

Compound 329:

This product is prepared by the Procedure-VII using the Intermediate-11 (71 mg, 0.2 mmol), 2-bromopyrimidine (48 mg, 0.3 mmol) and triethylamine (42 μL, 0.3 mmol) in DMF (2 mL) to give the title compound (41 mg, 49%). ES-MS: 434 $(M+H)^+$.

Compound 330:

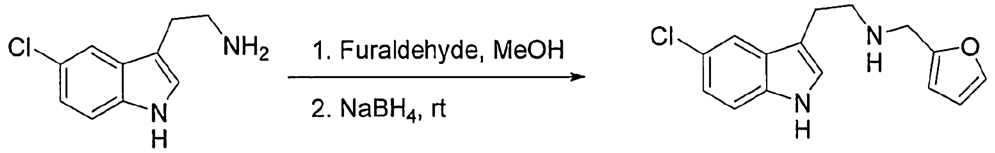
This product is prepared by the Procedure-II using the Intermediate-6 (65 mg, 0.2 mmol), 2-fluoroethyl chloroformate (38 μL, 0.3 mmol) and DIEA (70 μL, 0.4 mmol) in dichloromethane (2 mL) to give the title compound as white powder (34 mg, 41%). ES-MS: 415 $(M+H)^+$.

Compound 332:

This product is prepared by the Procedure-II using the Intermediate-7 (36 mg, 0.1 mmol), 4-methoxyphenyl chloroformate (22 μL, 0.15 mmol) and DIEA (26 μL, 0.15 mmol) in dichloromethane (2 mL) to give the title compound as white powder (41 mg, 81%). ES-MS: 511 $(M+H)^+$.

Example 1B – Certain Starting Materials, Scheme Ia

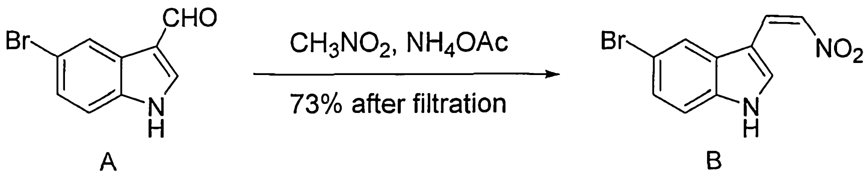
Scheme Ia can be used when in conjunction with Scheme I (above) to generate starting materials when R_2 is a $-CH_2$-furanyl group, as follows.



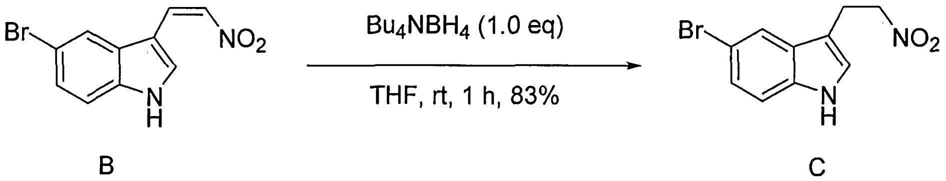
2-furaldehyde (0.05 mL, 1.1 eq) is added to a solution of 5-chlorotryptamine (114 mg, 0.586 mmol) in 2 mL of MeOH. The reaction mixture is stirred at room temperature for about 1 hour. $NaBH_4$ (110 mg, 5 eq) is added slowly. The reaction mixture is stirred at room temperature for about 30 min. MeOH is evaporated and the residue is partitioned between water and methylene chloride. The organic layer is separated and dried over K_2CO_3. The collected organic layer is concentrated to give 134.9 mg of viscous oil (84%).

Example 1C – Compounds of Formula I, Scheme Ib

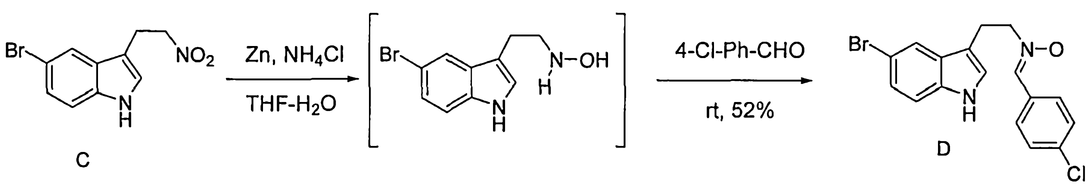
Alternatively, certain compounds of Formula I may be prepared according to **Scheme Ib** as follows.



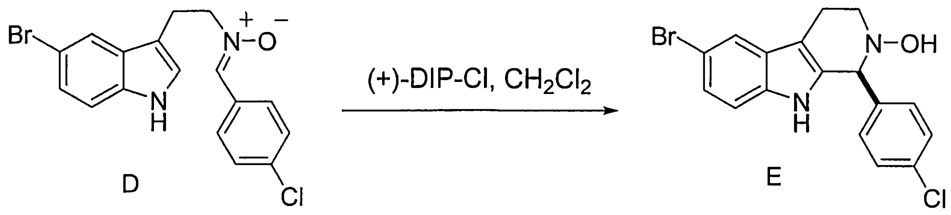
A suspension of reaction material **A** (8.05g, 35.9 mmol) and CH_3COONH_4 (4.15g, 1.5 eq) in 60 mL of CH_3NO_2 is refluxed in oil bath at about 110°C. After about 30 minutes, the reaction mixture is cooled with ice-bath. The precipitated solid is filtered and washed with water (3X100 mL), followed by hexane (2X50 mL) to give crude indole product **B**. The collected solid is dried under vacuum at about 40°C for about 30 min to give 6.97g of brown solid (73%).



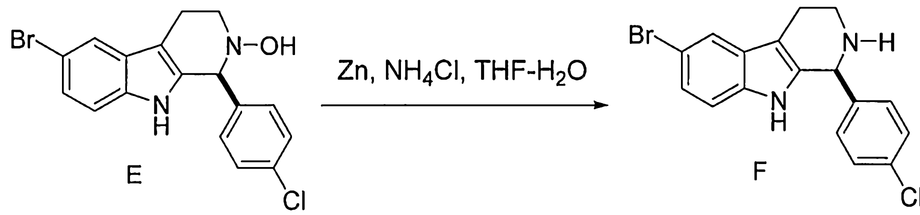
A solution of indole product **B** (12.32g, 46.1 mmol) in THF (130 mL) is then treated with a solution of tetrabutylammonium borohydride (11.9g, 1 eq) in 75 mL of THF slowly for about 60 minutes at about –5°C. The reaction is stirred at room temperature for about 1 hour and diluted with dichloromethane (200 mL). The organic layer is washed with water twice and brine. The combined organic layers are dried and evaporated under vacuum. The residue is purified on silica gel to give 10.28g of solid **C** (83%).



Ammonium chloride (9.9 mL of aqueous solution (100 mg/mL), 2 eq) and Zn (725 mg, 1.2 eq) are then added to a solution of indole product **C** (2.49g, 9.24 mmol) in 161 mL of THF. The reaction mixture is stirred at room temperature for about 10 min and Zn (725 mg, 1.2 eq) is then added. After about 30 min, additional Zn (967 mg, 1.6 eq) is added and stirred for about 2 hours, followed by the addition of further Zn (845 mg, 1.4 eq). After stirring at room temperature for about 15 min, Zn is filtered off and the residue is concentrated and dissolved in THF. The resulting solution is then treated with p-chlorobenzaldehyde (0.7 eq) and stirred at room temperature for about 15 hours. The reaction mixture is concentrated under vacuum and purified on silica gel to give 953.5 mg of the desired nitrone product **D**.



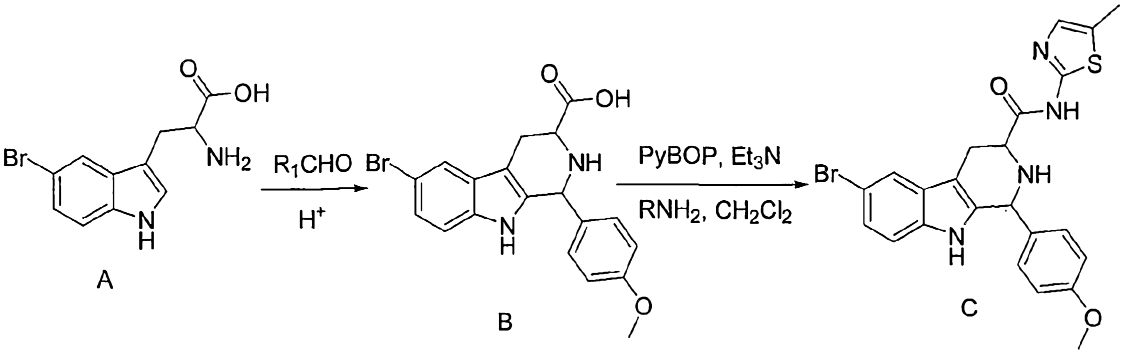
(+)-DIP-Cl (6.93 mL, 2 eq, 85.8 mg / mL in CH_2Cl_2) is then added to a solution of nitrone product **D** (350 mg, 0.93 mmol) in 60 mL of dichloromethane. The reaction mixture is stirred at about –78°C for about 10 days and quenched with a mixture of 10% $NaHCO_3$ (7mL) and 10 mL of water. The aqueous layer is extracted with dichloromethane three times. Combined organic layers are concentrated and purified on silica gel to give the desired hydroxylamine product **E** (>98 % ee).



Water (11.5 mL), NH_4Cl (2.5 mL, 5 eq) and Zn (908 mg, 15 eq) are then added to a solution of hydroxylamine product **E** (0.927 mmol) in THF (28 mL). The reaction mixture is stirred at room temperature for about 1 day. Additional THF (10 mL), NH_4Cl (5 mL, 10 eq) and Zn (1.8g, 30 eq) are then added and stirred for about another 21 hours. Again, THF (10 mL), NH4Cl (5 mL, 10 eq) and Zn (1.8g, 30 eq) are added and stirred for about another 20 hours. The reaction mixture is then filtered through celite and washed with MC. The collected dichloromethane layer is washed with water and brine. The organic layer is dried and concentrated to give a boron complex of beta-carboline. This product is dissolved in 20 mL of THF. This solution is loaded into prepacked cation exchange resin (preconditioned with MeOH and THF) and washed with THF. The combined THF solution is concentrated to give 390 mg of free amine. The solid is then washed with ether and hexane consecutively to yield 130 mg of the enantiomerically pure compound **F**.

Example 1D – Compounds of Formula I, Scheme II

Compounds of Formula I-h may be prepared according to **Scheme II** as follows.

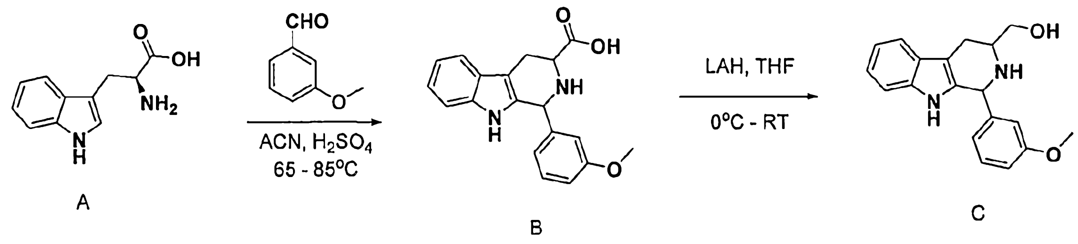


p-anisaldehyde (2.16g, 15.9 mmol, 1.93 mL) is added to a suspension of 5-Bromotryptophan **A** (3g, 10.6 mmol) in 100 mL of Acetic acid at room temperature. The reaction mixture is then heated to reflux at about 125 °C in silicon oil bath and maintained at that temperature for about 3 hours 20 minutes. The resultant solution is concentrated under vacuum. The residue is triturated with dichloromethane, diethyl ether and hexane to yield a powdery brown solid. The acetic salts of the intermediate product **B** is collected and washed with hexane three times.

The intermediate product **B** is suspended (70 mg, 0.174 mmol) in 2 mL of dichloromethane, and triethylamine (52.8 mg, 0.522 mmol), 5-methyl-2-aminothiazole (37.6 mg, 0.26 mmol) and PyBOP (135.8 mg, 0.26 mmol) is added to the suspension. The reaction mixture is stirred at room temperature for about 6 hour and quenched with sat. $NaHCO_3$ solution. The aqueous layer is extracted with dichloromethane. The combined organic layers are dried over K_2CO_3 and concentrated. Purification on silica gel with 40% ethyl acetate in hexane yields 8.1 mg of the desired amide **C**. LCMS [MH^+] 498, Rt = 2.54.

Example 1E – Compounds of Formula I, Scheme III

Compounds of Formula I-i may be prepared according to **Scheme III** as follows.

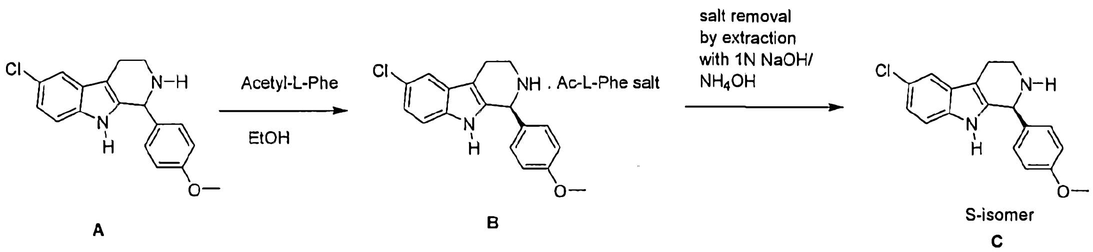


Tryptophan **A** (1.0 g, 5.0 mmol) and 3-methoxybenzaldehyde (670 μL, 5.5 mmol) are suspended / dissolved in acetonitrile (100 mL) and concentrated sulfuric acid (100 μL) is added. The reaction is heated to reflux until all the aldehyde was consumed (overnight). The solvent was removed in vacuo and the residue was dissolved in 5 mL of ethanol. The product was precipitated out with ether, filtered, and washed with 10 mL of ether. The desired β-carboline product/ intermediate **B** (1-(3-Methoxy-phenyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid) is isolated as a beige solid (1.2 g, 76%). LC/MS RT = 2.33 min. M/Z+ 323, 100%.

The β-carboline product/intermediate **B** (200 mg, 0.62 mmol) is then dissolved in 5 mL of dry THF and cooled to about 0°C. Lithium aluminum hydride (LAH) solution (1.2 mL, 1.0M in ether, 1.2 mmol) is added to the cooled reaction mixture under nitrogen. After the addition is complete (about 10 minutes), the reaction is allowed to warm to room temperature for about 4 hours. The reaction mixture is then cooled back to 0°C, and saturated sodium sulfate solution (750 μL) is added and the mixture stirred for about 5 minutes at 0°C. The reaction mixture is then filtered and washed with THF (100 mL). The solvent is removed *in vacuo*, and the crude product purified by preparative HPLC. The product **C** ([1-(3-Methoxy-phenyl)-2,3,4,9-tetrahydro-1H-b-carbolin-3-yl]-methanol) is isolated as a white solid (106 mg, 55%). LC/MS RT = 2.25 min. M/Z+ 309, 100%.

Example 1F - Chemical resolution of Compounds of the Invention

Compounds of the invention may optionally be chemical resolved to enantiomerically pure compositions, preferably enantiomerically pure (*S*) isomer compositions as follows.

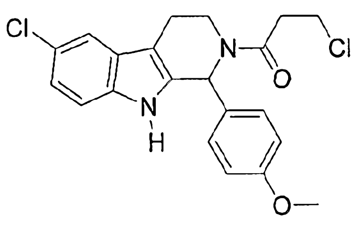
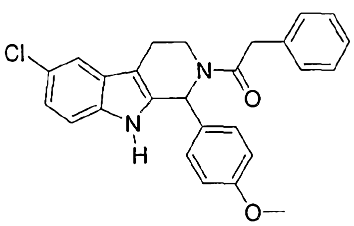
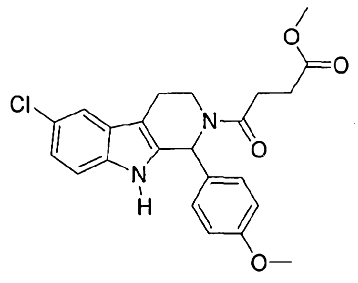
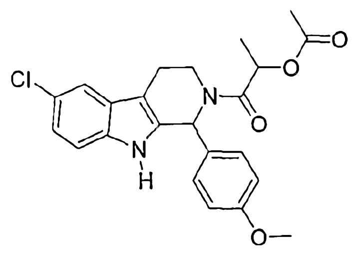


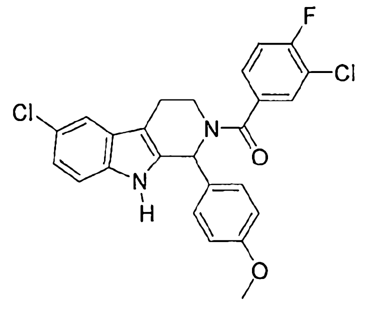
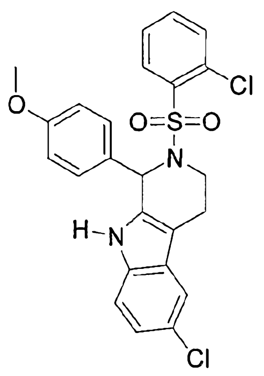
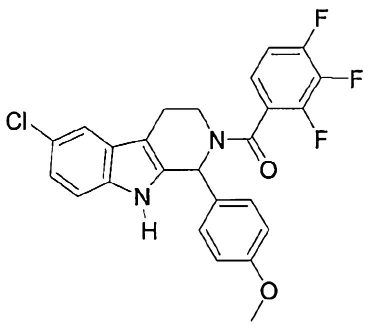
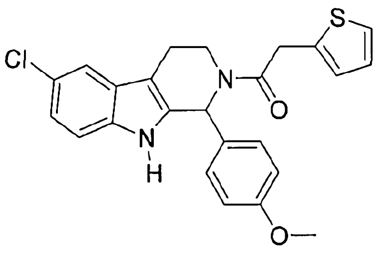
The racemic amine **A** (18.21 g, 58.2 mmol) is mixed with N-acetyl-L-phenylalanine (12.05 g, 58.2 mmol) in EtOH (1.28 L) and refluxed to get a clear solution. The solution is then allowed to cool to room temperature. After overnight standing, the precipitated solid is filtered and washed with EtOH (200 mL) to give the salt **B** (16.4 g). The salt **B** is taken in EtOAc (500 mL) and washed with aqueous 1N NaOH (300 mL x 2) or NH_4OH (200 mL x 2), dried and evaporated to give the S-isomer of the free amine **C** (7.4 g). The R-isomer is prepared by similar procedure using N-acetyl-D-phenylalanine.

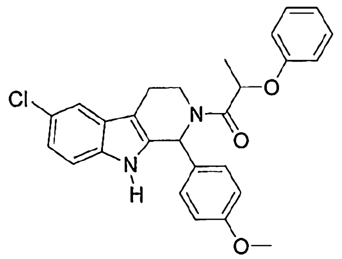
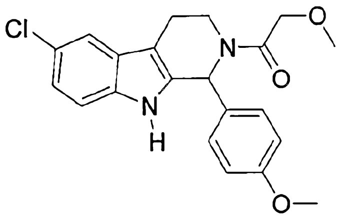
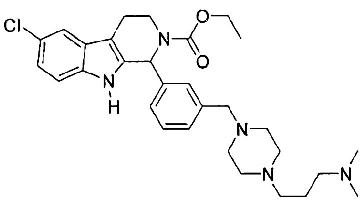
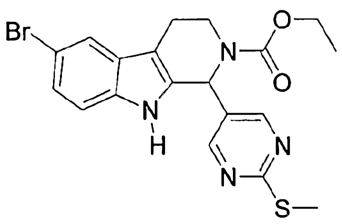
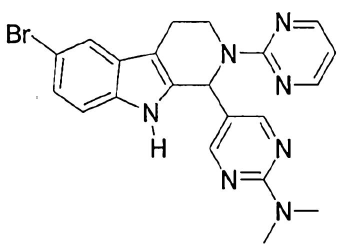
Example 1G - Further Exemplary Compounds of the Invention

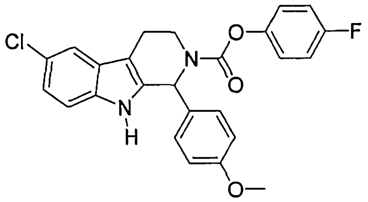
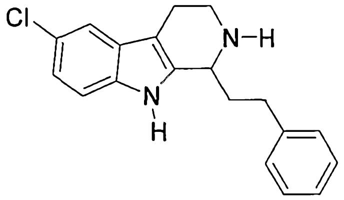
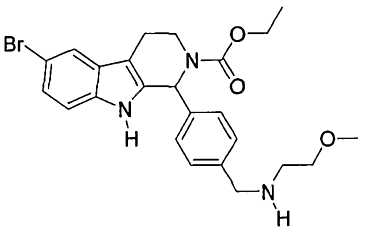
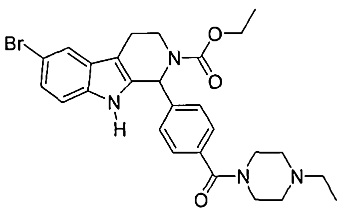
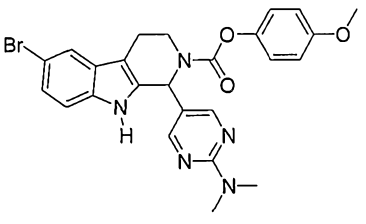
By way of further non-limiting example, the following compounds (Table 5) may be prepared by similar methodology to that described above, as will be recognized by one of skill in the art.

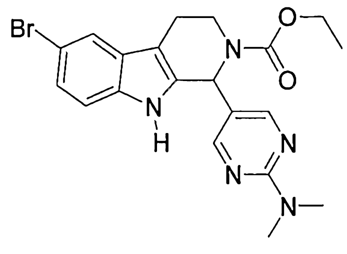
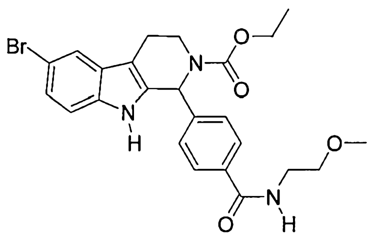
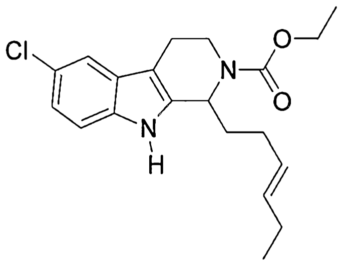
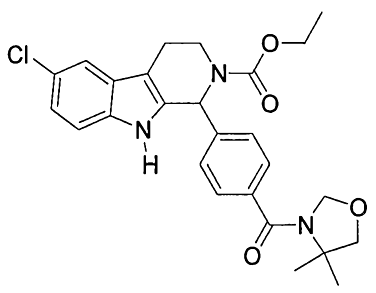
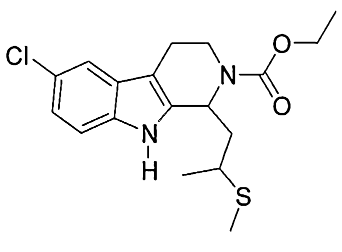
Table 5

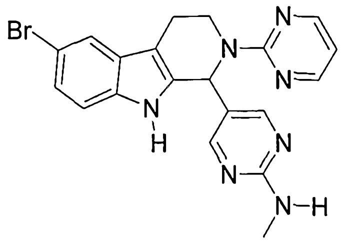
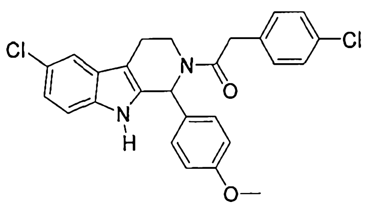
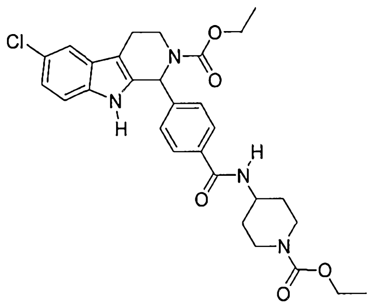
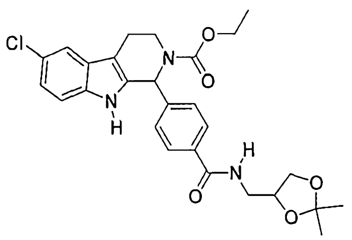
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **367**	(CDCl3, 400MHz), δ 8.16 (s, 1H), 7.48 (s, 1H), 7.22 (d, J=8.8Hz, 1H), 7.19 (d, J=8.8Hz, 2H), 7.13 (d, J=8.8Hz, 1H), 6.94 (s, 1H), 6.80 (d, J=8.8Hz, 2H), 3.92-3.91 (m, 1H), 3.86 (t, J=7.2Hz, 2H), 3.77 (s, 3H), 3.46-3.39 (m, 1H), 3.11-3.09 (m, 1H), 2.91-2.83 (m, 3H)	402.8	4.37
 **368**	(CDCl3, 400MHz), δ 8.29 (s, 1H), 7.47-7.09 (m, 10H), 6.98 (s, 1H), 6.77 (d, J=8.8Hz, 2H), 3.93 (dd, J=13.6Hz and 4.8Hz, 1H), 3.82-3.80 (m, 2H), 3.77 (s, 3H), 3.38-3.30 (m, 1H), 2.69-2.65 (m, 1H), 2.53-2.45 (m, 1H)	430.9	4.79
 **369**	(CDCl3, 400MHz), δ 8.21 (s, 1H), 7.46 (s, 1H), 7.22 (d, J=8.4Hz, 1H), 7.17 (d, J=8.4Hz, 2H), 7.12 (dd, J=8.4Hz and 2.0Hz, 1H), 6.92 (s, 1H), 6.77 (d, J=8.4Hz, 2H), 3.94 (dd, J=13.2Hz and 4.4Hz, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.43-3.35 (m, 1H), 2.87-2.62 (m, 6H)	427.0	4.06
 **370**	(CDCl3, 400MHz), δ 8.23, 8.12 (s, 1H), 7.48, 7.42 (d, J= 1.6Hz, 1.2Hz, 1H), 7.22-7.10 (m, 4H), 6.94, 6.88 (s, 1H), 6.79 (d, J=8.8Hz, 2H), 5.48-5.45 (m, 1H), 3.96-3.80 (m, 1H), 3.77 (s, 3H), 3.47-3.36 (m, 1H), 3.08-2.77 (m, 2H), 2.14, 2.09 (s, 3H), 1.48, 1.41 (d, J=6.8Hz, 6.4Hz, 3H)	427.0	3.99

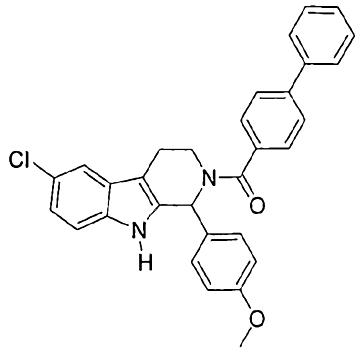
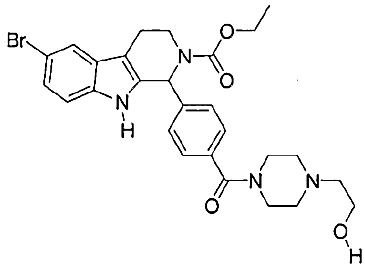
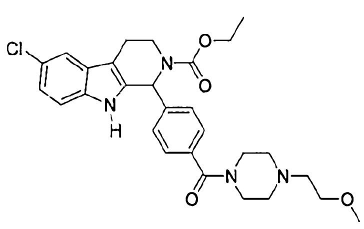
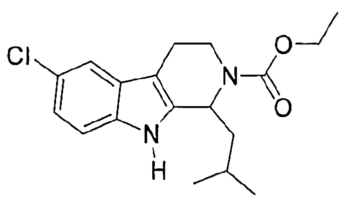
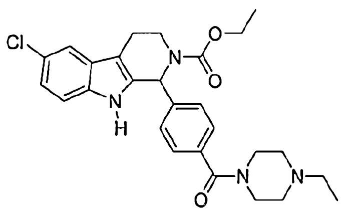
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 371	(CDCl3, 400MHz), δ 7.87 (s, 1H), 7.51 (s, 1H), 7.47 (dd, J=6.8Hz and 1.6Hz, 1H), 7.30-7.15 (m, 6H), 6.98 (b, 1H), 6.76 (d, J=8.8Hz, 2H), 3.80 (s, 3H), 3.77-3.74 (m, 1H), 3.49-3.39 (m, 1H), 2.93-2.82 (m, 2H)	469.0	5.27
 372	(CDCl3, 400MHz), δ 8.07 (dd, J=7.6Hz and 1.2Hz, 1H), 7.74 (s, 1H), 7.45-7.32 (m, 4H), 7.18 (d, J=8.4Hz, 1H), 7.12 (dd, J=8.8Hz and 2.0Hz, 1H), 7.07 (d, J=8.4Hz, 2H), 6.76 (d, J=8.8Hz, 2H), 6.35 (s, 1H), 3.97 (dd, J=14.8Hz and 5.2Hz, 1H), 3.77 (s, 3H), 3.49-3.41 (m, 1H), 2.67 (dd, J=15.6Hz and 3.2Hz, 1H), 2.57-2.53 (m, 1H)	486.9	4.96
 373	(CDCl3, 400MHz), δ 7.95 (s, 1H), 7.48 (s, 1H), 7.30 (d, J=8.4Hz, 2H), 7.23 (d, J=8.8Hz, 1H), 7.16 (dd, J=8.8Hz and 1.6Hz, 1H), 7.05 (b, 3H), 6.86 (d, J=8.4Hz, 2H), 3.80 (s, 3H), 3.61 (dd, J=13.6Hz and 5.2Hz, 1H), 3.52-3.44 (m, 1H), 2.91-2.88 (m, 1H), 2.78 (dd, J=15.2Hz and 3.2Hz, 1H)	470.8	5.01
 374	(CDCl3, 400MHz), δ 8.09 (s, 1H), 7.45 (s, 1H), 7.21-7.17 (m, 4H), 7.12 (d, J=8.8Hz, 1H), 6.98 (s, 1H), 6.91 (d, J=4Hz, 1H), 6.80 (s, 1H), 6.79 (d, J=8.4Hz, 2H), 3.99 (s, 2H), 3.96 (d, J=4.4Hz, 1H), 3.77 (s, 3H), 3.43-3.38 (m, 1H), 2.77-2.63 (m, 2H)	436.9	4.66

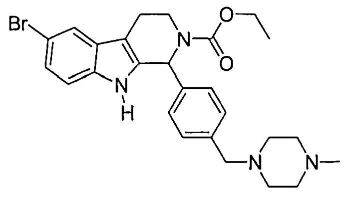
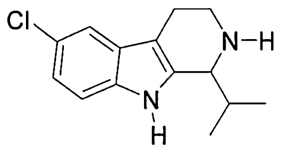
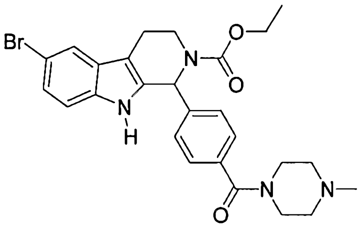
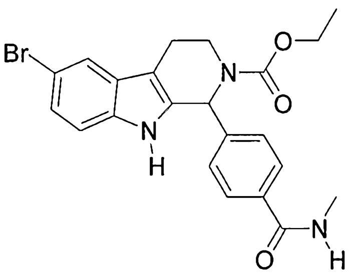
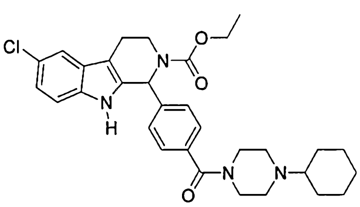
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 375	(CDCl3, 400MHz), δ 8.19, 8.16 (s, 1H), 7.48, 8.42 (s, 1H), 7.24-7.09 (m, 6H), 6.94 (t, J=7.8Hz, 2H), 6.85 (t, J=8.2Hz, 2H), 6.77 (d, J=8.4Hz, 1H), 6.72 (d, J=8.4Hz, 1H), 5.09-4.98 (m, 1H), 4.39-4.17 (m, 1H), 3.77, 3.75 (s, 3H), 3.41-3.28 (m, 1H), 3.02-2.65 (m, 2H), 1.61-1.59 (m, 3H)	461	4.92
 376	(CDCl3, 400MHz), δ 8.39 (s, 1H), 7.48 (s, 1H), 7.23 (d, J=8.4Hz, 1H), 7.19 (d, J=8.4Hz, 2H), 7.13 (dd, J=8.8Hz and 1.6Hz, 1H), 6.89 (s, 1H), 6.77 (d, J=8.4Hz, 2H), 4.17 (q, J=12.8Hz, 2H), 3.88 (d, J=10Hz, 1H), 3.75 (s, 3H), 3.41 (s, 3H), 3.38-3.34 (m, 1H), 2.95-2.81 (m, 2H)	385	3.79
 389	(CD3OD, 400MHz), δ 7.48-7.46 (m, 4H), 7.35 (b, 1H), 7.23 (d, J=8.8Hz, 1H), 7.07 (dd, J=8.8Hz and 2.0Hz, 1H), 6.46 (b, 1H), 4.35-4.14 (m, 5H), 3.52-3.47 (m, 2H), 3.22-3.19 (m, 7H), 2.98-2.93 (m, 3H), 2.89 (s, 6H), 2.67-2.63 (m, 5H), 2.06-1.96 (m, 2H), 1.31 (t, J=7.2Hz, 3H)	538.3	4.29
 393	(DMSO, 400MHz), δ 11.00 (s, 1H), 8.47 (s, 2H), 7.67 (s, 1H), 7.26 (d, J=8.4Hz, 1H), 7.19 (dd, J=8.8Hz and 2.0Hz, 1H), 6.26 (b, 1H), 4.25 (b, 1H), 4.11 (t, J=6.8Hz, 2H), 3.22-3.17 (m, 1H), 2.86-2.81 (m, 1H), 2.77-2.66 (m, 1H), 2.50 (b, 3H), 1.21 (t, J=6.8Hz, 3H)	447.1	6.55
 394	(CD3OD, 400MHz), δ8.43-8.41 (m, 4H), 7.63 (d, J=1.2Hz, 1H), 7.22 (d, J=8.8Hz, 1H), 7.19 (dd, J=8.4Hz and 1.6Hz, 1H), 7.04 (s, 1H), 6.67 (t, J=4.8Hz, 1H), 5.01 (dd, J=14.0Hz and 3.6Hz, 1H), 3.29-3.26 (m, 1H), 3.21 (s, 6H), 2.91-2.86 (m, 2H)	450.1	5.48

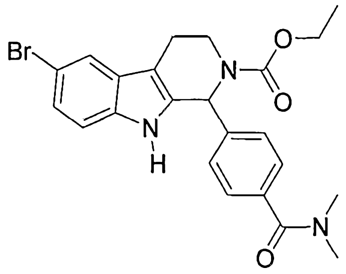
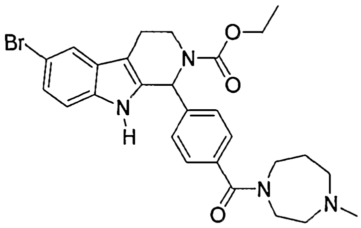
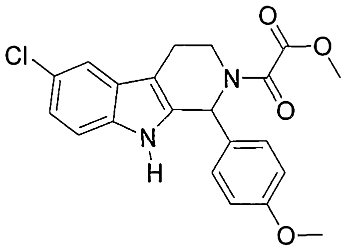
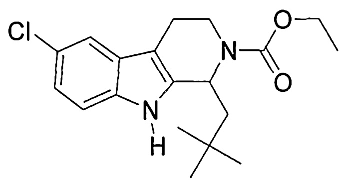
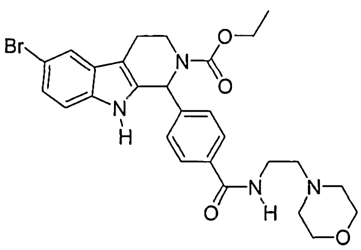
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **410**	(DMSO, 400MHz), δ 11.15, 11.05 (b, 1H), 7.53 (d, J=1.6Hz, 1H), 7.29 (d, J=8.8Hz, 1H), 7.20-7.18 (m, 6H), 7.06 (dd, J=8.8Hz and 2Hz, 1H), 6.93 (d, J=7.2Hz, 2H), 6.45-6.37 (m, 1H), 4.30 (b, 1H), 3.72 (s, 3H), 3.18 (b, 1H), 2.82 (b, 2H)	451.3	3.99
 HCl salt **416**	(CD3OD, 400MHz), δ 10.98 (b, 1H), 7.49 (d, J=2.0Hz, 1H), 7.34-7.30 (m, 5H), 7.25-7.21 (m, 1H), 7.13 (dd, J=8.8Hz and 2.0Hz, 1H), 4.81-4.79 (m, 1H), 3.82-3.76 (m, 1H), 3.54-3.49 (m, 1H), 3.11-3.07 (m, 2H), 2.91-2.87 (m, 2H), 2.59-2.55 (m, 1H), 2.24-2.20 (m, 1H)	311.1	4.39
 **420**	(CD3OD, 400MHz), δ 7.61 (s, 1H), 7.46 (d, J=8.0Hz, 2H), 7.38 (d, J=8.0Hz, 2H), 7.19 (s, 2H), 6.47 (s, 1H), 4.32-4.19 (m, 5H), 3.62 (t, J=3.9Hz, 2H), 3.42 (s, 1H), 3.19-3.10 (m, 3H), 2.29-2.76 (m, 2H), 1.30 (s, 3H)	486.6	3.45
 **425**	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.49 (d, J=8.4Hz, 2H), 7.42 (d, J=8.4Hz, 2H), 7.19 (s, 2H), 6.49 (b, 1H), 4.34-4.19 (m, 4H), 3.60 (b, 4H), 3.29-3.17 (m, 6H), 2.89-2.75 (m, 2H), 1.36 (t, J=7.2Hz, 3H), 1.30 (b, 3H)	539.2	3.11
 **431**	(CDCl3, 400MHz), δ 8.56 (b, 1H), 8.40 (b, 2H), 7.68 (s, 1H), 7.28 (d, J=2.0Hz, 1H), 7.14 (d, J=8.4Hz, 1H), 7.00 (d, J=9.2Hz, 2H), 6.80 (d, J=8.4Hz, 2H), 6.48-6.38 (m, 1H), 4.55-4.52 (m, 1H), 3.81-3.74 (m, 4H), 3.24 (s, 6H), 3.00-2.91 (m, 1H), 2.88-2.84 (m, 1H)	522.2	5.05

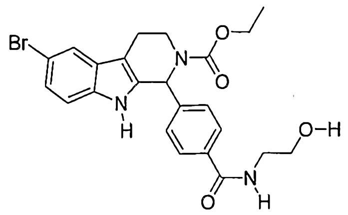
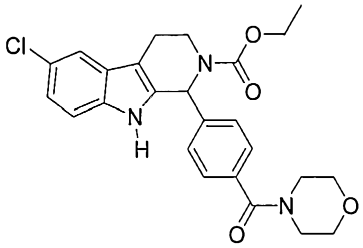
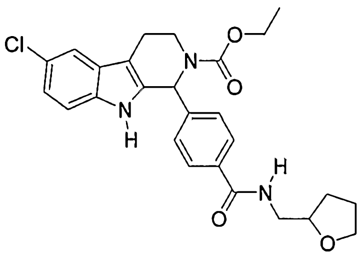
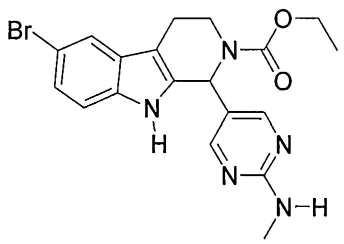
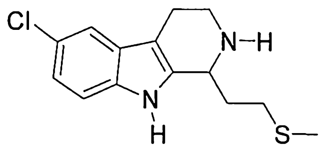
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **435**	(DMSO, 400MHz), δ 11.00 (s, 1H), 8.14 (s, 2H), 7.64 (s, 1H), 7.23 (d, J=8.4Hz, 1H), 7.18 (d, J=8.8Hz, 1H), 6.14 (s, 1H), 4.23 (b, 1H), 4.11-4.08 (m, 2H), 3.14-3.10 (m, 1H), 3.08 (s, 6H), 2.81-2.77 (m, 1H), 2.70-2.66 (m, 1H), 1.21 (t, J=6.8Hz, 3H)	444.3	3.95
 **438**	(CD3OD, 400MHz), δ 7.79 (d, J=8.4Hz, 2H), 7.63 (s, 1H), 7.37 (d, J=8.4Hz, 2H), 7.20 (s, 2H), 6.51 (b, 1H), 4.32-4.22 (m, 3H), 3.54 (s, 3H), 3.36 (s, 2H), 3.30 (s, 2H), 3.21-3.11 (m, 1H), 2.90-2.77 (m, 2H), 1.32 (s, 3H)	500.1	4.35
 **439**	(CDCl3, 400MHz), δ 7.98, 7.81 (s, 1H), 7.42 (s, 1H), 7.21 (d, J=8.4Hz, 1H), 7.11 (d, J=8.4Hz, 1H), 5.40-5.23 (m, 3H), 4.55-4.35 (m, 1H), 4.20-4.11 (m, 2H), 3.24-3.13 (m, 1H), 2.79-2.63 (m, 2H), 2.22 (d, J=6.8Hz, 2H), 2.08 (b, 2H), 1.89-1.81 (m, 2H), 1.30 (b, 3H), 0.97 (b, 3H)	361.2	5.95
 **441**	(CD3OD, 400MHz), δ 7.47 (d, J=1.6Hz, 1H), 7.43 (d, J=7.6Hz, 2H), 7.37 (d, J=8.0Hz, 2H), 7.24 (d, J=8.8Hz, 1H), 7.06 (dd, J=8.4Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.83 (s, 4H), 3.19-3.10 (m, 1H), 2.90-2.79 (m, 2H), 1.57 (b, 6H), 1.32 (s, 3H)	482.1	5.11
 **442**	(CDCl3, 400MHz), δ 8.48-8.09 (m, 1H), 7.44-7.42 (m, 1H), 7.24 (t, J=9Hz, 1H), 7.11-7.09 (m, 1H), 5.59-5.40 (m, 1H), 4.54-4.34 (m, 1H), 4.21-4.18 (m, 2H), 3.23-3.13 (m, 1H), 2.87-2.81 (m, 2H) , 2.76-263 (m, 1H), 2.17 (s, 3H), 2.12-1.90 (m, 2H), 1.42-1.24 (m, 6H)	367.1	2.92

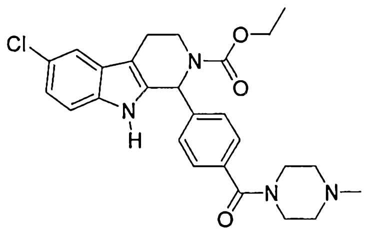
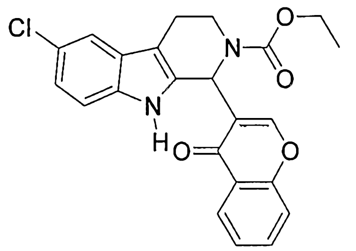
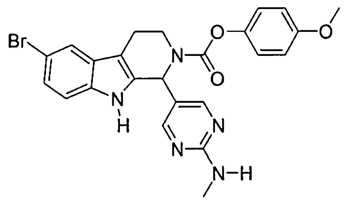
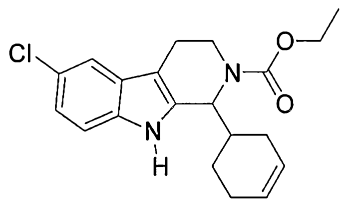
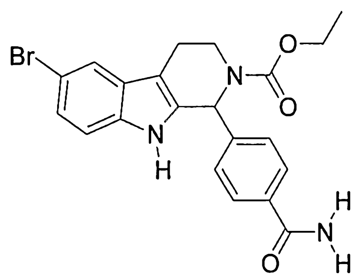
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **443**	(CD3OD, 400MHz), δ 8.62 (d, J=4.4Hz, 2H), 8.59 (s, 2H), 7.84 (s, 1H), 7.43-7.39 (m, 2H), 7.24 (s, 1H), 6.88 (t, J=8.0Hz, 1H), 5.24-5.20 (m, 1H), 3.47-3.44 (m, 1H), 3.16 (s, 3H), 3.11-3.05 (m, 2H)	436.2	5.25
 **447**	(CDCl3, 400MHz), δ 8.12 (s, 1H), 7.45 (s, 1H), 7.26 (d, J=8Hz, 2H), 7.18 (d, J=8.8Hz, 2H), 7.14-7.12 (m, 4H), 6.97 (s, 1H), 6.78 (d, J=8.8Hz, 2H), 3.89 (dd, J=14Hz and 1.2Hz, 1H), 3.80-3.78 (m, 5H), 3.41-3.33 (m, 1H), 2.73 (dd, J=15.2Hz and 3.2Hz, 1H), 2.64-2.60 (m, 1H)	464.9	5.11
 **453**	(CD3OD, 400MHz), δ 7.78 (d, J=8.0Hz, 2H), 7.47 (d, J=1.6Hz, 1H), 7.37 (d, J=8.0Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.06 (dd, J=8.8Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.31-4.05 (m, 8H), 3.20-3.11 (m, 1H), 3.00-2.77 (m, 4H), 1.94-1.90 (m, 2H), 1.54-1.45 (m, 2H), 1.31 (b, 3H), 1.25 (t, J=7.2Hz, 3H)	553.1	6.13
 **461**	(CD3OD, 400MHz), δ 7.80 (d, J=8.0Hz, 2H), 7.48 (d, J=1.6Hz, 1H), 7.38 (d, J=8.4Hz, 2H), 7.25 (d, J=8.8Hz, 1H), 7.07 (dd, J=8.4Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.31-4.21 (m, 4H), 4.06 (t, J=8.4Hz, 1H), 3.74 (t, J=8.0Hz, 1H), 3.51 (d, J=5.2Hz, 2H), 3.21-3.11 (m, 1H), 2.90-2.79 (m, 2H), 2.26 (s, 1H), 1.39 (s, 3H), 1.32 (s, 6H)	454.3	5.98

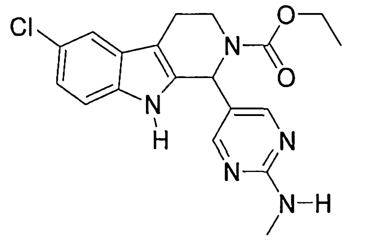
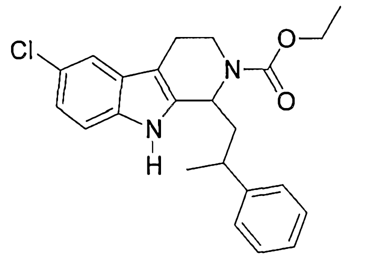
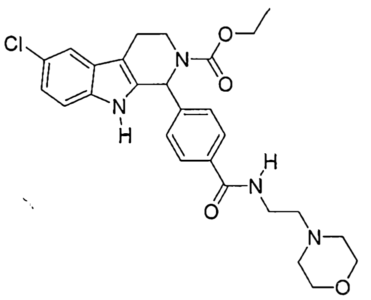
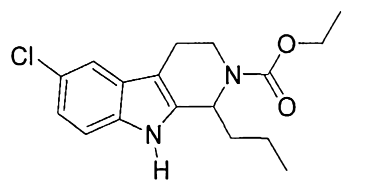
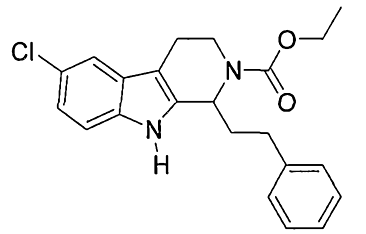
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 464	(CDCl3, 400MHz), δ 8.29 (b, 1H), 7.64 (d, J=8.0Hz, 2H), 7.61 (d, J=7.2Hz, 2H), 7.50-7.45 (m, 5H), 7.39 (d, J=7.6Hz, 1H), 7.33 (d, J=7.6Hz, 2H), 7.19 (d, J=8.8Hz, 1H), 7.14 (dd, J=8.4Hz and 1.6Hz, 1H), 7.08 (s, 1H), 6.84 (d, J=8Hz, 2H), 3.87 (d, J=9.2Hz, 1H), 3.79 (s, 3H), 3.45-3.40 (m, 1H), 2.96-2.94 (m, 1H), 2.80-2.76 (m, 1H)	493.0	5.71
 466	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.48 (d, J=8.4Hz, 2H), 7.42 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.33-4.22 (b, 3H), 3.89 (t, J=5.2Hz, 2H), 3.50 (b, 4H), 3.21-3.11 (m, 2H), 2.91-2.78 (m, 2H), 1.31 (s, 3H)	555.2	3.14
 469	(CD3OD, 400MHz), δ 7.47 (d, J=2.0Hz, 1H), 7.39 (s, 4H), 7.23 (d, J=8:8Hz, 1H), 7.06 (dd, J=8.4Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.75 (b, 2H), 3.53 (t, J=5.4Hz, 2H), 3.44 (b, 2H), 3.26-3.30 (m, 4H), 3.22-3.13 (m, 1H), 2.89-2.78 (m, 2H), 2.60 (t, J=5.4Hz, 4H), 2.46 (b, 2H), 1.32 (s, 3H)	525.2	5.07
 472	(CDCl3, 400MHz), δ 7.80, 7.75 (s 1H), 7.43, 7.41 (s, 1H), 7.21 (d, J=8.4Hz, 1H), 7.10 (d, J=8.0Hz, 1H), 5.43, 5.27 (d, J=7.2Hz, 1H), 4.51-4.30 (m, 1H), 4.21-4.10 (m, 2H), 3.18 (q, J=12.8Hz,1H), 2.82-2.76 (m, 1H) , 2.64-2.61 (m, 1H), 1.82-1.76 (m, 2H), 1.55-1.53 (m, 1H), 1.29-1.24 (m, 3H), 1.08 (b, 3H), 0.98 (d, J=6.8Hz, 3H)	335.3	5.52
 473	(CD3OD, 400MHz), δ 7.47 (d, J=2.0Hz, 1H), 7.39 (s, 4H), 7.23 (d, J=8.8Hz, 1H), 7.05 (dd, J=8.4Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.32-4.20 (m, 3H), 3.76 (b, 2H), 3.46 (b, 2H), 3.21-3.13 (m, 1H), 2.90-2.78 (m, 2H), 2.54 (b, 2H), 2.49-2.43 (m, 4H), 1.32 (b, 3H), 1.10 (t, J=7.2Hz, 3H)	495.3	4.68

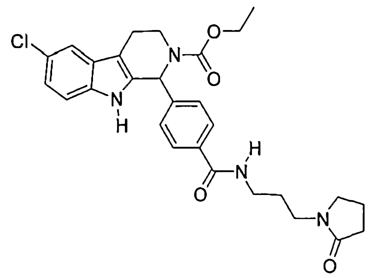
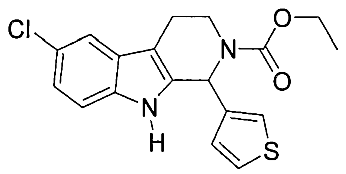
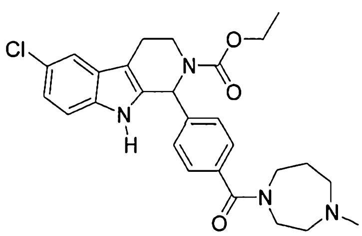
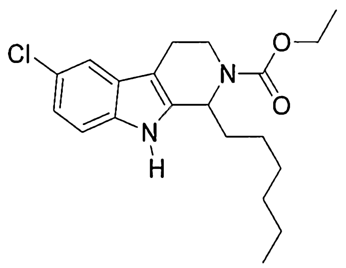
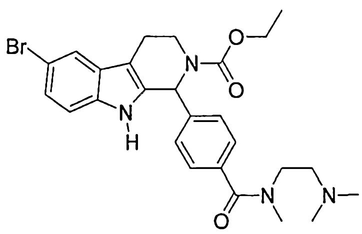
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **474**	((CD3OD, 400MHz), δ 7.61 (s, 1H), 7.44 (d, J=8.0Hz, 2H), 7.35 (d, J=8.0Hz, 2H), 7.20-7.16 (m, 2H), 6.45 (b, 1H), 4.28-4.14 (m, 3H), 4.11 (s, 2H), 3.47 (s, 4H), 3.26 (s, 4H), 3.19-3.12 (m, 1H), 2.91 (s, 3H), 2.88-2.79 (m, 2H), 1.30 (s, 3H)	511.2	4.99
 HCl salt **477**	(CD3OD, 400MHz) δ 7.48 (d, J=1.6Hz, 1H), 7.34 (d, J=8.4Hz, 1H), 7.12 (dd, J=8.8Hz and 2.0Hz, 1H), 4.68 (s, 1H), 3.77-3.72 (m, 1H), 3.47-3.44 (m, 1H), 3.10-3.03 (m, 2H), 2.65-2.61 (m, 1H), 1.25 (d, J=7.2Hz, 3H), 0.96 (d, J=7.2Hz, 3H)	249.1	3.67
 **478**	CD3OD, 400MHz), δ 7.63 (s, 1H), 7.48 (d, J=8.0Hz, 2H), 7.42 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.32-4.21 (m, 3H), 3.50 (b, 4H), 3.21-3.15 (m, 3H), 2.92 (s, 3H), 2.90-2.73 (m, 2H), 1.32 (s, 3H)	525.1	3.25
 **480**	(CD3OD, 400MHz), δ 7.78 (d, J=8.0Hz, 2H), 7.63 (s, 1H), 7.37 (d, J=8.4Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.31-4.22 (m, 3H), 3.19-3.11 (m, 1H), 2.90 (s, 3H), 2.86-2.77 (m, 2H), 1.32(s, 3H)	456.1	4.26
 **481**	(CD3OD, 400MHz), δ 7.48 (d, J=2Hz, 1H), 7.41-7.36 (m, 4H), 7.23 (d, J=8.4Hz, 1H), 7.06 (dd, J=8.8Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.64 (b, 2H), 3.45 (b, 2H), 3.20-3.11 (m, 1H), 2.92-2.78 (m, 2H), 2.68 (b, 2H), 2.55 (b, 2H), 1.92-1.80 (m, 4H), 1.66-1.62 (m, 1H), 1.32-1.22 (m, 8H)	549.3	5.29

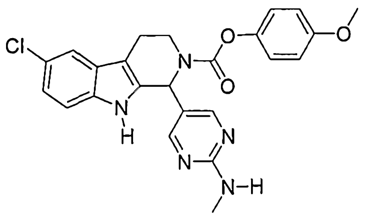
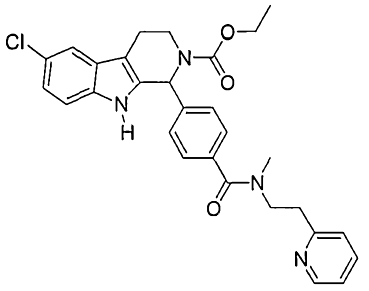
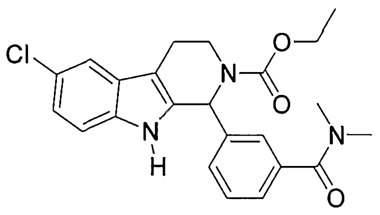
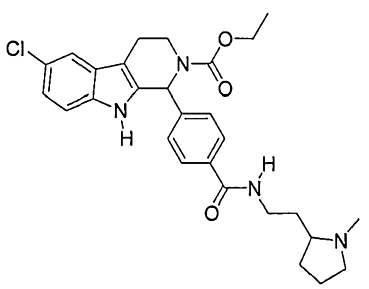
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **483**	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.41 (d, J=8.4Hz, 2H), 7.37 (d, J=8.0Hz, 2H), 7.19 (s, 2H), 6.49 (b, 1H), 4.35-4.22 (m, 3H), 3.22-3.13 (m, 1H), 3.08 (s, 3H), 2.98 (s, 3H), 2.89-2.77 (m, 2H), 1.32(s, 3H)	470.1	4.46
 **484**	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.48 (d, J=7.2Hz, 2H), 7.40 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.35-4.22 (m, 4H), 3.82-3.50 (m, 6H), 3.45 (b, 1H), 3.21-3.11 (m, 1H), 3.00-2.78 (m, 5H), 2.25-2.15 (m, 2H), 1.32 (s, 3H)	539.2	3.02
 **485**	(CDCl3, 400MHz), δ 8.06 7.98 (s, 1H), 7.50, 7.49 (s, 1H), 7.22 (d, J=6.0Hz, 1H), 7.21 (d, J=6.4Hz, 2H), 7.15 (dd, J=8.8Hz and 1.6Hz, 1H), 6.81 (d, J=8.4Hz, 2H), 6.77 (s, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.72 (d, J=5.2Hz, 1H), 3.51-3.43 (m, 1H), 3.02-2.96 (m, 1H), 2.86-2.81 (m, 1H)	398.9	4.18
 **486**	(CDCl3, 400MHz), δ 7.77, 7.70 (s, 1H), 7.42, 7.39 (s, 1H), 7.20 (dd, J=8.4Hz and 1.6Hz, 1H), 7.09 (d, J=8.0Hz, 1H), 5.52-5.36 (m, 1H), 4.44-4.17 (m, 3H), 3.28-3.20 (m, 1H), 2.88-2.77 (m, 1H), 2.60 (d, J=15.2Hz, 1H), 2.05-1.88 (m, 1H), 1.58-1.54 (m, 1H), 1.30-1.26 (m, 3H), 1.04 (d, J=2Hz, 9H)	349.1	6.03
 **488**	(CD3OD, 400MHz), δ 7.85 (d, J=8.0Hz, 2H), 7.64 (s, 1H), 7.41 (d, J=8.4Hz, 2H), 7.20 (s, 2H), 6.52 (b, 1H), 4.33-4.22 (b, 3H), 4.07 (b, 2H), 3.77 (t, J=5.6Hz, 4H), 3.65 (b, 2H), 3.39 (t, J=5.6Hz, 2H), 3.21-3.11 (m, 3H), 2.91-2.78 (m, 2H), 1.32 (s, 3H)	555.2	3.34

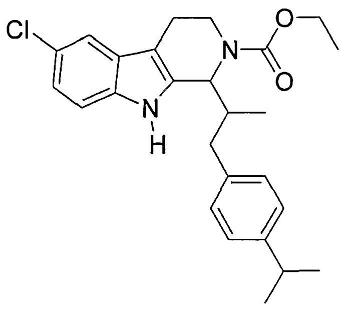
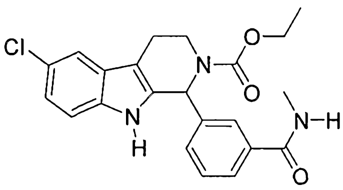
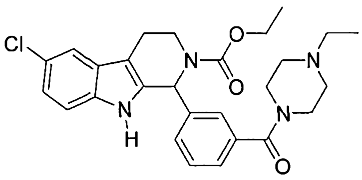
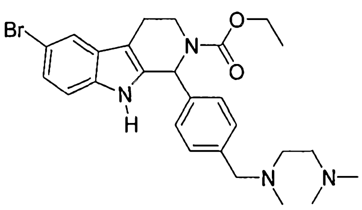
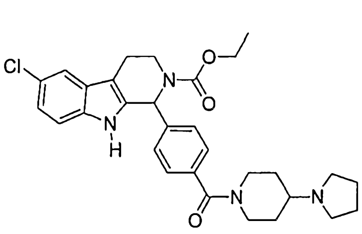
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 490	(CD3OD, 400MHz), δ 7.81 (d, J=8.4Hz, 2H), 7.63 (s, 1H), 7.37 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.51 (b, 1H), 4.32-4.22 (m, 3H), 3.69 (t, J=5.8Hz, 2H), 3.48 (t, J=5.6Hz, 2H), 3.21-3.11 (m, 1H), 2.90-2.77 (m, 2H), 1.32 (s, 3H)	486.1	3.80
 492	(CD3OD, 400MHz), δ 7.47 (s, 1H), 7.41-7.38 (m, 4H), 7.23 (d, J=8.8Hz, 1H), 7.06 (dd, J=8.8Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.73-3.62 (m, 6H), 3.44 (b, 2H), 3.19-3.10 (m, 1H), 2.91-2.78 (m, 2H), 1.32 (b, 3H)	468	5.52
 494	(DMSO, 400MHz), δ 11.19 (b, 1H), 8.49 (b, 1H), 7.81 (d, J=8.0Hz, 2H), 7.51 (d, J=1.6Hz, 1H), 7.30 (d, J=8.4Hz, 2H), 7.29 (d, J=14.0Hz, 1H), 7.07 (dd, J=8.4Hz and 1.6Hz, 1H), 6.39 (b, 1H), 4.21-4.16 (m, 3H), 3.93 (t, J=6.4Hz, 1H), 3.74 (q, J=6.8Hz, 1H), 3.59 (q, J=6.8Hz, 1H), 3.28 (s, 2H), 3.08-3.01 (m, 1H), 2.81-2.70 (m, 2H), 1.91-1.79 (m, 3H), 1.59-1.52 (m, 1H), 1.21 (s, 3H)	482.2	5.74
 496	(CD3OD, 400MHz), δ 11.05 (s, 1H), 8.09 (s, 2H), 7.64 (s, 1H), 7.32 (b, 1H), 7.24 (d, J=8.4Hz, 1H), 7.17 (dd, J=8.8Hz and 2.0Hz, 1H), 6.24 (s, 1H), 4.22 (b, 1H), 4.12-4.09 (m, 2H), 3.15-3.09 (m, 1H), 2.83-2.65 (m, 5H), 1.21 (t, J=6.8Hz, 3H)	430.2	3.65
 HCl salt 497	(CD3OD, 400MHz), δ 7.49 (d, J=1.6Hz, 1H), 7.34 (d, J=8.8Hz, 1H), 7.13 (dd, J=8.8Hz and 2.0Hz, 1H), 3.77-3.72 (m, 1H), 3.52-3.45 (m, 1H), 3.15-3.01 (m, 2H), 2.80-2.74 (m, 2H), 2.60-2.52 (m, 1H), 2.27-2.20 (m, 4H)	281.0	3.84

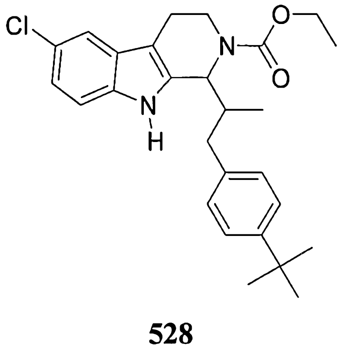
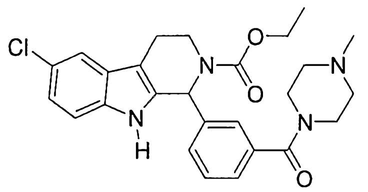
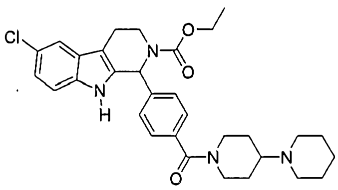
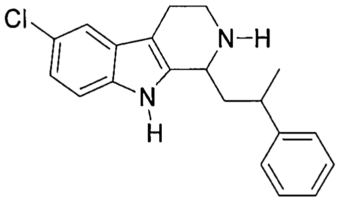
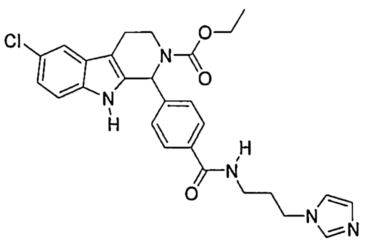
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 498	(CDCl3, 400MHz), δ 8.35 (b, 1H), 7.51 (s, 1H), 7.32-7.26 (m, 4H), 7.20 (d, J=8.4Hz, 1H), 7.13 (dd, J=8.8Hz and 2.4Hz, 1H), 6.39 (b, 1H), 4.25-4.21 (m, 2H), 3.80 (b, 2H), 3.47 (b, 2H), 3.16-3.10 (m, 1H), 2.96-2.88 (m, 3H), 2.79-2.75 (m, 1H), 2.54-2.36 (m, 6H), 1.32 (s, 3H)	481.4	4.81
 499	(DMSO, 400MHz), δ 10.86 (s, 1H), 8.17 (s, 1H), 8.03 (d, J=7.6Hz, 1H), 7.81 (t, J=8.0Hz, 1H), 7.65 (d, J=8.4Hz, 1H), 7.50 (b, 2H), 7.26 (d, J=8.4Hz, 1H), 7.02 (d, J=8.8Hz, 1H), 6.24 (s, 1H), 4.35 (b, 1H), 4.09-4.05 (m, 2H), 3.61-3.49 (m, 1H), 2.78-2.65 (m, 2H), 1.45(t, J=6.8Hz, 3H)	423.3	5.15
 503	(CD3OD, 400MHz), δ 8.33 (s, 2H), 7.67 (s, 1H), 7.23 (s, 2H), 7.05 (d, J=8.4Hz, 2H), 6.91 (d, J=8.8Hz, 2H), 6.54-6.38 (m, 1H), 4.52 (b, 1H), 3.78 (s, 3H), 3.36-3.34 (m, 1H), 2.99 (s, 3H), 2.92-2.88 (m, 2H)	508.2	5.72
 504	(CDCl3, 400MHz), δ 7.88-7.77 (m, 1H), 7.43 (d, J=8.0Hz, 1H), 7.23 (d, J=8.8Hz, 1H), 7.11 (d, J=8.8Hz 1H), 5.70-7.68 (m, 2H), 5.19-4.97 (m, 1H), 4.60-4.38 (m, 1H), 4.19-4.07 (m, 2H), 2.82-2.80 (m, 1H), 2.68-2.64 (m, 1H), 2.29-1.84 (m, 6H), 1.55-1.46 (m, 1H), 1.36-1.24 (m, 3H)	359.1	5.65
 505	(CD3OD, 400MHz), δ 7.84 (d, J=8.0Hz, 2H), 7.63 (s, 1H), 7.38 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.31-4.22 (m, 3H), 3.19-3.11 (m, 1H), 2.89-2.77 (m, 2H), 1.32(s, 3H)	442.0	4.06

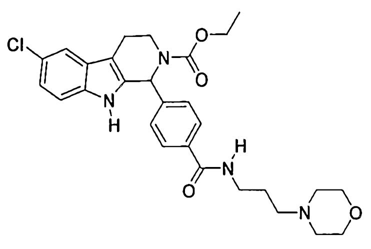
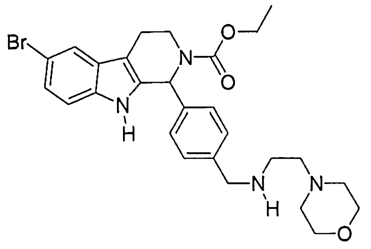
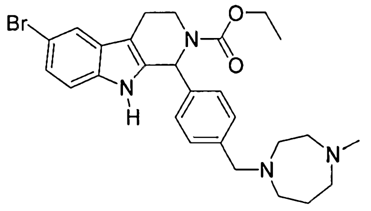
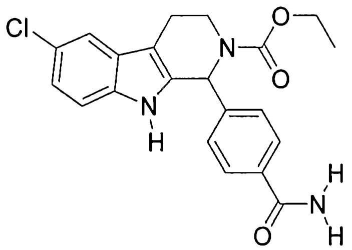
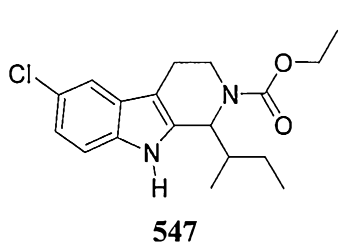
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 506	(CD3OD, 400MHz), δ 8.44 (s, 2H), 7.67 (d, J=2.0Hz, 1H), 7.44 (d, J=8.8Hz, 1H), 7.28 (dd, J=8.8Hz and 2.0Hz, 1H), 6.52 (s, 1H), 4.58-4.55 (m, 1H), 4.43-4.40 (m, 2H), 3.41-3.31 (m, 1H), 3.15 (s, 3H), 3.03-3.01 (m, 2H), 1.32 (b, 3H)	386.3	5.32
 508	(CDCl3, 400MHz), δ 7.66 (d, J=24.8Hz, 1H), 7.39-6.89 (m, 8H), 5.44-5.02 (m, 1H), 4.49-4.10 (m, 3H), 3.23-2.94 (m, 2H), 2.83-2.74 (m, 1H), 2.64-2.58 (m, 1H), 2.26-1.98 (m, 2H), 1.47-1.26 (m, 6H)	397.1	5.97
 509	(CD3OD, 400MHz), δ 7.80 (d, J=8.4Hz, 2H), 7.47 (d, J=1.6Hz, 1H), 7.38 (d, J=8.0Hz, 2H), 7.24 (d, J=8.8Hz, 1H), 7.07 (dd, J=8.0Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.69 (t, J=4.6Hz, 4H), 3.53 (t, J=6.8Hz, 2H), 3.19-3.10 (m, 1H), 2.90-2.78 (m, 2H), 2.59 (t, J=6.6Hz, 4H), 2.53 (s, 2H), 1.32 (s, 3H)	511.4	5.05
 510	(CDCl3, 400MHz), δ 8.09, 7.83 (s, 1H), 7.42 (s, 1H), 7.21 (d, J=8.4Hz, 1H), 7.09 (dd, J=8.4Hz and 1.2Hz, 1H), 5.33-5.21 (m, 1H), 4.50-4.34 (m, 1H), 4.21-4.10 (m, 2H), 3.19-3.17 (m, 1H), 2.77-2.74 (m, 1H), 2.67-2.61 (m, 1H), 1.81 (s, 2H), 1.52 (s, 2H), 1.29-1.23 (m, 3H), 0.96 (s, 3H)	321.4	5.19
 511	(CDCl3, 400MHz), δ 7.73-7.52 (m, 1H), 7.47 (s, 1H), 7.42-7.18 (m, 6H), 7.09 (dd, J=8.8Hz and 2.0Hz, 1H), 5.41-5.26 (m, 1H), 4.56-4.32 (m, 1H), 4.23-4.10 (m, 2H), 3.21 (b, 1H), 2.85-2.72 (m, 3H), 2.65 (d, J=14.2Hz, 1H) , 2.23-2.10 (m, 2H), 1.38 (b, 3H)	383.1	5.75

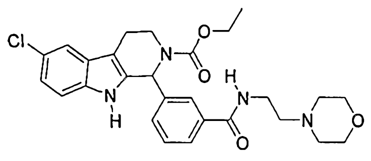
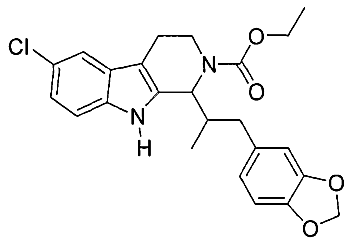
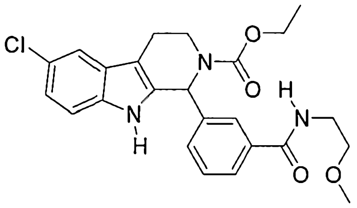
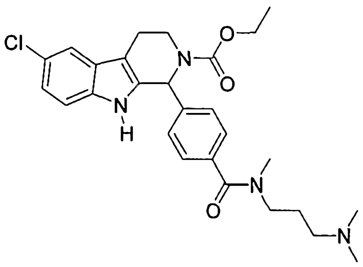
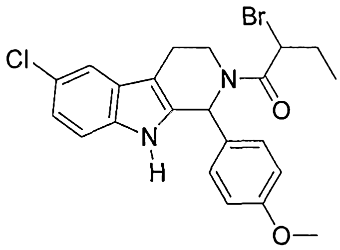
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **512**	(CD3OD, 400MHz), δ 7.80 (d, J=8.4Hz, 2H), 7.47 (d, J=1.6Hz, 1H), 7.37 (d, J=8.0Hz, 2H), 7.24 (d, J=8.8Hz, 1H), 7.06 (dd, J=8.8Hz and 2.0Hz, 1H), 6.50 (b, 1H), 4.32-4.21 (m, 3H), 3.47 (t, J=7.2Hz, 2H), 3.38-3.34 (m, 4H), 3.19-3.10 (m, 1H), 2.89-2.78 (m, 2H), 2.39 (t, J=8.4Hz, 2H), 2.09-2.00 (m, 2H), 1.86-1.80 (m, 2H), 1.32 (b, 3H)	523.1	5.69
 **513**	(CDCl3, 400MHz), δ 7.81 (s, 1H), 7.51 (d, J=6.8Hz, 1H), 7.29 (dd, J=12.0Hz and 2.8Hz, 1H), 7.21 (d, J=8.4Hz, 1H), 7.13 (dd, J=8.4Hz and 2.0Hz, 1H), 7.12-7.08 (m, 1H), 7.07 (s, 1H), 6.50 (b, 1H), 4.49-4.21 (m, 3H), 3.17-3.09 (m, 1H), 2.91-2.85 (m, 1H), 2.77-2.73 (m, 1H), 1.39 (s, 3H)	361.1	5.12
 **514**	(CD3OD, 400MHz), δ 7.47 (d, J=2.0Hz, 1H), 7.46-7.37 (m, 4H), 7.23 (d, J=8.4Hz, 1H), 7.06 (dd, J=8.8Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.77-3.69 (m, 2H), 3.55-3.45 (m, 2H), 3.20-3.11 (m, 1H), 2.90-2.78 (m, 3H), 2.67-2.55 (m, 3H), 2.39-2.31 (m, 3H), 2.01-1.95 (m, 1H), 1.82-1.79 (m, 1H), 1.32 (s, 3H)	495.3	4.67
 **515**	(CDCl3, 400MHz), δ 7.92, 7.82 (s, 1H), 7.42 (s, 1H), 7.22 (dd, J=8.4Hz and 1.2Hz, 1H), 7.10 (d, J=8.8Hz, 1H), 5.31, 5.19 (s, 1H), 4.52, 4.32 (d, J=10.8Hz, 1H), 4.20-4.12 (m, 2H), 3.19-3.12 (m, 1H), 2.81-2.62 (m, 2H), 1.81 (d, J=6.8Hz, 2H), 1.48-22 (m, 12H), 0.88 (s, 3H)	363.5	6.34
 **516**	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.50 (d, J=8.0Hz, 2H), 7.40 (d, J=8.0Hz, 2H), 7.20 (s, 2H), 6.49 (b, 1H), 4.30-4.20 (m, 3H), 3.89 (s, 2H), 3.45 (b, 2H), 3.20-3.10 (m, 1H), 3.03-3.01 (m, 9H), 2.91-2.80 (m, 2H), 1.32 (s, 3H)	527.1	3.16

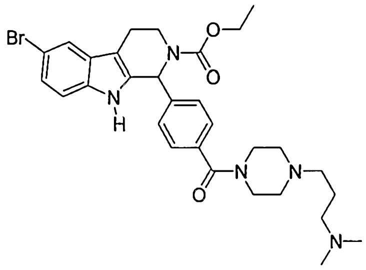
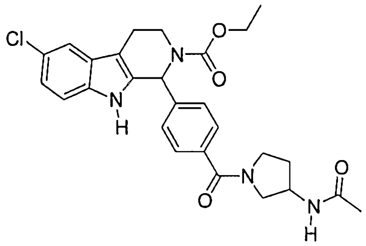
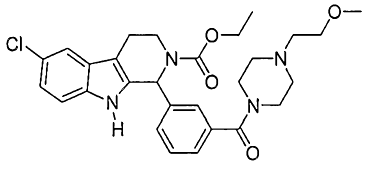
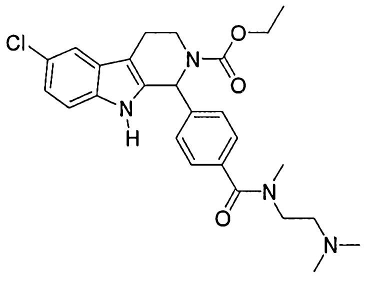
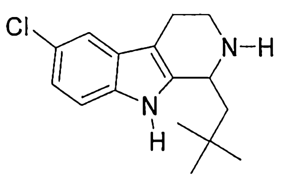
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 517	(CD3OD, 400MHz), δ 8.27 (s, 2H), 7.52 (d, J=2Hz, 1H), 7.27 (d, J=8.8Hz, 1H), 7.17 (d, J=8.8Hz, 1H), 7.10 (dd, J=8.8Hz and 2.4Hz, 1H), 7.05 (d, J=8.8Hz, 2H), 6.95 (d, J=9.2Hz, 2H), 6.92 (s, 1H), 6.58-6.38 (m, 1H), 4.52 (b, 1H), 3.80 (s, 1H), 3.79 (s, 3H), 3.31-3.30 (m, 1H), 2.95 (s, 3H), 2.92-2.88 (m, 1H)	464.2	5.86
 518	(CD3OD, 400MHz), δ 8.49, 8.29 (d, J=4.4Hz, 2.8Hz, 1H), 7.82, 7.70 (t, J=2.0Hz, 1H), 7.46 (s, 1H), 7.38-7.23 (m, 5H), 7.15 (d, J=7.6Hz, 1H), 7.07 (d, J=8.4Hz, 1H), 6.98 (d, J=6.8Hz, 1H), 6.46 (b, 1H), 4.35-4.21 (m, 3H), 3.88 (t, J=7.0Hz, 1H), 3.71-3.67 (m, 1H), 3.20-3.11 (m, 3H), 3.01-2.80 (m, 4H), 1.32 (s, 3H)	517.6	5.03
 520	(DMSO, 400MHz), δ 11.15 (s, 1H), 7.51 (d, J=2.0Hz, 1H), 7.42 (t, J=7.6Hz, 1H), 7.35 (d, J=7.6Hz, 1H), 7.30 (d, J=8.8Hz, 2H), 7.16 (s, 1H), 7.06 (dd, J=8.4Hz and 2.0Hz, 1H), 6.36 (b, 1H), 4.18-4.10 (m, 3H), 3.09-3.00 (m, 1H), 2.91-2.64 (m, 8H), 1.21 (t, J=6.6Hz, 3H)	426.2	4.29
 521	(CD3OD, 400MHz), δ 7.81 (d, J=8.4Hz, 2H), 7.47 (d, J=1.6Hz, 1H), 7.39 (d, J=8.4Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.07 (dd, J=8.4Hz and 2.0Hz, 1H), 6.50 (b, 1H), 4.35-4.29 (m, 3H), 3.70-3.60 (m, 1H), 3.51-3.47 (m, 2H), 3.37-3.29 (m, 1H), 3.19-3.11 (m, 2H), 2.92 (s, 3H), 2.88-2.78 (m, 2H), 2.51-2.41 (m, 1H), 2.29-2.20 (m, 1H), 2.17-2.00 (m, 2H), 1.89-1.78 (m, 2H), 1.32 (s, 3H)	509.4	4.99

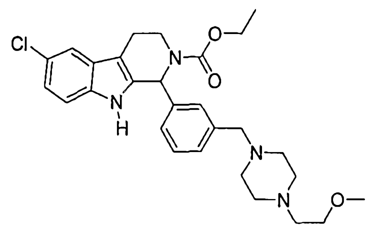
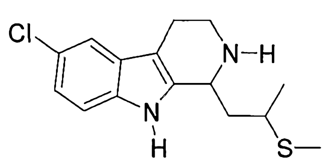
Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **523**	(CDCl3, 400MHz), δ 7.91,7.72 (s, 1H), 7.50-7.43 (s, 1H), 7.22-7.06 (m, 6H), 5.28-5.19 (m, 1H), 4.64-4.45 (m, 1H), 4.20 (b, 2H), 3.27-3.10 (m, 2H), 2.91-2.72 (m, 2H), 2.70-2.66 (m, 1H), 2.49-2.28 (m, 2H), 1.38-1.24 (m, 9H), 1.01, 0.96 (d, J=6.8Hz, 3H)	439.0	6.11
 **524**	(DMSO, 400MHz), δ 11.10 (s, 1H), 8.42 (s, 1H), 7.75 (d, J=7.2Hz, 1H), 7.67 (s, 1H), 7.51 (d, J=1.6Hz, 1H), 7.43 (t, J=7.2Hz, 1H), 7.35 (d, J=8.0Hz, 1H), 7.29 (d, J=8.4Hz, 1H), 7.06 (dd, J=8.8Hz and 2.4Hz, 1H), 6.39 (b, 1H), 4.13-4.09 (m, 3H), 3.10-3.04 (m, 1H), 2.81-2.72 (m, 5H), 1.21 (s, 3H)	412.1	4.13
 **525**	(CD3OD, 400MHz), δ 7.53-7.46 (m, 4H), 7.29 (b, 1H), 7.25 (d, J=8.8Hz, 1H), 7.08 (dd, J=8.8Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.34-4.23 (m, 3H), 3.53-3.42 (m, 2H), 3.18-3.12 (m, 5H), 2.91-2.74 (m, 3H), 1.32 (t, J=7.2Hz, 6H)	4.95.3	3.46
 **526**	(CD3OD, 400MHz), δ 7.63 (s, 1H), 7.51 (d, J=8.0Hz, 2H), 7.41 (d, J=8.4Hz, 2H), 7.19 (d, J=1.2Hz, 2H), 6.46 (b, 1H), 4.31 (s, 2H), 4.23-4.20 (m, 3H), 3.62-3.50 (m, 4H), 3.19-3.11 (m, 1H), 2.92 (s, 6H), 2.87-2.81 (m, 2H), 2.76 (s, 3H), 1.31 (s, 3H)	513.2	4.43
 **527**	(CD3OD, 400MHz), δ 7.47 (d, J=2Hz, 1H), 7.46-7.37 (m, 4H), 7.24 (d, J=8.8Hz, 1H), 7.07 (d, J=8.8Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.75 (b, 1H), 4.35-4.21 (m, 3H), 3.85 (b, 1H), 3.64 (b, 2H), 3.45-3.37 (m, 1H), 3.19-3.12 (m, 4H), 2.91-2.80 (m, 3H), 2.28-2.00 (m, 6H), 2.12-2.05 (m, 2H), 1.61 (b, 2H), 1.32 (s, 3H)	535.3	4.94

Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 **528**	(CDCl3, 400MHz), δ 7.89-7.69 (m, 1H), 7.43 (b, 1H), 7.33-7.30 (m, 2H), 7.20-7.06 (m, 4H), 5.29-5.19 (m, 1H), 4.64-4.45 (m, 1H), 4.20 (b, 2H), 3.27-3.10 (m, 2H), 2.91-2.72 (m, 2H), 2.70-2.66 (m, 1H), 2.50 (b, 2H), 2.29 (b, 1H), 1.32-1.31 (m, 12H), 1.02, 0.90 (d, J=6.8Hz, 3H)	453.0	6.30
 **529**	(CD3OD, 400MHz), δ 7.52-7.45 (m, 4H), 7.31 (b, 1H), 7.25 (d, J=8.4Hz, 1H), 7.08 (dd, J=8.4Hz and 2.0Hz, 1H), 6.48 (b, 1H), 4.34-4.23 (m, 3H), 3.45 (b, 3H), 3.23-3.13 (m, 4H), 2.92-2.80 (m, 5H), 1.32 (s, 3H)	481.3	3.43
 **531**	(CD3OD, 400MHz) δ 7.48 (d, J=1.6Hz, 1H), 7.43 (d, J=8.4Hz, 2H), 7.40 (d, J=8.4Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.07 (dd, J=8.4Hz and 2.0Hz, 1H), 6.50 (b, 1H), 4.35-4.29 (m, 3H), 3.90 (b, 1H), 3.52-3.47 (m, 3H), 3.20-3.16 (m, 2H), 3.01 (t, J=12.0Hz, 2H), 2.91-2.79 (m, 3H), 2.20 (b, 1H), 2.00-1.97 (m, 3H), 1.82-1.71 (m, 6H), 1.56-1.48 (m, 1H), 1.32 (b, 3H)	549.6	5.21
 HCl salt **532**	(DMSO, 400MHz), δ 11.39 (s, 1H), 9.80 (b, 1H), 9.40 (b, 1H), 7.52 (d, J=1.6Hz, 1H), 7.48 (s, 1H), 7.37-7.31 (m, 4H), 7.25-7.19 (m, 1H), 7.00 (dd, J=8.8Hz and 2Hz, 1H), 4.76 (d, J=5.6Hz, 1H), 3.61-3.53 (m, 1H), 3.25-3.20 (m, 1H), 2.94-2.92 (m, 2H), 2.13-1.97 (m, 1H), 1.35, 1.24 (d, J= 6.8Hz, 3H)	325.3	4.75
 **533**	(CD3OD, 400MHz), δ 8.99 (s, 1H), 7.80 (d, J=8.0Hz, 2H), 7.71 (d, J=1.2Hz, 1H), 7.57 (s, 1H), 7.47 (d, J=1.6Hz, 1H), 7.39 (d, J=8.0Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.07 (d, J=8.0Hz, 1H), 6.51 (b, 1H), 4.32 (t, J=4.8Hz, 3H), 4.23-4.21 (m, 2H), 3.43 (t, J=6.4Hz, 2H), 3.20-3.11 (m, 1H), 2.91-2.78 (m, 2H), 2.23-2.17 (m, 2H), 1.32 (b, 3H)	506.2	4.96

Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 534	(CD3OD, 400MHz), δ 7.79 (d, J=8.4Hz, 2H), 7.48 (s, 1H), 7.38 (d, J=8.0Hz, 2H), 7.25 (d, J=8.8Hz, 1H), 7.07 (dd, J=8.4Hz and 2.0Hz, 1H), 6.51 (b, 1H), 4.35-4.21 (m, 3H), 3.67 (t, J=4.6Hz, 4H), 3.41 (q, J=4.8Hz, 2H), 3.20-3.11 (m, 1H), 2.91-2.79 (m, 2H), 2.62 (s, 1H), 2.46-2.42 (m, 5H), 1.83-1.79 (m, 2H), 1.32 (s, 3H)	525.2	4.76
 535	(CD3OD, 400MHz), δ 7.62 (s, 1H), 7.49 (d, J=8.0Hz, 2H), 7.39 (d, J=8.4Hz, 2H), 7.19 (s, 2H), 6.48 (s, 1H), 4.27-4.18 (m, 5H), 3.87 (t, J=4.6Hz, 4H), 3.47 (t, J=6.8Hz, 2H), 3.34-3.30 (m, 2H), 3.16-3.12 (m, 5H), 2.89-2.75 (m, 2H), 1.30 (s, 3H)	541.2	3.51
 541	(CD3OD, 400MHz), δ 7.60 (s, 1H), 7.51 (d, J=8.0Hz, 2H), 7.40 (d, J=8.0Hz, 2H), 7.21-7.16 (m, 2H), 6.46 (b, 1H), 4.41 (s, 2H), 4.28-4.19 (m, 3H), 3.79-3.74 (m, 4H), 3.51-3.49 (m, 4H), 3.19-3.11 (m, 1H), 2.95 (s, 3H), 2.88-2.75 (m, 2H), 2.30 (s, 2H), 1.30 (s, 3H)	525.2	4.42
 542	(CD3OD, 400MHz), δ 7.84 (d, J=8.0Hz, 2H), 7.47 (d, J=2.0Hz, 1H), 7.37 (d, J=8.4Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.06 (dd, J=8.4Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.35-4.16 (m, 3H), 3.21-3.10 (m, 1H), 2.90-2.71 (m, 2H), 1.32 (b, 3H)	398.1	3.95
 547	(CDCl3, 400MHz), δ 7.92-7.77 (m, 1H), 7.42-7.39 (m, 8H), 7.26-7.21 (m, 1H), 7.10 (d, J=8.4Hz, 1H), 5.16-4.97 (m, 1H), 4.56-4.36 (m, 1H), 4.19-4.11 (m, 2H), 3.27-3.19 (m, 1H), 2.78-2.63 (m, 2H), 1.90 (d, J=5.6Hz, 1H), 1.74 (b, 1H), 1.49-1.26 (m, 4H), 1.10-0.91 (m, 6H)	335.2	5.45

Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 552	(CD3OD, 400MHz), δ 7.82 (s, 1H), 7.80 (s, 1H), 7.55-7.48 (m, 3H), 7.23 (d, J=8.4Hz, 1H), 7.07 (dd, J=8.4Hz and 2.0Hz, 1H), 6.49 (b, 1H), 4.33-4.21 (m, 3H), 4.05 (b, 2H), 3.5-3.73 (m, 4H), 3.61 (b, 2H), 3.37 (t, J=5.8Hz, 2H), 3.25-3.17 (m, 3H), 2.92-2.80 (m, 2H), 1.32 (s, 3H)	511.3	3.56
 553	(CDCl3, 400MHz), δ 8.01, 7.91 (s, 1H), 7.43 (s, 1H), 7.23 (d, J=8.4Hz, 1H), 7.11 (d, J=7.2Hz, 1H), 6.71 (d, J=7.6Hz, 1H), 6.63 (s, 1H), 6.57 (d, J=7.6Hz, 1H), 5.92 (s, 2H), 5.18-5.07 (m, 1H), 4.63-4.41 (m, 1H), 4.30-4.11 (m, 2H), 3.36-3.31 (m, 1H), 2.91-2.83 (m, 2H), 2.70-2.61 (m, 1H), 2.38-2.15 (m, 2H), 1.38-1.30 (m, 3H), 1.09-1.01 (m, 3H)	440.9	5.75
 556	(CD3OD, 400MHz), δ 7.76 (s, 1H), 7.75 (s, 1H), 7.52-7.43 (m, 2H), 7.23 (d, J=8.4Hz, 1H), 7.06 (d, J=7.6Hz, 1H), 6.47 (b, 1H), 4.30-4.21 (m, 3H), 3.52 (s, 4H), 3.33 (s, 3H), 3.26-3.18 (m, 1H), 2.91-2.80 (m, 2H), 1.32 (s, 3H)	456.1	4.21
 558	(CD3OD, 400MHz), δ 7.48 (s, 1H), 7.46 (d, J=8.8Hz, 2H), 7.40 (d, J=7.6Hz, 2H), 7.24 (d, J=8.4Hz, 1H), 7.07 (d, J=8.0Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.64-3.61 (m, 2H), 3.20-3.11 (m, 3H), 3.01 (s, 3H), 2.93 (s, 5H), 2.89-2.78 (m, 3H), 2.12-2.05 (m, 2H), 1.32 (s, 3H)	497.2	4.69
 559	(CDCl3, 400MHz), δ 8.17, 8.00 (s, 1H), 7.50 (s, 1H), 7.23-7.13 (m, 4H), 6.97, 6.92 (s, 1H), 6.80 (d, J=8.4Hz, 2H), 4.43, 4.34 (t, J=7.0Hz, 1H), 4.04-3.98 (m, 1H), 3.77 (s, 3H), 3.47-3.41 (m, 1H), 3.25-2.81 (m, 2H), 2.23-2.06 (m, 2H), 1.02 (t, J=6.2Hz, 3H)	460.8	4.96

Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 560	(DMSO, 300MHz), δ 7.63 (s, 1H), 7.49 (d, J=6.3Hz, 2H), 7.42 (d, J=6.0Hz, 2H), 7.20 (s, 2H), 6.49 (s, 1H), 4.32-4.21 (m, 3H), 3.85 (b, 4H), 3.39-3.30 (m, 3H), 3.26-3.15 (m, 5H), 2.92-2.73 (m, 9H), 2.26-2.20 (m, 2H), 1.31 (s, 3H)	596.3	4.45
 561	(CD3OD, 400MHz), δ 7.52 (d, J=8.4Hz, 2H), 7.47 (s, 1H), 7.39-7.36 (m, 2H), 7.24 (d, J=8.8Hz, 1H), 7.06 (dd, J=8.4Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.45-4.23 (m, 4H), 3.84-3.45 (m, 4H), 3.20-3.12 (m, 1H), 2.91-2.78 (m, 2H), 2.25-2.10 (m, 1H), 1.98-1.89 (m, 4H), 1.32 (s, 3H)	509.2	5.18
 562	(CD3OD, 400MHz), δ 7.52-7.45 (m, 4H), 7.32 (b, 1H), 7.25 (d, J=8.4Hz, 1H), 7.08 (dd, J=8.4Hz and 1.6Hz, 1H), 6.49 (b, 1H), 4.34-4.23 (m, 4H), 3.69 (s, 3H), 3.31-3.30 (m, 8H), 3.21-3.12 (m, 3H), 2.91-2.74 (m, 2H), 1.32 (s, 3H)	525.3	3.52
 563	(CD3OD, 400MHz), δ 7.51-7.48 (m, 3H), 7.40 (d, J=8.0Hz, 2H), 7.24 (d, J=8.8Hz, 1H), 7.07 (dd, J=8.4Hz and 1.2Hz, 1H), 6.49 (b, 1H), 4.35-4.21 (m, 3H), 3.89 (b, 2H), 3.45 (b, 2H), 3.19-3.10 (m, 1H), 3.05-3.01 (m, 9H), 2.91-2.78 (m, 2H), 1.32 (b, 3H)	483.1	4.96
 565	(CD3OD, 400MHz), δ 7.47 (d, J=1.6Hz 1H), 7.35 (d, J=8.4Hz, 1H), 7.12 (dd, J=8.4Hz and J=2.0Hz, 1H), 4.87 (s, 1H), 3.75-3.72 (m, 1H), 3.50-3.47 (m, 1H), 3.09-3.03 (m, 2H), 2.22 (dd, J=15.6Hz and J=2.4Hz, 1H), 1.84 (dd, J=15.6Hz and 8.4Hz, 1H), 1.17 (s, 9H)	276.9	4.00

Compound	NMR	Mass Spec (LCMS)	Reten. Time (min)
 567	(CD3OD, 400MHz), δ 7.48 (d, J=1.6Hz, 1H), 7.41-7.32 (m, 3H), 7.23 (d, J=8.4Hz, 2H), 7.07 (dd, J=8.4Hz and 2.0Hz, 1H), 6.46 (b, 1H), 4.32-4.17 (m, 3H), 3.80 (s, 2H), 3.67 (t, J=5.0Hz, 2H), 3.39 (s, 3H), 3.30-15 (m, 6H), 2.88-2.83 (m, 6H), 1.32 (s, 3H)	511.4	4.71
 HCl salt 568	(DMSO, 400MHz),δ11.39 (d, J=2.8Hz, 1H), 9.75 (s, 1H), 9.34 (s, 1H), 7.53 (s, 1H), 7.36 (dd, J=8.4Hz and 4.0Hz, 1H), 7.10 (dd, J=8.8Hz and 2.0Hz, 1H), 4.82-4.71 (m, 1H), 3.62-3.56 (m, 1H), 3.14 (b, 1H), 3.00-2.83 (m, 2H), 2.35-2.23 (m, 1H), 2.18-1.82 (m, 4H), 1.34 (q, J=6.4Hz, 3H)	295.0	4.14

Example 2: Assay to Evaluate Affect 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 may be monitored by an ELISA assay (R&D Systems). Briefly, HeLa cells may be 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 may then be assayed by ELISA, and the concentration of VEGF calculated from the standard ELISA curve of each assay.

A dose-response analysis may be 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 Cell Titer 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 0.5, and even more preferably less than 0.01.

Figure 1 shows the ability of a typical compound of the invention, Compound No. 7, to inhibit endogenous VEGF production in tumor cells under hypoxic conditions. The ELISA EC_{50} is 0.0025 μM, while its CC_{50} (50% cytotoxicity) is greater than 0.2 μM. The EC_{50} for a series of preferred compounds of the invention is provided in **Table 5**.

Table 5

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
1	391.20	3.67	****
2	385.28	4.01	*****
3	479.18	4.35	*****
4	435.23	4.28	*****
5	391.28	4.05	*****
6	425.28	4.07	*****
7	443.28	4.61	*****
# 8	415.26	4.25	*****
9	431.25	4.07	*****
# 10	467.15	4.51	*****
11	389.24	4.24	*****
12	414.31	3.94	*****
13	411.24	4.89	*****
14	397.22	4.57	*****
15	457.3	4.24	*****
16	435.19	4.47	*****
17	447.14	4.44	*****
18	431.14	4.55	*****
19	437.26	4.54	*****
20	389.24	4.22	*****
21	391.28	4.04	*****
22	425.28	4.11	*****
23	373.23	4.04	*****
24	411.24	4.8	*****
25	449.23	4.03	*****
26	437.15	4.52	*****
27	399.25	4.11	*****
28	399.19	4.2	*****
29	435.09	4.14	*****
30	413.22	4.42	*****
31	423.17	4.32	*****
32	467.25	4.26	*****
33	457.15	4.29	*****
34	383.19	4.42	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
35	425.28	4.14	*****
36	383.2	4.37	*****
37	423.3	4.24	*****
38	355.24	4.07	*****
39	391.28	4.12	*****
40	403.15	4.45	*****
41	449.11	4.59	*****
42	383.19	4.44	*****
43	371.31	3.89	*****
44	479.18	4.35	*****
45	394.16	4.09	*****
46	421.19	4.22	****
47	449.07	4.54	****
48	403.32	4.2	****
49	403.15	4.51	****
50	405.18	3.81	****
51	373.23	4.11	****
52	355.3	4.07	****
53	375.26	3.92	****
54	435.23	4.3	****
55	425.27	4.26	****
56	414.14	4.19	****
57	399.19	4.2	****
58	469.22	4.32	****
59	444.12	4.12	****
60	433.17	4.27	****
61	419.28	4.04	****
62	409.14	4.22	****
63	435.09	4.16	****
64	435.12	4.27	****
65	387.2	3.95	****
66	414.17	4.24	****
67	429.3	4.47	****
68	359.19	3.89	****
69	449.08	4.55	****
70	375.25	4.19	****
71	394.16	4.12	****
72	403.15	4.49	****
73	381.09	3.59	****
# 74	400.15	4.05	****
75	387.22	4.29	****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
76	449.26	4.3	****
77	391.28	4.19	****
78	435.12	4.24	****
79	437.19	4.49	****
80	437.2	3.84	****
81	375.03	3.57	****
82	391.28	4.05	****
83	425.28	4.16	****
84	359.22	3.95	****
85	437.15	4.44	****
86	399.19	4.22	****
87	403.15	4.44	****
88	399.19	4.17	****
89	434.07	4.04	****
90	387.23	4.26	****
91	369.27	4.17	****
92	377.29	4.04	****
93	435.23	4.29	****
94	369.17	4.24	****
95	449.06	4.51	****
96	341.27	3.89	****
97	387.19	4.2	****
98	405.18	3.79	****
99	469.22	4.29	****
100	461.32	4.61	****
101	369.17	4.26	****
102	413.28	4.02	****
103	407.1	4.05	****
104	375.27	4.11	****
105	387.21	4.19	****
106	373.18	4.04	****
107	385.28	4.02	****
108	359.16	3.92	****
109	369.34	4.16	****
110	374.24	3.07	****
111	386.19	3.89	****
112	369.27	2.63	****
113	399.13	4.01	****
114	389.3	4.05	****
115	435.13	4.14	****
116	407.16	4.09	****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
117	419.28	4.05	****
118	366.29	3.79	****
119	521.19	4.16	****
120	380.31	3.92	****
121	403.32	4.27	****
122	383.31	4.37	****
123	319.2	2.19	****
124	351.14	2.53	***
125	409.3	4.14	***
126	423.3	3.95	***
127	371.31	3.9	***
128	371.31	3.62	***
129	449.13	3.81	***
130	401.23	3.56	***
131	385.22	3.74	***
132	363.06	2.31	***
133	385.15	3.86	***
134	377.3	4.04	***
135	397.15	2.42	***
136	443.33	4.11	***
137	361.07	2.53	***
138	345.07	3.15	***
139	400.27	4.01	***
140	488.23	4.36	***
141	425.21	4.37	***
142	462.15	4.11	***
143	369.23	3.74	***
144	415.33	3.84	***
145	361.3	4.39	***
146	400.21	3.81	***
147	438.21	3.97	***
148	469.01	4.42	***
149	425.25	4.24	***
150	504.2	4.68	***
151	397.01	2.44	***
152	369.21	3.59	***
153	372.21	2.36	***
154	377.29	3.97	***
155	363.11	2.32	***
156	341.21	2.46	***
157	407.14	1.78	***

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
158	428.11	3.85	***
159	351.13	2.47	***
160	450.15	3.95	***
161	363.05	2.32	***
162	325.26	2.66	***
163	319.2	2.24	***
164	462.19	3.87	***
165	371.31	3.65	***
166	354.28 (-Boc)	3.95	***
167	432.16	3.87	***
168	351.08	2.4	***
169	385.35	4.09	***
170	351.07	2.51	***
171	363.09	2.68	**
172	384.21	3.52	**
173	319.2	2.24	**
174	N/A	2.38	**
175	443.33	4.09	**
176	417.30	2.77	**
177	398.17	3.67	**
178	363.11	2.31	**
179	450.14	3.89	**
180	421.19	2.65	**
181	363.15	2.46	**
182	419.14	4.14	**
183	389.29	4.14	**
184	431.27	4.1	**
185	328.02	2.41	**
186	462.19	3.81	**
187	443.28	3.99	**
188	446.19	3.81	**
189	405.19	3.8	**
190	317.16	2.7	**
191	369.23	3.89	**
192	495.28	4.89	**
193	297.2	2.53	**
194	319.21	2.19	**
195	494.25	2.79	**
196	419.22	4.09	**
197	317.16	2.41	**
198	317.08	2.53	**

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
199	448.24	3.95	**
200	363.09	2.45	**
201	365.09	2.36	**
202	464.2	4.32	**
203	301.18	2.27	**
204	429.23	3.57	**
205	301.15	2.27	**
206	476.3	4.33	**
207	395.17	2.55	**
208	367.36	2.72	**
209	353.33	3.97	**
210	313.21	2.33	**
211	415.26	4.07	**
212	389.2	2.88	**
213	407.1	2.46	**
214	357.07	2.48	**
215	319.23	2.24	**
216	283.1	2.41	**
217	418.17	3.62	**
218	435.23	3.77	**
220	308.23	2.37	**
221	460.29	4.05	**
222	365.11	2.52	**
223	441.02	2.6	**
224	341.27	2.6	**
225	467.25	4.18	**
226	369.34	4.01	**
227	327.16	2.26	**
228	369.34	2.64	**
229	373.29	4.04	*
230	401.23	3.2	*
231	313.12	2.43	*
232	433.25	2.73	*
233	430.38 (-Boc)	4.34	*
234	351.17	2.4	*
235	351.25	3.79	*
236	379.35	2.74	*
237	439.11	4.41	*
238	479.24	3.77	*
239	328.16	2.35	*
240	307.27	3.87	*

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
241	523.19	3.7	*
242	438.27	4.14	*
243	323.20	3.49	*
244	512	2.27	*
245	485	2.62	*
246	498	2.54	*
247	471	2.36	*
248	283.23	2.24	*
249	339.17	3.07	*
250	355.30	3.57	*
251	297.26	2.26	*
252	341.21	2.44	*
253	301.27	2.29	*
254	301.25	2.27	*
255	281.31	2.2	*
256	345.2	2.26	*
257	335.21	2.34	*
258	459.27	3.72	*
259	479.24	3.52	*
260	287.26	2.36	*
261	287.26	2.56	*
262	380.24	3.92	*
263	503.50	3.20	*
264	369.36	2.52	*
265	355.26	2.54	*
266	355.26	2.42	*
267	370.22	3.61	*
268	355.26	2.42	*
269	355.27	2.37	*
270	370.23	3.19	*
271	369.34	2.62	*
272	374.31	2.90	*
273	492.25	2.76	*
274	451.30	3.17	*
275	374.31	2.61	*
276	374.31	2.72	*
277	349.28	1.5	*
278	457.28	4.11	*
279			*****
280	407.10	3.92	*
281	508.15	4.74	*

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
282	507.08	4.42	*
283	422.32	3.86	*
284	373.29	4.01	*
285	385.24	2.25	*
286	297.2	2.52	*
287	289.22	2.48	*
288	461.26	2.57	*
289	380.29	3.82	*
290	396.27	3.60	*
291	299.17	2.43	*
292	385.18	2.6	*
293	413.22	3.8	*
294	340.25	2.27	*
295	404.34	3.84	*
296	299.17	2.23	*
297	326.24	2.4	*
298	235.13	2.18	*
299	351.16	2.62	*
300	401	2.57	*
301	313.21	2.35	*
302	398.28	3.74	*
303	355.22	2.58	*
304	440.32	4.09	*
305	341.08	2.48	*
306	364.3	3.65	*
307	350.32	3.35	*
308	432.27	3.92	*
309	474.26	3.02	****
310	289.03	2.35	*
311	345.19	2.58	*
312	420.28	4.12	*
313	279.28	2.18	*
314	293.24	2.20	*
315	297.26	2.17	*
316	472.26	3.85	*
317	428.25	3.95	*
318	309	2.25	*
319	284.09	2.1	*
320	356.21	2.37	*
321	279.2	2.1	*
322	279.2	1.76	*

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
323	309.23	1.82	*
324	280.19	1.76	*
325	279.2	1.76	*
326	263.17	1.93	*
327	343.18	2.33	*
328	~0.005	4.16	*
329	0.0036	4.26	*
330	0.0047	4.24	*
331	~ 0.010	2.94	*
#332	~ 0.010	4	*
333	410.27	3.64	**
334	426.24	3.39	*
335	466.23	4.64	***
336	438.31	4.31	**
337	454.24	4.63	***
338	474.32	4.33	**
339	412.3	3.83	*
340	446.33	4.49	*
341	447.26	4.25	***
342	371.31	3.88	***
343	371.31	3.61	*
344	459.31	4.91	****
345	383.35	4.44	****
346	587	4.04	****
347	451.16	3.93	*****
348	479.28	4.13	*****
349	481.21	3.74	****
350	462.17	3.66	*****
351	471.17	3.93	****
352	403.29	3.98	****
353	497.16	3.94	*****
354	525.2	4.19	*****
355	511.21	3.81	*****
356	490.3	3.93	**
357	534.23	3.93	***
358	433.2	3.45	***
359	511.25	3.64	***
360	516	3.82	****
361	474.26	3.02	****
362	427	4.2	*****
363	412.4	1.80	*

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
364	484.3	2.49	*****
365	457.3	4.06	***
366	553.3	4.42	*
367	402.8	4.37	****
368	430.9	4.79	**
369	427.0	4.06	**
370	427.0	3.99	*****
371	469.0	5.27	***
372	486.9	4.96	*
373	470.8	5.01	***
374	436.9	4.66	***
375	461	4.92	**
376	385	3.79	**
377			*
378			*
379			*
380			*
381			*
382			*
383	417.2	4.93	*****
384	403.22	4.65	*****
385	509.51	2.57	****
386	465.26	2.52	*****
387	465.26	2.52	*****
388	495.4	3.94	*****
389	538.3	4.29	*****
390	480.5	3.23	*****
391	562.55	3.63	*****
392	443.4	3.88	*****
393	447.1	6.55	*****
394	450.1	5.48	*****
395	481.32	3.51	*****
396	411.3	3.99	*****
397	535.3	4.29	*****
398	481.3	4.23	*****
399	429.3	3.81	*****
400	493.3	4.43	*****
401	451.3	3.99	*****
402	494.4	3.71	*****
403	479.3	4.23	*****
404	473.6	3.78	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
405	551.17	4.58	*****
406	425.4	4.13	*****
407	457.4	4.04	*****
408	425.4	4.09	*****
409	477.4	4.18	*****
410	451.3	3.99	*****
411	443.4	3.86	*****
412	473.4	4.23	*****
413	459.3	4.16	*****
414	439.4	4.31	*****
415	637.64	2.82	*****
416	311.1	4.39	*****
417	562.47	4.15	*****
418	511.3	4.13	*****
419	491.4	3.98	*****
420	486.6	3.45	*****
421	553.30	4.05	*****
422	359.29	4.17	*****
423	447.4	3.56	*****
424	594.2 [M-H]	4.58	*****
425	539.2	3.11	*****
426	535.27	4.29	*****
427	554.3	4.45	*****
428	563.55	4.64	*****
429	564.42	2.77	*****
430	431.3	3.41	*****
431	522.2	5.05	*****
432	489.4	4.14	*****
433	578.44	2.82	*****
434	467.18	4.11	*****
435	444.3	3.95	*****
436	477.4	3.93	*****
437	543.4	3.92	*****
438	500.1	4.35	*****
439	361.2	5.95	*****
440	536.43	3.95	*****
441	482.1	5.11	****
442	367.1	2.92	****
443	436.2	5.25	****
444	455.28	3.73	****
445	478	3.67	****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
446	383.3	4.10	****
447	464.9	5.11	****
448	501.27	3.65	****
449	482.24	2.62	****
450	587	4.04	****
451	644.3 [M-H]	4.80	****
452	439.3	3.56	****
453	553.1	6.13	****
454	579.3	2.75	****
455	583	3.84	****
456	474.3	2.44	****
457	455	3.4	****
458	456.3	2.51	****
459	470.3	2.61	****
460	509.30	4.16	****
461	454.3	5.98	****
462	580.56	2.85	****
463	495.44	4.13	****
464	493.0	5.71	****
465	507.4	3.98	****
466	555.2	3.14	****
467	524.2	4.02	****
468	582.2	2.81	****
469	525.2	5.07	****
470	554.3	3.90	****
471	620.18	3.85	****
472	335.3	5.52	****
473	495.3	4.68	***
474	511.2	4.99	***
475	483	3.87	***
476	400	3.45	***
477	249.1	3.67	***
478	525.1	3.25	***
479	538.3	2.76	***
480	456.1	4.26	***
481	549.3	5.29	***
482	522.3	3.95	***
483	470.1	4.46	***
484	539.2	3.02	***
485	398.9	4.18	***
486	349.1	6.03	***

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
487	505	3.66	***
488	555.2	3.34	***
489	538.3	4.15	***
490	486.1	3.80	***
491	537.31	2.64	***
492	468	5.52	***
493	504.3	2.68	***
494	482.2	5.74	***
495	403.3	4.16	***
496	430.2	3.65	***
497	281.0	3.84	***
498	481.4	4.81	***
499	423.3	5.15	***
500	506.29	3.85	***
501	534.3	2.68	***
502	518.3	2.76	***
503	508.2	5.72	***
504	359.1	5.65	***
505	442.0	4.06	***
506	386.3	5.32	***
507	450	3.19	***
508	397.1	5.97	***
509	511.4	5.05	***
510	321.4	5.19	***
511	383.1	5.75	***
512	523.1	5.69	***
513	361.1	5.12	***
514	495.3	4.67	***
515	363.5	6.34	**
516	527.1	3.16	**
517	464.2	5.86	**
518	517.6	5.03	**
519	527.2	3.88	**
520	426.2	4.29	**
521	509.4	4.99	**
522	383.3	4.10	**
523	439.0	6.11	**
524	412.1	4.13	**
525	4.95.3	3.46	**
526	513.2	4.43	**
527	535.3	4.94	**

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
528	453.0	6.30	**
529	481.3	3.43	**
530	466.28	3.21	**
531	549.6	5.21	**
532	325.3	4.75	**
533	506.2	4.96	**
534	525.2	4.76	**
535	541.2	3.51	**
536	482.29	3.29	**
537	476.3	2.51	**
538	516.37	3.49	**
539	337.3 [M-H]	2.14	**
540	428.28	3.43	**
541	525.2	4.42	**
542	398.1	3.95	**
543	466.34	3.29	**
544	723.58	3.92	*****
545	466.31	3.28	**
546	426.3	2.26	**
547	335.2	5.45	**
548	516.37	3.46	**
549	414	2.89	**
550	496	4.58	**
551	544.5	2.78	**
552	511.3	3.56	**
553	440.9	5.75	**
554	482.32	3.41	**
555	372	2.89	**
556	456.1	4.21	**
557	538.4	3.71	**
558	497.2	4.69	**
559	460.8	4.96	**
560	596.3	4.45	*
561	509.2	5.18	*
562	525.3	3.52	*
563	483.1	4.96	*
564	432	2.18	*
565	276.9	4.00	*
566	384.4	1.73	*
567	511.4	4.71	*
568	295.0	4.14	*

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
569	480.21	3.50	*****
570	549.22	4.59	*****
571	497.13	3.50	**
572	525.29	4.14	*****
573	341.34	2.14	****
574	427.37	2.23	*
575	437.33	3.16	**
576	575.43	3.71	***
577	453.28	3.34	***
578	610.45	3.94	***
579	481.32	3.51	*****
580	495.29	3.64	*****
581	465.43	3.64	*
582	516.34	3.31	*
583	512.26	3.39	***
584	466.37	3.34	***
585	516.33	3.46	***
586	387.27	2.13	*****
587	467.29	3.66	***
588	455.26	3.69	***
589	471.3	3.83	***
590	495.31	3.64	****
591	541.35	3.73	*****
592	523.42	3.58	*****
593	541.38	3.69	****
594	505.38	3.83	***
595	431.21	4.01	****
596	431.24	3.99	*****
597	445.24	4.19	*****
598	459.24	4.36	*****
599	513.17	4.19	****
600	479.23	3.99	*****
601	504.21	3.79	****
602	493.2	4.18	****
603	513.16	4.19	****
604	446.18	2.86	*
605	503.23	3.84	*****
606	461.19	3.46	***
607	442.25	3.46	***
608	489.2	3.72	***
609	433.27	3.98	**

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
610			****
611			**
612	491.23	3.56	***
613	513.14	4.18	****
614	463	3.88	**
615	381	3.48	***
616	540	4.17	**
617	621.57	4.13	****
618	493.6	2.63	*****
619	521.6	2.80	*****
620	445.5	3.23	****
621	459.5	3.40	*****
622	459.5	3.38	*****
623	473.5	3.57	*****
624	479.5	3.28	****
625	507.6	3.53	*****
626	493.6	3.48	****
627	511.6	3.53	*****
628	527.4	3.62	***
629	527.5	3.72	*****
630	573.5	3.75	*****
631	507.6	3.65	*****
632	538.6	3.53	****
633	443.5	3.32	*****
634	457.6	3.30	*****
635	523.6	3.47	****
636	463.6	3.12	*****
637	621.62	2.77	*****
638	580.56	2.80	*****
639	496.54	3.28	*****
640	552.64	2.48	****
641	445.55	4.13	*****
642	381.49	3.97	*****
643	397.47	3.95	*****
644	395.45	3.78	*****
645	521.15	4.17	*****
646	531.11	4.58	****
647	505.18	4.7	*****
648	437.19	4.15	****
649	477.21	4.1	*****
650	487.18	4.3	****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
651	548.3	2.53	****
652	419.23	4.15	****
653	449.24	4.12	****
654	433.26	4.3	*****
655	453.19	4.33	****
656	444.17	4.02	*****
657	464.22	4.08	*****
658	461.6	4.30	*****
659	489.7	4.78	*****
660	543.7	4.92	*****
661	459.5	3.63	*****
662	471.5	3.87	*****
663	491.6	3.63	*****
664	507.6	3.80	*****
665	485.6	3.85	****
666	485.6	3.83	*****
667	486.6	3.95	*****
668	503.6	3.58	*****
669	521.6	3.88	*****
670	521.6	4.02	*****
671	501.6	4.13	*****
672	501.6	4.10	*****
673	539.6	4.02	
674	555.6	4.13	****
675	555.6	4.22	****
676	535.6	4.05	****
677	535.6	4.15	****
678	551.6	3.98	***
679	487.6	3.93	****
680	599.5	4.27	*****
681	566.6	4.02	****
682	496.5	2.13	**
683	486.5	2.03	***
684	484.6	2.67	***
685	514.6	2.15	***
686	512.6	2.12	****
687	510.6	2.13	***
688	525.6	1.85	***
689	494.5	3.12	***
690	524.6	2.32	***
691	514.6	2.23	***

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
692	512.6	2.35	***
693	542.6	2.35	****
694	540.6	2.27	****
695	538.6	2.35	****
696	553.6	2.07	***
697	522.6	3.95	*****
698	578.5	2.43	****
699	568.5	2.35	****
700	566.6	2.45	****
701	596.6	2.47	****
702	594.6	2.43	****
703	592.6	2.48	****
704	607.6	2.20	***
705	575.5	2.47	****
706	576.5	3.58	*****
707	477.51	2.77	*****
708	491.53	2.73	*****
709	503.55	2.68	*****
710	495.45	4.42	*****
711	475.51	4.62	*****
712	513.50	4.42	*****
713	529.46	4.62	****
714	509.51	4.43	*****
715	482.46	4.28	*****
716	457.47	4.05	****
717	459.59	4.33	*****
718	491.5	4.10	*****
719	527.5	4.47	*****
720	489.5	4.75	*****
721	517.5	4.26	*****
722	519.5	3.84	*****
723	555.4	4.09 (non polar)	*****
724	541.54	2.90	*****
725	478.47	3.58	*****
726	516.5	2.67	**
727	526.5	2.78	****
728	544.5	2.80	***
729	542.5	2.72	*****
730	540.5	2.83	****
731	555.6	2.43	***
732	580.6	2.40	***

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
733	523.5	2.78	*****
734	524.5	3.40	*****
735	552.5	2.98	*****
736	562.5	3.15	*****
737	580.6	3.17	****
738	578.5	3.02	*****
739	576.6	3.17	*****
740	591.6	2.75	***
741	616.5	2.62	***
742	559.5	3.13	*****
743	560.5	3.83	*****
744	514.6	2.80	*****
745	524.6	2.92	*****
746	512.5	2.93	*****
747	542.6	2.93	*****
748	540.5	2.85	*****
749	538.6	2.93	*****
750	553.6	2.55	*****
751	521.5	2.92	****
752	522.5	3.87	*****
753	542.6	2.98	****
754	552.6		*****
755	540.6	3.17	****
756	570.6	3.17	****
757	568.6	3.07	*****
758	566.6	3.17	***
759	581.6	2.78	***
760	549.6	3.13	*****
761	550.5	4.17	*****
762	544.5	2.68	****
763	554.5	2.77	*****
764	542.6	2.78	****
765	572.5	2.75	****
766	570.6	2.70	*****
767	568.6	2.82	****
768	583.6	2.47	****
769	608.6	2.38	***
770	551.5	2.73	*****
771	552.5	3.65	*****
772	580.5	3.03	*****
773	590.6	3.12	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 µM
774	578.5	3.12	****
775	608.6	3.05	*****
776	606.5	3.05	*****
777	604.6	3.12	*****
778	619.6	2.77	*****
779	644.5	2.63	***
780	587.5	3.10	*****
781	588.5	4.05	*****
782	596.5	3.10	*****
783	606.5	3.18	*****
784	594.5	3.27	*****
785	624.5	3.22	*****
786	622.5	3.12	*****
787	620.5	3.20	*****
788	635.6	2.85	****
789	660.5	2.68	***
790	603.5	3.22	*****
791	604.5	4.25	*****
792	480.50	2.98	*****
793	494.50	2.97	****
794	494.50	2.97	***
795	496.48	2.97	****
796	563.50	2.41	****
797	522.48	2.50	*****
798	538.48	2.92	*****
799	535.49	2.35	***
800	503.40	2.52	****
801	504.43	3.42	*****
802	504.42	3.37	*****
803	579.48	2.42	****
804	538.48	2.43	*****
805	584.50	2.52	*****
806	554.40	2.47	*****
807	540.47	2.50	*****
808	551.48	2.33	****
809	516.45	2.47	*****
810	520.40	3.21	*****
811	520.40	3.12	*****
812	466.4	3.27	*****
813	466.4	3.18	*****
814	465.4	2.38	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
815	465.4	3.45	*****
# 816	497.4	2.70	*****
# 817	511.4	2.62	*****
# 818	491.4	2.43	****
819	494.4	3.53	*****
820	494.4	3.47	****
821	493.4	2.55	****
822	493.4	3.73	*****
# 823	525.4	2.95	*****
# 824	539.4	2.83	*****
# 825	519.4	2.58	*
826	496.4	3.07	***
827	496.4	2.98	****
828	495.4	2.32	***
829	495.4	3.28	***
# 830	527.4	2.53	*****
# 831	541.4	2.50	*****
# 832	521.4	2.35	
833	532.4	3.50	***
834	532.4	3.42	****
835	531.4	2.57	***
836	531.4	3.67	****
# 837	563.4	2.93	*****
# 838	577.4	2.82	*****
839	548.3	3.63	****
840	548.3	3.58	****
# 841	579.3	3.08	*****
# 842	593.3	2.95	*****
# 843	573.4	2.75	*****
844	451.91	3.58	***
845	648.48	4.45	***
846	526.45	2.57	***
847	568.37	3.40	****
848	585.30	3.57	*****
849	604.37	3.52	****
850	540.39	2.60	***
851	495.06	4.37	*****
852	539.08	4.17	*****
853	549.09	4.38	*****
854	523.17	4.73	*****
855	455.19	4.15	****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
856	495.18	4.10	*****
857	505.16	4.30	*****
858	566.3	2.57	*****
859	437.22	4.15	*****
860	467.2	4.13	*****
861	451.12	4.10	****
862	471.17	4.32	*****
863	514.55	4.38	*****
864	462.28	4.00	****
865	482.13	4.08	****
866	447.37	4.04	*****
867	577.43	2.85	****
868	477.14	4.37	*****
869	504.53	3.62	*****
870	493.55	2.80	*****
871	489.54	2.72	*****
872	493.55	2.80	*****
873	503.54	2.73	*****
874	479.2	2.74	*****
875	425.52	4.27	*****
876	492.52	3.57	*****
877	489.54	2.72	*****
878	508.55	3.82	*****
879	507.55	2.90	*****
880	459.49	4.24	*****
881	471.45	4.22	*****
882	542.51	3.87	*****
883	494.50	3.67	*****
884	544.27	2.79	*****
885	490.54	3.54	*****
886	494.57	3.68	*****
887	521.62	2.93	*****
888	558.54	3.70	*****
889	545.55	2.93	*****
890	490.49	3.48	*****
891	528.49	3.69	*****
892	546.50	3.75	*****
893	461.49	4.36	*****
894	580.47	2.72	*****
895	491.51	2.77	*****
896	576.49	4.00	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
897	504.51	3.52	*****
898	457.53	4.25	*****
899	481.37	4.17	*****
900	541.55	3.00	*****
901	575.54	2.98	*****
902	471.49	4.12	*****
903	621.39	2.72	*****
904	596.54	2.85	*****
905	542.54	3.78	*****
906	489.53	4.82	*****
907	514.47	3.54	*****
908	582.43	2.79	*****
909	514.21	2.75	*****
910	539.45	3.97	*****
911	527.54	2.88	*****
912	530.53	2.67	*****
913	626.6	2.88	*****
914	514.55	2.60	*****
915	509.56	4.63	*****
916	626.40	2.82	*****
917	561.46	2.95	*****
918	642.56	2.85	*****
919	543.45	4.82	*****
920	557.57	2.87	*****
921	527.39	4.52	*****
922	561.53	2.85	*****
923	612.51	2.92	*****
924	498.20	2.71	*****
925	596.54	2.88	*****
926	5.62	3.85	*****
927	540.65	4.25	*****
928	510.52	3.10	*****
929	506.46	2.95	*****
930	500.48	2.83	*****
931	467.39	4.17	*****
932	548.49	3.17	*****
933	596.37	2.79	*****
934	561.53	2.95	*****
935	496.54	3.37	*****
936	582.6	2.83	*****
937	555.61	2.55	*****

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
938	582.53	2.85	*****
939	560.63	2.68	*****
940	541.43	2.45	*****
941	562.55	3.63	*****
942	623.35	2.73	****
943	499	2.72	****
944	525.56	4.36	****
945	509.43	4.73	****
946	566.53	2.77	****
947	510	2.44	****
948	482.47	2.88	****
949	524.55	3.22	****
950	506.46	2.87	****
951	544.53	3.27	****
952	530.53	3.12	****
953	552.46	2.90	****
954	403	4.11	****
955	397	3.9	****
956	484.55	2.42	****
957	495.52	2.62	****
958	542.36	3.84	****
959	496.24	2.81	****
960	639.57	2.70	****
961	593.52	2.64	****
962	516.59	2.65	****
963	593.61	2.72	****
964	598.55	2.83	****
965	544.53	3.15	****
966	564.45	3.32	****
967	491.57	4.00	****
968	512.51	2.73	****
969	492.46	2.90	****
970	609.54	2.72	****
971	468.46	2.78	****
972	496.47	3.02	****
973	578.47	3.80	****
974	528.34	3.79	***
975	431.5	3.10	***
976	564.46	3.23	***
977	568.53	2.85	***
978	578.45	3.30	***

Compound	LCMS [M+H]	LCMS Retention Time (min)	ELISA EC50 μM
979	470.55	2.45	***
980	527.61	2.50	***
981	560.51	3.12	***
982	425.60	3.78	***
983	375.37	2.27	***
984	5.06.19	3.97	**
985	407.31	1.82	*
986	531.56	2.17	*
987	497.1	4.4	*****
988	605.62	2.52	*****
989	564.61	2.55	*****
990	610.62	2.67	*****
991	580.58	2.60	***
992	566.61	2.60	***
993	577.61	2.45	*****
994	545.54	2.57	*****
995	546.57	3.53	*****
996	578.46	3.71	*****

(*S*) Isomer prepared and tested.

Wherein:
1 star, > 1uM (1000 nM)
2 stars, 0.2 to 1 uM (200 nM to 1000 nM)
3 stars, 0.04 uM to 0.2 uM (40 nM to 200 nM)
4 stars, 0.008 uM to 0.04 uM (8 nM to 40 nM)
5 stars, < 0.008 uM (< 8 nM)

Example 3: Compounds of the Invention Inhibit VEGF Expression and Tumor Growth in an In Vivo Tumor Growth 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 may be administrated compounds orally at a desired dosage range, *e.g.*, 200mg/kg/day, for seven days. The tumors may then be excised from mice and homogenized in Tris-HCl buffer containing proteinase inhibitors. Moulder *et al.*, *Cancer Res.* 61(24):8887-95 (2001). 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).

Example 4: Compounds of the Invention Do Not Affect the Activity of PDE5.

The compounds of the invention are tested to assess their effect on phosphodiesterase 5 (PDE5) activity. The effect on PDE5 activity is determined using the High-Efficiency Fluorescence Polarization Assay (HEFP) kit from Molecular Devices. The HEFP assay measures the activity of PDE-5 by using fluorescein-labeled derivatives of cGMP as a substrate. When hydrolyzed by PDE-5, fluorescein-labeled cGMP derivatives are able to bind to a binding reagent. The cGMP substrate:binding reagent complex results in a highly polarized fluorescent state.

FIG. 2 shows the results of the compounds of the invention on PDE-5 activity. After combining recombinant PDE5 (CalBioChem) and the cGMP substrate, the mixture is incubated at room temperature for 45 minutes in the presence or absence of compounds or a positive control (Tadalafil). The reaction is stopped upon addition of the binding reagent. Fluorescence polarization is determined on a Viewlux using a setting recommended by the manufacturer. As is evident from FIG. 2, the compounds of the invention do not inhibit the activity of PDE-5 in comparison to the positive control.

All publications and patent applications cited herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the claims of the invention.

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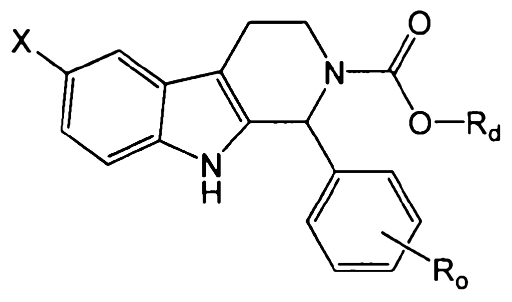
The claims defining the invention are as follows:

1. A compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt, racemate or stereoisomer thereof, wherein,

X is hydrogen; C_1 to C_6 alkyl optionally substituted with one or more halogen; hydroxyl; halogen; or C_1 to C_5 alkoxy optionally substituted with phenyl;

R_0 is halogen; cyano; nitro; sulfonyl substituted with C_1 to C_6 alkyl or morpholinyl; amino optionally substituted with C_1 to C_6 alkyl, -C(O)-R_b, -C(O)O-R_b, alkylsulfonyl, morpholinyl or tetrahydropyranyl; C_1 to C_6 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen or amino; -C(O)-R_n; or -OR_a;

R_a is hydrogen; C_2 to C_8 alkenyl; -C(O)O-R_b; -C(O)-NH-R_b; C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen, C_1 to C_4 alkoxy, C_1 to C_4 alkoxy-C_1 to C_4 alkoxy, amino, alkylamino, dialkylamino, acetamide, -C(O)-R_b, -C(O)O-R_b, aryl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxolan-2-one, oxiranyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3-triazole, 1,2,4-triazole, furan, imidazole, isoxazole, isothiazole, oxazole, pyrazole, thiazole, thiophene or tetrazole;

wherein amino is optionally substituted with C_1 to C_4 alkoxycarbonyl, imidazole, isothiazole, pyrazole, pyridine, pyrazine, pyrimidine, pyrrole, thiazole, wherein pyridine and thiazole are each optionally substituted with C_1 to C_4 alkyl;

wherein alkylamino and dialkylamino are each optionally substituted on alkyl with hydroxyl, C_1 to C_4 alkoxy, imidazole, pyrazole, pyrrole or tetrazole; and wherein morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl and oxiranyl are each optionally substituted with -C(O)-R_n, -C(O)O-R_n or C_1 to C_4 alkyl, wherein C_1 to C_4 alkyl is optionally substituted with hydroxyl;

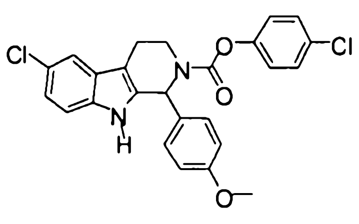
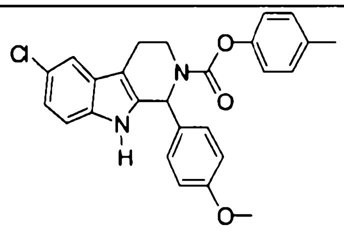
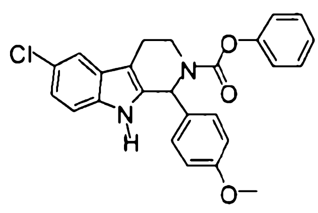
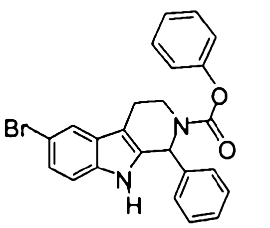
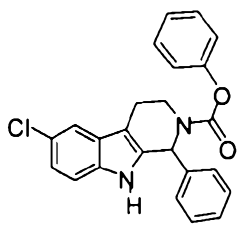
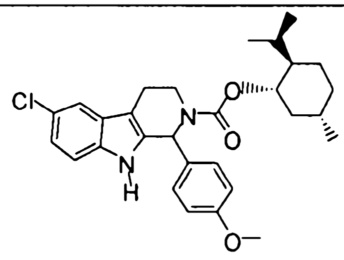
R_b is hydroxyl; amino; alkylamino, optionally substituted on alkyl with hydroxyl, amino, alkylamino or C_1 to C_4 alkoxy; C_1 to C_4 alkoxy; C_2 to C_8 alkenyl; C_2 to C_8 alkynyl; aryl optionally substituted with one or more substituents independently selected from halogen and C_1 to C_4 alkoxy; furan; or C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from C_1 to C_4 alkoxy, aryl, amino, morpholinyl, piperidinyl or piperazinyl;

R_d is phenyl substituted by one or more substituents independently selected from halogen, nitro, C_1 to C_6 alkyl, -C(O)O-R_e, and -OR_e;

R_e is hydrogen; C_1 to C_6 alkyl optionally substituted with one or more substituents independently selected from halogen and alkoxy; or phenyl, wherein phenyl is optionally substituted with one or more substituents independently selected from halogen and alkoxy; and

R_n is hydroxyl, C_1 to C_4 alkoxy, amino or C_1 to C_6 alkyl.

2. A compound, wherein said compound is selected from the group consisting of

 10	 17	 60
 76	 121	 192

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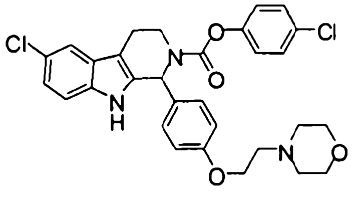
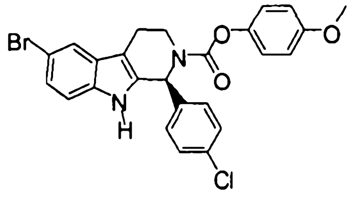
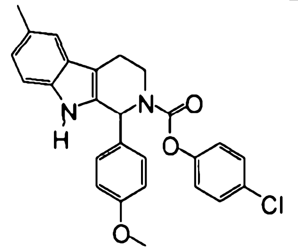
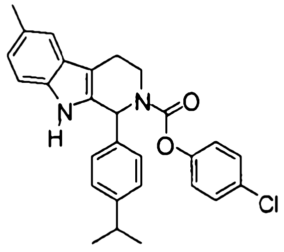
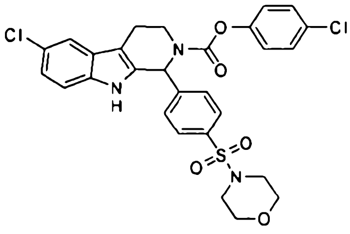
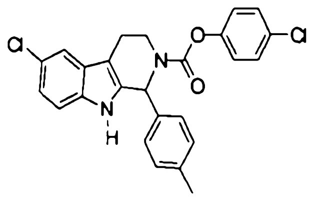
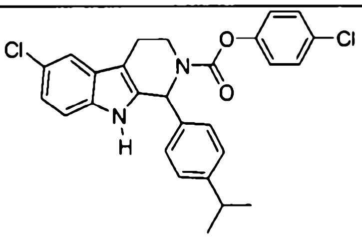
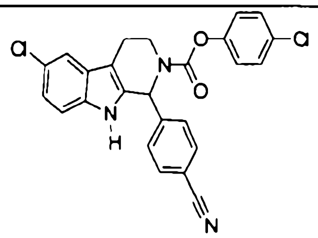
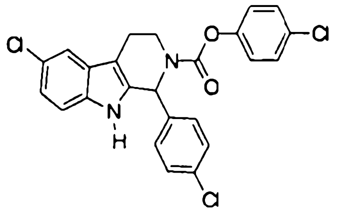
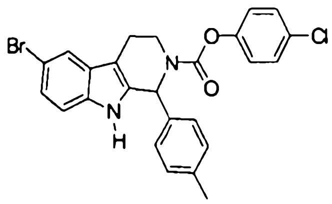
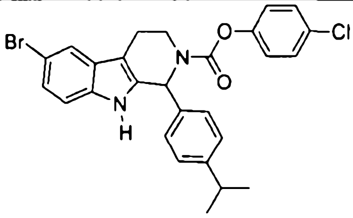
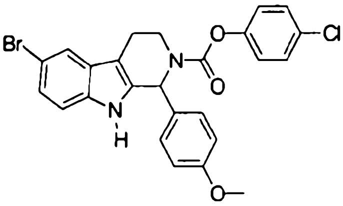
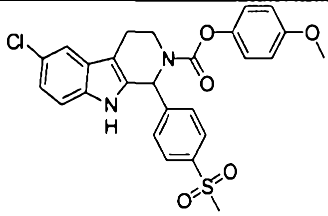
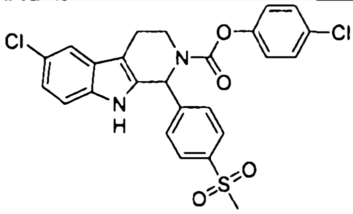
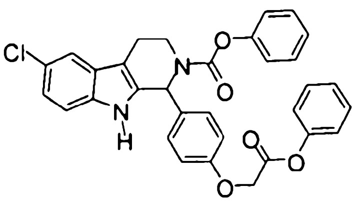
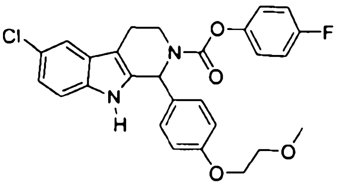
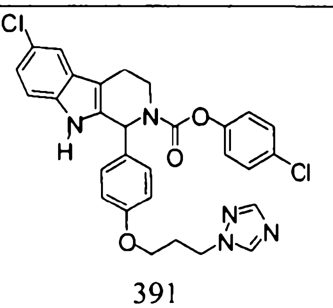
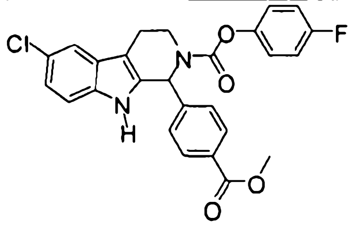
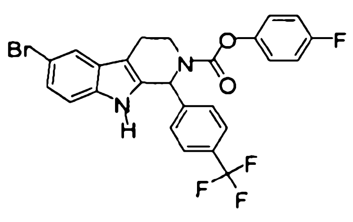
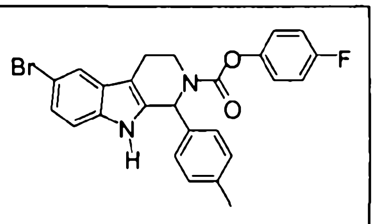
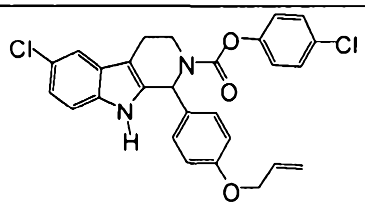
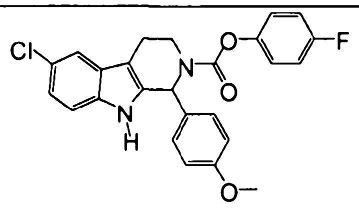
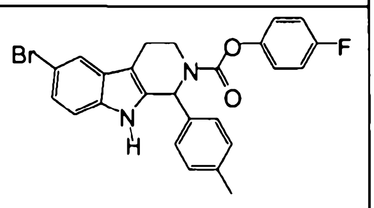
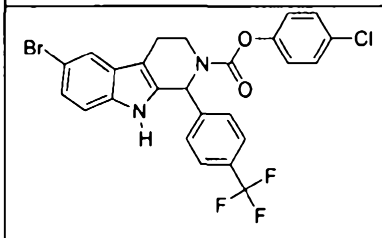
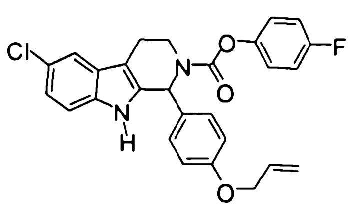
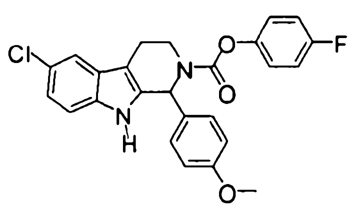
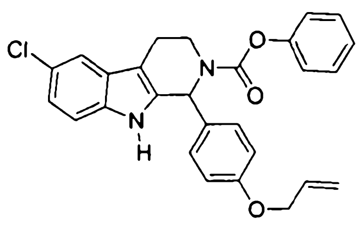
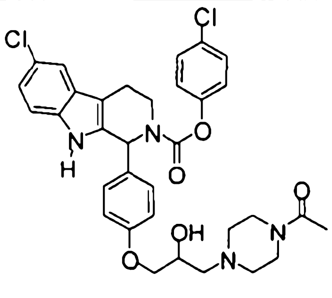
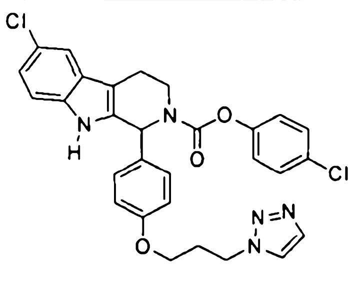
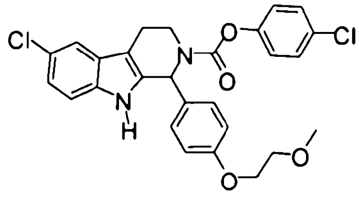
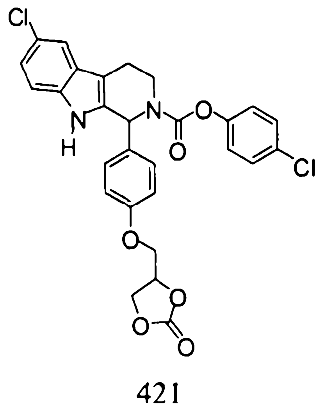
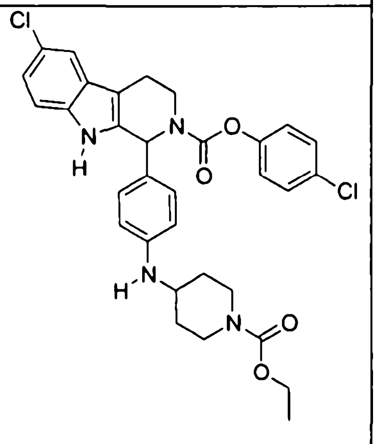
 331	 332	 341
 344	 346	 347
 348		 350
 351	 353	 354
 355	 359	 360
 366	 388	 391

 395	 397	 398
 400	 401	 403
 405	 409	 410
 413	 415	 417
 418	 421	 422

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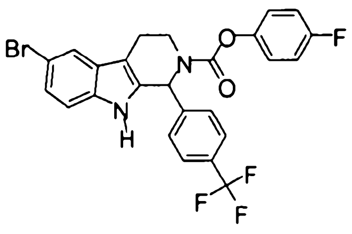
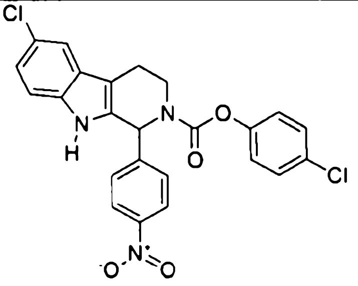
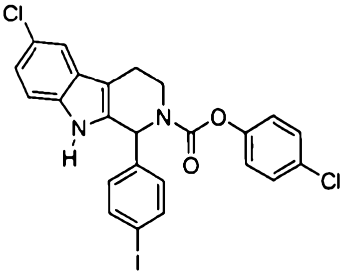
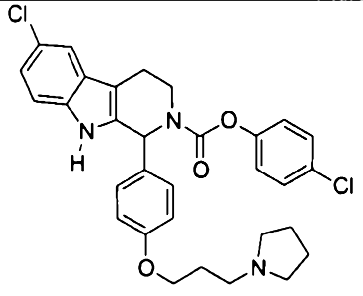
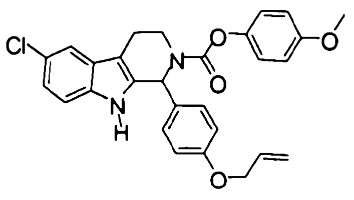
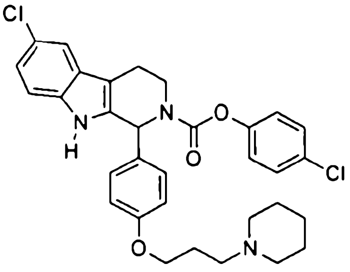
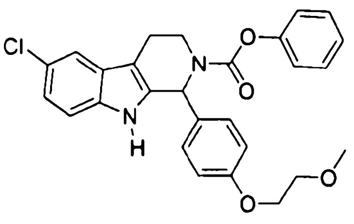
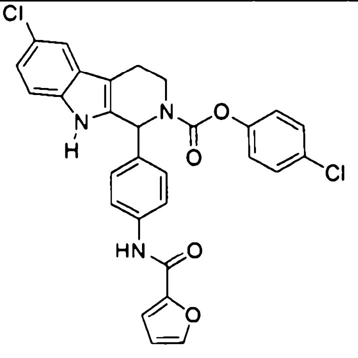
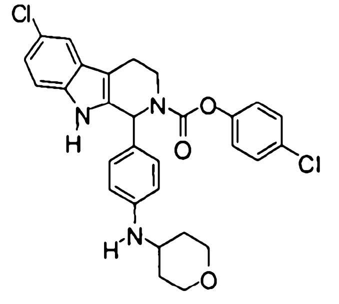
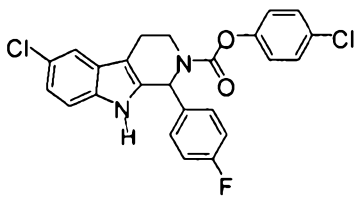
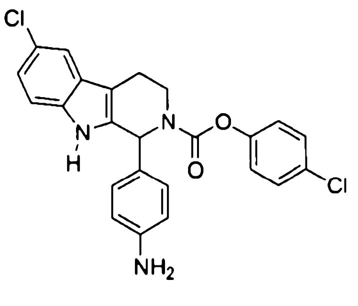
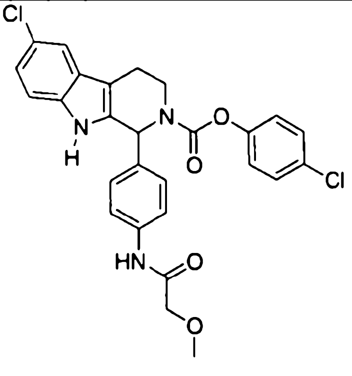
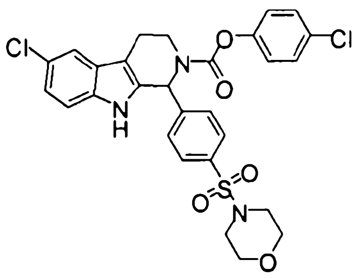
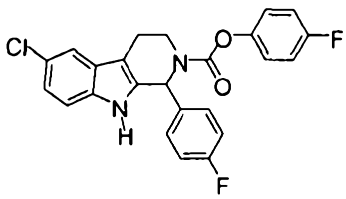
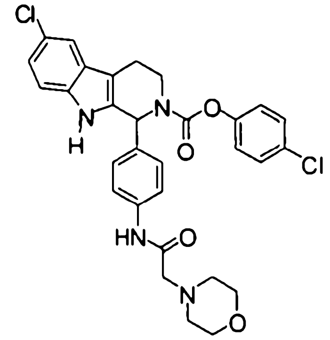
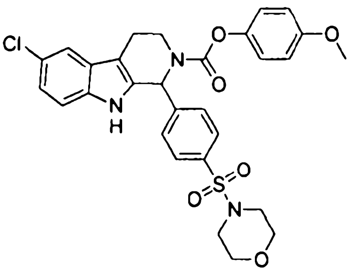
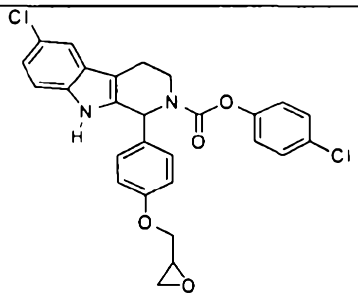
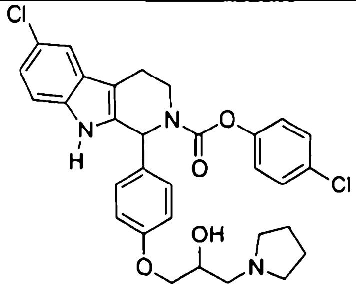
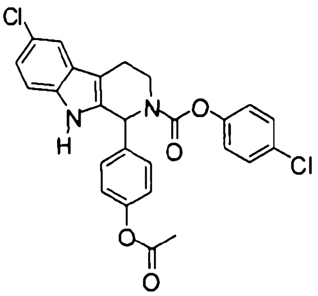
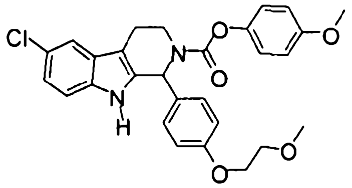
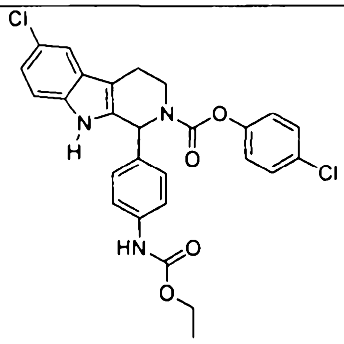
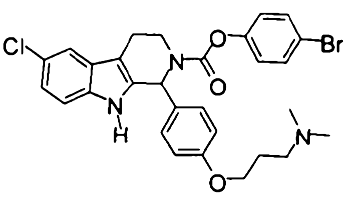
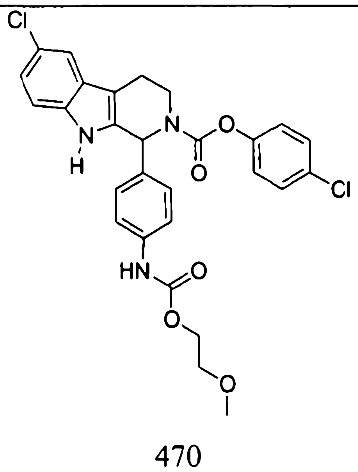
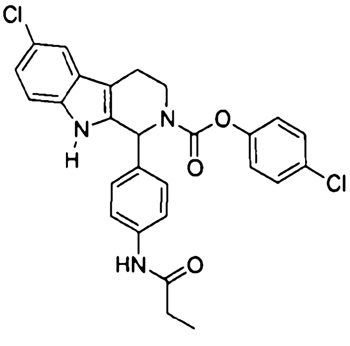
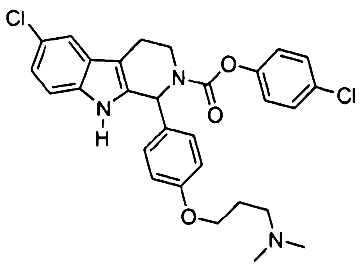
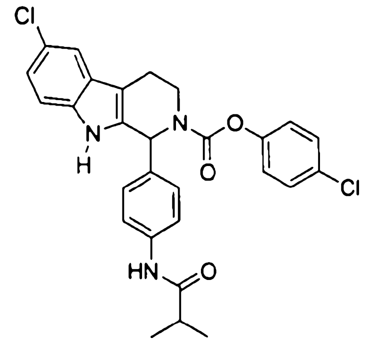
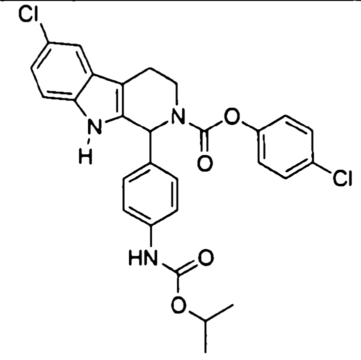
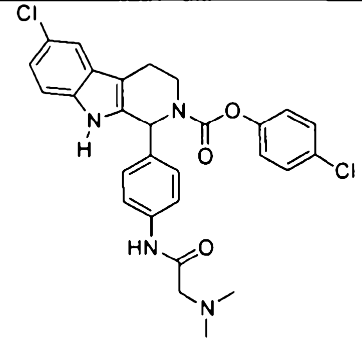
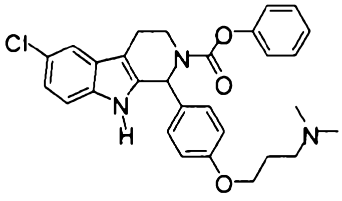
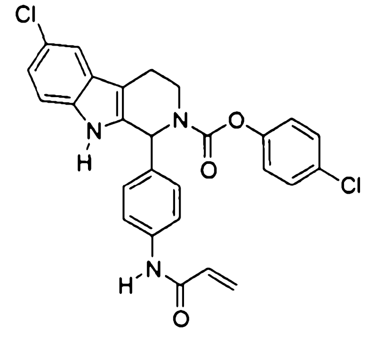
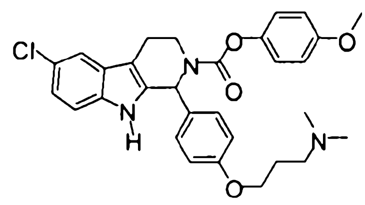
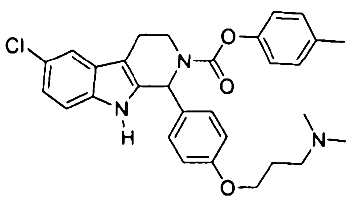
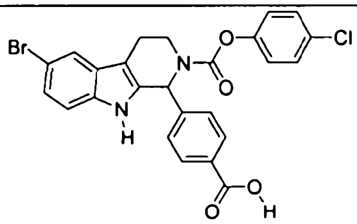
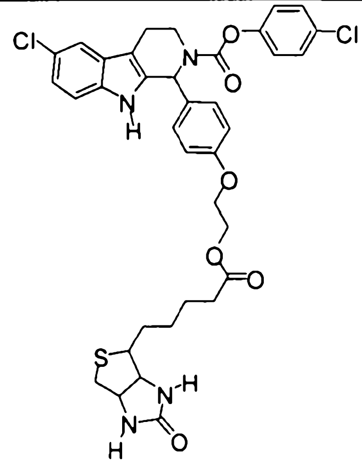
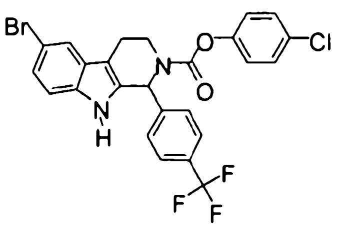
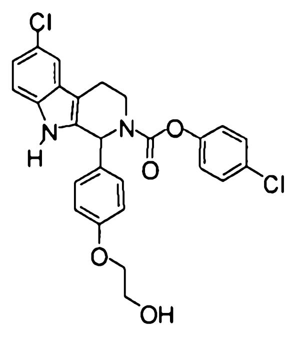
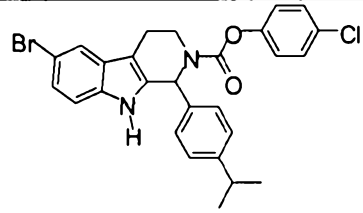
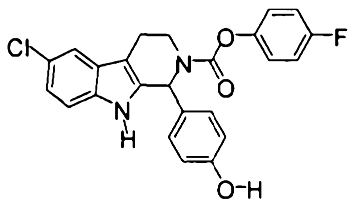
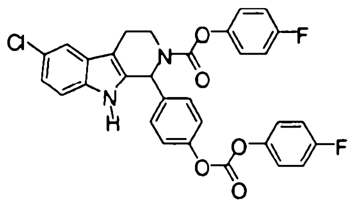
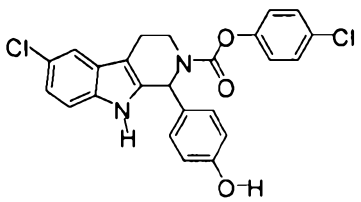
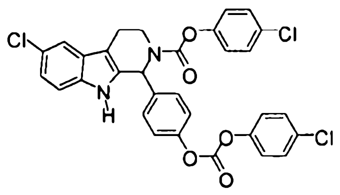
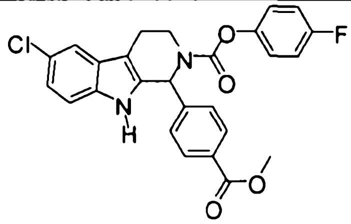
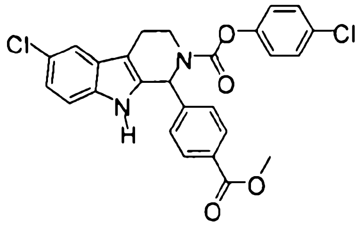
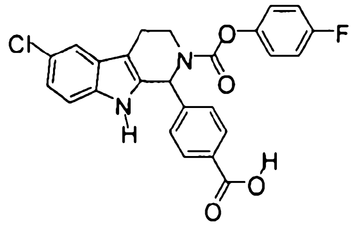
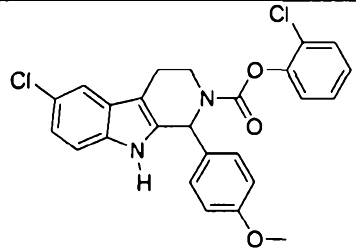
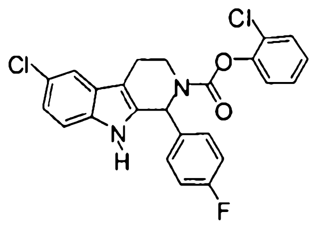
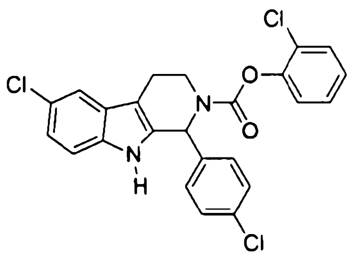
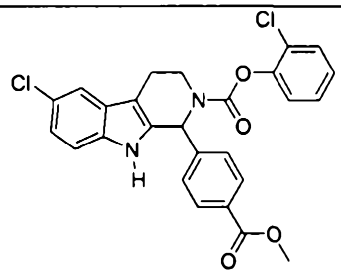
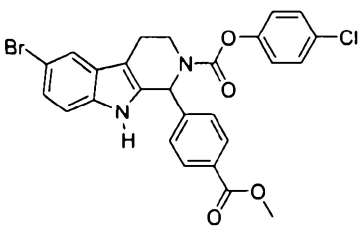
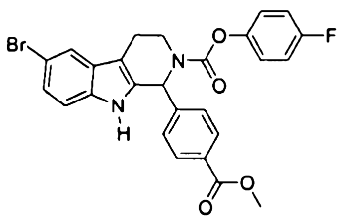
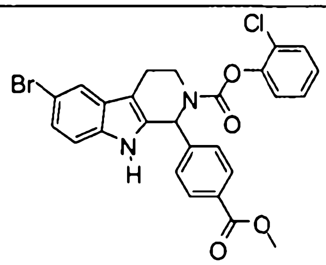
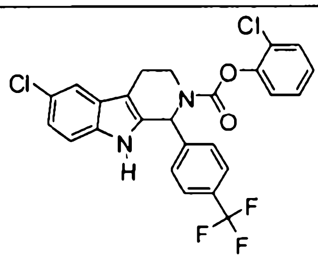
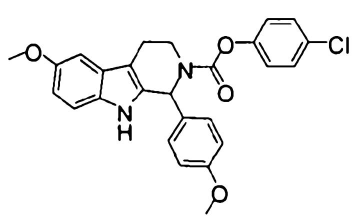
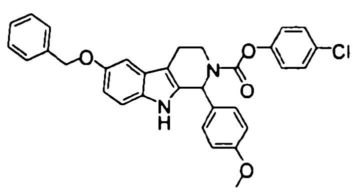
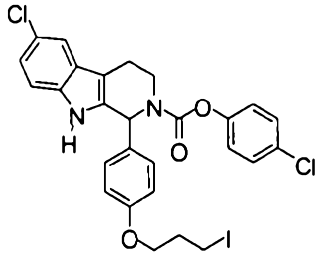
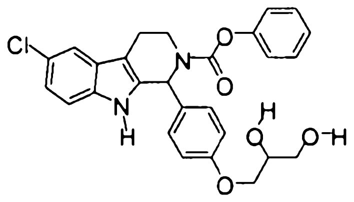
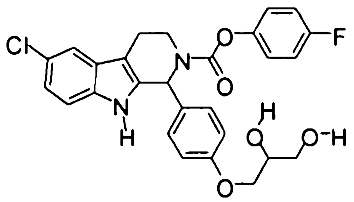
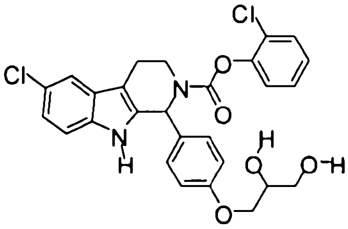
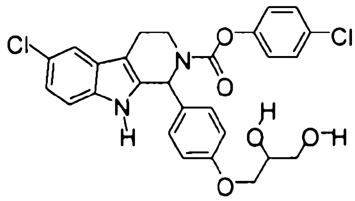
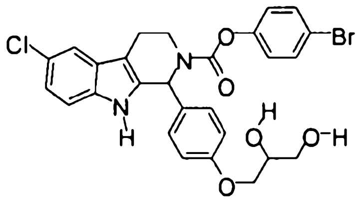
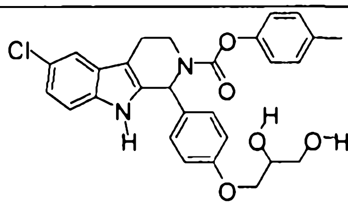
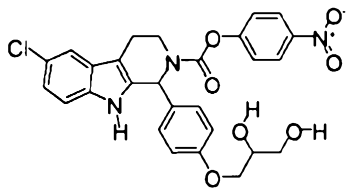
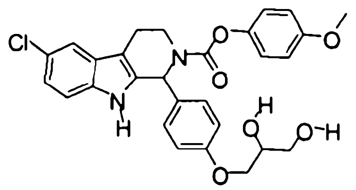
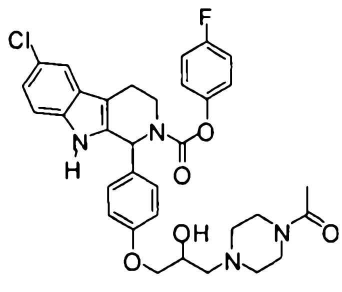
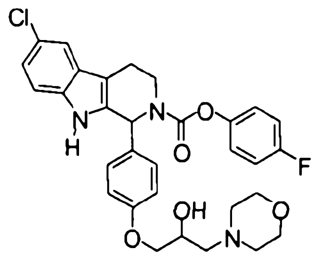
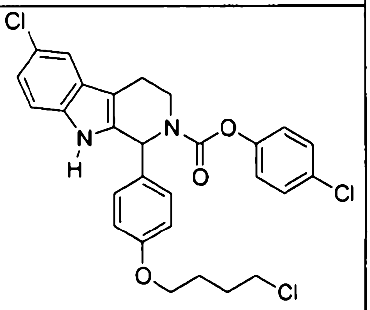
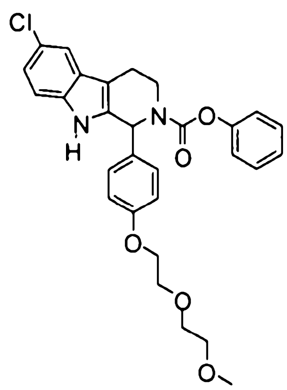
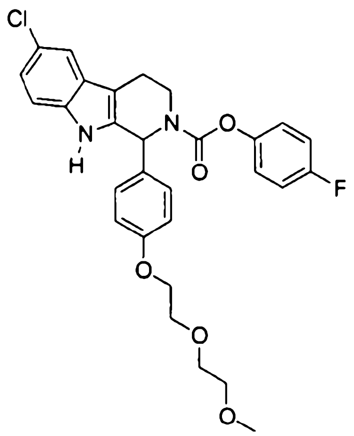
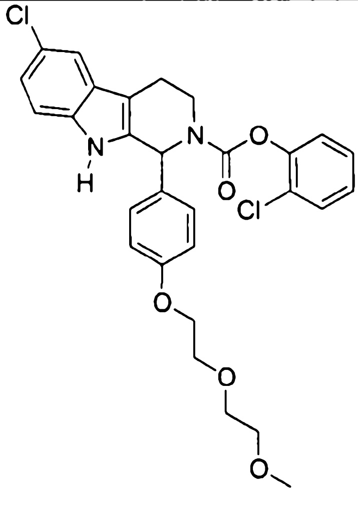
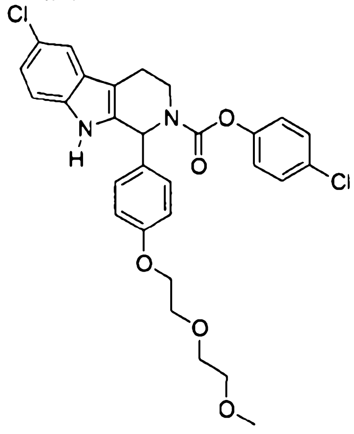
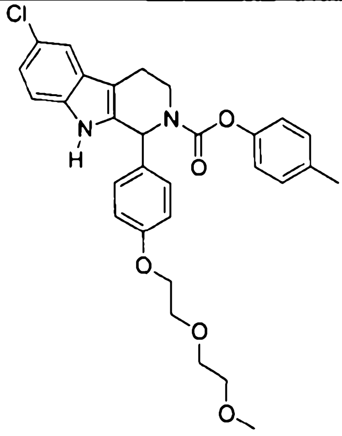
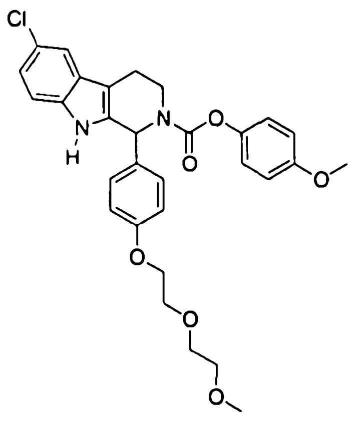
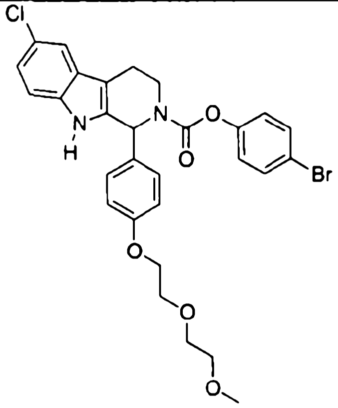
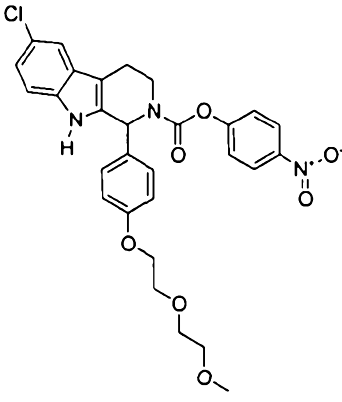
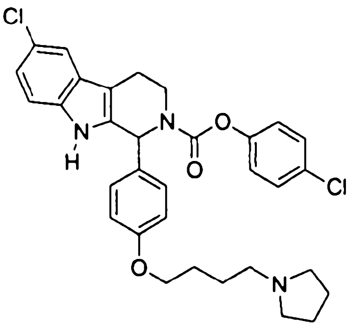
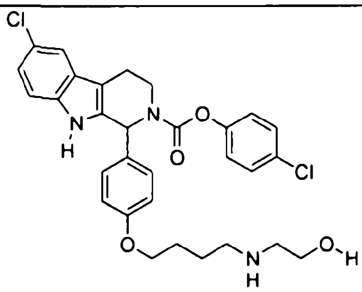
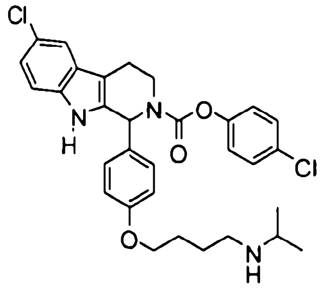
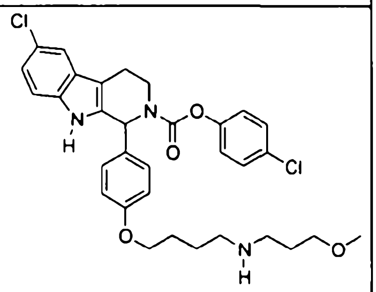
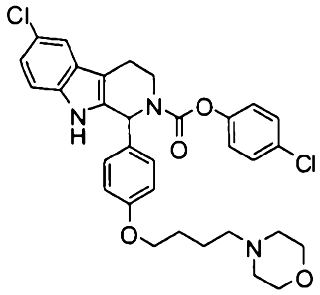
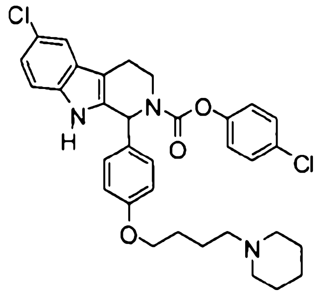
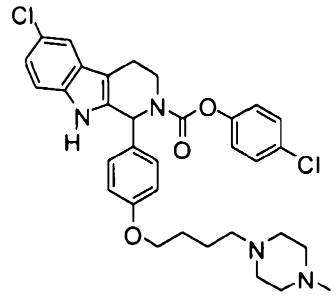
 426	 427	 428
 429	 432	 433
 436	 437	 440
 444	 446	 448

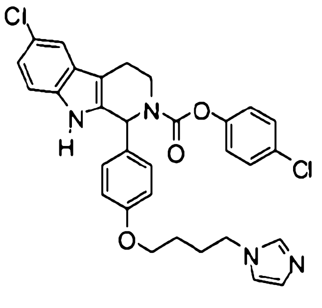
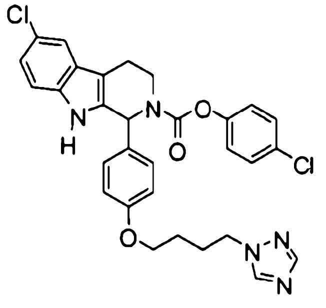
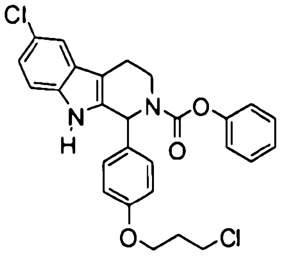
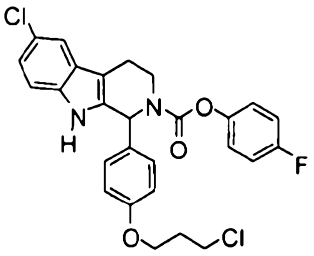
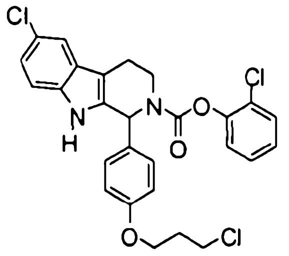
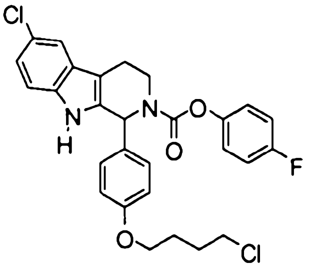
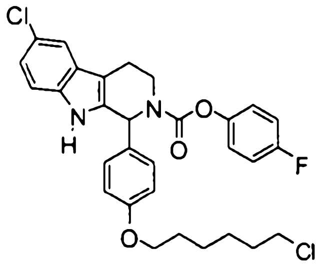
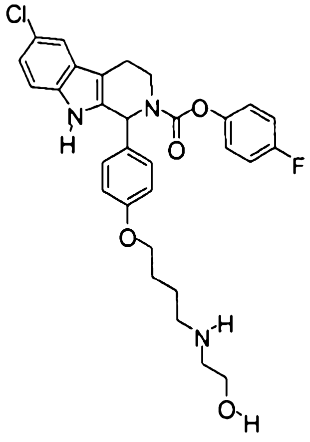
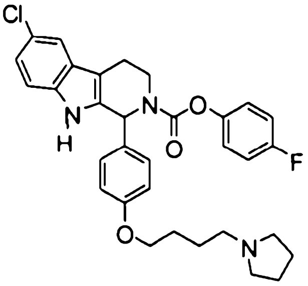
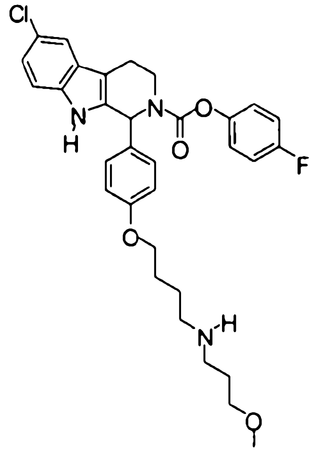
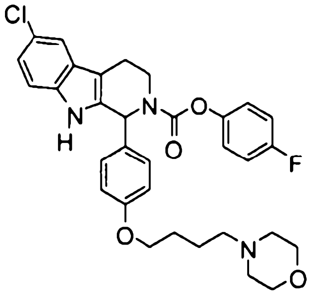
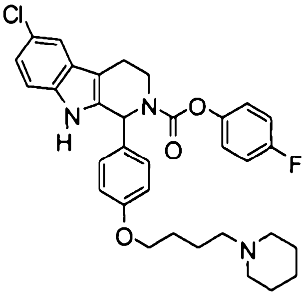
 450	 452	 454
 455	 460	 462
 463	 465	 467
 468	 470	 471

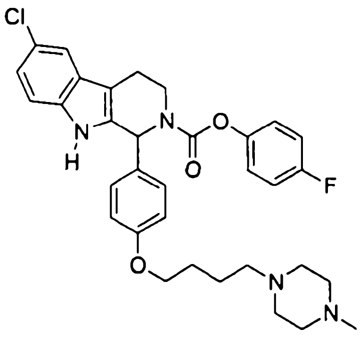
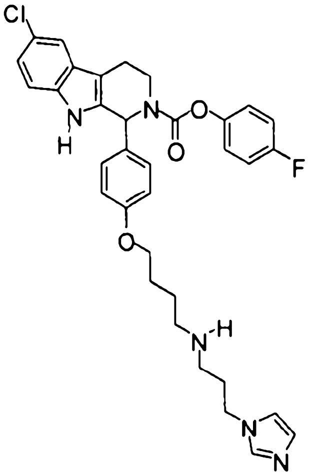
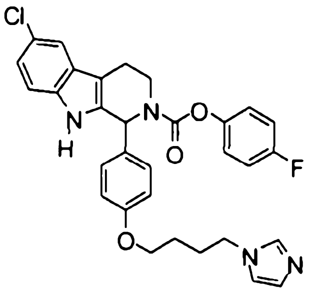
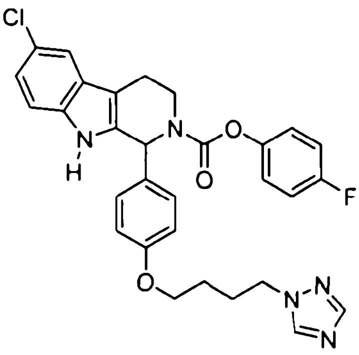
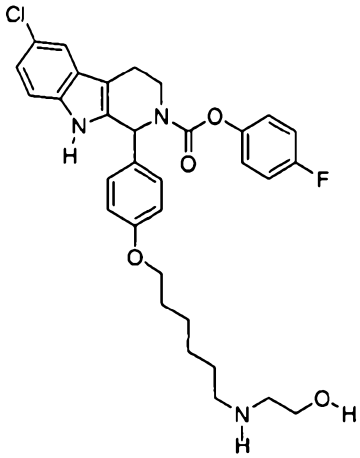
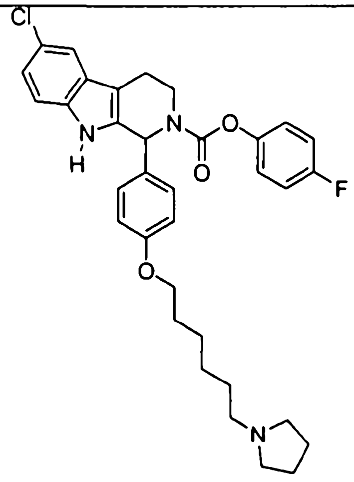
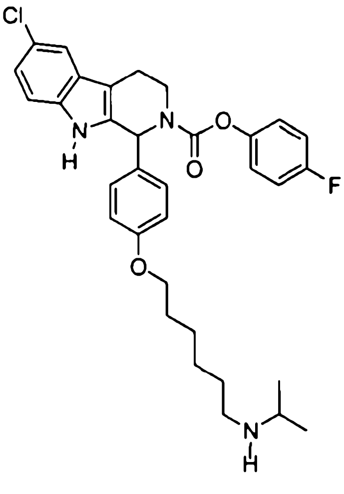
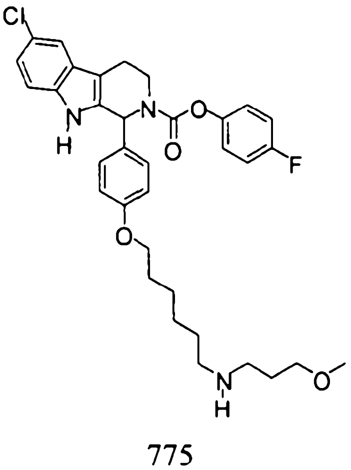
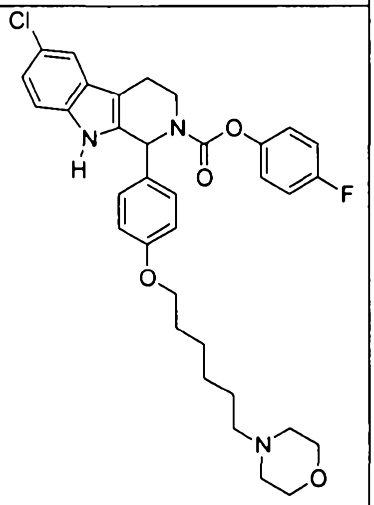
 479	 482	 489
 491	 493	 500
 501	 502	 519
 544	 570	 571

 572	 575	 576
 577	 578	 579
 580	 581	 587
 588	 589	 590
 591	 592	 593
 594	 614	 616

 617	 626	 627
 628	 629	 630
 631	 632	 635
 637	 638	 660
 670	 673	 674

 675	 677	 678
 680	 681	 698
 699	 700	 701
 702	 703	 704

 705	 706	 710
 712	 713	 719
 723	 735	 736
 737	 738	 739

 740	 741	 742
 743	 772	 773
 774	 775	 776

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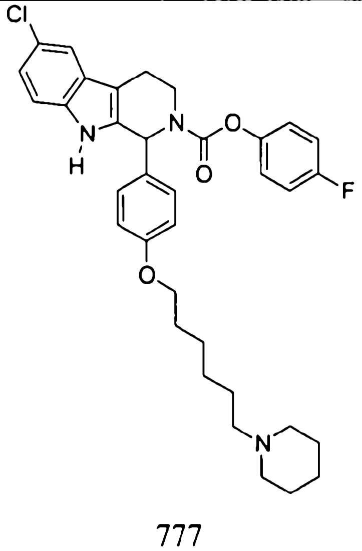
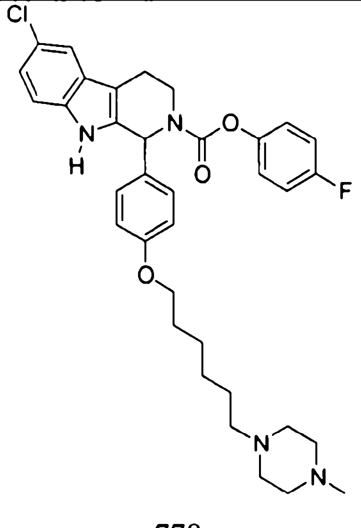
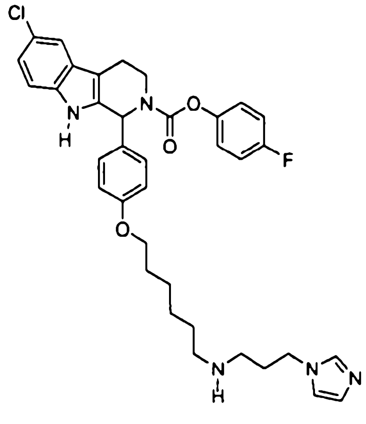
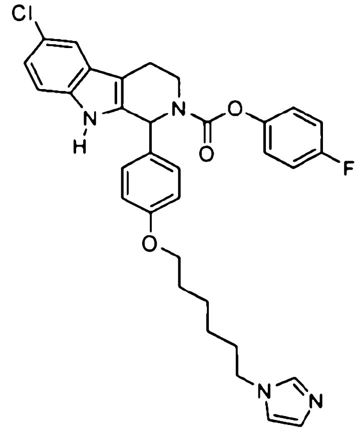
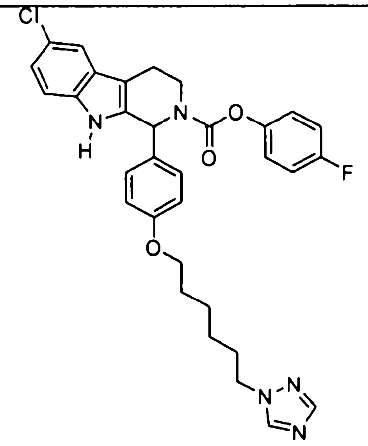
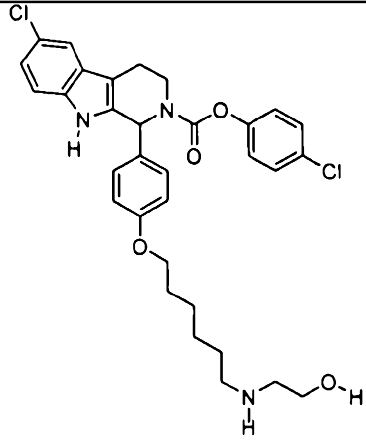
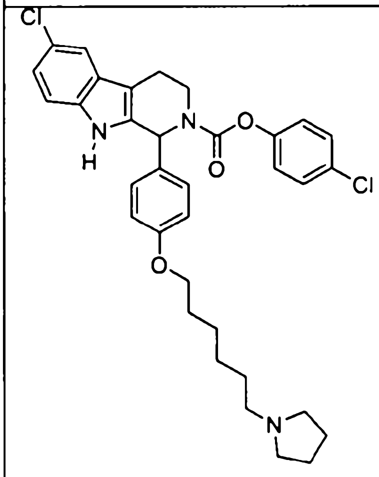
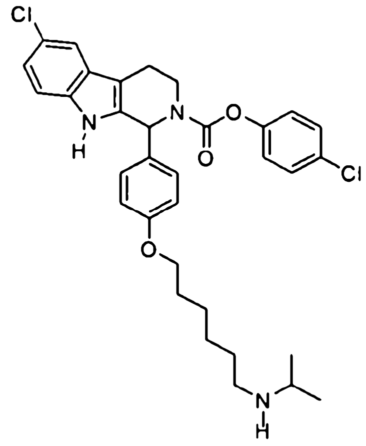
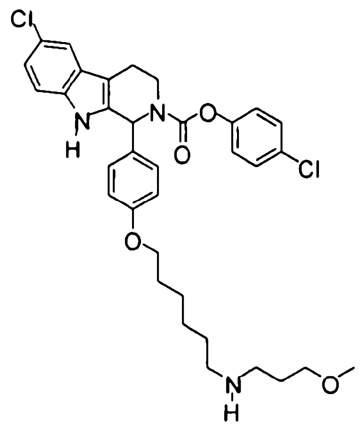
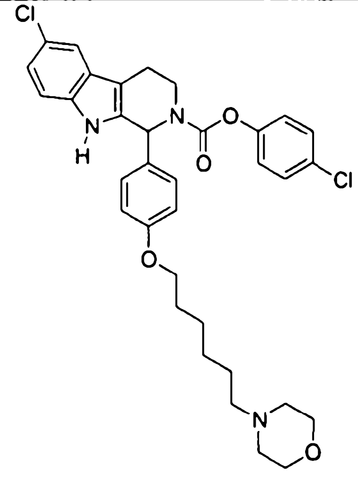
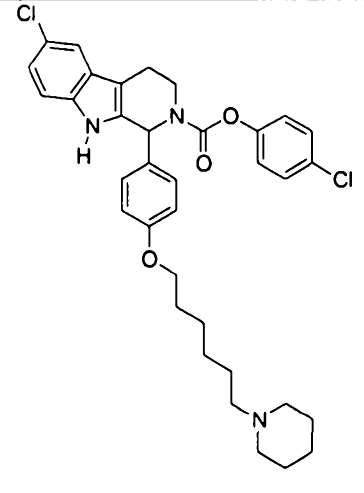
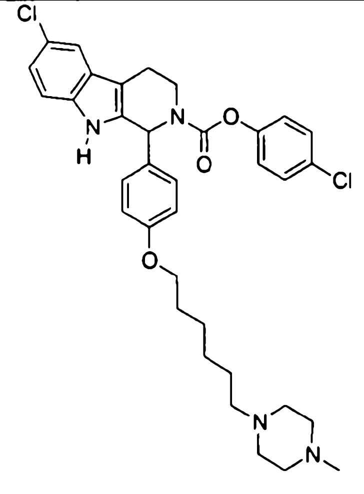
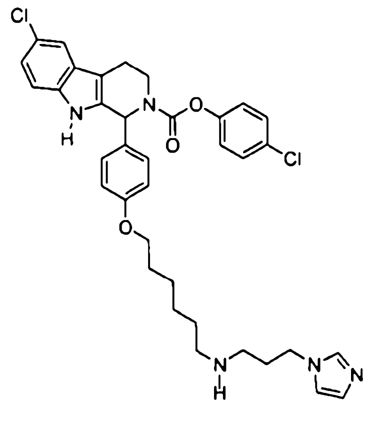
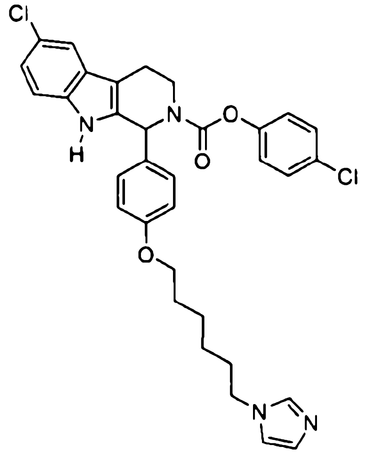
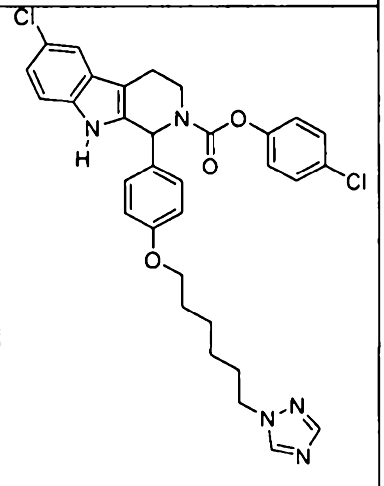
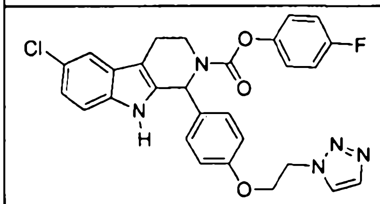
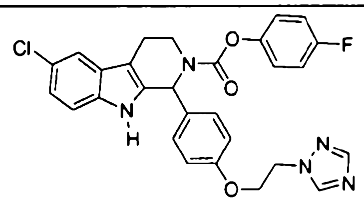
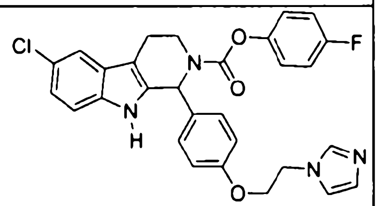
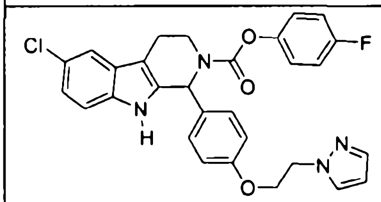
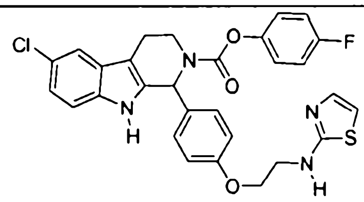
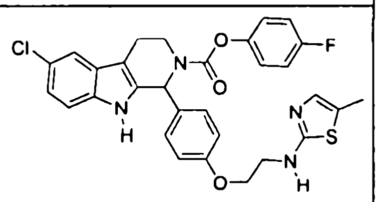
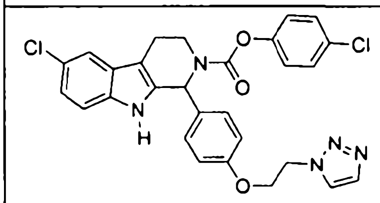
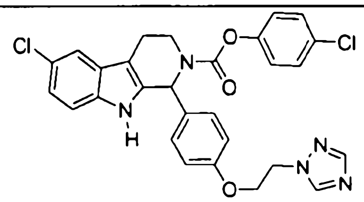
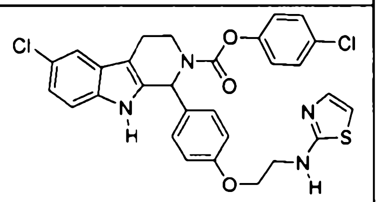
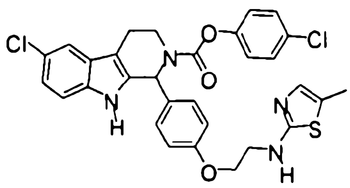
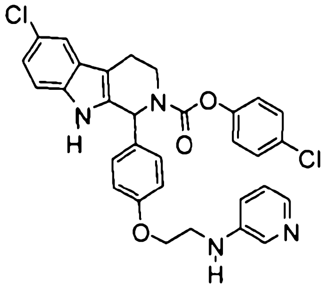
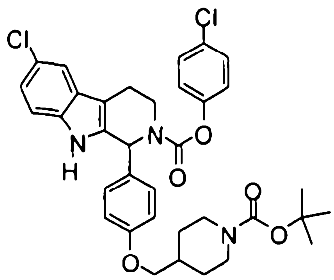
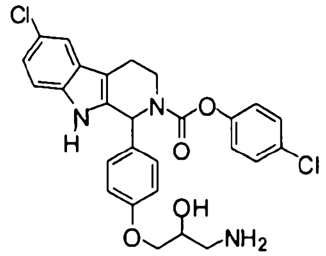
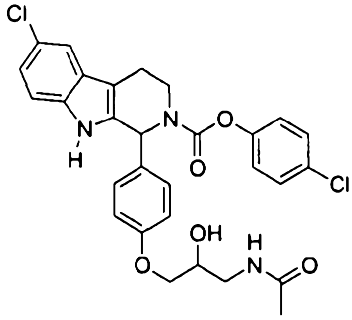
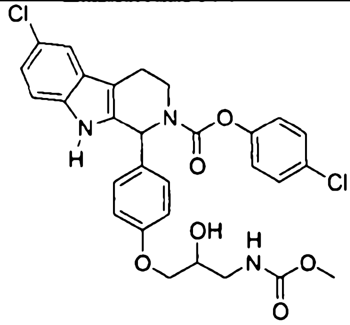
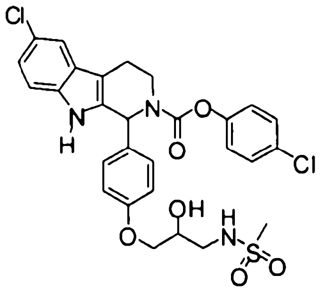
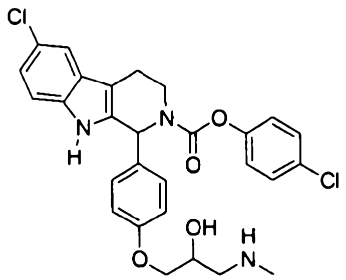
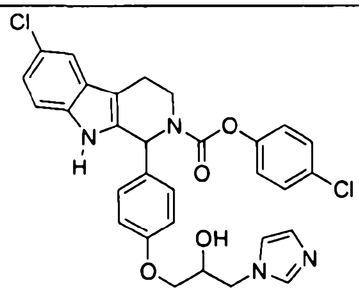
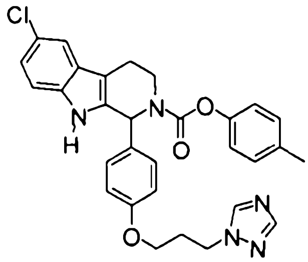
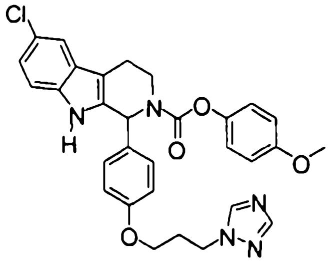
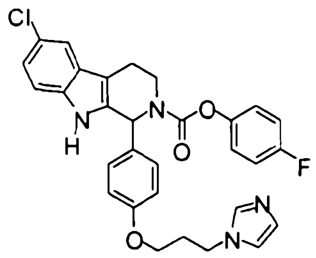
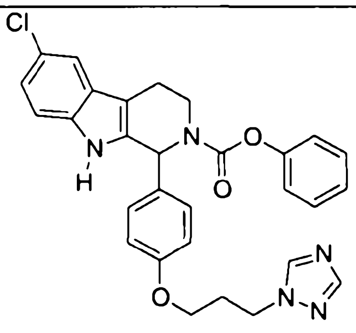
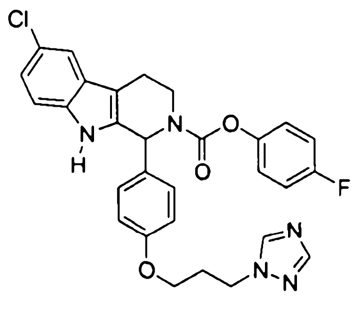
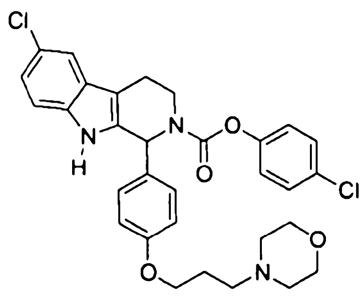
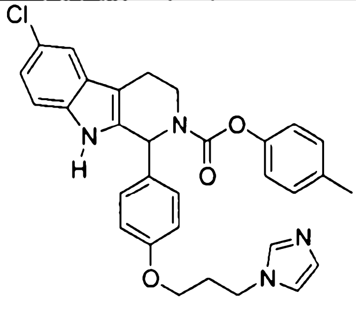
 777	 778	 779
 780	 781	 782
 783	 784	 785

 786	 787	 788
 789	 790	 791
 833	 834	 835
 836	 837	 838
 839	 840	 841

 842	 843	 845
 846	 847	 848
 849	 850	 867
 882	 888	 889
 891	 892	 894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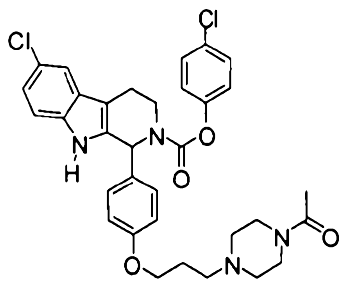
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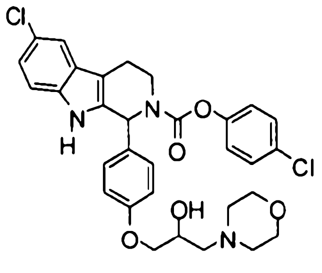
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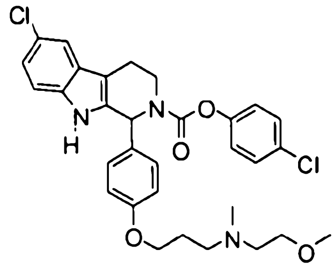
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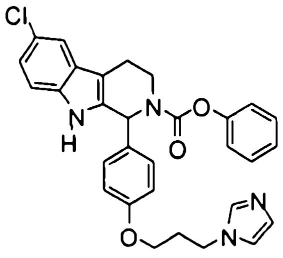
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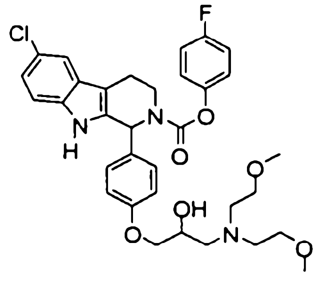
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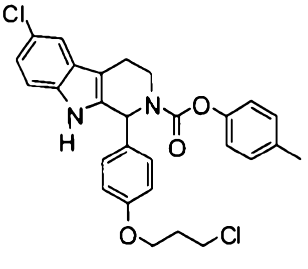
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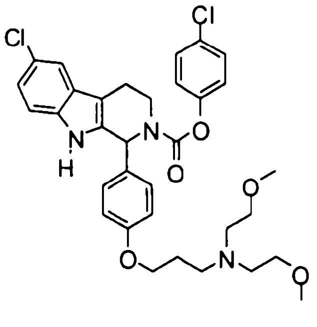
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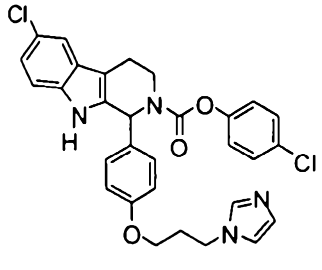
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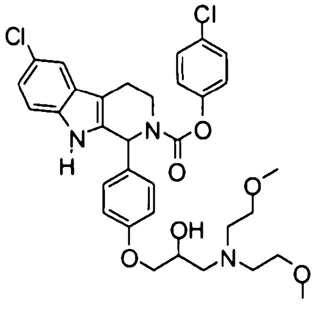
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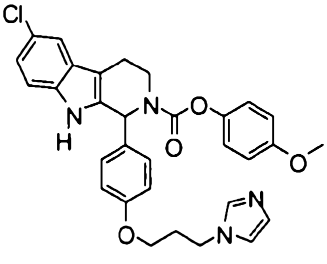
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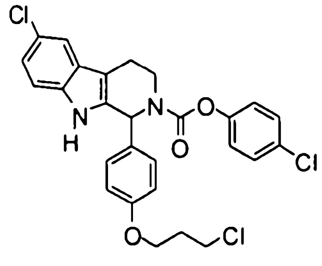
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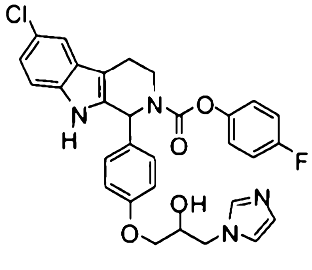
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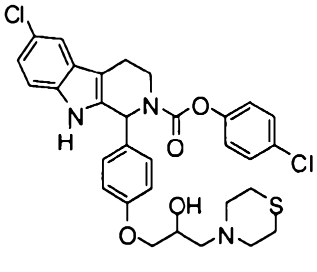
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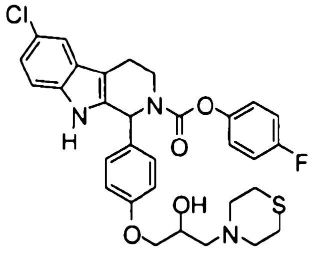
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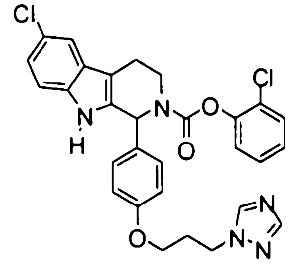
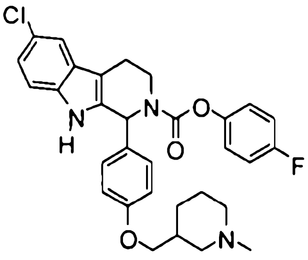
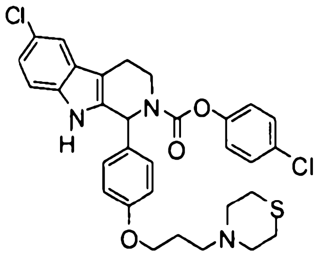
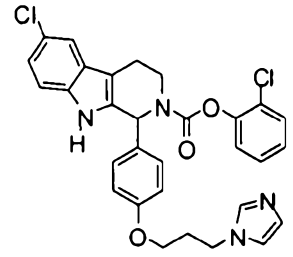
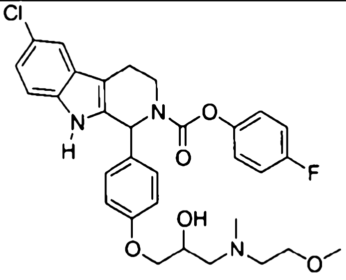
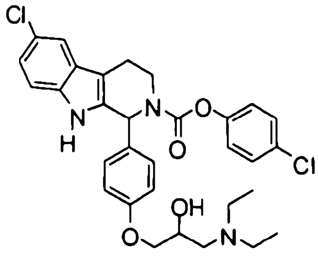
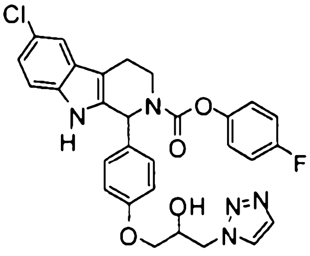
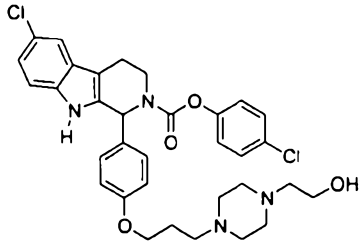
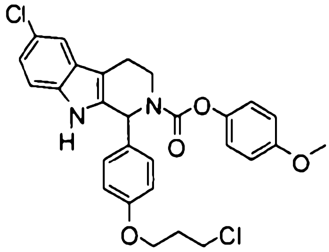
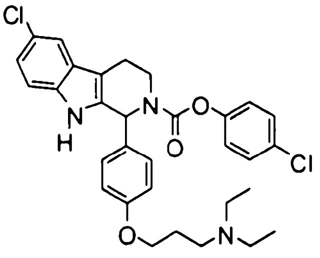
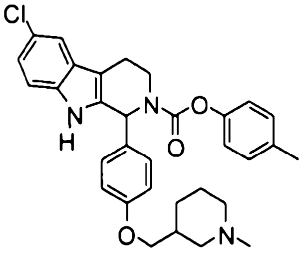
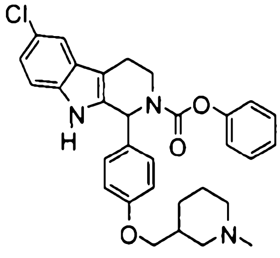
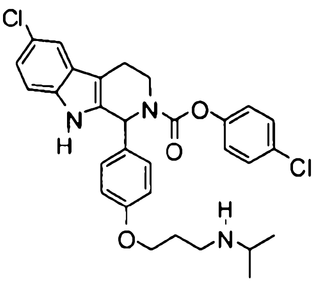
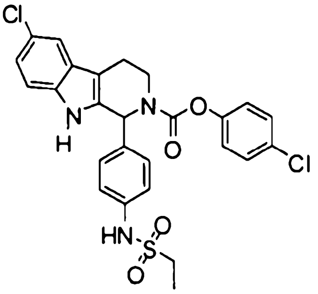
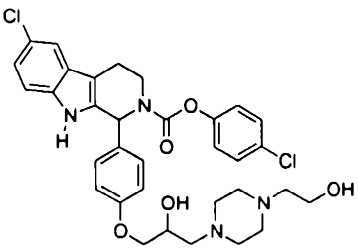
 926	 932	 933
 934	 936	 938
 941	 942	 944
 946	 951	 952
 953	 958	 960

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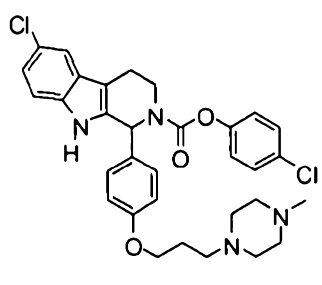
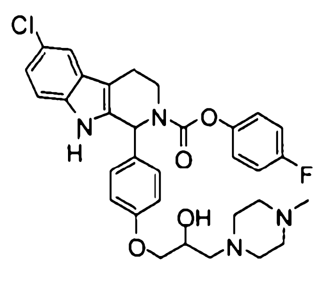
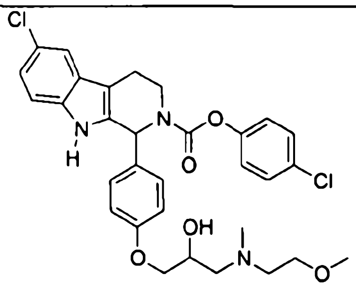
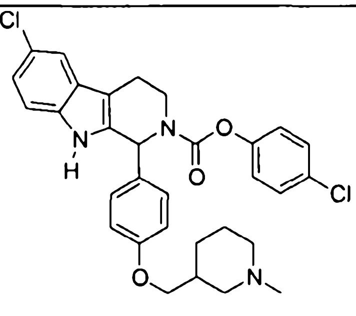
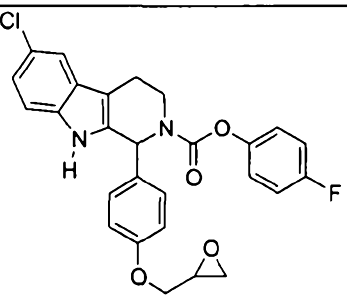
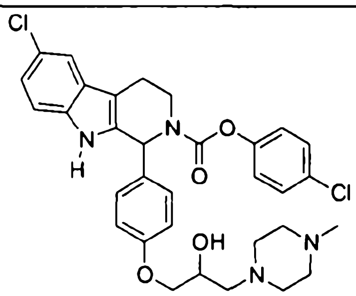
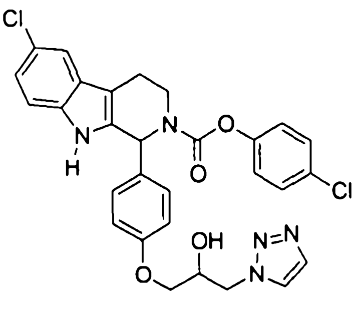
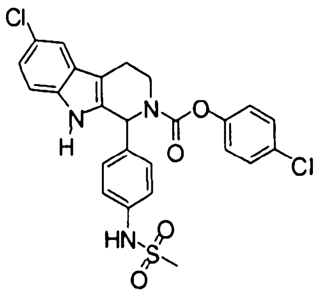
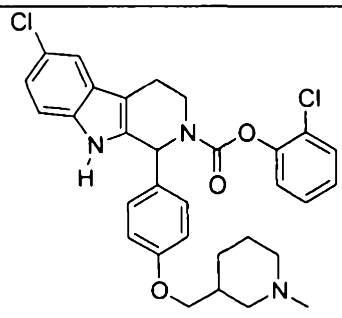
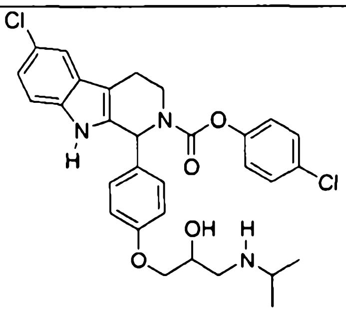
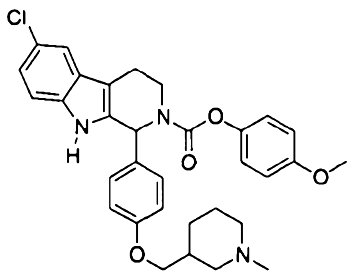
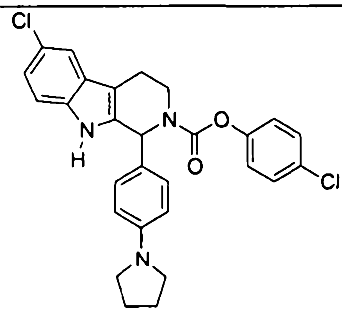
 961	 963	 964
 966	 967	 970
 973	 974	 976
 977	 981	 984

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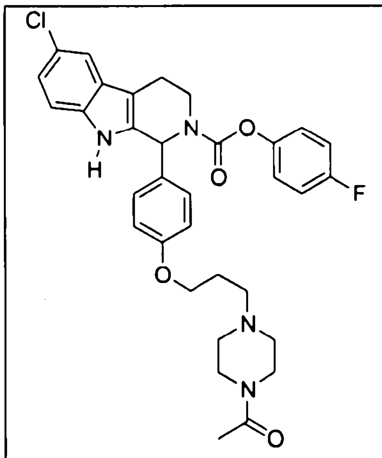
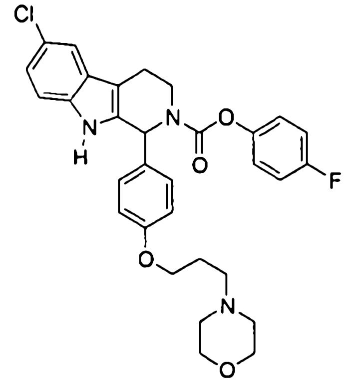
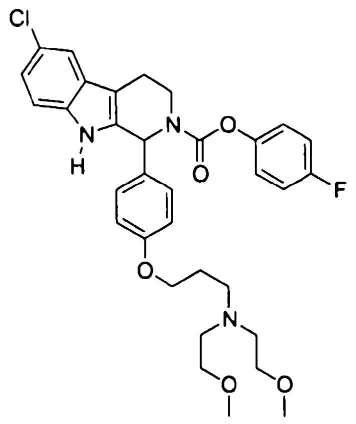
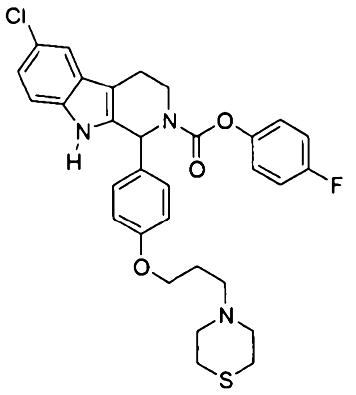
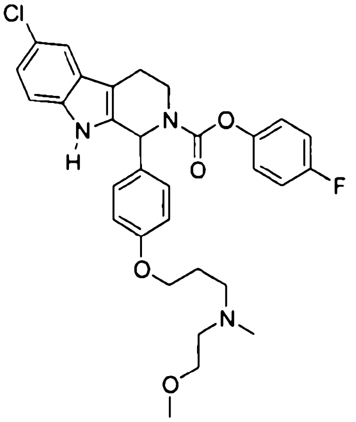
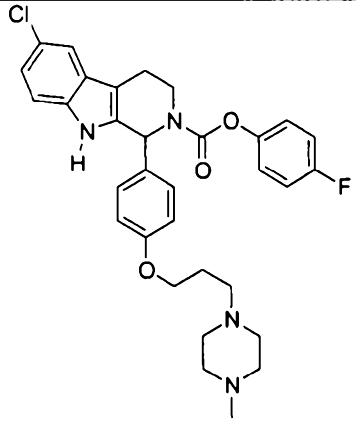
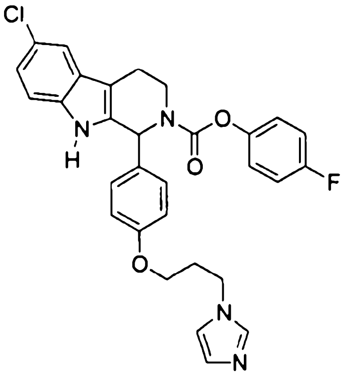
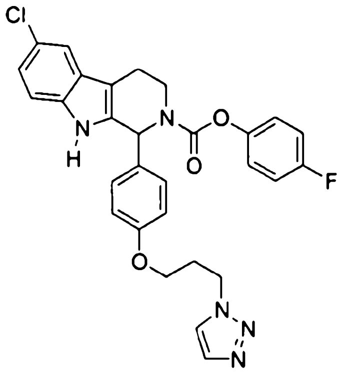
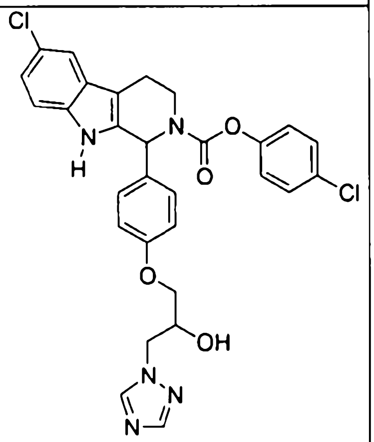
 988	 989	 990
 991	 992	 993
 994	 995	 996

or a pharmaceutically acceptable salt, racemate or stereoisomer thereof.

3. The compound of claim 1, wherein

X is C_1 to C_6 alkyl optionally substituted with one or more halogen; halogen; or C_1 to C_5 alkoxy optionally substituted with phenyl;

R_0 is halogen; cyano; nitro; sulfonyl substituted with C_1 to C_6 alkyl or morpholinyl; amino optionally substituted with C_1 to C_6 alkyl, -C(O)-R_b,

-C(O)O-R_b, alkylsulfonyl and tetrahydropyranyl; C_1 to C_6 alkyl optionally substituted with one or more halogen substituents; -C(O)-R_n; or -OR_a;

R_a is hydrogen; C_2 to C_8 alkenyl; -C(O)O-R_b; C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen, C_1 to C_4 alkoxy, C_1 to C_4 alkoxy-C_1 to C_4 alkoxy, amino, alkylamino, dialkylamino, acetamide, -C(O)-R_b, -C(O)O-R_b, aryl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxolan-2-one, oxiranyl, 1,2,3-triazole, 1,2,4-triazole, imidazole or pyrazole;

wherein amino is optionally substituted with C_1 to C_4 alkoxycarbonyl, pyridine, thiazole, wherein pyridine and thiazole are each optionally substituted with C_1 to C_4 alkyl;

wherein alkylamino and dialkylamino are each optionally substituted on alkyl with hydroxyl, C_1 to C_4 alkoxy or imidazole; and

wherein morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl and oxiranyl are each optionally substituted with -C(O)-R_n, -C(O)O-R_n or C_1 to C_4 alkyl, wherein C_1 to C_4 alkyl is optionally substituted with hydroxyl;

R_b is hydroxyl; C_1 to C_4 alkoxy; C_2 to C_8 alkenyl; phenyl optionally substituted with one or more halogen substituents; furan; or C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from C_1 to C_4 alkoxy, phenyl, amino or morpholinyl; and,

R_d is phenyl substituted by one or more substituents independently selected from halogen, nitro, C_1 to C_6 alkyl and -OR_e; and,

wherein all other variables are as previously defined.

4. The compound of claim 3, wherein

X is C_1 to C_6 alkyl; halogen; or C_1 to C_5 alkoxy optionally substituted with phenyl;

R_0 is halogen; cyano; nitro; sulfonyl substituted with C_1 to C_6 alkyl or morpholinyl; amino optionally substituted with -C(O)-R_b, -C(O)O-R_b, alkylsulfonyl and tetrahydropyranyl; C_1 to C_6 alkyl optionally substituted with one or more halogen substituents; -C(O)-R_n; or -OR_a;

R_a is hydrogen; C_2 to C_8 alkenyl; -C(O)O-R_b; C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from hydroxyl, halogen, C_1 to C_4 alkoxy, C_1 to C_4 alkoxy-C_1 to C_4 alkoxy, amino, alkylamino, dialkylamino, acetamide, -C(O)O-R_b, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, 1,3-dioxolan-2-one, oxiranyl, 1,2,3-triazole, 1,2,4-triazole, imidazole or pyrazole;

wherein amino is optionally substituted with C_1 to C_4 alkoxycarbonyl, pyridine, thiazole, wherein pyridine and thiazole are each optionally substituted with C_1 to C_4 alkyl;

wherein alkylamino and dialkylamino are each optionally substituted on alkyl with hydroxyl, C_1 to C_4 alkoxy or imidazole; and,

wherein morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl and oxiranyl are each optionally substituted with -C(O)-R_n, -C(O)O-R_n or C_1 to C_4 alkyl, wherein C_1 to C_4 alkyl is optionally substituted with hydroxyl; and,

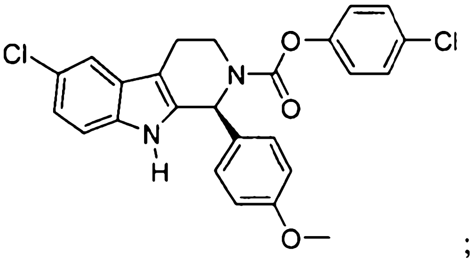
R_b is hydroxyl; C_1 to C_4 alkoxy; C_2 to C_8 alkenyl; phenyl optionally substituted with one or more halogen substituents; furan; or C_1 to C_8 alkyl optionally substituted with one or more substituents independently selected from C_1 to C_4 alkoxy or morpholinyl; and,

wherein all other variables are as previously defined.

5. The compound of any one of claims 1, 3 or 4 wherein said compound has a chiral carbon at the point of attachment of the R_0 substituted phenyl and said compound is an (S) isomer at said chiral carbon.

6. The compound of claim 2, wherein said compound has a chiral carbon at the point of attachment of the phenyl ring directly attached to the tricyclic core and said compound is an (S) isomer at said chiral carbon.

7. The compound of claim 6, wherein said compound is selected from the group consisting of:



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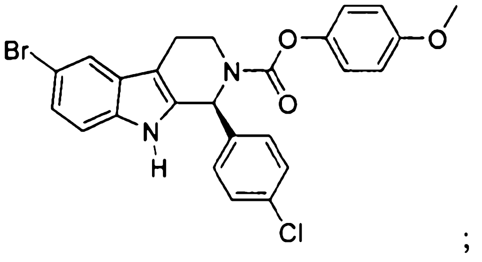

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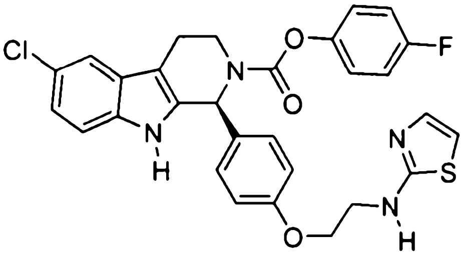
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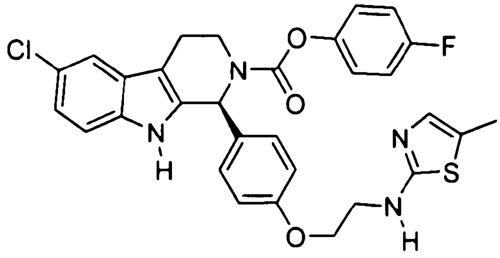
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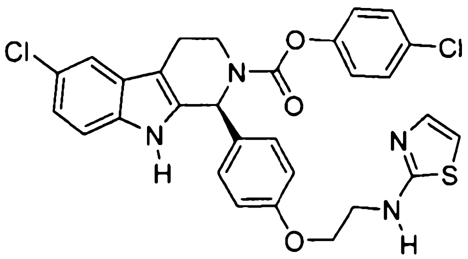
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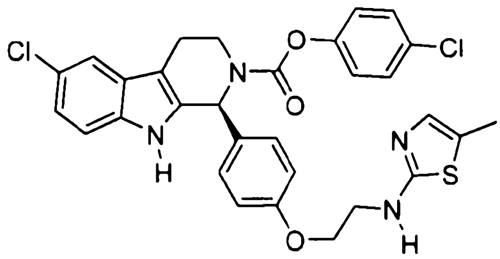
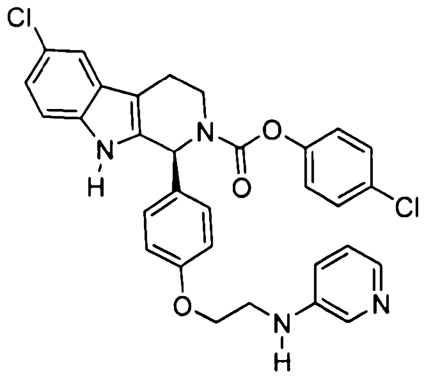

; and

,

or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound of any one of claims 1-6 or a pharmaceutically acceptable salt, racemate or stereoisomer thereof and a pharmaceutically acceptable excipient.

9. A pharmaceutical composition comprising a compound of claim 7 or a pharmaceutically acceptable salt, racemate or stereoisomer thereof and a pharmaceutically acceptable excipient.

10. A compound of claim 1, substantially as hereinbefore described with reference to any one of the examples.

11. A compound of claim 2, substantially as hereinbefore described with reference to any one of the examples.

12. A pharmaceutical composition of claim 8, substantially as hereinbefore described with reference to any one of the examples.

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13. A pharmaceutical composition of claim 9, substantially as hereinbefore described with reference to any one of the examples.

Dated 29 January, 2010

PTC Therapeutics, Inc.

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

FIG. 1

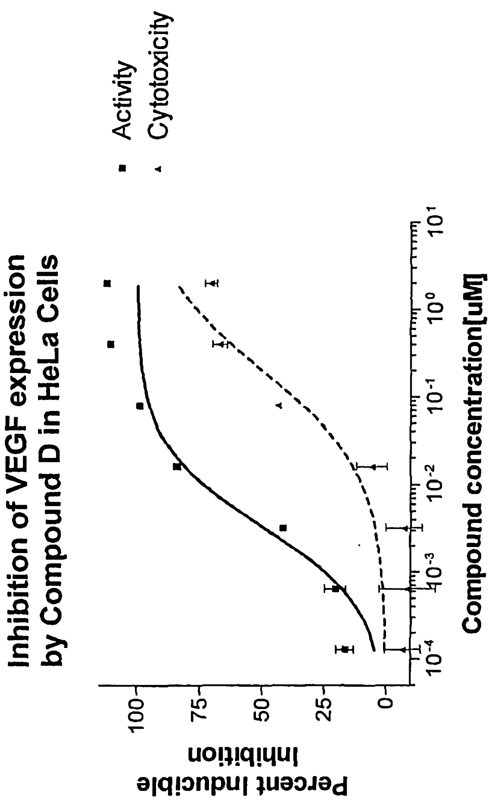
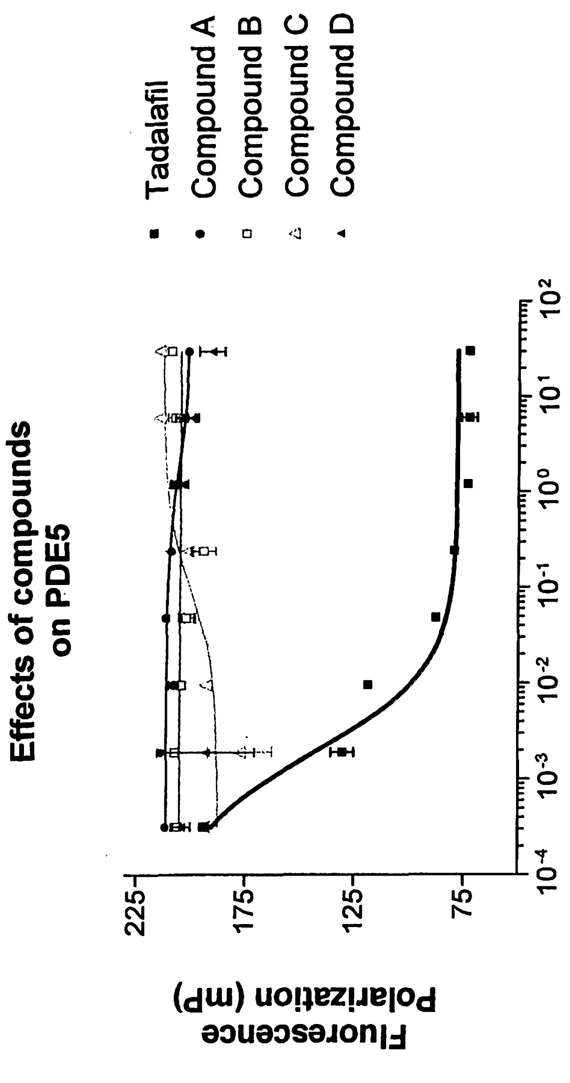

Inhibition of VEGF expression
by Compound D in HeLa Cells
Percent Inducible
Inhibition
100
75
50
25
0
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
Compound concentration[uM]
Activity
Cytotoxicity

FIG. 2


Effects of compounds on PDE5
Fluorescence Polarization (mP)
225
175
125
75
Compound concentration [uM]
10^-4
10^-3
10^-2
10^-1
10^0
10^1
10^2
Tadalafil
Compound A
Compound B
Compound C
Compound D