1,6-NAPHTHYRIDINE DERIVATIVES AS ANTIDIABETICS

The present invention relates to 1,6-naphthyridine derivatives, pharmaceutical compositions containing them, and their use for treating diabetes and related disorders in a subject.

DESCRIPTION OF THE RELATED ART

Diabetes is characterized by impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in the diabetic patient. Underlying defects lead to a classification of diabetes into two major groups: type 1 diabetes, or insulin dependent diabetes mellitus (IDDM), arises when patients lack insulin-producing beta-cells in their pancreatic glands. Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), occurs in patients with impaired beta-cell function and alterations in insulin action.

The current treatment for type 1 diabetic patients is the injection of insulin, while the majority of type 2 diabetic patients are treated with agents that stimulate beta-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin. The drugs presently used to treat type 2 diabetes include alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and metformin.

Over time almost one-half of type 2 diabetic subjects lose their response to these agents. Insulin treatment is instituted after diet, exercise, and oral medications have failed to adequately control blood glucose. The drawbacks of insulin treatment are the need for drug injection, the potential for hypoglycemia, and weight gain.

Because of the problems with current treatments, new therapies to treat type 2 diabetes are needed. In particular, new treatments to retain normal (glucose-dependent) insulin secretion are needed. Such new drugs should have the following characteristics: dependency on glucose for promoting insulin secretion, *i.e.*, compounds that stimulate

insulin secretion only in the presence of elevated blood glucose; low primary and secondary failure rates; and preservation of islet cell function. The strategy to develop the new therapy disclosed herein is based on the cyclic adenosine monophosphate (cAMP) signaling mechanism and its effects on insulin secretion.

Metabolism of glucose promotes the closure of ATP-dependent K+ channels, which leads to cell depolarization and subsequent opening of Ca++ channels. This in turn results in the exocytosis of insulin granules. cAMP is a major regulator of glucose-stimulated insulin secretion. However, it has little if any effects on insulin secretion in the absence of or at low glucose concentrations (Weinhaus, A., *et al.*, Diabetes 47: 1426-1435 (1998)). The effects of cAMP on insulin secretion are thought to be mediated by a protein kinase A pathway.

Endogenous secretagogues like pituitary adenylate cyclase activating peptide (PACAP), VIP, and GLP-1 use the cAMP system to regulate insulin secretion in a glucose-dependent fashion (Komatsu, M., *et al.*, Diabetes 46: 1928-1938, (1997)). Also, phosphodiesterases (PDEs) are known to be involved in the regulation of the cAMP system.

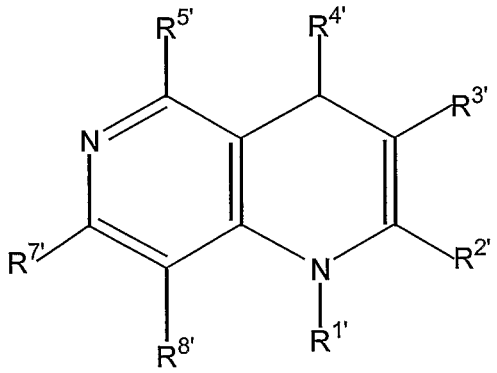
PACAP is a potent stimulator of glucose-dependent insulin secretion from pancreatic beta cells. Three different PACAP receptor types (R1, R2, and R3) have been described (Harmar, A., *et al.*, Pharmacol. Reviews 50: 265-270 (1998)). The insulinotropic action of PACAP is mediated by the GTP binding protein Gs. Accumulation of intracellular cAMP in turn activates nonselective cation channels in beta cells increasing [Ca++]i, and promoting the exocytosis of insulin-containing secretory granules.

Vasoactive intestinal peptide (VIP) is a 28 amino acid peptide that was first isolated from hog upper small intestine (Said and Mutt, Science 169: 1217-1218, 1970; U.S. Patent No. 3,879,371). This peptide belongs to a family of structurally related, small polypeptides that includes helodermin, secretin, the somatostatins, and glucagon. The biological effects of VIP are mediated by the activation of membrane-bound receptor proteins that are coupled to the intracellular cAMP signaling system. These receptors were originally known as VIP-R1 and VIP-R2, however, they were later found to be the same receptors as PACAP-R2 and PACAP-R3.

GLP-1 is released from the intestinal L-cell after a meal and functions as an incretin hormone (*i.e.*, it potentiates glucose-induced insulin release from the pancreatic beta cell). It is a 37-amino acid peptide that is differentially expressed by the glucagon gene, depending upon tissue type. The clinical data that support the beneficial effect of raising cAMP levels in β-cells have been collected with GLP-1. Infusions of GLP-1 in poorly controlled type 2 diabetics normalized their fasting blood glucose levels (Gutniak, M., *et al.*, New Eng. J. Med. 326:1316-1322, (1992)) and with longer infusions improved the beta cell function to those of normal subjects (Rachman, J. *et al.*, Diabetes 45: 1524-1530, (1996)). A recent report has shown that GLP-1 improves the ability of β-cells to respond to glucose in subjects with impaired glucose tolerance (Byrne M., *et al.*, Diabetes 47: 1259-1265 (1998)). All of these effects, however, are short-lived because of the short half-life of the peptide.

SUMMARY OF THE INVENTION

The invention provides compounds, pharmaceutical compositions, and methods of using the same for treating diabetes and related disorders. Compounds of the invention include compounds of formula (II)



(II)

wherein

$R^{1'}$ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

$R^{1'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms,

cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{10} is selected from nitro, nitrile, hydroxy, halogen, acyl of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, $NR^{11}R^{12}$, $C(=O)OR^{11}$, $C(=O)NHR^{11}$, $NHC(=O)R^{13}$, $NHS(=O)_2R^{13}$, $S(=O)_{0-2}R^{13}$, $S(=O)_2NHR^{11}$, cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O);

R^{13} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

R^{11} and R^{12} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

A is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and haloalkyl of 1-8 carbon atoms;

R^9 is selected from hydroxy, alkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, O-A-R^{14}, $NR^{11}R^{12}$; or

R^9 is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, all of which may be substituted with 1-3 of R^{10}, or

R^9 is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{14} is selected from cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

with the proviso for $R^{1'}$ that when A is CH_2, R^9 is not optionally substituted biphenyl;

$R^{2'}$ is selected from $NR^{15}R^{16}$, $S(O)_{0-2}R^{17}$, and OR^{17};

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, $S(=O)_2NHR^{18}$;

R^{18} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms

and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, and alkynyl of 2-6 carbon atoms, all of which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9;

R^{16} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

R^{16} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{17} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms, A-R^9, or

R^{17} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms

and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{3'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$, and O, cycloalkenyl of 4-8 carbon atoms, and heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$, and A-R^{20};

R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^9, or

R^{19} and R^{20} are independently selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{4'}$ is selected from =O, =S, and OR^{21};

R^{21} is hydrogen, or

R^{21} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7

membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, cycloalkoxy of 3-8 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$;

Q is selected from O and $S(=O)_{0-2}$;

R^{22} is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms, and cycloalkyl of 3-8 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, and cycloalkoxy of 3-8 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

with the proviso for $A(OR^{22})$-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, and cycloalkoxy of 3-8 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said

heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, C(=O)R^{24}, C(=O)OR^{26}, C(=O)$NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A(OR^{22})-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$

and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, all of which may be substituted with 1-3 of R^{10};

R^{29} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)$NR^{24}R^{25}$, A-$NR^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

and pharmaceutically acceptable salts thereof.

Another aspect of the invention includes compounds of formula (II), wherien $R^{1'}$ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

$R^{1'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms

and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{10} is selected from nitro, nitrile, hydroxy, halogen, acyl of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, $NR^{11}R^{12}$, $C(=O)OR^{11}$, $C(=O)NHR^{11}$, $NHC(=O)R^{13}$, $NHS(=O)_2R^{13}$, $S(=O)_{0-2}R^{13}$, $S(=O)_2NHR^{11}$, cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O);

R^{13} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

R^{11} and R^{12} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

A is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and haloalkyl of 1-8 carbon atoms;

R^9 is selected from hydroxy, alkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, O-A-R^{14}, $NR^{11}R^{12}$; or

R^9 is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, all of which may be substituted with 1-3 of R^{10}, or

R^9 is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{14} is selected from cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

with the proviso for $R^{1'}$ that when A is CH_2, R^9 is not optionally substituted biphenyl;

$R^{2'}$ is $NR^{15}R^{16}$;

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, $S(=O)_2NHR^{18}$;

R^{18} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, and alkynyl of 2-6 carbon atoms, all of which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9;

R^{16} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

R^{16} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$ and A-R^{20};

R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^9, or

R^{19} and R^{20} are independently selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{4'}$ is selected from =O, =S, and OR^{21};

R^{21} is hydrogen, or

R^{21} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{5'}$ is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{5'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms,

alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$;

Q is selected from O and $S(=O)_{0-2}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

with the proviso for A(OR^{22})-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $C(=O)R^{24}$, $C(=O)OR^{26}$, $C(=O)NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A(OR^{22})-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}; and

R^{29} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, A-$C(=O)NR^{24}R^{25}$, A-$NR^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}.

$R^{7'}$ and $R^{8'}$ are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{7'}$ and $R^{8'}$ are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$;

and pharmaceutically acceptable salts thereof.

Methods of the invention provide for the treatment or prevention of diabetes, inlcuding Type 1 and Type 2 diabetes, and related disorders by administration of a compound of the invention. Related disorders include maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), gestational diabetes, and metabolic syndrome X.

In other embodiments, methods of the invention provide for the administration of a compound of the invention in combination with a PPAR agonist, an insulin sensitizer, a sulfonylurea, an insulin secretagogue, a hepatic glucose output lowering compound, an α-glucosidase inhibitor or insulin. PPAR agonist includes rosiglitazone and pioglitazone. Sulfonylureas include glibenclamide, glimepiride, chlorpropamide, and glipizide. Insulin secretagogues include GLP-1, GIP, PAC/VPAC receptor agonists, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, and glipizide. α-glucosidase inhibitors include acarbose, miglitol and voglibose. A hepatic glucose output lowering compound is metformin.

In another embodiment, methods of the invention provide for the administration of a compound of the invention in combination with an HMG-CoA reductase inhibitor, nicotinic acid, a bile acid sequestrant, a fibric acid derivative, antihypertensive drug, or an anti-obesity drug. Anti-obesity drugs include a β-3 agonist, a CB-1 antagonist, and a lipase inhibitor.

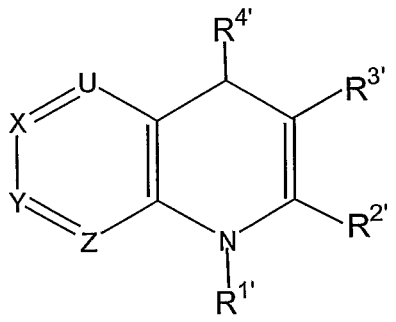
In another embodiment of the invention, methods are provided for the treatment or prevention of secondary causes of diabetes, such as glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes.

Finally, methods of the invention provide for increasing the sensitivity of pancreatic beta cells to an insulin secretagogue, by administering a compound of the invention. Insulin secretagogues include GLP-1, GIP, PAC/VPAC receptor agonists, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, and glipizide.

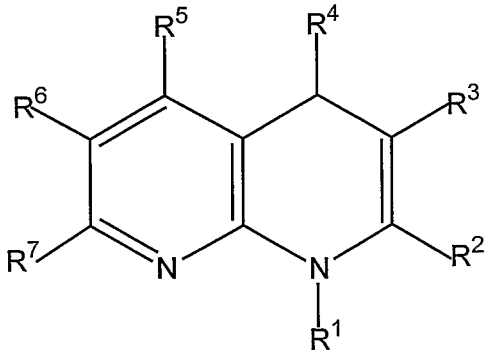
The present invention therefore provides compounds and methods for the treatment of diabetes and related disorders. These and other aspects of the invention will be more apparent from the following description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates generally to naphthyridine derivatives of the formula



wherein one of U, X, Y and Z is nitrogen and the others are C-R, where R is hydrogen or a substituent such as $R^{5'}$, $R^{7'}$ or $R^{8'}$, as described above for formula (II). $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are as defined above for formula (II). The invention relates to compounds of formula (II), as described above, and to compounds of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 correspond to $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{7'}$ and $R^{8'}$, respectively, of formula (II). Such compounds may be used in the treatment of diabetes and related disorders.

In one embodiment, the invention relates to compounds of formula (II), as described above. In another embodiment, the invention relates to compounds of formula

(II), wherein $R^{1'}$ is phenyl, which may be substituted with 1-3 of R^{10}, $R^{2'}$ is $NR^{15}R^{16}$, $R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or $R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$ and A-R^{20}, and $R^{4'}$ is =O.

In another embodiment, the invention relates to methods of treating diabetes and related disorders by administration of compounds of formula (II). Preferred methods relate to the treatment of Type 2 diabetes. In methods of the invention, compounds of formula (II) may be administered in combination with PPAR agonist, insulin sensitizers, sulfonylureas, insulin secretagogues, metformin, α-glucosidase inhibitors and insulin. In another embodiment, compounds of formula (II) are administered in combination with an HMG-CoA reductase inhibitor, nicotinic acid, a bile acid sequestrant, a fibric acid derivative, an anti-hypertensive drug or an anti-obesity drug.

In other methods of the invention, compounds of formula (II) are administered to treat or prevent secondary causes of diabetes or to increase the sensitivity of pancreatic beta cells to an insulin secretagogue.

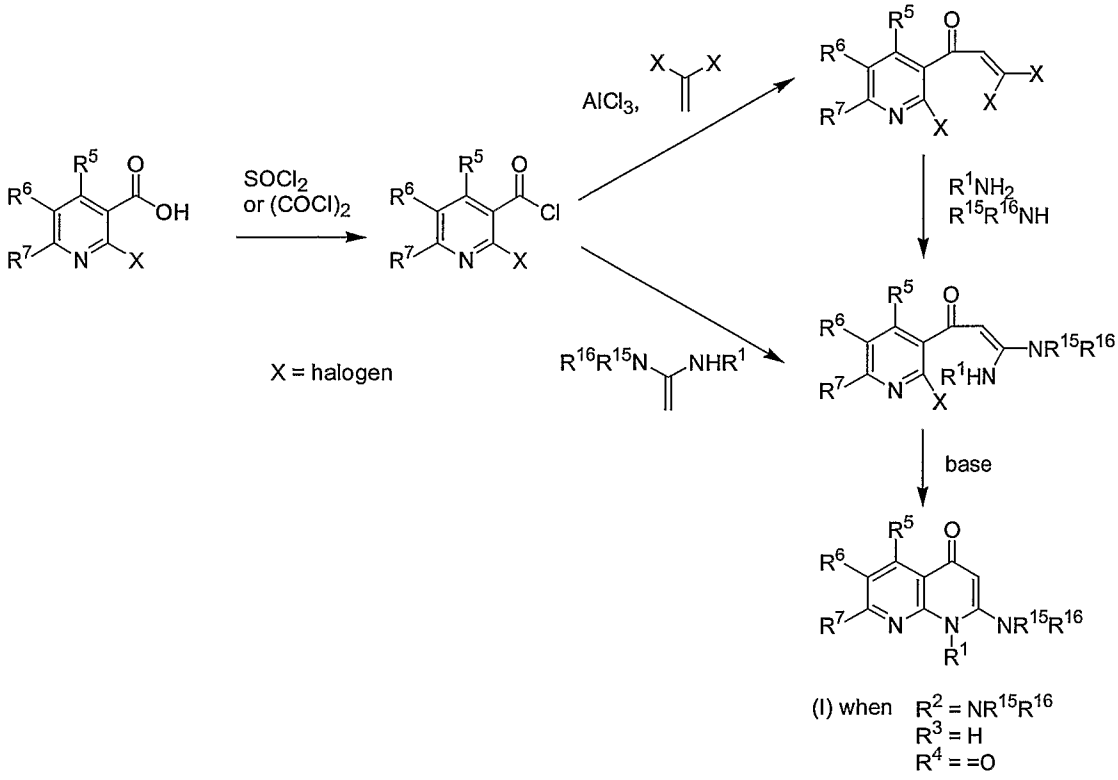
General Preparative Methods

The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general synthetic schemes are presented to aid the reader in synthesizing compounds of this invention, with more detailed particular examples being presented below in the experimental section describing the working examples.

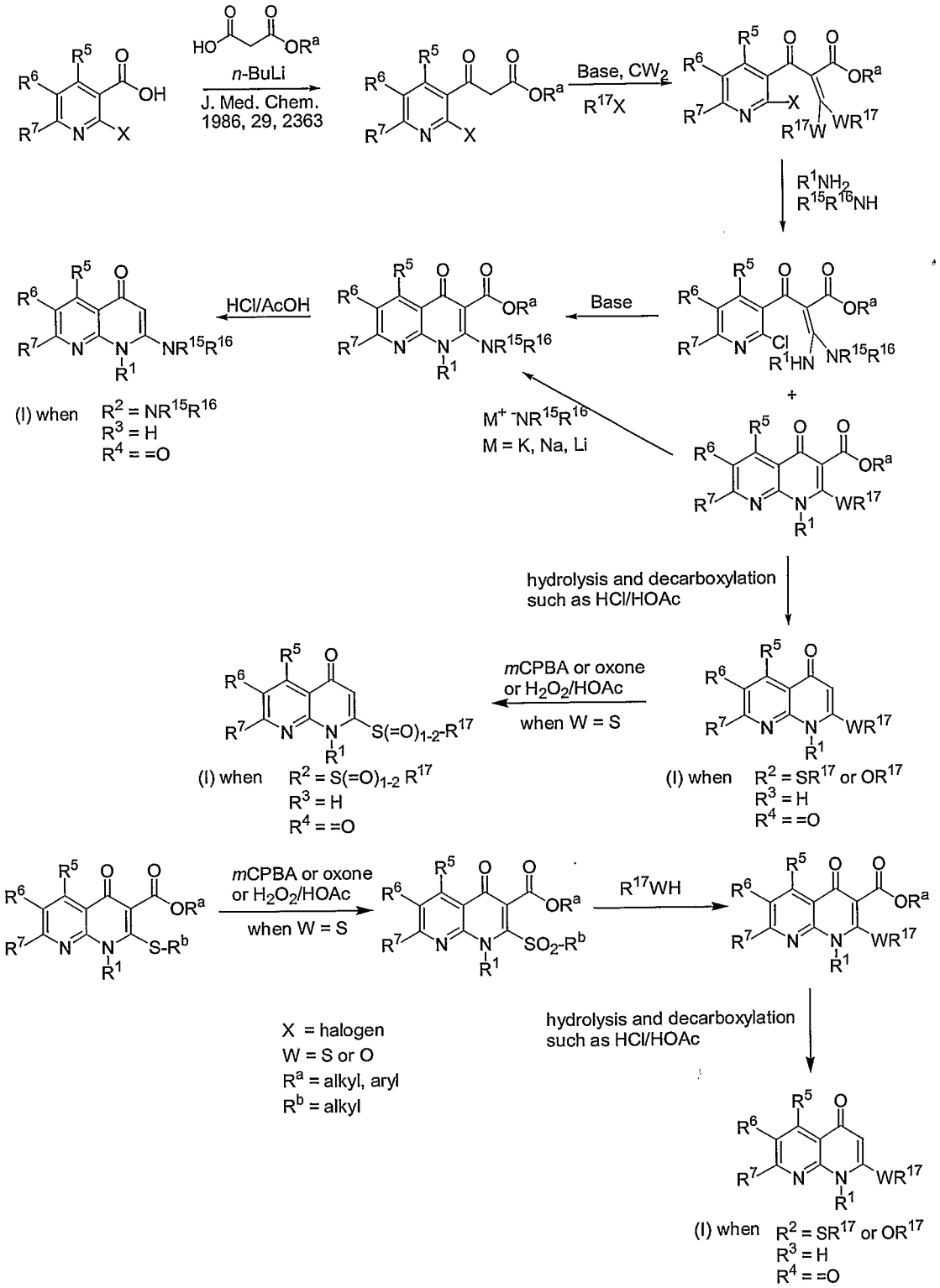
In general, compounds of Formula (I) (R^4 is =O) may be prepared from the appropriately substituted nicotinic acid through several routes summarized in **Flow Diagram I** to **IV**. Compounds of Formula (II) ($R^{4'}$ is =O) may be prepared from the appropriately substituted nicotinic acid through the route summarized in **Flow diagram V**. The close analogy between **Flow Diagram I** and **V** demonstrates that the routes used to synthesize Formula (I) may be applied to synthesize Formula (II). The routes shown in

Flow Diagram II to **IV** maybe used to synthesize Formula (II) from appropriately substituted nicotinic acid.

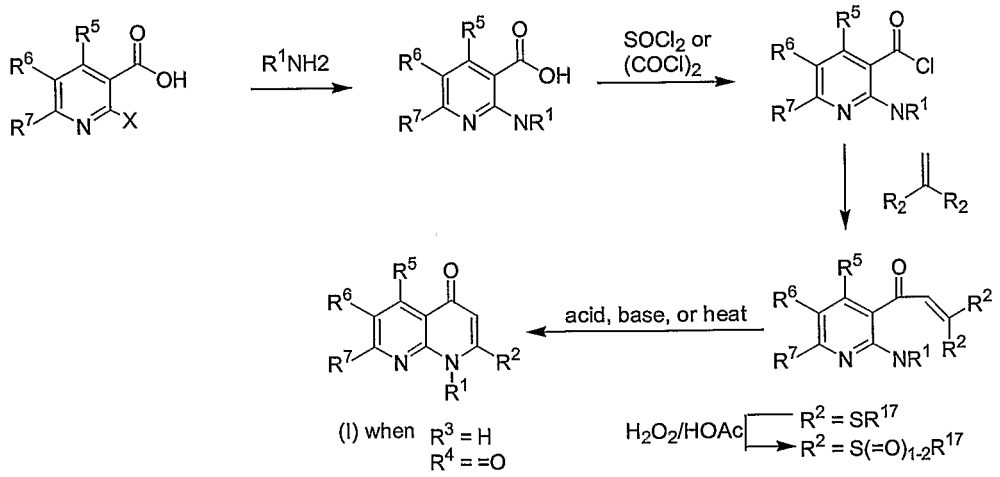
Flow Diagram I



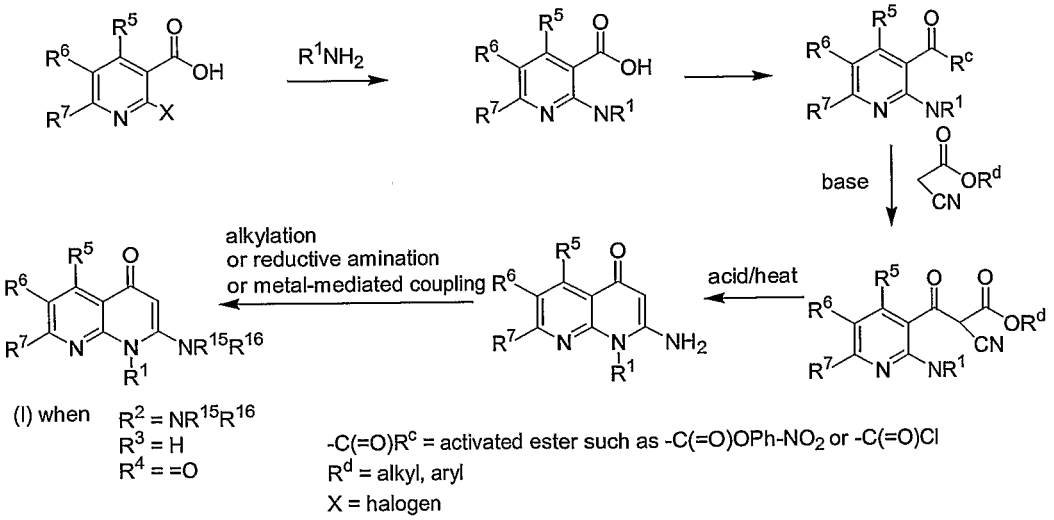
Flow Diagram II



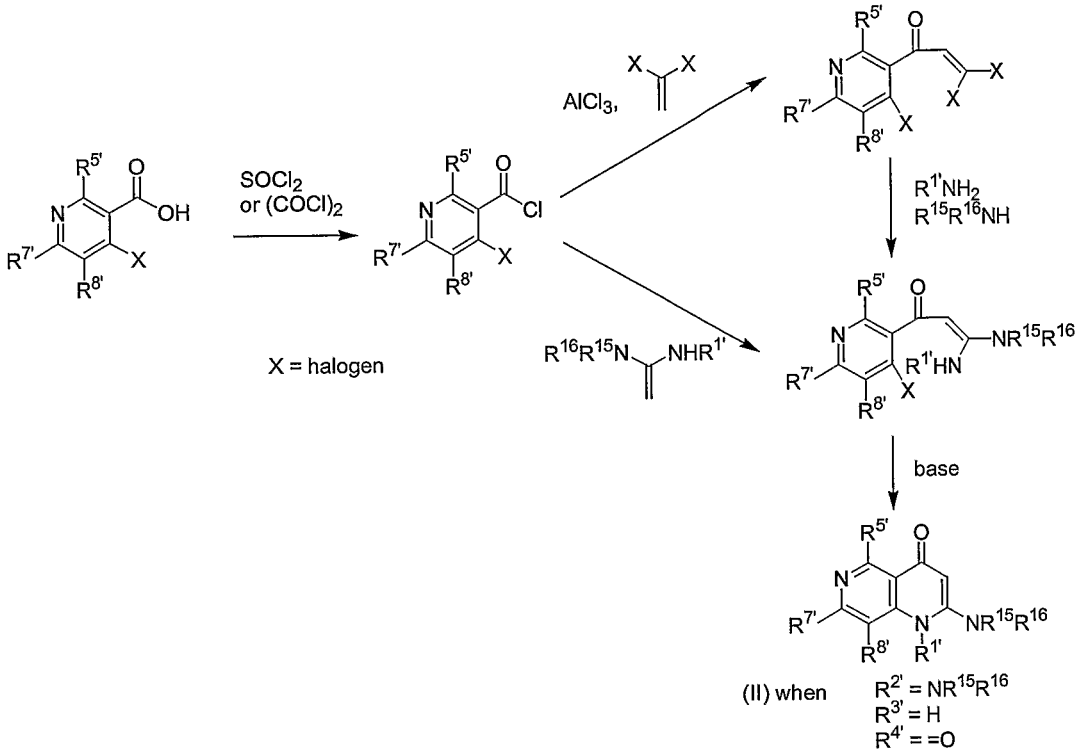
Flow Diagram III



Flow Diagram IV

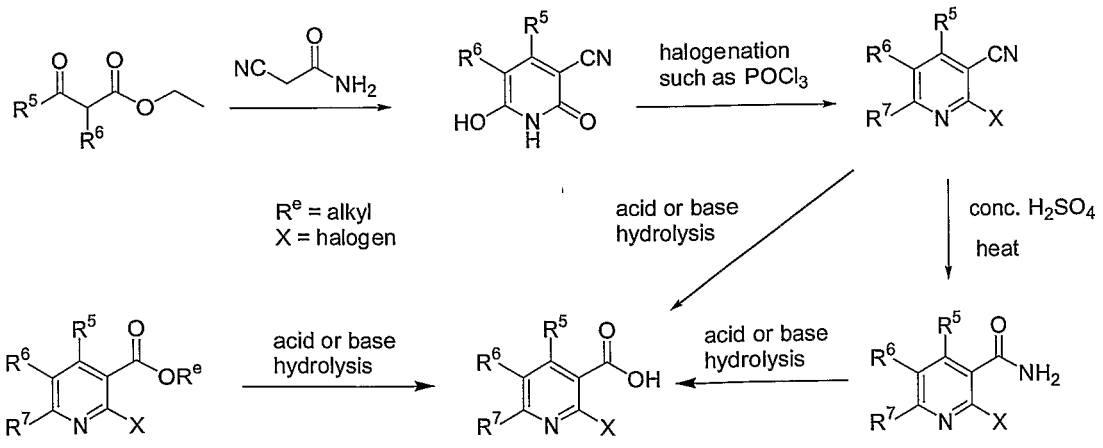


Flow Diagram V



The nicotinic acids used in the above flow diagrams could be purchased from commercial sources, prepared according to **Flow Diagram VI**, or prepared according to literature in this field (*Biorg. Med. Chem. Lett.* **2001**, 475-477; *J. Prakt. Chem.* **2002**, 33; *Eur. J. Org. Chem.* **2001**, 1371; *J. Org. Chem.* **2000**, *65*, 4618; *J. Med. Chem.* **1997**, *40*, 2674; *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1151; US patent 3838156, etc.).

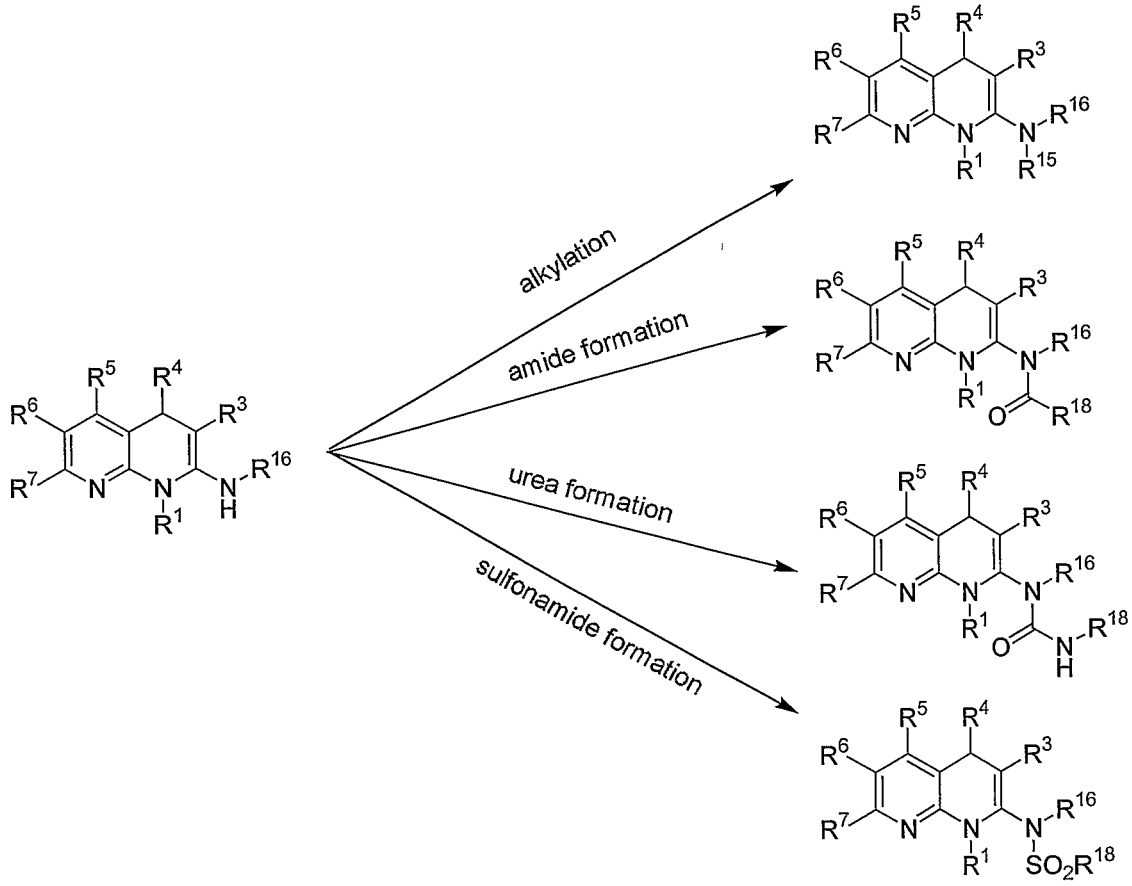
Flow Diagram VI



Further manipulations of Formula (I) (when R^4 is =O) and (II) (when $R^{4'}$ is =O) could lead to more diversely substituted compounds. These manipulations include aromatic nucleophilic substitutions, metal-mediated couplings, reductions, oxidations, amide formations, *etc.*

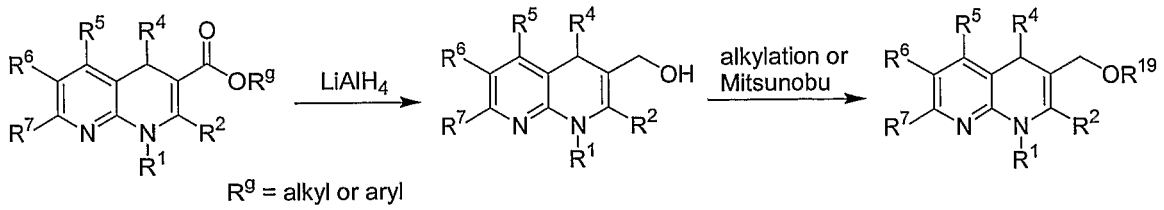
Flow Diagram VII illustrates alkylation, and amide, urea, and sulfonamide formations in Formula (I) when $R^2 = NHR^{16}$. Similar transformations could be carried out in Formula (II) when $R^{2'} = NHR^{16}$.

Flow Diagram VII

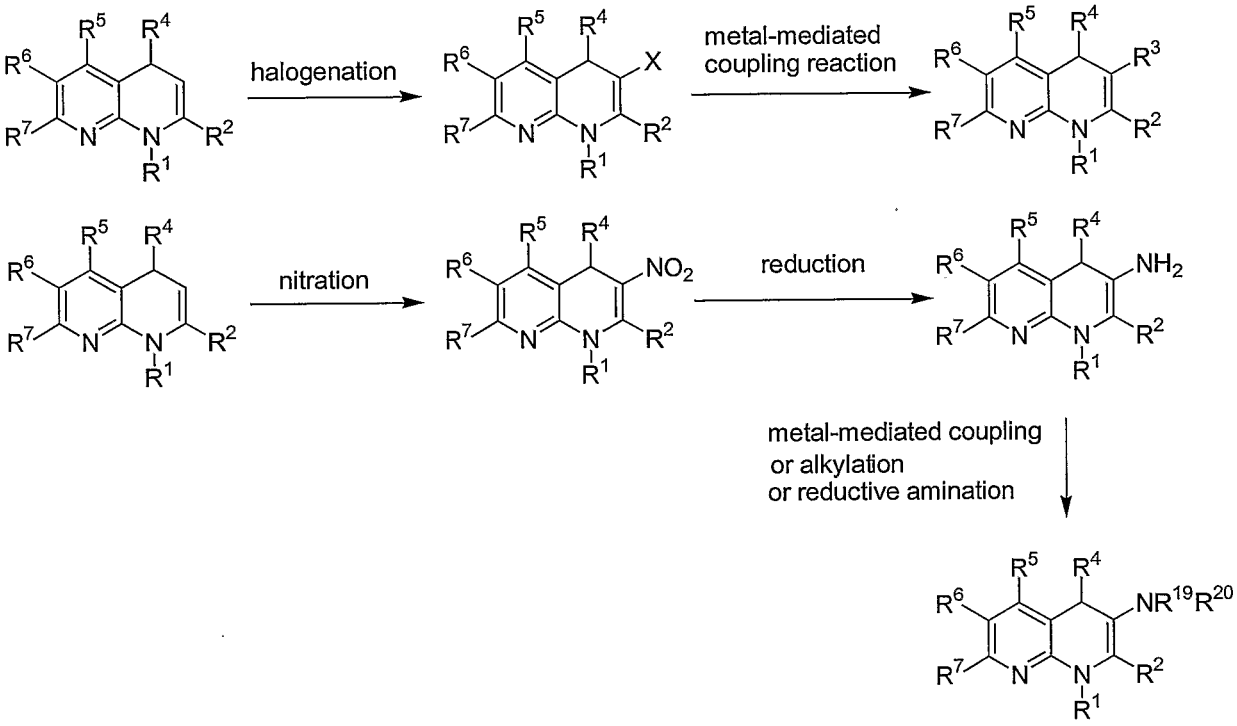


Flow Diagram VIII and **IX** illustrate transformations at R^3 in Formula (I). These transformations could also be applied to $R^{3'}$ in Formula (II).

Flow Diagram VIII

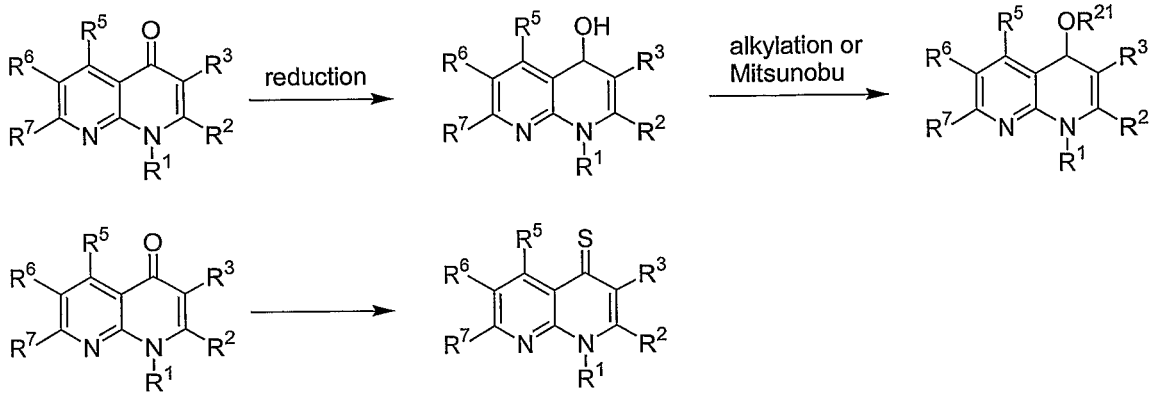


Flow Diagram IX



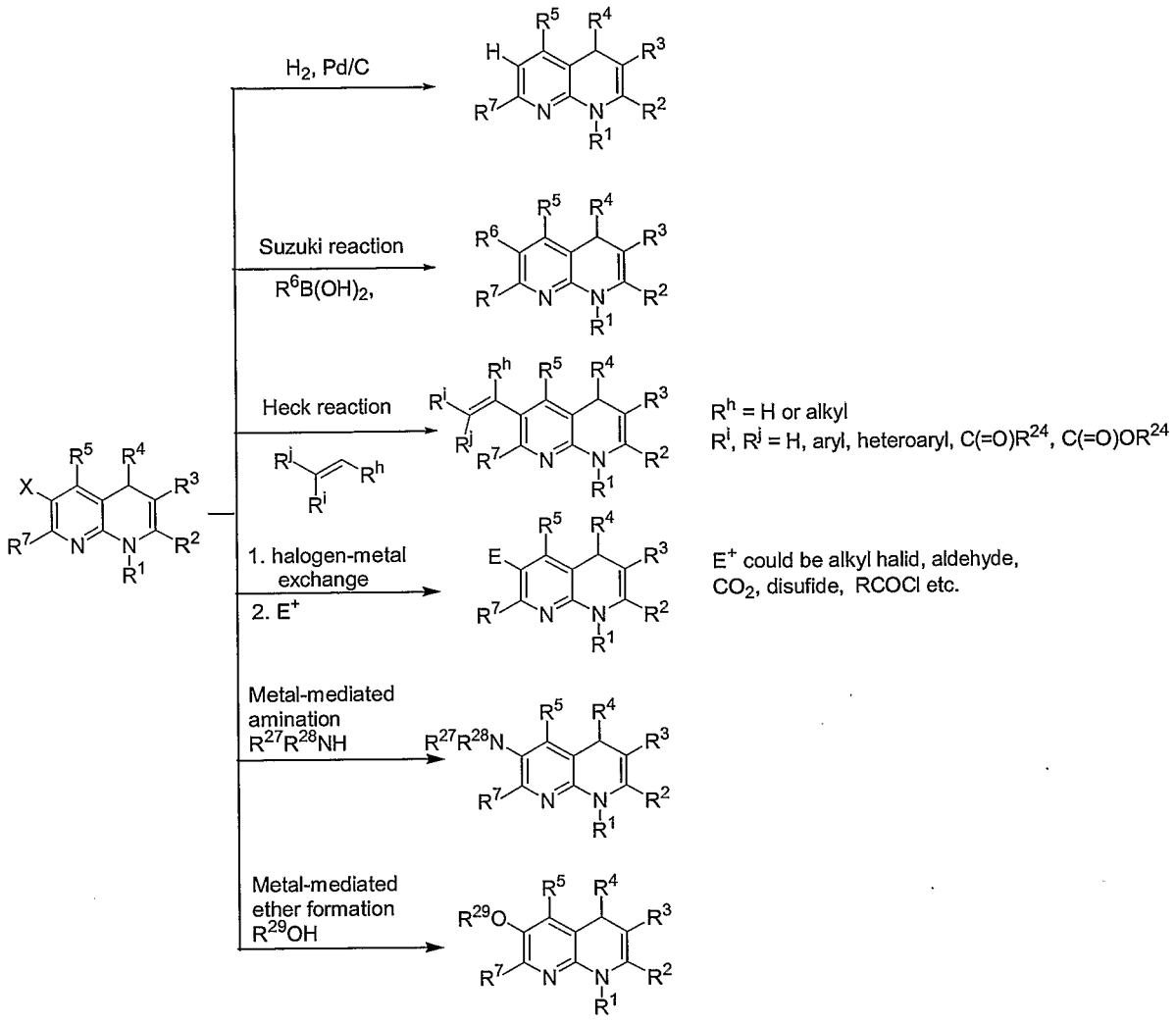
Flow Diagram X illustrates manipulations of R^4 in formula (I), which could also be used on $R^{4'}$ in formula (II).

Flow Diagram X



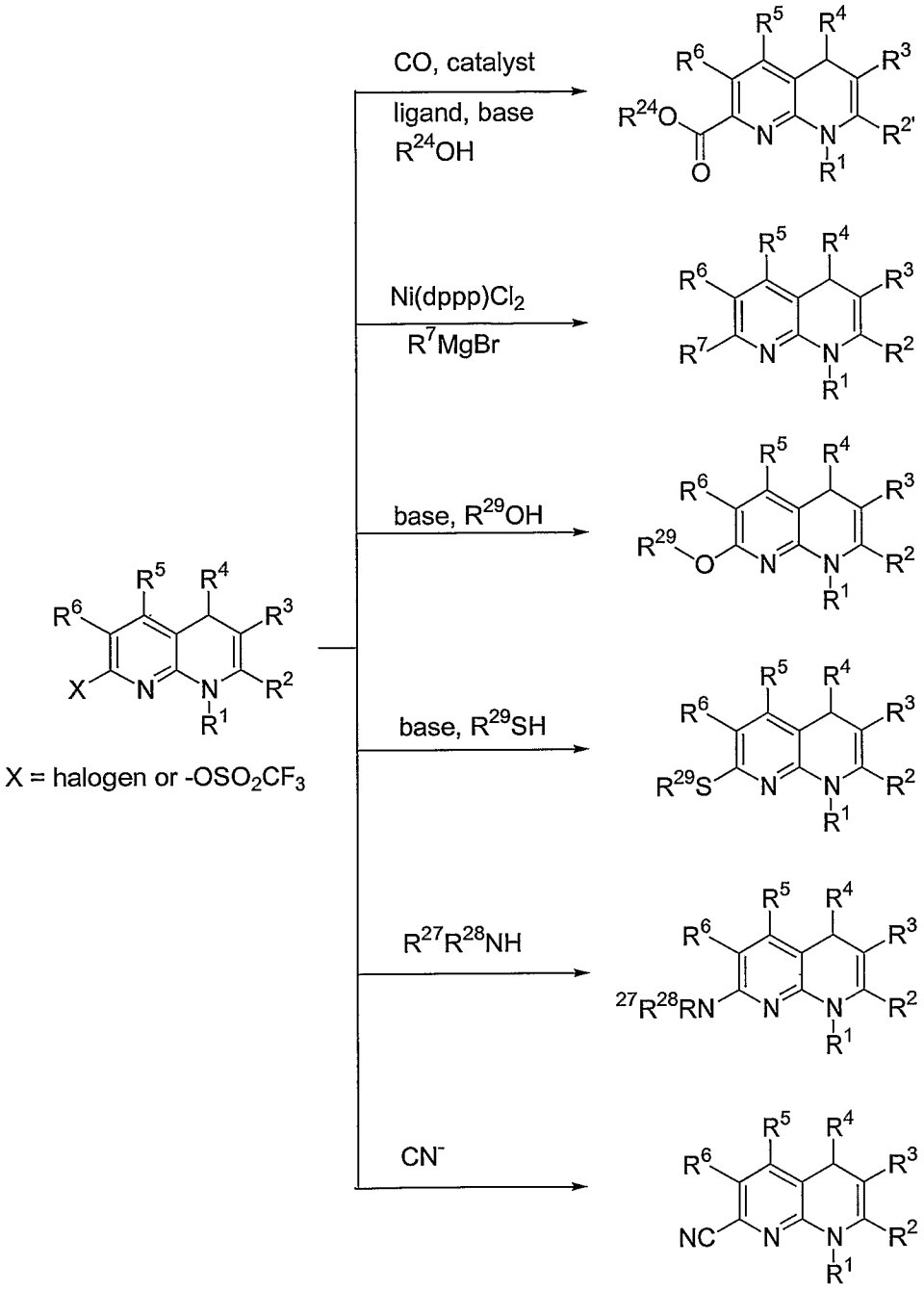
Flow Diagram XI illustrates manipulations of R^6 in formula (I). These manipulations could also be applied to R^5 and R^7 in formula (I), $R^{5'}$, $R^{7'}$, and $R^{8'}$ in formula (II).

Flow Diagram XI



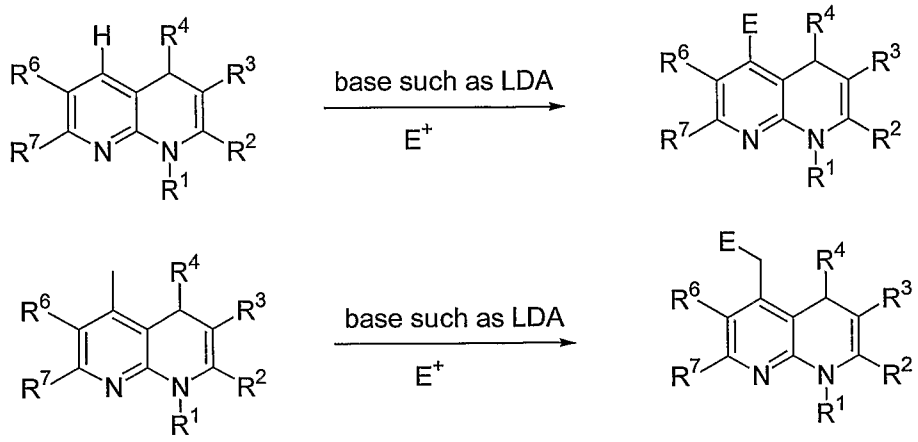
Flow Diagram XII illustrates manipulations on R^7 of formula (I). These manipulations could also be applied to R^5 in formula (I), $R^{5'}$ and $R^{7'}$ in formula (II).

Flow Diagram XII



Flow Diagram XIII illustrates manipulations on R^5 of formula (I). These manipulations could also be applied to R^7 in formula (I), $R^{5'}$ and $R^{7'}$ in formula (II).

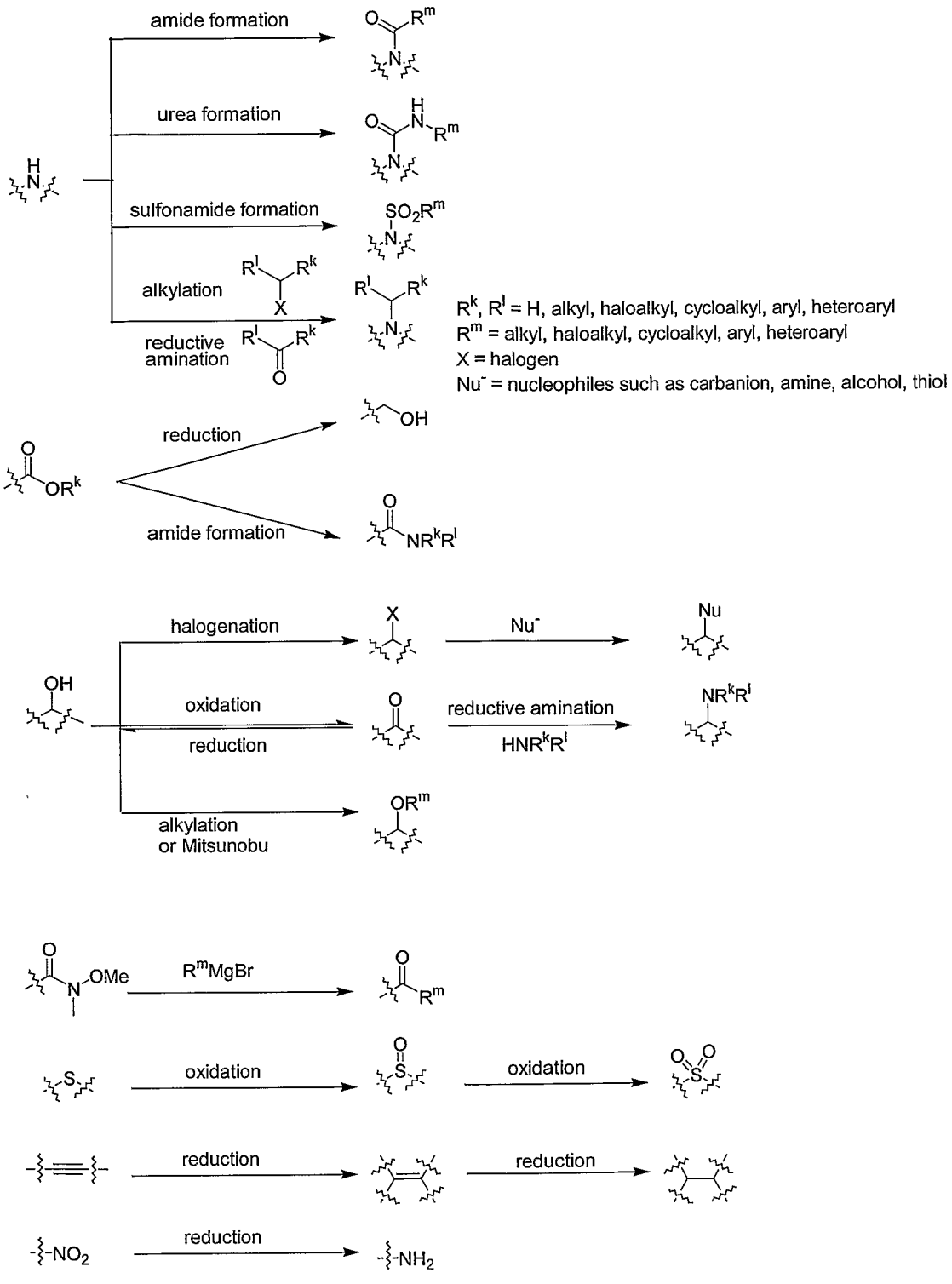
Flow Diagram XIII



E^+ is alkyl halide, aldehydes, halogen, CO_2, O_2, activated ester, etc.

Flow Diagram XIV illustrates the transformations of some functional groups which are present in Formula (I) or (II).

Flow Diagram XIV



Alternative Forms Of Novel Compounds

Also included in the compounds of the present invention are (a) the stereoisomers thereof, (b) the pharmaceutically-acceptable salts thereof, (c) the tautomers thereof, (d) the protected acids and the conjugate acids thereof, and (e) the prodrugs thereof.

(a) The Stereoisomers

The stereoisomers of these compounds may include, but are not limited to, enantiomers, diastereomers, racemic mixtures and combinations thereof. Such stereoisomers can be prepared and separated using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention. Isomers may include geometric isomers. Examples of geometric isomers include, but are not limited to, cis isomers or trans isomers across a double bond. Other isomers are contemplated among the compounds of the present invention. The isomers may be used either in pure form or in admixture with other isomers of the inhibitors described above.

(b) The Pharmaceutically-Acceptable Salts

Pharmaceutically-acceptable salts of the compounds of the present invention include salts commonly used to form alkali metal salts or form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, , heterocyclic, carboxylic and sulfonic classes of organic acids. Examples of organic and sulfonic classes of organic acids includes, but are not limited to, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic,

sulfanilic, cyclohexylaminosulfonic, stearic, algenic, N-hydroxybutyric, salicyclic, galactaric and galacturonic acid and combinations thereof.

(c) The Tautomers

Tautomers of the compounds of the invention are encompassed by the present invention. Thus, for example, a carbonyl includes its hydroxy tautomer.

(d) The Protected Acids and the Conjugate Acids

The protected acids include, but are not limited to, esters, hydroxyamino derivatives, amides and sulfonamides.

(e) The Prodrugs

The present invention includes the prodrugs and salts of the prodrugs. Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 11-13, (1996), which is hereby incorporated by reference).

Dosages And Treatment Regimen

Dosage levels of the compounds of this invention typically are from about 0.001 mg to about 10,000 mg daily, preferably from about 0.005 mg to about 1,000 mg daily. On the basis of mg/kg daily dose, either given in a single dose or in divided doses, dosages

typically range from about 0.001/75 mg/kg to about 10,000/75 mg/kg, preferably from about 0.005/75 mg/kg to about 1,000/75 mg/kg.

The total daily dose of each drug can be administered to the patient in a single dose, or in multiple subdoses. Typically, subdoses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Doses can be in immediate release form or sustained release form sufficiently effective to obtain the desired control over the diabetic condition.

The dosage regimen to prevent, treat, give relief from, or ameliorate a diabetic condition or disorder, or to otherwise protect against or treat a diabetic condition with the combinations and compositions of the present invention is selected in accordance with a variety of factors. These factors include, but are not limited to, the type, age, weight, sex, diet, and medical condition of the subject, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular inhibitors employed, whether a drug delivery system is utilized, and whether the inhibitors are administered with other active ingredients. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Pharmaceutical Compositions

For the prophylaxis or treatment of the conditions and disorders referred to above, the compounds of this invention can be administered as the compound *per* se. Alternatively, pharmaceutically-acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to that of the parent compound.

The compounds of the present invention also can be administered with an acceptable carrier in the form of a pharmaceutical composition. The carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be intolerably deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 0.05% to about 95% by

weight of the active compound(s) based on a total weight of the dosage form. Other pharmacologically active substances can also be present, including other compounds useful in the treatment of a diabetic condition.

The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a therapeutically effective dose for the treatment intended. The active compounds and compositions, for example, may be administered orally, sublingually, nasally, pulmonarily, mucosally, parenterally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Unit dose formulations, particularly orally administrable unit dose formulations such as tablets or capsules, generally contain, for example, from about 0.001 to about 500 mg, preferably from about 0.005 mg to about 100 mg, and more preferably from about 0.01 to about 50 mg, of the active ingredient. In the case of pharmaceutically acceptable salts, the weights indicated above for the active ingredient refer to the weight of the pharmaceutically active ion derived from the salt.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, a capsule, a suspension, an emulsion, a paste, a solution, a syrup or other liquid form. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. If administered by mouth, the compounds may be admixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration.

Oral delivery of the compounds of the present invention can include formulations, as are well known in the art, to provide immediate delivery or prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. Immediate delivery formulations include, but are not limited to, oral solutions, oral suspensions, fast-dissolving tablets or capsules, sublingual tablets, disintegrating tablets and the like. Prolonged or sustained delivery formulations include, but are not limited to, pH sensitive release of the active ingredient from the dosage form based on the changing pH of the

small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the inhibitor(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the inhibitor(s) with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the inhibitors, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made, for example, by molding the powdered compound in a suitable machine.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the inhibitors in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations for parenteral administration, for example, may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Pharmaceutically acceptable carriers encompass all the foregoing and the like. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, such as admixing the components. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks.

Methods Of Use

The present invention also includes methods for the treatment of diabetes and related diseases and conditions. One such method comprises the step of administering to a subject in need thereof, a therapeutically effective amount of one or more compounds of formula (II).

Compounds of formula (II) may be used in methods of the invention to treat diseases, such as diabetes, including both Type 1 and Type 2 diabetes. Such methods may also delay the onset of diabetes and diabetic complications. Other diseases and conditions that may be treated or prevented using compounds of formula (II) in methods of the invention include: Maturity-Onset Diabetes of the Young (MODY) (Herman, *et al.*, Diabetes 43:40 (1994)), Latent Autoimmune Diabetes Adult (LADA) (Zimmet, *et al.*, Diabetes Med. 11:299 (1994)), impaired glucose tolerance (IGT) (Expert Committee on

Classification of Diabetes Mellitus, Diabetes Care 22 (Supp. 1) S5 (1999)), impaired fasting glucose (IFG) (Charles, *et al.*, Diabetes 40:796 (1991)), gestational diabetes (Metzger, Diabetes, 40:197 (1991), and metabolic syndrome X.

Compounds of formula (II) may also be used in methods of the invention to treat secondary causes of diabetes (Expert Committee on Classification of Diabetes Mellitus, Diabetes Care 22 (Supp. 1), S5 (1999)). Such secondary causes include glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes. Drugs that may induce diabetes include, but are not limited to, pyriminil, nicotinic acid, glucocorticoids, phenytoin, thyroid hormone, β-adrenergic agents, α-interferon and drugs used to treat HIV infection.

The methods and compounds of the present invention may be used alone or in combination with additional therapies and/or compounds known to those skilled in the art in the treatment of diabetes and related disorders. Alternatively, the methods and compounds described herein may be used, partially or completely, in combination therapy.

Compounds of formula (II) may also be administered in combination with other known therapies for the treatment of diabetes, including PPAR agonists, sulfonylurea drugs, non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compounds, insulin and anti-obesity drugs. Such therapies may be administered prior to, concurrently with or following administration of the compound of formula (II). Insulin includes both long and short acting forms and formulations of insulin. PPAR agonist may include agonists of any of the PPAR subunits or combinations thereof. For example, PPAR agonist may inlcude agonists of PPAR-α, PPAR-γ, PPAR-δ or any combination of two or three of the subunits of PPAR. PPAR agonists include, for example, rosiglitazone and pioglitazone. Sulfonylurea drugs include, for example, glyburide, glimepiride, chlorpropamide, and glipizide. α-glucosidase inhibitors that may be useful in treating diabetes when administered with a compound of formula (II) include acarbose, miglitol and voglibose. Insulin sensitizers that may be useful in treating diabetes when administered with a compound of formula (II) include thiazolidinediones and non-thiazolidinediones. Hepatic glucose output lowering compounds that may be useful in treating diabetes when

administered with a compound of formula (II) include metformin, such as Glucophage and Glucophage XR. Insulin secretagogues that may be useful in treating diabetes when administered with a compound of formula (II) include sulfonylurea and non-sulfonylurea drugs: GLP-1, GIP, PAC/VPAC receptor agonists, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, glipizide. GLP-1 includes derivatives of GLP-1 with longer half-lives than native GLP-1, such as, for example, fatty-acid derivatized GLP-1 and exendin. In one embodiment of the invention, compounds of formula (II) are used in combination with insulin secretagogues to increase the sensitivity of pancreatic beta cells to the insulin secretagogue.

Compounds of formula (II) may also be used in methods of the invention in combination with anti-obesity drugs. Anti-obesity drugs include β-3 agonists, CB-1 antagonists, appetite suppressants, such as, for example, sibutramine (Meridia), and lipase inhibitors, such as, for example, orlistat (Xenical).

Compounds of formula (II) may also be used in methods of the invention in combination with drugs commonly used to treat lipid disorders in diabetic patients. Such drugs include, but are not limited to, HMG-CoA reductase inhibitors, nicotinic acid, bile acid sequestrants, and fibric acid derivatives. Compounds of formula (II) may also be used in combination with anti-hypertensive drugs, such as, for example, β-blockers and ACE inhibitors.

Such co-therapies may be administered in any combination of two or more drugs (*e.g.*, a compound of formula (I) in combination with an insulin sensitizer and an anti-obesity drug). Such co-therapies may be administered in the form of pharmaceutical compositions, as described above.

Terms

As used herein, various terms are defined below.

When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having"

are intended to be inclusive and mean that there may be additional elements other than the listed elements.

The term "subject" as used herein includes mammals (*e.g.*, humans and animals).

The term "treatment" includes any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

The phrase "therapeutically-effective" means the amount of each agent administered that will achieve the goal of improvement in a diabetic condition or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.

The term "pharmaceutically acceptable" means that the subject item is appropriate for use in a pharmaceutical product.

The term "prodrug" includes a compound that is a drug precursor that, following administration to a subject and subsequent absorption, is converted to an active species *in vivo*. Conversion to the active, species *in vivo* is typically via some process, such as metabolic conversion. An example of a prodrug is an acylated form of the active compound.

The following definitions pertain to the structure of the compounds: In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified, for example, alkyl of 1-8 carbon atoms or C1-C8 alkyl. The use of a term designating a monovalent radical where a divalent radical is appropriate shall be construed to designate the divalent radical and *vice versa*. Unless otherwise specified, conventional definition of terms controls and conventional stable atom valences are presumed and achieved in all formulas and groups.

When symbols such as "A-Q-R" is used, it refers to a group which is formed by linking group A, group Q and group R in the designated order and the attachment of this

group "A-Q-R" is any position on group A to form a stable structure. Group Q may be linked to any position on group A to form a stable structure and group R may be linked to any position on group Q to form a stable structure.

When symbols such as "A(OR')-R" is used, it refers to a group which is formed by susbstituting group A with both group OR' and group R and the attachment of this group "A(OR')-R" is any position on group A to form a stable structure. Group OR' and group R maybe linked to any position on group A to form a stable structure.

The term "halogen" refers to a halogen radical selected from fluoro, chloro, bromo or iodo.

The term "alkyl" refers to a saturated aliphatic hydrocarbon radical. "Alkyl" refers to both branched and unbranched alkyl groups. Examples of "alkyl" include alkyl groups that are straight chain alkyl groups containing from one to ten carbon atoms and branched alkyl groups containing from three to ten carbon atoms. Other examples include alkyl groups that are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. This term is examplified by groups such as methyl, ethyl, *n*-propyl, 1-methylethyl (isopropyl), 1,1-dimethylethyl (*tert*-butyl), and the like. It may be abbreviated "Alk". It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkylthio", "alkylamino" refer to alkyl groups linked to a second group via an oxygen, sulfur, or nitrogen atom, respectively.

The term "haloalkyl" refers to an alkyl group in which one or more hydrogen atoms are replaced with halogen atoms. This term in examplified by groups such as trifluomethyl. The more preferred haloalkyl groups are alkyl groups substituted with one or more fluro or chloro. The term "haloalkoxy" refers to haloalkyl groups linked to a second group via an oxygen atom.

The term "alkenyl" refers to a mono or polyunsatuarted aliphatic hydrocarbon radical. The mono or polyunsaturated aliphatic hydrocarbon radical contains at least one

carbon-carbon double bond. "Alkenyl" refers to both branched and unbranched alkenyl groups, each optionally partially or fully halogenated. Examples of "alkenyl" include alkenyl groups that are straight chain alkenyl groups containing from two to ten carbon atoms and branched alkenyl groups containing from three to ten carbon atoms. Other examples include alkenyl groups which are straight chain alkenyl groups containing from two to six carbon atoms and branched alkenyl groups containing from three to six carbon atoms. This term is exemplified by groups such as ethenyl, propenyl, *n*-butenyl, isobutenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, decenyl, and the like.

The term "alkynyl" refers to a mono or polyunsatuarted aliphatic hydrocarbon radical. The mono or polyunsaturated aliphatic hydrocarbon radical contains at least one carbon-carbon triple bond. "Alkynyl" refers to both branched and unbranched alkynyl groups, each optionally partially or fully halogenated. Examples of "alkynyl" include alkynyl groups that are straight chain alkynyl groups containing from two to ten carbon atoms and branched alkynyl groups containing from four to ten carbon atoms. Other examples include alkynyl groups that are straight chain alkynyl groups containing from two to six carbon atoms and branched alkynyl groups containing from four to six carbon atoms. This term is exemplified by groups such as ethynyl, propynyl, octynyl, and the like.

The term "cycloalkyl" refers to the mono- or polycyclic analogs of an alkyl group, as defined above. Unless otherwise specified, the cycloalkyl ring may be attached at any carbon atom that results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Examples of cycloalkyl groups are saturated cycloalkyl groups containing from three to ten carbon atoms. Other examples include cycloalkyl groups containing three to six carbon atoms. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cyclononyl, cyclodecyl, norbornane, adamantyl, and the like.

The term "cycloalkenyl" refers to the mono- or polycyclic analogs of an alkenyl group, as defined above. Unless otherwise specified, the cycloalkenyl ring may be attached at any carbon atom that results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Examples of

cycloalkenyl groups are cycloalkenyl groups containing from four to ten carbon atoms. Other examples include cycloalkenyl groups containing four to six carbon atoms. Exemplary cycloalkenyl groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, norbornene, and the like.

The term "heterocycloalkyl" refers to the mono- or polycyclic structures of "cycloalkyl" where one or more of the carbon atoms are replaced by one or more atoms independently chosen from nitrogen, oxygen, or sulfur atoms. Any nitrogen atom maybe optionally oxidized or quanternized, and any sulfur atom maybe optionally oxidized. Unless otherwise specified, the heterocycloalkyl ring may be attached at any carbon atom or heteroatom that results in a stable structure and, if substituted, may be substituted at any suitable carbon atom or heteroatom which results in a stable structure. Examples of heterocycloalkyl groups are saturated heterocycloalkyl groups containing from two to nine carbon atoms and one to four heteroatoms chosen independently from nitrogen, oxygen, or sulfur atoms. Examples of heterocycloalkyl groups include morpholino, pyrazino, tetrahydrofurano, and the like.

The term "heterocycloalkenyl" refers to the mono- or polycyclic structures of "cycloalkenyl" where one or more of the carbon atoms are replaced by one or more atoms independently chosen from nitrogen, oxygen, or sulfur atoms. Any nitrogen atom maybe optionally oxidized or quanternized, and any sulfur atom maybe optionally oxidized. Unless otherwise specified, the heterocycloalkenyl ring may be attached at any carbon atom or heteroatom that results in a stable structure and, if substituted, may be substituted at any suitable carbon atom or heteroatom which results in a stable structure. Examples of heterocycloalkenyl groups are saturated heterocycloalkenyl groups containing from two to nine carbon atoms and one to four heteroatoms chosen independently from nitrogen, oxygen, or sulfur atoms. Examples of heterocycloalkenyl groups include dihydropyran, dihydrofuran, and the like.

The term "cycloalkyloxy" refers to a monovalent radical of the formula –O-cycloalkyl, *i.e.*, a cycloalkyl group linked to a second group via an oxygen atom.

The term "acyl" refers to a monovalent radical of the formula –C(=O)-alkyl and –C(=O)-cycloalkyl, *i.e.*, an alkyl or cycloakyl group linked to a second group via caronyl group C(=O), wherein said alkyl maybe further substituted with cycloalkyl, aryl, or heteroaryl. Examples of acyl groups include –C(=O)Me (acetyl), -C(=O)CH_2-cyclopropyl (cyclopropylacetyl), - C(=O)CH_2Ph (phenylacetyl), and the like.

The term "aryl" refers to 6-10 membered mono- or polycyclic aromatic carbocycles, for example, phenyl and naphthyl. Unless otherwise specified, the aryl ring may be attached at any carbon atom that results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. The term "aryl" refers to non-substituted aryls and aryls optionally substituted with one or more of the following groups: halogen, C1-C6 alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, C4-C6 cycloalkenyl, C2-C6 alkynyl, nitro, cyano, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkoxy, amino, C1-C6 alkylamino (for example, -NHMe and -$N(Me)_2$), C1-C6 acyl, thiol, alkylthio, carboxylic acid. All the above subtsitutions can further be substituted with optionally selected groups to form a stable structure. It may be abbreviated "Ar". It should be understood that any combination term using an "ar" or "aryl" prefix refers to analogs according to the above definition of "aryl". For example, terms such as "aryloxy", "arylthio", "arylamino" refer to aryl groups linked to a second group via an oxygen, sulfur, or nitrogen atom, respectively.

The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical. Each heteroaryl contains 1-10 carbon atoms and from 1 to 5 heteroatoms independently chosen from nitrogen, oxygen and sulfur, wherein any sulfur heteroatom may optionally be oxidized and any nitrogen heteroatom may optionally be oxidized or quaternized. Unless otherwise specified, the heteroaryl ring may be attached at any suitable heteroatom or carbon atom that results in a stable structure and, if substituted, may be substituted at any suitable heteroatom or carbon atom which results in a stable structure. The term "heteroaryl" includes heteroaryl groups that are non-substituted or those optionally substituted with one or more of the following groups: halogen, C1-C6 alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, C4-C6 cycloalkenyl, C2-C6 alkynyl, nitro, cyano, hydroxyl, C1-C6 alkoxy, C3-C6 cycloalkoxy, amino, C1-C6 alkylamino (for example, -NHMe and -$N(Me)_2$), C1-C6 acyl,

thiol, alkylthio, carboxylic acid. Examples of "heteroaryl" include radicals such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl. Terms such as "heteroaryloxy", "heteroarylthio", "heteroarylamino" refer to heteroaryl groups linked to a second group via an oxygen, sulfur, or nitrogen atom, respectively.

The terms "optional" or "optionally" mean that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

A comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

Abbreviations and Acronyms

When the following abbreviations are used throughout the disclosure, they have the following meaning:

CH_2Cl_2	methylene chloride
THF	tetrahydrofuran
CH_3CN	acetonitrile

Na_2SO_4	anhydrous sodium sulfate
$MgSO_4$	anhydrous magnesium sulfate
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
H_2	hydrogen
CO	carbon monoxide
HCl	hydrochloric acid
Hex	hexanes
^1H NMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
K_2CO_3	potassium carbonate
Cs_2CO_3	cesium carbonate
NH_4Cl	ammonium chloride
LC/MS	liquid chromatography / mass spectroscopy
MeOH	methanol
MS ES	mass spectroscopy with electrospray
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
RT	retention time
h	hour
min	minutes
$Pd(OAc)_2$	palladium acetate
$Ni(dppp)Cl_2$	[1,3-bis(diphenylphosphino)propane]dichloronickel(II)
DMF	*N,N*-dimethylformamide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
LTMP	Lithium tetramethylpiperidine
BuLi	butyllithium
TLC	thin layer chromatography
TFA	trifluoacetic acid
TMEDA	tetramethylethylenediamine

BINAP	2,2'-bis(diphenylphosphino)-1,1'binaphthyl
HOBt	1-hydroxybenzotriazole hydrate
NaH	sodium hydride
MeMgBr	methylmagnesium bromide
DPPP	(diphenylphosphino)propane
DME	dimethoxyethane
$AlCl_3$	aluminum chloride
TEA	triethyl amine
CS_2	carbon disulfide
MeI	methyl iodide
t-BuOK	potassium tert-butoxide
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
NaOBr	sodium hypobromite
Br_2	bromine
Conc.	Concentrated
Pd/C	palladium on carbon
EtOH	ethanol
NH_3	ammonia
NaOMe	sodium methoxide
PPh_3	triphenylphosine
NaH	sodium hydride
LDA	lithium diisopropylamide
$SOCl_2$	thionyl chloride
MsCl	methanesulfonyl chloride
DMAP	4-dimethylaminopyridine
NMM	4-methylmorpholine
AcOH	acetic acid
$Na_2S_2O_3$	sodium thiosulfate
H_2SO_4	sulfuric acid
$CHCl_3$	chloroform
MnO_2	manganese(IV) oxide
LAH	lithium aluminum hydride

ADDP	1,1'-(azodicarbonyl)-dipiperidine
EDTA	ethylenediaminetetraacetic acid
CCl_2FCClF_2	1,1,2-trichlorotrifluoroethane
$NaNO_2$	sodium nitrite

Preparative Examples

Examples of preparations of compounds of the invention are provided in the following detailed synthetic procedures. In tables 1A and 2A, the synthesis of each compound is referenced back to these exemplary preparative steps. In tables 1B and 2B, the proposed synthesis of each compound is referenced back to these exemplary preparative steps.

All reactions were carried out under a positive pressure of dry argon or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification.

Unless otherwise stated, the term 'concentration under reduced pressure' refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by volume.

Proton (^1H) nuclear magnetic resonance (NMR) spectra were measured with a Varian Mercury (300 MHz) or a Bruker Avance (500 MHz) spectrometer with either Me_4Si (δ 0.00) or residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. The NMR data of the synthesized examples, which are not disclosed in the following detailed charaterizations, are in agreements with their corresponding structural assignements.

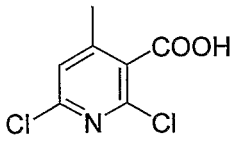
The HPLC–MS spectra were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% CH_3CN in water with 0.02% TFA and B: 2% water in CH_3CN with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Elemental analyses were conducted by Robertson Microlit Labs, Madison NJ. The results of elemental analyses, if conducted but not disclosed in the following detailed charaterizations, are in agreements with their corresponding structural assignements.

The following specific examples are presented to illustrate the invention related to Formula (I) as described herein, but they should not be construed as limiting the scope of the invention in any way.

Intermediate A:

2,6-dichloro-4-methyl-nicotinic acid



Method 1

A solution of sodium nitrite (2.73 g, 39.6 mmol) in water (15 mL) was added slowly to a solution of commercially available (Maybridge) 2,6-dichloro-4-methyl-nicotinamide (4.5 g, 22 mmol) in concentrated sulfuric acid resulting in evolution of heat and brown gas. The mixture was stirred at room temperature for 15 min, and then heated to 60 °C for 7 h. The solution was cooled to 0 °C and then water (15 mL) was added. The resulting white precipitate was collected by filtration and washed with hexane. The aqueous filtrate was extracted with EtOAc (3X) and the combined organic extracts were

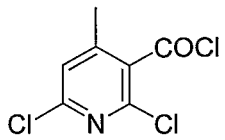
dried over $MgSO_4$ and concentrated *in vacuo*. The residue was combined with the white precipitate to afford 2,6-dichloro-4-methyl-nicotinic acid (4.39 g, 97%) as a white solid: LCMS RT: 1.20 min, MH^+: 206.3.

Method 2

Concentrated nitric acid (14 mL) was added to cooled (0 °C) concentrated sulfuric acid (43 mL) maintaining the internal temperature below 10 °C. After addition, the acid mixture was heated to 70 °C and commercially available (Avocado) 2,6-dichloro-4-methylnicotinonitrile (20.0 g, 107 mmol) was added. The temperature was raised until the internal temperature of the reaction reached 105 °C. At this point the heating was stopped and after 2 h, TLC analysis revealed that the reaction was complete. The reaction mixture was cooled to room temperature, and slowly added to ice (100 g) with strong agitation. The solid was filtered and washed with cold water (10 mL). The solid was dissolved in EtOAc (100 mL) and the solution was dried over Na_2SO_4 and concentrated to give 2,6-dichloro-4-methyl-nicotinic acid (21.0 g, 96%) as a white solid: R_f = 0.20 (1:1 EtOAc:Hex).

Intermediate B:

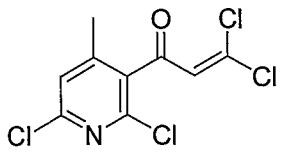
2,6-dichloro-4-methyl-nicotinoyl chloride



A solution of 2,6-dichloro-4-methyl-nicotinic acid (3.94 g, 19.1 mmol) in thionyl chloride (18 mL) was heated to 80 °C for 2 h. After cooling, the solution was concentrated *in vacuo* to give 2,6-dichloro-4-methyl-nicotinoyl chloride as yellow oil. It was carried on to the next step without further purification. This transformation can also be accomplished using oxalyl chloride with catalytic DMF in place of thionyl chloride.

Intermediate C:

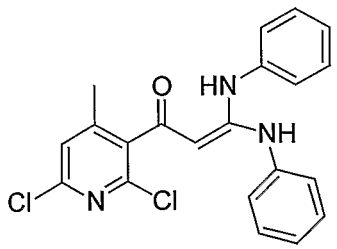
3,3-dichloro-1-(2,6-dichloro-4-methyl-pyridin-3-yl)-propenone



A solution of the 2,6-dichloro-4-methyl-nicotinoyl chloride from the previous reaction in CH_2Cl_2 (10 mL) was added slowly to a cooled (0 °C) and stirred slurry solution of $AlCl_3$ (2.54 g, 19.1 mmol) in CH_2Cl_2 (54 mL). After 15 min, vinylidene chloride (1.5 mL, 1.85 g, 19.1 mmol) was added to the mixture dropwise. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was poured over ice and the ice slurry was acidified using 1 N HCl (50 mL). Stirring was continued for 20 min and then the product was extracted with CH_2Cl_2 (3X). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 3,3-dichloro-1-(2,6-dichloro-4-methyl-pyridin-3-yl)-propenone (4.22 g, 77 %) as a yellow oil: LCMS RT: 3.25, MH^+: 284.3, $R_f = 0.47$ (4:1 Hex:EtOAc).

Intermediate D:

1-(2,6-Dichloro-4-methyl-pyridin-3-yl)-3,3-bis-phenylamino-propenone

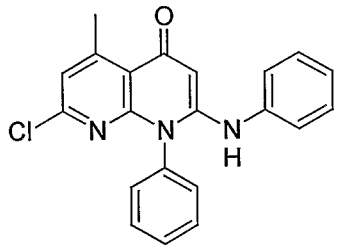


A solution of aniline (4.04 mL, 44.4 mmol) in TEA (6.2 mL, 44.4 mmol) was added slowly to a cooled (0 °C) and stirred solution of 3,3-dichloro-1-(2,6-dichloro-4-methyl-pyridin-3-yl)-propenone (4.22 g, 14.8 mmol) in dioxane (50 mL). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated *in vacuo* until most of the solvent was removed and then the residue was

diluted with water and extracted with EtOAc (3X). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 7:1 EtOAc:Hex gave 1-(2,6-dichloro-4-methyl-pyridin-3-yl)-3,3-bis-phenylamino-propenone as yellow solid (2.22 g, 40 %): LCMS RT: 3.21 min; MH^+: 398.2, R_f = 0.27 (2:1 Hex:EtOAc).

Intermediate E:

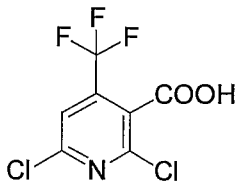
7-Chloro-5-methyl-1-phenyl-2-phenylamino-1H-[1,8]-naphthyridin-4-one



A mixture of 1-(2,6-dichloro-4-methyl-pyridin-3-yl)-3,3-bis-phenylamino-propenone (2.17 g, 5.45 mmol) and *t*-BuOK (1.10 g, 9.81 mmol) in dioxane (55 mL) was heated to 80 °C overnight. The reaction was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 1:1 EtOAc:Hex provided 7-chloro-5-methyl-1-phenyl-2-phenylamino-1H-[1,8]naphthyridin-4-one (1.297 g, 66%) as an orange solid: LCMS RT: 2.52 min, MH^+: 362.3, R_f = 0.18 (1:1 EtOAc:Hex) This transformation can also be accomplished by using the combination of other aprotic solvents such as DMF, and THF with other bases such as NaH.

Intermediate F:

2,6-dichloro-4-(trifluoromethyl)nicotinic acid



Method 1

A solution of $NaNO_2$ (9.59 g, 139 mmol) in water (95 mL) was added slowly to a solution of commercially available (Oakwood) 2,6-dichloro-4-(trifluoromethyl)nicotinamide (20.0 g, 77 mmol) in conc. H_2SO_4 resulting in evolution of heat and brown gas. The mixture was stirred at room temperature for 15 min, and then heated to 60 °C for 18 h. The solution was cooled to 0 °C and then water (15 mL) was added. The resulting mixture was extracted with Et_2O (3X) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with hexanes and vacuum-filtered to afford 2,6-dichloro-4-(trifluoromethyl)nicotinic acid (19 g, 95%) as an off-white solid: R_f = 0.30 (9:1 CH_2Cl_2:MeOH), ^{1}H-NMR (d_6-DMSO, 300 MHz) δ 8.18 (s, 1H).

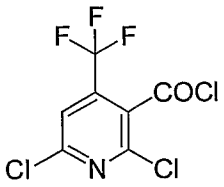
Method 2

Conc. HNO_3 (13.3 mL) was added to cooled (0 °C) conc. H_2SO_4 (60 mL) maintaining the internal temperature below 10 °C. After addition, the acid mixture was heated to 70 °C and commercially available (Maybridge) 2,6-dichloro-4-(trifluoromethyl)nicotinonitrile (20.0 g, 83 mmol) was added. The temperature was raised until the internal temperature of the reaction reached 100 °C. After heating for 1 h TLC analysis revealed that the reaction was complete. The reaction mixture was cooled to room temperature, and slowly added to ice (100 g) with strong agitation and extracted with Et_2O (3X). The organic layers were combined and washed with brine. The solution was

dried over Na_2SO_4 and concentrated *in vacuo* to give 2,6-dichloro-4-(trifluoromethyl)nicotinic acid (19.1 g, 89%) as an off-white solid: R_f = 0.30 (9:1 CH_2Cl_2:MeOH), ^{1}H-NMR (d_6-DMSO, 300 MHz) δ 8.18 (s, 1H).

Intermediate G:

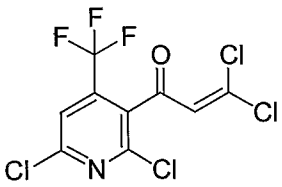
2,6-dichloro-4-(trifluoromethyl)nicotinoyl chloride



A solution of 2,6-dichloro-4-(trifluoromethyl)nicotinic acid (3.22 g, 13.2 mmol) in thionyl chloride (9 mL) was heated at reflux for 3 h. After cooling, the solution was concentrated *in vacuo* to give 2,6-dichloro-4-(trifluoromethyl)nicotinoyl chloride as a yellow oil which was carried on to the next step without further purification. This transformation can also be accomplished using oxalyl chloride with catalytic DMF in place of thionyl chloride.

Intermediate H:

3,3-dichloro-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one

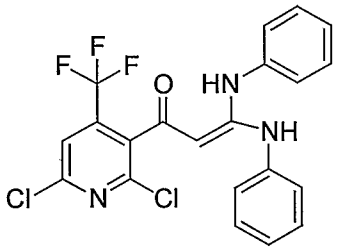


A solution of the 2,6-dichloro-4-(trifluoromethyl)nicotinoyl chloride from the previous reaction in CH_2Cl_2 (14 mL) was added slowly to a cooled (0 °C) and stirred slurry solution of $AlCl_3$ (4.4 g, 33.0 mmol) in CH_2Cl_2 (14 mL). After 15 min, vinylidene chloride (2.6 mL, 33.0 mmol) was added to the mixture dropwise. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was poured over ice and partitioned with CH_2Cl_2. The organic layer was collected and cooled to 0 °C

before TEA (4.6 mL, 33 mmol)was added. After 15 min, the ice bath was removed and the reaction was allowed to warm to room temperature and stirred for an additional 30 min. The solution was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was passed through a pad of silica gel and concentrated *in vacuo* to afford 3,3-dichloro-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one: (4.3 g, 95%) as a brown oil: LCMS RT: 3.59, MH^+: 488.1, R_f= 0.44 (EtOAc).

Intermediate I:

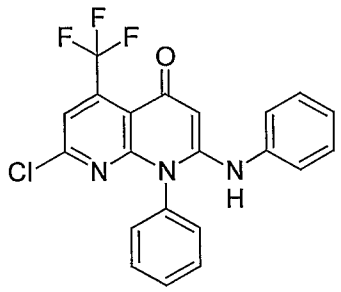
3,3-dianilino-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one



A solution of aniline (18.4 mL, 202 mmol) in TEA (28.2 mL, 202 mmol) was added slowly to a cooled (0 °C) and stirred solution of 3,3-dichloro-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one (22.9 g, 67.4 mmol) in dioxane (220 mL). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was treated with 10% HCl and extracted with Et_2O (3X). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 6:1 Hex:EtOAc gave 3,3-dianilino-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one as an off-white solid (13.10 g, 43%): ^{1}H-NMR (d_6-DMSO, 300 MHz) δ12.24 (br s, 1H), 9.20 (br s, 1H), 7.95 (s, 1H), 7.12- 7.42 (m, 10H), 4.82 (s, 1H); R_f= 0.60 (6:1 Hex:EtOAc).

Intermediate J:

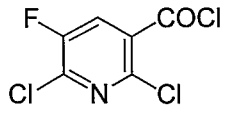
2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one



A mixture of 3,3-dianilino-1-[2,6-dichloro-4-(trifluoromethyl)-3-pyridinyl]-2-propen-1-one (12.9 g, 28.5 mmol) and *t*-BuOK (28.5 mL, 28.5 mmol, 1M in THF) in dioxane (200 mL) was heated at reflux overnight. The reaction was cooled, concentrated *in vacuo*, treated with saturated NH_4Cl and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 6:1 Hex:EtOAc provided 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (11.2 g, 95%) as an off-white solid: LCMS RT: 3.00 min, MH^+: 416.7, R_f = 0.25 (3:1 Hex:EtOAc). This transformation can be accomplished by using the combination of other aprotic solvents such as DMF, and THF with other bases such as NaH.

Intermediate K:

2,6-dichloro-5-fluoronicotinoyl chloride

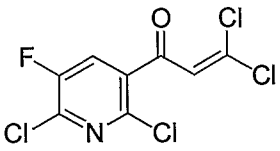


A solution of commercially available (Aldrich) 2,6-dichloro-5-fluoronicotinic acid (5.00 g, 23.8 mmol) in thionyl chloride (15 mL) was heated at reflux for 3 h. After cooling, the solution was concentrated *in vacuo* to give 2,6-dichloro-5-fluoronicotinoyl chloride as a brown oil which was carried on to the next step without further purification.

This transformation can also be accomplished using oxalyl chloride with catalytic DMF in place of thionyl chloride.

Intermediate L:

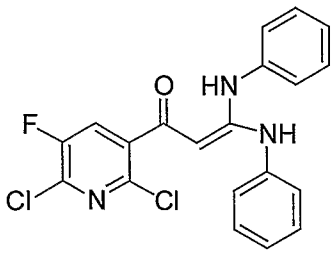
3,3-dichloro-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one



A solution of the 2,6-dichloro-5-fluoronicotinoyl chloride from the previous reaction in CH_2Cl_2 (25 mL) was added slowly to a cooled (0 °C) and stirred slurry solution of $AlCl_3$ (7.9 g, 59.5 mmol) in CH_2Cl_2 (25 mL). After 15 min, vinylidene chloride (4.75 mL, 59.5 mmol) was added to the mixture dropwise. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was poured over ice and partitioned with CH_2Cl_2. The organic layer was collected and cooled to 0 °C before TEA (8.3 mL, 59.5 mmol) was added. After 15 min, the ice bath was removed and the reaction was allowed to warm to room temperature and stirred for an additional 30 min. The solution was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was passed through a pad of silica gel and concentrated *in vacuo* to afford 3,3-dichloro-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one: (6.1 g, 90%) as a brown oil: ^{1}H-NMR (d_6-DMSO, 300 MHz) δ 8.43 (d, 1H, J = 8.4 Hz), 7.56 (s, 1H), R_f = 0.76 (3:1 Hex:EtOAc).

Intermediate M:

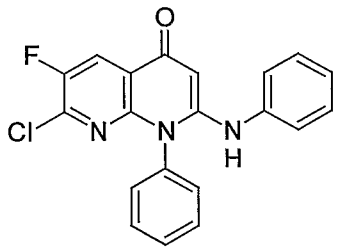
3,3-dianilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one



To a 0 °C solution of 3,3-dichloro-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one (6.70 g, 23.2 mmol) in dioxane (50 mL) was added TEA (9.7 mL, 69.6) followed by aniline (6.3 mL, 69.6 mmol). After 1 h the reaction was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated *in vacuo* until most of the solvent was removed and then the residue was diluted with water and extracted with CH_2Cl_2 (2X). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by silica gel Biotage chromatography provided 3,3-dianilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one as yellow solid (4.2 g, 49%): LCMS RT: 3.47 min; MH^+: 402.6.

Intermediate N:

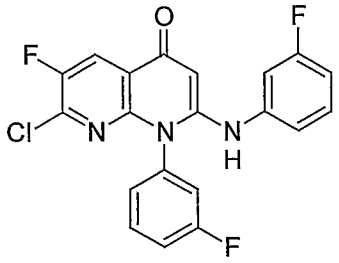
2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1H)-one



A mixture of 3,3-dianilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one (2.3 g, 5.7 mmol) and *t*-BuOK (1.28 g, 11.4 mmol) in dioxane (80 mL) was stirred at 80 °C overnight. The reaction was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue provided 2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1H)-one (1.0 g, 50%) as a light yellow solid: LCMS RT: 2.60 min, MH^+: 366.8. This transformation can be accomplished by using the combination of other aprotic solvents such as DMF, and THF with other bases such as NaH.

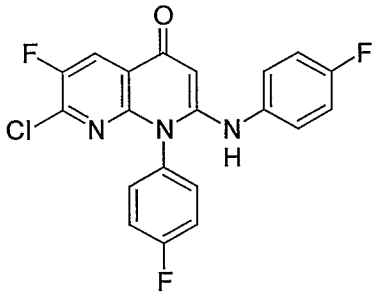
Intermediates N_1-N_{12} were synthesized from 3,3-dichloro-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one as above for Intermediate N using the appropriate amine:

Intermediate N_1:



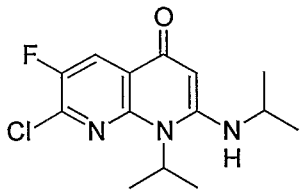
LCMS RT: 2.81 min, MH^+: 402.3

Intermediate N_2:



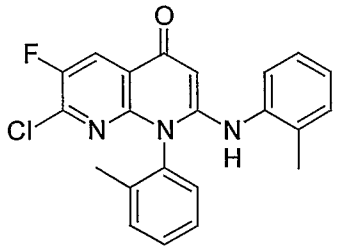
LCMS RT: 2.73 min, MH^+: 402.4

Intermediate N_3:



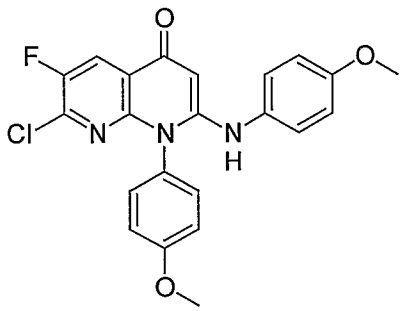
LCMS RT: 2.30 min, MH^+: 298.1

Intermediate N_4:



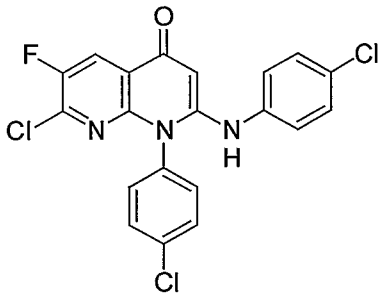
LCMS RT: 2.88 min, MH^+: 394.3

Intermediate N_5:



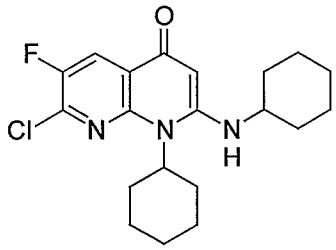
LCMS RT: 2.78 min, MH^+: 426.3

Intermediate N_6:



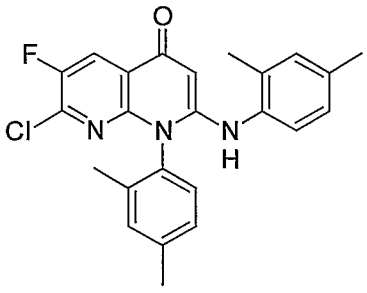
LCMS RT: 3.09 min, MH^+: 434.5

Intermediate N_7:



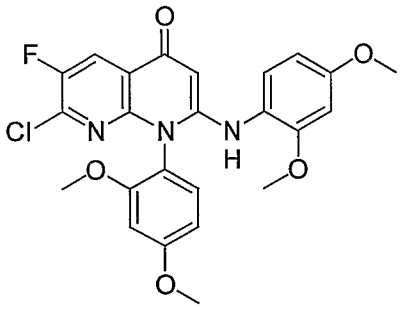
LCMS RT: 3.07 min, MH^+: 378.2

Intermediate N_8:



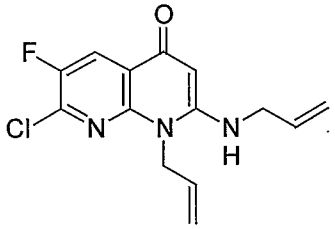
LCMS RT: 3.15 min, MH^+: 422.4

Intermediate N_9:



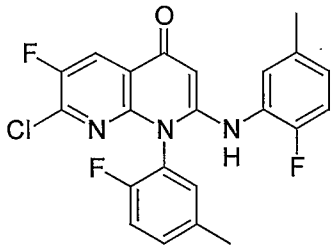
LCMS RT: 2.90 min, MH^+: 486.3

Intermediate N_{10}:



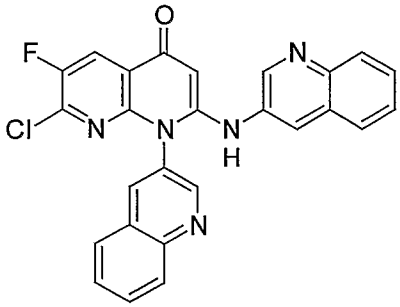
LCMS RT: 2.22 min, MH^+: 294.2

Intermediate N_{11}:



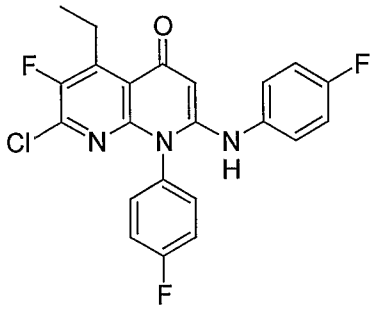
LCMS RT: 3.05 min, MH^+: 430.4

Intermediate N_{12}:



LCMS RT: 2.51 min, MH^+: 468.3

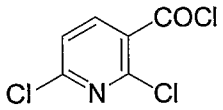
Intermediate N_{13}



LCMS RT: 3.10 min, MH^+: 430.4

Intermediate O:

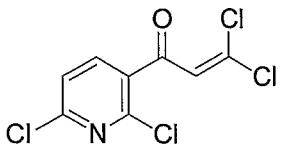
2,6-dichloronicotinoyl chloride



A solution of commercially available (Aldrich) 2,6-dichloro-nicotinic acid (2.0 g, 10.4 mmol) in thionyl chloride (10 mL) was heated to 80 °C for 2 h. After cooling, the solution was concentrated *in vacuo* to give 2,6-dichloro-nicotinoyl chloride as yellow oil which was carried on to the next step without further purification. This transformation can also be accomplished using oxalyl chloride with catalytic DMF in place of thionyl chloride.

Intermediate P:

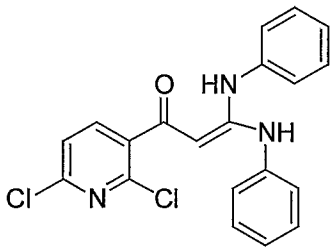
3,3-dichloro-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one



A solution of the 2,6-dichloro-nicotinoyl chloride (1.0 g, 4.76 mmol) from the previous reaction in CH_2Cl_2 (5 mL) was added slowly to a cooled (0 °C) and stirred slurry solution of $AlCl_3$ (0.64 g, 4.76 mmol) in CH_2Cl_2 (20 mL). After 15 min, vinylidene chloride (0.38 mL, 0.46 g, 4.76 mmol) was added to the mixture dropwise. The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was then poured over ice and was acidified using 1 N HCl (15 mL). Stirring was continued for 20 min and the product was extracted with CH_2Cl_2 (3X). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 3,3-dichloro-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one (0.88 g, 68%) as a light yellow oil: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.38, d, J = 8.4, 1H). 7.40 (d, J = 8.4, 1H), 7.10 (s, 1H); R_f = 0.51 (4:1 Hex:EtOAc).

Intermediate Q:

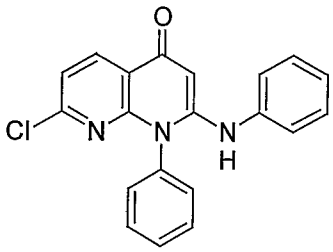
3,3-dianilino-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one



A solution of aniline (1.01 mL, 11.1 mmol) in TEA (1.55 mL, 11.1 mmol) was added slowly to a cooled (0 °C) and stirred solution of 3,3-dichloro-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one (1.0 g, 3.69 mmol) in dioxane (20 mL). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was concentrated *in vacuo* until most of the solvent was removed. The residue was diluted with water and extracted with EtOAc (3X). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 6:1 EtOAc:Hex gave 3,3-dianilino-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one as pale yellow solid (0.69 g, 49%): LCMS RT: 3.81 min; MH^+: 384.2.

Intermediate R:

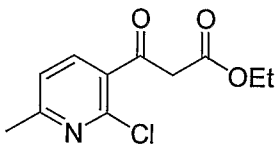
2-anilino-7-chloro-1-phenyl-2,3-dihydro-1,8-naphthyridin-4(1H)-one



A mixture of 3,3-dianilino-1-(2,6-dichloro-3-pyridinyl)-2-propen-1-one (0.08 g, 0.21 mmol) and NaH (0.009 g, 0.23 mmol) in THF (6 mL) was heated to 80 °C overnight. The reaction was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 3:1 Hex:EtOAc provided 2-anilino-7-chloro-1-phenyl-2,3-dihydro-1,8-naphthyridin-4(1H)-one (49 mg, 68%) as an off- white solid: LC-MS RT: 2.56 min, MH^+: 348.2. This transformation can be accomplished by using the combination of other aprotic solvents such as dioxane and DMF with other bases such as *t*-BuOK.

Intermediate S:

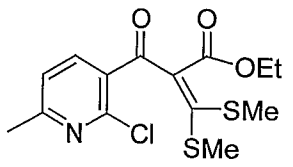
Ethyl 3-(2-chloro-6-methyl(3-pyridyl))-3-oxopropanoate



Ethyl 3-(2-chloro-6-methyl(3-pyridyl))-3-oxopropanoate was prepared by the general procedure described in the *Journal of Medicinal Chemistry*, **1986**, *29*, 2363. The product had: MH^+: 242.1, LCMS RT: 2.33 and 3.06 min (keto-enol).

Intermediate T:

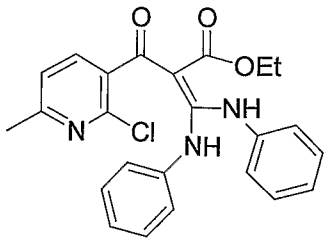
Ethyl (2Z)-2-[(2-chloro-6-methyl(3-pyridyl))carbonyl]-3,3-dimethylthio-prop-2-enoate



Cs_2CO_3 (24.0 g, 72.5 mmol) was added to a solution of ethyl 3-(2-chloro-6-methyl(3-pyridyl))-3-oxopropanoate (7.0 g, 29 mmol) in THF (290 mL). The reaction mixture was cooled to −10 °C and after 15 min, CS_2 (8.7 mL, 145 mmol) was added. Stirring was continued for 2 h and MeI (4.5 mL, 72.5 mmol) was added. The reaction was slowly warmed to room temperature over 18 h and filtered. The filtrate was concentrated *in vacuo* to provide ethyl (2Z)-2-[(2-chloro-6-methyl(3-pyridyl))carbonyl]-3,3-dimethylthioprop-2-enoate as a yellow oil that was used without purification. LCMS RT: 2.79 min, MH^+: 345.8. A variety of alkyl halides can be used to quench the generated sulfur anion.

Intermediate U:

Ethyl (2*E*)-3,3-bis(phenylamino)-2-[(2-chloro-6-methyl(3-pyridyl))-carbonyl]prop-2-enoate

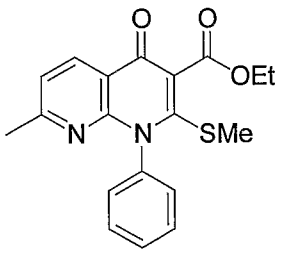


A solution of ethyl (2Z)-2-[(2-chloro-6-methyl(3-pyridyl))carbonyl]-3,3-dimethylthioprop-2-enoate (100. mg, 0.28 mmol) and aniline (0.076 mL, 0.83 mmol) in THF (1.4 mL) was heated at reflux for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 1:1

EtOAc:Hex provided ethyl (2*E*)-3,3-bis(phenylamino)-2-[(2-chloro-6-methyl(3-pyridyl))carbonyl]prop-2-enoate (55.6 mg, 44%): LCMS RT: 3.56 min, MH^+: 436.3.

Intermediate V:

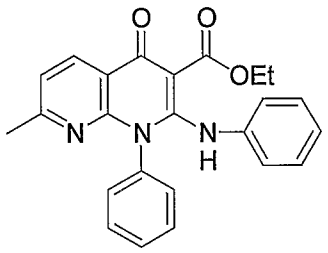
Ethyl 7-methyl-2-methylthio-4-oxo-1-phenylhydropyridino[2,3-b]-pyridine-3-carboxylate



Aniline (3.96 mL, 43.5 mmol) was added to a solution of ethyl (2*Z*)-2-[(2-chloro-6-methyl(3-pyridyl))carbonyl]-3,3-dimethylthioprop-2-enoate (5.13 g, 14.5 mmol) in DMSO (72.5 mL). The reaction solution was heated to 70 °C for 18 h and then cooled to room temperature. The solution was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Trituration of the resulting orange oil with Et_2O afforded some desired product as a yellow solid. Additional product was obtained by silica gel flash chromatography of the mother liquor using 1:1 EtOAc:Hex. The two purifications provided ethyl 7-methyl-2-methylthio-4-oxo-1-phenylhydropyridino[2,3-b]pyridine-3-carboxylate (2.87 g, 56%) as a yellow solid: LCMS RT: 2.85 min, MH^+: 355.0.

Intermediate W:

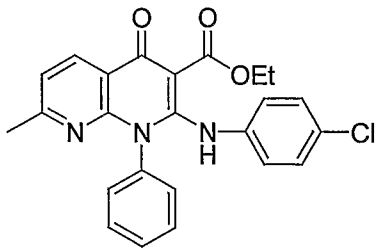
Ethyl 7-methyl-4-oxo-1-phenyl-2-(phenylamino)hydro-pyridino[2,3-b]-pyridine-3-carboxylate



A solution of ethyl (2*E*)-3,3-bis(phenylamino)-2-((2-chloro-6-methyl(3-pyridyl))carbonyl)prop-2-enoate (85.0 mg, 0.195 mmol) and *t*-BuOK (67 mg, 0.60 mmol) in dioxane (2 mL) was heated at reflux for 48 h. The reaction was cooled to room temperature and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 3:1 Hex:EtOAc to 100% EtOAc gave ethyl 7-methyl-4-oxo-1-phenyl-2-(phenylamino)hydropyridino[2,3-b]pyridine-3-carboxylate (39 mg, 49%) as a white solid: LCMS RT: 2.80 min, MH^+ 400.0. This transformation can be accomplished by using the combination of other aprotic solvents such as DMF and THF with other bases such as NaH.

Intermediate X:

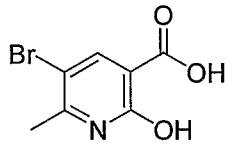
Ethyl 2-[(4-chlorophenyl)amino]-7-methyl-4-oxo-1-phenyl-hydropyridino-[2,3-b]pyridine-3-carboxylate



KHMDS (0.5 M in toluene, 0.84 mL, 0.42 mmol) was added to a cooled (-78 °C) solution of 4-chloroaniline (71.4 mg, 0.560 mmol) in THF (0.70 mL). After 2 h, a solution of ethyl 7-methyl-2-methylthio-4-oxo-1-phenylhydropyridino[2,3-b]pyridine-3-carboxylate (100 mg, 0.28 mmol) in THF (0.70 mL) was added resulting in immediate formation of an orange solution. The reaction was slowly warmed to room temperature, stirred for 21 h, and quenched with saturated aqueous NH_4Cl. The aqueous solution was extracted with Et_2O (3X) and the combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 1:1 EtOAc:Hex gave ethyl 2-[(4-chlorophenyl)amino]-7-methyl-4-oxo-1-phenylhydropyridino[2,3-b]pyridine-3-carboxylate (30.0 mg, 25%) as a white solid: LCMS RT: 2.98 min, MH^+ 434.0.

Intermediate Y:

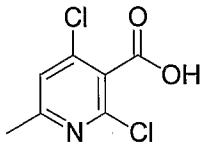
5-Bromo-2-hydroxy-6-methylnicotinc acid



A solution of NaOBr was prepared by adding Br_2 (11.4 g, 3.66 mL, 71.3 mmol) to a cooled (0 °C) and stirred solution of NaOH (7.8 g, 196 mmol) in water (90 mL). This solution was warmed to room temperature and was then added to a solution of commercially available (Aldrich) 2-hydroxy-6-methylpyridine-3-carboxylic acid (10.0 g, 65.1 mmol) and NaOH (7.8 g, 196 mmol) in water (30 mL). After stirring for 5 min, the mixture was cooled to 0 °C and carefully acidified with conc. HCl. The precipitate was filtered and dried over $MgSO_4$ to afford 5-bromo-2-hydroxy-6-methylnicotinc acid (15.0 g, 99%): ^1H NMR (DMSO-d_6) 8.25 (s, 1H), 2.41 (s, 3H); MH^+: 232.0. Elemental analysis calculated for $C_7H_6BrNO_3$: C, 36.23; H, 2.61; N, 6.04; Br, 34.44; Found: C, 36.07; H, 2.44; N, 5.91; Br, 34.43.

Intermediate Z (Same as Intermediate BA):

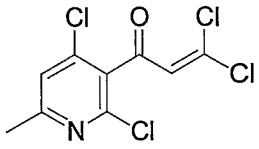
2,4-dichloro-6-methylnicotinic acid



A solution of commercially available (Maybridge) ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (1.0 g, 4.3 mmol) and NaOH (342 mg, 8.6 mmol) in water (1.7 mL) and MeOH (1.5 mL) was heated to 80 °C for 4 h. The mixture was acidified using 50% H_2SO_4 and filtered. The solid was washed with cold water and dried to give of 2,4-dichloro-6- methylpyridine-3-carboxylic acid (582 mg, 66%): LCMS RT: 0.70 min, MH^+: 206.2.

Intermediate AA (Same as Intermediate BB):

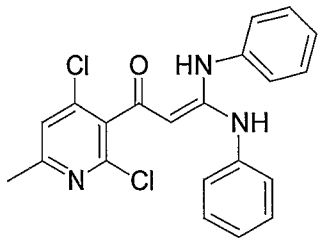
3,3-dichloro-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one



The compound was prepared according to the procedure described for Intermediate BB below. LCMS RT: 3.13 min, MH^+: 284.6.

Intermediate AB (Same as Intermediate BC):

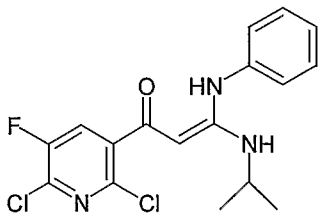
3,3-dianilino-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one



The compound was prepared according to the procedure described for Intermediate BC below: LCMS RT: 3.06 min, MH^+: 398.7.

Intermediate AC:

(2Z)-3-anilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-3-(isopropylamino)-2-propen -1-one

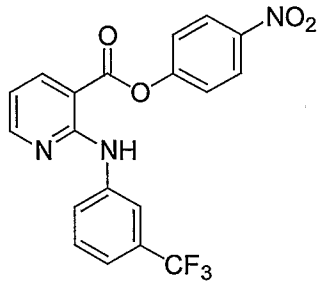


3,3-dichloro-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-2-propen-1-one (374.0 mg, 1.29 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 10 °C. Aniline (120.0 mg, 1.29 mmol) and isopropylamine (76.5 mg, 1.29 mmol) were added dropwise as a mixture in 3 mL of 1,4-dioxane. TEA (0.897 mL, 6.45 mmol) was added and the reaction mixture was warmed to room temperature and left to stir for 2 h. The dioxane was removed *in vacuo* and the brown residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue using Biotage silica gel chromatography eluting with 6:1 to 7:3 Hex:EtOAc

provided (2Z)-3-anilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-3-(isopropylamino)-2-propen-1-one (45 mg, 10%) as an off-white solid: LCMS RT: 3.63 min, MH^+: 368.2.

Intermediate AD:

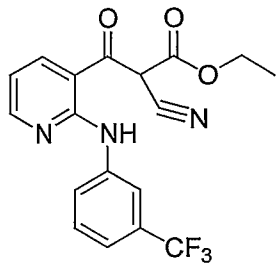
4-Nitrophenyl 2-{[3-(trifluoromethyl)phenyl]amino}nicotinate



To a warmed (40 °C) suspension of niflumic acid (10.0 g, 35.4 mmol) and 4-nitrophenol (4.9 g, 35.4 mmol) in CH_2Cl_2 (80 mL) was added a suspension of EDCI (6.8 g, 35.4 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred for 16 h, and then cooled to room temperature. The solution was quenched with water (50 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by trituration with Hex:CH_2Cl_2 to afford 4-Nitrophenyl 2-{[3-(trifluoromethyl)phenyl]amino}nicotinate (4.5 g, 31%): LCMS RT: 4.03 min, MH^+: 404.1.

Intermediate AE:

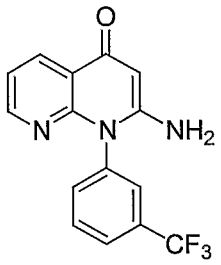
Ethyl 2-cyano-3-oxo-3-(2-{[3-(trifluoromethyl)phenyl]amino}-3-pyridinyl)propanoate



To a stirred mixture of NaH (524 mg, 21.8 mmol) in toluene (20 mL) was added dropwise ethyl cyanoacetate (3.7 g, 32.7 mmol, 3.5 mL). The slurry was stirred for 1 h and then 4-nitrophenyl 2-{[3-(trifluoromethyl)phenyl]amino}nicotinate (4.4 g, 10.9 mmol) was added. The reaction mixture was stirred for 1 h and then quenched with water (20 mL). CH_2Cl_2 (30 mL) was added and the layers were partitioned. The organic layer was washed with brine (2X) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by silica gel flash chromatography (5:1 to 2:1 Hex:EtOAc) to afford 3 Ethyl 2-cyano-3-oxo-3-(2-{[3-(trifluoromethyl)phenyl]amino}-3-pyridinyl)propanoate.(6 g, 87%): LCMS RT: 2.83 min, MH^+: 378.0.

Intermediate AF:

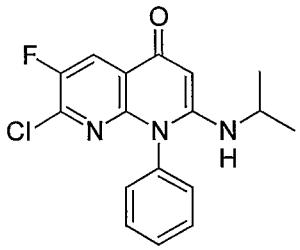
2-Amino-1-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-4(1H)-one



Ethyl 2-cyano-3-oxo-3-(2-{[3-(trifluoromethyl)phenyl]amino}-3-pyridinyl) propanoate (2.0 g, 5.3 mmol) was heated to 120 °C in a mixture of conc. HCl (4 mL) and glacial acetic acid (2 mL) for 3 h. The reaction mixture was cooled to room temperature, and neutralized by slow addition of NaOH pellets. The mixture was extracted with CH_2Cl_2 (3X). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by prep-HPLC (YMC-Pack Pro C18 Column, 150 x 20 mm I.D.; 30-70% CH_3CN in water, 20 min.) to afford 2-Amino-1-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-4(1H)-one (880 mg, 55%): LCMS RT: 2.03 min, MH^+: 306.3.

Intermediate AG:

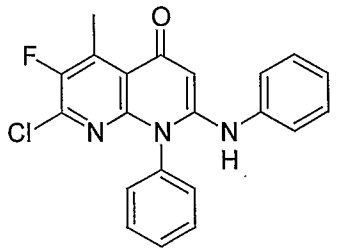
7-chloro-6-fluoro-2-(isopropylamino)-1-phenyl-1,8-naphthyridin-4(1H)-one



(2Z)-3-Anilino-1-(2,6-dichloro-5-fluoro-3-pyridinyl)-3-(isopropylamino)-2-propen-1-one (40.0 mg, 0.109 mmol) was dissolved in 4 mL of DMF. NaH (8.70 mg, 0.217 mmol, 60% dispersion in oil) was added and the reaction was heated to 85 °C under argon for 2 h. The reaction mixture was cooled to room temperature and diluted with water and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue using Biotage silica gel chromatography eluting with 100% EtOAc to 95:5 EtOAc:MeOH provided 7-chloro-6-fluoro-2-(isopropylamino)-1-phenyl-1,8-naphthyridin-4(1H)-one (21 mg, 64%) as a white solid: LCMS RT: 2.57 min, MH^+: 332.2.

Intermediate AH:

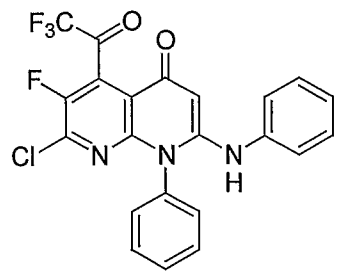
2-anilino-7-chloro-6-fluoro-5-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one



A solution of LTMP [freshly prepared at 0 °C from tetramethylpiperidine (227.2 mg, 1.62 mmol), TMEDA (188.3 mg, 1.62 mmol) and n-BuLi (1 mL, 1.62 mmol)] in THF (5 mL) was added to a cooled (-40 °C) and stirred solution of 2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1*H*)-one (200 mg, 0.54 mmol) in THF (10 mL). The reaction mixture was warmed to 0 °C, for 1 h and then re-cooled to -40 °C. MeI (766 mg, 5.35 mmol) was added and the reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched carefully with water (50 mL) and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 1:1 EtOAc:Hex afforded 2-anilino-7-chloro-6-fluoro-5-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (184 mg, 88%) as a white solid: LCMS RT: 2.74 min, MH^+: 380.3. This transformation can also be accomplished by using other amide bases such as LDA.

Intermediate AI:

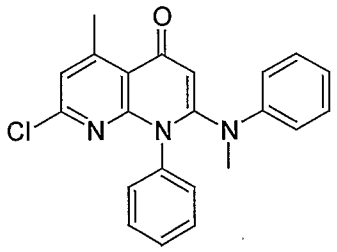
2-anilino-7-chloro-6-fluoro-1-phenyl-5-(trifluoroacetyl)-1,8-naphthyridin-4(1*H*)-one



A solution of LTMP [freshly prepared at 0 °C from tetramethylpiperidine (154 mg, 1.10 mmol), TMEDA (127.8 mg, 1.10 mmol) and n-BuLi (0.688 mL, 1.10 mmol)] in THF (5 mL) was added to a cooled (-40 °C) stirred solution of 2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1*H*)-one (100 mg, 0.273 mmol) in THF(10 mL). The reaction was stirred for 1 h and then cooled to -78 °C. Methyl trifluoroacetate (350 mg, 2.74 mmol) was added and stirring was continued for 2 h. The reaction was quenched carefully with water (50 mL), warmed to room temperature and extracted with EtOAc . The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 3:1 Hex:EtOAc gave 2-anilino-7-chloro-6-fluoro-1-phenyl-5-(trifluoroacetyl)-1,8-naphthyridin-4(1*H*)-one (71 mg, 56%) as a light yellow solid: LCMS RT: 3.43 min, MH^+: 462.3. The anion generated from LTMP deprotonation can be quenched with other electrophiles including carbon dioxide and 4-nitrophenyl acetate.

Intermediate AJ:

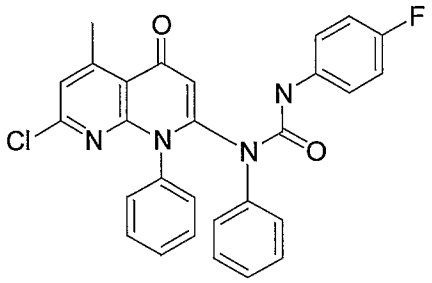
7-chloro-5-methyl-2-[methyl(phenyl)amino]-1-phenyl-1,8-naphthyridin-4(1*H*)-one



MeI (0.10 mL, 228 mg, 1.6 mmol) was added to a stirred suspension of K_2CO_3 (23.5 mg, 0.17 mmol) and 2-anilino-7-chloro-5-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (50 mg, 0.14 mmol) in THF (3 mL). The suspension was heated to 40 °C and stirred was overnight. The reaction was quenched with water (5.0 mL) and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Recrystallization of the residue using EtOAc afforded 7-chloro-5-methyl-2-[methyl(phenyl)amino]-1-phenyl-1,8-naphthyridin-4(1*H*)-one (18 mg, 35%): LCMS RT: 2.24 min, MH^+: 376.6, R_f = 0.76 (4:1 Hex:EtOAc).

Intermediate AK:

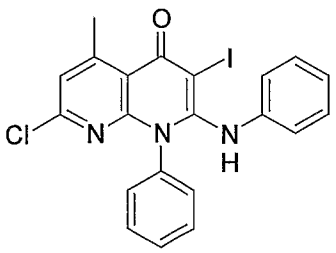
N-(7-chloro-5-methyl-4-oxo-1-phenyl-1,4-dihydro-1,8-naphthyridin-2-yl)-N'-(4-fluorophenyl)-N-phenylurea



4-Fluorophenyl isocyanate (45.0 mg, 0.33 mmol) was added to a stirred solution of 2-anilino-7-chloro-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.276 mmol) in CH_2Cl_2 (3 mL). After 16 h, an additional equivalent of 4-fluorophenyl isocyanate (45.0 mg) was added, and the reaction stirred for an additional 16 h. The reaction was concentrated *in vacuo* and the residue was dissolved in EtOAc. The solution was washed with 1 N HCl, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue using reverse phase prep-HPLC afforded N-(7-chloro-5-methyl-4-oxo-1-phenyl-1,4-dihydro-1,8-naphthyridin-2-yl)-N'-(4-fluorophenyl)-N-phenylurea (2.2 mg, 1.6%): LCMS RT: 3.47 min, MH^+: 499.1, R_f = 0.52 (1:1 EtOAc:Hex).

Intermediate AL:

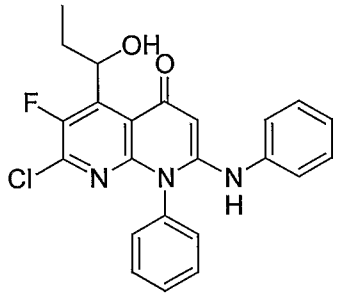
2-anilino-7-chloro-3-iodo-5-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one



K_2CO_3 (210 mg, 1.52 mmol) and I_2 (390 mg, 1.52 mmol,) were added to a solution 2-anilino-7-chloro-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (500 mg, 1.38 mmol) in DMF (10 mL). The mixture was stirred for 30 min and then poured into an aqueous solution of saturated $Na_2S_2O_3$ (10 mL). The aqueous solution was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 4:1 to 1:1 Hex:EtOAc afforded 2-anilino-7-chloro-3-iodo-5-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (380 mg, 56%): LCMS RT: 3.45 min, MH^+: 488.2, R_f = 0.5 (2:1 Hex:EtOAc).

Intermediate AM:

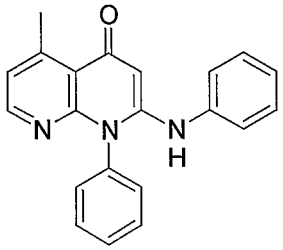
2-anilino-7-chloro-6-fluoro-5-(1-hydroxypropyl)-1-phenyl-1,8-naphthyridin-4(1H)-one



A -40 °C solution of 2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.274 mmol) in THF (10 mL) was treated with LTMP (1.10 mmol, freshly prepared by mixing 2,2,6,6-Tetramethyl piperidine and n-BuLi at 0 °C for 30 min.). The mixture was then allowed to warm to 0 °C for 2 h. The reaction mixture was cooled to -30 °C and propionaldehyde (159 mg, 2.74 mmol) was added. The reaction was stirred at -30 °C for 2 h before it was slowly quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography to afford 2-anilino-7-chloro-6-fluoro-5-(1-hydroxypropyl)-1-phenyl-1,8-naphthyridin-4(1H)-one (120 mg, 97%) as a white solid: LCMS RT: 3.14 min, MH^+: 424.2. Other electrophiles such as disulfide may be used to quench the anion.

Example 1:

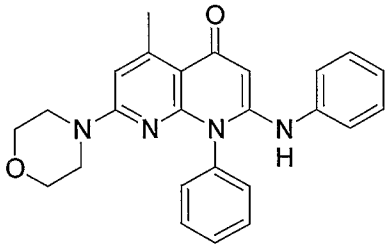
2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



A solution of 2-anilino-7-chloro-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (95.0 mg, 0.263 mmol), TEA (0.65 mmol), and 10% Pd/C in EtOAc (2.5 mL) and EtOH (2.5 mL) was stirred under H_2 (1 atm) for 3.5 h. The reaction mixture was filtered through a pad of Celite using EtOH and EtOAc to rinse. The combined filtrates were concentrated *in vacuo*, and purified with Biotage silica gel chromatography using 1:1 EtOAc:Hex to afford 2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (84 mg, 98%) as a pale yellow solid. LCMS RT: 2.26 min, MH^+: 328.4, R_f = 0.1 (1:1 EtOAc:Hex),

Example 2:

5-Methyl-7-morpholin-4-yl-1-phenyl-2-phenylamino-1H-[1,8]-naphthyridin-4one

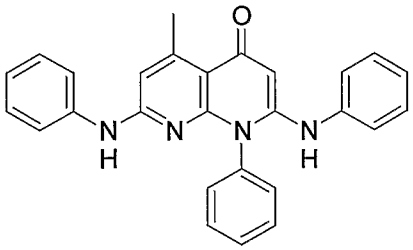


A mixture of 7-chloro-5-methyl-1-phenyl-2-phenylamino-1H-[1,8]naphthyridin-4-one (68.3 mg, 0.189 mmol) and morpholine (0.05 mL, 0.48 mmol) in dioxane (3 mL) was heated to 80 °C for 2 d. The reaction was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give 5-methyl-7-morpholin-4-yl-1-

phenyl-2-phenylamino-1H-[1,8]naphthyridin-4-one (67 mg, 92%) as yellow solid: LCMS RT: 2.33 min, MH^+: 413.4, R_f = 0.49 (EtOAc).

Example 3:

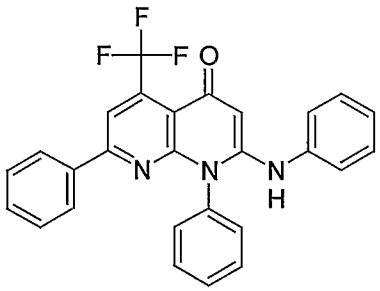
5-Methyl-1-phenyl-2,7-bis-phenylamino-1H-[1,8]naphthyridin-4-one



A mixture of 7-chloro-5-methyl-1-phenyl-2-phenylamino-1H-[1,8]naphthyridin-4-one (15.1 mg, 0.042 mmol), aniline (2 drops), $Pd(OAc)_2$ (0.27 mg, 0.001 mmol), Cs_2CO_3 (19.5 mg, 0.06 mmol), and BINAP (1.68 mg, 0.003 mmol) in THF (0.5 mL) was heated at reflux for 16 h. The reaction was quenched with water and extracted with EtOAc (3X). The combined organic extracts were washed brine, dried over Na_2SO_4, and concentrated *in vacuo* to give 5-methyl-1-phenyl-2,7-bis-phenylamino-1H-[1,8]naphthyridin-4-one (6.0 mg, 38%): LCMS RT: 2.57 min, MH^+: 419.5, R_f = 0.18 (EtOAc).

Example 4:

2-anilino-1,7-diphenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one

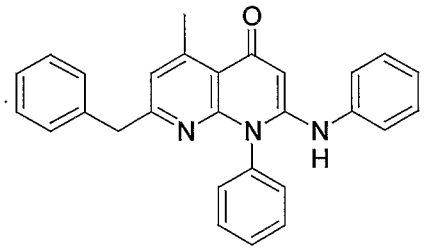


A solution of 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (10.0 mg, 0.241 mmol), Ph_3P (6.00 mg, 0.024 mmol) and phenylboronic acid (36.0 mg, 0.290 mmol) in DME was treated with 2M K_2CO_3 (0.482 mL, 0.964 mmol) and

$Pd(OAc)_2$ (1.35 mg, 0.006 mmol). The mixture was heated at reflux for 24 h. After cooling to room temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided 2-anilino-1,7-diphenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (45.0 mg, 41%): LCMS RT: 3.76 min, MH^+: 458.4.

Example 5:

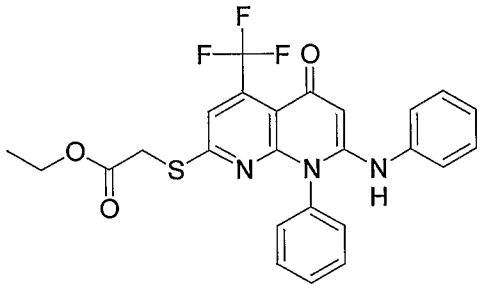
2-anilino-7-benzyl-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



To a solution of 2-anilino-7-chloro-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.277 mmol) in THF was added $Ni(dppp)Cl_2$ (37.0 mg, 0.069 mmol). After stirring for 5 min, benzylmagnesium chloride (2M , 1.45 mL, 2.90 mmol) was added dropwise via syringe and the mixture was allowed to stir for 24 h. The mixture was quenched with 1 N HCl and extracted with EtOAc. The organic layer was washed brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparative HPLC (10% MeNC in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided 2-anilino-7-benzyl-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (47.3 mg, 41%): LCMS RT: 2.85 min, MH^+: 418.3.

Example 6:

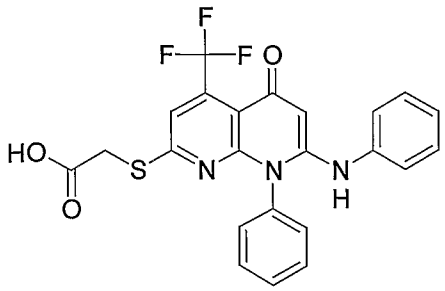
Ethyl{[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]sulfanyl}acetate



NaH (60% dispersion in oil, 18.0 mg, 0.434 mmol) was added to a cooled (0 °C) and stirred solution of ethyl mercaptoacetate (0.05 mL, 0.434 mmol) in DMF. After 0.5 h, 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (150.0 mg, 0.361 mmol) was added as a solid in a single portion. The mixture was allowed to warm to room temperature and was stirred for 24 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided ethyl {[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]sulfanyl}acetate (50 mg, 53%): LCMS RT: 3.91 min, MH^+: 500.2, R_f = 0.24 (1:1 EtOAc:Hex).

Example 7:

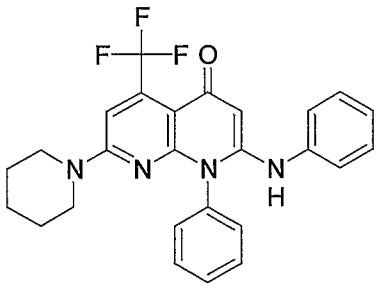
{[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]sulfanyl}acetic acid



NaOH (160 mg, 4.0 mmol) was added to a stirred solution of ethyl {[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl] sulfanyl} acetate (30.0 mg, 0.060 mmol) in aqueous EtOH (10mL EtOH in 4mL H_2O). The mixture was allowed to stir for 4 h and was then concentrated *in vacuo*. The reaction was acidified with 1N HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided {[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]sulfanyl}acetic acid (19.0 mg, 66%): LCMS RT: 2.50 min, MH^+: 472.1

Example 8

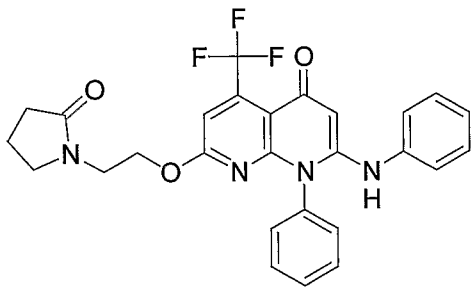
2-anilino-1-phenyl-7-(1-piperidinyl)-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one



To a solution of 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (100.0 mg, 0.241 mmol) in dioxane (2.5 mL) was added piperdine (40.9 mg, 0.481 mmol). The mixture was left to stir at 80 °C overnight. The mixture was cooled to room temperature, poured into 1N HCl (1 mL) and extracted with CH_2Cl_2. The organic extracts were combined, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by Biotage silica gel chrmoatography (1:1 EtOAc:Hex) to provide 2-anilino-1-phenyl-7-(1-piperidinyl)-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (89.5 mg, 80%) as a pale yellow solid: LCMS RT: 2.76 min, MH^+: 465.5.

Example 9:

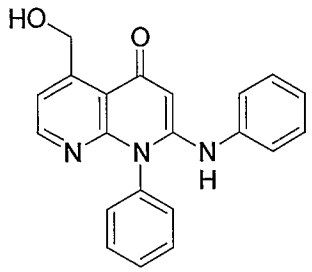
2-anilino-7-[2-(2-oxo-1-pyrrolidinyl)ethoxy]-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one



NaH (60% dispersion, 20.0 mg, 0.514 mmol) was added to a cooled (0 °C) and stirred solution of 1-(2-hydroxyethyl)-2-pyrrolidinone (0.06 mL, 0.514 mmol) in DMF. After 0.5 h, 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (178 mg, 0.428 mmol) was added as a solid in a single portion and the mixture was heated to 130 °C for 48 h. After cooling to room temperature the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided 2-anilino-7-[2-(2-oxo-1-pyrrolidinyl)ethoxy]-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (0.047 g, 64%): LCMS RT: 2.40 min, MH^+: 509.2. This transformation can be accomplished by using other aprotic solvents such as DMSO, THF and dioxane with temperatures appropriate for these solvents. Commercially available alkoxides can also be used in the absence of base.

Example 10:

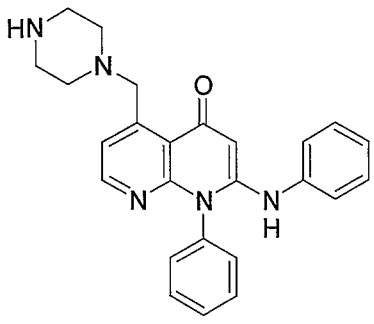
2-anilino-5-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one



A solution of LDA (38.2 mmol, freshly prepared from n-BuLi and diisopropylamine) in THF (53 mL) was added to a cooled (-78 °C) and stirred suspension of 2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (2.50 g, 7.64 mmol) in THF (100 mL). The resulting mixture was stirred for 1 h, and then oxygen gas was bubbled, through a fritted glass tube, into the bottom of the reaction vessel. The mixture was stirred overnight, with continued bubbling of oxygen with slow warming to room temperature. The reaction was quenched with water and 1M HCl (5 mL), and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford an orange solid which was recrystalized from EtOAc to obtain 2-anilino-5-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one (1.38 g, 53%): LCMS RT: 2.01 min, MH^+: 344.3, R_f = 0.22 (95:5 CH_2Cl_2:MeOH).

Example 11:

2-anilino-1-phenyl-5-(1-piperazinylmethyl)-1,8-naphthyridin-4(1H)-one

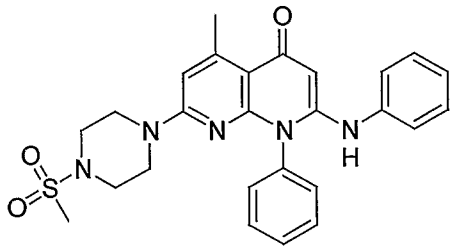


A solution of 2-anilino-5-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one (180 mg, 0.52 mmol), N,N-diisopropylethylamine (0.10 mL, 0.52 mmol) and $SOCl_2$ (0.12 mL, 1.57 mmol) in CH_2Cl_2 (7 mL) was stirred at room temperature for 2 h. Excess $SOCl_2$ and solvent were removed *in vacuo* to afford a brownish solid. Crude 2-anilino-5-(chloromethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one was used without further purification: LCMS RT: 2.50 min, MH^+: 362.3.

DMF (1 mL) was added to a stirred suspension of crude 2-anilino-5-(chloromethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one (15.0 mg, 0.041 mmol), N,N-diisopropylethylamine (0.036 mL, 0.21 mmol), and piperazine (36 mg, 0.21 mmol) in 1,4-dioxane (2 mL). The solution was heated to 50 °C overnight, cooled to room temperature and concentrated *in vacuo*. Reverse phase preparative HPLC (0.1% TFA in CH_3CN and water) of the residue gave 2-anilino-1-phenyl-5-(1-piperazinylmethyl)-1,8-naphthyridin-4(1H)-one (8.0 mg, 37%) as the TFA salt: LCMS RT: 0.71 min, MH^+: 412.2.

Example 12:

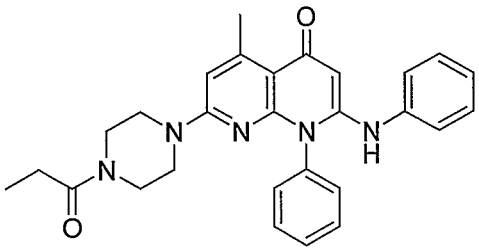
5-Methyl-1-phenyl-2-phenylamino-7-piperazin-1-yl-1H-[1,8]naphthyridin-4-one



A mixture of 5-methyl-1-phenyl-2-phenylamino-7-piperazin-1-yl-1H-[1,8]naphthyridin-4-one (22.6 mg, 0.055 mmol) and MsCl (0.083 mmol, 0.006 mL) in CH_2Cl_2 (0.8 mL) was stirred at room temperature overnight at which time the solvent was removed *in vacuo*. The resulting residue was purified by prep-TLC to give 7-(4-methanesulfonyl-piperazin-1-yl)-5-methyl-1-phenyl-2-phenylamino-1H-[1,8]naphthyridin-4-one (3.4 mg, 6%): LCMS RT: 2.36 min, MH^+: 490.3.

Example 13:

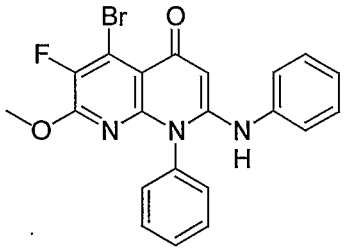
5-methyl-1-phenyl-2-phenylamino-7-(4-propionyl-piperazin-1-yl)-1H-[1,8]naphthyridin-4-one



A mixture of 5-methyl-1-phenyl-2-phenylamino-7-piperazin-1-yl-1H-[1,8]naphthyridin-4-one (21.0 mg, 0.052 mmol), propionic acid (0.004 mL, 0.055 mmol), EDCI (11.9 mg, 0.062 mmol), DMAP (7.6 mg, 0.062 mmol), and NMM (0.006 mL, 0.062) in CH_2Cl_2 (0.8 mL) was stirred at room temperature overnight. The reaction was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with 0.5 N HCl and brine and concentrated *in vacuo*. The residue was purified by prep-TLC eluting with 100% EtOAc to give 5-methyl-1-phenyl-2-phenylamino-7-(4-propionyl-piperazin-1-yl)-1H-[1,8]naphthyridin-4-one (9.0 mg, 37%): LCMS RT: 2.29 min, MH^+: 468.3.

Example 14:

2-anilino-5-bromo-6-fluoro-7-methoxy-1-phenyl-1,8-naphthyridin-4(1*H*)-one

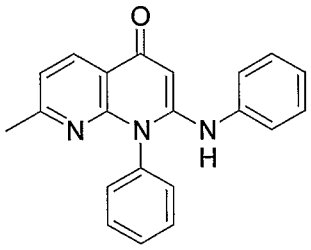


A solution of LTMP [freshly prepared at 0 °C from tetramethylpiperidine (785.4 mg, 5.6 mmol), TMEDA (651 mg, 5.6 mmol) and n-BuLi (3.5 mL, 5.6 mmol)] in THF (10 mL) was added to a cooled (-40 °C) stirred solution of 2-anilino-6-fluoro-7-methoxy-1-

phenyl-1,8-naphthyridin-4(1*H*)-one (507 mg, 104 mmol) in THF (20 mL). The reaction mixture was warmed to room temperature. After 1 h, the mixture was cooled to -30 °C and 1,2-dibromotetrachloroethane (457 mg, 1.4 mmol) was added. After 30 min, water (50 mL) was added slowly, and then the reaction was warmed to room temperature and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using EtOAc afforded 2-anilino-5-bromo-6-fluoro-7-methoxy-1-phenyl-1,8-naphthyridin-4(1*H*)-one (101 mg, 16%) as a light yellow solid: LCMS RT: 2.75 min, MH^+: 440.3.

Example 15:

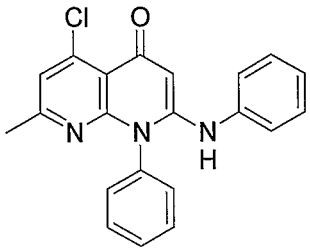
7-Methyl-1-phenyl-2-(phenylamino)hydropyridino[2,3-b]pyridin-4-one



Ethyl 7-methyl-4-oxo-1-phenyl-2-(phenylamino)hydropyridino[2,3-b]pyridine-3-carboxylate (67 mg, 0.17 mmol) was dissolved in a 2:1 HCl:AcOH solution (8.5 mL). The reaction was heated to 120 °C for 5 h then cooled to room temperature. The aqueous solution was washed with Et_2O and then neutralized with 2 N NaOH and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to provide 7-methyl-1-phenyl-2-(phenylamino)hydropyridino[2,3-b]pyridin-4-one (40 mg, 72%): LCMS RT: 2.28 min, MH^+:328.4.

Example 16:

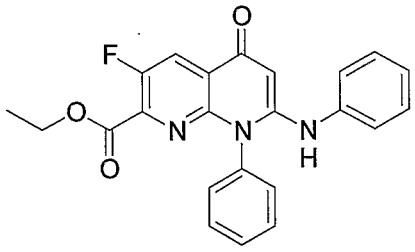
2-anilino-5-chloro-7-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



A mixture of 3,3-dianilino-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one(100 mg, 0.25 mmol) and *t*-BuOK (42 mg, 0.38 mmol) in anhydrous dioxane (4 mL) was heated to 80 °C for 4 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel flash chromatography of the residue using 1:1 EtOAc:Hex gave 2-anilino-5-chloro-7-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (13 mg, 14%): LCMS RT: 2.47 min, MH^+: 362.6. 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one was also isolated (68 mg, 75%): LCMS RT: 2.24 min, MH^+: 362.6. This transformation can be accomplished by using the combination of other aprotic solvents such as DMF and THF with other bases such as NaH.

Example 17:

Ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine carboxylate

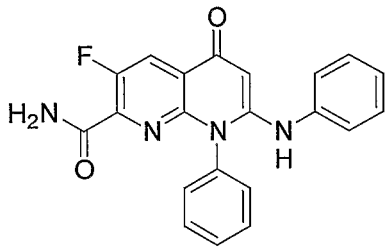


2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1H)-one (200 mg, 0.55 mmol), DPPP (12 mg, 0.030 mmol), $Pd(OAc)_2$ (6.0 mg, 0.028 mmol), and Cs_2CO_3 (114 mg, 0.42 mmol) was dissolved in a 1:1 mixture of EtOH (3 mL) / DMF (3 mL). A balloon filled with CO was attached to the flask and the solution was stirred vigorously. The

solution was saturated with CO by evacuating the flask followed by back filling the flask with CO. This was repeated 3 times before heating the solution to 70 °C. After 4 h of stirring all of the starting material had been consumed and the reaction was cooled to room temperature. The solution was diluted with EtOAc and was washed with water. The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo*. The crude solid was triturated with Et_2O, filtered and dried to give ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate as a light brown solid (900 mg, 81%): LCMS RT: 2.63 min, MH^+: 404.4

Example 18:

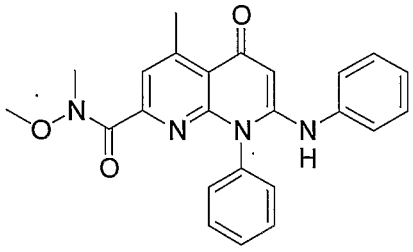
7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide



A suspension of ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate (50 mg, 0.12 mmol), and NH_4Cl (10 mg, 0.19 mmol) in concentrated NH_3 (3 mL) and MeOH (8 drops) was stirred for 16 h at room temperature. The solid was collected by filtration washing with water. Trituration with Et_2O, provided 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide as a yellow solid (32 mg, 71%): LCMS RT: 1.93 min, MH^+: 375.3. This trasformation can also be accomplished using EDCI/HOBT coupling with NH_3.

Example 19:

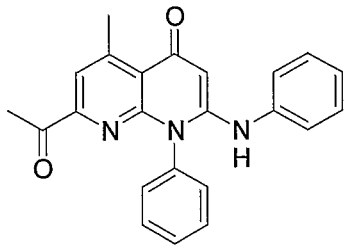
7-anilino-N-methoxy-N,4-dimethyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide



7-anilino-4-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylic acid (50 mg, 0.14 mmol), N,O-dimethylhydroxylamine hydrochloride (39 mg, 0.40 mmol), HOBT (28 mg, 0.21 mmol), EDCI (40 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (3 mL). To this solution was added TEA (78 uL, 0.56 mmol). The reaction was stirred for 1 h and was diluted with CH_2Cl_2, washed with 0.5N HCl, saturated $NaHCO_3$, and brine. The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo*. The solid obtained was triturated with Et_2O and dried to give 7-anilino-N-methoxy-N,4-dimethyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide as a light yellow solid (34 mg, 59%): LCMS RT: 2.28 min, MH^+: 415.2. This transformation can also be accomplished by coupling the appropriate amine with the corresponding acid chloride.

Example 20:

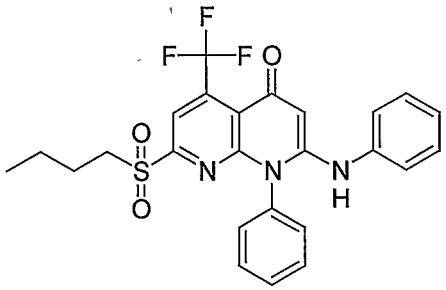
7-acetyl-2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



To a suspension of 7-anilino-N-methoxy-N,4-dimethyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide (100 mg, 0.24 mmol) in THF (5 mL) at 0 °C was added MeMgBr (3M in Et_2O, 322 uL, 0.97 mmol). The suspension became a red solution. As the reaction proceeded the solution lost its red color. After 1 h the reaction was quenched with saturated NH_4Cl, diluted with EtOAc, and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by a Biotage silica gel chromatography using EtOAc to afford 7-acetyl-2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one as a light yellow solid (65 mg, 74%): LCMS RT: 2.63 min, MH^+: 370.4.

Example 21:

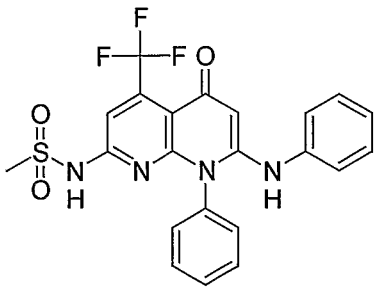
2-anilino-7-(butylsulfonyl)-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one



To a solution of montmorillonite K10 (107.5 mg) in $CHCl_3$ was added 13 uL of water. 2-anilino-7-(butylsulfanyl)-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (25 mg, 0.06 mmol) was then added followed by oxone (85.2 mg, 0.14 mmol). The reaction was allowed to stir for 24 h at room temperature. After 24 h the solution was bright bluish-green in color and was filtered and washed with copious amounts of $CHCl_3$. The filtrate was then concentrated *in vacuo*. Silica gel flash chromatography using 3:1 Hex:EtOAc provided 2-anilino-7-(butylsulfonyl)-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one as a yellow oil (13.8 mg, 46%): LCMS RT: 3.14, MH^+ 502.2.

Example 22:

N-[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]methanesulfonamide

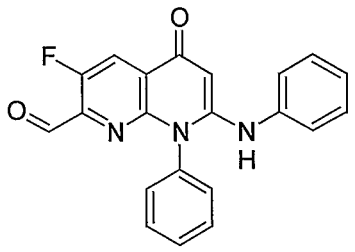


To a solution of 2-anilino-7-chloro-1-phenyl-5-(trifluoromethyl)-1,8-naphthyridin-4(1H)-one (100 mg, 0.241 mmol) in DMSO (5 mL) was added methyl sulfonamide and K_2CO_3 (76.5 mg, 0.554 mmol). The reaction was stirred at 120 °C for 24 h. The reaction

was then cooled to room temperature, quenched with water and extracted with Et_2O. The organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was then passed through a plug of silica gel eluting with 1:1 Hex:EtOAc to 9:1 CH_2Cl_2:MeOH to afford N-[7-anilino-5-oxo-8-phenyl-4-(trifluoromethyl)-5,8-dihydro-1,8-naphthyridin-2-yl]methanesulfonamide as a white solid (4.4 mg, 4%): LCMS RT: 2.45, MH^+: 475.2.

Example 23:

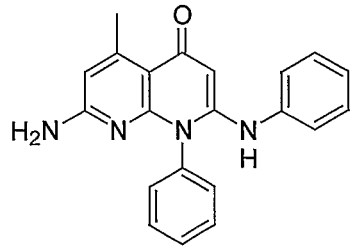
7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carbaldehyde



2-anilino-6-fluoro-7-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.277 mmol) was dissolved in 4.5 mL $CHCl_3$. MnO_2 (311 mg, 3.05 mmol) was added and the reaction was heated to 70 °C under argon for 3 d. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification by silica gel flash chromatography eluting with 3:1 to 100:0 EtOAc:Hex provided 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carbaldehyde (15 mg, 15%) as a white solid: LCMS RT: 2.18 min, MH^+: 360.2.

Example 24:

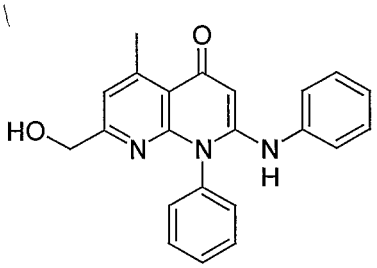
7-amino-2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



Pd/C (30 mg, 1.75 mmol, 10%) was added to a 25 mL round bottom flask and was blanketed with argon. 7-(allylamino)-2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (150 mg, 0.392 mmol) was dissolved in EtOH (2 mL) and was added to the Pd/C followed by methane sulfonic acid (0.041 mL, 0.63 mmol). The reaction was heated to 80 °C for 3 d at which time it was cooled to room temperature, diluted with EtOAc and filtered through celite. The filtrate was concentrated *in vacuo* and the residue was purified by Biotage silica gel chromatrography eluting with 100% EtOAc to provide 7-amino-2-anilino-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (182 mg, 41%) as a yellow solid: LCMS RT: 2.01 min, MH^+: 343.3.

Example 25:

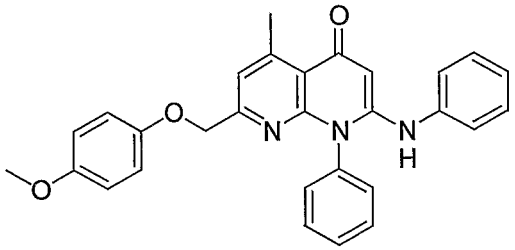
2-anilino-7-(hydroxymethyl)-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



To a 0 °C suspension of ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate (100.0 mg, 0.25 mmol) in THF (2.5 mL) was added LAH (0.750 mmol, 1M in THF) dropwise over 10 min. After 5 min. the reaction was slowly quenched with EtOAc (10 mL), was left to stir for 15 min and was concentrated *in vacuo*. The resiude was taken up in CH_2Cl_2 (10 mL) and 1N HCl (5 mL) and was left to stir for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Trituation with Et_2O provided 2-anilino-6-fluoro-7-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1*H*)-one (55.2 mg, 61%) as a tan solid: LCMS RT: 2.01 min, MH^+: 362.3.

Example 26:

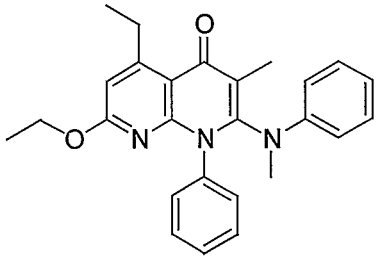
2-anilino-7-[(4-methoxyphenoxy)methyl]-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



2-anilino-6-fluoro-7-(hydroxymethyl)-1-phenyl-1,8-naphthyridin-4(1*H*)-one (62 mg, 0.175 mmol) was dissolved in CH_2Cl_2 (1.2 mL). 4-methoxyphenol (22 mg, 0.175 mmol) was added followed by Ph_3P (91.8 mg, 0.35 mmol), and ADDP (88.31 mg, 0.35 mmol). The reaction was left to stir overnight at room temperature under argon. Hexanes (5 mL) were added and the reaction was filtered. The filtrate was concentrated *in vacuo*. Purification of the residue using Biotage silica gel chromatography eluting with 7:3 to 9:1 EtOAc:Hex provided 2-anilino-6-fluoro-7-[(4-methoxyphenoxy)methyl]-1-phenyl-1,8-naphthyridin-4(1*H*)-one (30.0 mg, 37%) as a white solid: LCMS RT 2.87 min, MH^+: 464.2.

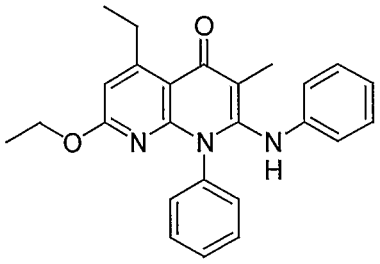
Example 27:

7-ethoxy-5-ethyl-2-[methyl(phenyl)amino]-1-phenyl-1,8-naphthyridin-4(1H)-one



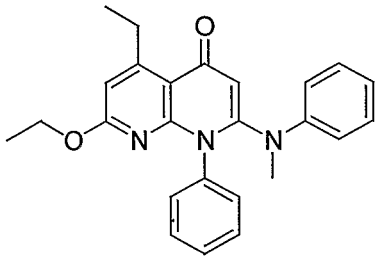
and Example 28:

2-anilino-7-ethoxy-5-ethyl-3-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



and Example 29:

7-ethoxy-5-ethyl-3-methyl-2-[methyl(phenyl)amino]-1-phenyl-1,8-naphthyridin-4(1H)-one

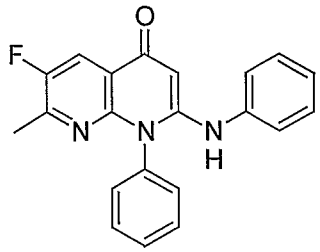


To a suspension of 2,2,6,6-tetramethylpiperidine (153 mg, 0.18 mL, 1.08 mmol) in THF (10 mL) at 0 °C, was added n-BuLi via syringe (1.6 M, 0.68 mL, 1.08 mmol) and TMEDA. The reaction mixture was stirred for 1 h under argon. The reaction mixture was cooled to -60 °C using an acetone/dry ice bath and 2-anilino-7-ethoxy-5-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.269 mmol) was added via syringe as a solution in THF (5 mL). The mixture was stirred for 1 h. MeI was added via syringe and the reaction was allowed to warm to room temperature and stirred for 18 h. A saturated aqueous solution of NH_4Cl (20 mL) and EtOAc (20 mL) was added, and the organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography using 7:3 to 100:0 EtOAc:Hex to give 3 products as follows:

Example 27: (35 mg, 32 %), Example 28: (11 mg, 10 %), Example 29: (16 mg, 14 %).

Example 30:

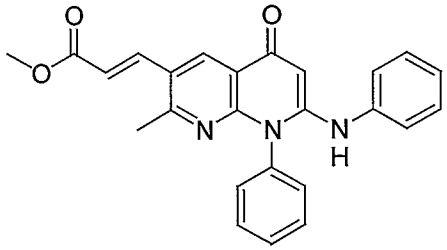
2-anilino-6-fluoro-7-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one



To 2-anilino-7-chloro-6-fluoro-1-phenyl-1,8-naphthyridin-4(1H)-one (100 mg, 0.273 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.001 mmol) and methyl zinc chloride (2M, 0.819 mL, 1.64 mmol) and the reaction was heated to 75 °C for 18 h. The reaction was then cooled to room temperature and poured into a solution of EDTA in water (2.5 g/20 mL) and extracted with Et_2O. The organic layer was washed with brine and concentrated *in vacuo*. The residue was then taken up in MeOH and filtered. The filtrate was concentrated *in vacuo* to give 2-anilino-6-fluoro-7-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (83.0 mg, 89%): LCMS RT: 2.43 min, MH^+: 346.4.

Example 31:

Methyl (2E)-3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridin-3-yl)-2-propenoate

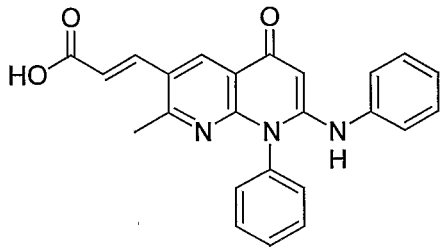


To a suspension of 2-anilino-6-bromo-7-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (41 mg, 0.1 mmol) in DMF (2.0 mL) were successively added $Pd(OAc)_2$ (0.70 mg, 0.003 mmol), Ph_3P (5.2 mg, 0.02 mmol), TEA (0.03 mL) and methyl acrylate (17.2 mg, 0.2 mmol). The suspension was heated at 120 °C in a sealed tube for 64 h. The residue obtained after concentration *in vacuo* was washed with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by prep-HPLC provided methyl (2E)-3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-

naphthyridin-3-yl)-2-propenoate (10.0 mg, 24%): LCMS RT: 2.61 min, MH^+: 412.3, R_f = 0.26 (1:1 EtOAc:Hex).

Example 32:

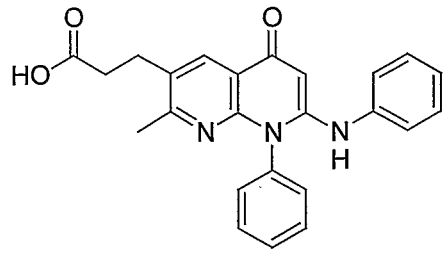
(2E)-3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridin-3-yl)-2-propenoic acid



To a suspension of 2-anilino-6-[(*E*)-3-methoxy-3-oxo-1-propenyl]-7-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (10 mg, 0.025 mmol) in CH_3CN (2.0 mL) was added 1N NaOH (2.0 mL). The suspension was stirred at room temperature for 18 h. The mixture was diluted with water (10 mL) and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford (2E)-3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridin-3-yl)-2-propenoic acid (6.2 mg, 63%): LCMS RT: 2.37 min, MH^+: 398.3, R_f = 0.51 (EtOAc).

Example 33:

3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridin-3-yl)propanoicacid

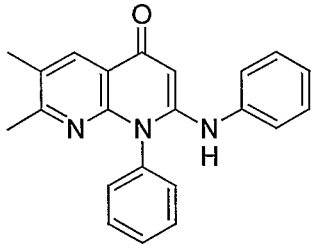


To a stirred suspension of 2-anilino-6-[(*E*)-3-hydroxy-3-oxo-1-propenyl]-7-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (40.0 mg, 0.100 mmol) in MeOH (2.0 mL), was added Pd/C (5.3 mg, 10% weight on carbon) under an argon atmosphere, followed by the addition of ammonia formate (19.0 mg, 0.30 mmol) in a single portion. The reaction

mixture was heated at reflux for 2 h, cooled and filtered. The filtrate was diluted with water (10 mL) and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was washed with water and dried *in vacuo* to afford 3-(7-anilino-2-methyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridin-3-yl)propanoicacid (34.5 mg, 86 %): LCMS RT: 2.31 min, MH^+: 400.4, R_f = 0.61 (4:1 EtOAc:MeOH).

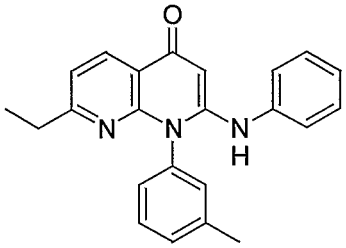
Example 34:

2-anilino-6,7-dimethyl-1-phenyl-1,8-naphthyridin-4(1H)-one



Example 35:

2-anilino-7-ethyl-1-(3-methylphenyl)-1,8-naphthyridin-4(1H)-one

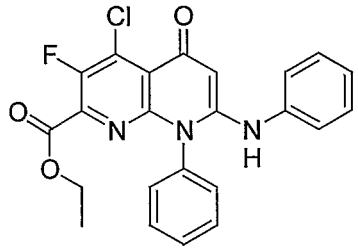


A suspension of 2-anilino-6-bromo-7-methyl-1-phenyl-1,8-naphthyridin-4(1*H*)-one (203 mg, 0.5 mmol) in THF (10 mL) in an atmosphere of argon was cooled to -78 °C. A solution of n-BuLi in hexanes (1.0 mL, 1.6 mmol, 1.6 M) was added and the suspension was stirred for 10 min at 0 °C until it became a clear solution. Excessive MeI (0.2 mL, 3.2 mmol) was added, and the reaction was stirred for another 10 min. The reaction was quenched with saturated aqueous NH_4Cl (2.0 mL) and water (10 mL) and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 2-anilino-6,7-dimethyl-1-phenyl-1,8-naphthyridin-4(1H)-one (55 mg, 32%): LCMS RT: 2.33 min, MH^+: 342.4, R_f = 0.39 (EtOAc). 2-anilino-7-ethyl-1-(3-methylphenyl)-1,8-naphthyridin-4(1H)-one (13.3 mg, 7.5%) was also obtained as a side product: LCMS RT: 2.54 min, MH^+: 356.3, R_f =

0.40 (EtOAc). Other electrophiles such as aldehydes, carbon dioxide, disulfides, trifluoroacetates acid chlorides and other alkyl halides can also be used to quench the generated aryl lithium.

Example 36:

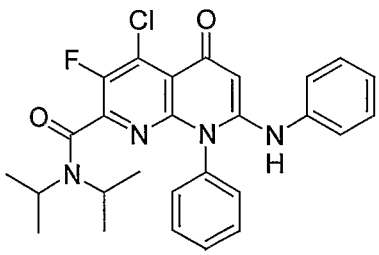
Ethyl 7-anilino-4-chloro-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate



A suspension of ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate (40.0 mg, 0.099 mmol) in anhydrous THF (10 mL) in an atmosphere of argon was cooled to -78 °C. LiHMDS (5 mL, 5 mmol) was then added to the suspension, and the suspension was stirred for 2 h at 0 °C and then cooled to -78 °C and treated with CCl_2FCClF_2 (94 mg, 0.5 mmol). The reaction was stirred for another hour at 0 °C before being quenched with saturated aqueous NH_4Cl (2.0 mL) and water (10 mL) and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by prep-HPLC provided Ethyl 7-anilino-4-chloro-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate (13.2 mg, 31%): LCMS RT: 2.80 min, MH^+: 437.1, R_f = 0.78 (EtOAc).

Example 37:

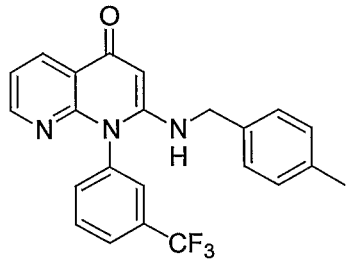
7-anilino-4-chloro-3-fluoro-N,N-diisopropyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide



LDA was made by adding n-BuLi (0.31 mL, 0.5 mmol, 1.6 M) to diisopropylamine (50 mg, 0.5 mmol) in THF (15 mL) at -15 °C. A suspension of ethyl 7-anilino-3-fluoro-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxylate (40.0 mg, 0.915 mmol) in anhydrous THF (10 mL) in an atmosphere of argon was cooled to -78 °C. LDA was added and the suspension was stirred for 2 h at 0 °C and then cooled to -78 °C and treated with CCl_2FCClF_2 (94 mg, 0.5 mmol). The reaction was stirred for another hour at 0 °C before being quenched with saturated aqueous NH_4Cl (2.0 mL) and water (10 mL). The aqueous solution was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by prep-HPLC provided 7-anilino-3-bromo-4-chloro-N,N-diisopropyl-5-oxo-8-phenyl-5,8-dihydro-1,8-naphthyridine-2-carboxamide (20 mg, 41%): LCMS RT: 3.02 min, MH^+: 493.3, R_f = 0.78 (EtOAc).

Example 38:

2-[(4-Methylbenzyl)amino]-1-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-4(1H)-one

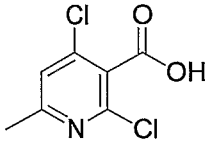


A mixture of 2-amino-1-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-4(1H)-one (50 mg, 0.16 mmol), $CsCO_3$ (160 mg, 0.49 mmol) and 4-methylbenzyl bromide (35 mg, 0.25 mmol) in THF (3 mL) was heated to 80 °C in a sealed tube for 16 h. The reaction was cooled to room temperature and quenched with water (3 mL). The mixture was extracted with CH_2Cl_2 (3X), and the combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC (YMC-Pack Pro C18 Column, 150 x 20 mm I.D.; first run: 20-80% CH_3CN in water, 11 min.; second run: 50-90% MeOH in water, 20 min.) to afford 2-[(4-Methylbenzyl)amino]-1-[3-(trifluoromethyl)phenyl]-1,8-naphthyridin-4(1H)-one (2.2 mg, 3%): LCMS RT: 2.75 min, MH^+: 410.2.

The following specific examples are presented to illustrate the invention related to Formula (II) as described herein, but they should not be construed as limiting the scope of the invention in any way.

Intermediate BA:

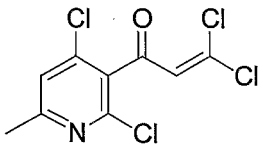
2,4-dichloro-6-methylnicotinic acid



A solution of commercially available (Maybridge) ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (1.0 g, 4.3 mmol) and NaOH (342 mg, 8.6 mmol) in water (1.7 mL) and MeOH (1.5 mL) was heated to 80 °C for 4 h. The mixture was acidified using 50% H_2SO_4 and then filtered. The solid collected was washed with cold water and dried to give of 2,4-dichloro-6- methylpyridine-3-carboxylic acid (582 mg, 66%): LCMS RT: 0.70 min, MH^+: 206.2.

Intermediate BB:

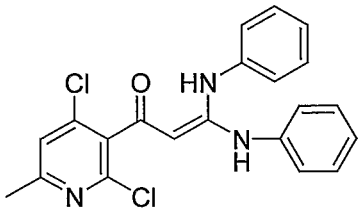
3,3-dichloro-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one



2,4-Dichloro-6-methylnicotinic acid (8.7 g, 43.0 mmol) was mixed with $SOCl_2$ (31 mL). The resulting mixture was heated to 80 °C for 2 h and concentrated *in vacuo* to give the acid chloride as yellow oil. The oil was then dissolved in CH_2Cl_2 (10 mL) and the solution was added to a cooled suspension of $AlCl_3$ (21.3 g, 160.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After 2 h at 0 °C, vinylidene chloride (2.16 mL, 80.0 mmol) was added to the above suspension. The resulting mixture was then left to warm to room temperature and stirred overnight. The reaction mixture was poured into crushed ice and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were cooled to 0 °C and TEA (14.9 mL) was added. After 1 h of stirring, the organic layer was washed with 10% aqueous HCl (100 mL), water (200 mL), brine (100 mL), and dried over Na_2SO_4. Solvents were removed *in vacuo* and the residue was purified by passing it through a pad of silica gel with 15% EtOAc in Hex as the eluent to provide 3,3-dichloro-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one (5.2 g, 46%): LCMS RT: 3.13 min, MH^+: 284.6. Alternatively, the acid chloride could be prepared by using oxalyl chloride with a catalytic amount of DMF.

Intermediate BC:

3,3-dianilino-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one

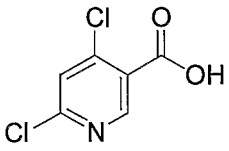


A solution of 3,3-dichloro-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one (5.2 g, 18.0 mmol) in 1,4-dioxane (25 mL) was cooled to 0 °C and aniline (5.1 mL, 55.0 mmol) and TEA (7.7 mL, 55.0 mmol) were added dropwise. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The solvents were removed *in vacuo*. The residue was purified by passing it through a pad of silica gel with EtOAc:Hex (1:5) as the eluent to provide 3,3-dianilino-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one (7.1 g, 99%): LCMS RT: 3.06 min, MH^+: 398.7.

Intermediates BA1, BB1, BC1, BA2, BB2, BC2 can be prepared in the same manner shown above for BA, BB and BC starting with the appropriate known starting nicotinic acid (*Eur. J. Org. Chem.* **2001**, 1371).

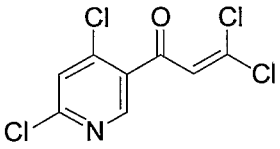
Intermediate BA1:

4,6-dichloronicotinic acid



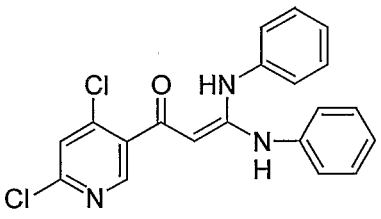
Intermediate BB1:

3,3-dichloro-1-(4,6-dichloro-3-pyridinyl)-2-propen-1-one



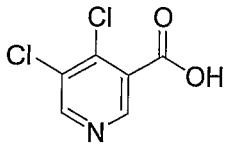
Intermediate BC1:

3,3-dianilino-1-(4,6-dichloro-3-pyridinyl)-2-propen-1-one



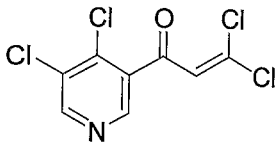
Intermediate BA2:

4,5-dichloronicotinic acid



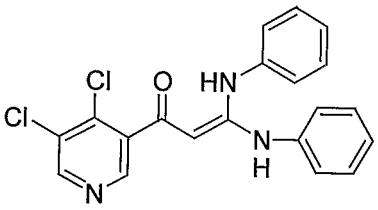
Intermediate BB2:

3,3-dichloro-1-(4,5-dichloro-3-pyridinyl)-2-propen-1-one



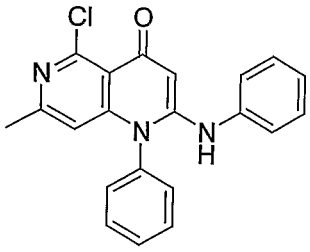
Intermediate BC2:

3,3-dianilino-1-(4,5-dichloro-3-pyridinyl)-2-propen-1-one



Example 39:

2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one



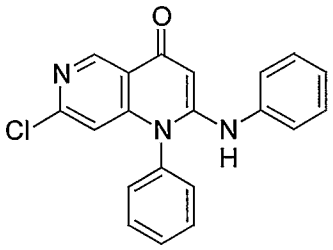
A mixture of 3,3-dianilino-1-(2,4-dichloro-6-methyl-3-pyridinyl)-2-propen-1-one (100 mg, 0.25 mmol) and *t*-BuOK (42 mg, 0.38 mmol) in anhydrous dioxane (4 mL) was heated to 80 °C for 4 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The solution was washed with water and brine, dried over $MgSO_4$, and concentrated *in vcaco*. Silica gel flash chromatography of the residue using 1:1

EtOAc:Hex gave 2-anilino-5-chloro-7-methyl-1-phenyl-1,8-naphthyridin-4(1H)-one (13 mg, 14%): LCMS RT: 2.47 min, MH^+: 362 and 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (68 mg, 75%): LCMS RT: 2.24 min, MH^+: 362.3. Alternatively, the cyclization could be achieved by using other bases such as NaH and other aprotic solvents such as THF and DMF.

Examples 40 and 41 can be prepared in the same manner as that for Example 39 above.

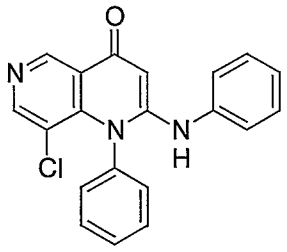
Example 40:

2-anilino-7-chloro-1-phenyl-1,6-naphthyridin-4(1H)-one



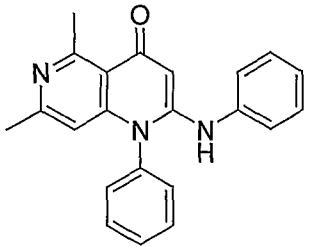
Example 41:

2-anilino-8-chloro-1-phenyl-1,6-naphthyridin-4(1H)-one



Example 42:

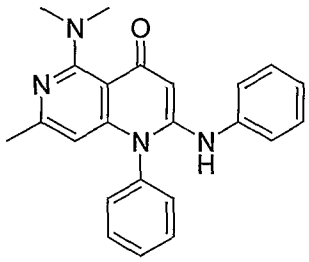
2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one



To a solution of 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (80 mg, 0.22 mmol) in THF (3mL) was added Ni(dppp)Cl_2 (24 mg, 0.044 mmol) at room temperature. After stirring for a few minutes MeMgBr (3M , 0.59 mL, 1.76 mmol) was added and the mixture was allowed to stir for 24 h. The mixture was quenched with 1N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by reverse-phase preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided 2-anilino-5,7-dimethyl-1-phenyl-1,6-naphthyridin-4(1H)-one (31 mg, 40%): LCMS RT: 1.51 min, MH^+: 342.4.

Example 43:

2-anilino-5-(dimethylamino)-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one

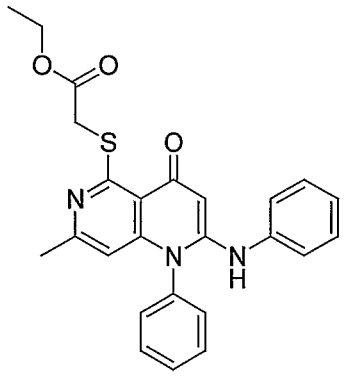


A mixture of 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (80 mg, 0.22 mmol) and dimethylamine (3M in THF, 0.73 mL, 2.20 mmol) in dioxane (3 mL) was heated to 80 °C for 24 h. The reaction mixture was cooled, concentrated *in vacuo*, diluted with water and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated

in vacuo to give 2-anilino-5-(dimethylamino)-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (74 mg, 91%): LCMS RT: 1.86 min, MH^+: 371.3

Example 44:

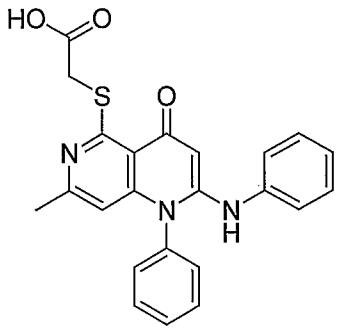
Ethyl[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetate



A solution of 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (200 mg, 0.55 mmol) in EtOH (10 mL) was added ethyl 2-mercaptoacetate (0.12 mL, 1.10 mmol) and TEA (0.23 mL, 1.65 mmol). The reaction was heated at reflux for 24 h. The reaction mixture was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, brine, and dried over Na_2SO_4. Solvents were removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) to provide ethyl[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetate (120 mg, 49%): LCMS RT: 3.07 min, MH^+: 446.2.

Example 45:

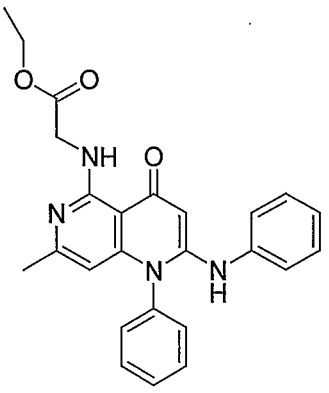
[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetic acid



Aqueous NaOH (2N, 1 mL) was added to a stirred solution of ethyl[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetate (100 mg, 0.23 mmol) in EtOH (8 mL) at room temperature. The mixture was allowed to stir for 4 h and was concentrated *in vacuo*. The reaction mixture was acidified with 1N HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by reverse-phase preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) provided [(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetic acid (56 mg, 60%): LCMS RT: 2.61 min, MH^+: 418.2.

Example 46:

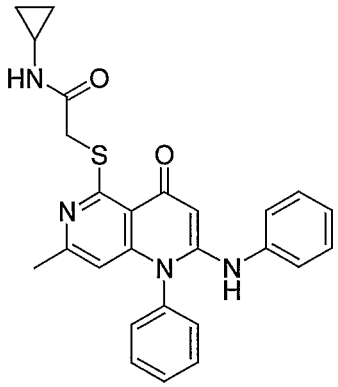
Ethyl N-(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)glycinate



To a solution of 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (80 mg, 0.22 mmol) in EtOH (8 mL) was added glycine ethyl ester hydrochloride (46 mg, 0.44 mmol) and TEA (0.23 mL, 1.65 mmol). The reaction was heated at reflux for 3 d. The reaction mixture was cooled, concentrated *in vacuo*, diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) to provide ethyl N-(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)glycinate (43 mg, 46%): LCMS RT: 2.16 min, MH^+: 429.3.

Example 47:

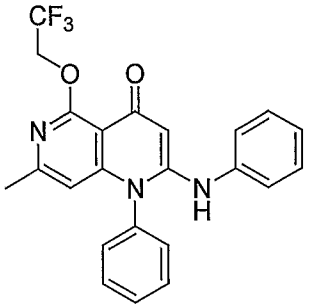
2-[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]-N-cyclopropylacetamide



To a mixture of [(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]acetic acid (20 mg, 0.05 mmol), EDCI (18 mg, 0.10 mmol), HOBT (13 mg, 0.10 mmol) and cyclopropylamine (0.004 mL, 0.06 mmol) in CH_2Cl_2 (5 mL) was added TEA (0.02 mL, 0.14 mmol). The reaction solution was stirred at room temperature for 24 h before the mixture was diluted with CH_2Cl_2, washed with 0.5N HCl, saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Solvents were removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (10% CH_3CN in water with 0.1% TFA to 95% CH_3CN in water, 10 mL/min, 10 min) to provide 2-[(2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridin-5-yl)sulfanyl]-N-cyclopropylacetamide (13 mg, 59%): LCMS RT: 2.55 min, MH^+: 457.1.

Example 48:

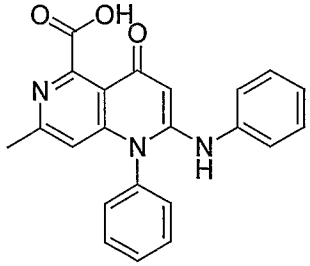
2-anilino-7-methyl-1-phenyl-5-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-4(1H)-one



Trifluoroethanol (0.08 mL, 1.1 mmol) was added to a suspension of NaH (60% oil dispersion, 44 mg, 1.1 mmol) in DMSO (4 mL) at 0 °C, and the mixture was heated at 60 °C for 1 h. The mixture was cooled to room temperature and a solution of 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (200 mg, 0.55 mmol) in DMSO (2 mL) was added. The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled, poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by a Biotage silica gel chromatography (2:1 EtOAc:Hex) to provide 2-anilino-7-methyl-1-phenyl-5-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-4(1H)-one (159 mg, 68%): LCMS RT: 2.65 min, MH^+: 426.4. This transformation can be accomplished by using other aprotic solvents such as DMF, THF and dioxane with temperatures appropriate for these solvents. Commercially available alkoxides can also be used in the absence of base.

Example 49:

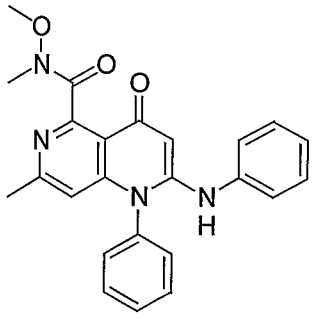
2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid



2-Anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (1.0 g, 2.8 mmol), DPPP (64 mg, 0.15 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), Cs_2CO_3 (580 mg, 4.20 mmol) were dissolved in EtOH (10 mL) and DMF (10 mL). A balloon filled with CO was attached to the flask and the solution was stirred vigorously. The flask was purged with CO for 5 min before it was heated to 70 °C. After 4 h the mixture was cooled to room temperature and diluted with EtOAc. The mixture was washed with water, brine, and dried over Na_2SO_4. Solvents were removed *in vacuo* and the residue was triturated with Et_2O to give ethyl 2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridine-5-carboxylate (800 mg, 71%). The ethyl ester was then dissolved in MeOH (5 mL), and THF (20 mL). To this stirring solution was added KOH (3N, 10 mL) and the mixture was stirred at room temperature for 6 h before it was extracted with Et_2O. The aqueous layer was acidified with 2N HCl to pH = 1 and the product precipitated out of the solution. The solid was filtered and dried to give 2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid as a white solid (683 mg, 92%): LCMS RT: 1.75 min, MH^+: 372.9.

Example 50:

2-anilino-N-methoxy-N,7-dimethyl-4-oxo-1-phenyl-1,4-dihydro-1,6 naphthyridine-5-carboxamide

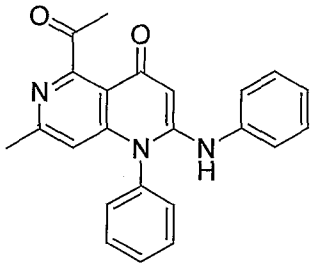


2-anilino-7-methyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridine-5-carboxylic acid (80 mg, 0.22 mmol), N,O-dimethylhydroxylamine hydrochloride (64 mg, 0.66 mmol), HOBT (89 mg, 0.66 mmol) and EDCI (126 mg, 0.66 mmol) were dissolved in CH_2Cl_2 (9 mL). To this solution was added TEA (120 uL, 0.88 mmol). The reaction was stirred for 1 h and was diluted with CH_2Cl_2, washed with 0.5N HCl, saturated $NaHCO_3$,

and brine. The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo*. The solid obtained was triturated with Et_2O and dried to give 2-anilino-N-methoxy-N,7-dimethyl-4-oxo-1-phenyl-1,4-dihydro-1,6 naphthyridine-5-carboxamide as a light yellow solid (50 mg, 55%): LCMS RT: 2.08 min, MH^+: 414.9. This transformation can also be accomplished by coupling the appropriate amine with the corresponding acid chloride.

Example 51:

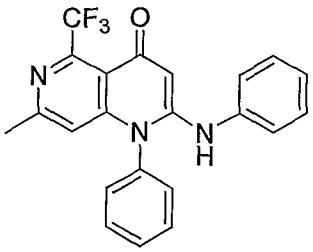
5-acetyl-2-anilino-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one



2-Anilino-*N*-methoxy-*N*,7-dimethyl-4-oxo-1-phenyl-1,4-dihydro-1,6-naphthyridine-5-carboxamide (60 mg, 0.14 mmol) was suspended in THF (5 mL). To this stirring suspension at 0 °C was added MeMgBr (0.19 mL, 0.56 mmol, 3M in Et_2O). The reaction was stirred at room temperature for 6 h and quenched with saturated aqueous NH_4Cl, diluted with EtOAc, and washed with brine. The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by Biotage silica gel chromatography using EtOAc as the eluent to provide 5-acetyl-2-anilino-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one as a light yellow solid (34 mg, 66%): LCMS RT: 2.20 min, MH^+: 370.4.

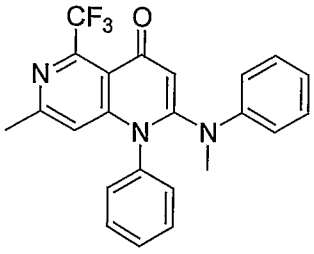
Example 52:

2-anilino-7-methyl-1-phenyl-5-(trifluoromethyl)-1,6-naphthyridin-4(1H)-one



and Example 53:

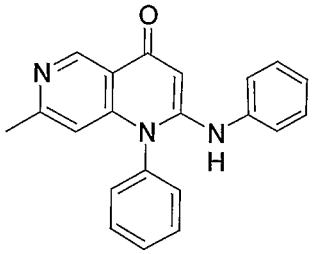
7-methyl-2-[methyl(phenyl)amino]-1-phenyl-5-(trifluoromethyl)-1,6-naphthyridin-4(1H)-one



A mixture of methyl fluorosulphonyldifluoroacetate (0.78 mL, 6.10 mmol) and 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (2.0 g, 5.50 mmol) in DMF (15 mL) was mixed with Copper(I) iodide (1.05 g, 5.50 mmol) at 80 °C for 6 h before the mixture was filtered and concentrated *in vacuo*. The residue was diluted with CH_2Cl_2, washed with water and brine, and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was purified by Biotage silica gel chromatography using 1:1 EtOAc:Hex to provide 2-anilino-7-methyl-1-phenyl-5-(trifluoromethyl)-1,6-naphthyridin-4(1H)-one as a light yellow solid (477 mg 22%): LCMS RT: 2.68 min, MH^+: 396.2. 7-Methyl-2-[methyl(phenyl)amino]-1-phenyl-5-(trifluoromethyl)-1,6-naphthyridin-4(1H)-one (270 mg, 12%) was also isolated: LCMS RT: 2.32 min, MH^+: 410.4.

Example 54:

2-anilino-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one

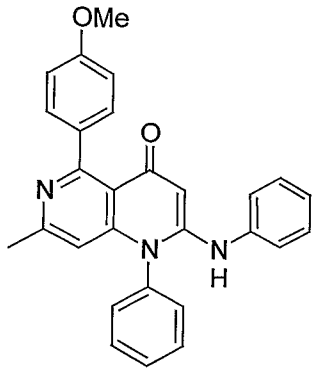


To a flask containing 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (10 mg, 0.03 mmol) in EtOAc (2 mL) and EtOH (2 mL) at room temperature was added a drop of TEA, and Pd/C (10 weight % on activated carbon Degussa type E101, 2 mg). The system was purged with H_2 and left stirring at room temperature overnight.

The reaction mixture was filtered and concentrated *in vacuo* to provide 2-anilino-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (8 mg, 91%): LCMS RT: 1.22 min, MH^+: 328.3.

Example 55:

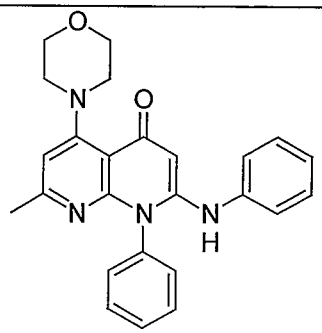
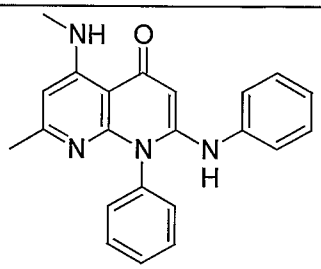
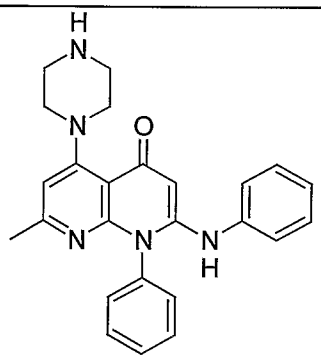
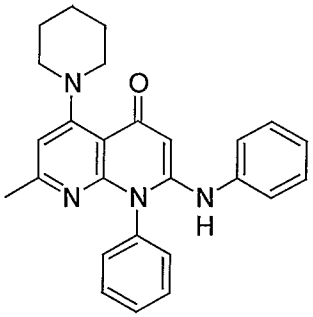
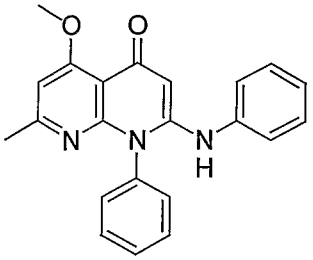
2-anilino-5-(4-methoxyphenyl)-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one

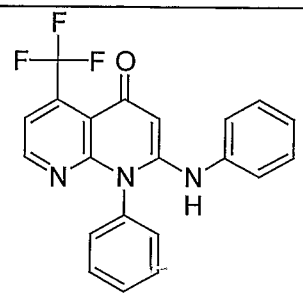
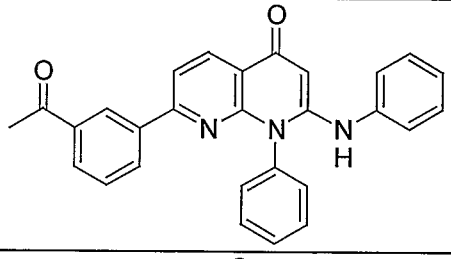
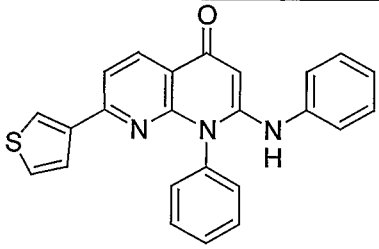
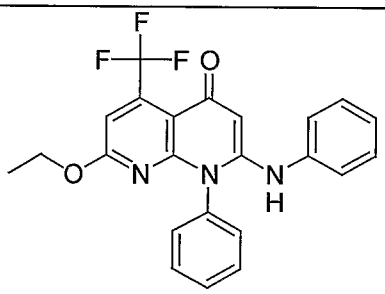
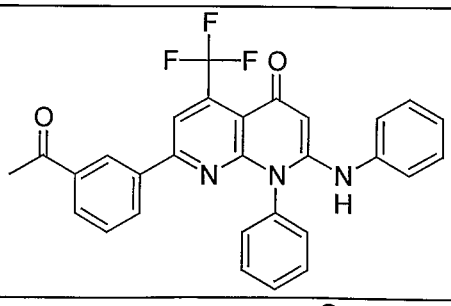
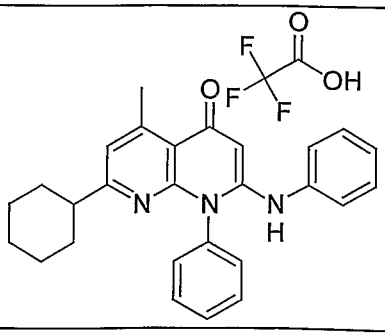


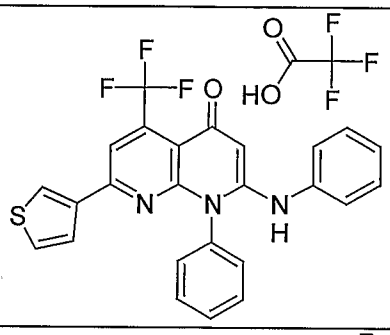
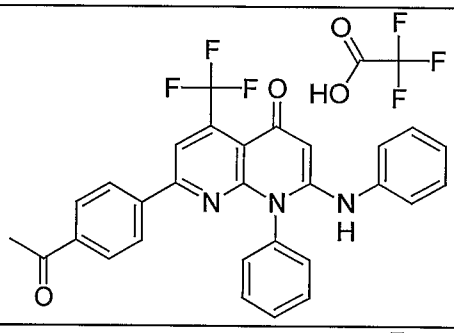
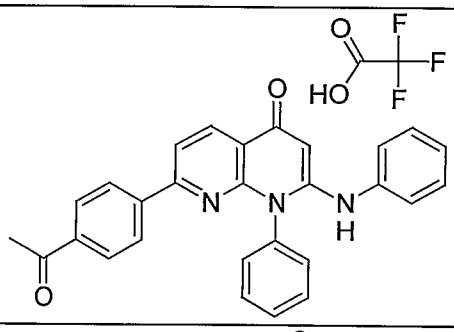
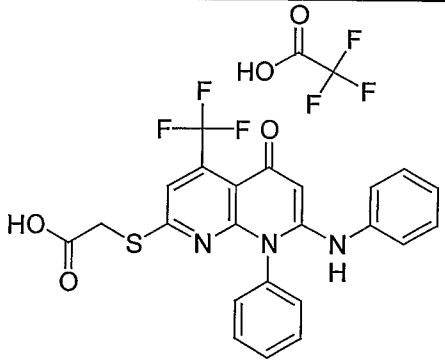
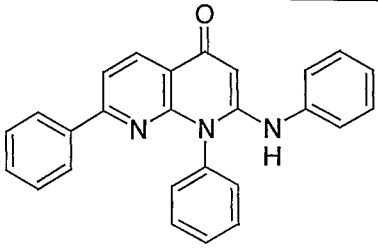
An 8-mL amber vial was charged with 2-anilino-5-chloro-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (72 mg, 0.20 mmol), 4-methoxyphenylboronic acid (36 mg, 0.24 mmol), $Pd(OAc)_2$ (1 mg, 0.02 mmol), Ph_3P (5 mg, 0.02 mmol), K_2CO_3 (110 mg, 0.8 mmol, 2 M), and DME (2 mL). The mixture was heated to 90 °C 2 d. Water was added to the reaction mixture and it was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. The residue after concentration *in vacuo* was triturated with Et_2O to provide 2-anilino-5-(4-methoxyphenyl)-7-methyl-1-phenyl-1,6-naphthyridin-4(1H)-one (54 mg, 63%): LCMS RT: 1.92 min, MH^+: 434.5.

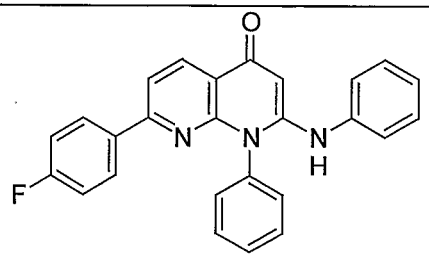
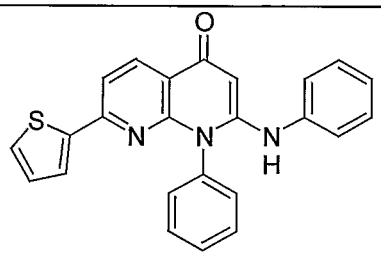
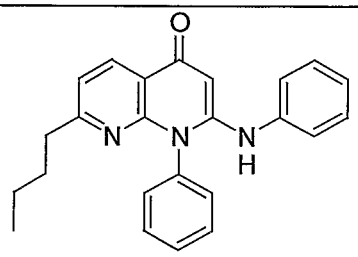
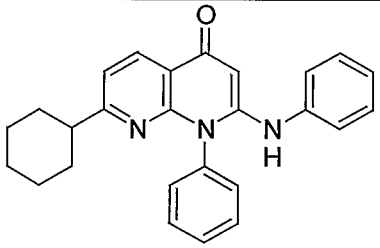
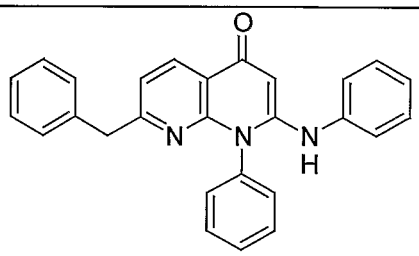
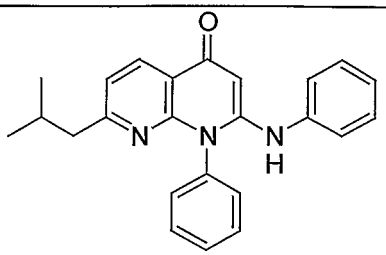
Utilizing the above described procedures for intermediates and examples alone or in combination, a variety of Formula I compounds were prepared using the appropriate starting material and the representative procedure described. These results are summarized in Table 1A.

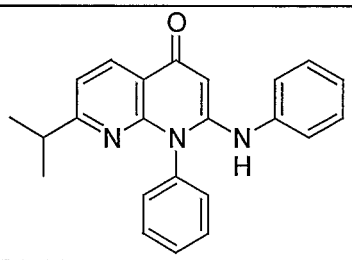
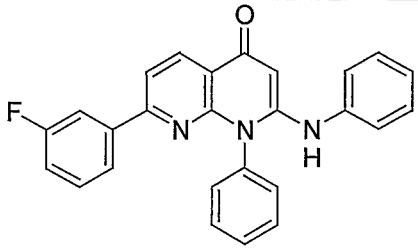
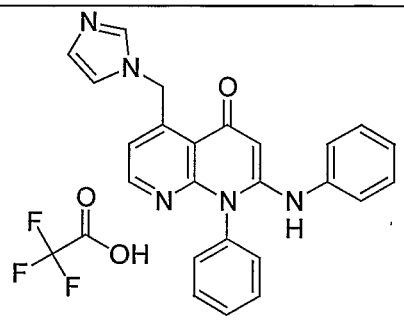
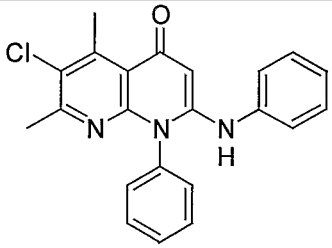
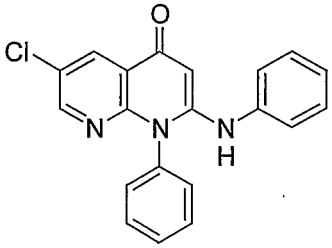
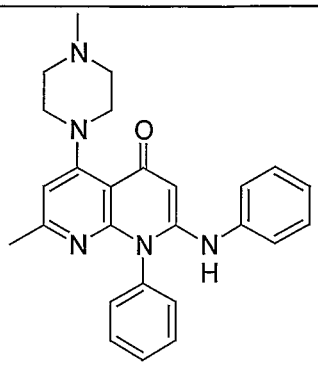
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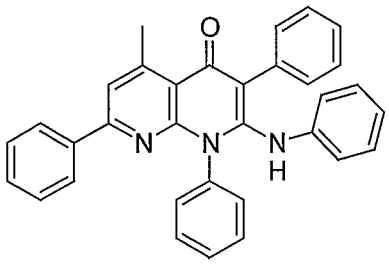
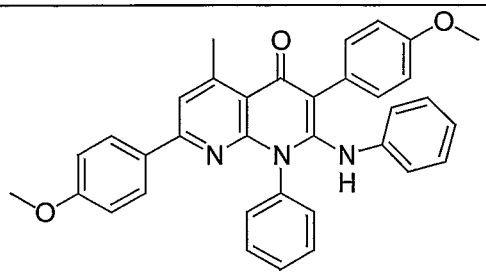
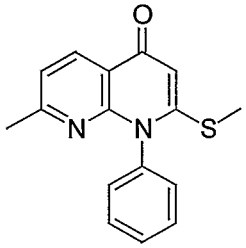
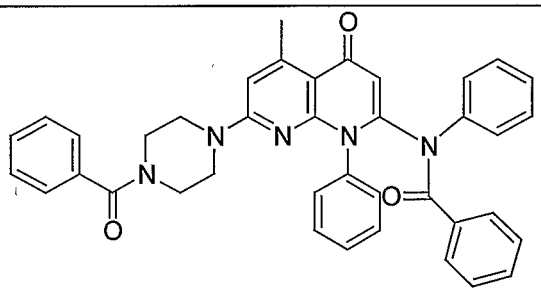
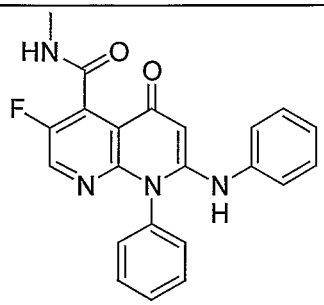
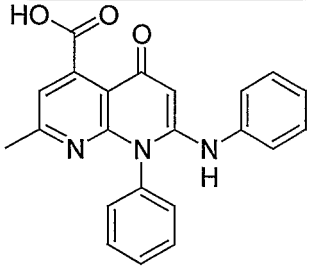
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
56		2.07	413.4	Intermediate Z, AA, AB and Example 16, 2
57		1.85	357.3	Intermediate Z, AA, AB and Example 16, 2
58		1.67	412.2	Intermediate Z, AA, AB and Example 16, 2
59		2.18	411.4	Intermediate Z, AA, AB and Example 16, 2
60		2.02	358.4	Intermediate Z, AA, AB and Example 16, 9

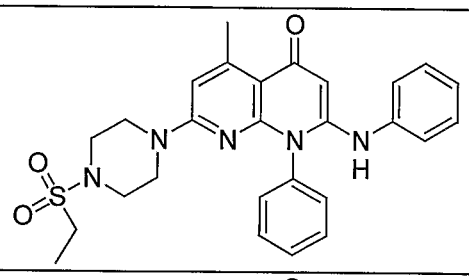
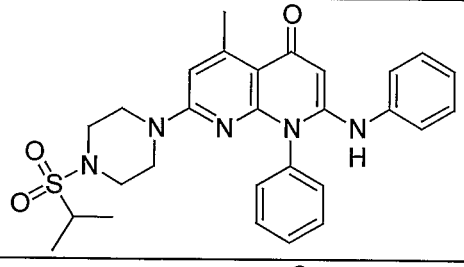
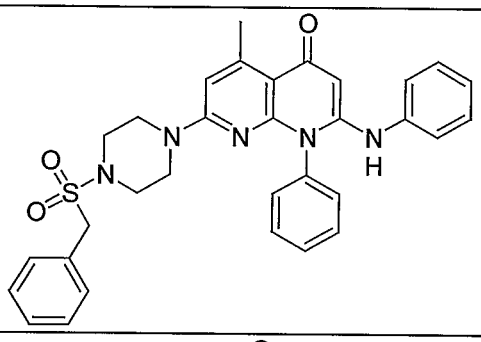
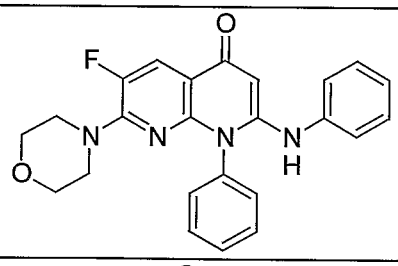
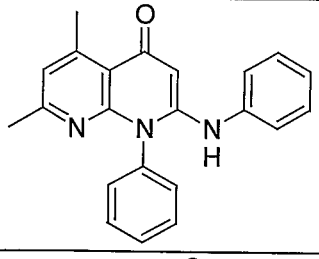
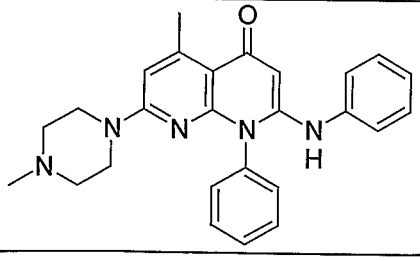
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
61		2.54	382.3	Intermediate F, G, H, I, J and Example 1
62		2.58	432.4	Intermediate O, P, Q, R and Example 4
63		2.63	296.3	Intermediate O, P, Q, R and Example 4
64		2.89	426.2	Intermediate F, G, H, I, J and Example 9
65		3.00	426.2	Intermediate Intermediate F, G, H, I, J and Example 4
66		3.02	410.4	Intermediate A, B, C, D, E and Example 5

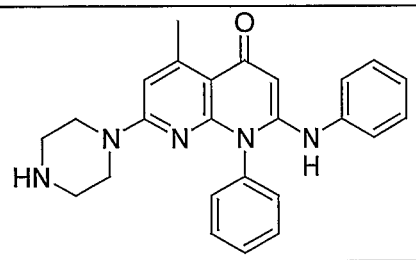
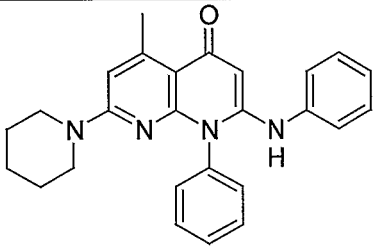
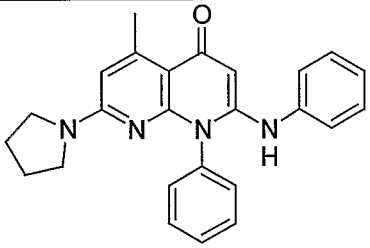
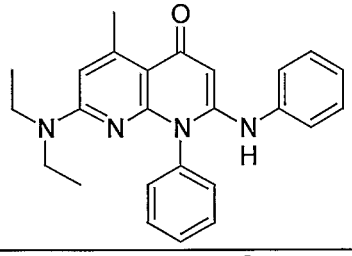
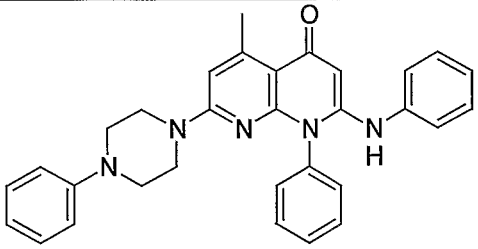
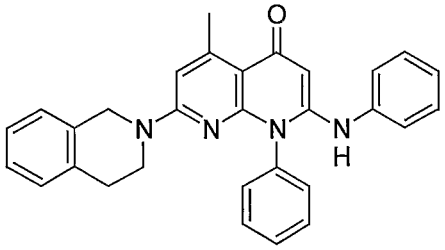
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
67		3.00	464.2	Intermediate F, G, H, I, J and Example 4
68		2.98	500.3	Intermediate F, G, H, I, J and Example 4
69		2.57	432.3	Intermediate O, P, Q, R and Example 4
70		2.50	471.1	Intermediate F, G, H, I, J and Example 6, 7
71		2.73	390.4	Intermediate O, P, Q, R and Example 4

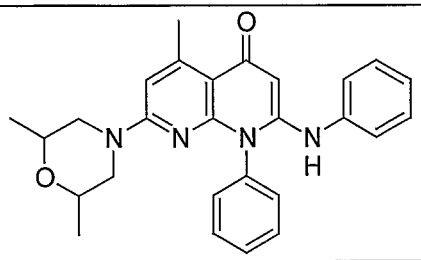
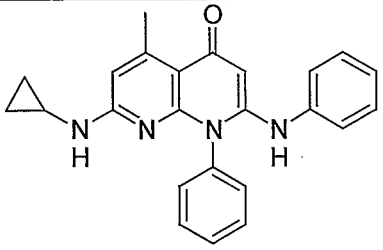
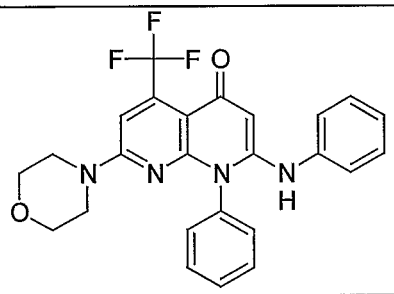
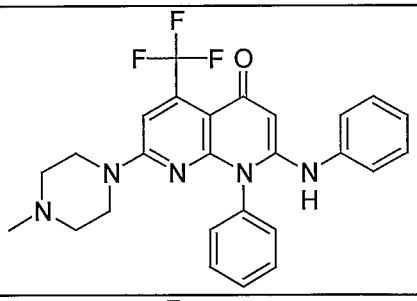
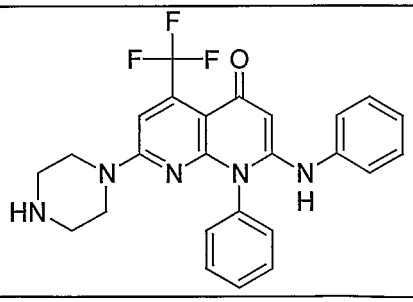
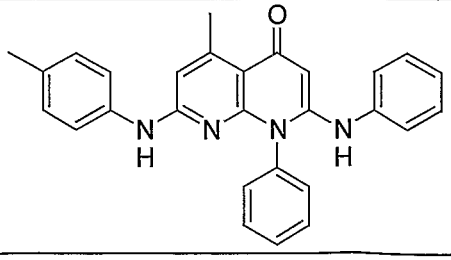
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
72		2.73	408.5	Intermediate O, P, Q, R and Example 4
73		3.30	396.4	Intermediate O, P, Q, R and Example 4
74		3.41	370.4	Intermediate O, P, Q, R and Example 5
75		3.56	396.5	Intermediate O, P, Q, R and Example 5
76		3.39	404.4	Intermediate O, P, Q, R and Example 5
77		2.69	370.3	Intermediate O, P, Q, R and Example 5

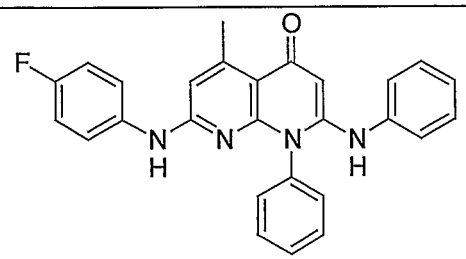
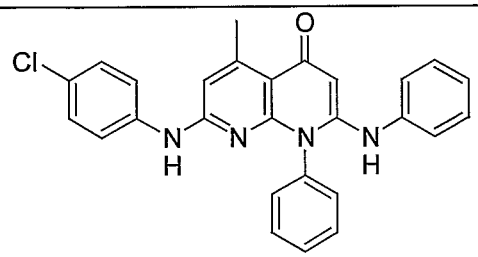
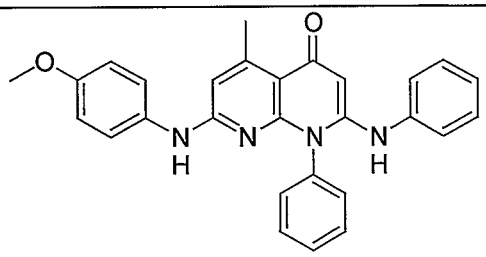
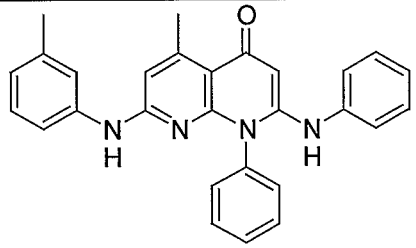
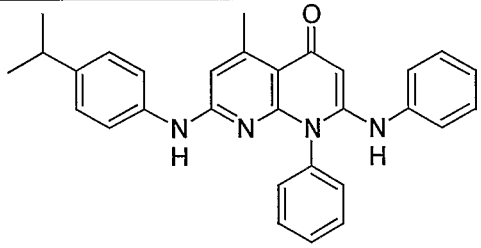
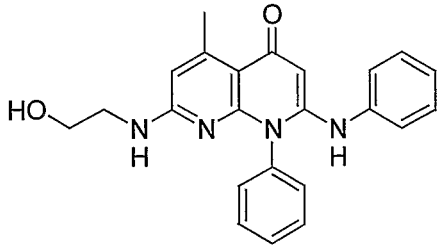
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
78		2.59	356.3	Intermediate O, P, Q, R and Example 5
79		2.74	408.4	Intermediate O, P, Q, R and Example 4
80		1.60	394.0	Intermediate A, B, C, D, E and Example 1, 10, 11
81		2.88	376.4	Intermediate S, T, U, W and Example 15
82		2.42	348.3	Intermediate S, T, U, W and Example 15
83		1.69	426.2	Intermediate Z, AA, AB and Example 16, 2

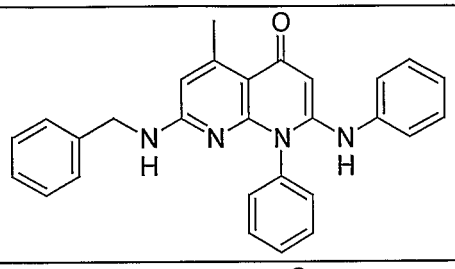
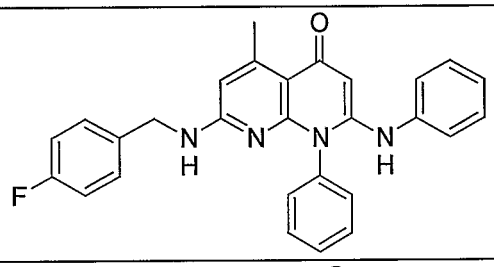
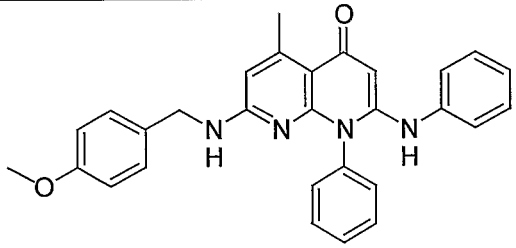
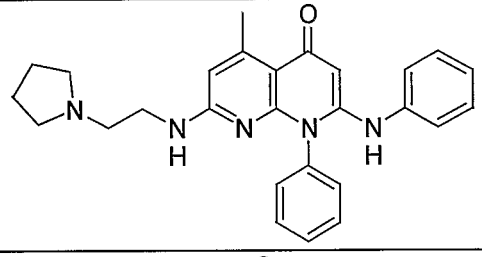
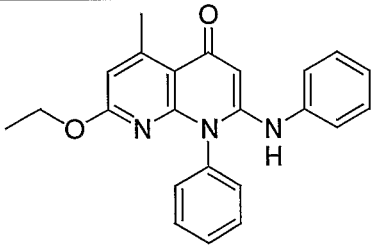
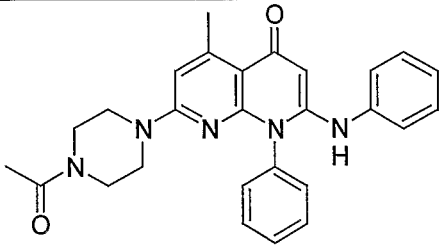
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
84		3.87	480.4	Intermediate A, B, C, D, E, AL and Example 4
85				Intermediate A, B, C, D, E, AL and Example 4
86		2.43	283.6	Intermediate S, T, V and Example 15
87		2.82	620.4	Intermediate A, B, C, D, E and Example 2, 13
88		1.86	389.1	Intermediate K, L, M, N, AM, and Example 1, 13
89		2.56	372.3	Intermediate Z, AA, AB and Example 16, 17, 7

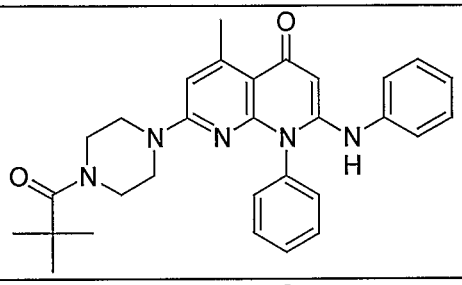
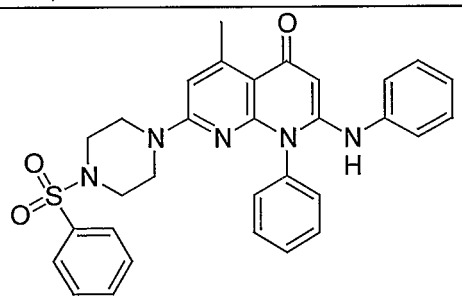
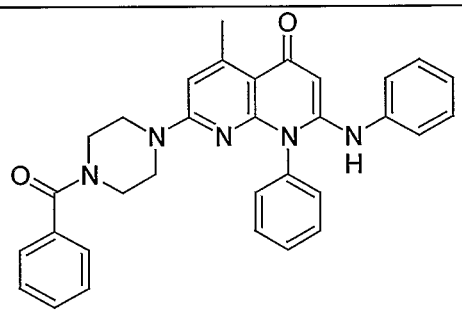
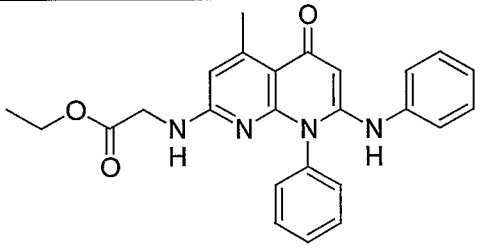
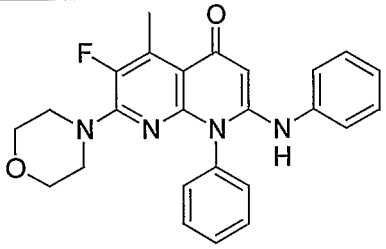
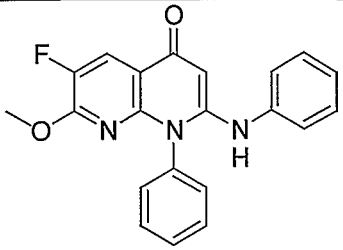
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
90		2.41	504.2	Intermediate A, B, C, D, E and Example 2, 12
91		2.50	518.3	Intermediate A, B, C, D, E and Example 2, 12
92		2.71	566.3	Intermediate A, B, C, D, E and Example 2, 12
93		2.54	417.4	Intermediate K, L, M, N, and Example 2
94		2.27	342.4	Intermediate S, T, U, W and Example 15
95		1.71	426.2	Intermediate A, B, C, D, E and Example 2

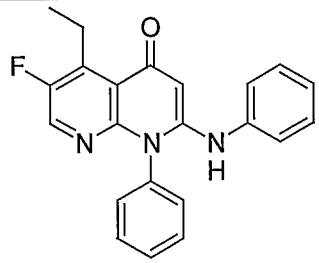
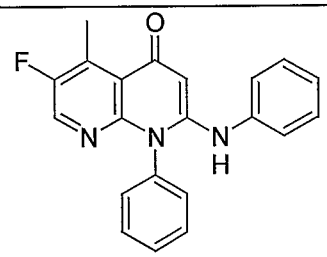
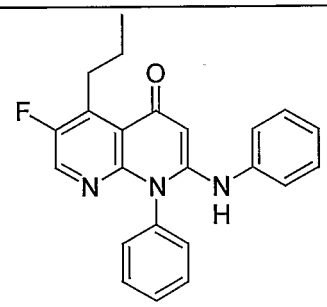
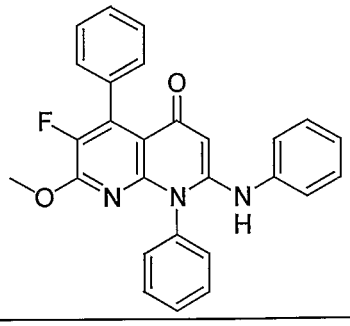
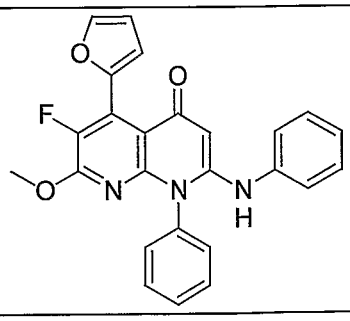
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
96		1.74	412.1	Intermediate A, B, C, D, E and Example 2
97		2.75	411.2	Intermediate A, B, C, D, E and Example 2
98		2.70	397.2	Intermediate A, B, C, D, E and Example 2
99		2.52	399.4	Intermediate A, B, C, D, E and Example 2
100		2.80	488.6	Intermediate A, B, C, D, E and Example 2
101		2.89	459.7	Intermediate A, B, C, D, E and Example 2

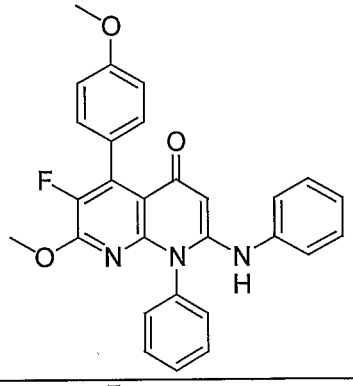
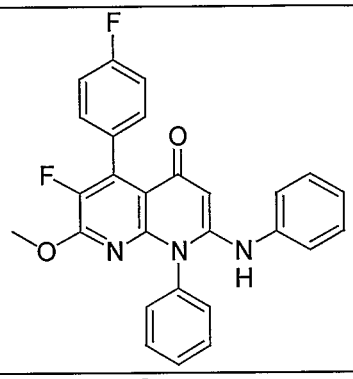
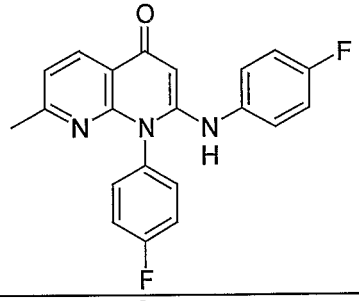
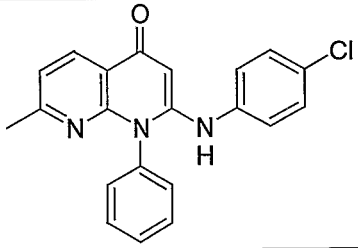
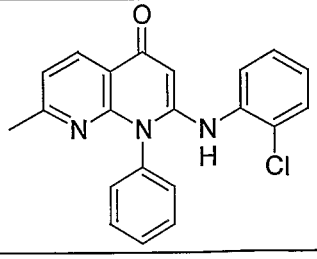
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
102		2.54	441.6	Intermediate A, B, C, D, E and Example 2
103		2.40	383.5	Intermediate A, B, C, D, E and Example 2
104		2.44	467.5	Intermediate F, G, H, I, J and Example 8
105		2.51	480.4	Intermediate F, G, H, I, J and Example 8
106		1.80	466.4	Intermediate F, G, H, I, J and Example 8
107		2.65	433.4	Intermediate A, B, C, D, E and Example 3

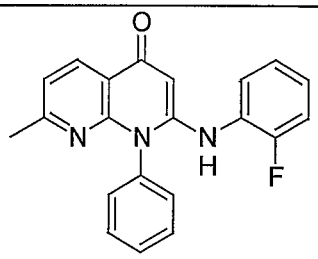
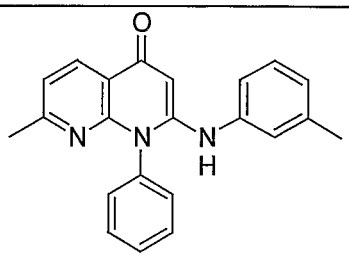
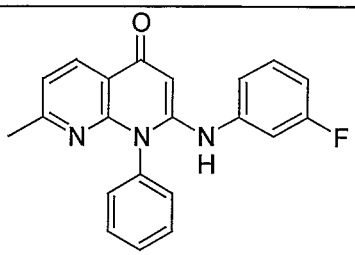
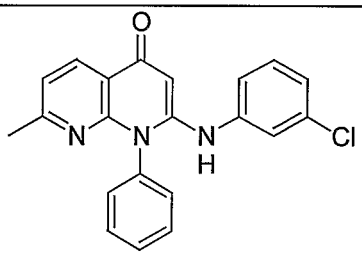
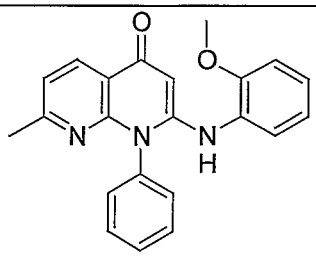
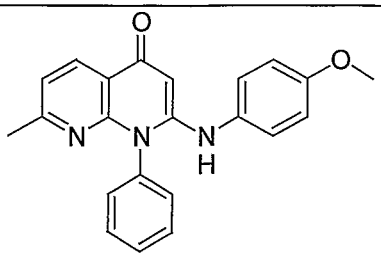
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
108		2.60	437.4	Intermediate A, B, C, D, E and Example 3
109		2.71	453.4	Intermediate A, B, C, D, E and Example 3
110		2.53	449.4	Intermediate A, B, C, D, E and Example 3
111		2.65	433.4	Intermediate A, B, C, D, E and Example 3
112		2.84	461.5	Intermediate A, B, C, D, E and Example 3
113		2.08	387.4	Intermediate A, B, C, D, E and Example 2

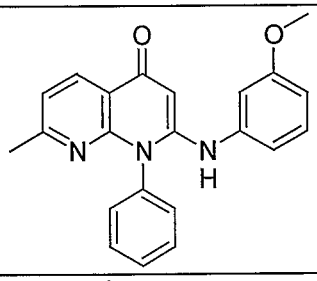
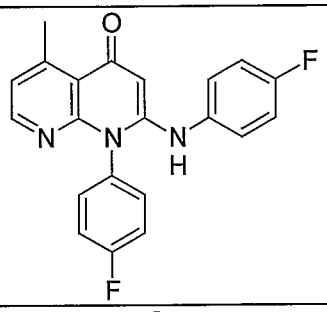
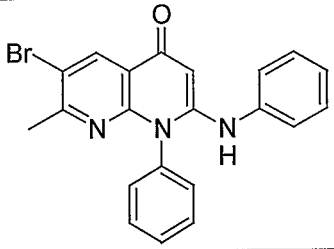
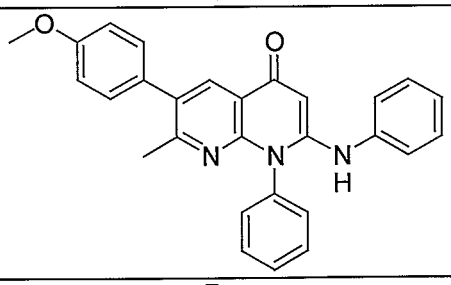
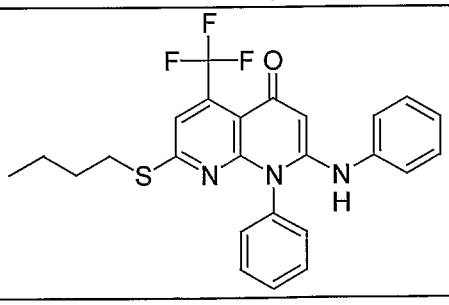
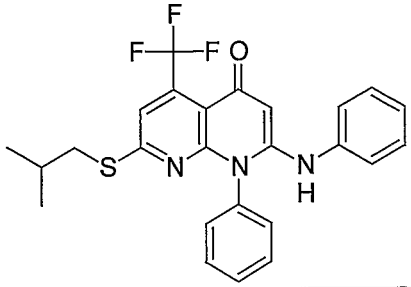
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
114		2.46	433.4	Intermediate A, B, C, D, E and Example 2
115		2.64	451.3	Intermediate A, B, C, D, E and Example 2
116		2.61	463.4	Intermediate A, B, C, D, E and Example 2
117		2.03	440.4	Intermediate A, B, C, D, E and Example 2
118		2.58	372.2	Intermediate A, B, C, D, E and Example 9
119		2.20	454.4	Intermediate A, B, C, D, E and Example 2, 13

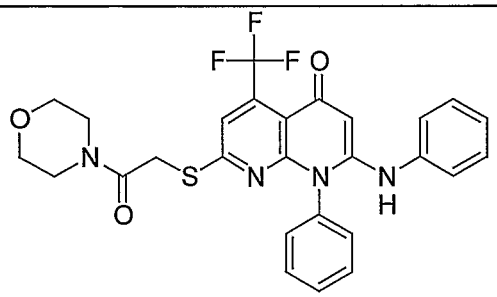
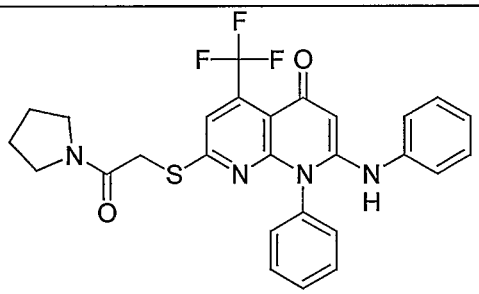
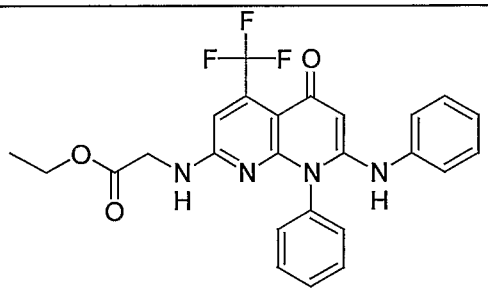
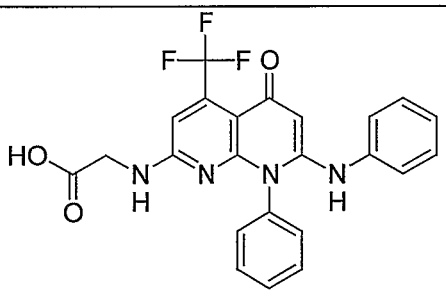
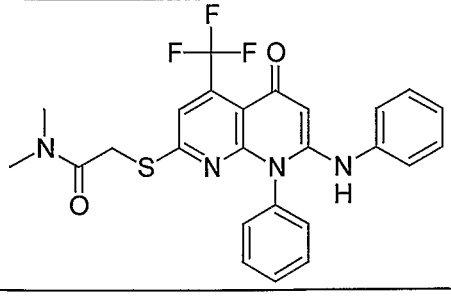
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
120		2.55	496.4	Intermediate A, B, C, D, E and Example 2, 13
121		2.52	552.2	Intermediate A, B, C, D, E and Example 2, 12
122		2.44	516.3	Intermediate A, B, C, D, E and Example 2, 13
123		2.28	429.3	Intermediate A, B, C, D, E and Example 3
124		2.45	431.4	Intermediate K, L, M, N, AH and Example 2
125		2.45	362.3	Intermediate K, L, M, N and Example 9

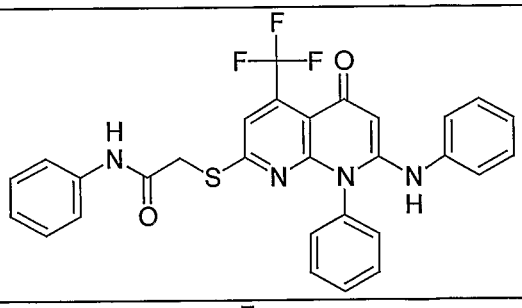
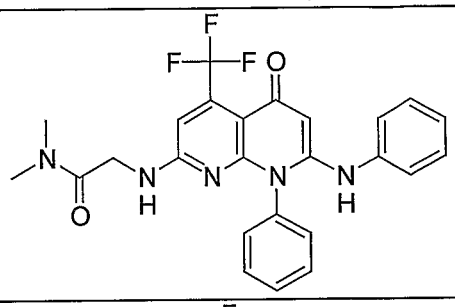
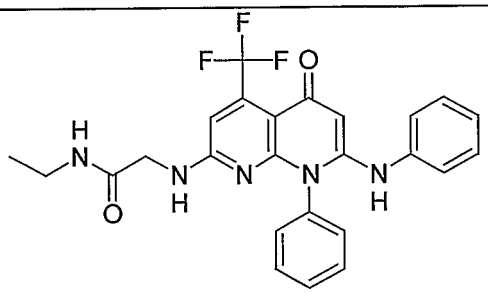
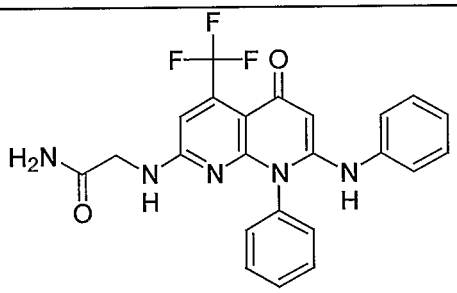
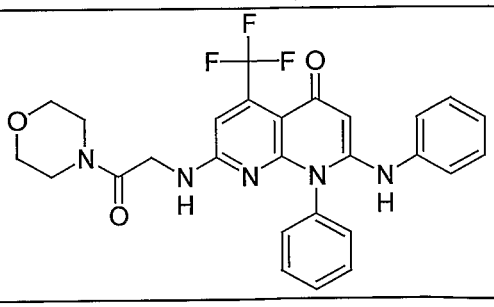
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
126		2.51	360.3	Intermediate K, L, M, N, AH and Example 1
127		2.30	346.4	Intermediate K, L, M, N, AH and Example 1
128		2.70	374.4	Intermediate K, L, M, N, AH and Example 1
129		2.69	438.3	Intermediate K, L, M, N and Example 9, 14, 4
130		2.64	428.3	Intermediate K, L, M, N and Example 9, 14, 4

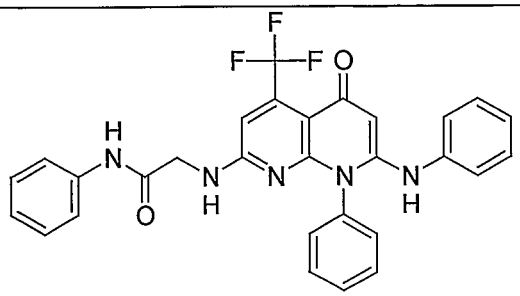
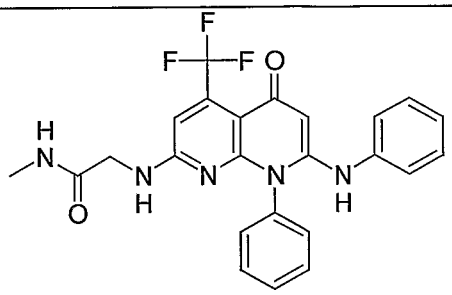
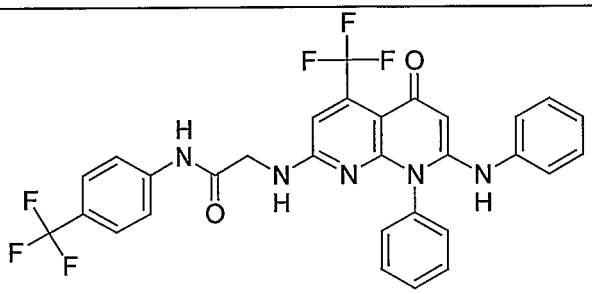
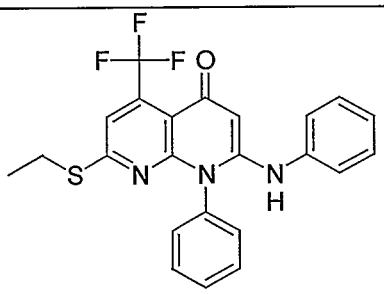
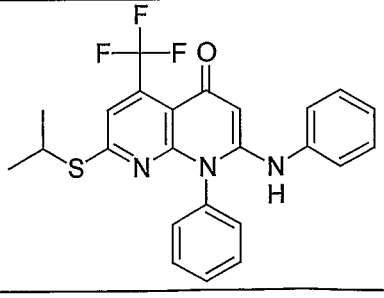
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
131		2.74	468.3	Intermediate 2 K, L, M, N and Example 9, 14, 4
132		2.77	456.4	Intermediate K, L, M, N and Example 9, 14, 4
133		2.37	364.3	Intermediate S, T, U, W and Example 15
134		2.40	362.3	Intermediate S, T, V, X and Example 15
135		2.46	362.2	Intermediate S, T, V, X and Example 15

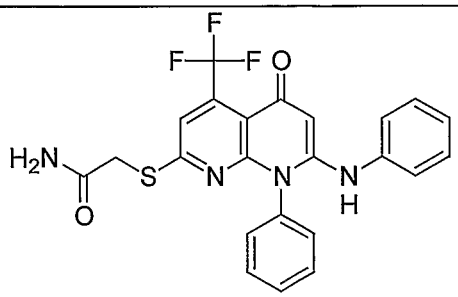
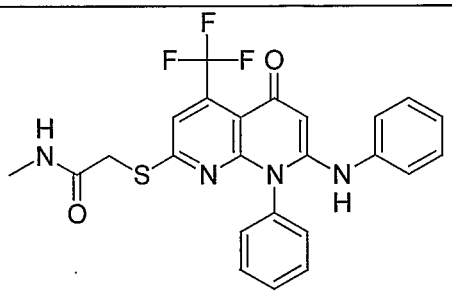
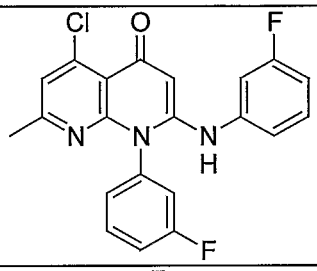
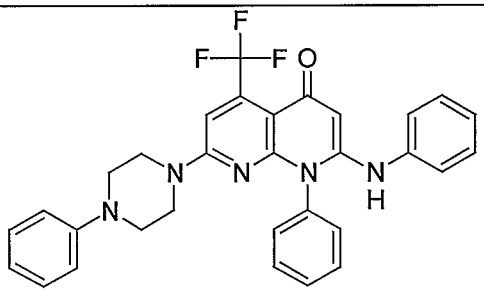
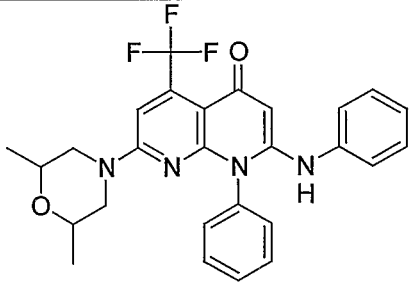
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
136		2.28	346.3	Intermediate S, T, V, X and Example 15
137		2.32	342.3	Intermediate S, T, V, X and Example 15
138		2.27	346.3	Intermediate S, T, V, X and Example 15
139		2.41	362.3	Intermediate S, T, V, X and Example 15
140		2.36	358.3	Intermediate S, T, V, X and Example 15
141		2.32	358.3	Intermediate S, T, V, X and Example 15

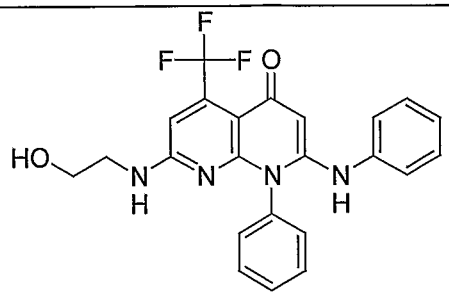
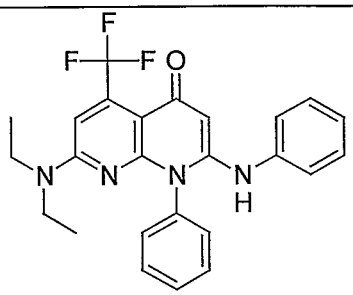
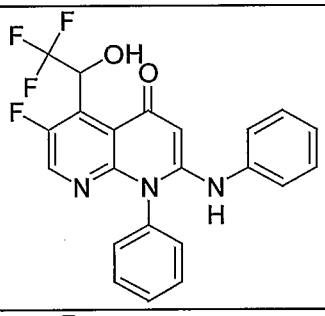
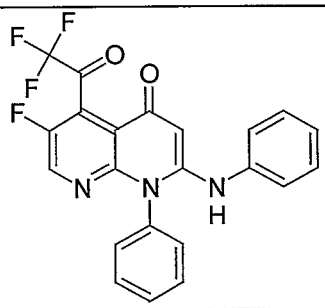
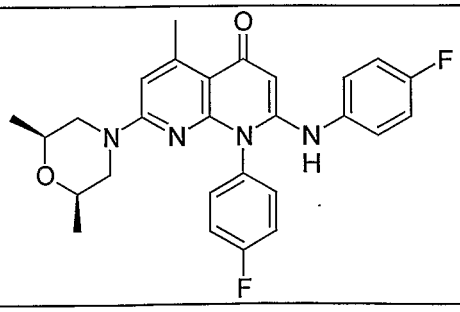
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
142		2.36	358.3	Intermediate S, T, V, X and Example 15
143		2.35	364.3	Intermediate A, B, C, D, E and Example 1
144		2.60	406.3	Intermediate Y, S, T, U, W and Example 15
145		5.35	434.4	Intermediate Y, S, T, U, W and Example 15, 4
146		3.43	470.3	Intermediate F, G, H, I, J and Example 6
147		3.43	470.3	Intermediate F, G, H, I, J and Example 6

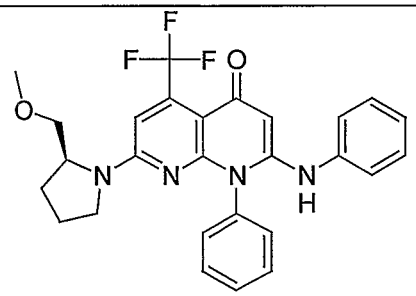
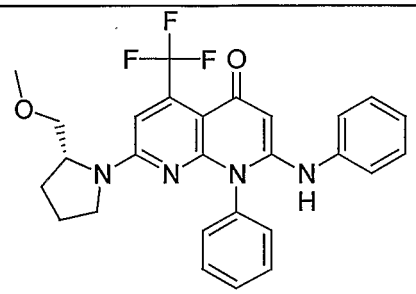
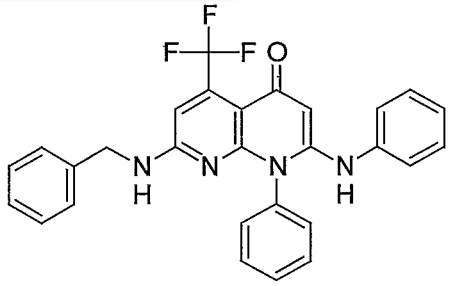
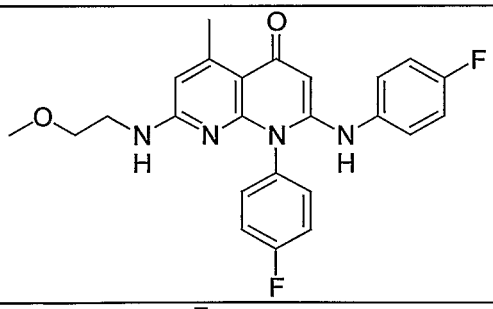
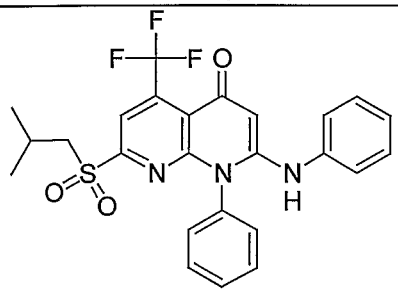
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
148		2.59	541.3	Intermediate F, G, H, I, J and Example 6, 7, 13
149		2.66	525.2	Intermediate F, G, H, I, J and Example 6, 7, 13
150		2.49	483.4	Intermediate F, G, H, I, J and Example 8
151		2.38	455.3	Intermediate F, G, H, I, J and Example 8, 7
152		2.60	499.4	Intermediate F, G, H, I, J and Example 6, 7, 13

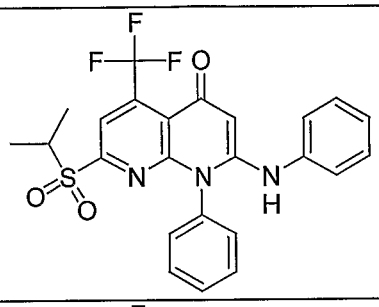
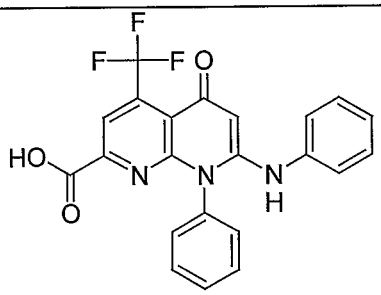
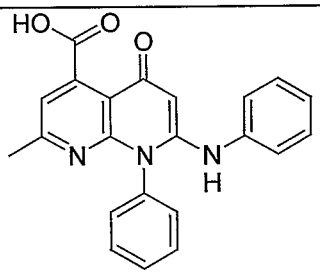
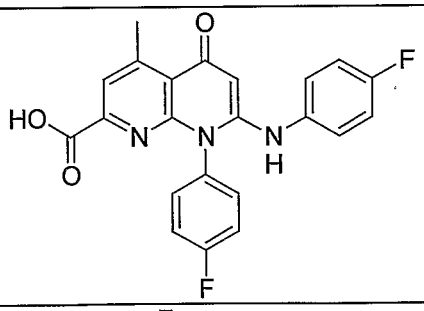
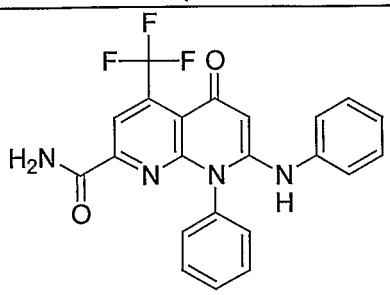
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
153		2.95	547.4	Intermediate F, G, H, I, J and Example 6, 7, 13
154		2.19	482.3	Intermediate F, G, H, I, J and Example 8, 7, 13
155		2.07	482.3	Intermediate F, G, H, I, J and Example 8, 7, 13
156		1.95	454.3	Intermediate F, G, H, I, J and Example 8, 7, 13
157		2.18	524.3	Intermediate F, G, H, I, J and Example 8, 7, 13

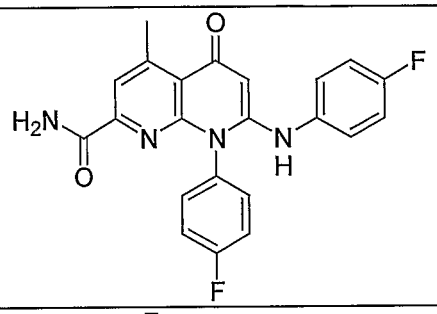
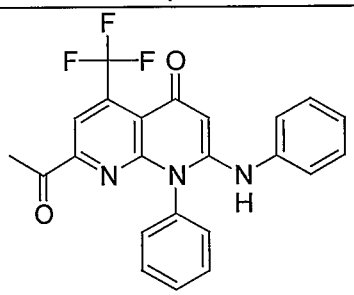
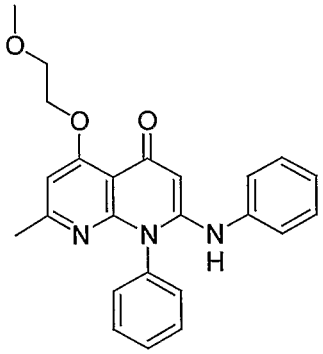
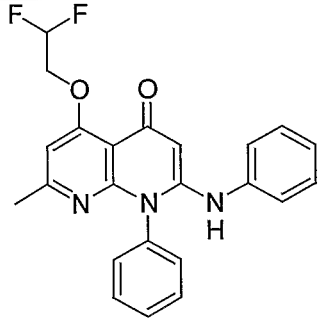
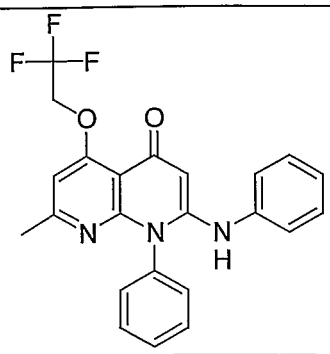
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
158		2.44	530.3	Intermediate F, G, H, I, J and Example 8, 7, 13
159		1.99	468.3	Intermediate F, G, H, I, J and Example 8, 7, 13
160		2.74	598.3	Intermediate F, G, H, I, J and Example 8, 7, 13
161		3.15	442.3	Intermediate F, G, H, I, J and Example 6
162		328	456.2	Intermediate F, G, H, I, J and Example 6

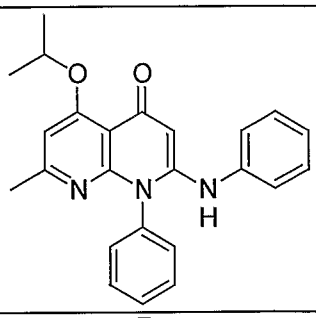
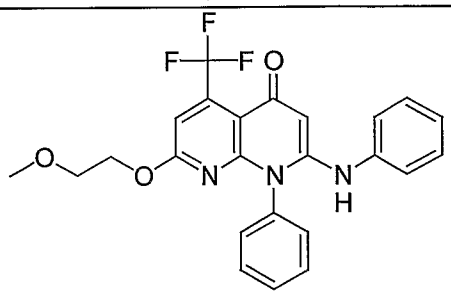
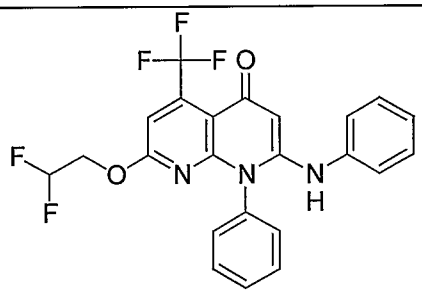
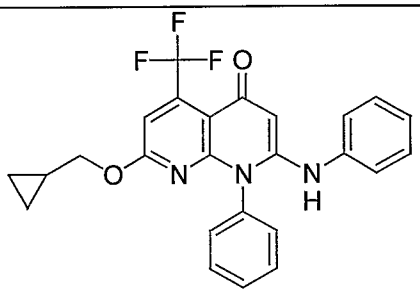
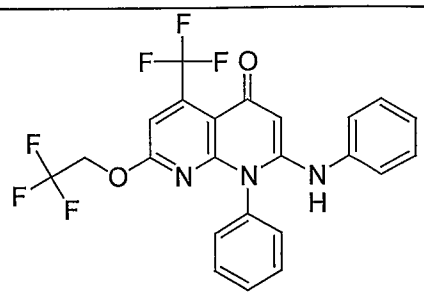
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
163		2.26	471.3	Intermediate F, G, H, I, J and Example 6, 7, 13
164		2.34	485.3	Intermediate F, G, H, I, J and Example 6, 7, 13
165		2.71	398.4	Intermediate Z, AA, AB and Example 16
166		2.88	542.6	Intermediate F, G, H, I, J and Example 8
167		2.66	495.6	Intermediate F, G, H, I, J and Example 8

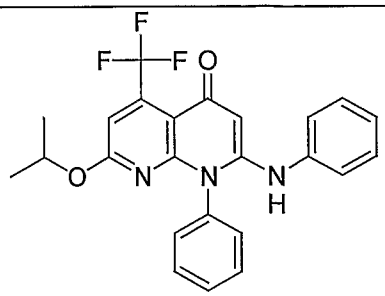
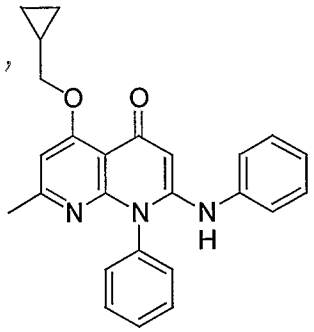
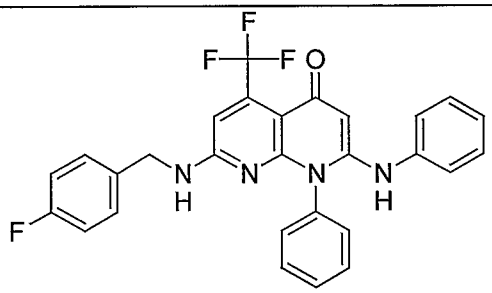
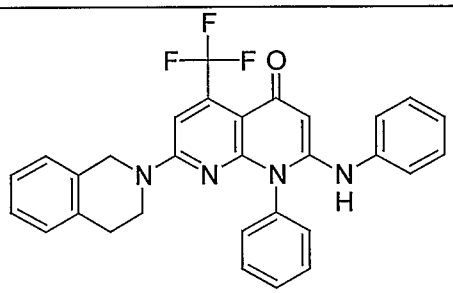
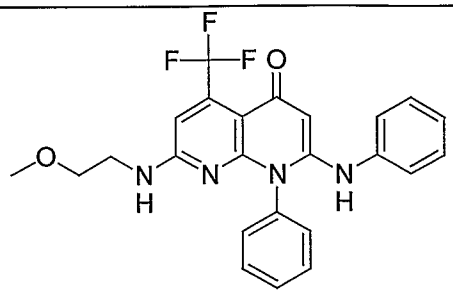
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
168		2.20	441.5	Intermediate F, G, H, I, J and Example 8
169		2.76	453.5	Intermediate F, G, H, I, J and Example 8
170		3.05	430.3	Intermediate K, L, M, N, AI and Example 1
171		3.14	428.4	Intermediate K, L, M, N, AI and Example 1
172		2.72	477.5	Intermediate A, B, C, D, E and Example 2

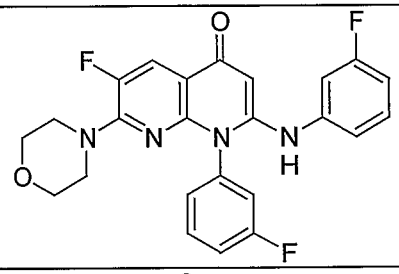
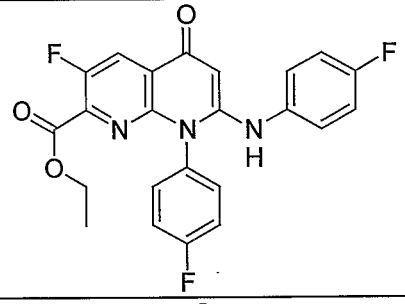
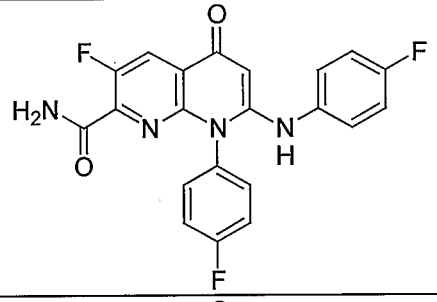
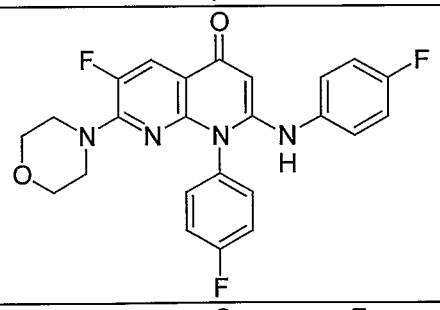
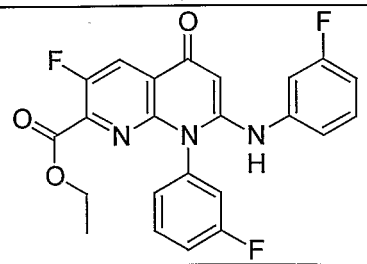
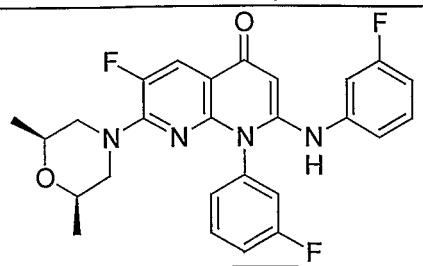
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
173		2.72	495.5	Intermediate F, G, H, I, J and Example 8
174		2.72	495.6	Intermediate F, G, H, I, J and Example 8
175		2.77	487.5	Intermediate F, G, H, I, J and Example 8
176		2.43	437.4	Intermediate A, B, C, D, E and Example 2
177		3.13	502.5	Intermediate F, G, H, I, J and Example 6, 21

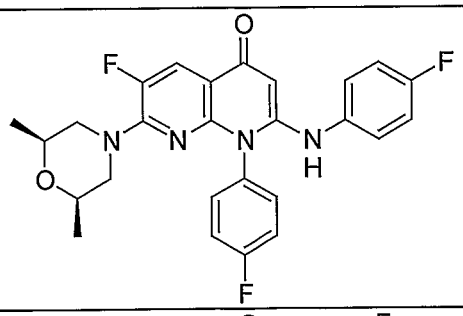
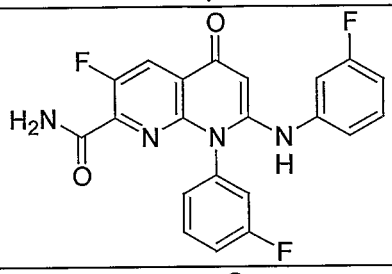
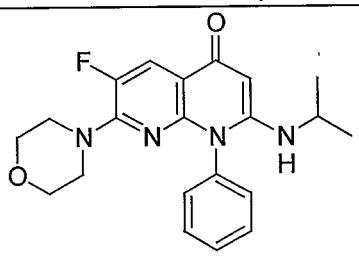
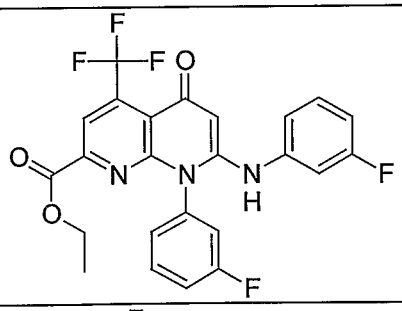
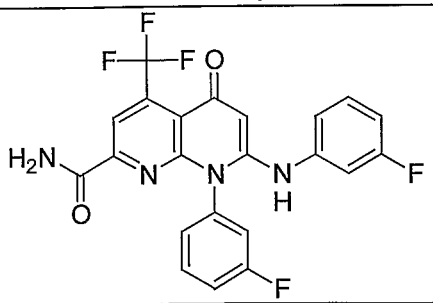
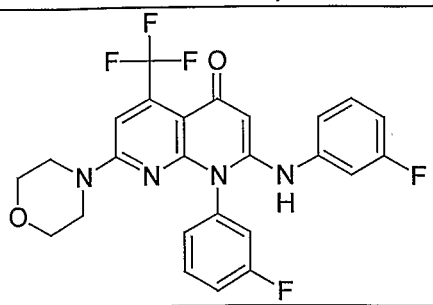
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
178		2.93	488.3	Intermediate F, G, H, I, J and Example 6, 21
179		2.41	426.3	Intermediate F, G, H, I, J and Example 17, 7
180		2.56	372.3	Intermediate Z, AA, AB and Example 16, 17, 7
181		2.19	408.2	Intermediate A, B, C, D, E and Example 17, 7
182		2.39	425.4	Intermediate F, G, H, I, J and Example 17, 18

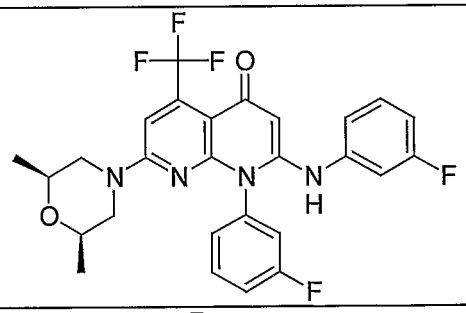
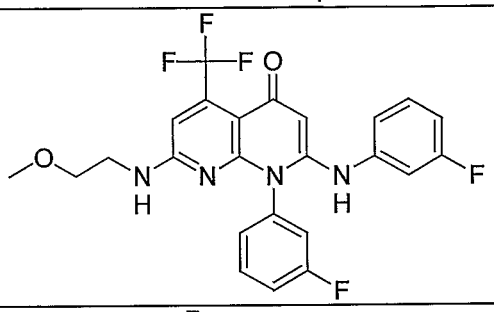
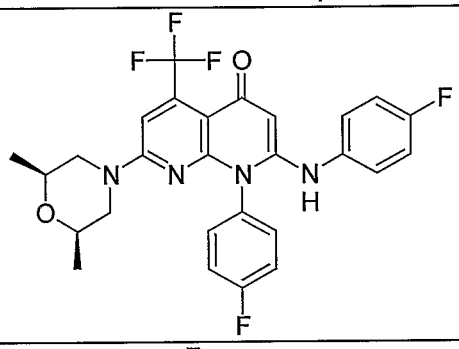
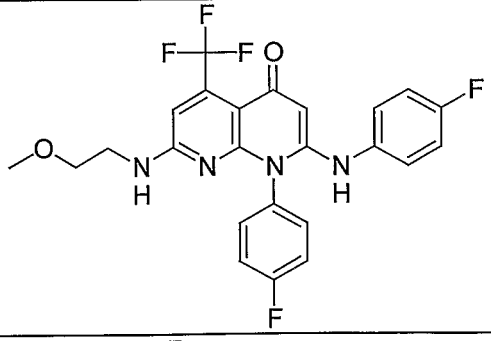
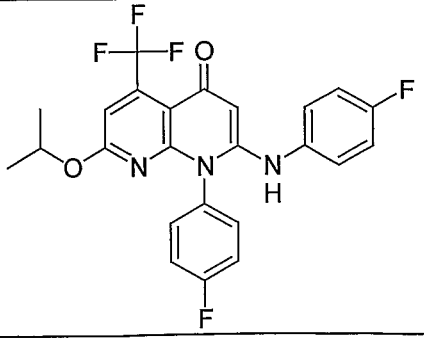
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
183		2.18	407.4	Intermediate A, B, C, D, E and Example 17, 18
184		2.88	424.4	Intermediate F, G, H, I, J and Example 17, 7, 19, 20
185		2.27	402.2	Intermediate Z, AA, AB and Example 16, 9
186		2.41	408.3	Intermediate Z, AA, AB and Example 16, 9
187		2.50	426.3	Intermediate Z, AA, AB and Example 16, 9

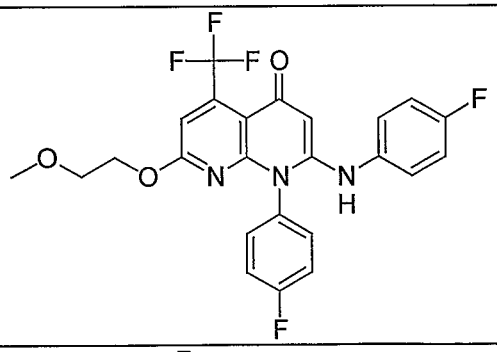
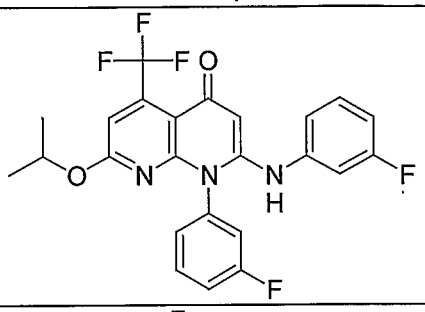
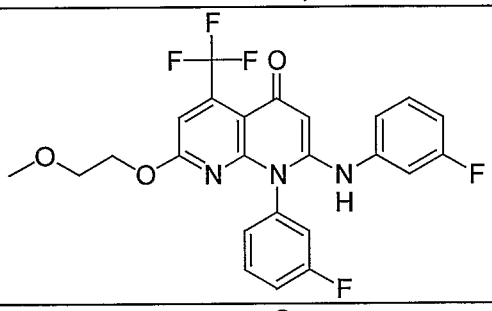
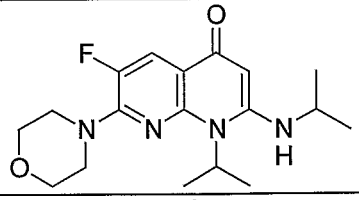
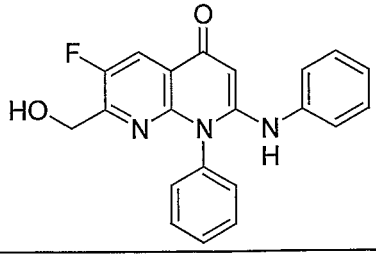
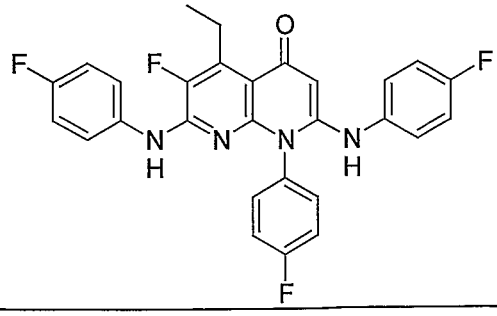
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
188		2.43	386.1	Intermediate Z, AA, AB and Example 16, 9
189		2.66	456.4	Intermediate F, G, H, I, J and Example 9
190		2.88	462.5	Intermediate F, G, H, I, J and Example 9
191		2.98	452.4	Intermediate F, G, H, I, J and Example 9
192		3.12	480.3	Intermediate F, G, H, I, J and Example 9

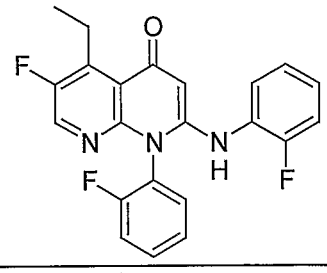
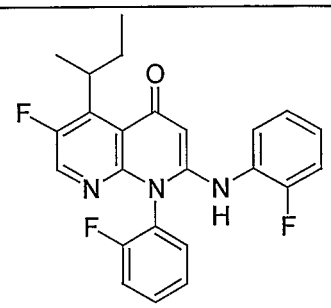
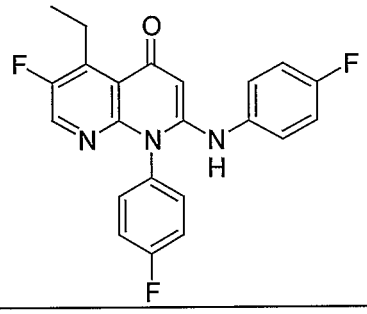
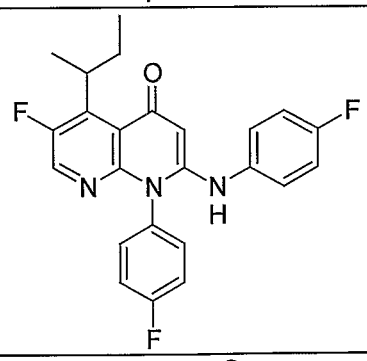
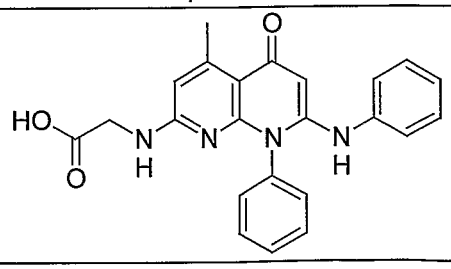
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
193		3.10	440.1	Intermediate F, G, H, I, J and Example 9
194		2.51	398.1	Intermediate Z, AA, AB and Example 16, 9
195		2.99	505.4	Intermediate F, G, H, I, J and Example 8
196		3.05	513.5	Intermediate F, G, H, I, J and Example 8
197		2.47	455.4	Intermediate F, G, H, I, J and Example 8

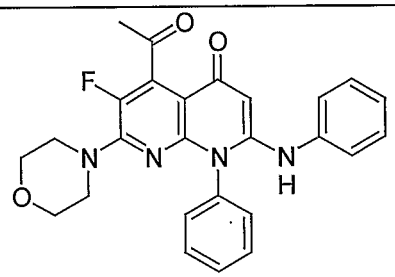
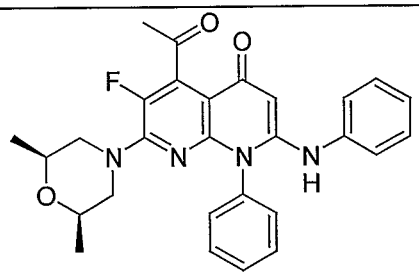
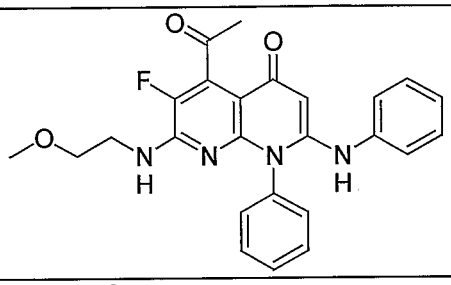
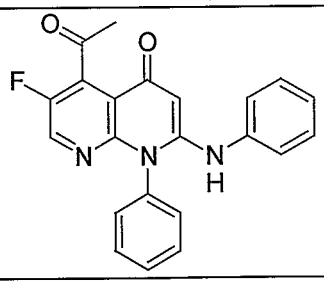
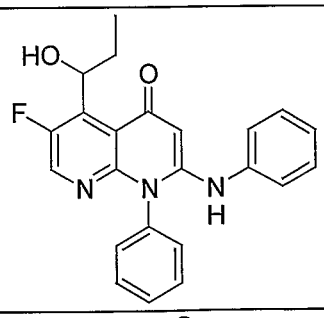
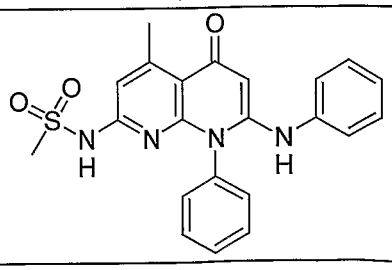
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
198		2.57	453.4	Intermediate K, L, M, N_1 and Example 2
199		2.70	440.2	Intermediate K, L, M, N_2 and Example 17
200		2.19	411.3	Intermediate K, L, M, N_2 and Example 17, 18
201		2.48	453.4	Intermediate K, L, M, N_2 and Example 2
202		2.76	440.2	Intermediate K, L, M, N_1 and Example 17
203		2.76	481.5	Intermediate K, L, M, N_1 and Example 2

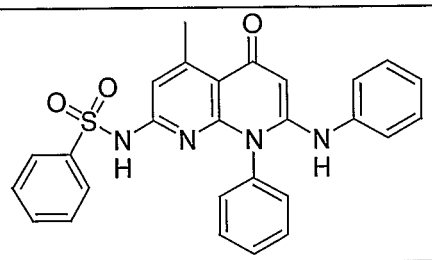
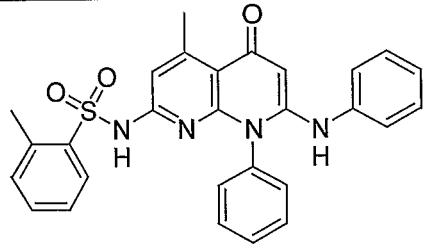
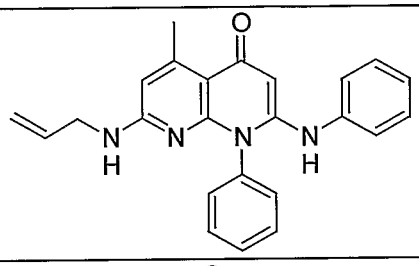
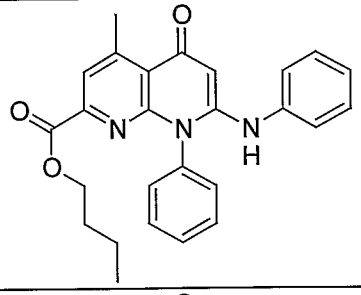
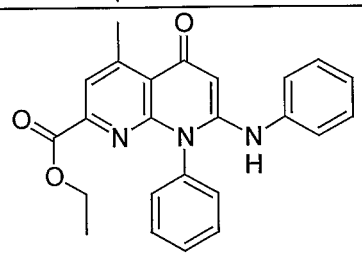
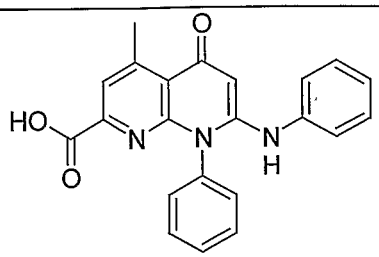
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
204		2.69	481.5	Intermediate K, L, M, N_2 and Example 2
205		2.23	411.3	Intermediate K, L, M, N_1 and Example 17, 18
206		2.27	383.4	Intermediate K, L, AC, AG and Example 2
207		3.12	490.3	Intermediate F, G, H, I, J and Example 17
208		2.55	461.3	Intermediate F, G, H, I, J and Example 17, 18
209		2.62	503.4	Intermediate F, G, H, I, J and Example 8

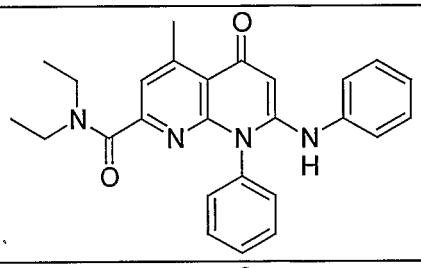
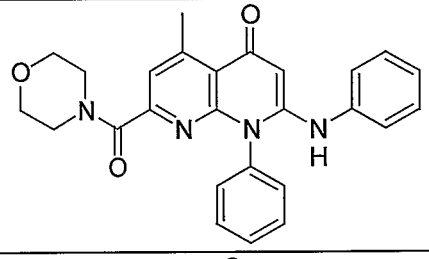
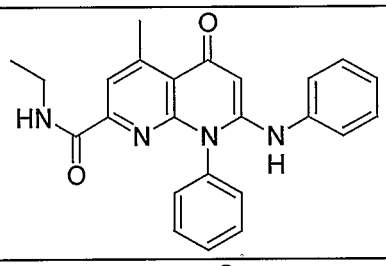
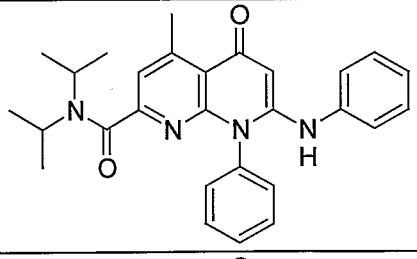
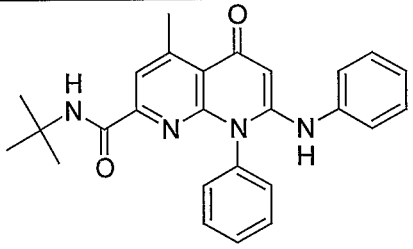
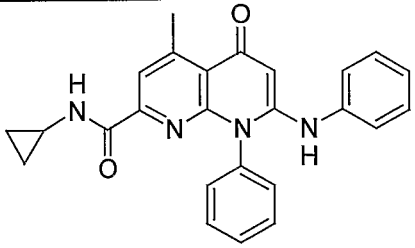
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
210		2.82	531.5	Intermediate F, G, H, I, J and Example 8
211		2.54	491.4	Intermediate F, G, H, I, J and Example 8
212		2.93	531.4	Intermediate F, G, H, I, J and Example 8
213		2.47	491.4	Intermediate F, G, H, I, J and Example 8
214		3.02	476.3	Intermediate F, G, H, I, J and Example 9

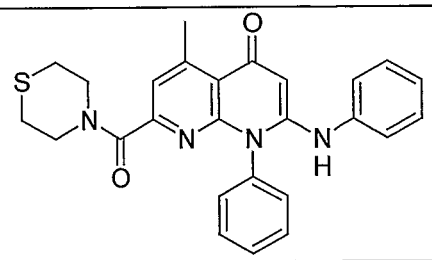
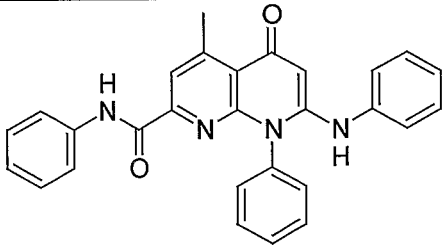
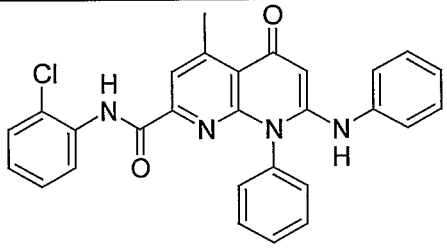
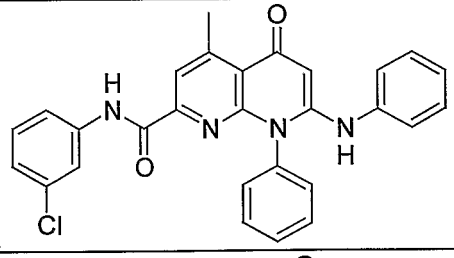
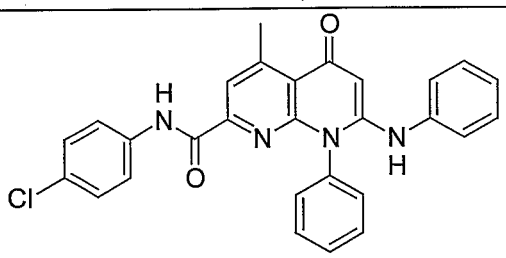
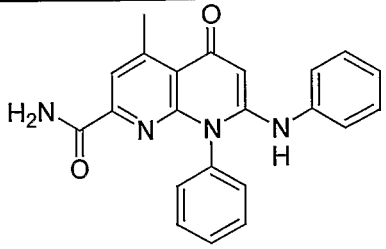
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
215		2.75	492.3	Intermediate F, G, H, I, J and Example 9
216		3.14	476.2	Intermediate F, G, H, I, J and Example 9
217		2.83	492.3	Intermediate F, G, H, I, J and Example 9
218		2.15	349.1	Intermediate K, L, M, N_3 and Example 2
219		2.01	362.3	Intermediate K, L, M, N and Example 17, 25
220		2.87	505.4	Intermediate AH, K, L, M, N_2

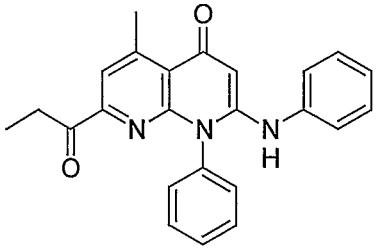
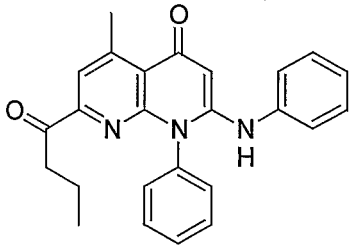
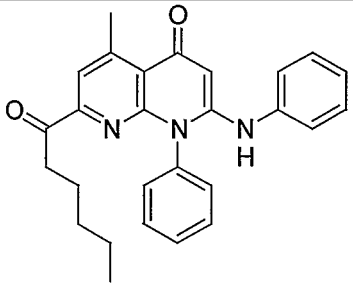
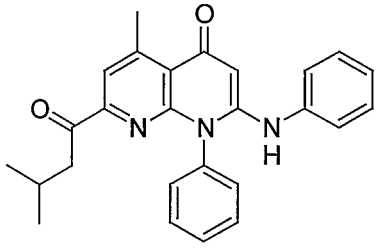
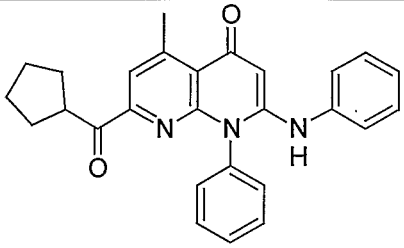
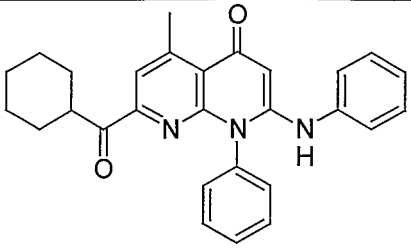
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
221		2.90	396.3	Intermediate AH, K, L, M, N and Example 1
222		3.23	424.3	Intermediate AH, K, L, M, N and Example 1
223		2.67	396.3	Intermediate AH, K, L, M, N_2 and Example 1
224		3.02	424.4	Intermediate AH, K, L, M, N_2 and Example, 1
225		2.12	401.3	Intermediate A, B, C, D, E and Example 3, 7

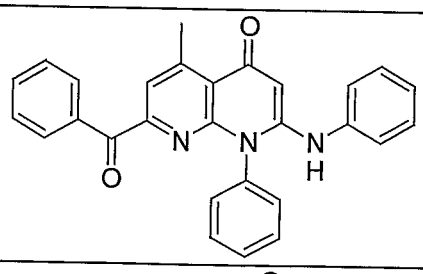
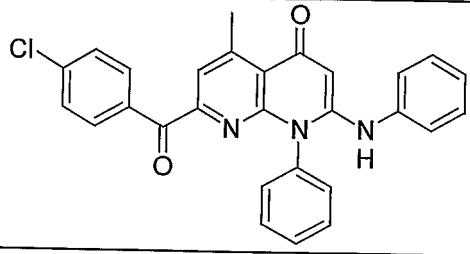
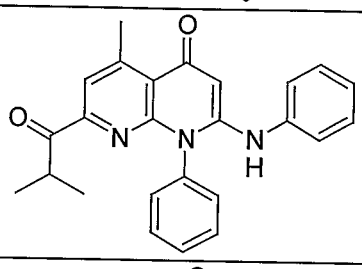
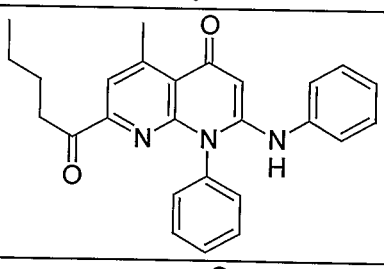
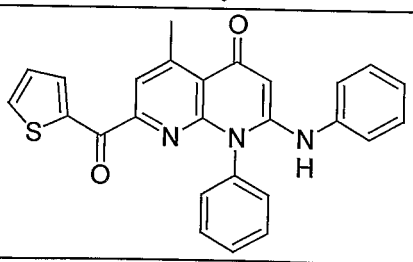
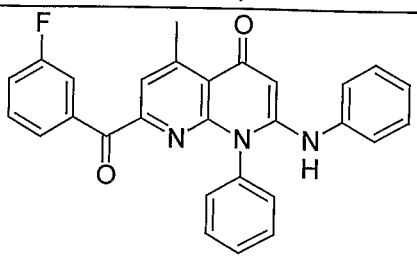
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
226		2.45	459.4	Intermediate K, L, M, N, AI and Example 2
227		2.69	487.5	Intermediate K, L, M, N, AI and Example 2
228		2.37	447.4	Intermediate K, L, M, N, AI and Example 2
229		2.60	374.3	Intermediate K, L, M, N, AI and Example 1
230		2.78	390.1	Intermediate K, L, M, N, AM and Example 1
231		2.09	421.2	Intermediate A, B, C, D, E and Example 22

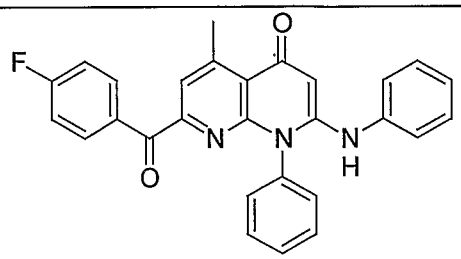
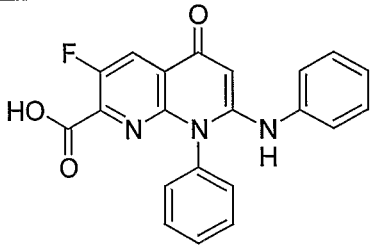
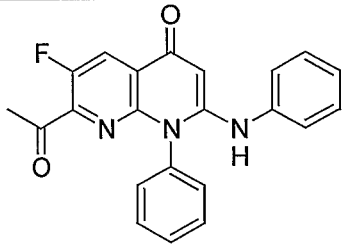
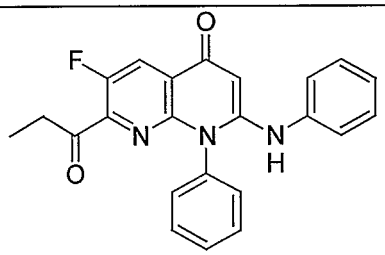
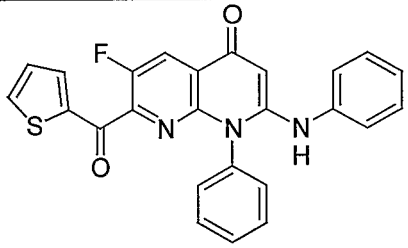
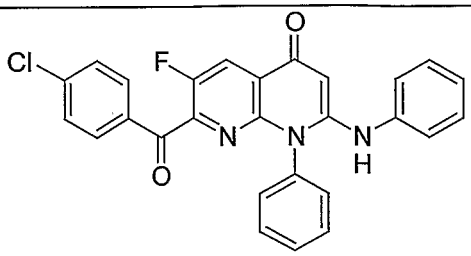
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
232		2.44	483.2	Intermediate A, B, C, D, E and Example 22
233		2.51	497.2	Intermediate A, B, C, D, E and Example 22
234		2.44	383.2	Intermediate A, B, C, D, E and Example 3
235		2.84	428.4	Intermediate A, B, C, D, E and Example 17
236		2.77	400.3	Intermediate A, B, C, D, E and Example 17
237		2.30	372.2	Intermediate A, B, C, D, E and Example 17, 7

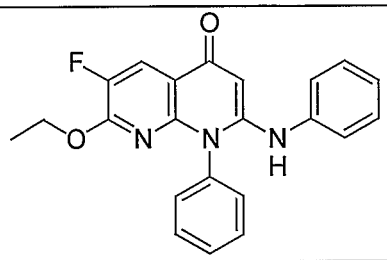
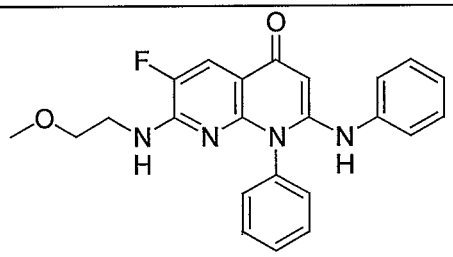
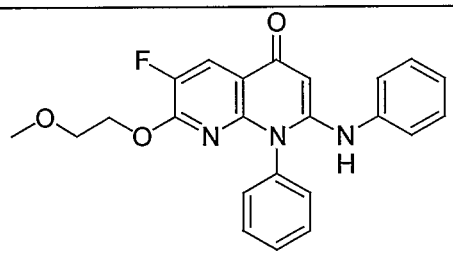
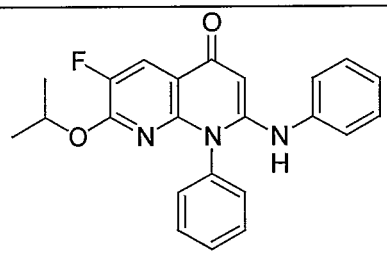
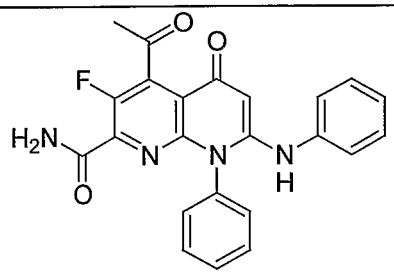
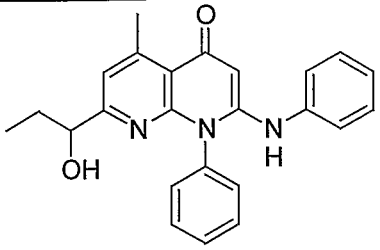
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
238		2.50	427.4	Intermediate A, B, C, D, E and Example 17, 7, 13
239		2.18	441.5	Intermediate A, B, C, D, E and Example 17, 7, 13
240		2.44	399.4	Intermediate A, B, C, D, E and Example 17, 7, 13
241		2.66	455.5	Intermediate A, B, C, D, E and Example 17, 7, 13
242		2.79	427.3	Intermediate A, B, C, D, E and Example 17, 7, 13
243		2.58	411.3	Intermediate A, B, C, D, E and Example 17, 7, 13

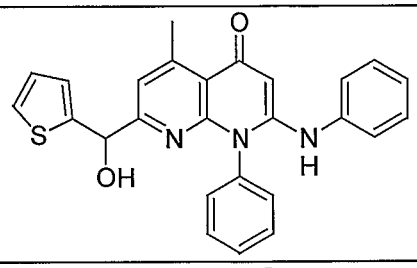
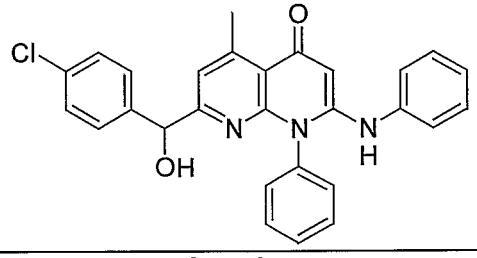
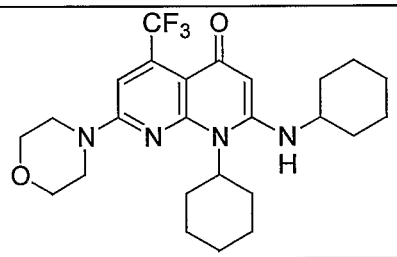
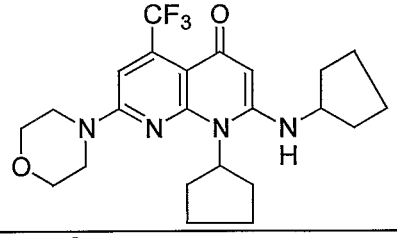
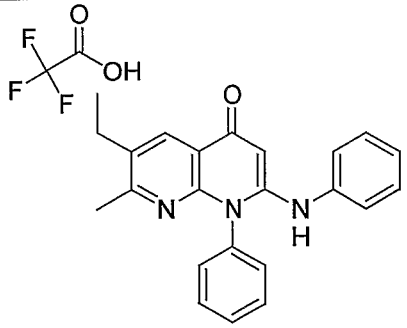
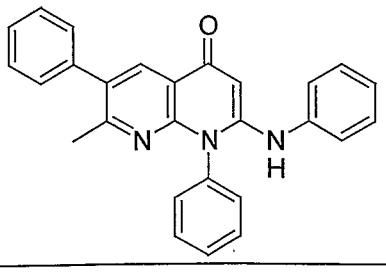
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
244		2.58	457.3	Intermediate A, B, C, D, E and Example 17, 7, 13
245		2.80	447.5	Intermediate A, B, C, D, E and Example 17, 7, 13
246		2.97	481.8	Intermediate A, B, C, D, E and Example 17, 7, 13
247		3.30	481.3	Intermediate A, B, C, D, E and Example 17, 7, 13
248		3.05	481.7	Intermediate A, B, C, D, E and Example 17, 7, 13
249		1.99	371.4	Intermediate A, B, C, D, E and Example 17, 18

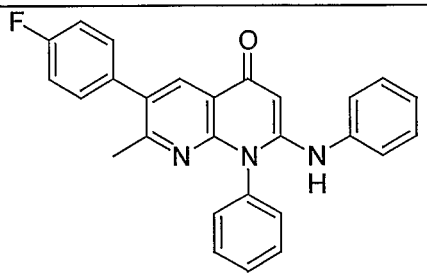
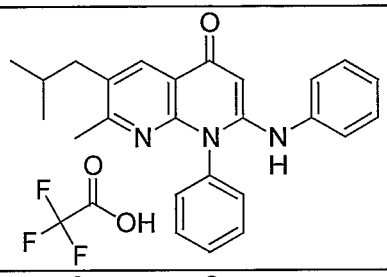
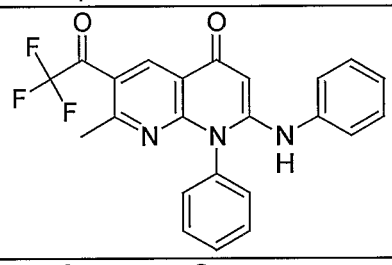
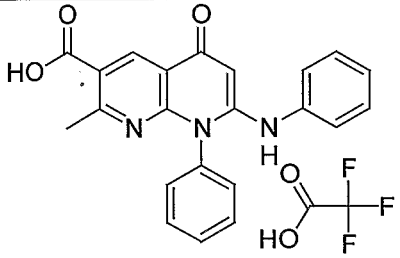
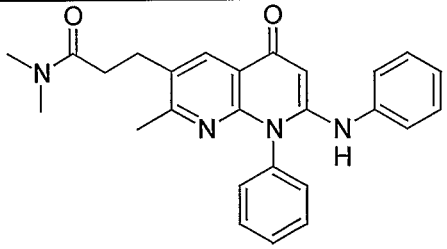
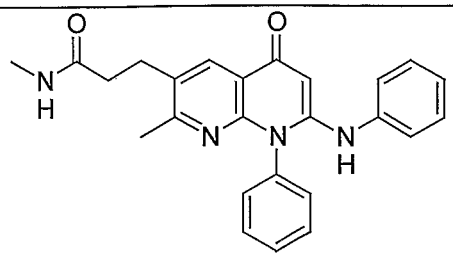
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
250		2.82	384.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
251		2.94	398.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
252		3.22	426.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
253		3.05	412.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
254		3.10	424.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
255		3.19	438.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20

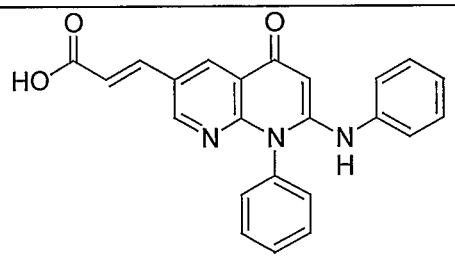
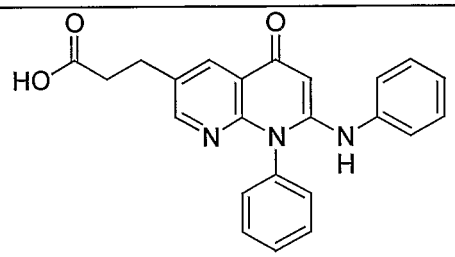
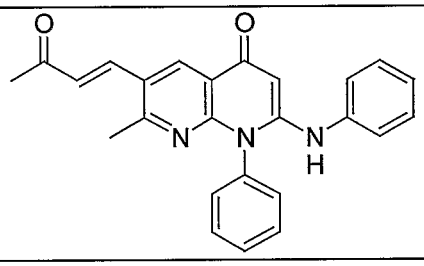
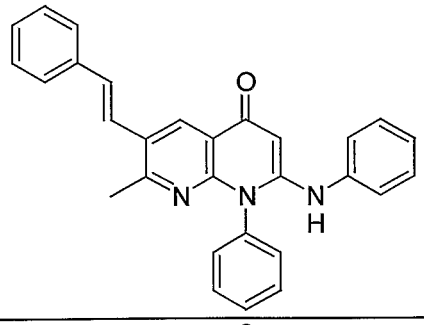
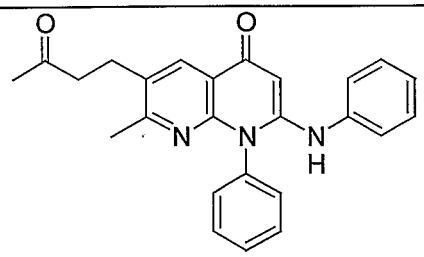
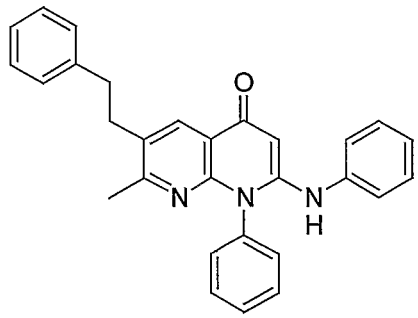
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
256		2.96	432.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
257		3.16	466.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
258		2.80	398.5	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
259		2.95	412.5	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
260		2.80	438.6	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
261		3.06	450.3	Intermediate A, B, C, D, E and Example 17, 7, 19, 20

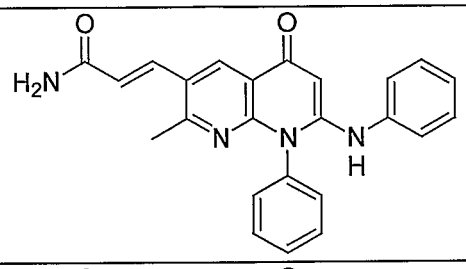
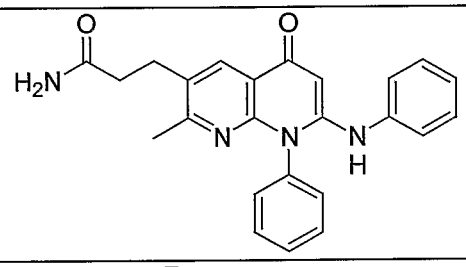
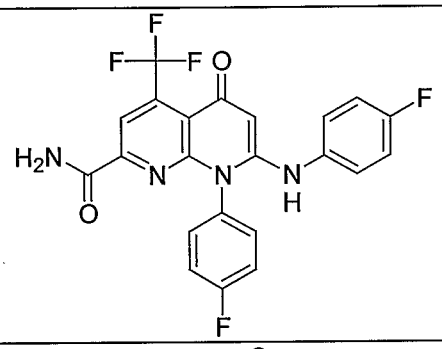
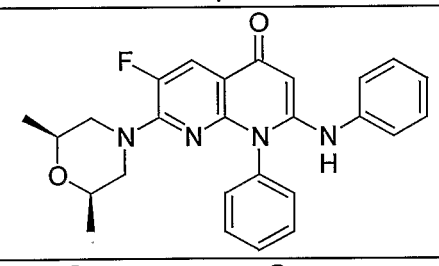
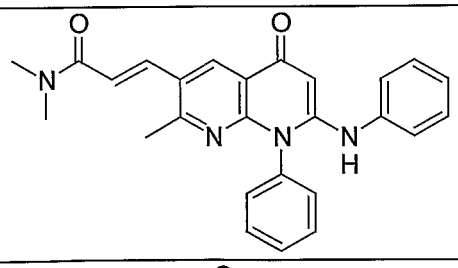
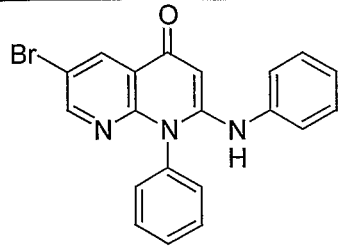
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
262		3.05	450.4	Intermediate A, B, C, D, E and Example 17, 7, 19, 20
263		1.94	376.2	Intermediate K, L, M, N and Example 17, 7
264		2.44	374.4	Intermediate K, L, M, N and Example 17, 7, 19, 20
265		2.59	388.3	Intermediate K, L, M, N and Example 17, 7, 19, 20
266		2.68	442.4	Intermediate K, L, M, N and Example 17, 7, 19, 20
267		2.97	470.5	Intermediate K, L, M, N and Example 17, 7, 19, 20

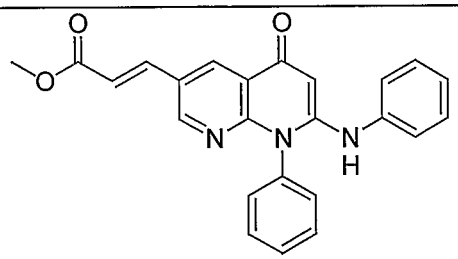
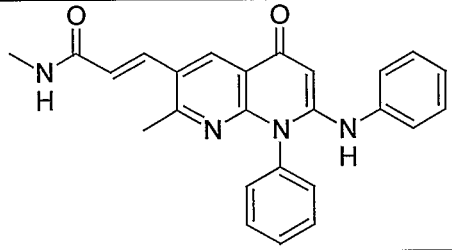
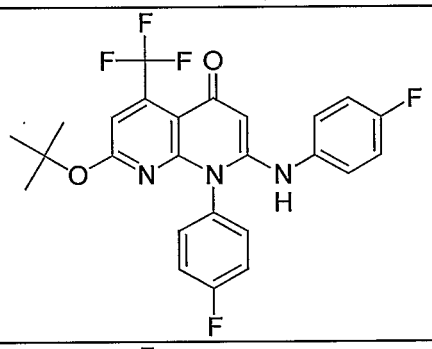
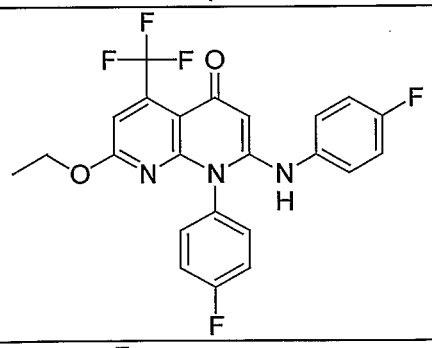
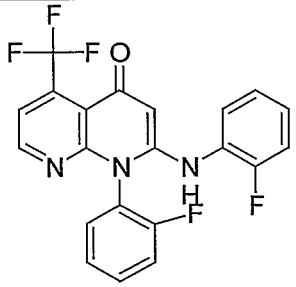
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
268		2.53	376.3	Intermediate K, L, M, N and Example 9
269		2.28	405.4	Intermediate K, L, M, N and Example 2
270		2.35	406.2	Intermediate K, L, M, N and Example 9
271		2.70	390.2	Intermediate K, L, M, N and Example 9
272		2.20	417.3	Intermediate K, L, M, N, AI and Example 17, 18
273		2.38	386.3	Intermediate A, B, C, D, E and Example 17, 7, 19, 20, 25

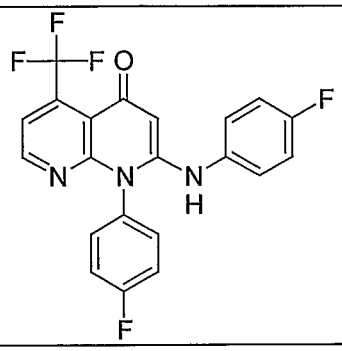
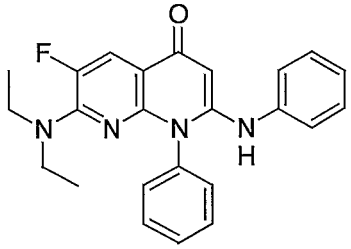
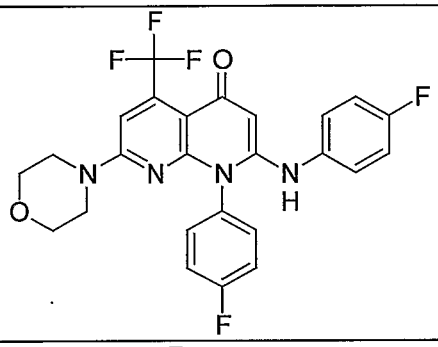
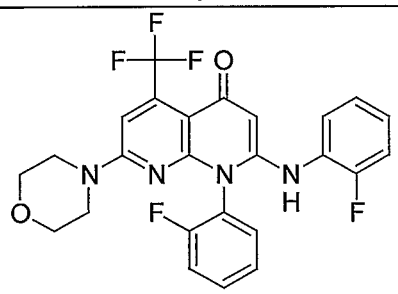
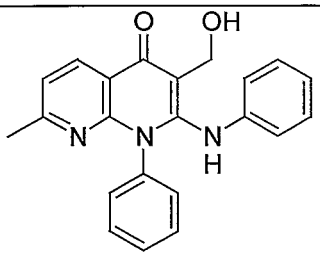
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
274		2.63	440.3	Intermediate A, B, C, D, E and Example 17, 7, 19, 20, 25
275		2.83	468.3	Intermediate A, B, C, D, E and Example 17, 7, 19, 20, 25
276		2.79	479.3	Intermediate F, G, H, I, J and Example 8
277		2.58	451.2	Intermediate F, G, H, I, J and Example 8
278		2.58	356.4	Intermediate Y, S, T, U, W and Example 15, 34
279		2.79	404.4	Intermediate Y, S, T, U, W and Example 15, 4

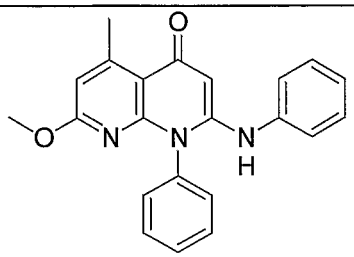
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
280		2.93	422.4	Intermediate Y, S, T, U, W and Example 15, 4
281		2.78	384.4	Intermediate Y, S, T, U, W and Example 15, 34
282		2.50	442.2 (423 + H2O + 1)	Intermediate Y, S, T, U, W and Example 15, 34
283		2.26	372.4	Intermediate Y, S, T, U, W and Example 15, 34
284		2.29	427.4	Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13
285		2.19	413.4	Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13

Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
286		2.15	384.4	Intermediate Y, S, T, U, W and Example 15, 31, 32
287		2.01	386.4	Intermediate Y, S, T, U, W and Example 15, 31, 32, 33
288		2.42	396.5	Intermediate Y, S, T, U, W and Example 15, 31
289		2.97	430.6	Intermediate Y, S, T, U, W and Example 15, 31
290		2.33	398.6	Intermediate Y, S, T, U, W and Example 15, 31, 33
291		2.87	432.4	Intermediate Y, S, T, U, W and Example 15, 31, 33

Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
292		2.01	397.3	Intermediate Y, S, T, U, W and Example 15, 31, 32, 13
293		2.00	399.5	Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13
294		2.63	461.3	Intermediate F, G, H, I, J and Example 17, 18
295		2.54	445.5	Intermediate K, L, M, N and Example 2
296		2.27	425.3	Intermediate Y, S, T, U, W and Example 15, 31, 32, 13
297		2.43	392.3	Intermediate Y, S, T, U, W and Example 15

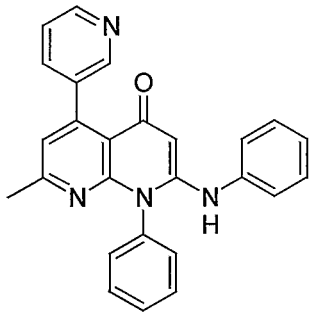
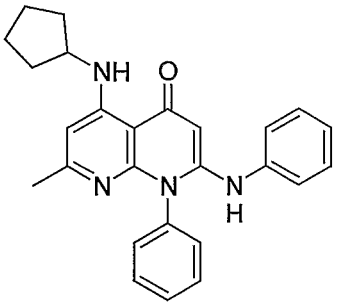
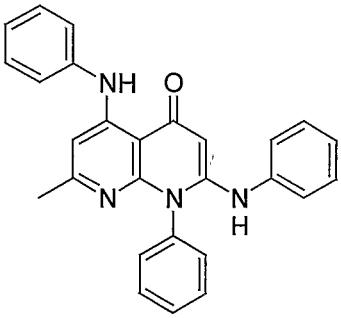
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
298		2.40	398.5	Intermediate Y, S, T, U, W and Example 15, 31
299		2.28	411.4	Intermediate Y, S, T, U, W and Example 15, 31, 32, 13
300		3.18	490.0	Intermediate F, G, H, I, J and Example 9
301		2.90	462.3	Intermediate F, G, H, I, J and Example 9
302		2.90	418.3	Intermediate F, G, H, I, J and Example 1

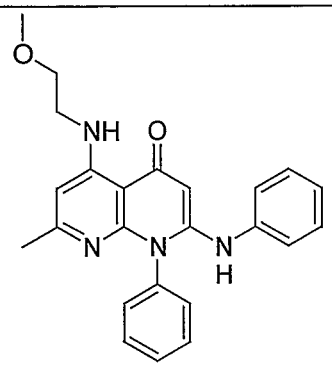
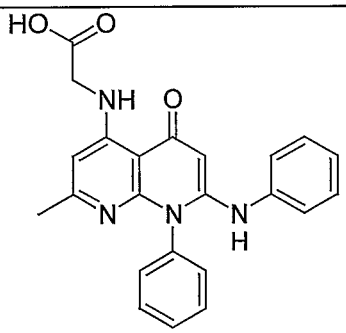
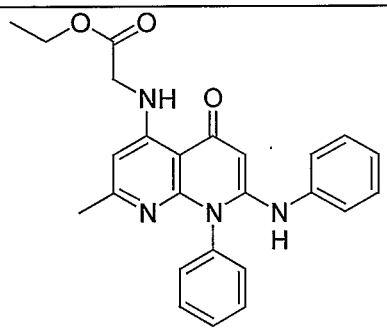
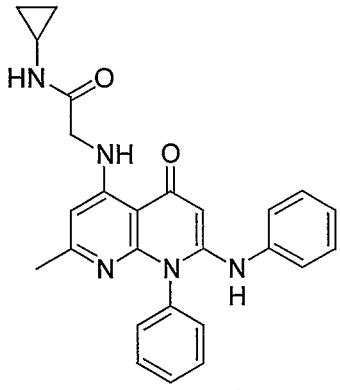
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
303		2.66	418.3	Intermediate F, G, H, I, J and Example 1
304		2.70	403.6	Intermediate K, L, M, N and Example 2
305		2.52	503.6	Intermediate F, G, H, I, J and Example 8
306		3.03	502.2	Intermediate F, G, H, I, J and Example 8
307		2.68	358.0	Intermediate S, T, U, W and Example 25

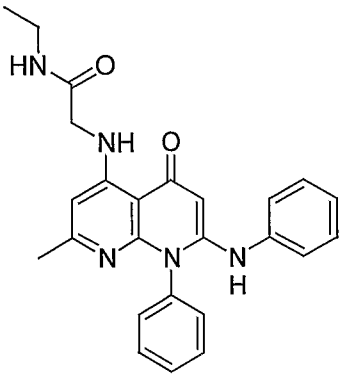
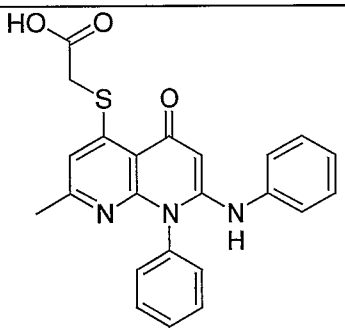
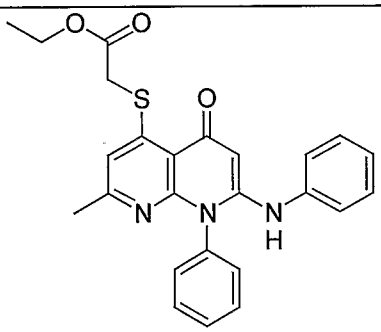
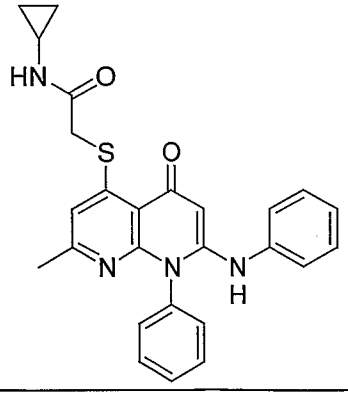
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
308		2.40	358.4	Intermediate A, B, C, D, E and Example 9

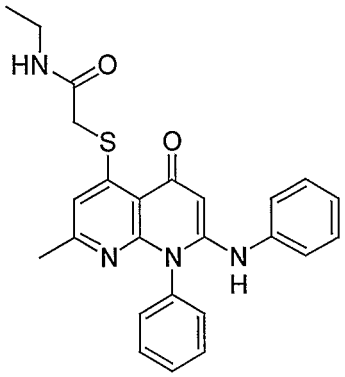
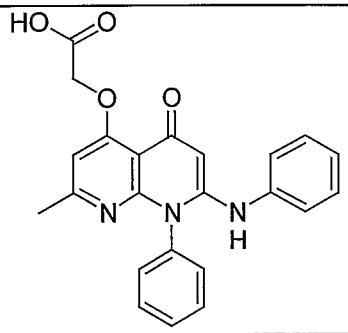
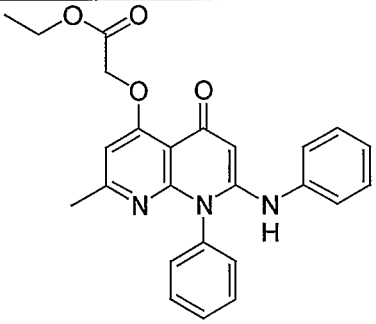
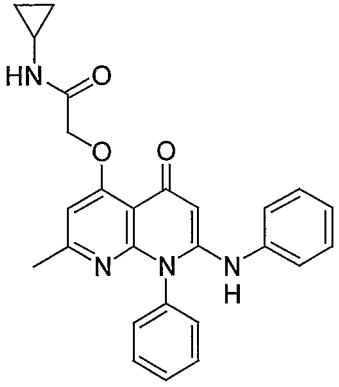
Utilizing the above described procedures for intermediates and examples alone or in combination, a variety of Formula I compounds can be prepared using the appropriate starting material and the representative procedure described. These compounds are summarized in Table 1B.

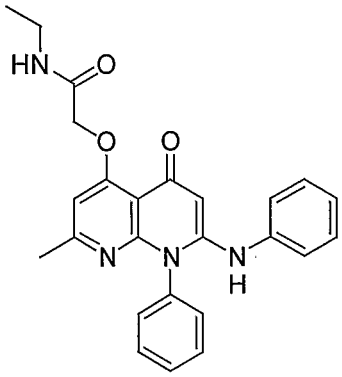
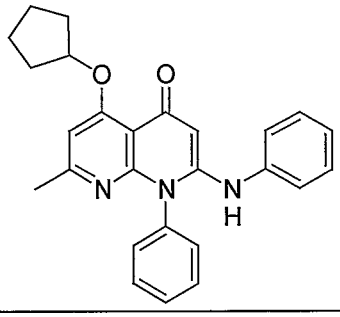
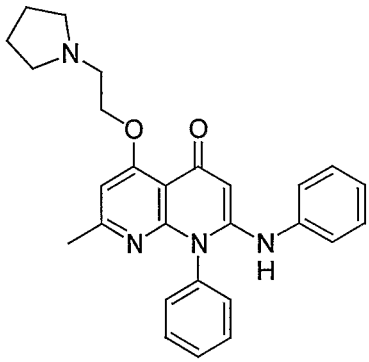
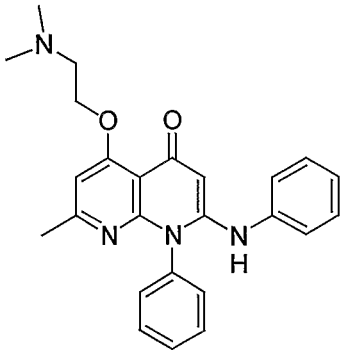
Table 1B

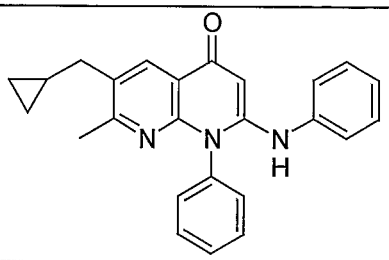
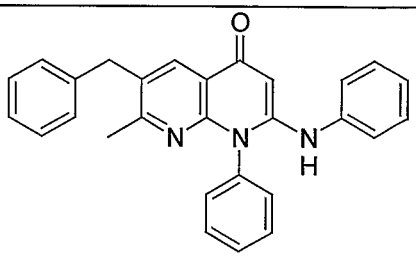
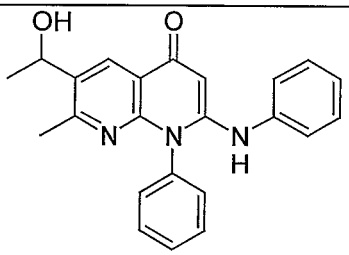
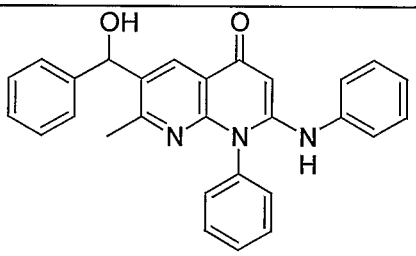
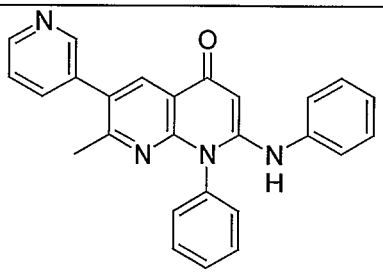
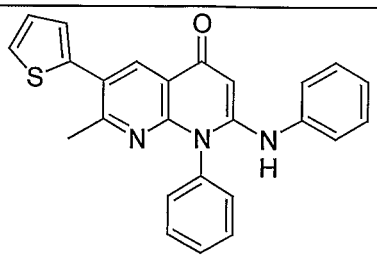
Example	Structure	Representative Procedure
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310		Intermediate Z, AA, AB and Example 16, 2
311		Intermediate Z, AA, AB and Example 16, 3

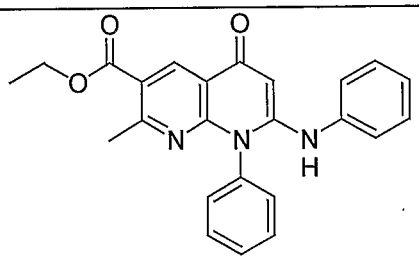
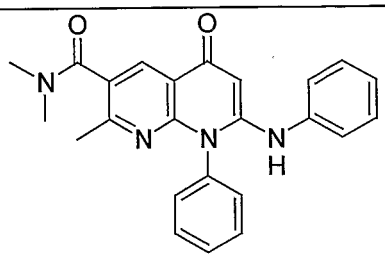
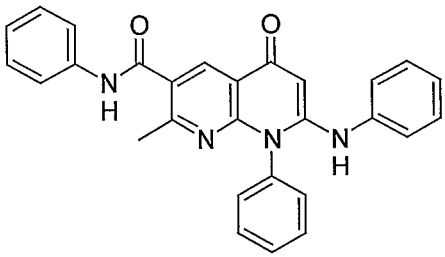
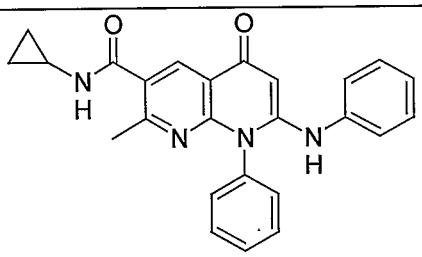
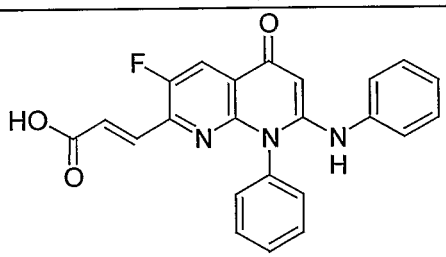
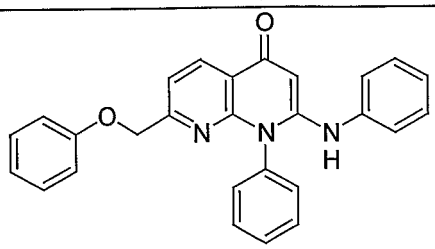
Example	Structure	Representative Procedure
312		Intermediate Z, AA, AB and Example 16, 2
313		Intermediate Z, AA, AB and Example 16, 2, 7
314		Intermediate Z, AA, AB and Example 16, 2
315		Intermediate Z, AA, AB and Example 16, 2, 7, 13

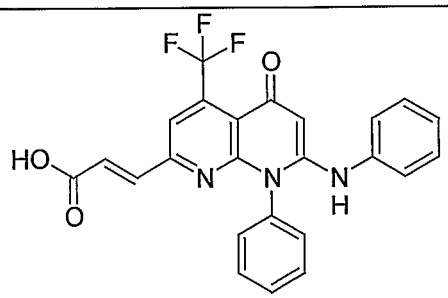
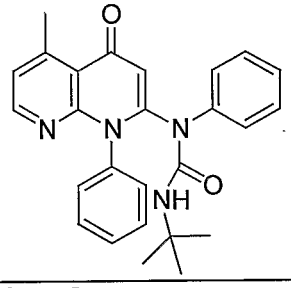
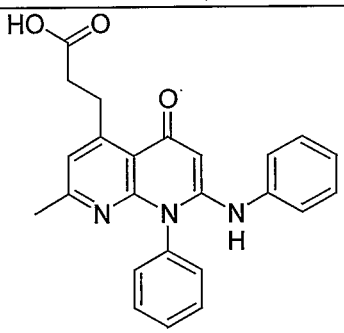
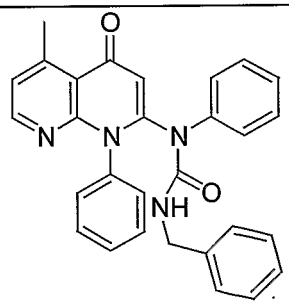
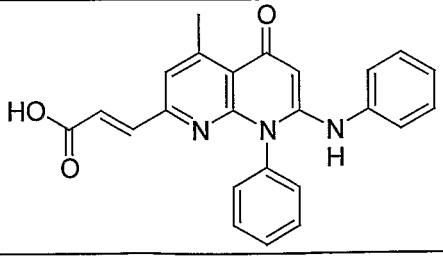
Example	Structure	Representative Procedure
316		Intermediate Z, AA, AB and Example 16, 2, 7, 13
317		Intermediate Z, AA, AB and Example 16, 6, 7
318		Intermediate Z, AA, AB and Example 16, 6
319		Intermediate Z, AA, AB and Example 16, 6, 7, 13

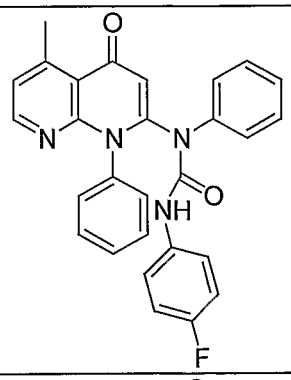
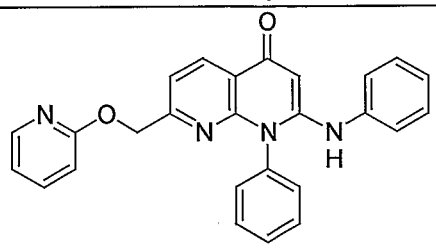
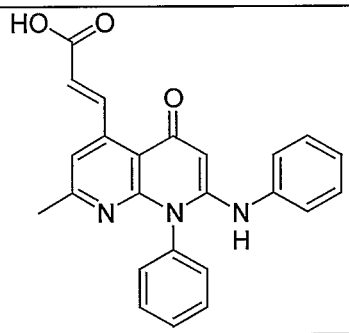
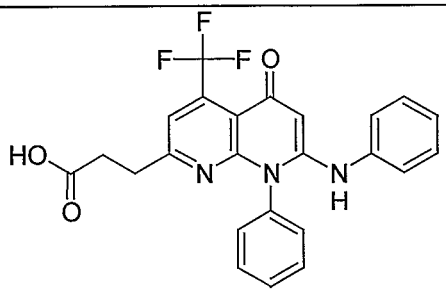
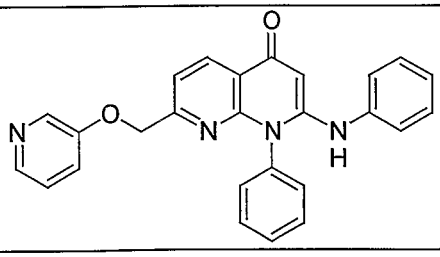
Example	Structure	Representative Procedure
320		Intermediate Z, AA, AB and Example 16, 6, 7, 13
321		Intermediate Z, AA, AB, and Example 16, 9, 7
322		Intermediate Z, AA, AB, and Example 16, 9
323		Intermediate Z, AA, AB, and Example 16, 9, 7, 13

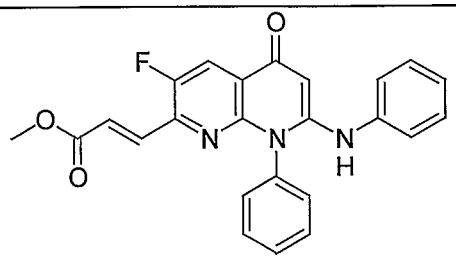
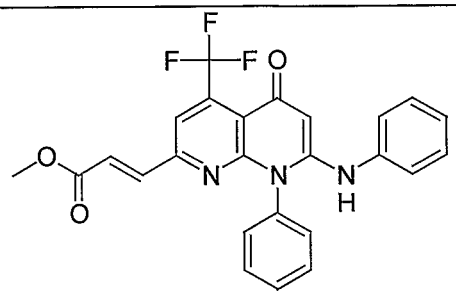
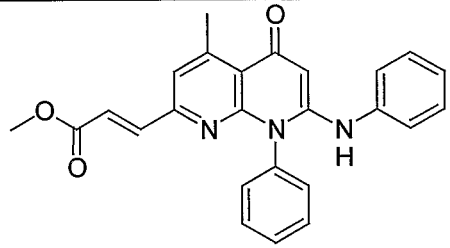
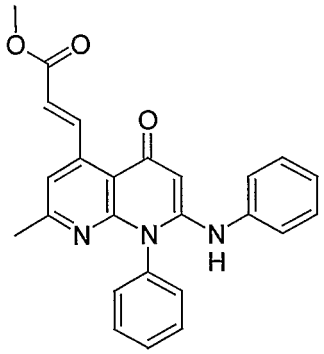
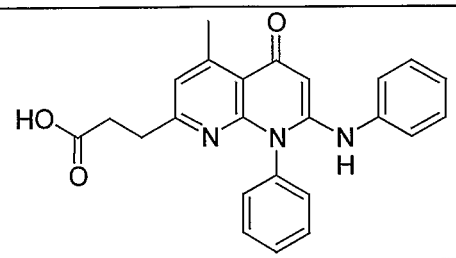
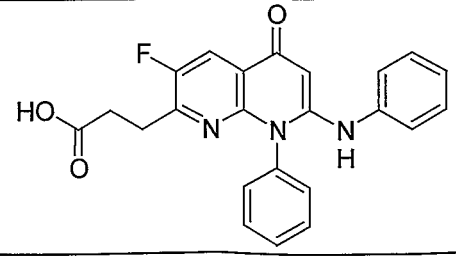
Example	Structure	Representative Procedure
324		Intermediate Z, AA, AB, and Example 16, 9, 7, 13
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326		Intermediate Z, AA, AB, and Example 16, 9
327		Intermediate Z, AA, AB, and Example 16, 9

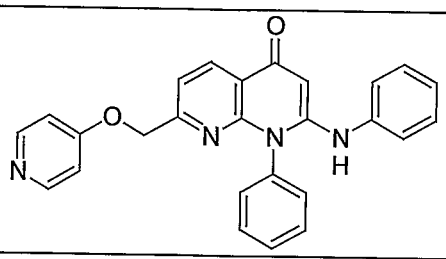
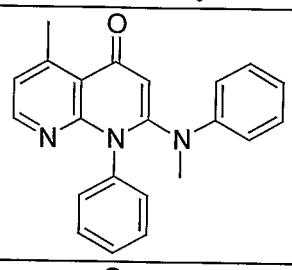
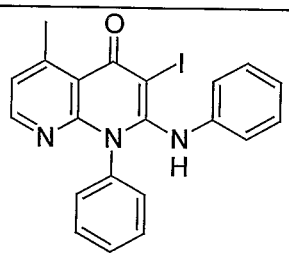
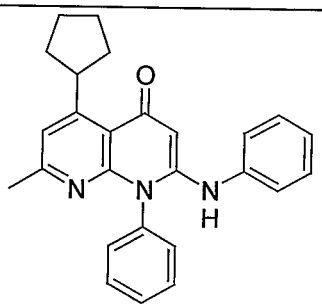
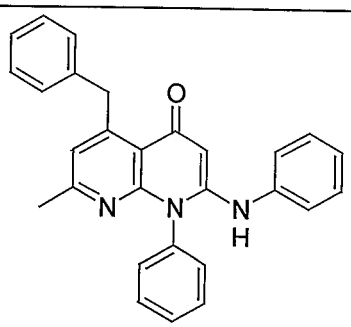
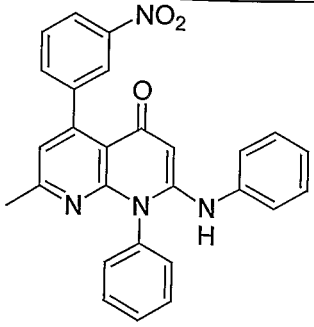
Example	Structure	Representative Procedure
328		Intermediate Y, S, T, U, W and Example 15, 34
329		Intermediate Y, S, T, U, W and Example 15, 34
330		Intermediate Y, S, T, U, W and Example 15, 34
331		Intermediate Y, S, T, U, W and Example 15, 34
332		Intermediate Y, S, T, U, W and Example 15, 4
333		Intermediate Y, S, T, U, W and Example 15, 4

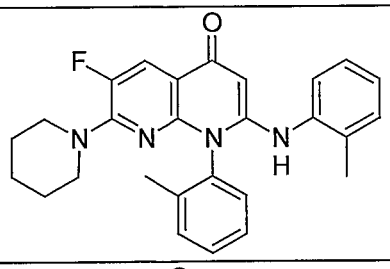
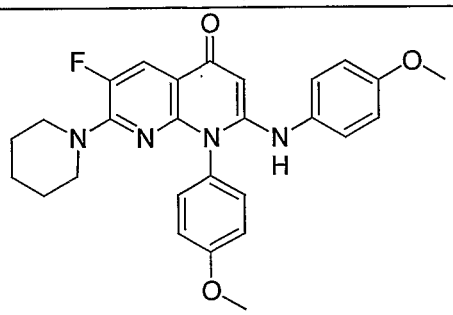
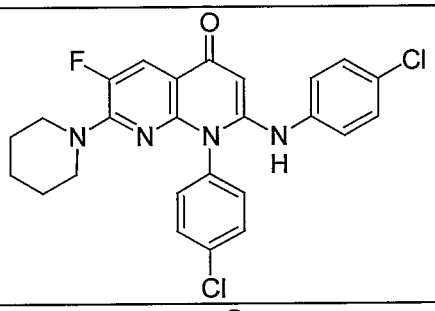
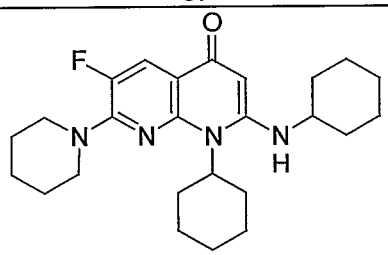
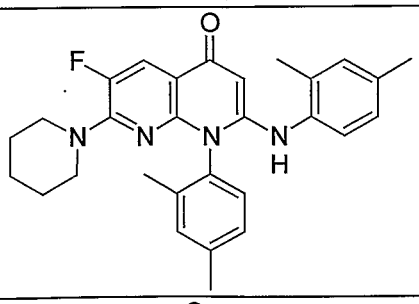
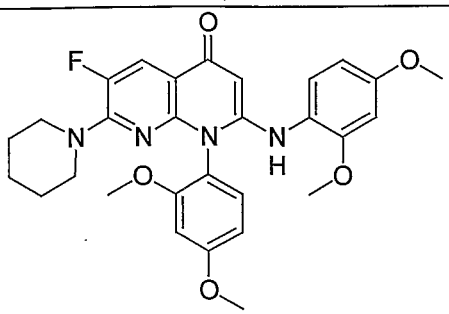
Example	Structure	Representative Procedure
334		Intermediate Y, S, T, U, W and Example 15, 34
335		Intermediate Y, S, T, U, W and Example 15, 34, 13
336		Intermediate Y, S, T, U, W and Example 15, 34, 13
337		Intermediate Y, S, T, U, W and Example 15, 34, 13
338		Intermediate K, L, M, N Example 31, 32
339		Intermediate O, P, Q, R and Example 17, 25, 26

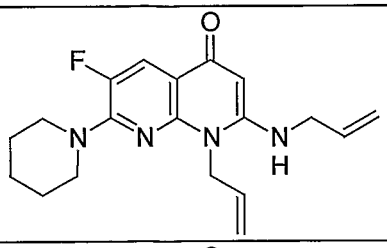
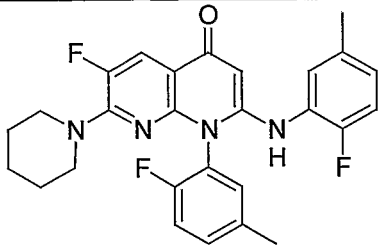
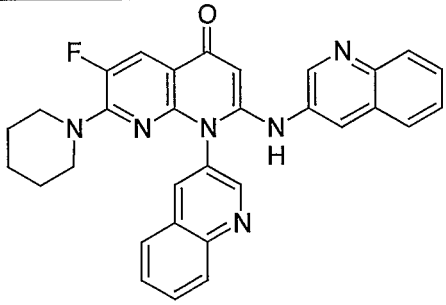
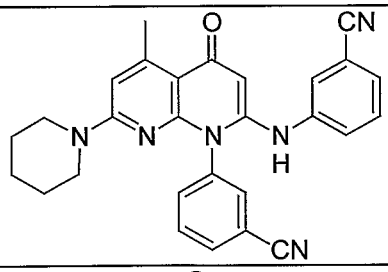
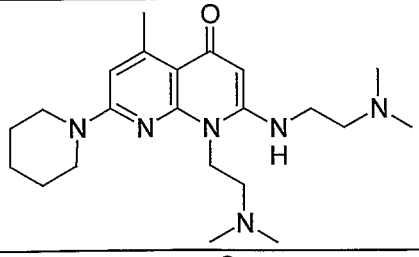
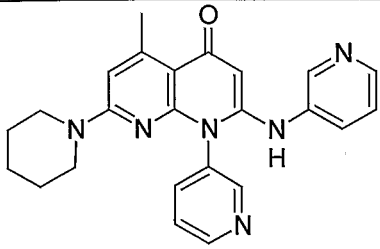
Example	Structure	Representative Procedure
340		Intermediate F, G, H, I, J and Example 31, 32
341		Intermediate A, B, C, D, E and Example 1 and Intermediate AK
342		Intermediate Z, AA, AB and Example 16, 31, 32, 33
343		Intermediate A, B, C, D, E and Example 1 and Intermediate AK
344		Intermediate A, B, C, D, E and Example 31, 32

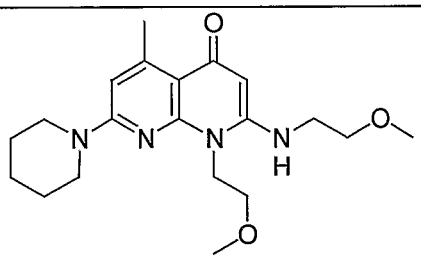
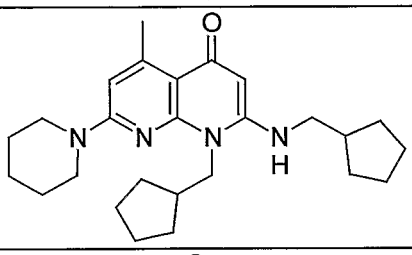
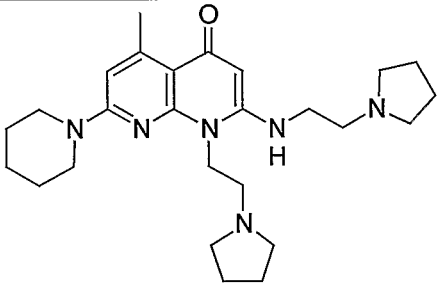
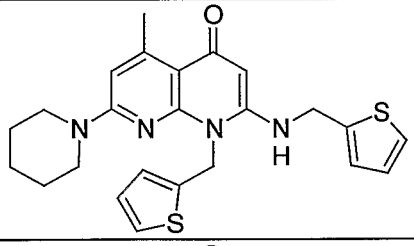
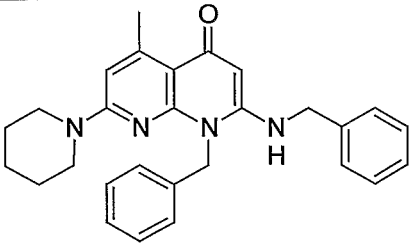
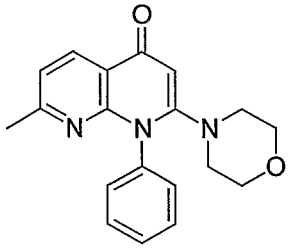
Example	Structure	Representative Procedure
345		Intermediate A, B, C, D, E and Example 1 and Intermediate AK
346		Intermediate O, P, Q, R and Example 17, 25, 26
347		Intermediate Z, AA, AB, and Example 16, 31, 32
348		Intermediate F, G, H, I, J and Example 31, 32, 33
349		Intermediate O, P, Q, R and Example 17, 25, 26

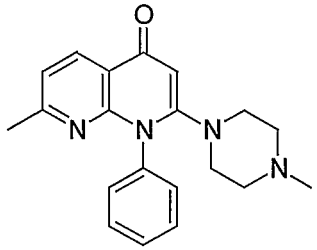
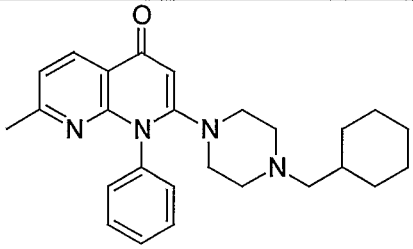
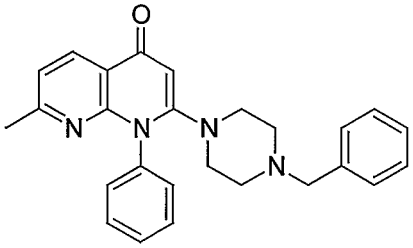
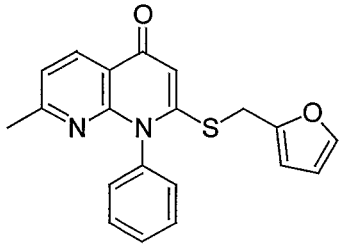
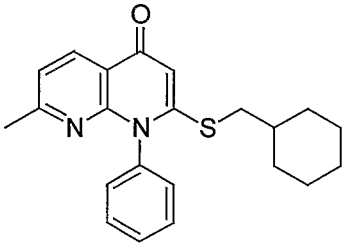
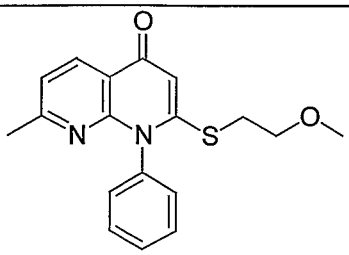
Example	Structure	Representative Procedure
350		Intermediate K, L, M, N and Example 31
351		Intermediate F, G, H, I, J and Example 31
352		Intermediate A, B, C, D, E and Example 31
353		Intermediate Z, AA, AB and Example 16, 31
354		Intermediate A, B, C, D, E and Example 31, 32, 33
355		Intermediate K, L, M, N and Example 31, 32, 33

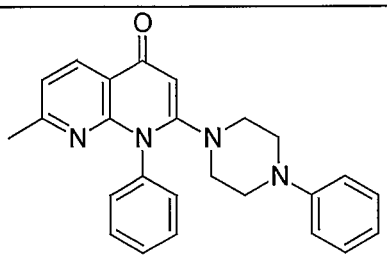
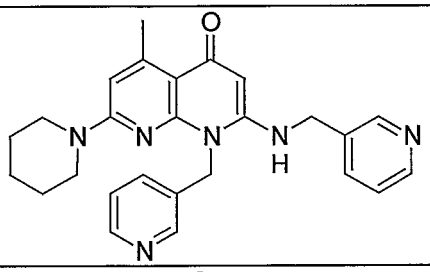
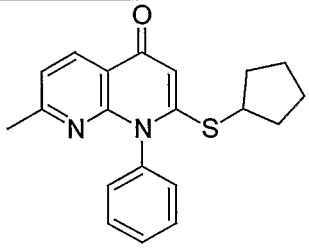
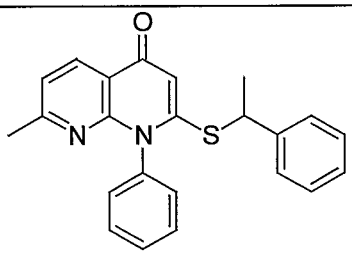
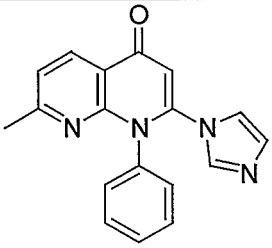
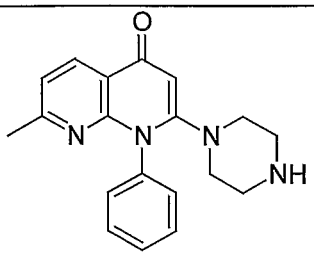
Example	Structure	Representative Procedure
356		Intermediate O, P, Q, R and Example 17, 25, 26
357		Intermediate A, B, C, D, E AJ and Example 1
358		Intermediate A, B, C, D, E and Example 1 and Intermediate AL
359		Intermediate Z, AA, AB, and Example 16, 5
360		Intermediate Z, AA, AB, and Example 16, 5
361		Intermediate Z, AA, AB, and Example 16, 4

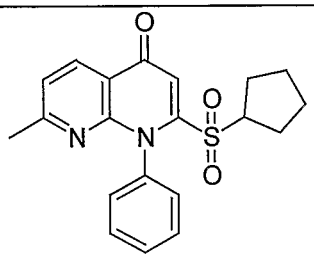
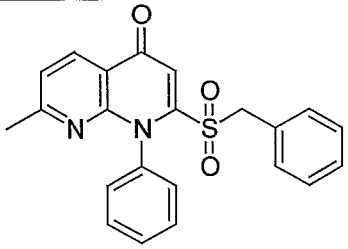
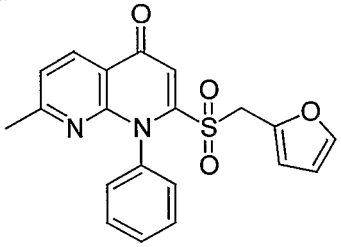
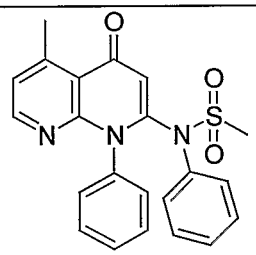
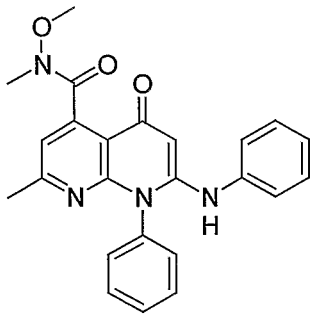
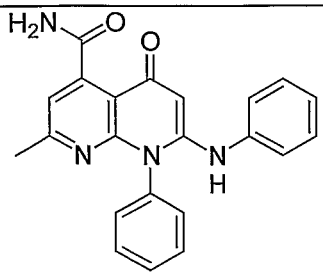
Example	Structure	Representative Procedure
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363		Intermediate K, L, M, N, and Example 2
364		Intermediate K, L, M, N, and Example 2
365		Intermediate K, L, M, N, and Example 2
366		Intermediate K, L, M, N, and Example 2
367		Intermediate K, L, M, N, and Example 2

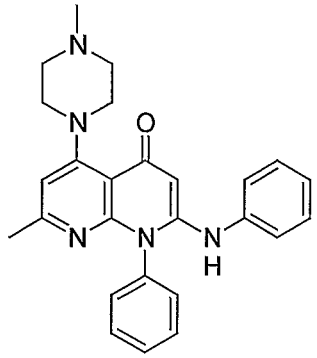
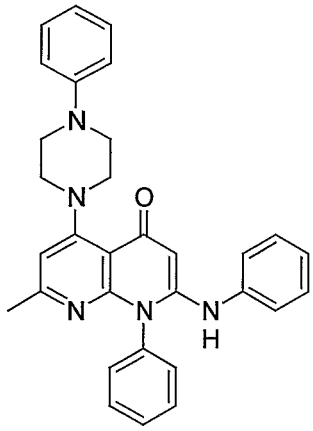
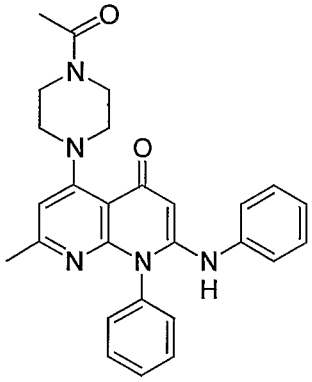
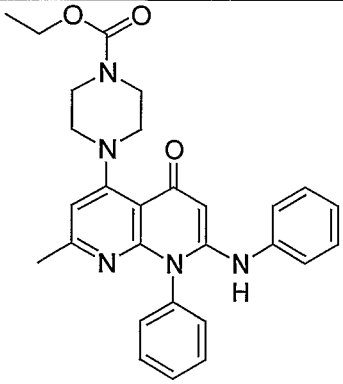
Example	Structure	Representative Procedure
368		Intermediate K, L, M, N, and Example 2
369		Intermediate K, L, M, N, and Example 2
370		Intermediate K, L, M, N, and Example 2
371		Intermediate A, B, C, D, E and Example 2
372		Intermediate A, B, C, D, E and Example 2
373		Intermediate A, B, C, D, E and Example 2

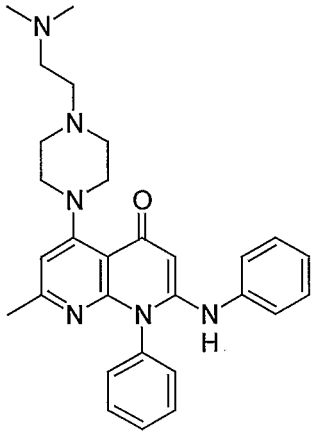
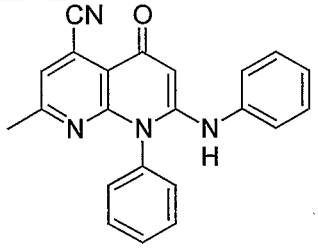
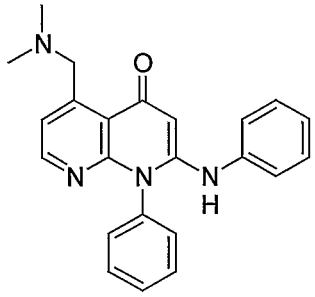
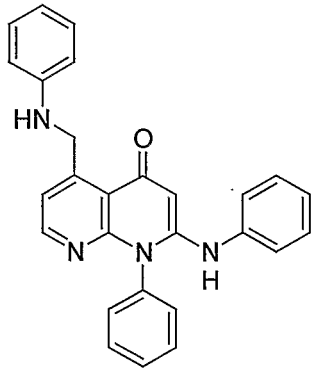
Example	Structure	Representative Procedure
374		Intermediate A, B, C, D, E and Example 2
375		Intermediate A, B, C, D, E and Example 2
376		Intermediate A, B, C, D, E and Example 2
377		Intermediate A, B, C, D, E and Example 2
378		Intermediate A, B, C, D, E and Example 2
379		Intermediate S, T, V, X and Example 15

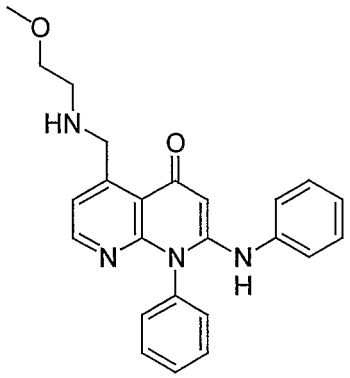
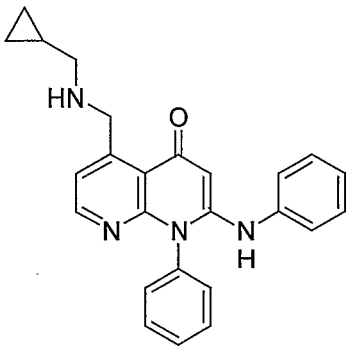
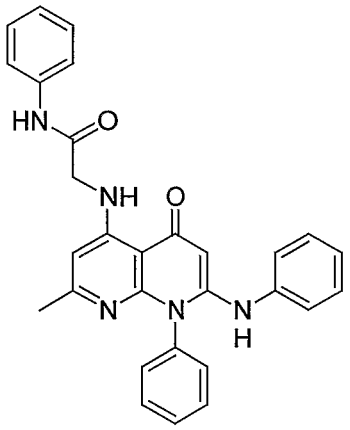
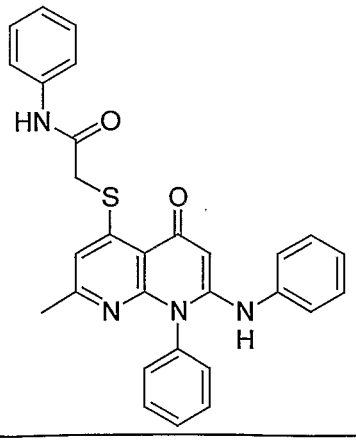
Example	Structure	Representative Procedure
380		Intermediate S, T, V, X and Example 15
381		Intermediate S, T, V, X and Example 15 and Intermediate AJ
382		Intermediate S, T, V, X and Example 15 and Intermediate AJ
383		Intermediate S, T, V and Example 15
384		Intermediate S, T, V and Example 15
385		Intermediate S, T, V and Example 15

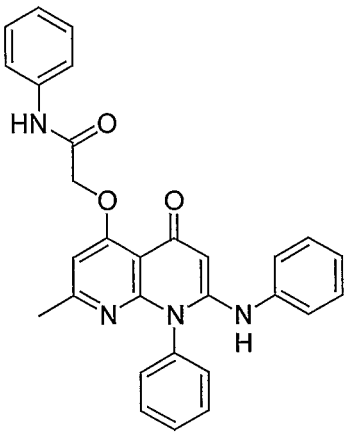
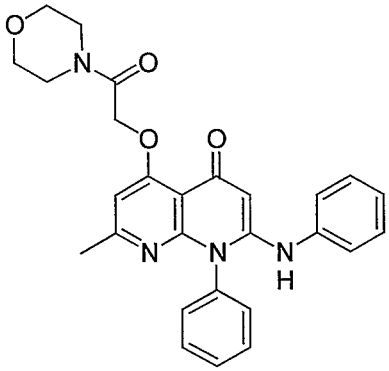
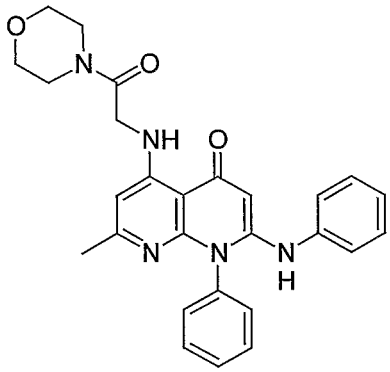
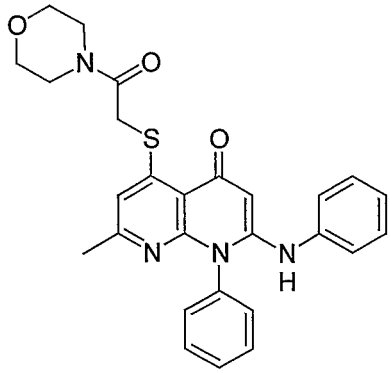
Example	Structure	Representative Procedure
386		Intermediate S, T, V, X and Example 15
387		Intermediate A, B, C, D, E and Example 2
388		Intermediate S, T, V and Example 15
389		Intermediate S, T, V and Example 15
390		Intermediate S, T, V, X and Example 15
391		Intermediate S, T, V, X and Example 15

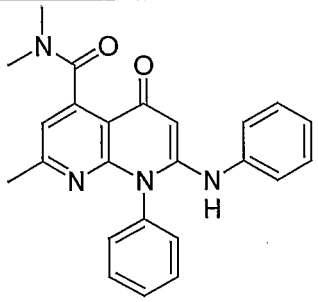
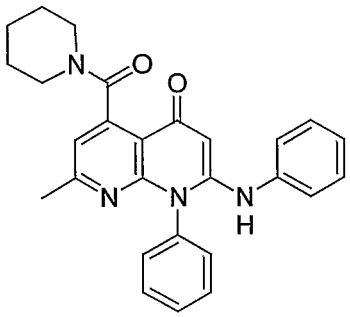
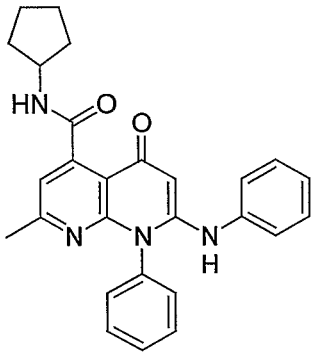
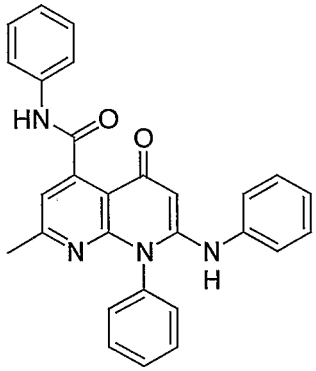
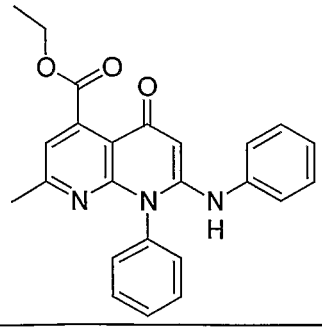
Example	Structure	Representative Procedure
392		Intermediate S, T, V and Example 15, 21
393		Intermediate S, T, V and Example 15, 21
394		Intermediate S, T, V and Example 15, 21
395		Intermediate A, B, C, D, E and Example 1, 12
396		Intermediate Z, AA, AB and Example 16, 17, 7, 19
397		Intermediate Z, AA, AB and Example 16, 17, 18

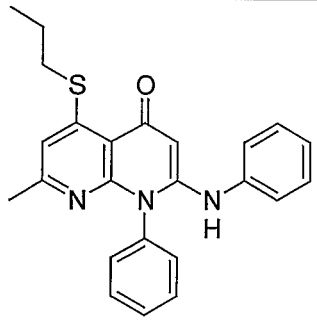
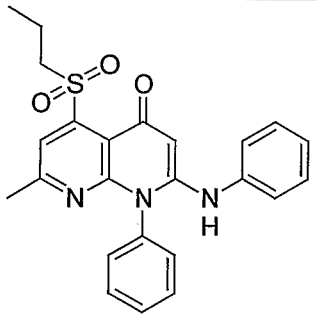
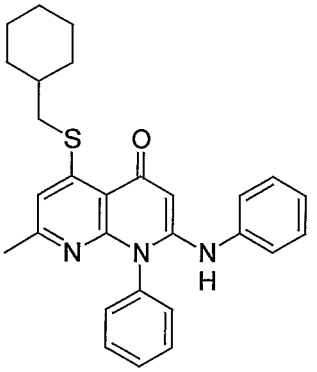
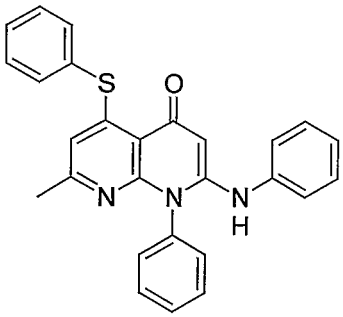
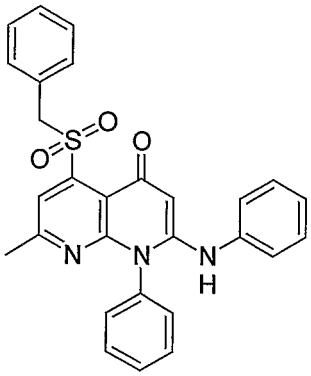
Example	Structure	Representative Procedure
398		Intermediate Z, AA, AB and Example 16, 2
399		Intermediate Z, AA, AB and Example 16, 2
400		Intermediate Z, AA, AB and Example 16, 2, 13
401		Intermediate Z, AA, AB and Example 16, 2

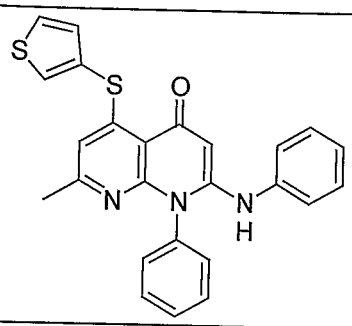
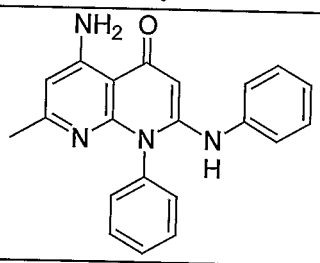
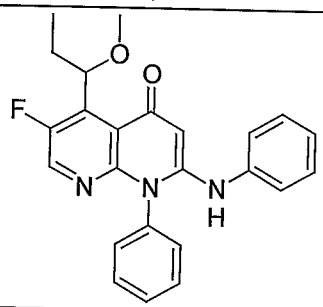
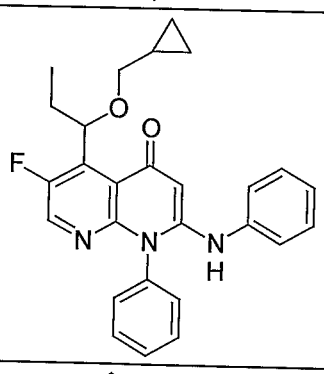
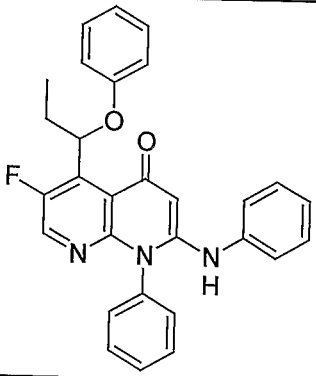
Example	Structure	Representative Procedure
402		Intermediate Z, AA, AB and Example 16, 2
403		Intermediate Z, AA, AB and Example 16, 9
404		Intermediate A, B, C, D, E and Example 1, 10, 11
405		Intermediate A, B, C, D, E and Example 1, 10, 11

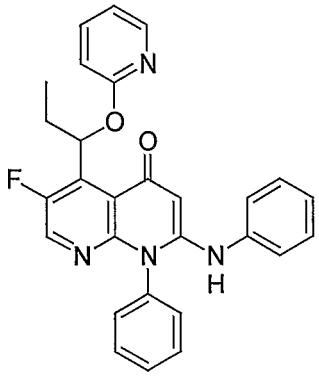
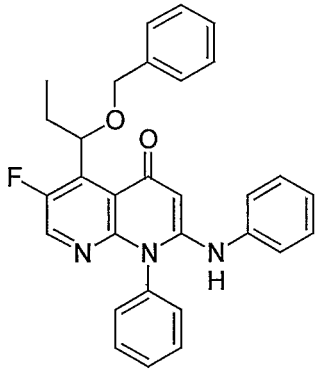
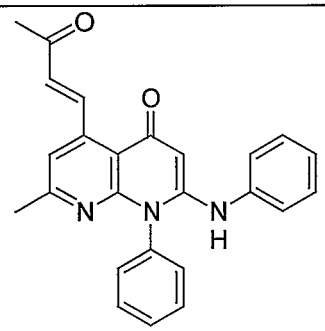
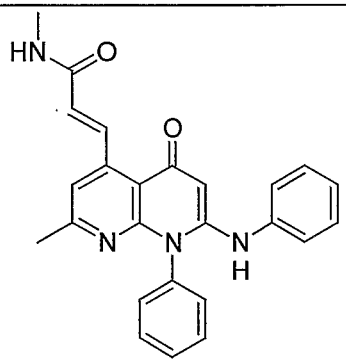
Example	Structure	Representative Procedure
406		Intermediate A, B, C, D, E and Example 1, 10, 11
407		Intermediate A, B, C, D, E and Example 1, 10, 11
408		Intermediate Z, AA, AB and Example 16, 2, 7, 13
409		Intermediate Z, AA, AB and Example 16, 6, 7, 13

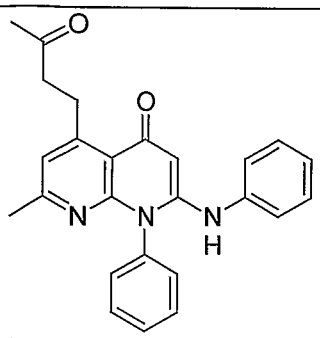
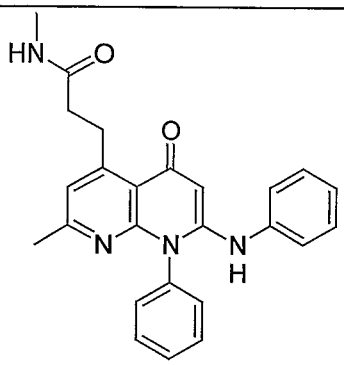
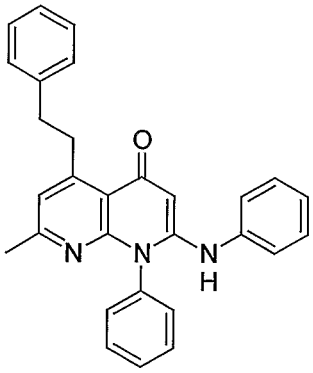
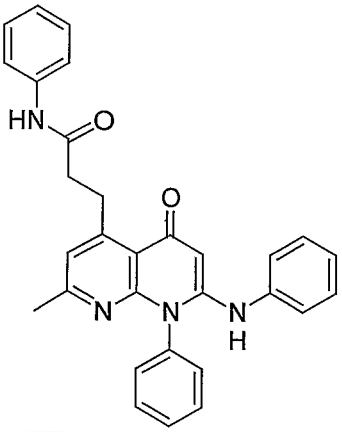
Example	Structure	Representative Procedure
410		Intermediate Z, AA, AB and Example 16, 9, 7, 13
411		Intermediate Z, AA, AB and Example 16, 9, 7, 13
412		Intermediate Z, AA, AB and Example 16, 2, 7, 13
413		Intermediate Z, AA, AB and Example 16, 6, 7, 13

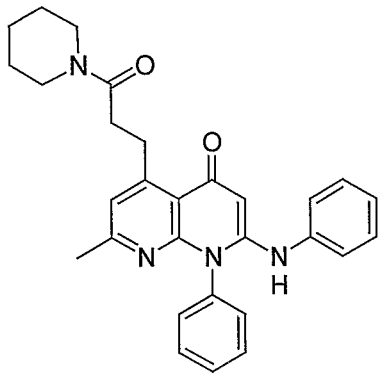
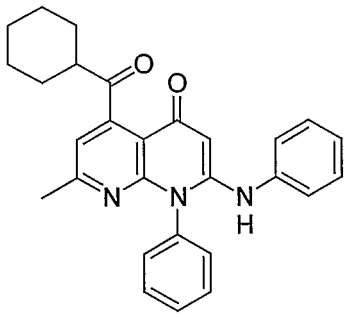
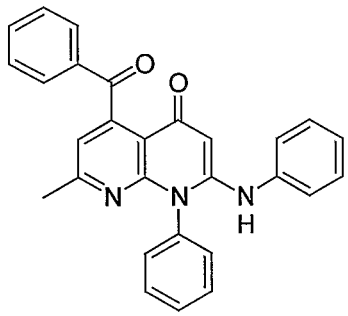
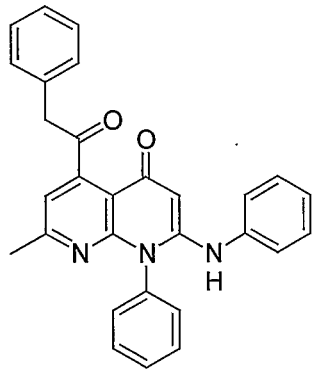
Example	Structure	Representative Procedure
414		Intermediate Z, AA, AB and Example 16, 17, 7, 13
415		Intermediate Z, AA, AB and Example 16, 17, 7, 13
416		Intermediate Z, AA, AB and Example 16, 17, 7, 13
417		Intermediate Z, AA, AB and Example 16, 17, 7, 13
418		Intermediate Z, AA, AB and Example 16, 17

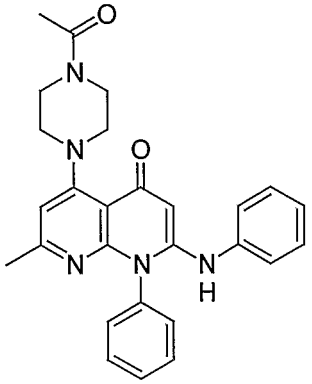
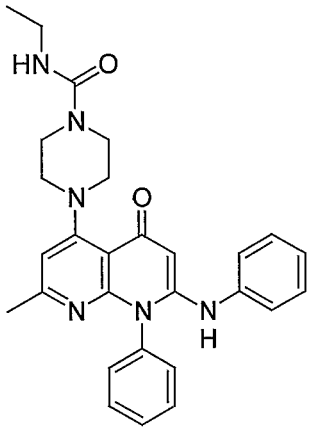
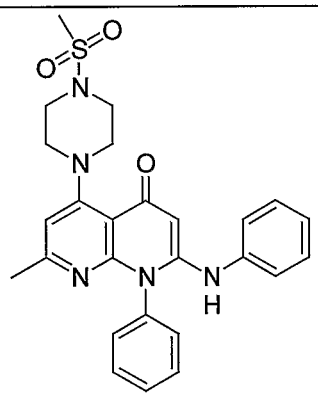
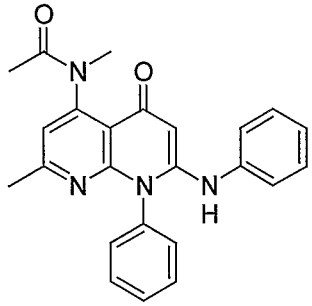
Example	Structure	Representative Procedure
419		Intermediate Z, AA, AB and Example 16, 6
420		Intermediate Z, AA, AB and Example 16, 6, 21
421		Intermediate Z, AA, AB and Example 16, 6
422		Intermediate Z, AA, AB and Example 16, 6
423		Intermediate Z, AA, AB and Example 16, 6, 21

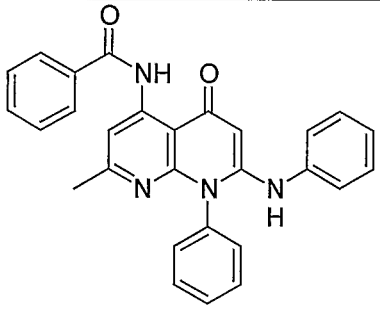
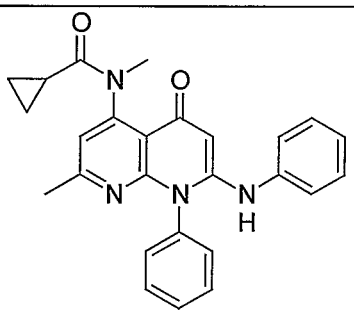
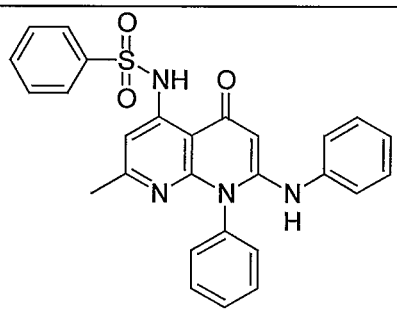
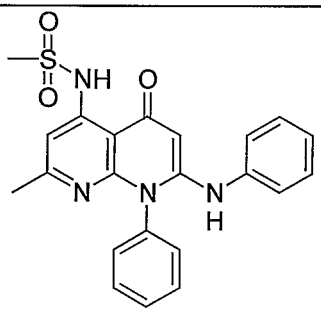
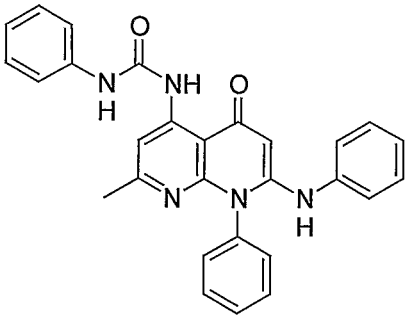
Example	Structure	Representative Procedure
424		Intermediate Z, AA, AB and Example 16, 6
425		Intermediate Z, AA, AB and Example 16, 3, 24
426		Intermediate K, L, M, N, AM and Example 1 and Intermediate AJ
427		Intermediate K, L, M, N, AM and Example 1 and Intermediate AJ
428		Intermediate K, L, M, N, AM and Example 1, 26

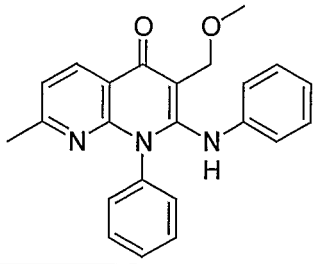
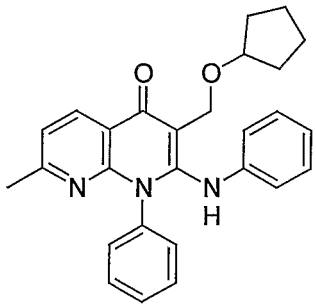
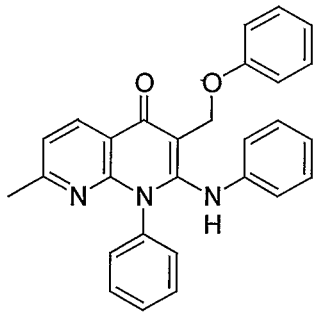
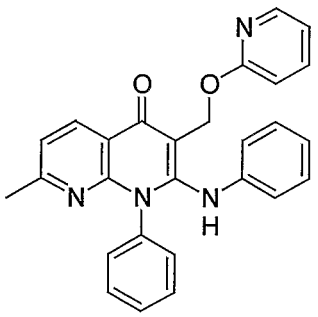
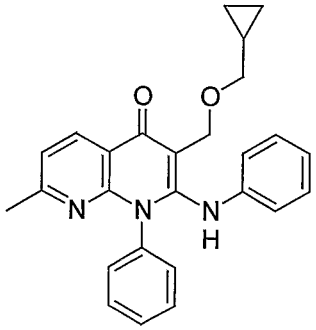
Example	Structure	Representative Procedure
429		Intermediate K, L, M, N, AM and Example 1, 26
430		Intermediate K, L, M, N, AM and Example 1 and Intermediate AJ
431		Intermediate Z, AA, AB and Example 16, 31
432		Intermediate Z, AA, AB and Example 16, 31, 32, 13

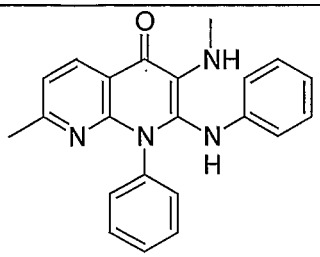
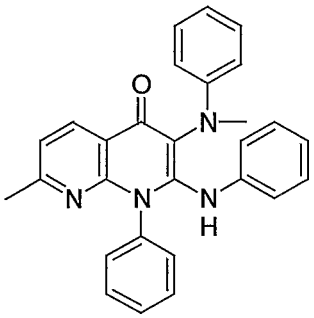
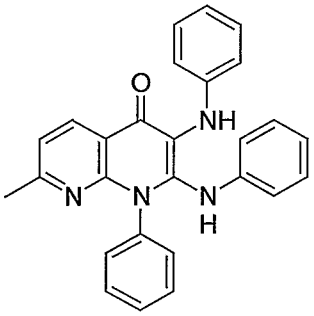
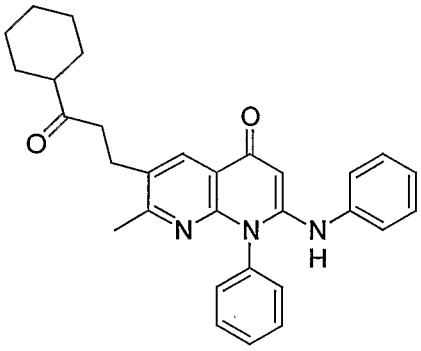
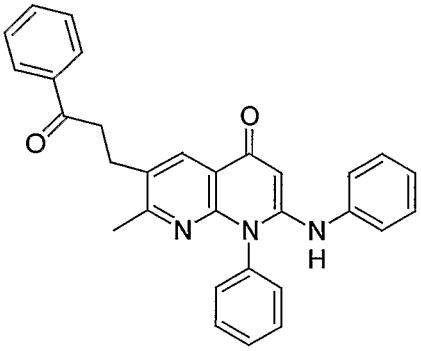
Example	Structure	Representative Procedure
433		Intermediate Z, AA, AB and Example 16, 31, 33
434		Intermediate Z, AA, AB and Example 16, 31, 32, 33, 13
435		Intermediate Z, AA, AB and Example 16, 31, 33
436		Intermediate Z, AA, AB and Example 16, 31, 32, 33, 13

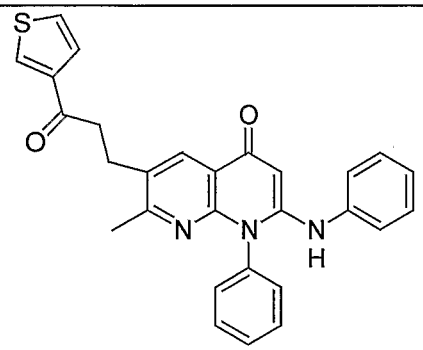
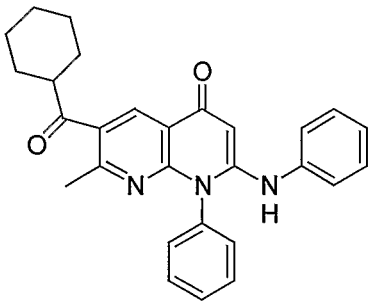
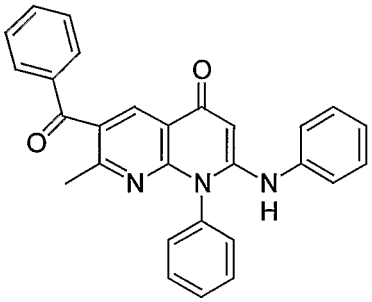
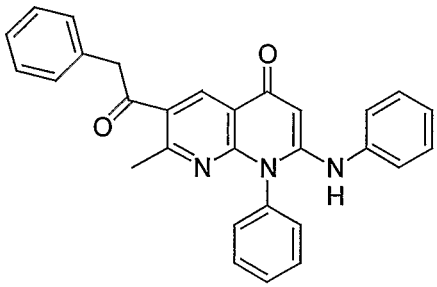
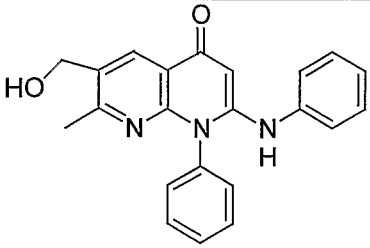
Example	Structure	Representative Procedure
437		Intermediate Z, AA, AB and Example 16, 31, 32, 33, 13
438		Intermediate Z, AA, AB and Example 16, 17, 7, 19, 20
439		Intermediate Z, AA, AB and Example 16, 17, 7, 19, 20
440		Intermediate Z, AA, AB and Example 16, 17, 7, 19, 20

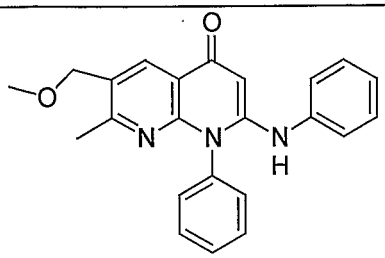
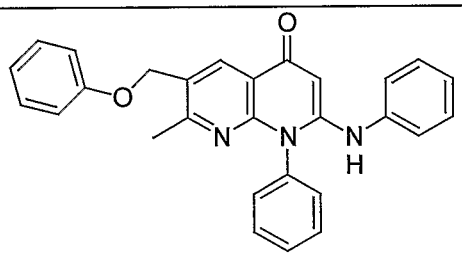
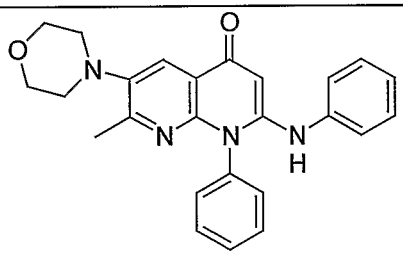
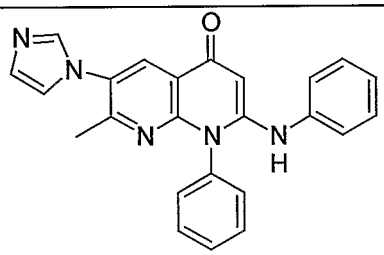
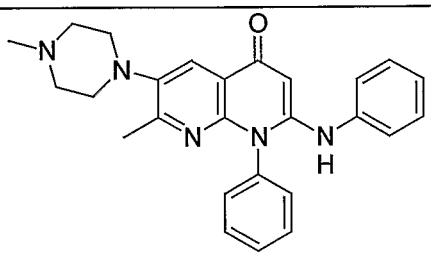
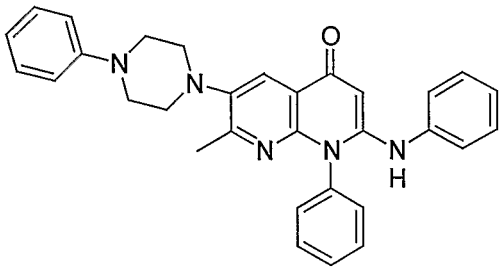
Example	Structure	Representative Procedure
441		Intermediate Z, AA, AB and Example 16, 2, 13
442		Intermediate Z, AA, AB and Example 16, 2 and Intermediate AK
443		Intermediate Z, AA, AB and Example 16, 2, 12
444		Intermediate Z, AA, AB and Example 16, 2, 13

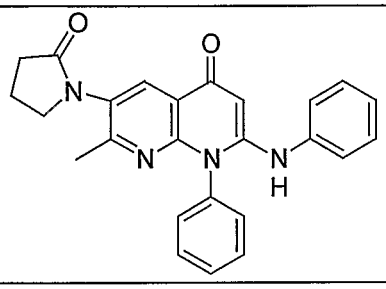
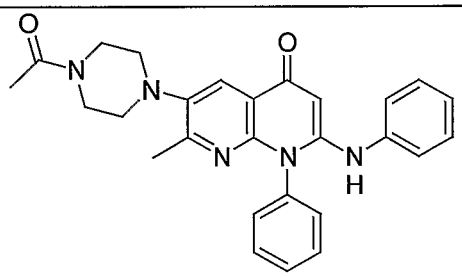
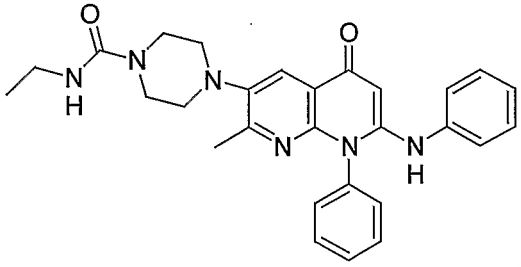
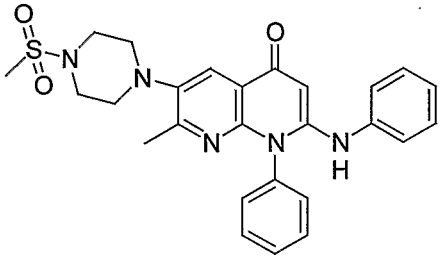
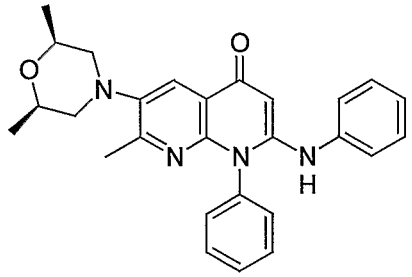
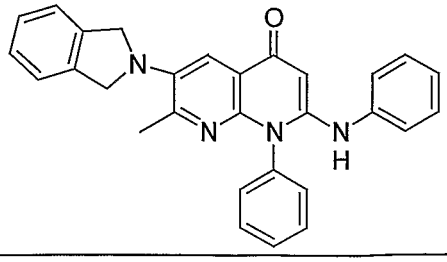
Example	Structure	Representative Procedure
445		Intermediate Z, AA, AB and Example 16, 3, 24, 13
446		Intermediate Z, AA, AB and Example 16, 2, 13
447		Intermediate Z, AA, AB and Example 16, 22
448		Intermediate Z, AA, AB and Example 16, 22
449		Intermediate Z, AA, AB and Example 16, 3, 24 and Intermediate AK

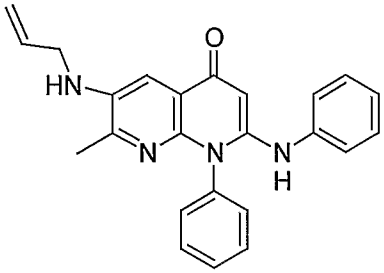
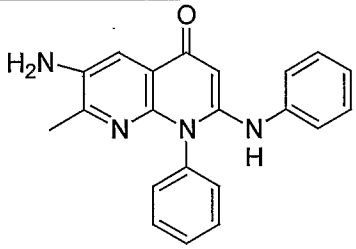
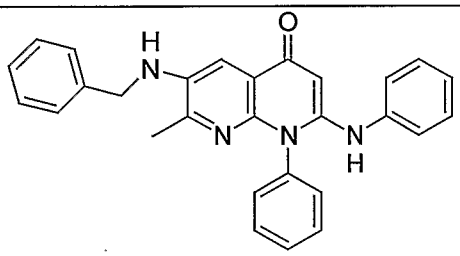
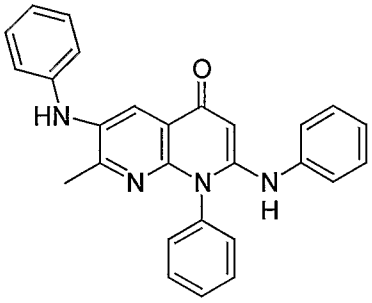
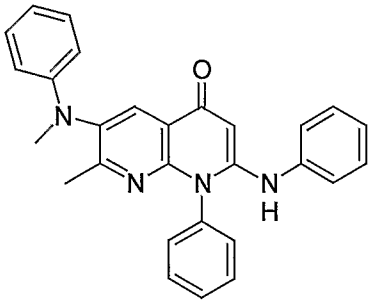
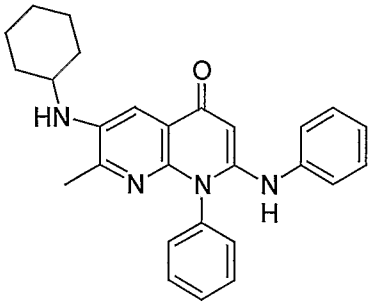
Example	Structure	Representative Procedure
450		Intermediate S, T, U, W and Example 25 and Intermediate AJ
451		Intermediate S, T, U, W and Example 25 and Intermediate AJ
452		Intermediate S, T, U, W and Example 25, 26
453		Intermediate S, T, U, W and Example 25, 26
454		Intermediate S, T, U, W and Example 25 and Intermediate AJ

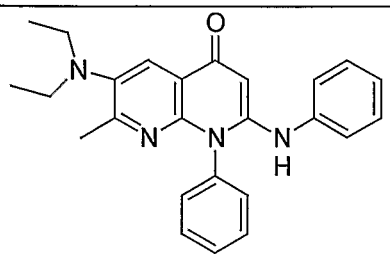
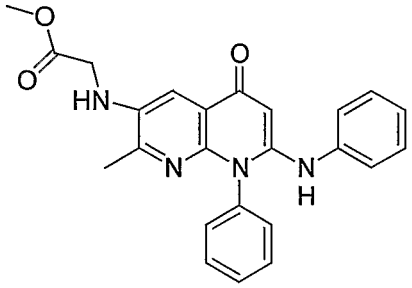
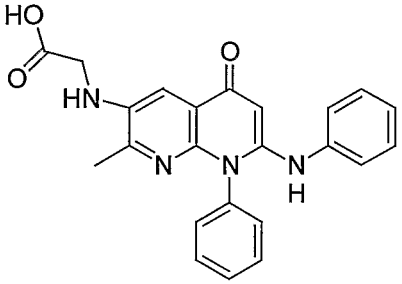
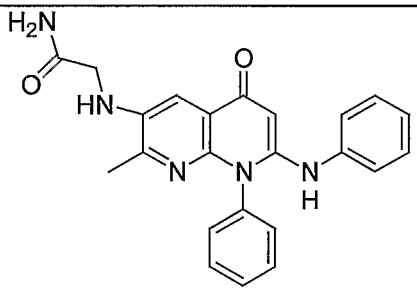
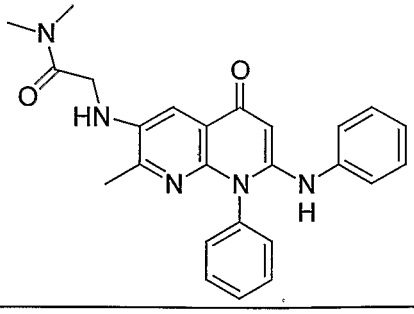
Example	Structure	Representative Procedure
455		Intermediate S, T, U, W and Example 15 and Intermediate AL and Example 3
456		Intermediate S, T, U, W and Example 15 and Intermediate AL and Example 3
457		Intermediate S, T, U, W and Example 15 and Intermediate AL and Example 3
458		Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 19, 20
459		Intermediate Y, S, T, U, W and Example 15, 31, 33

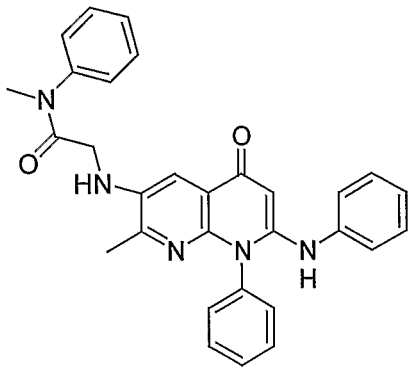
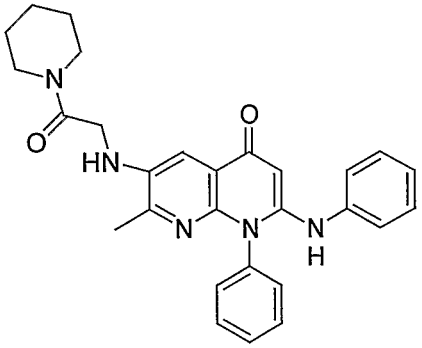
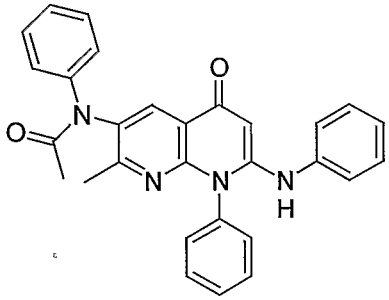
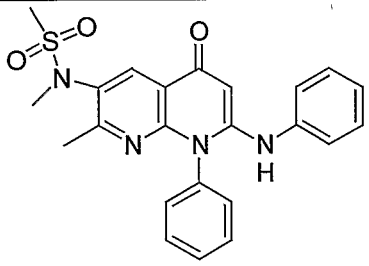
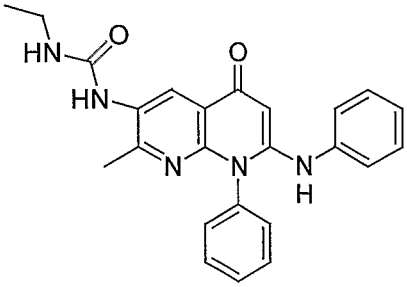
Example	Structure	Representative Procedure
460		Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 19, 20
461		Intermediate Y, S, T, U, W and Example 15, 17, 7, 19, 20
462		Intermediate Y, S, T, U, W and Example 15, 17, 7, 19, 20
463		Intermediate Y, S, T, U, W and Example 15, 17, 7, 19, 20
464		Intermediate Y, S, T, U, W and Example 15, 17, 25

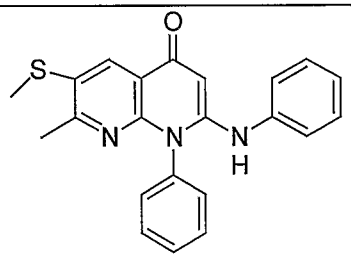
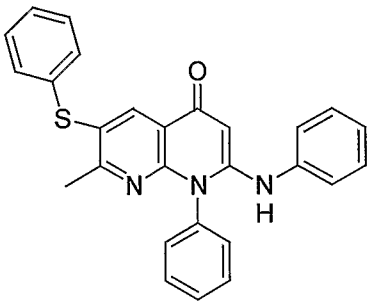
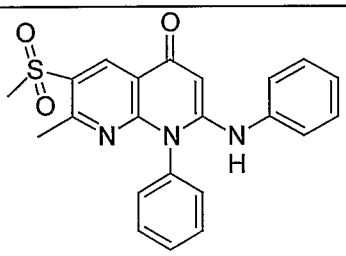
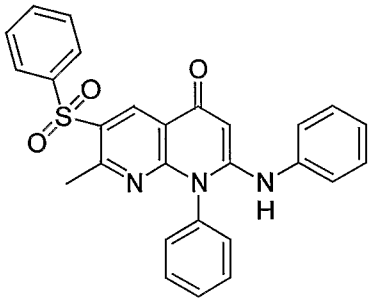
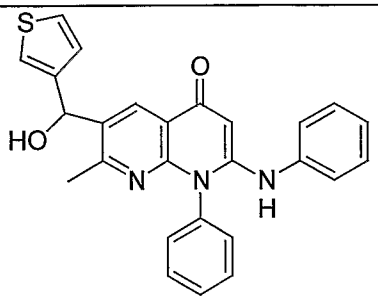
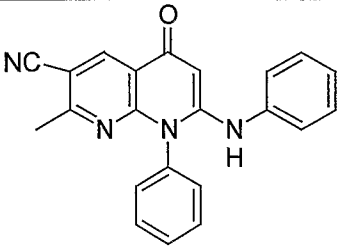
Example	Structure	Representative Procedure
465		Intermediate Y, S, T, U, W and Example 15, 17, 25 and Intermediate AJ
466		Intermediate Y, S, T, U, W and Example 15, 17, 25, 26
467		Intermediate Y, S, T, U, W and Example 15, 3
468		Intermediate Y, S, T, U, W and Example 15, 3
469		Intermediate Y, S, T, U, W and Example 15, 3
470		Intermediate Y, S, T, U, W and Example 15, 3

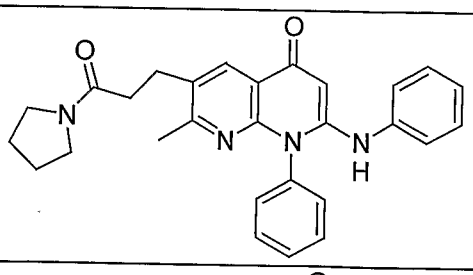
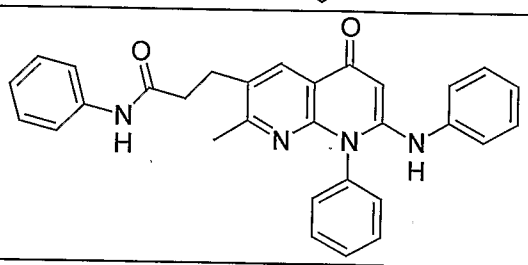
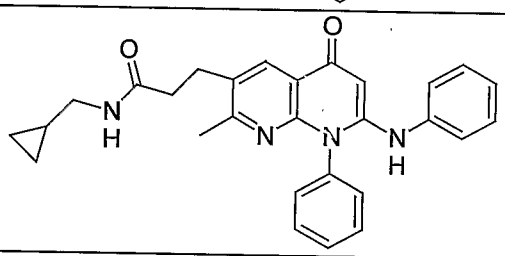
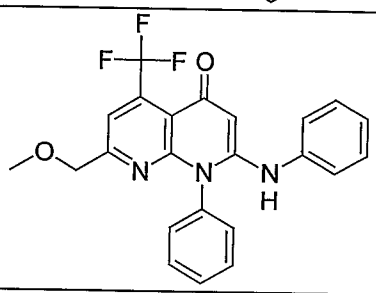
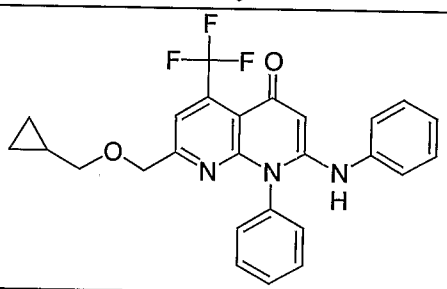
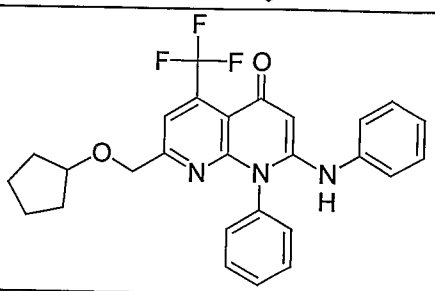
Example	Structure	Representative Procedure
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472		Intermediate Y, S, T, U, W and Example 15, 3, 13
473		Intermediate Y, S, T, U, W and Example 15, 3 and Intermediate AK
474		Intermediate Y, S, T, U, W and Example 15, 3, 12
475		Intermediate Y, S, T, U, W and Example 15, 3
476		Intermediate Y, S, T, U, W and Example 15, 3

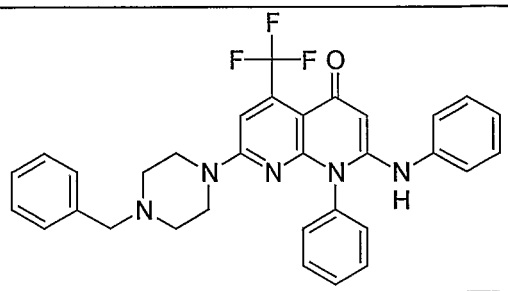
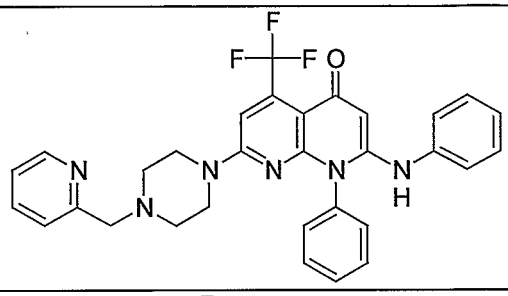
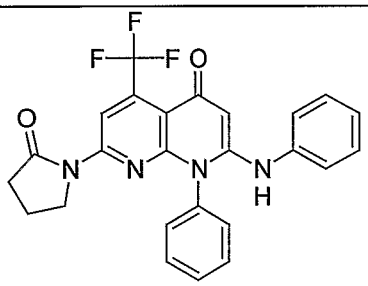
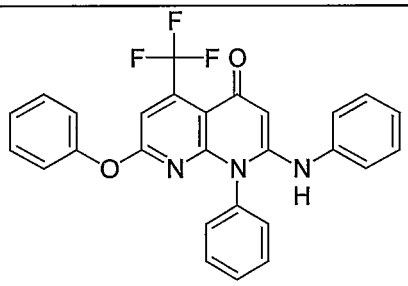
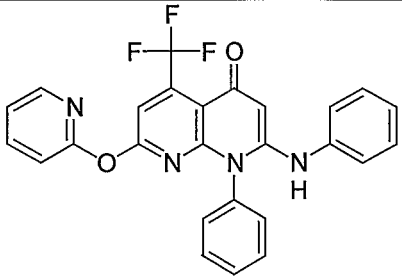
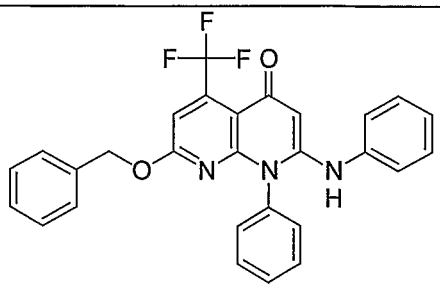
Example	Structure	Representative Procedure
477		Intermediate Y, S, T, U, W and Example 15, 3
478		Intermediate Y, S, T, U, W and Example 15, 3, 24
479		Intermediate Y, S, T, U, W and Example 15, 3
480		Intermediate Y, S, T, U, W and Example 15, 3
481		Intermediate Y, S, T, U, W and Example 15, 3
482		Intermediate Y, S, T, U, W and Example 15, 3

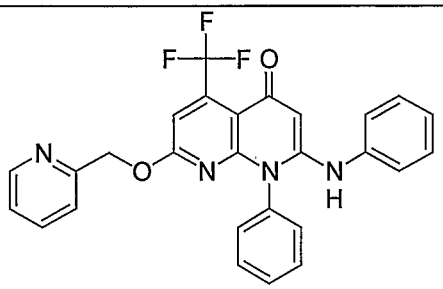
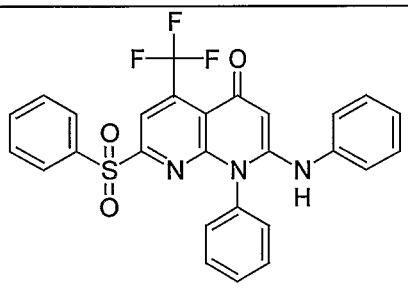
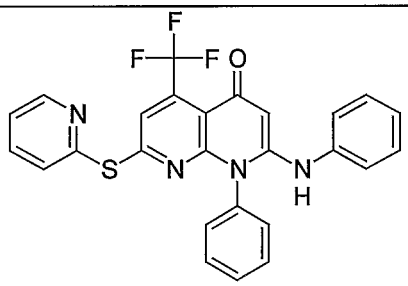
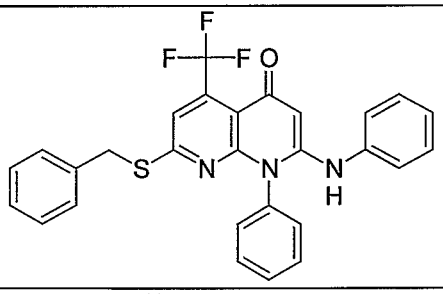
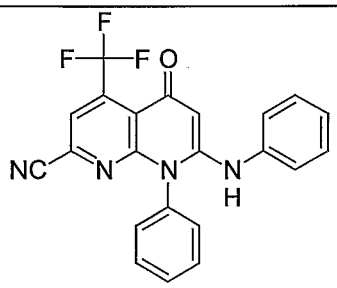
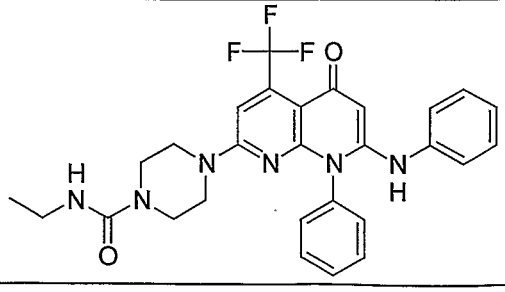
Example	Structure	Representative Procedure
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484		Intermediate Y, S, T, U, W and Example 15, 3
485		Intermediate Y, S, T, U, W and Example 15, 3, 7
486		Intermediate Y, S, T, U, W and Example 15, 3, 18
487		Intermediate Y, S, T, U, W and Example 15, 3, 7, 13

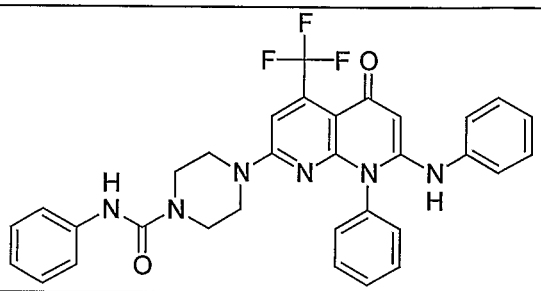
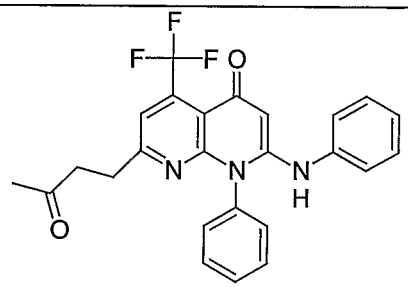
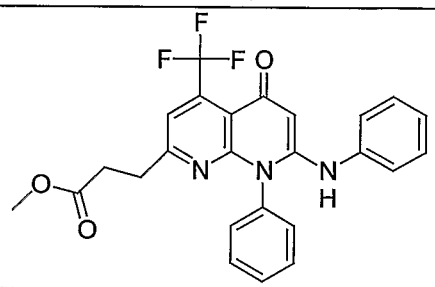
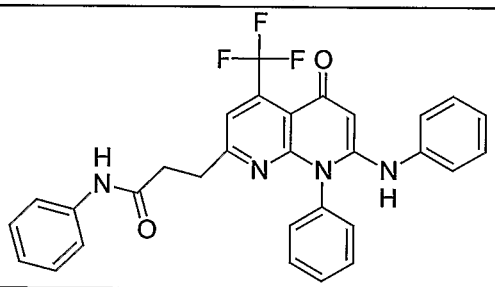
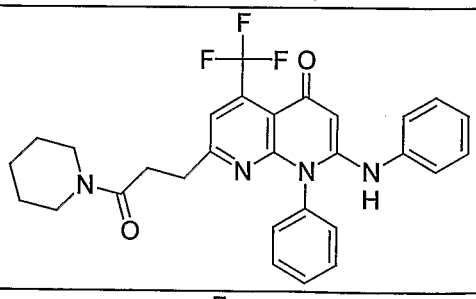
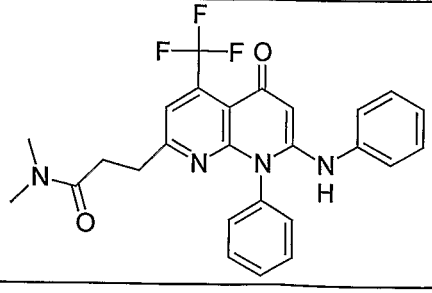
Example	Structure	Representative Procedure
488		Intermediate Y, S, T, U, W and Example 15, 3, 7, 13
489		Intermediate Y, S, T, U, W and Example 15, 3, 7, 13
490		Intermediate Y, S, T, U, W and Example 15, 3, 13
491		Intermediate Y, S, T, U, W and Example 15, 3, 12
492		Intermediate Y, S, T, U, W and Example 15, 3, 24 and Intermediate AK

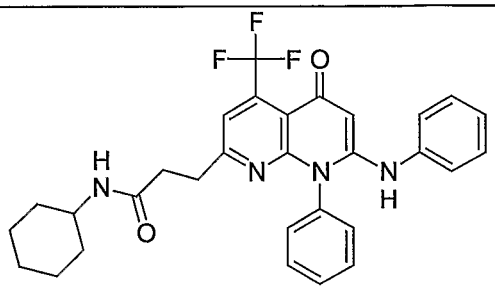
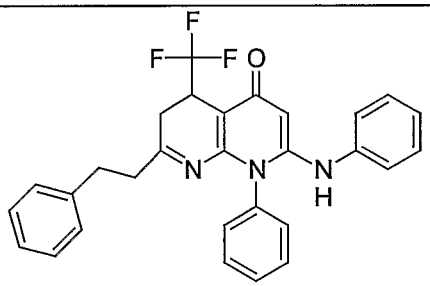
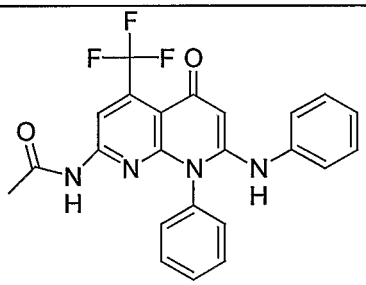
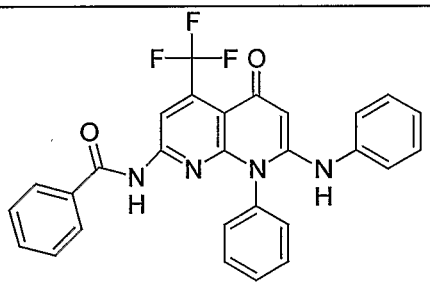
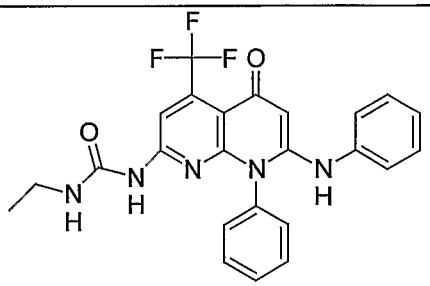
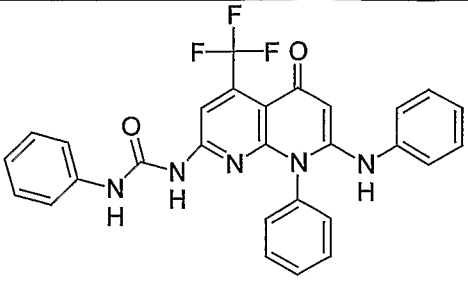
Example	Structure	Representative Procedure
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494		Intermediate Y, S, T, U, W and Example 15, 34
495		Intermediate Y, S, T, U, W and Example 15, 34, 21
496		Intermediate Y, S, T, U, W and Example 15, 34, 21
497		Intermediate Y, S, T, U, W and Example 15, 34
498		Intermediate S, T, U, W and Example 15

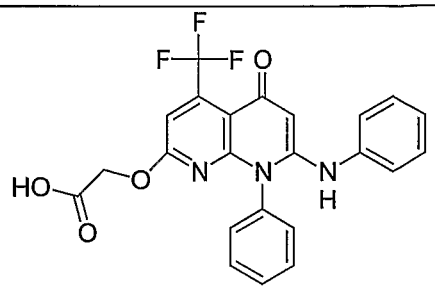
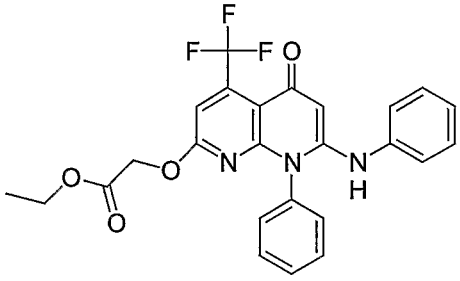
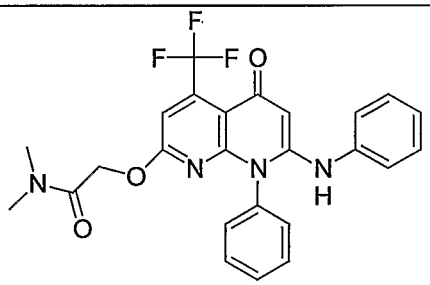
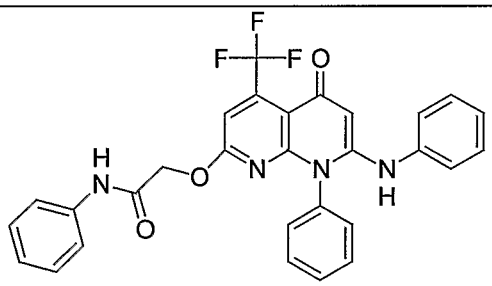
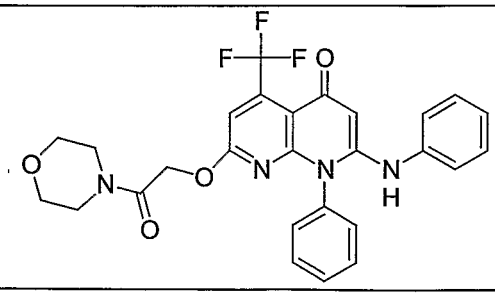
Example	Structure	Representative Procedure
499		Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13
500		Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13
501		Intermediate Y, S, T, U, W and Example 15, 31, 32, 33, 13
502		Intermediate F, G, H, I, J and Example 17, 25 and Intermediate AJ
503		Intermediate F, G, H, I, J and Example 17, 25 and Intermediate AJ
504		Intermediate F, G, H, I, J and Example 17, 25 and Intermediate AJ

Example	Structure	Representative Procedure
505		Intermediate F, G, H, I, J and Example 8
506		Intermediate F, G, H, I, J and Example 8
507		Intermediate F, G, H, I, J and Example 8
508		Intermediate F, G, H, I, J and Example 9
509		Intermediate F, G, H, I, J and Example 9
510		Intermediate F, G, H, I, J and Example 9

Example	Structure	Representative Procedure
511		Intermediate F, G, H, I, J and Example 9
512		Intermediate F, G, H, I, J and Example 6, 21
513		Intermediate F, G, H, I, J and Example 6
514		Intermediate F, G, H, I, J and Example 6
515		Intermediate F, G, H, I, J and Example 9
516		Intermediate F, G, H, I, J and Example 8 and Intermediate AK

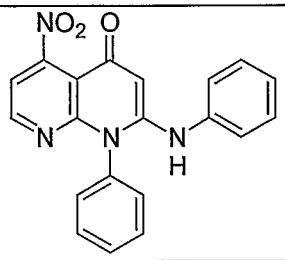
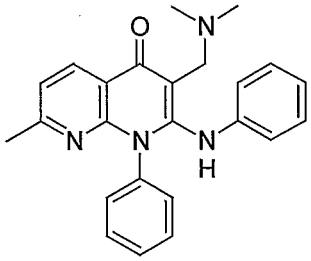
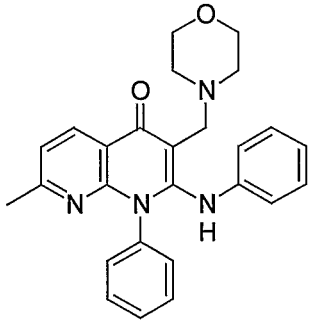
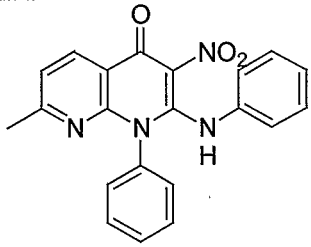
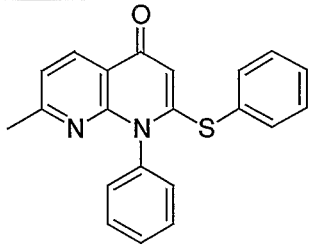
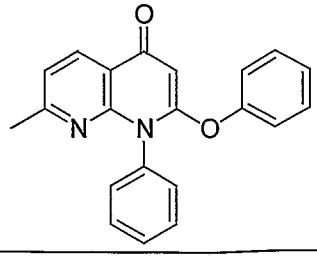
Example	Structure	Representative Procedure
517		Intermediate F, G, H, I, J and Example 8 and Intermediate AK
518		Intermediate F, G, H, I, J and Example 31, 33
519		Intermediate F, G, H, I, J and Example 31, 33
520		Intermediate F, G, H, I, J and Example 31, 32, 33, 13
521		Intermediate F, G, H, I, J and Example 31, 32, 33, 13
522		Intermediate F, G, H, I, J and Example 31, 32, 33, 13

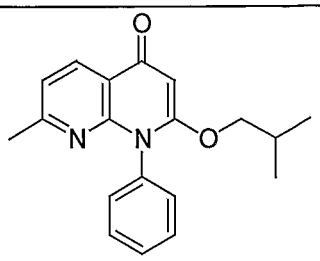
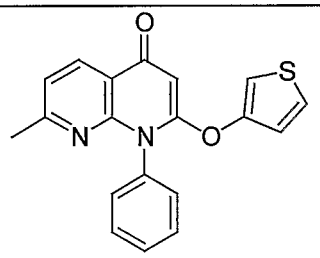
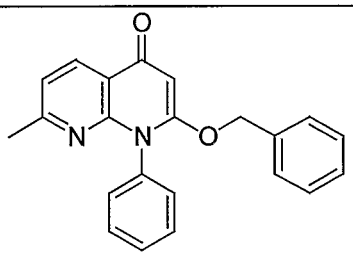
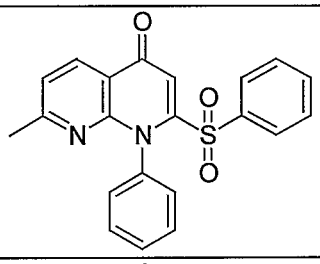
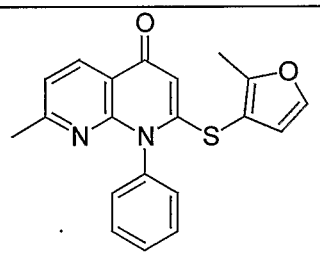
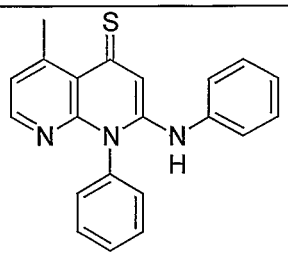
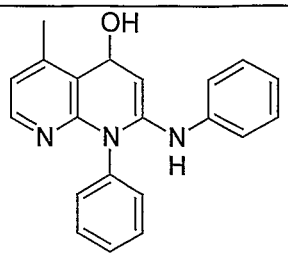
Example	Structure	Representative Procedure
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524		Intermediate F, G, H, I, J and Example 31, 33
525		Intermediate F, G, H, I, J and Example 3, 24, 13
526		Intermediate F, G, H, I, J and Example 3, 24, 13
527		Intermediate F, G, H, I, J and Example 3, 24 and Intermediate AK
528		Intermediate F, G, H, I, J and Example 3, 24 and Intermediate AK

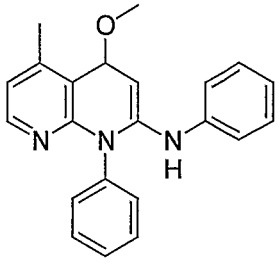
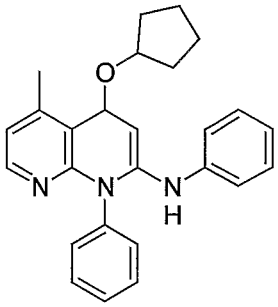
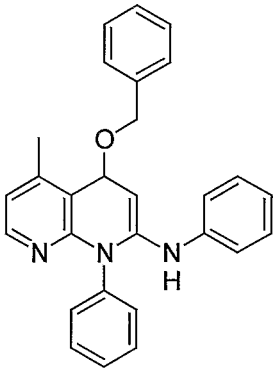
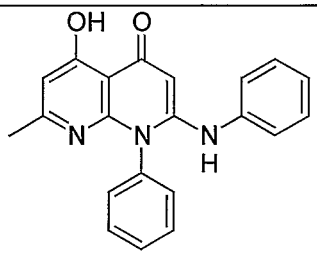
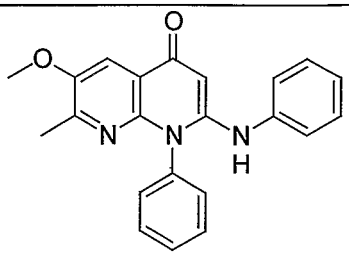
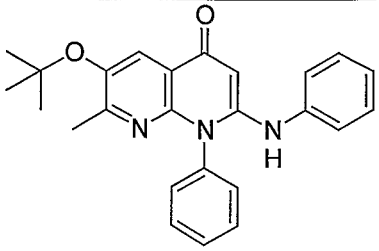
Example	Structure	Representative Procedure
529		Intermediate F, G, H, I, J and Example 9, 7
530		Intermediate F, G, H, I, J and Example 9
531		Intermediate F, G, H, I, J and Example 9, 7, 13
532		Intermediate F, G, H, I, J and Example 9, 7, 13
533		Intermediate F, G, H, I, J and Example 9, 7, 13

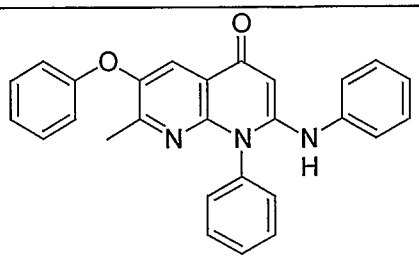
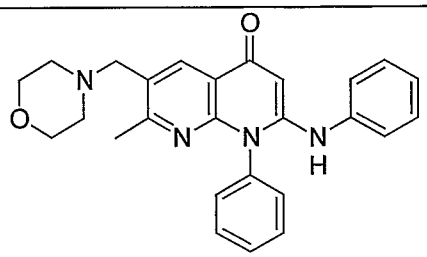
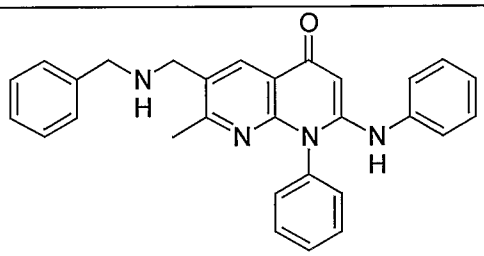
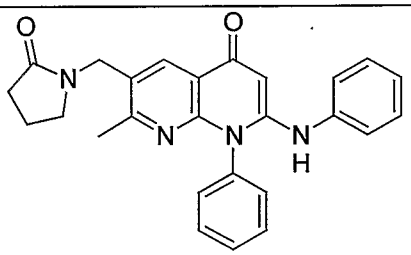
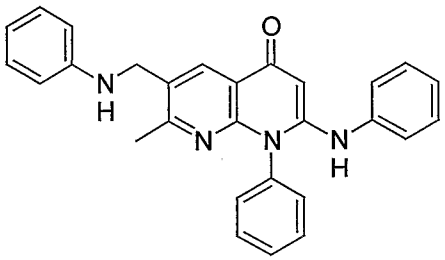
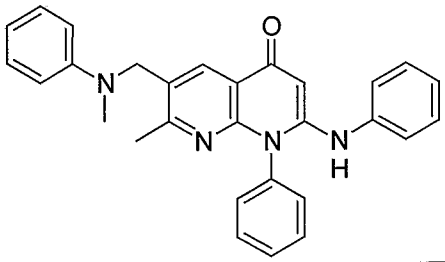
Utilizing the above described procedures for intermediates and examples and Flow Diagrams I - XIV alone or in combination, a variety of Formula I compounds can be prepared using the appropriate starting material. These compounds are summarized in Table 1C.

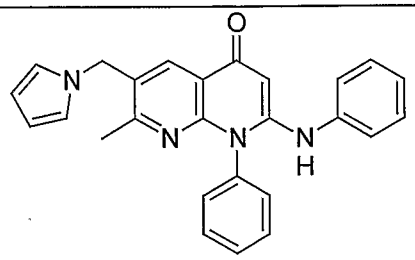
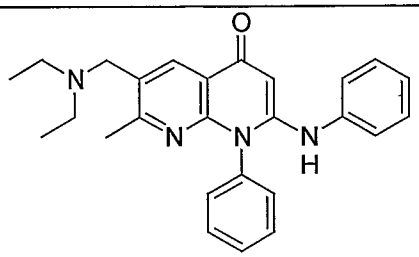
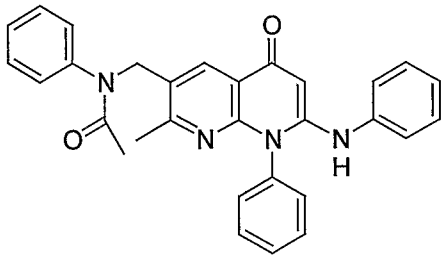
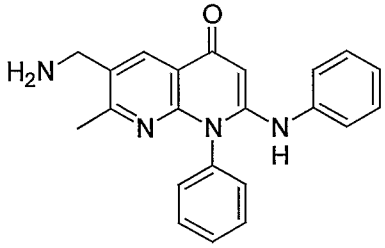
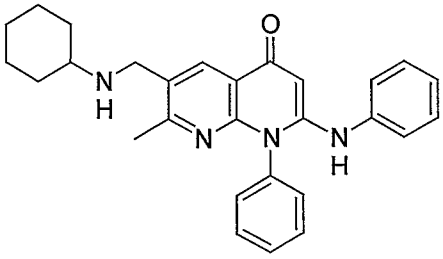
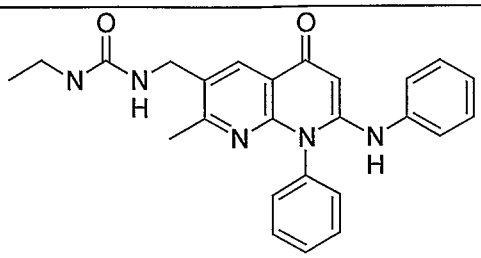
Table 1C

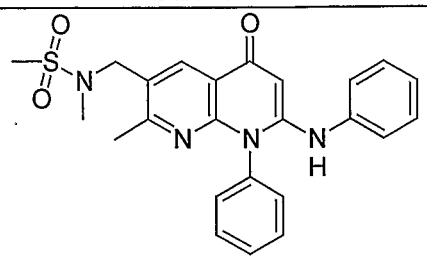
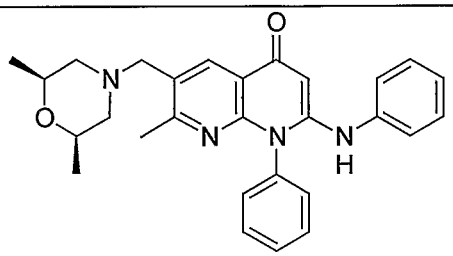
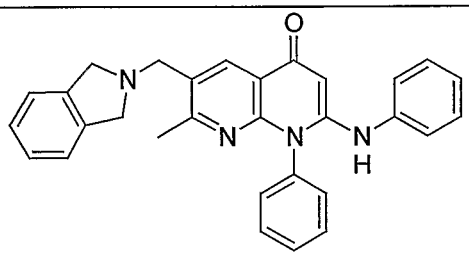
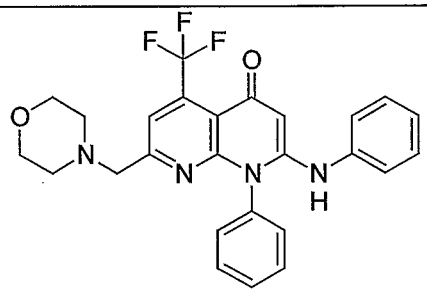
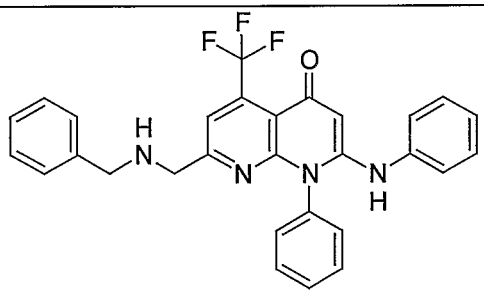
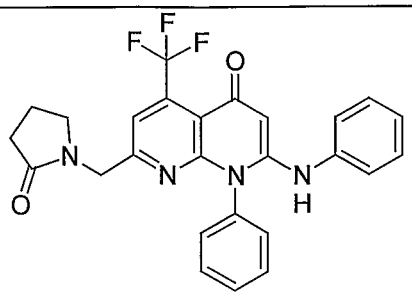
Example	Structure
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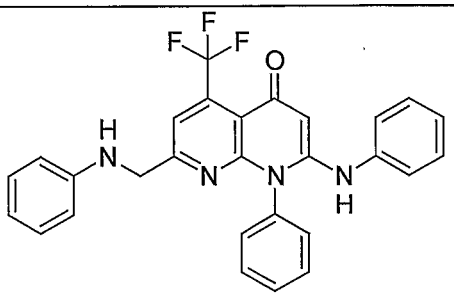
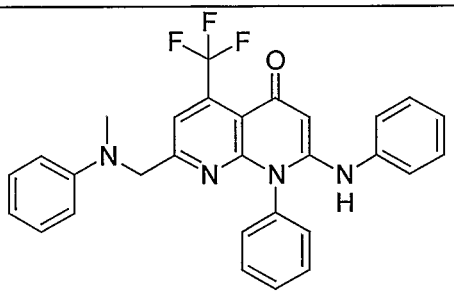
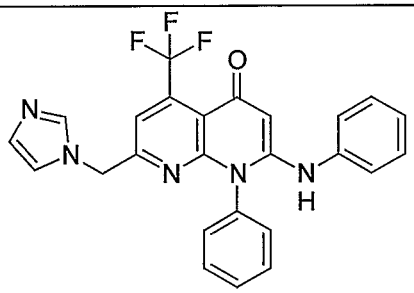
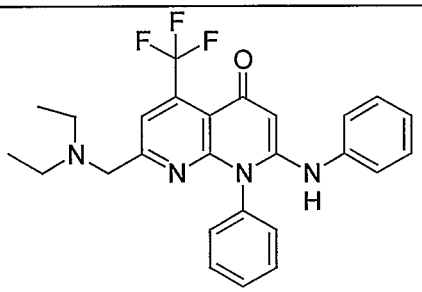
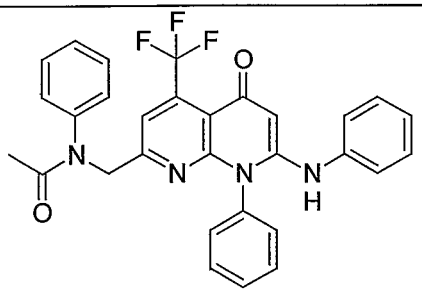
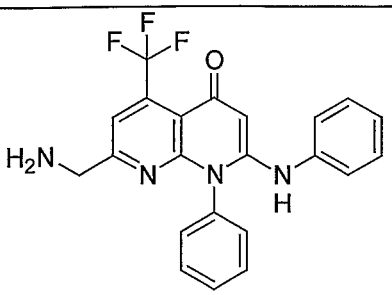
Example	Structure
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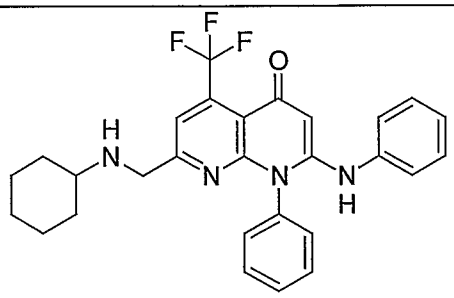
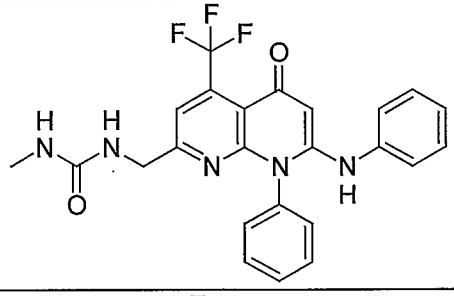
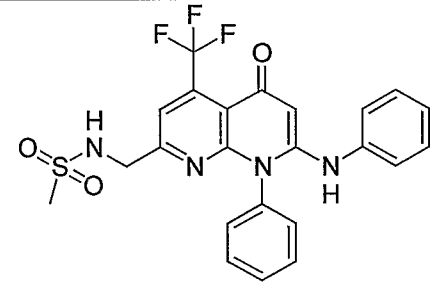
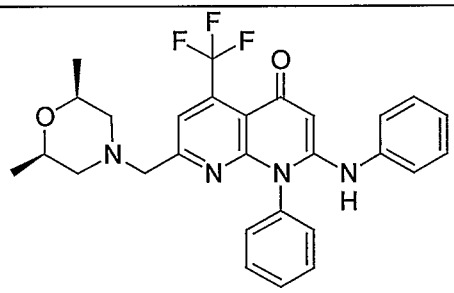
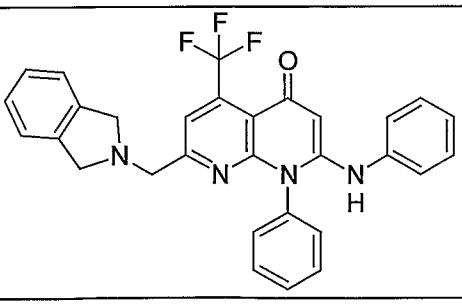
Example	Structure
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Example	Structure
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Example	Structure
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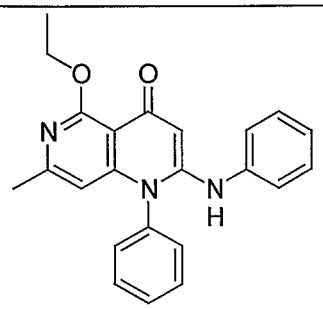
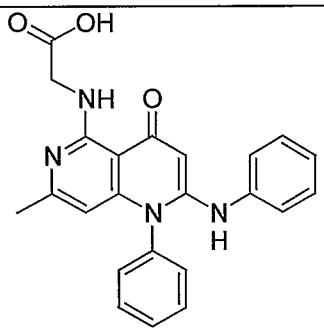
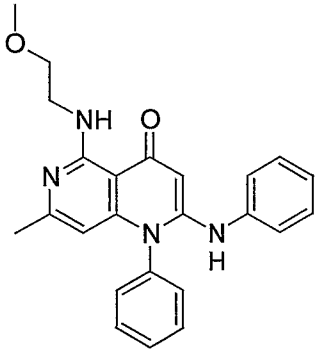
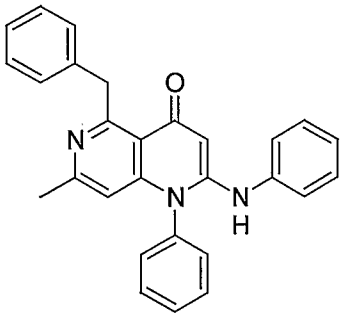
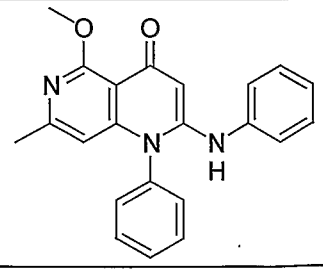
Example	Structure
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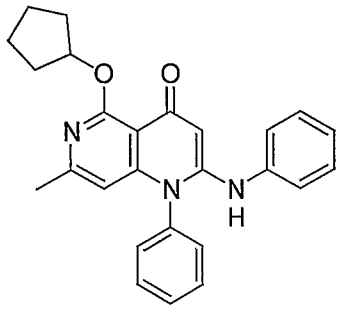
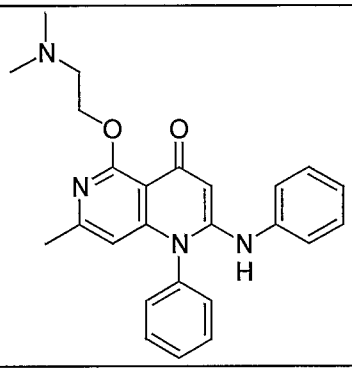
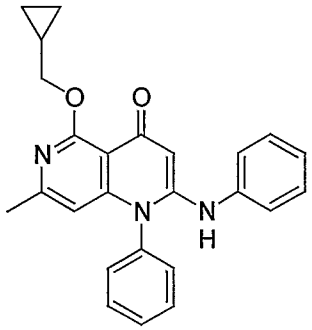
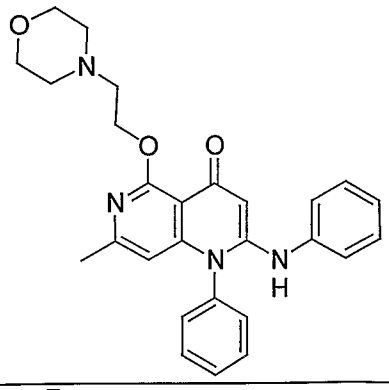
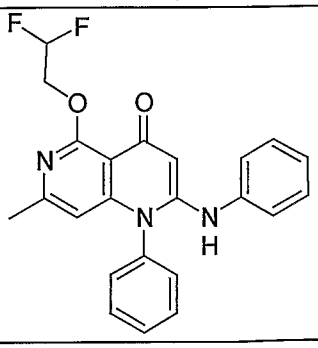
Example	Structure
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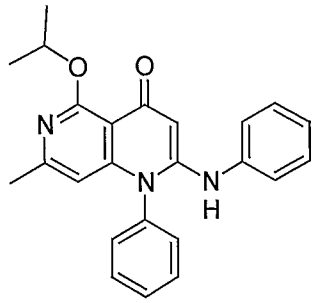
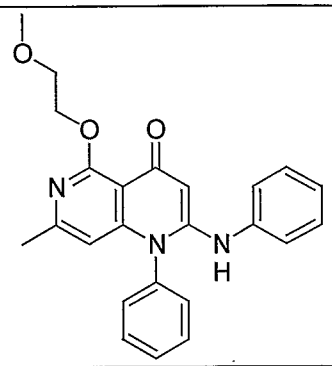
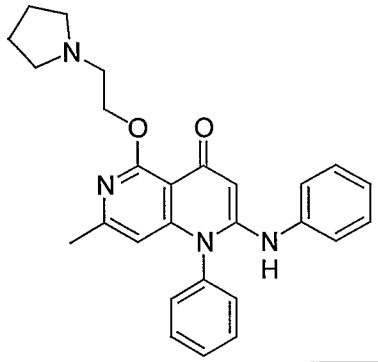
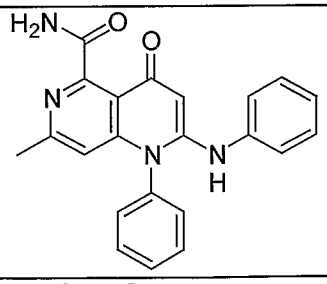
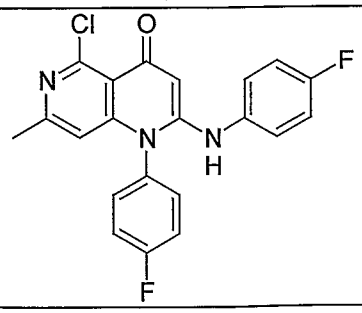
Example	Structure
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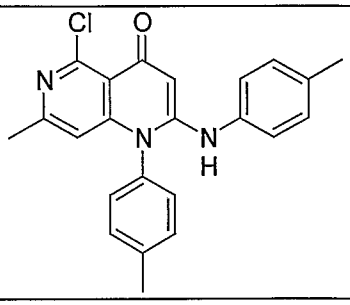
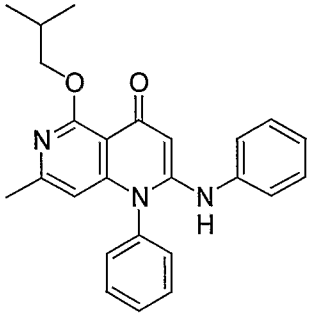
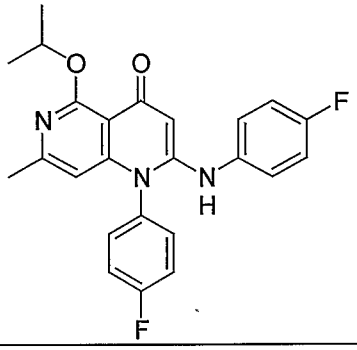
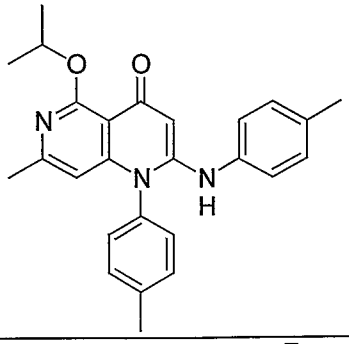
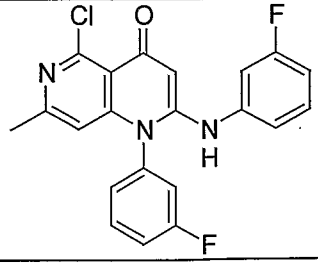
Utilizing the above described procedures for intermediates and examples alone or in combination, a variety of Formula II compounds were prepared using the appropriate starting material and the representative procedure described. These results are summarized in Table 2A.

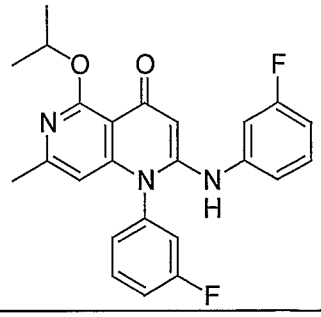
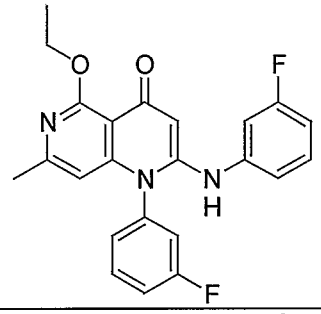
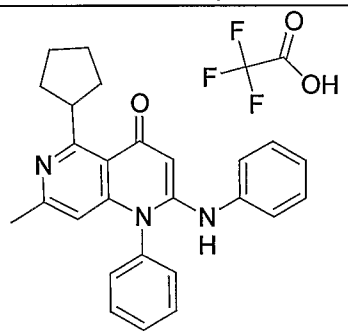
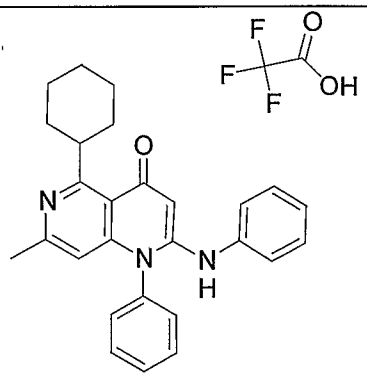
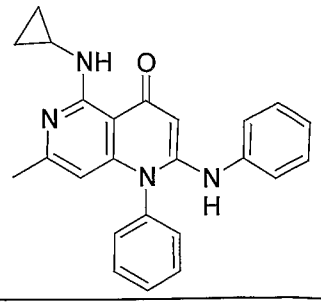
Table 2A

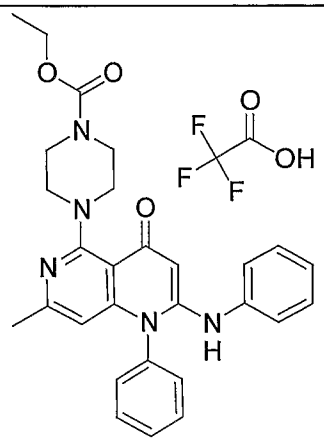
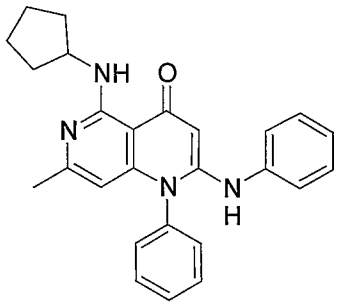
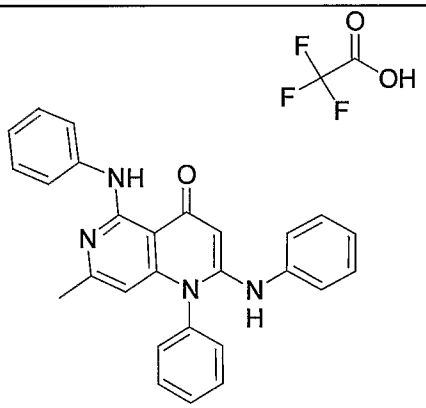
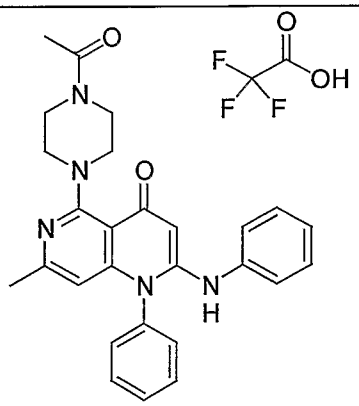
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
582		2.39	372.3	Intermediate BA, BB, BC and Example 39, 48
583		2.05	401.2	Intermediate BA, BB, BC and Example 39, 46, 45
584		1.93	401.3	Intermediate BA, BB, BC and Example 39, 43
585		2.04	418.3	Intermediate BA, BB, BC and Example 39, 42
586		2.25	358.4	Intermediate BA, BB, BC and Example 39, 48

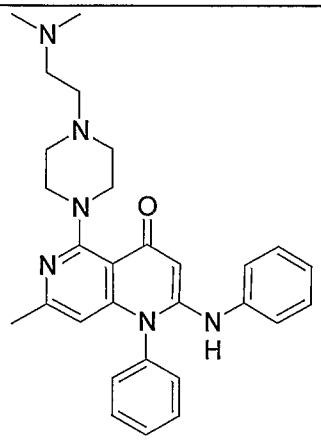
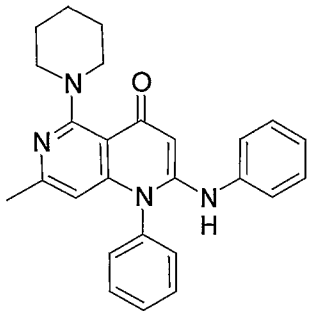
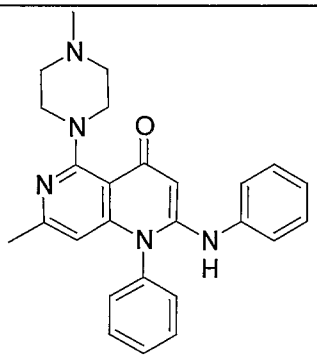
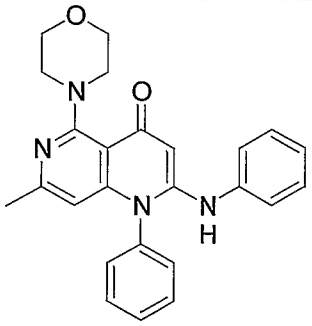
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
587		2.89	412.1	Intermediate BA, BB, BC and Example 39, 48
588		1.89	415.3	Intermediate BA, BB, BC and Example 39, 48
589		2.57	398.3	Intermediate BA, BB, BC and Example 39, 48
590		1.92	457.2	Intermediate BA, BB, BC and Example 39, 48
591		2.41	408.4	Intermediate BA, BB, BC and Example 39, 48

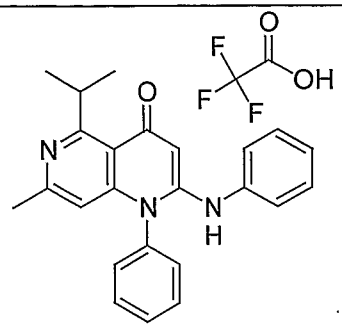
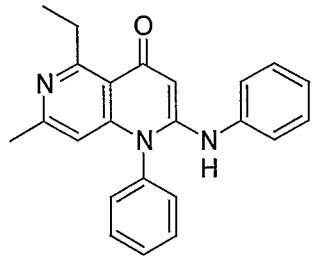
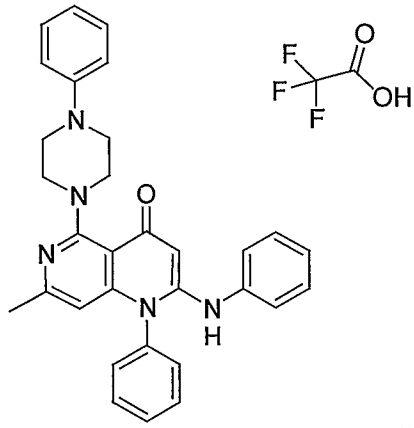
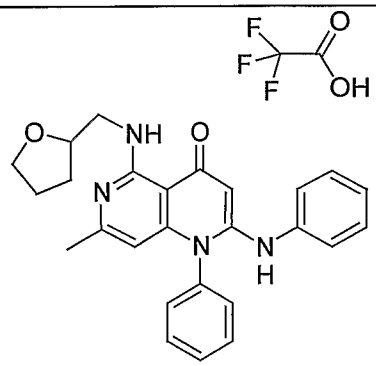
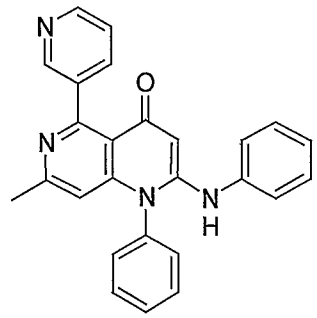
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
592		2.52	386.1	Intermediate BA, BB, BC and Example 39, 48
593		2.46	402.2	Intermediate BA, BB, BC and Example 39, 48
594		2.12	441.1	Intermediate BA, BB, BC and Example 39, 48
595		1.79	371.9	Intermediate BA, BB, BC and Example 39, 49, 47
596		2.36	398.3	Intermediate BA, BB, BC and Example 39

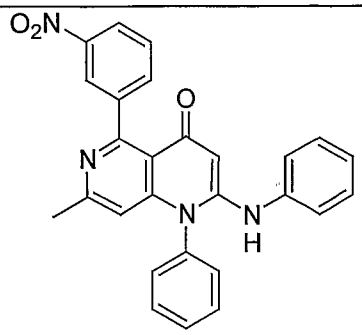
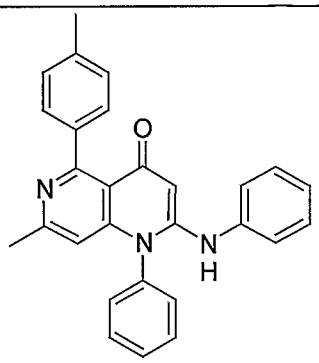
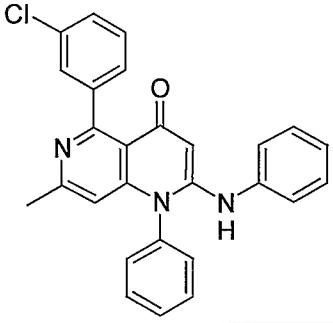
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
597		2.57	390.4	Intermediate BA, BB, BC and Example 39
598		3.28	400.2	Intermediate BA, BB, BC and Example 39, 48
599		2.56	422.0	Intermediate BA, BB, BC and Example 39, 48
600		2.74	414.1	Intermediate BA, BB, BC and Example 39, 48
601		2.43	398.4	Intermediate BA, BB, BC and Example 39

Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
602		2.57	422.1	Intermediate BA, BB, BC and Example 39, 48
603		2.45	408.2	Intermediate BA, BB, BC and Example 39, 48
604		2.02	396.3	Intermediate BA, BB, BC and Example 39, 42
605		2.15	410.3	Intermediate BA, BB, BC and Example 39, 42
606		1.96	383.3	Intermediate BA, BB, BC and Example 39, 43

Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
607		2.20	484.3	Intermediate BA, BB, BC and Example 39, 43
608		2.19	411.3	Intermediate BA, BB, BC and Example 39, 43
609		2.33	419.4	Intermediate BA, BB, BC and Example 39, 43
610		1.86	454.3	Intermediate BA, BB, BC and Example 39, 43

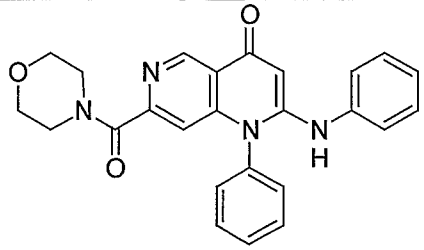
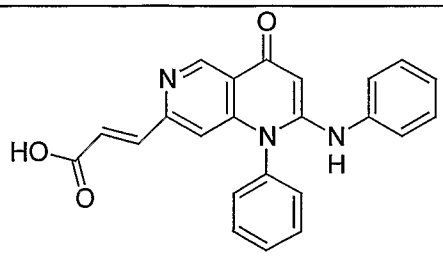
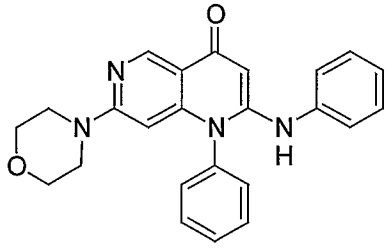
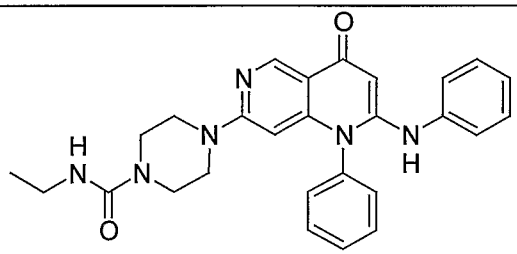
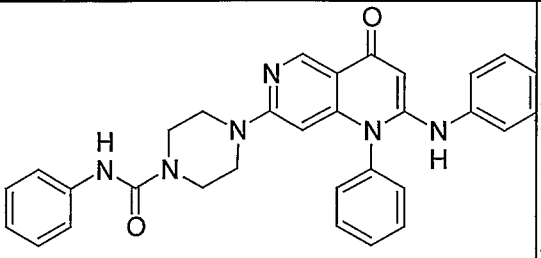
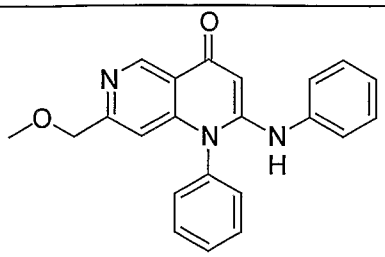
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
611		1.22	483.2	Intermediate BA, BB, BC and Example 39, 43
612		2.11	411.4	Intermediate BA, BB, BC and Example 39, 43
613		1.55	426.0	Intermediate BA, BB, BC and Example 39, 43
614		1.98	413.0	Intermediate BA, BB, BC and Example 39, 43

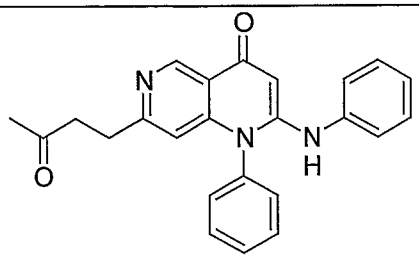
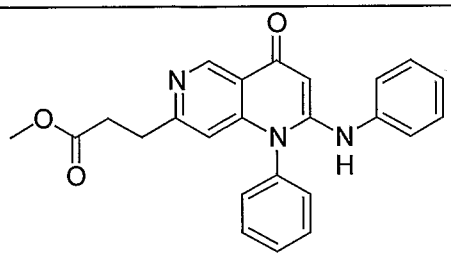
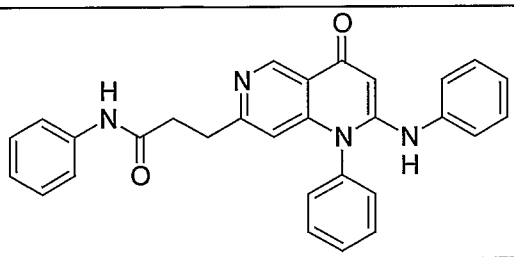
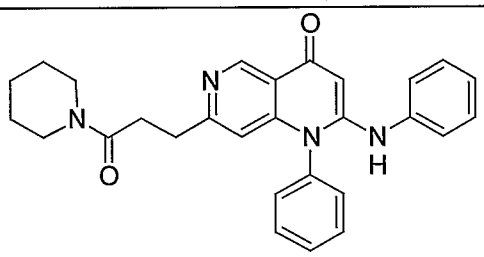
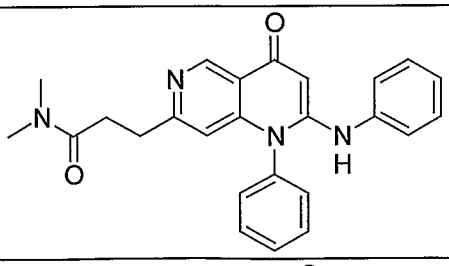
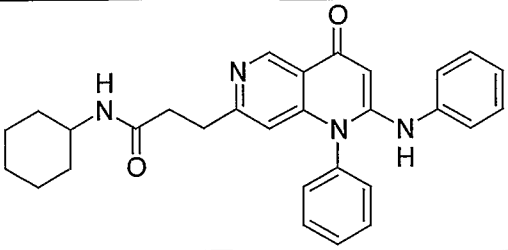
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
615		1.88	370.3	Intermediate BA, BB, BC and Example 39, 42
616		1.73	356.3	Intermediate BA, BB, BC and Example 39, 42
617		2.53	488.3	Intermediate BA, BB, BC and Example 39, 43
618		2.30	427.3	Intermediate BA, BB, BC and Example 39, 43
619		1.68	405.4	Intermediate BA, BB, BC and Example 39, 55

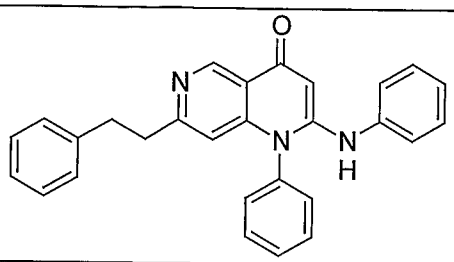
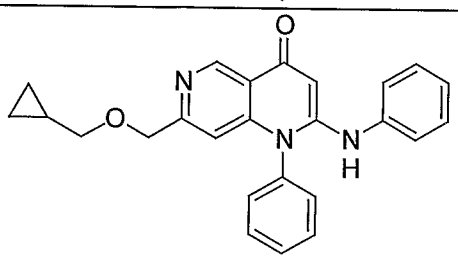
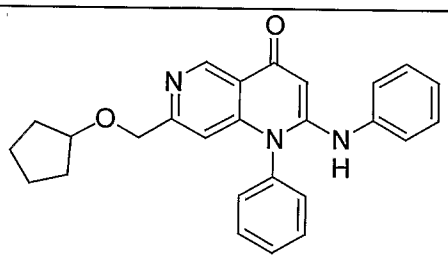
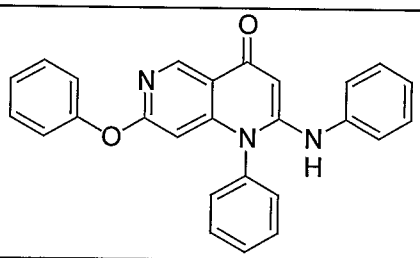
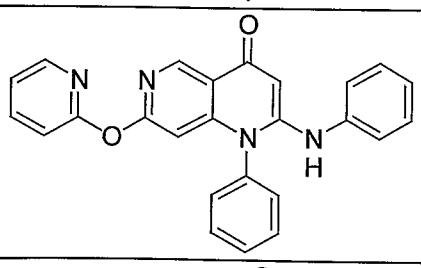
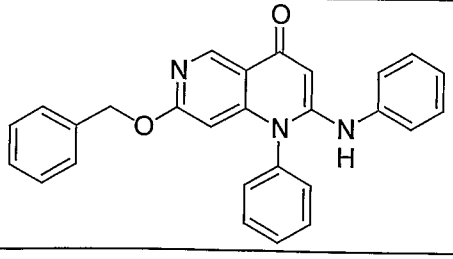
Example	Structure	LCMS RT (min)	[M+H]	Representative Procedure
620		2.25	449.2	Intermediate BA, BB, BC and Example 39, 55
621		2.00	418.5	Intermediate BA, BB, BC and Example 39, 55
622		2.19	438.3	Intermediate BA, BB, BC and Example 39, 55

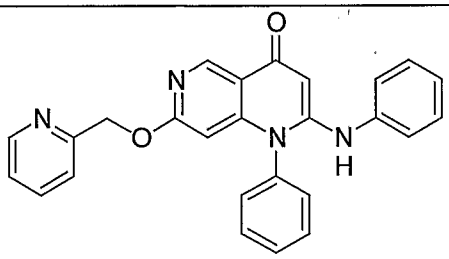
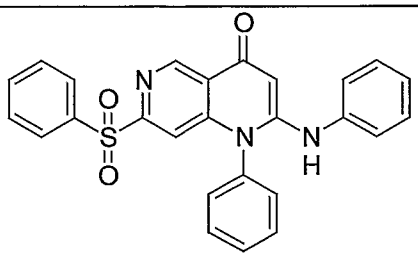
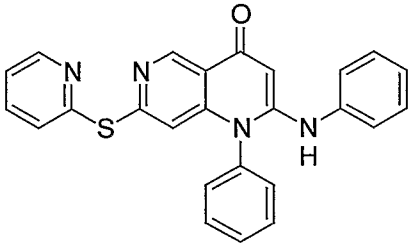
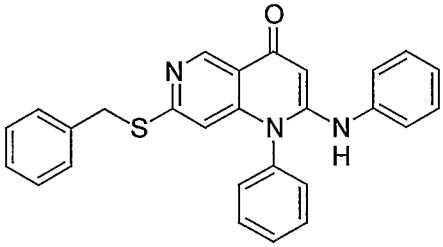
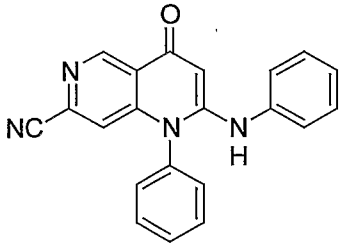
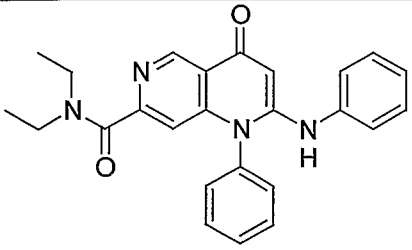
Utilizing the above described procedures for intermediates and examples alone or in combination, a variety of Formula II compounds can be prepared using the appropriate starting material and the representative procedure described. These compounds are summarized in Table 2B.

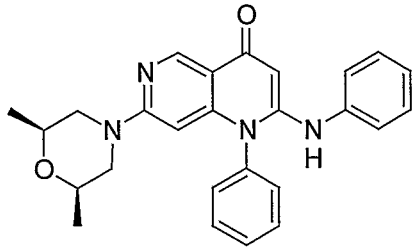
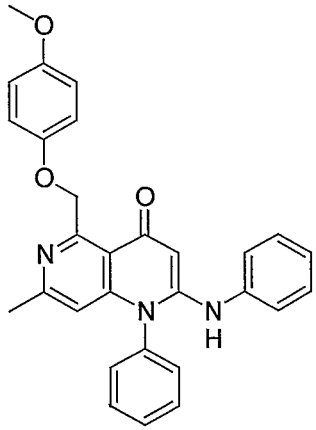
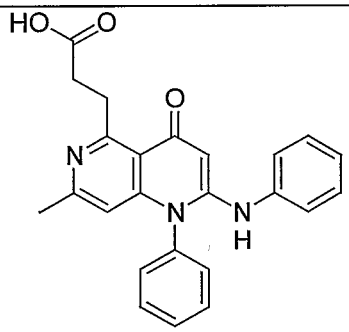
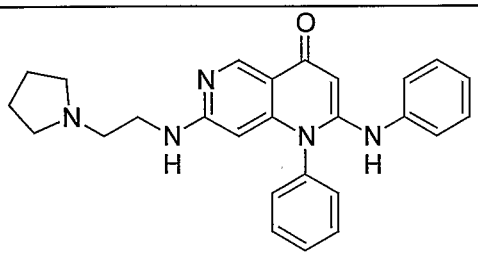
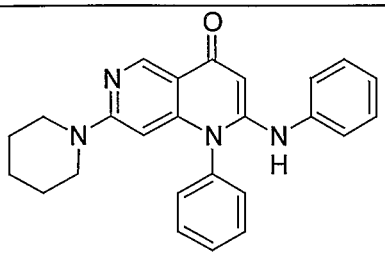
Table 2B

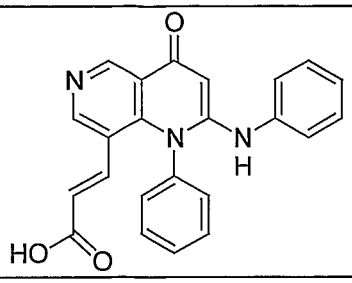
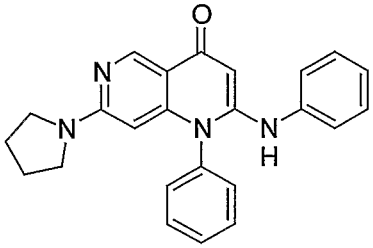
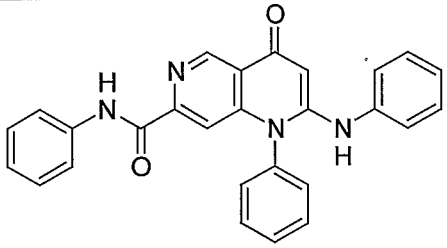
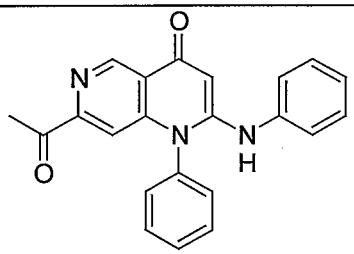
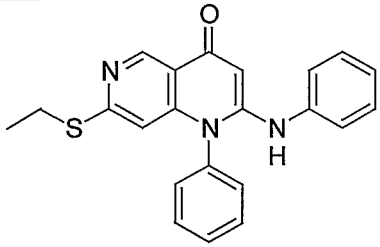
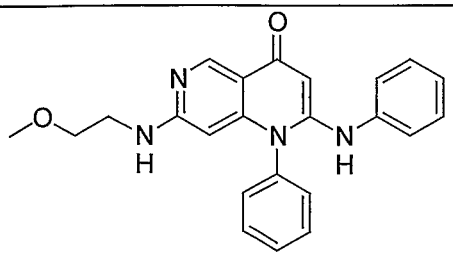
Example	Stucture	Representative Procedure
623		Intermediate BA1, BB1, BC1 and Example 40, 49, 47
624		Intermediate BA1, BB1, BC1 and Example 40, 31, 32
625		Intermediate BA1, BB1, BC1 and Example 40, 43
626		Intermediate BA1, BB1, BC1 and Example 40, 43 and Intermediate AK
627		Intermediate BA1, BB1, BC1 and Example 40, 43 and Intermediate AK
628		Intermediate BA1, BB1, BC1 and Example 40, 17, 25 and Intermediate AJ

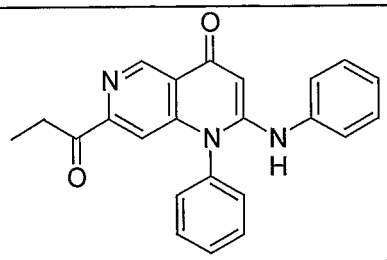
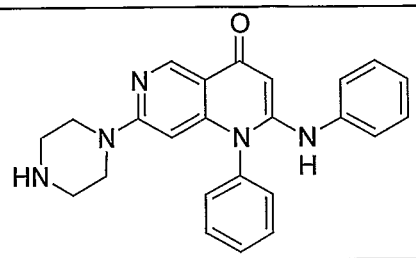
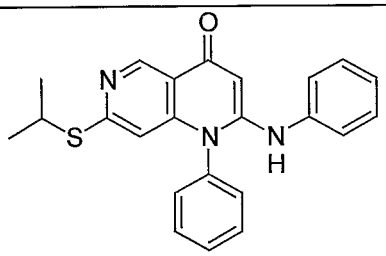
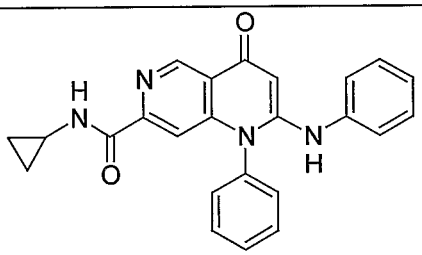
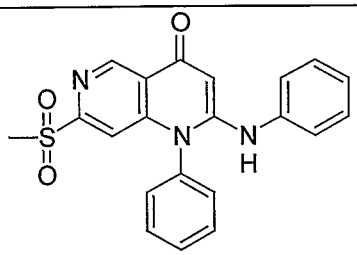
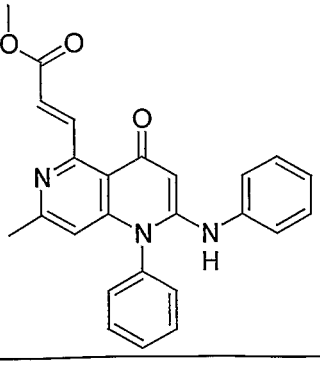
Example	Stucture	Representative Procedure
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630		Intermediate BA1, BB1, BC1 and Example 40, 31, 33
631		Intermediate BA1, BB1, BC1 and Example 40, 31, 32, 33, 47
632		Intermediate BA1, BB1, BC1 and Example 40, 31, 32, 33, 47
633		Intermediate BA1, BB1, BC1 and Example 40, 31, 32, 33, 47
634		Intermediate BA1, BB1, BC1 and Example 40, 31, 32, 33, 47

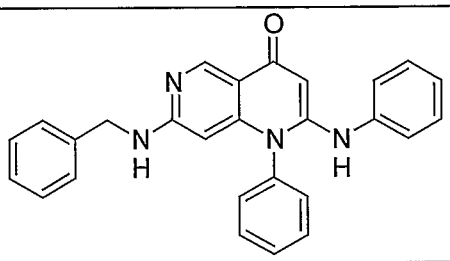
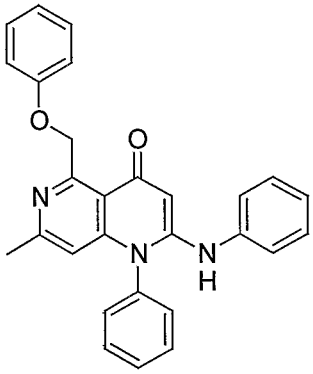
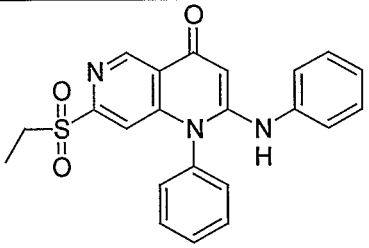
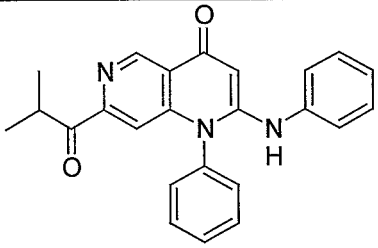
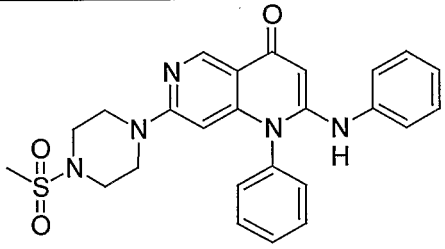
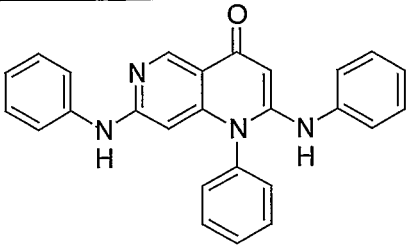
Example	Stucture	Representative Procedure
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636		Intermediate BA1, BB1, BC1 and Example 40, 17, 25 and Intermediate AJ
637		Intermediate BA1, BB1, BC1 and Example 40, 17, 25 and Intermediate AJ
638		Intermediate BA1, BB1, BC1 and Example 40, 48
639		Intermediate BA1, BB1, BC1 and Example 40, 48
640		Intermediate BA1, BB1, BC1 and Example 40, 48

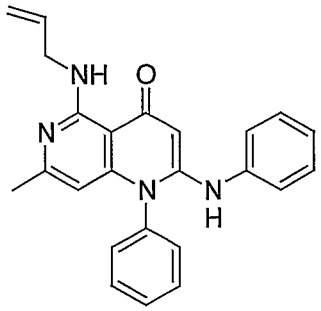
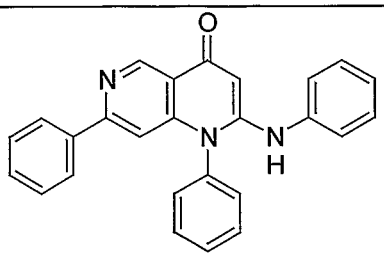
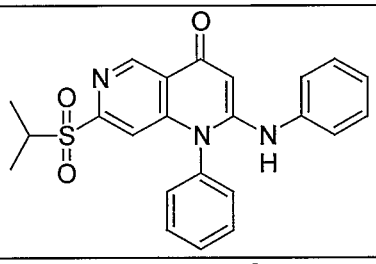
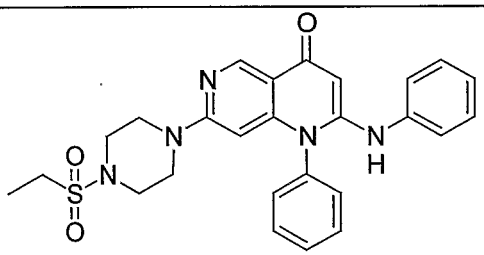
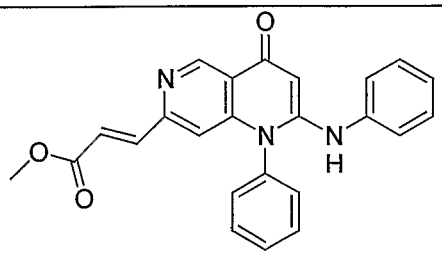
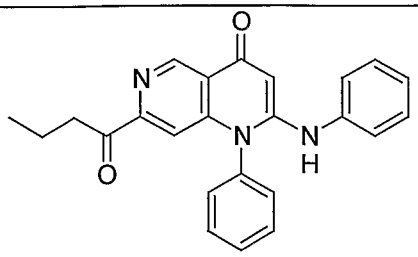
Example	Stucture	Representative Procedure
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642		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
643		Intermediate BA1, BB1, BC1 and Example 40, 44
644		Intermediate BA1, BB1, BC1 and Example 40, 44
645		Intermediate BA1, BB1, BC1 and Example 40, 43
646		Intermediate BA1, BB1, BC1 and Example 40, 49, 47

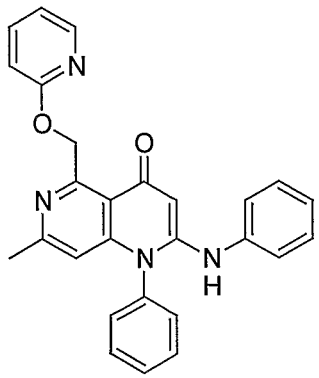
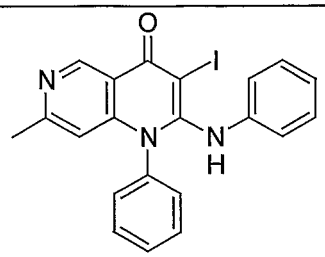
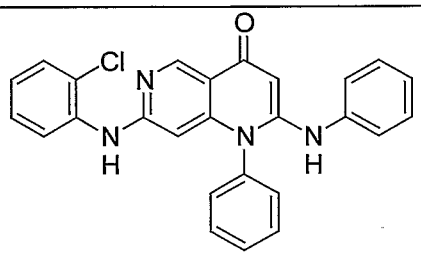
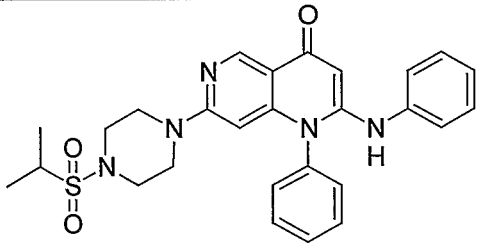
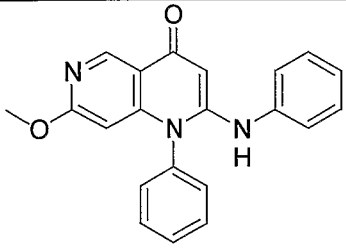
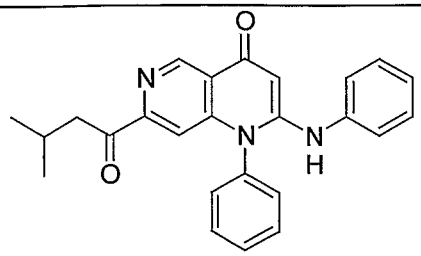
Example	Stucture	Representative Procedure
647		Intermediate BA1, BB1, BC1 and Example 40, 43
648		Intermediate BA, BB, BC and Example 39, 17, 25, 26
649		Intermediate BA, BB, BC and Example 39, 31, 32, 33
650		Intermediate BA1, BB1, BC1 and Example 40, 43
651		Intermediate BA1, BB1, BC1 and Example 40, 43

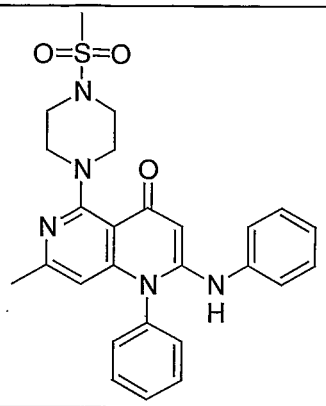
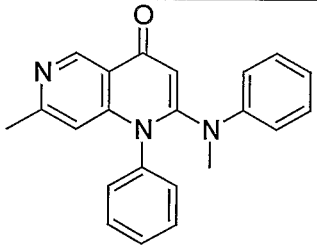
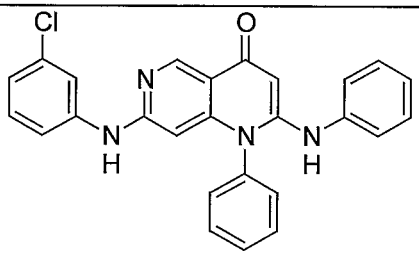
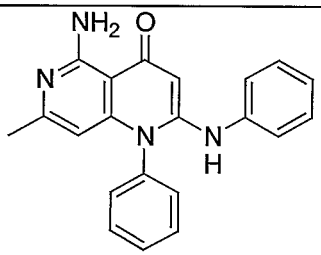
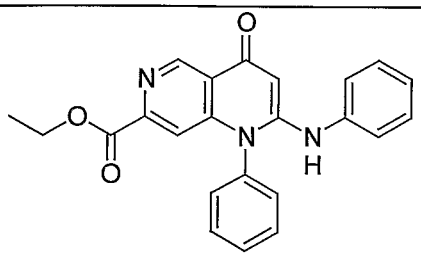
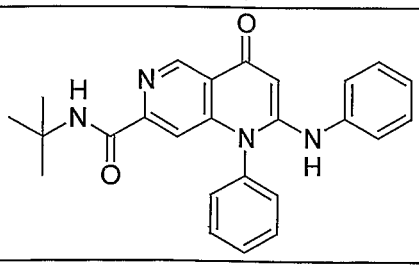
Example	Stucture	Representative Procedure
652		Intermediate BA2, BB2, BC2 and Example 40, 31, 32
653		Intermediate BA1, BB1, BC1 and Example 40, 43
654		Intermediate BA1, BB1, BC1 and Example 40, 49, 47
655		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51
656		Intermediate BA1, BB1, BC1 and Example 40, 44
657		Intermediate BA1, BB1, BC1 and Example 40, 43

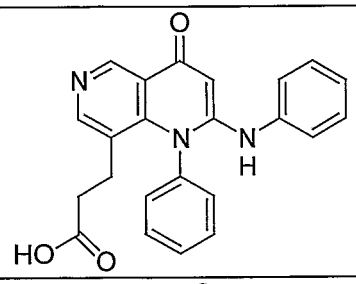
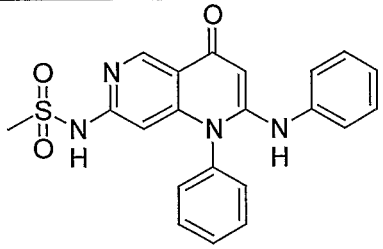
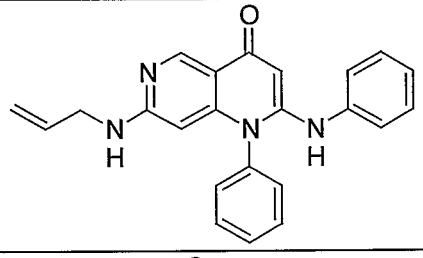
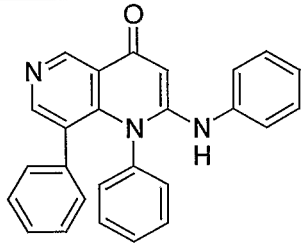
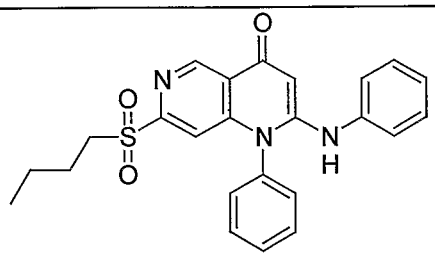
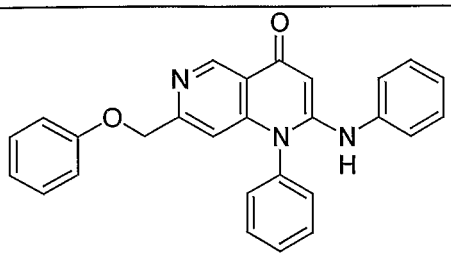
Example	Stucture	Representative Procedure
658		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51
659		Intermediate BA1, BB1, BC1 and Example 40, 43
660		Intermediate BA1, BB1, BC1 and Example 40, 44
661		Intermediate BA1, BB1, BC1 and Example 40, 49, 47
662		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
663		Intermediate BA, BB, BC and Example 39, 31

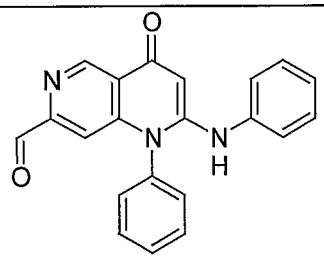
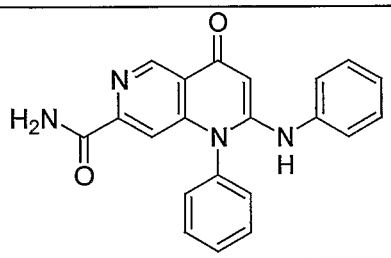
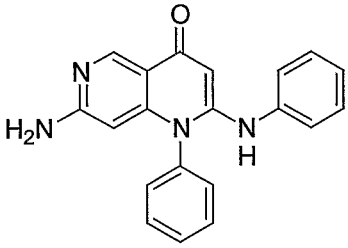
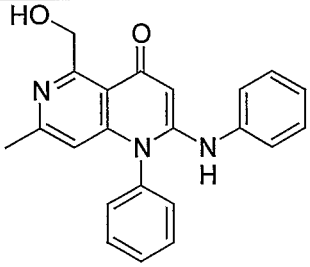
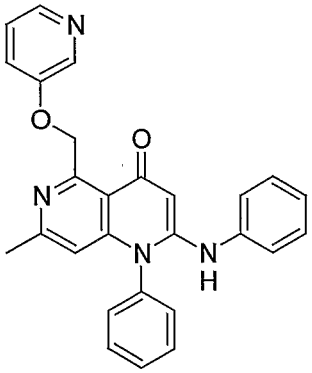
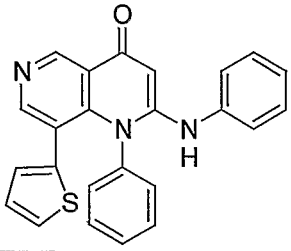
Example	Stucture	Representative Procedure
664		Intermediate BA1, BB1, BC1 and Example 40, 43
665		Intermediate BA, BB, BC and Example 39, 17, 25, 26
666		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
667		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51
668		Intermediate BA1, BB1, BC1 and Example 40, 43, 12
669		Intermediate BA1, BB1, BC1 and Example 40, 3

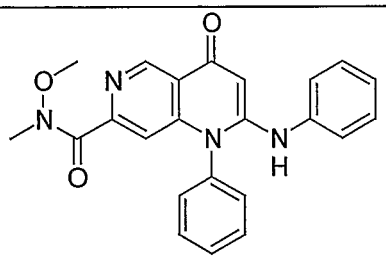
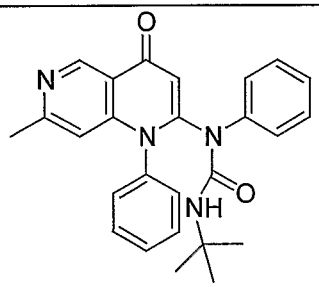
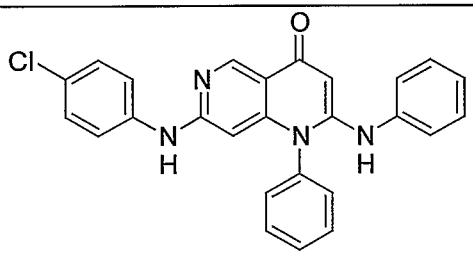
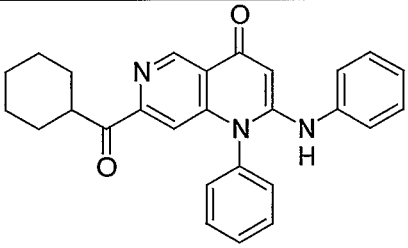
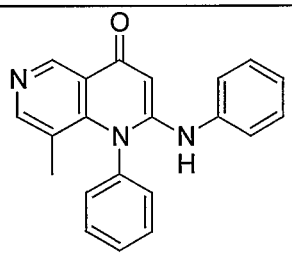
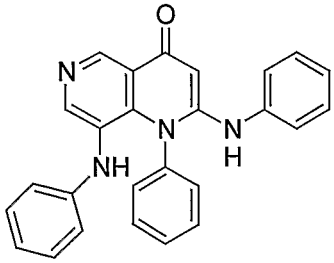
Example	Stucture	Representative Procedure
670		Intermediate BA, BB, BC and Example 39, 3
671		Intermediate BA1, BB1, BC1 and Example 40, 55
672		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
673		Intermediate BA1, BB1, BC1 and Example 40, 43, 12
674		Intermediate BA1, BB1, BC1 and Example 40, 31
675		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51

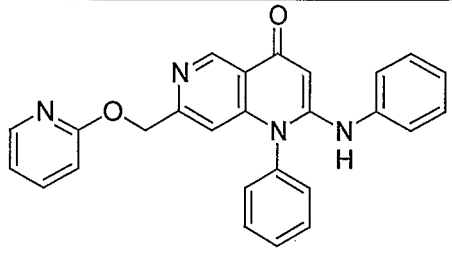
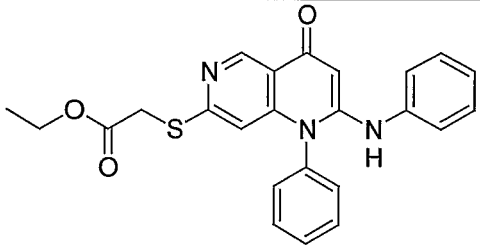
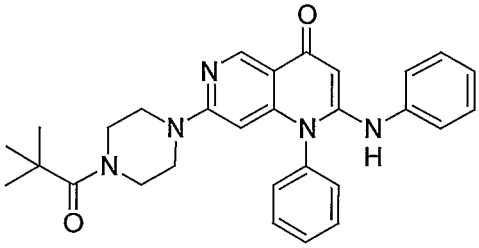
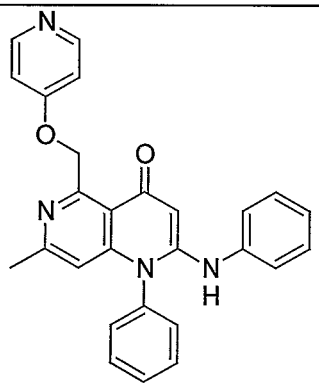
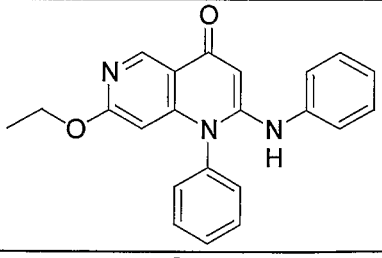
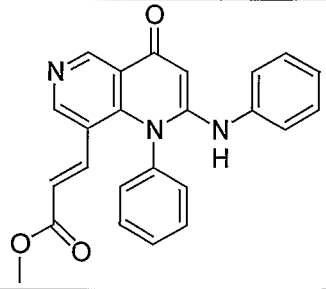
Example	Stucture	Representative Procedure
676		Intermediate BA, BB, BC and Example 39, 17, 25, 26
677		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL
678		Intermediate BA1, BB1, BC1 and Example 40, 3
679		Intermediate BA1, BB1, BC1 and Example 40, 43, 12
680		Intermediate BA1, BB1, BC1 and Example 40, 48
681		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51

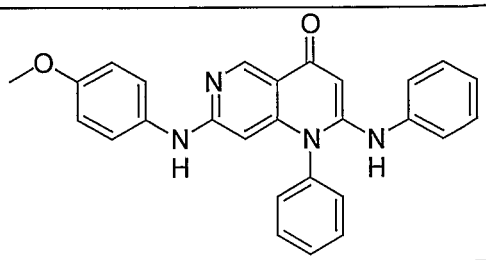
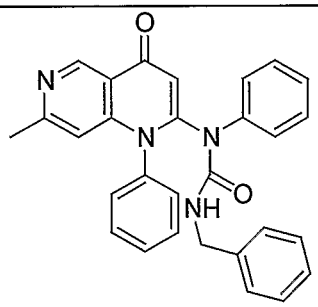
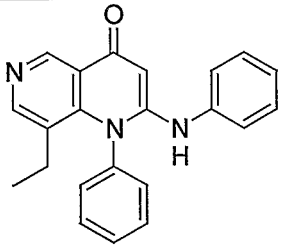
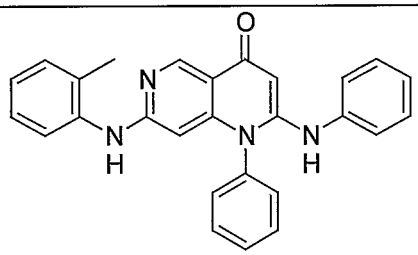
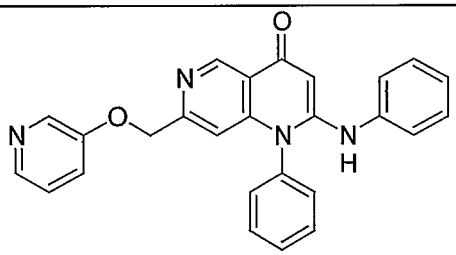
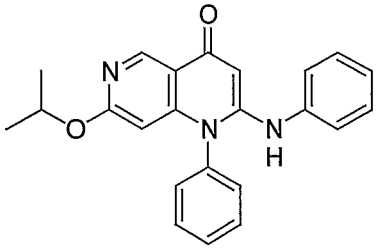
Example	Stucture	Representative Procedure
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683		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AJ
684		Intermediate BA1, BB1, BC1 and Example 40, 3
685		Intermediate BA, BB, BC and Example 39, 3, 24
686		Intermediate BA1, BB1, BC1 and Example 40, 17
687		Intermediate BA1, BB1, BC1 and Example 40, 49, 47

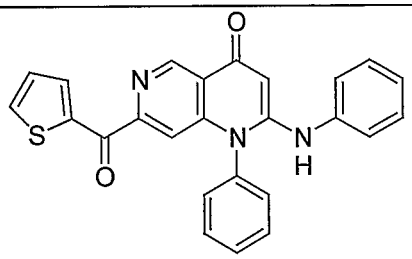
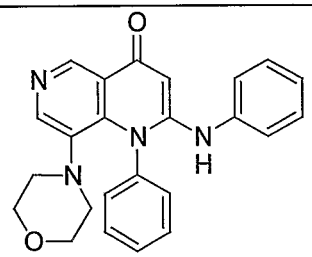
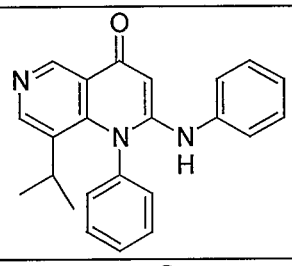
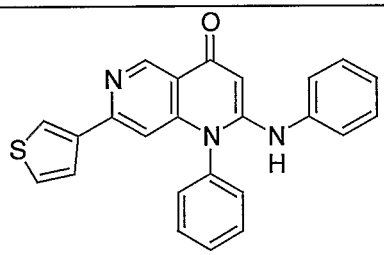
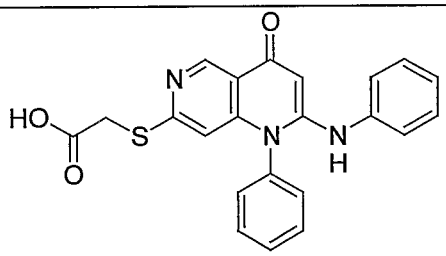
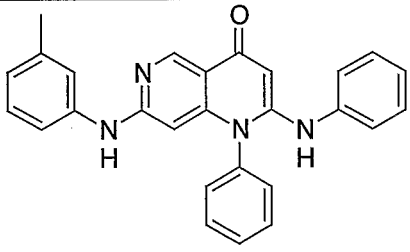
Example	Stucture	Representative Procedure
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689		Intermediate BA1, BB1, BC1 and Example 40, 22
690		Intermediate BA1, BB1, BC1 and Example 40, 3
691		Intermediate BA2, BB2, BC2 and Example 41, 55
692		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
693		Intermediate BA1, BB1, BC1 and Example 40, 17, 25, 26

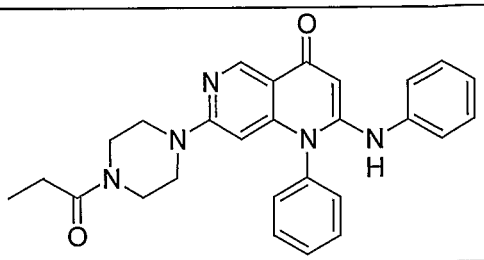
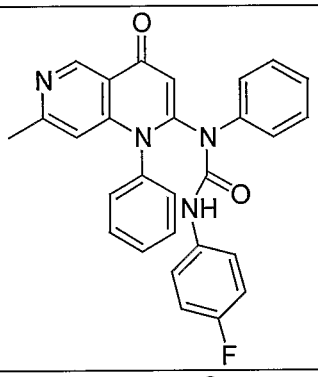
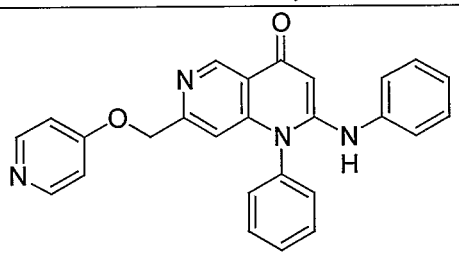
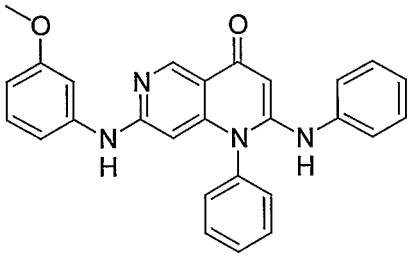
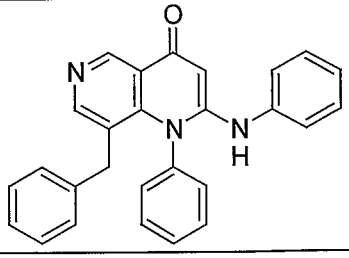
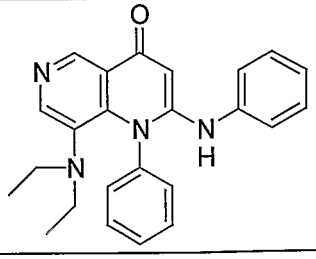
Example	Stucture	Representative Procedure
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695		Intermediate BA1, BB1, BC1 and Example 40, 17, 18
696		Intermediate BA1, BB1, BC1 and Example 40, 3, 24
697		Intermediate BA, BB, BC and Example 39, 17, 25
698		Intermediate BA, BB, BC and Example 39, 17, 25, 26
699		Intermediate BA2, BB2, BC2 and Example 41, 55

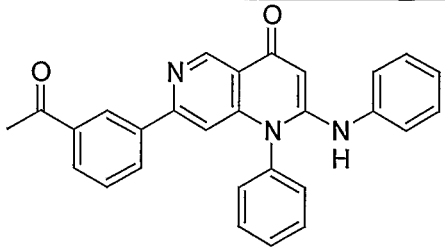
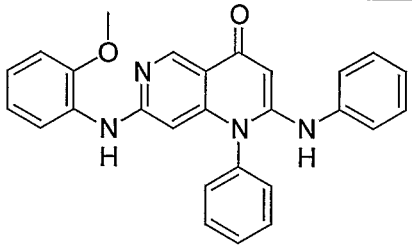
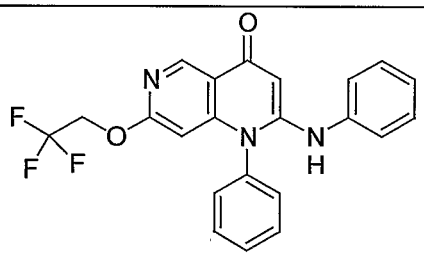
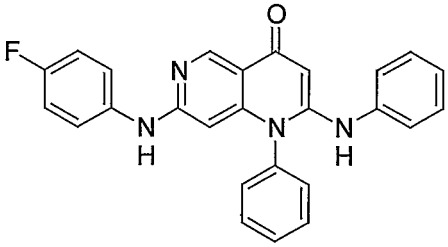
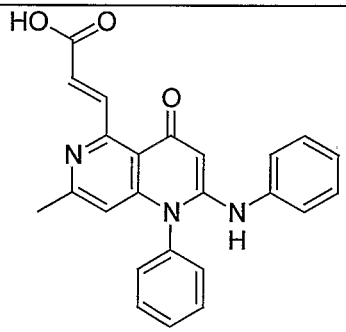
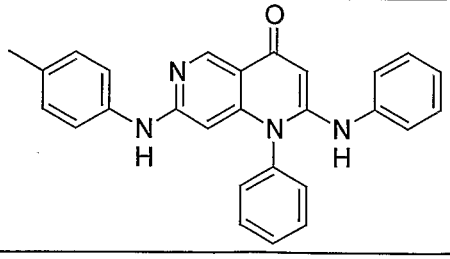
Example	Stucture	Representative Procedure
700		Intermediate BA1, BB1, BC1 and Example 40, 49, 50
701		Intermediate BA, BB, BC and Example 39 54, and Intermediate AK
702		Intermediate BA1, BB1, BC1 and Example 40, 3
703		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51
704		Intermediate BA2, BB2, BC2 and Example 41, 34
705		Intermediate BA2, BB2, BC2 and Example 41, 3

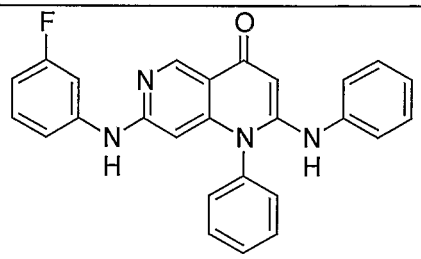
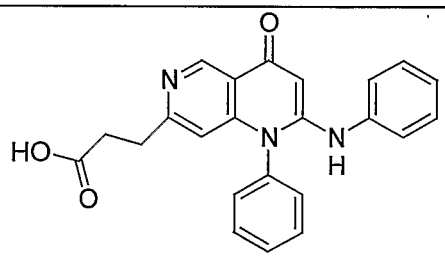
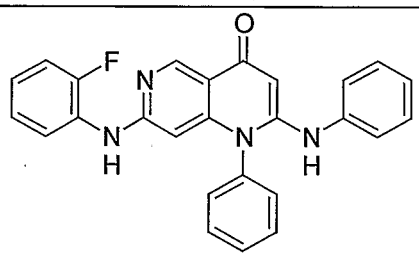
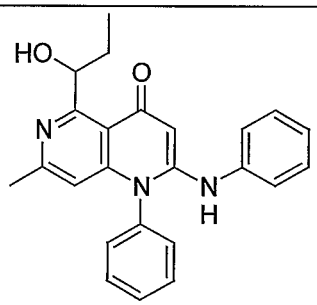
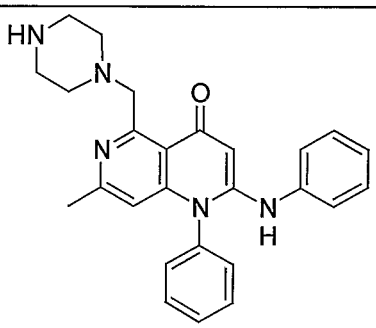
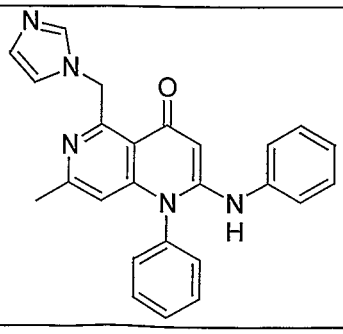
Example	Stucture	Representative Procedure
706		Intermediate BA1, BB1, BC1 and Example 40, 17, 25, 26
707		Intermediate BA1, BB1, BC1 and Example 40, 44
708		Intermediate BA1, BB1, BC1 and Example 40, 43, 47
709		Intermediate BA, BB, BC and Example 39, 17, 25, 26
710		Intermediate BA1, BB1, BC1 and Example 40, 48
711		Intermediate BA2, BB2, BC2 and Example 41, 31

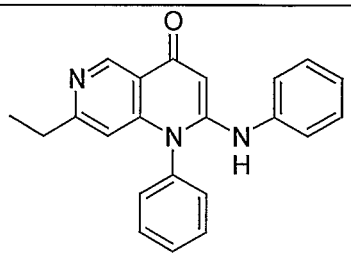
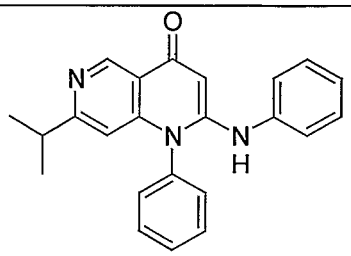
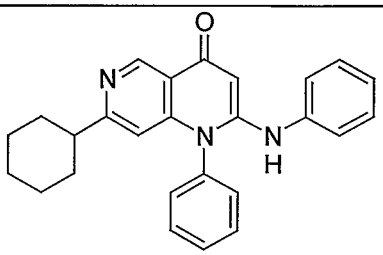
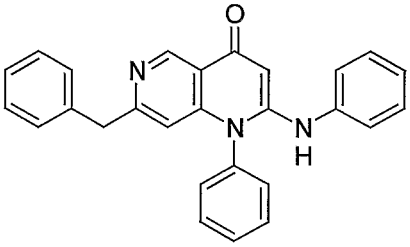
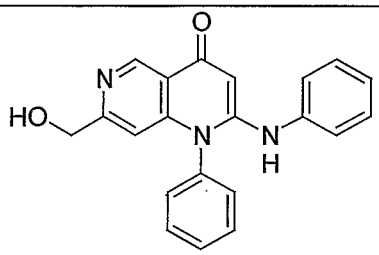
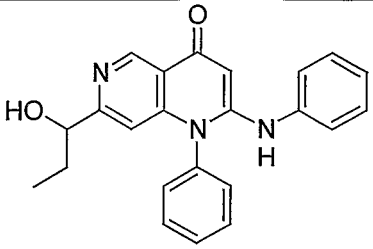
Example	Stucture	Representative Procedure
712		Intermediate BA1, BB1, BC1 and Example 40, 3
713		Intermediate BA, BB, BC and Example 39 54 and Intermediate AK
714		Intermediate BA2, BB2, BC2 and Example 41, 34
715		Intermediate BA1, BB1, BC1 and Example 40, 3
716		Intermediate BA1, BB1, BC1 and Example 40, 17, 25, 26
717		Intermediate BA1, BB1, BC1 and Example 40, 48

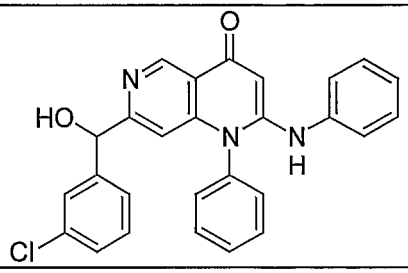
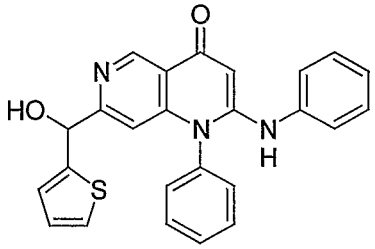
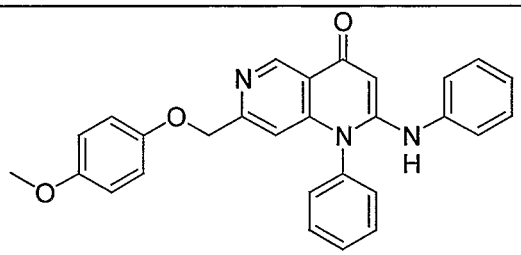
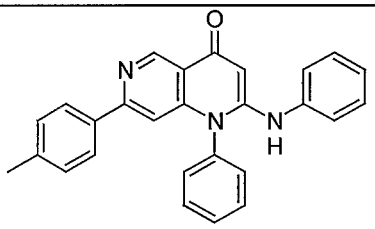
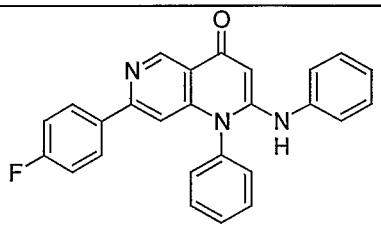
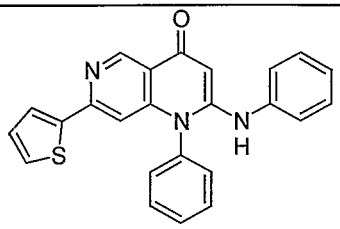
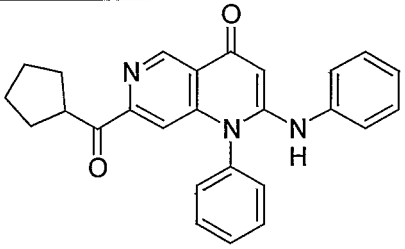
Example	Stucture	Representative Procedure
718		Intermediate BA1, BB1, BC1and Example 40, 49, 50, 51
719		Intermediate BA2, BB2, BC2 and Example 41, 3
720		Intermediate BA2, BB2, BC2 and Example 41, 34
721		Intermediate BA1, BB1, BC1 and Example 40, 55
722		Intermediate BA1, BB1, BC1 and Example 40, 44, 45
723		Intermediate BA1, BB1, BC1 and Example 40, 3

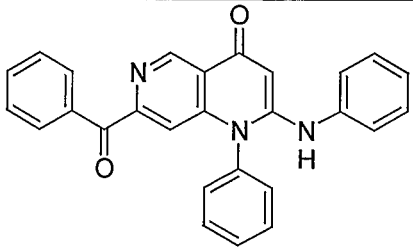
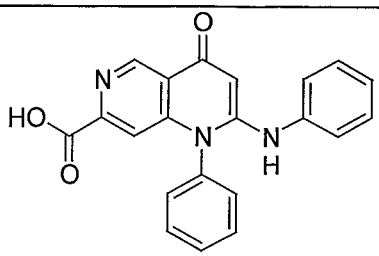
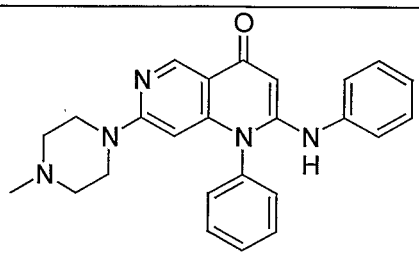
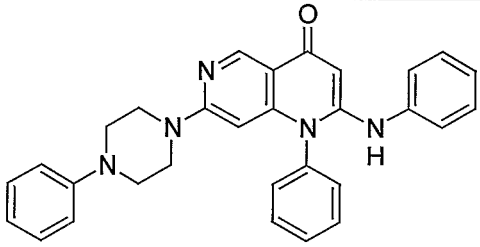
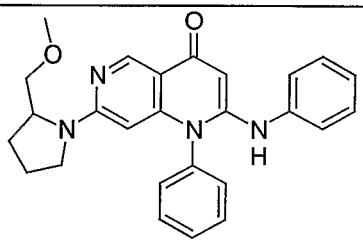
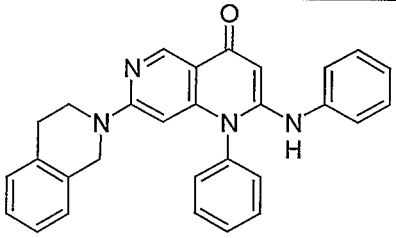
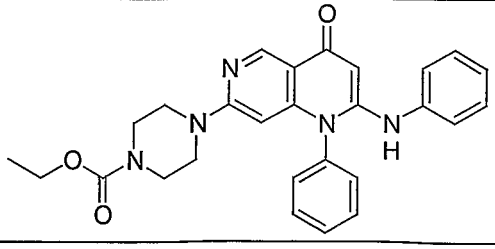
Example	Stucture	Representative Procedure
724		Intermediate BA1, BB1, BC1 and Example 40, 43, 47
725		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AK
726		Intermediate BA1, BB1, BC1 and Example 40, 17, 25, 26
727		Intermediate BA1, BB1, BC1 and Example 40, 3
728		Intermediate BA2, BB2, BC2 and Example 41, 34
729		Intermediate BA2, BB2, BC2 and Example 41, 3

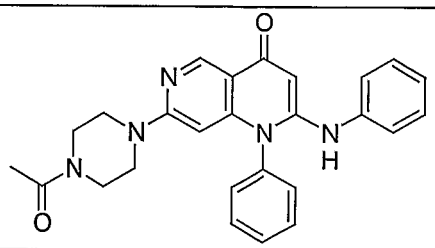
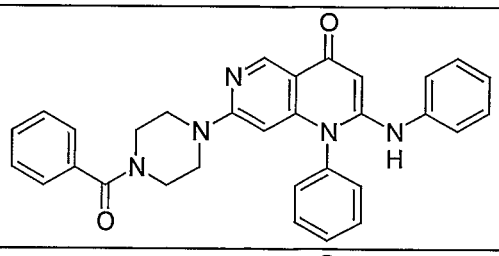
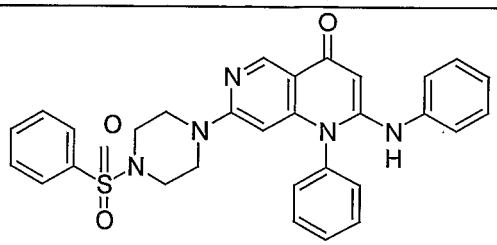
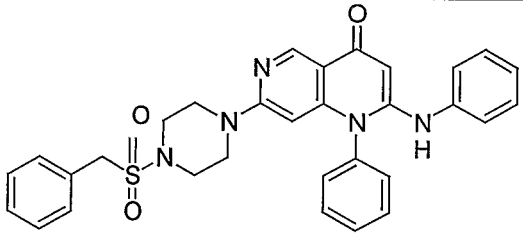
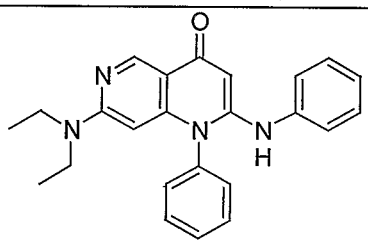
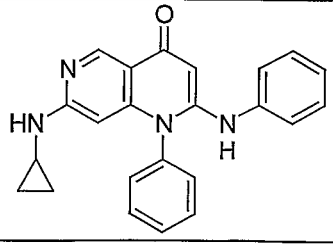
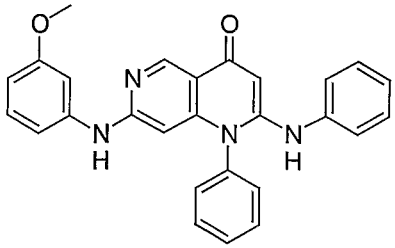
Example	Stucture	Representative Procedure
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731		Intermediate BA1, BB1, BC1 and Example 40, 3
732		Intermediate BA1, BB1, BC1 and Example 40, 48
733		Intermediate BA1, BB1, BC1 and Example 40, 3
734		Intermediate BA, BB, BC and Example 39, 31, 32
735		Intermediate BA1, BB1, BC1 and Example 40, 3

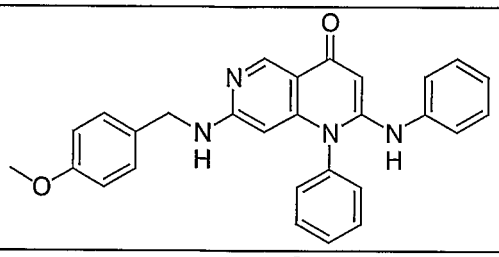
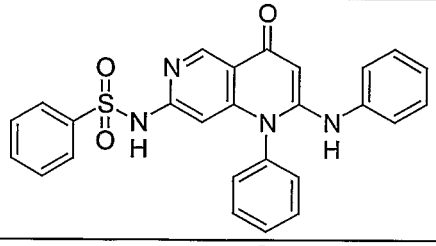
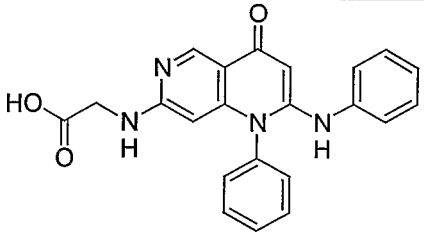
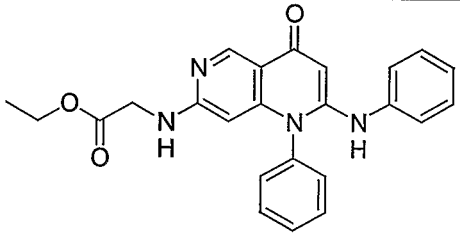
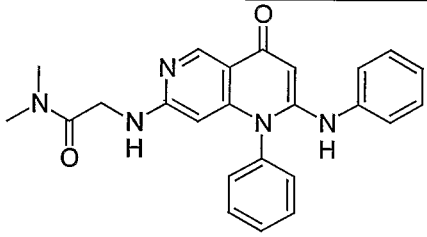
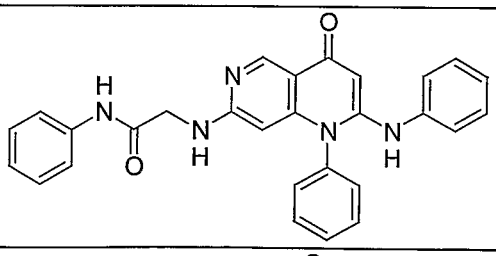
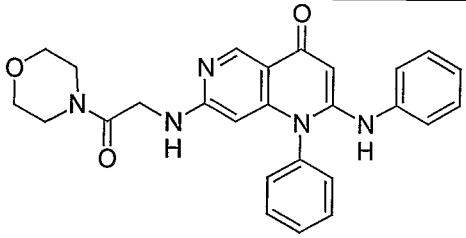
Example	Stucture	Representative Procedure
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737		Intermediate BA1, BB1, BC1 and Example 40, 31, 32, 33
738		Intermediate BA1, BB1, BC1 and Example 40, 3
739		Intermediate BA, BB, BC and Example 39, 49, 50, 51, 25
740		Intermediate BA, BB, BC and Example 39, 17, 25, 11
741		Intermediate BA, BB, BC and Example 39, 17, 25, 11

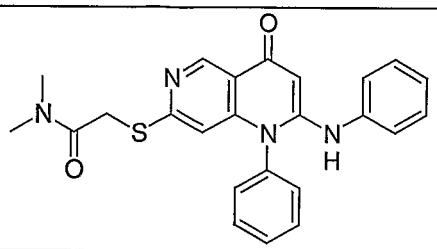
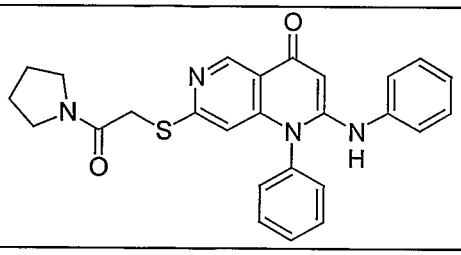
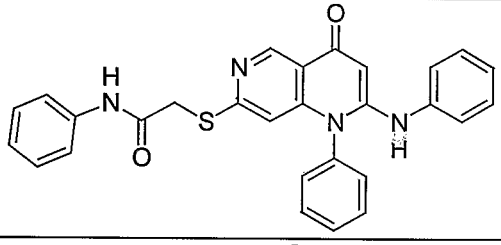
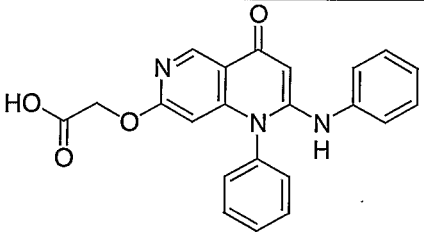
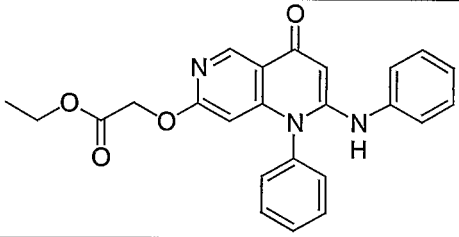
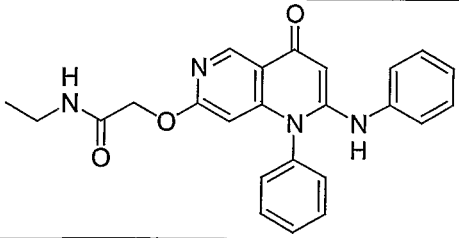
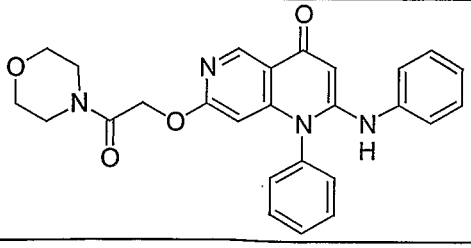
Example	Stucture	Representative Procedure
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743		Intermediate BA1, BB1, BC1 and Example 40, 42
744		Intermediate BA1, BB1, BC1 and Example 40, 42
745		Intermediate BA1, BB1, BC1 and Example 40, 42
746		Intermediate BA1, BB1, BC1 and Example 40, 17, 25
747		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51, 25

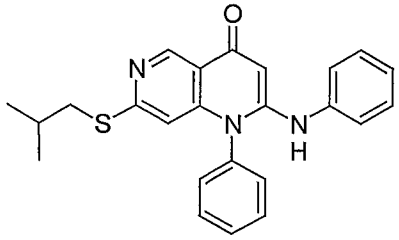
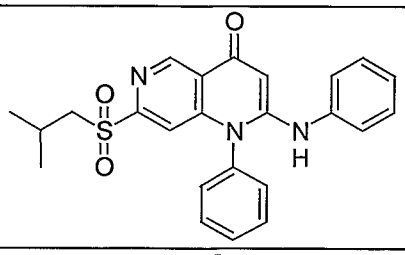
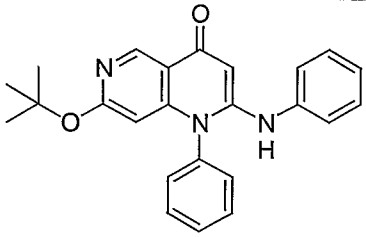
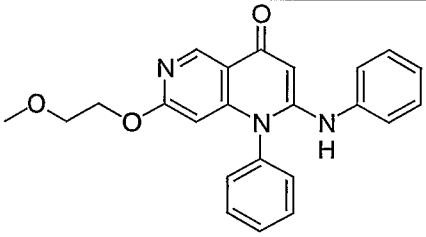
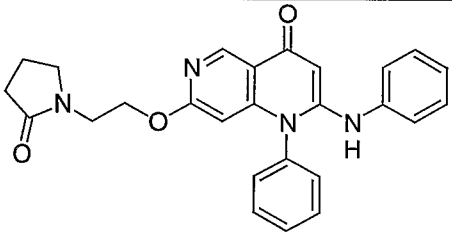
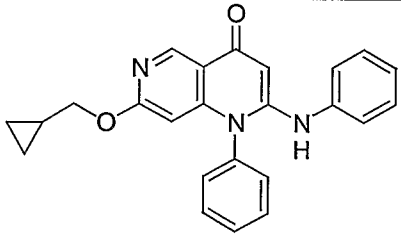
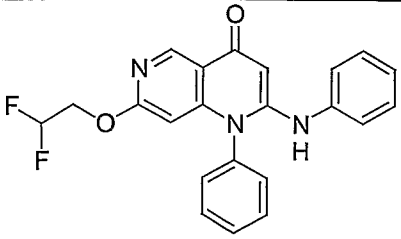
Example	Stucture	Representative Procedure
748		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51, 25
749		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51, 25
750		Intermediate BA1, BB1, BC1 and Example 40, 17, 25, 26
751		Intermediate BA1, BB1, BC1 and Example 40, 55
752		Intermediate BA1, BB1, BC1 and Example 40, 55
753		Intermediate BA1, BB1, BC1 and Example 40, 55
754		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51

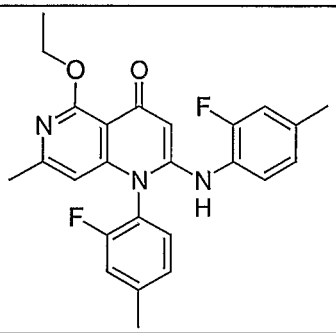
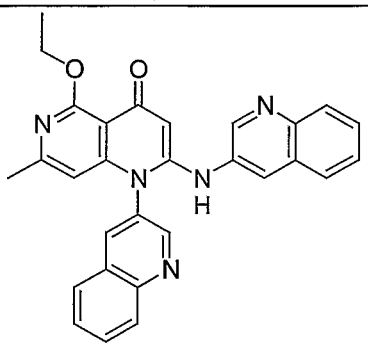
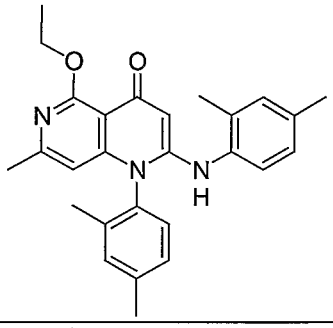
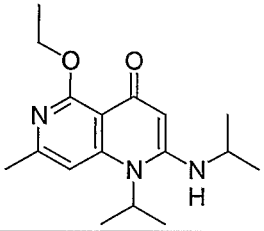
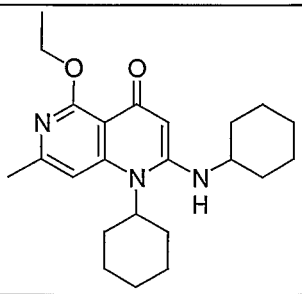
Example	Stucture	Representative Procedure
755		Intermediate BA1, BB1, BC1 and Example 40, 49, 50, 51
756		Intermediate BA1, BB1, BC1 and Example 40, 49
757		Intermediate BA1, BB1, BC1 and Example 40, 43
758		Intermediate BA1, BB1, BC1 and Example 40, 43
759		Intermediate BA1, BB1, BC1 and Example 40, 43
760		Intermediate BA1, BB1, BC1 and Example 40, 43
761		Intermediate BA1, BB1, BC1 and Example 40, 43

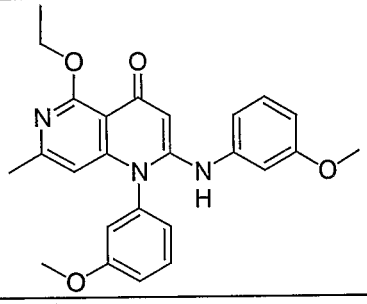
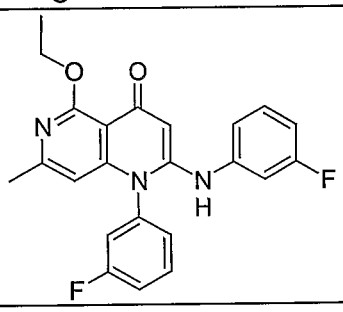
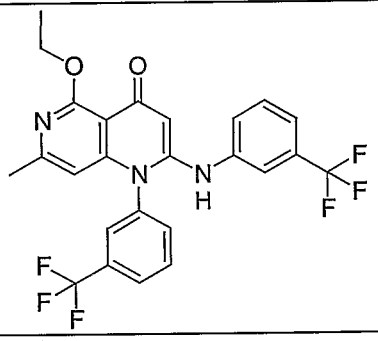
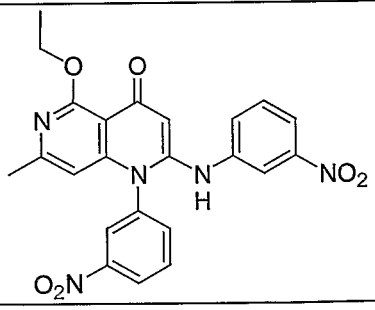
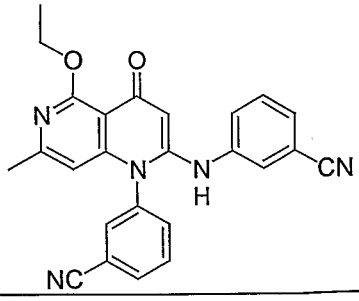
Example	Stucture	Representative Procedure
762		Intermediate BA1, BB1, BC1 and Example 40, 43
763		Intermediate BA1, BB1, BC1 and Example 40, 43, 47
764		Intermediate BA1, BB1, BC1 and Example 40, 43, 12
765		Intermediate BA1, BB1, BC1 and Example 40, 43, 12
766		Intermediate BA1, BB1, BC1 and Example 40, 43
767		Intermediate BA1, BB1, BC1 and Example 40, 43
768		Intermediate BA1, BB1, BC1 and Example 40, 3

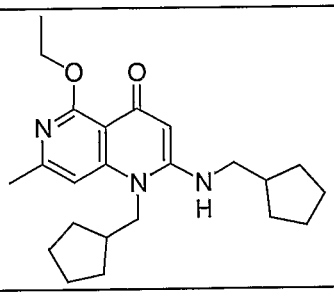
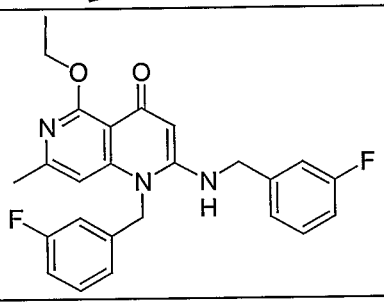
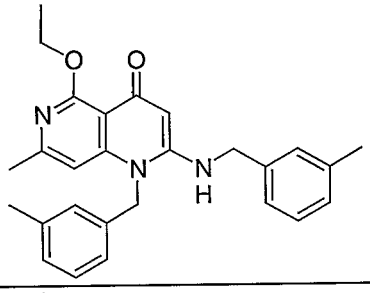
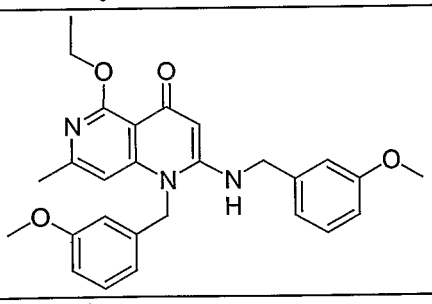
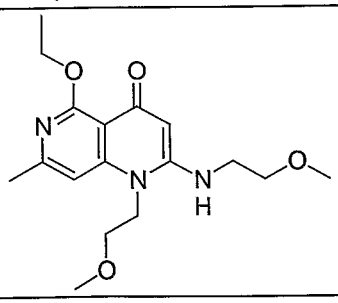
Example	Stucture	Representative Procedure
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770		Intermediate BA1, BB1, BC1 and Example 40, 22
771		Intermediate BA1, BB1, BC1 and Example 40, 46, 45
772		Intermediate BA1, BB1, BC1 and Example 40, 46
773		Intermediate BA1, BB1, BC1 and Example 40, 46, 45, 47
774		Intermediate BA1, BB1, BC1 and Example 40, 46, 45, 47
775		Intermediate BA1, BB1, BC1 and Example 40, 46, 45, 47

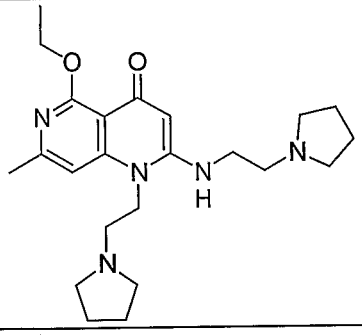
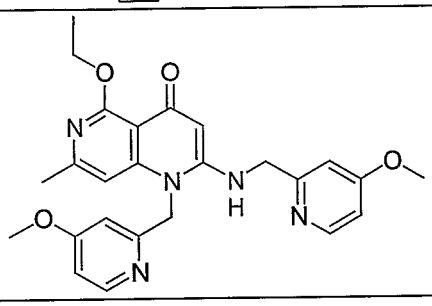
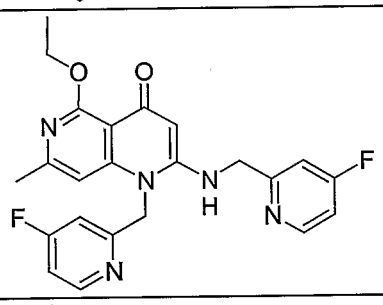
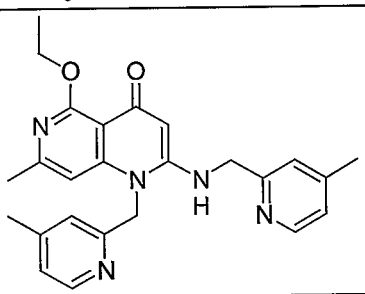
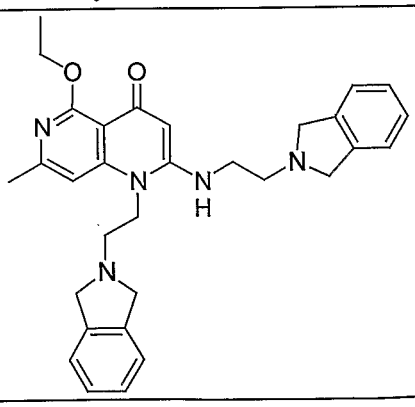
Example	Stucture	Representative Procedure
776		Intermediate BA1, BB1, BC1 and Example 40, 44, 45, 47
777		Intermediate BA1, BB1, BC1 and Example 40, 44, 45, 47
778		Intermediate BA1, BB1, BC1 and Example 40, 44, 45, 47
779		Intermediate BA1, BB1, BC1 and Example 40, 48, 45
780		Intermediate BA1, BB1, BC1 and Example 40, 48
781		Intermediate BA1, BB1, BC1 and Example 40, 48, 45, 47
782		Intermediate BA1, BB1, BC1 and Example 40, 48, 45, 47

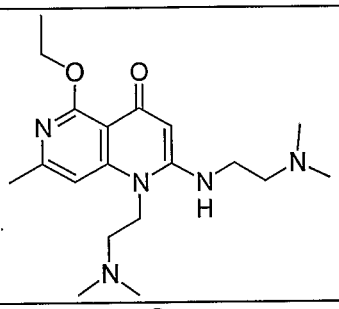
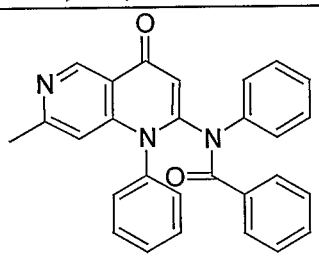
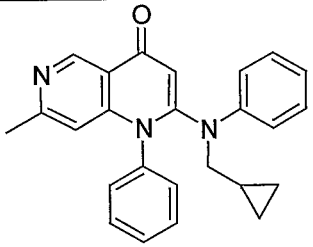
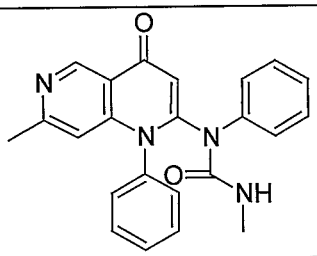
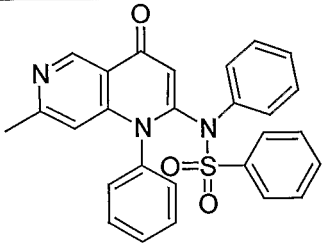
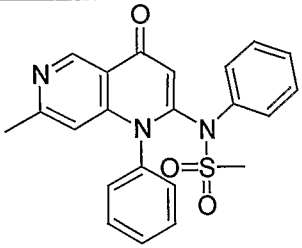
Example	Stucture	Representative Procedure
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784		Intermediate BA1, BB1, BC1 and Example 40, 44, 21
785		Intermediate BA1, BB1, BC1 and Example 40, 48
786		Intermediate BA1, BB1, BC1 and Example 40, 48
787		Intermediate BA1, BB1, BC1 and Example 40, 48
788		Intermediate BA1, BB1, BC1 and Example 40, 48
789		Intermediate BA1, BB1, BC1 and Example 40, 48

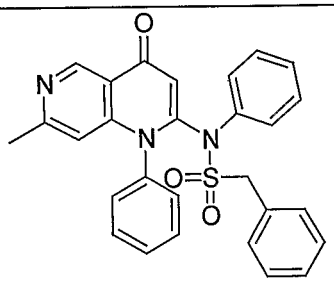
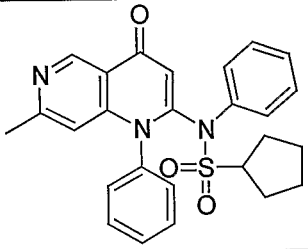
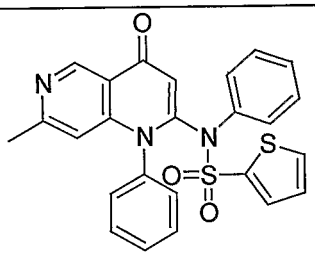
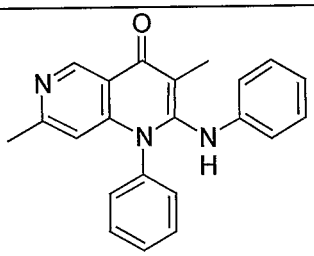
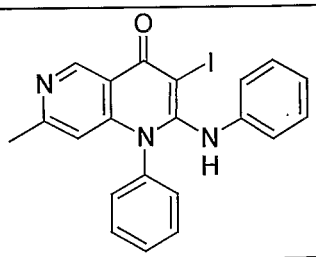
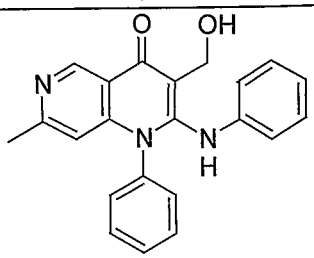
Example	Stucture	Representative Procedure
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791		Intermediate BA, BB, BC and Example 39, 48
792		Intermediate BA, BB, BC and Example 39, 48
793		Intermediate BA, BB, BC and Example 39, 48
794		Intermediate BA, BB, BC and Example 39, 48

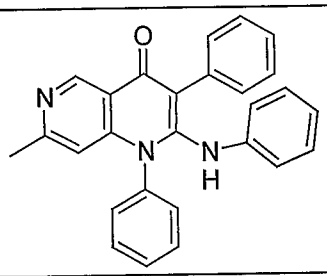
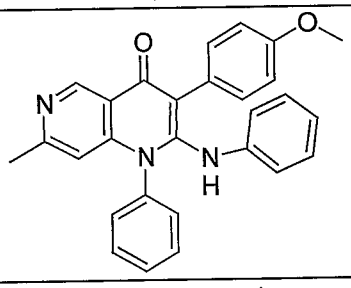
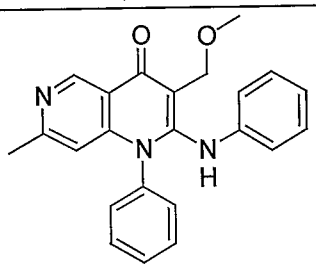
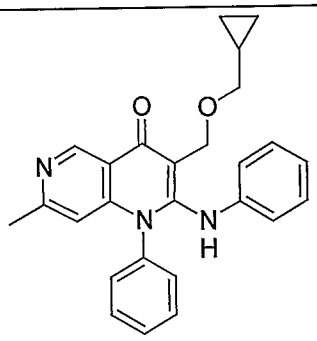
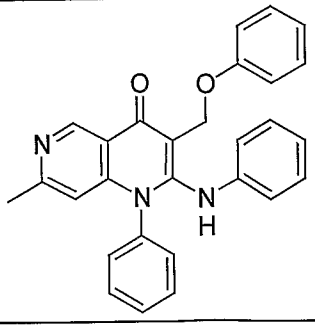
Example	Stucture	Representative Procedure
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796		Intermediate BA, BB, BC and Example 39, 48
797		Intermediate BA, BB, BC and Example 39, 48
798		Intermediate BA, BB, BC and Example 39, 48
799		Intermediate BA, BB, BC and Example 39, 48

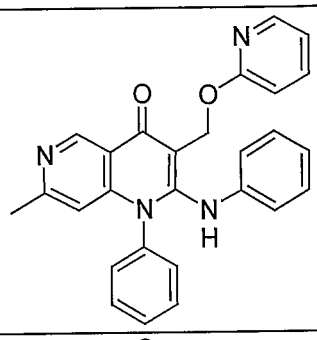
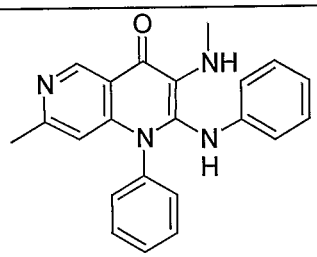
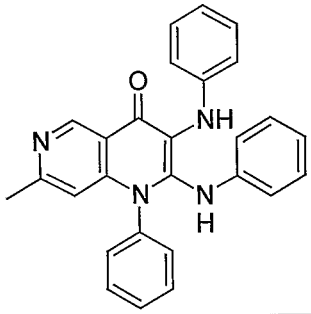
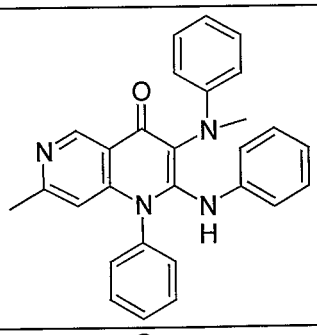
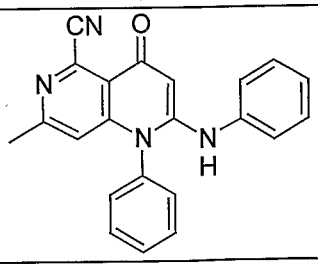
Example	Stucture	Representative Procedure
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801		Intermediate BA, BB, BC and Example 39, 48
802		Intermediate BA, BB, BC and Example 39, 48
803		Intermediate BA, BB, BC and Example 39, 48
804		Intermediate BA, BB, BC and Example 39, 48

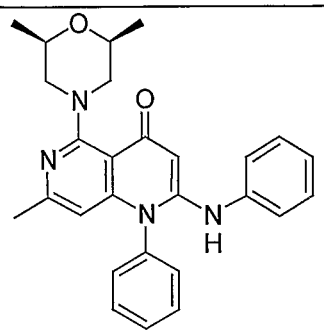
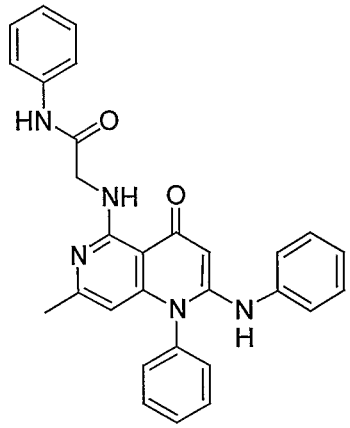
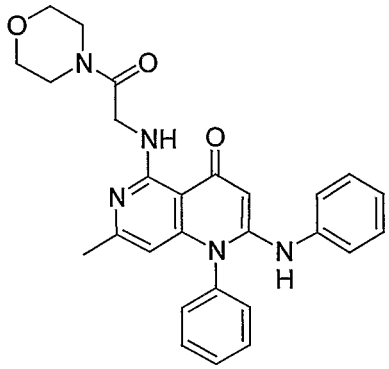
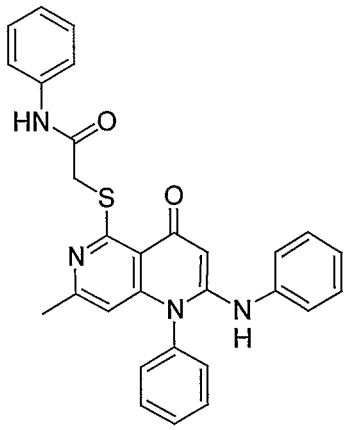
Example	Stucture	Representative Procedure
805		Intermediate BA, BB, BC and Example 39, 48
806		Intermediate BA, BB, BC and Example 39, 48
807		Intermediate BA, BB, BC and Example 39, 48
808		Intermediate BA, BB, BC and Example 39, 48
809		Intermediate BA, BB, BC and Example 39, 48

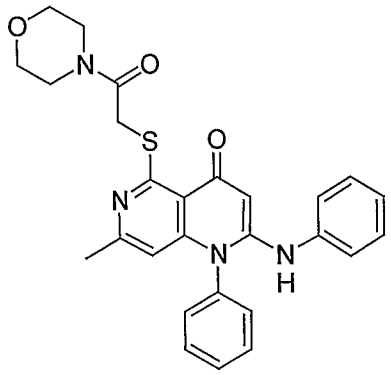
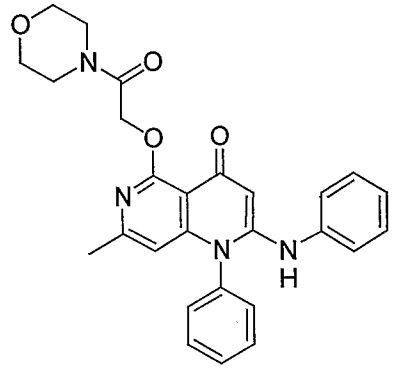
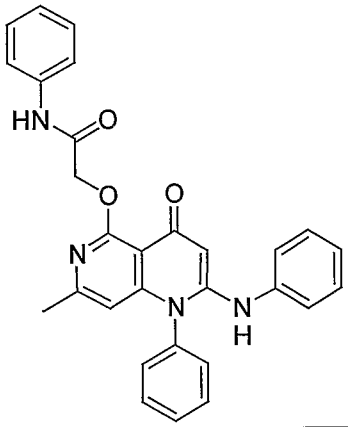
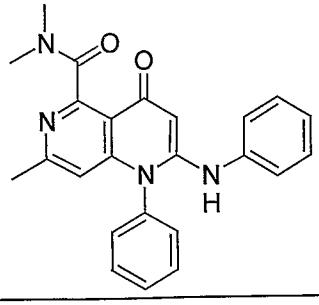
Example	Stucture	Representative Procedure
810		Intermediate BA, BB, BC and Example 39, 48
811		Intermediate BA, BB, BC and Example 39, 54, 47
812		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AJ
813		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AK
814		Intermediate BA, BB, BC and Example 39, 54, 12
815		Intermediate BA, BB, BC and Example 39, 54, 12

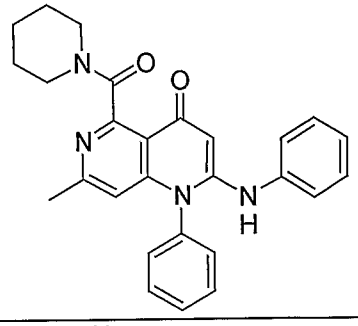
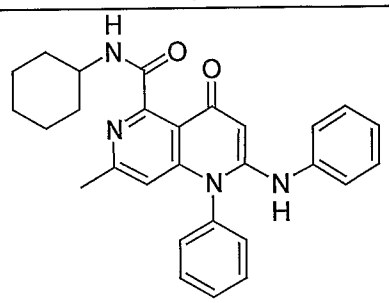
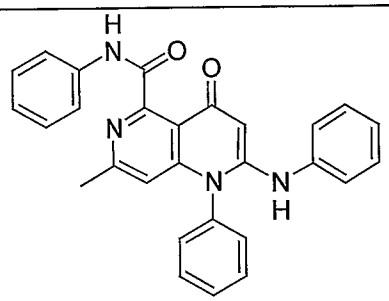
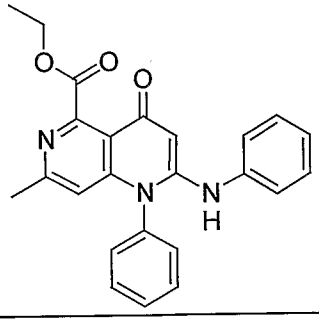
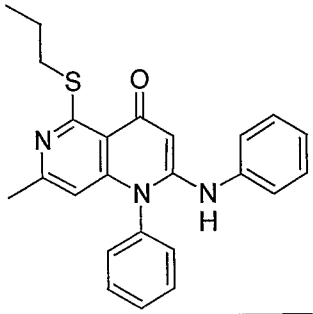
Example	Stucture	Representative Procedure
816		Intermediate BA, BB, BC and Example 39, 54, 12
817		Intermediate BA, BB, BC and Example 39, 54, 12
818		Intermediate BA, BB, BC and Example 39, 54, 12
819		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 42
820		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL
821		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 17, 25

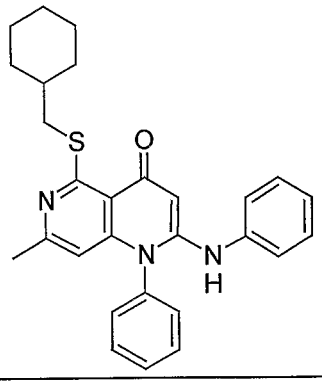
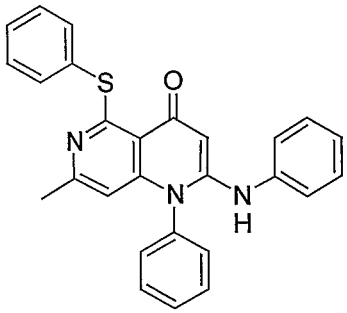
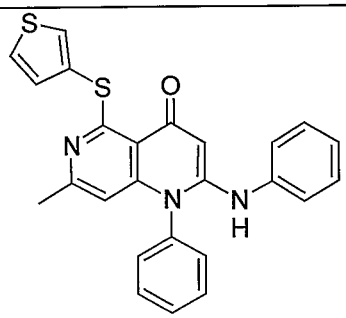
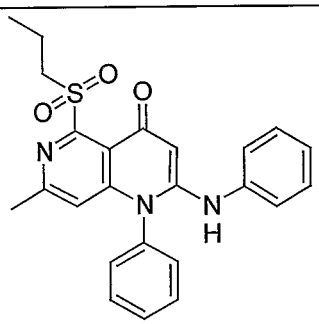
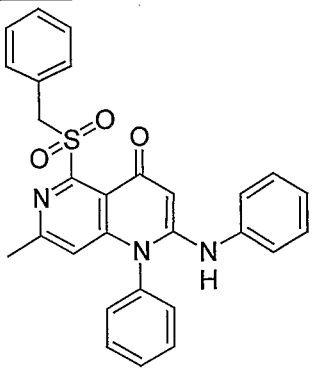
Example	Stucture	Representative Procedure
822		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and example 55
823		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 55
824		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 17, 25 and Intermediate AJ
825		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 17, 25 and Intermediate AJ
826		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 17, 25, 26

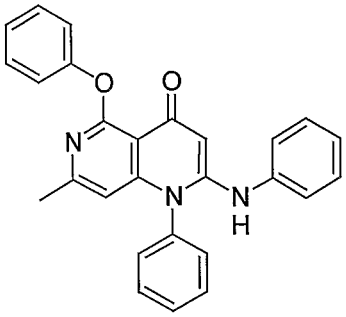
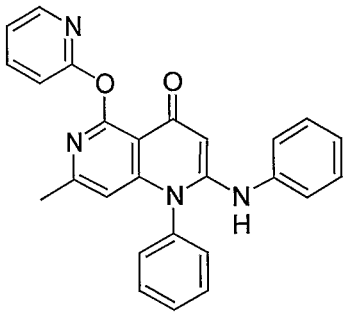
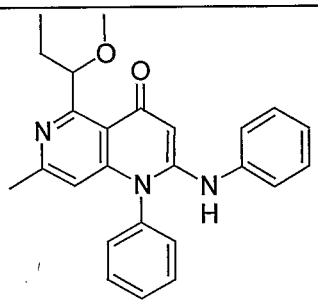
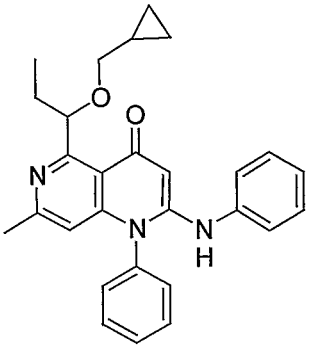
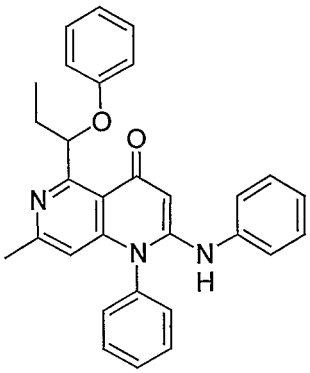
Example	Stucture	Representative Procedure
827		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 17, 25, 26
828		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 3
829		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 3
830		Intermediate BA, BB, BC and Example 39, 54 and Intermediate AL and Example 3
831		Intermediate BA, BB, BC and Example 39, 43

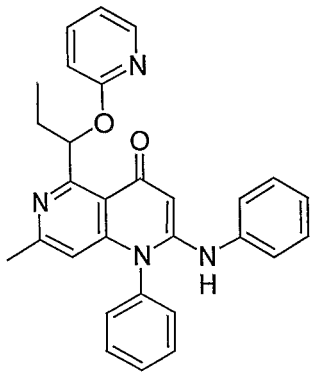
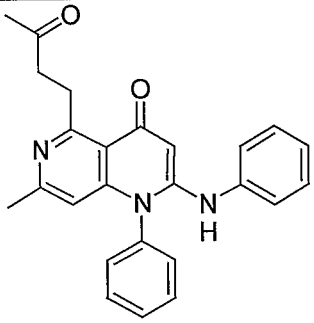
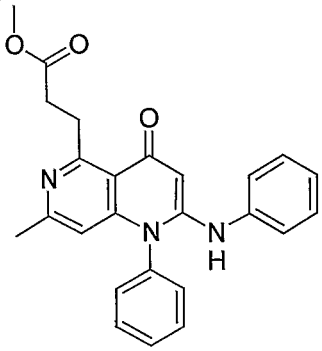
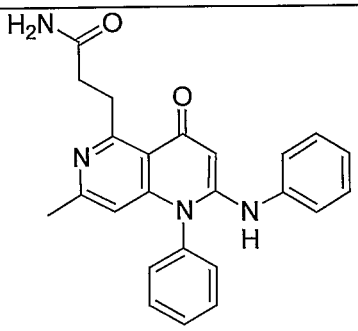
Example	Stucture	Representative Procedure
832		Intermediate BA, BB, BC and Example 39, 43
833		Intermediate BA, BB, BC and Example 39, 46, 45, 47
834		Intermediate BA, BB, BC and Example 39, 46, 45, 47
835		Intermediate BA, BB, BC and Example 39, 44, 45, 47

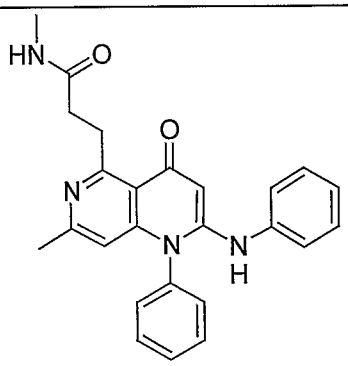
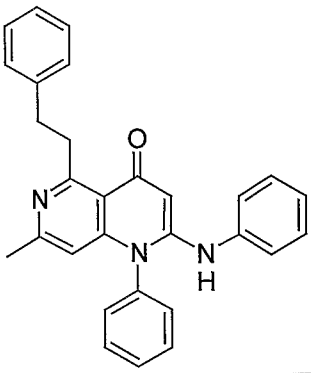
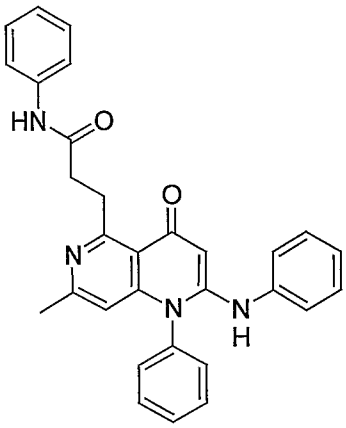
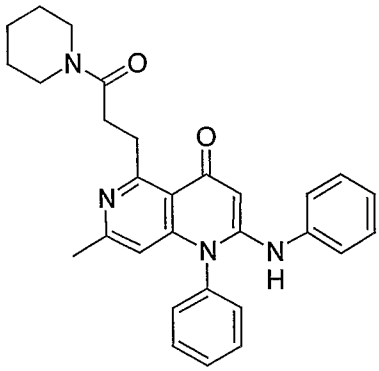
Example	Stucture	Representative Procedure
836		Intermediate BA, BB, BC and Example 39, 44, 45, 47
837		Intermediate BA, BB, BC and Example 39, 48, 45, 47
838		Intermediate BA, BB, BC and Example 39, 48, 45, 47
839		Intermediate BA, BB, BC and Example 39, 49, 47

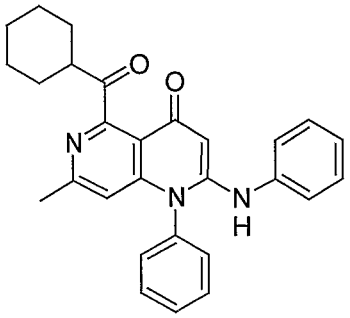
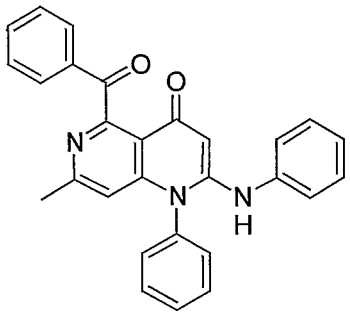
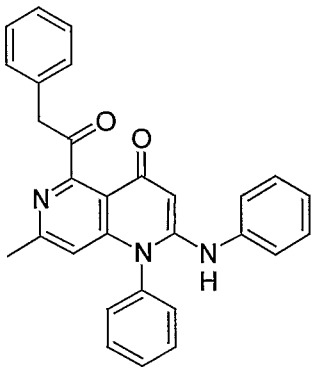
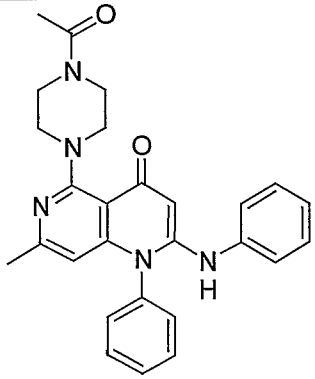
Example	Stucture	Representative Procedure
840		Intermediate BA, BB, BC and Example 39, 49, 47
841		Intermediate BA, BB, BC and Example 39, 49, 47
842		Intermediate BA, BB, BC and Example 39, 49, 47
843		Intermediate BA, BB, BC and Example 39, 17
844		Intermediate BA, BB, BC and Example 39, 44

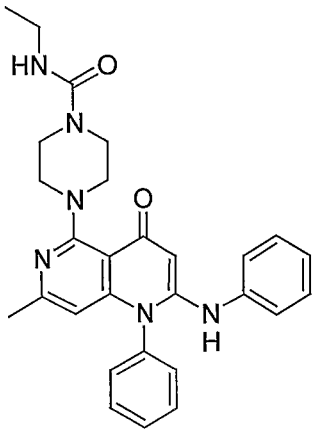
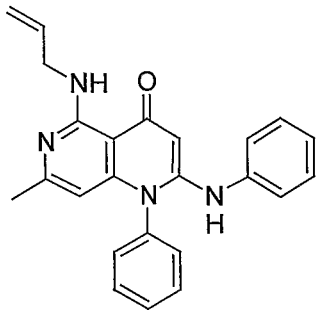
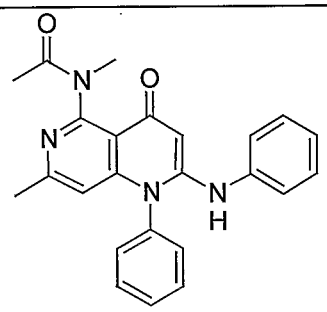
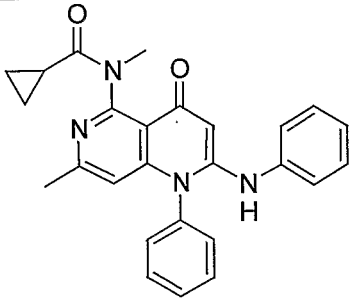
Example	Stucture	Representative Procedure
845		Intermediate BA, BB, BC and Example 39, 44
846		Intermediate BA, BB, BC and Example 39, 44
847		Intermediate BA, BB, BC and Example 39, 44
848		Intermediate BA, BB, BC and Example 39, 44, 21
849		Intermediate BA, BB, BC and Example 39, 44, 21

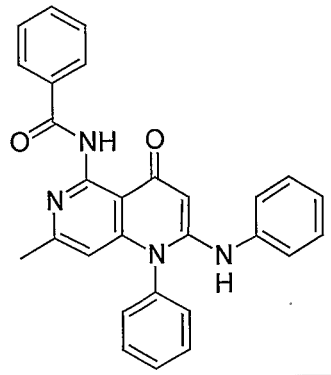
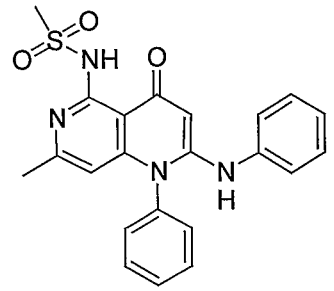
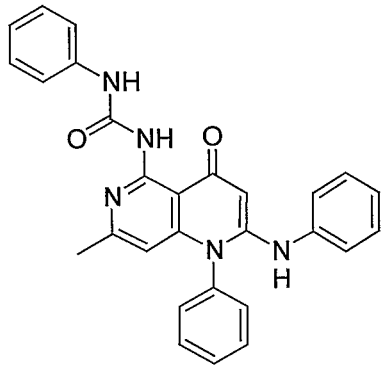
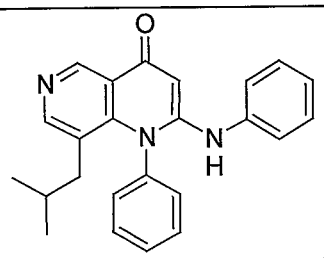
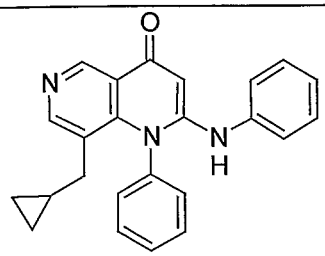
Example	Stucture	Representative Procedure
850		Intermediate BA, BB, BC and Example 39, 48
851		Intermediate BA, BB, BC and Example 39, 48
852		Intermediate BA, BB, BC and Example 39, 49, 50, 51, 25 and Intermediate AJ
853		Intermediate BA, BB, BC and Example 39, 49, 50, 51, 25 and Intermediate AJ
854		Intermediate BA, BB, BC and Example 39, 49, 50, 51, 25, 26

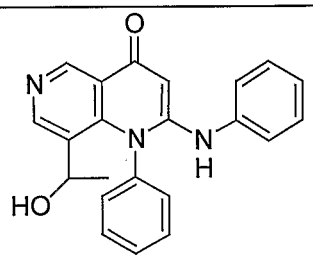
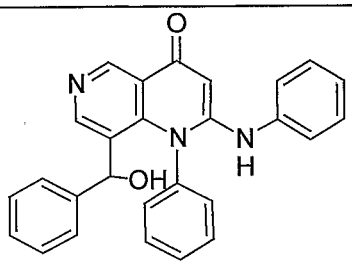
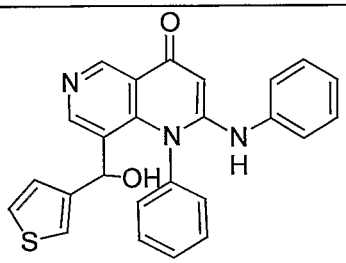
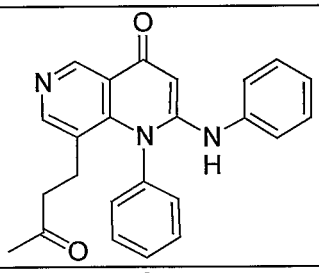
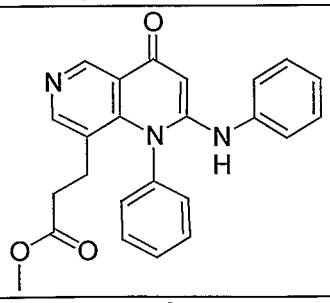
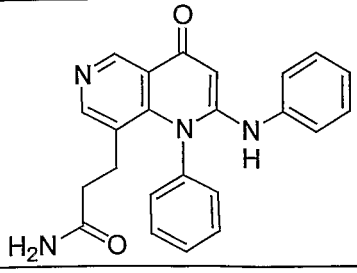
Example	Stucture	Representative Procedure
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856		Intermediate BA, BB, BC and Example 39, 31, 33
857		Intermediate BA, BB, BC and Example 39, 31, 33
858		Intermediate BA, BB, BC and Example 39, 31, 32, 33, 47

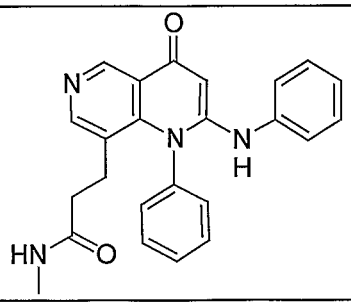
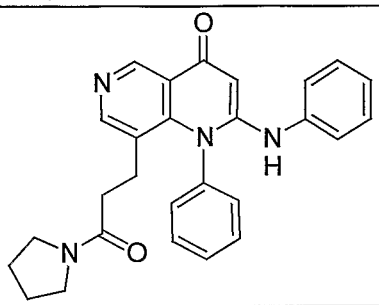
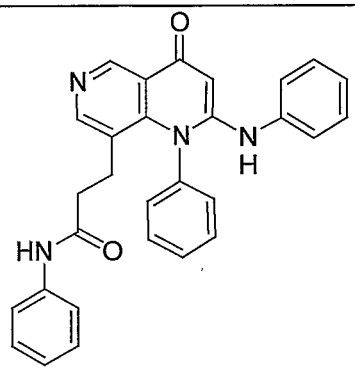
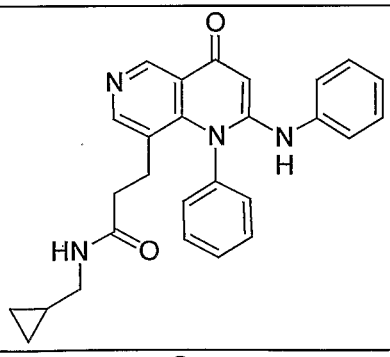
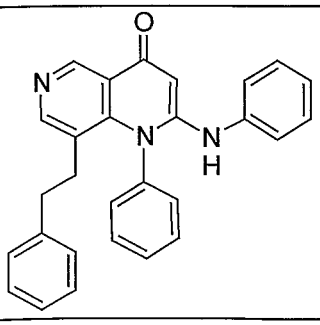
Example	Stucture	Representative Procedure
859		Intermediate BA, BB, BC and Example 39, 31, 32, 33, 47
860		Intermediate BA, BB, BC and Example 39, 31, 33
861		Intermediate BA, BB, BC and Example 39, 31, 32, 33, 47
862		Intermediate BA, BB, BC and Example 39, 31, 32, 33, 47

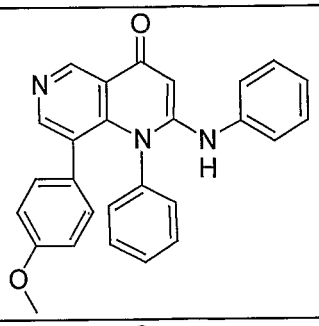
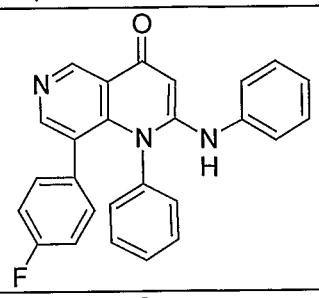
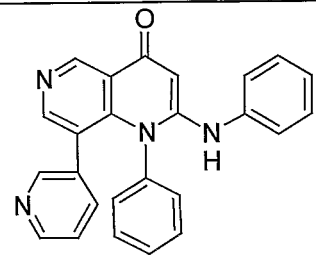
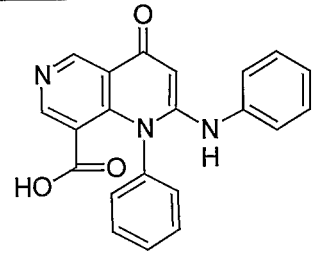
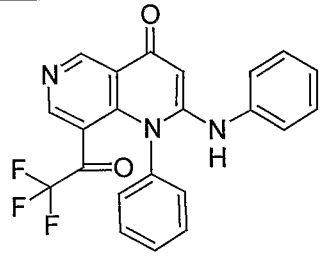
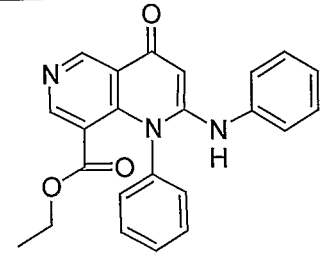
Example	Stucture	Representative Procedure
863		Intermediate BA, BB, BC and Example 39, 49, 50, 51
864		Intermediate BA, BB, BC and Example 39, 49, 50, 51
865		Intermediate BA, BB, BC and Example 39, 49, 50, 51
866		Intermediate BA, BB, BC and Example 39, 43, 47

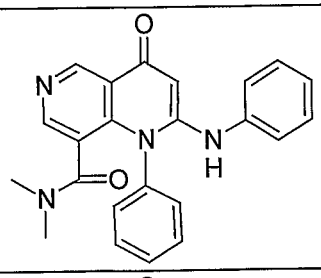
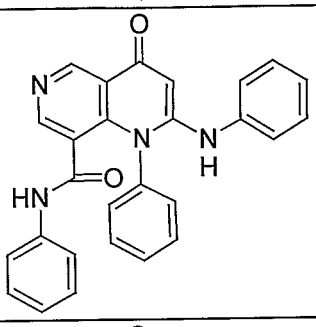
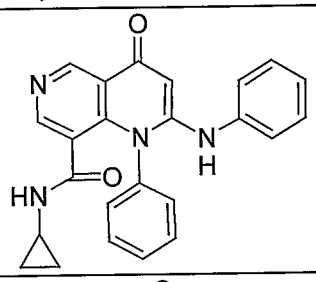
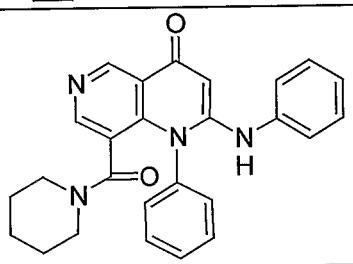
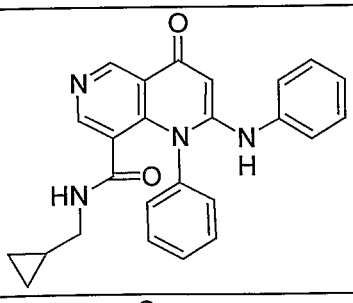
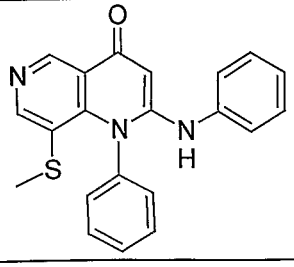
Example	Stucture	Representative Procedure
867		Intermediate BA, BB, BC and Example 39, 43 and Intermediate AK
868		Intermediate BA, BB, BC and Example 39, 3
869		Intermediate BA, BB, BC and Example 39, 43, 47
870		Intermediate BA, BB, BC and Example 39, 43, 47

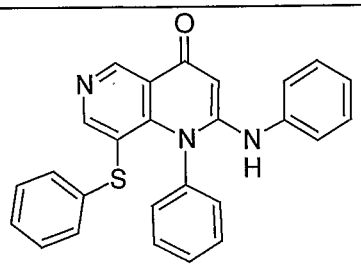
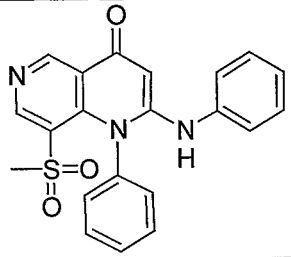
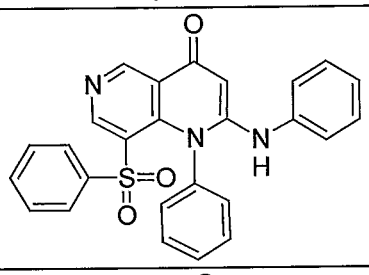
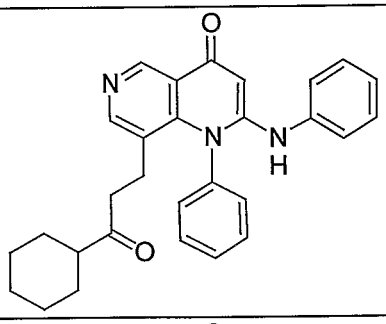
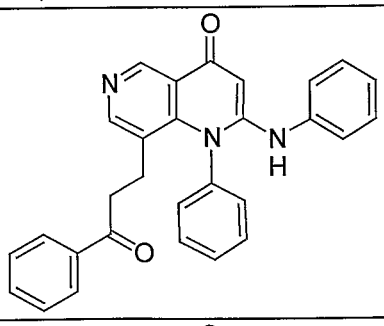
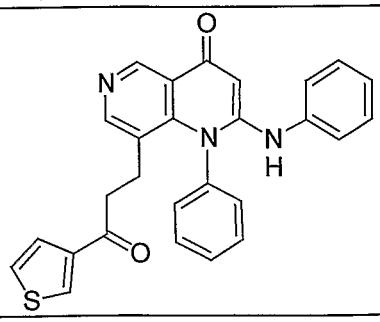
Example	Stucture	Representative Procedure
871		Intermediate BA, BB, BC and Example 39, 22
872		Intermediate BA, BB, BC and Example 39, 3, 24, 12
873		Intermediate BA, BB, BC and Example 39, 3, 24 and Intermediate AK
874		Intermediate BA2, BB2, BC2 and Example 41, 34
875		Intermediate BA2, BB2, BC2 and Example 41, 34

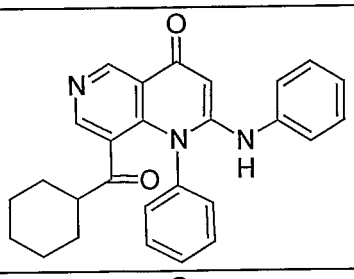
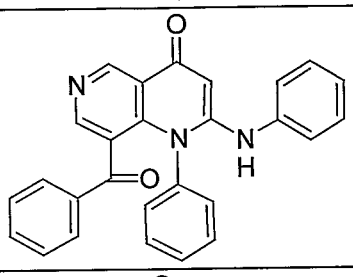
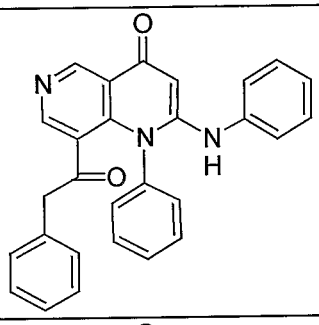
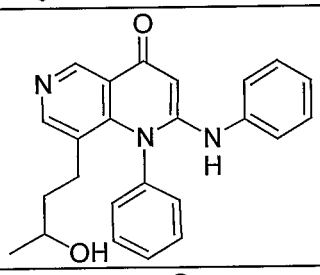
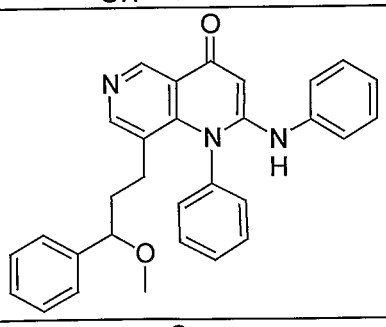
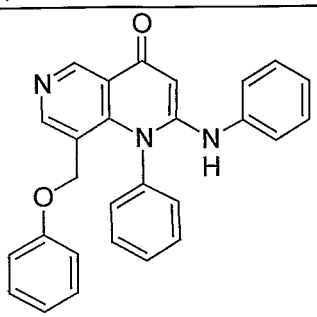
Example	Stucture	Representative Procedure
876		Intermediate BA2, BB2, BC2 and Example 41, 34
877		Intermediate BA2, BB2, BC2 and Example 41, 34
878		Intermediate BA2, BB2, BC2 and Example 41, 34
879		Intermediate BA2, BB2, BC2 and Example 41, 31, 33
880		Intermediate BA2, BB2, BC2 and Example 41, 31, 33
881		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 47

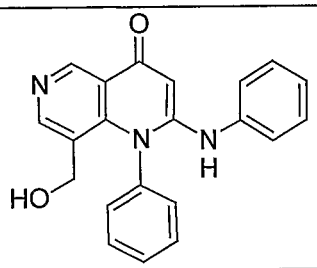
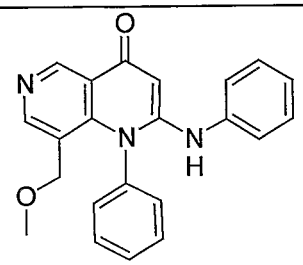
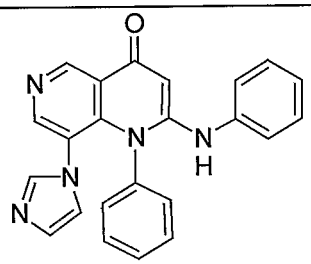
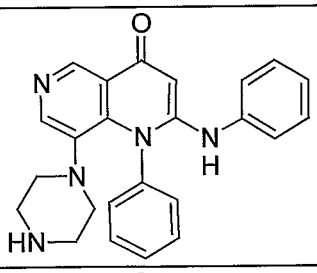
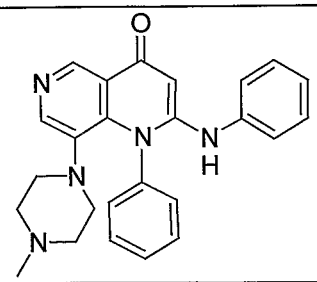
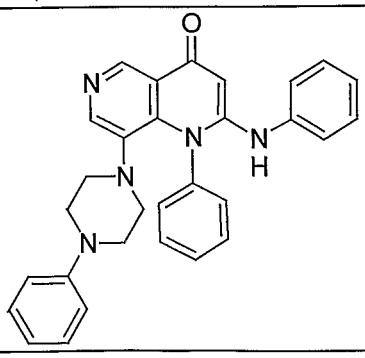
Example	Stucture	Representative Procedure
882		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 47
883		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 47
884		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 47
885		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 47
886		Intermediate BA2, BB2, BC2 and Example 41, 31, 33

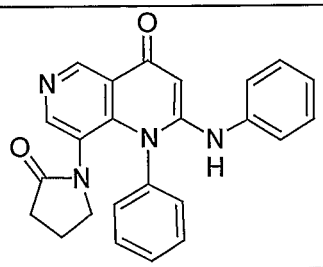
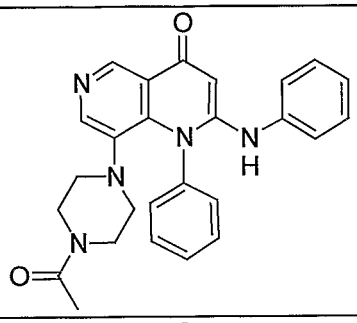
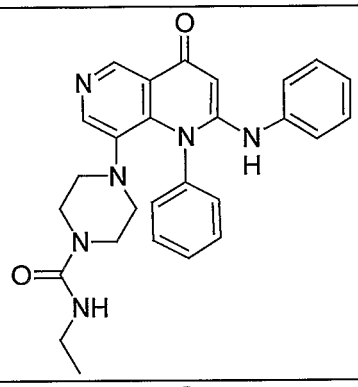
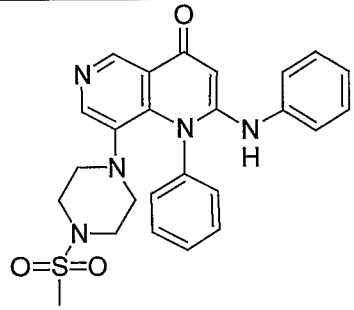
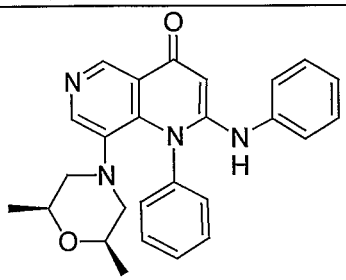
Example	Stucture	Representative Procedure
887		Intermediate BA2, BB2, BC2 and Example 41, 55
888		Intermediate BA2, BB2, BC2 and Example 41, 55
889		Intermediate BA2, BB2, BC2 and Example 41, 55
890		Intermediate BA2, BB2, BC2 and Example 41, 49
891		Intermediate BA2, BB2, BC2 and Example 41, 34
892		Intermediate BA2, BB2, BC2 and Example 41, 17

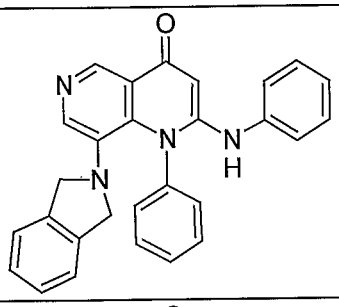
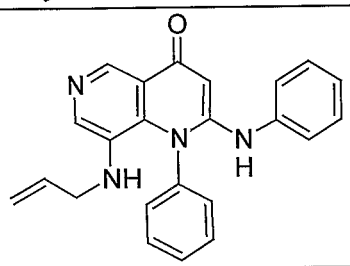
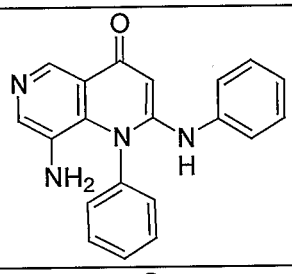
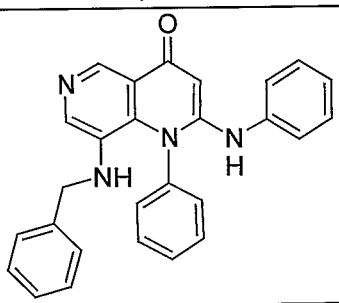
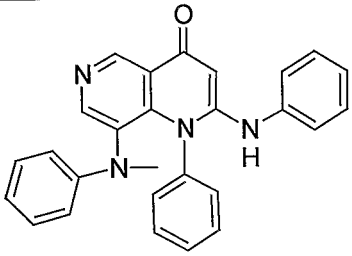
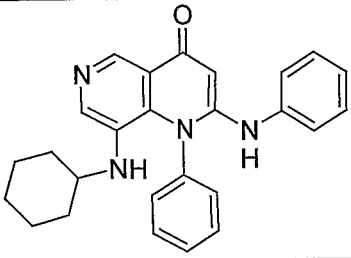
Example	Stucture	Representative Procedure
893		Intermediate BA2, BB2, BC2 and Example 41, 49, 47
894		Intermediate BA2, BB2, BC2 and Example 41, 49, 47
895		Intermediate BA2, BB2, BC2 and Example 41, 49, 47
896		Intermediate BA2, BB2, BC2 and Example 41, 49, 47
897		Intermediate BA2, BB2, BC2 and Example 41, 49, 47
898		Intermediate BA2, BB2, BC2 and Example 41, 34

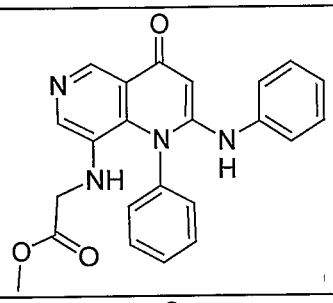
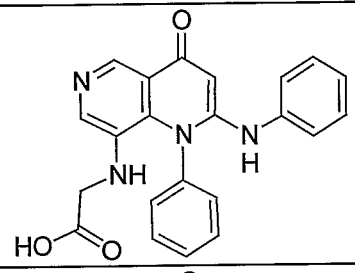
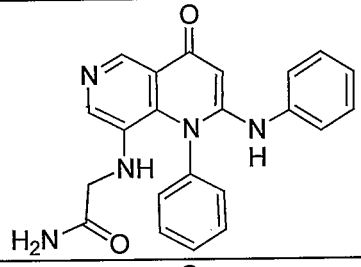
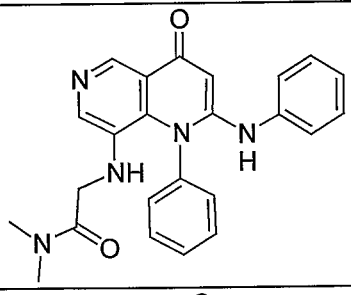
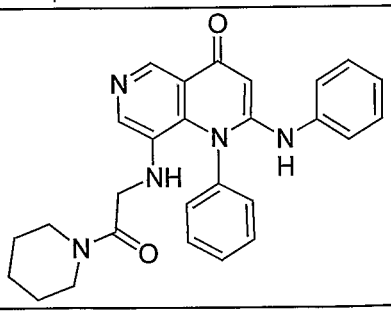
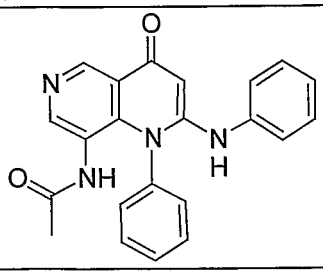
Example	Stucture	Representative Procedure
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900		Intermediate BA2, BB2, BC2 and Example 41, 34, 21
901		Intermediate BA2, BB2, BC2 and Example 41, 34, 21
902		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 50, 51
903		Intermediate BA2, BB2, BC2 and Example 41, 31, 33
904		Intermediate BA2, BB2, BC2 and Example 41, 31, 32, 33, 50, 51

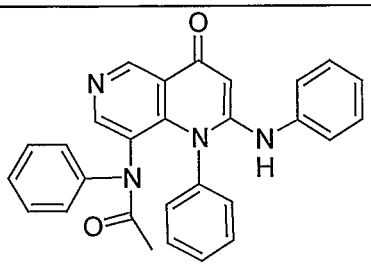
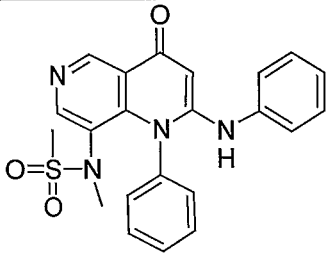
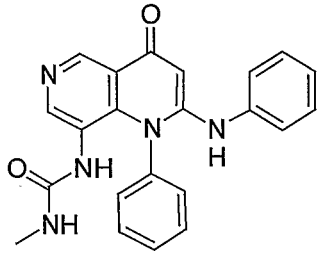
Example	Stucture	Representative Procedure
905		Intermediate BA2, BB2, BC2 and Example 41, 49, 50, 51
906		Intermediate BA2, BB2, BC2 and Example 41, 49, 50, 51
907		Intermediate BA2, BB2, BC2 and Example 41, 49, 50, 51
908		Intermediate BA2, BB2, BC2 and Example 41, 31, 33, 25
909		Intermediate BA2, BB2, BC2 and Example 41, 31, 33, 25 and Intermediate AJ
910		Intermediate BA2, BB2, BC2 and Example 41, 17, 25, 26

Example	Stucture	Representative Procedure
911		Intermediate BA2, BB2, BC2 and Example 41, 17, 25
912		Intermediate BA2, BB2, BC2 and Example 41, 17, 25 and Intermediate AJ
913		Intermediate BA2, BB2, BC2 and Example 41, 3
914		Intermediate BA2, BB2, BC2 and Example 41, 3
915		Intermediate BA2, BB2, BC2 and Example 41, 3
916		Intermediate BA2, BB2, BC2 and Example 41, 3

Example	Stucture	Representative Procedure
917		Intermediate BA2, BB2, BC2 and Example 41, 3
918		Intermediate BA2, BB2, BC2 and Example 41, 3
919		Intermediate BA2, BB2, BC2 and Example 41, 3 and Intermediate AK
920		Intermediate BA2, BB2, BC2 and Example 41, 3, 12
921		Intermediate BA2, BB2, BC2 and Example 41, 3

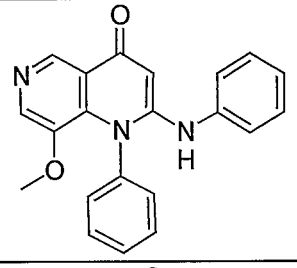
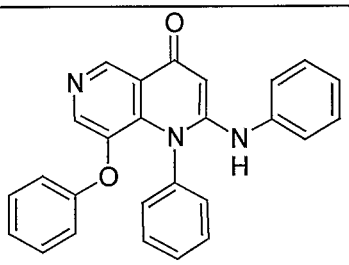
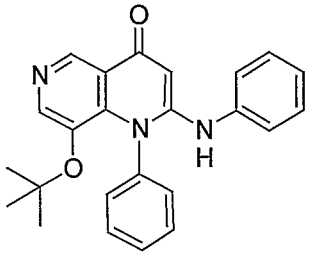
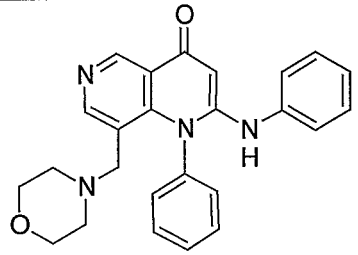
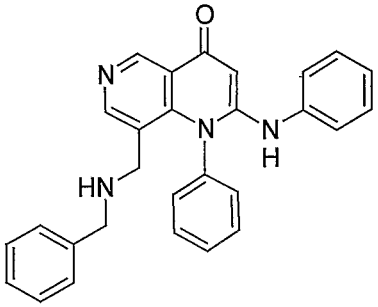
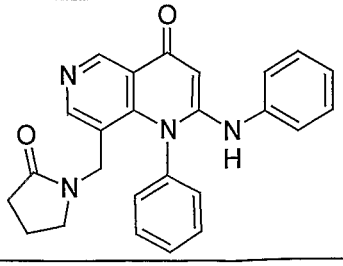
Example	Stucture	Representative Procedure
922		Intermediate BA2, BB2, BC2 and Example 41, 3
923		Intermediate BA2, BB2, BC2 and Example 41, 3
924		Intermediate BA2, BB2, BC2 and Example 41, 3, 24
925		Intermediate BA2, BB2, BC2 and Example 41, 3
926		Intermediate BA2, BB2, BC2 and Example 41, 3
927		Intermediate BA2, BB2, BC2 and Example 41, 3

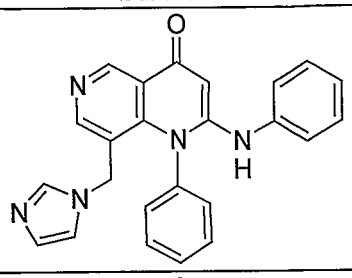
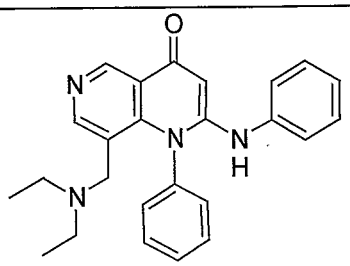
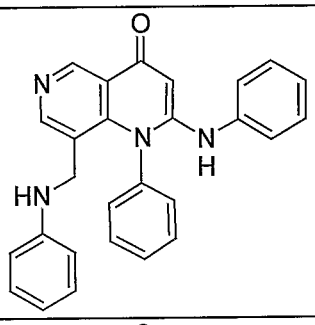
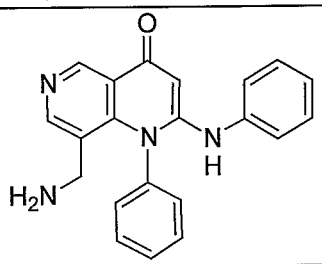
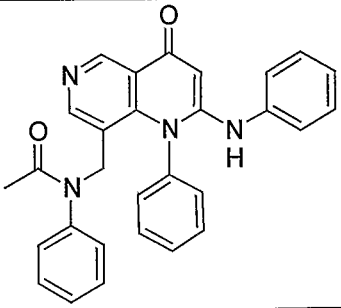
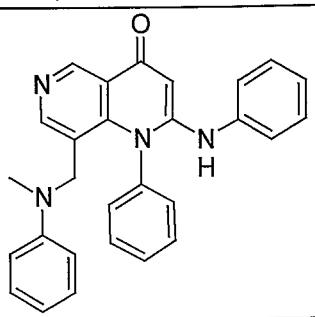
Example	Stucture	Representative Procedure
928		Intermediate BA2, BB2, BC2 and Example 41, 3
929		Intermediate BA2, BB2, BC2 and Example 41, 3, 45
930		Intermediate BA2, BB2, BC2 and Example 41, 3, 18
931		Intermediate BA2, BB2, BC2 and Example 41, 3, 45, 47
932		Intermediate BA2, BB2, BC2 and Example 41, 3, 45, 47
933		Intermediate BA2, BB2, BC2 and Example 41, 3, 24, 47

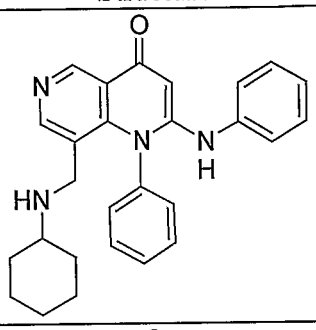
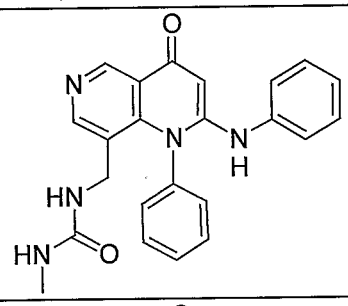
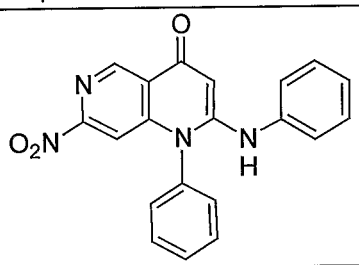
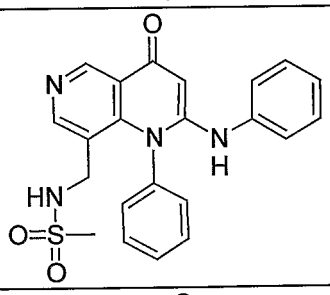
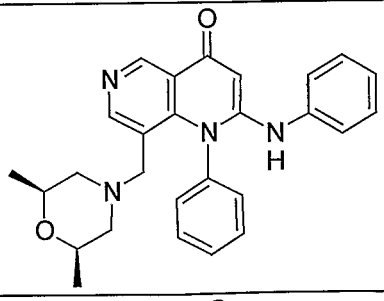
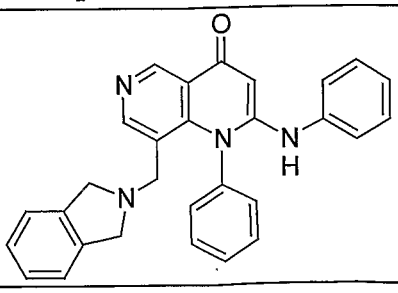
Example	Stucture	Representative Procedure
934		Intermediate BA2, BB2, BC2 and Example 41, 3, 47
935		Intermediate BA2, BB2, BC2 and Example 41, 3, 12
936		Intermediate BA2, BB2, BC2 and Example 41, 3, 24 and Intermediate AK

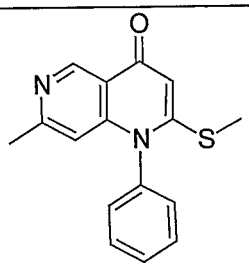
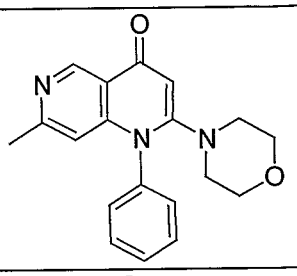
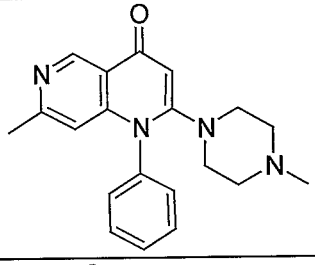
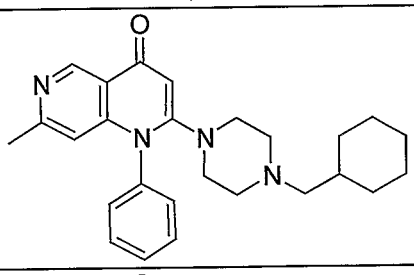
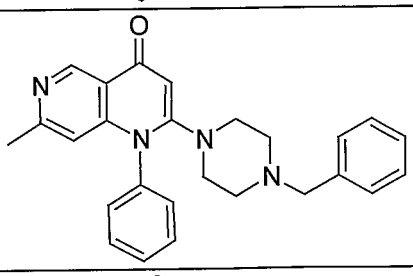
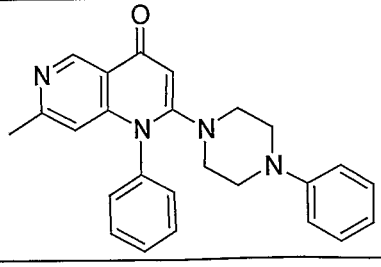
Utilizing the above described procedures for intermediates and examples, and Flow Diagrams I - XIV alone or in combination, a variety of Formula II compounds can be prepared using the appropriate starting material. These compounds are summarized in Table 2C

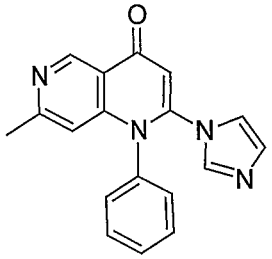
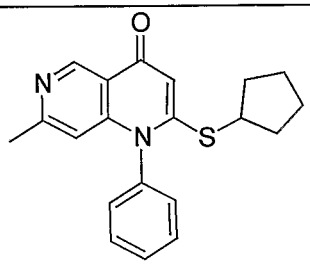
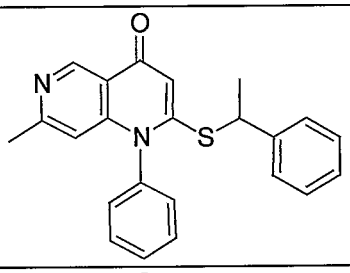
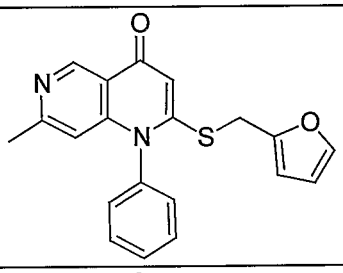
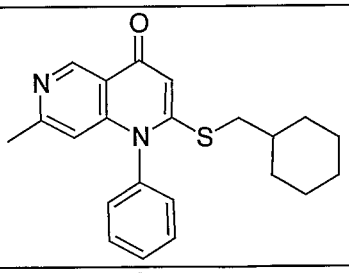
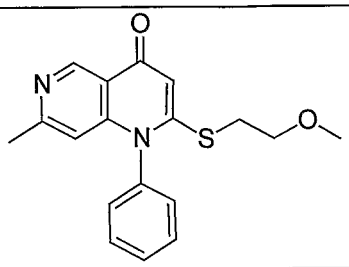
Table 2C

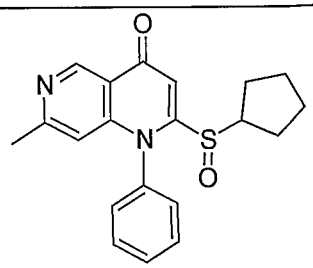
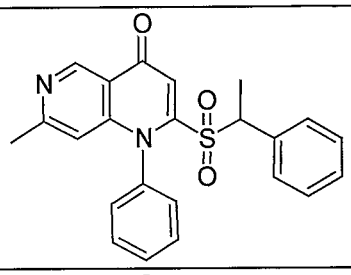
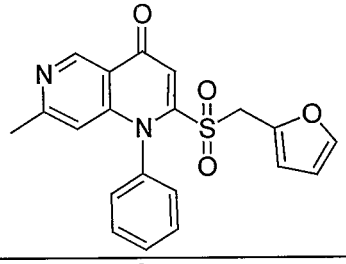
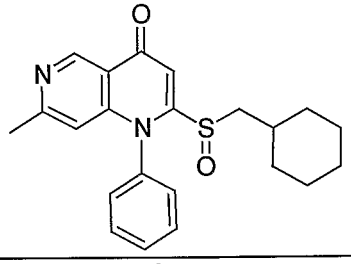
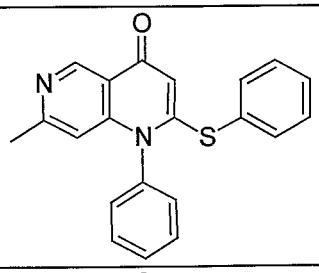
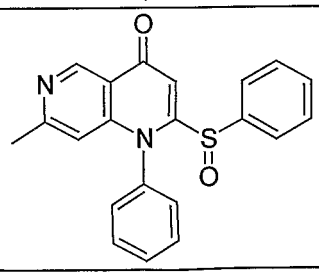
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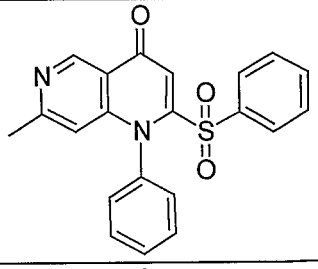
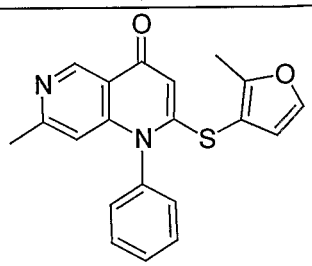
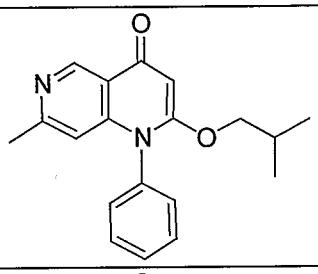
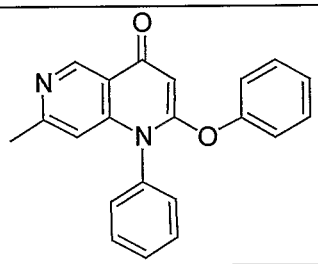
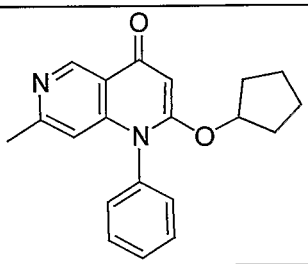
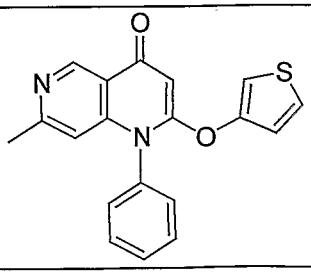
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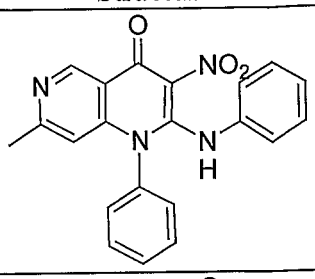
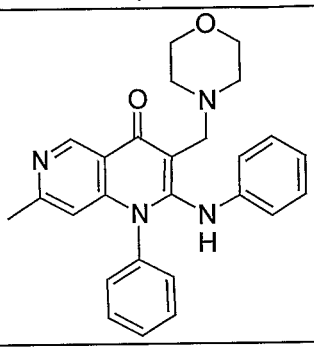
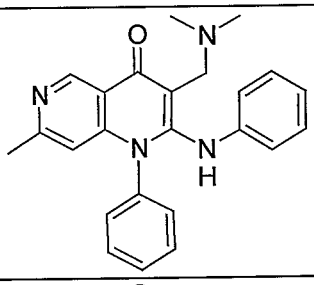
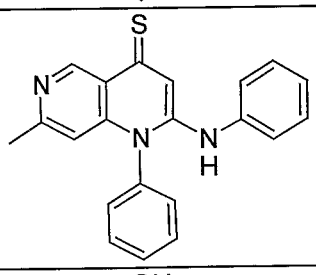
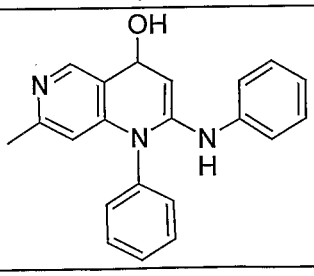
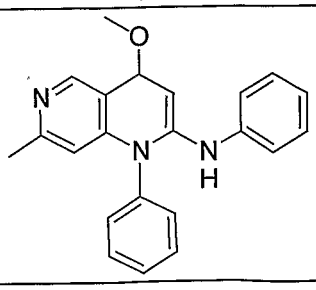
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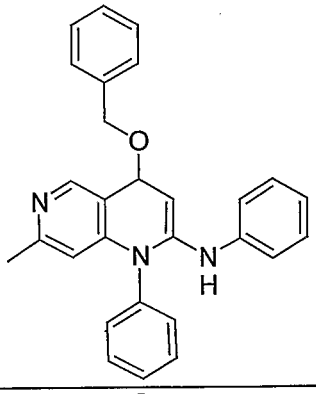
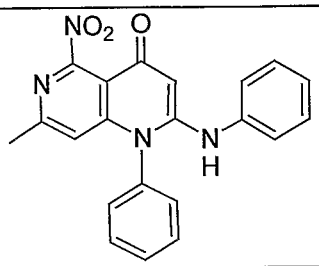
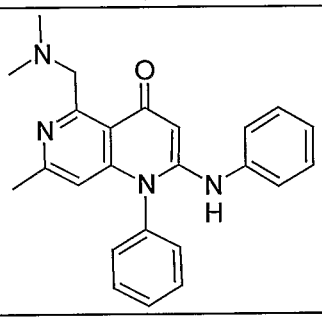
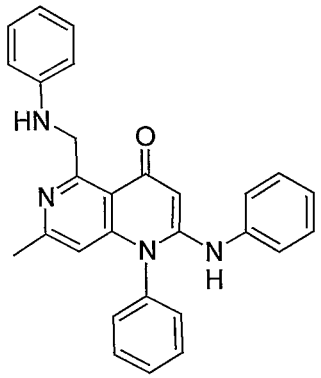
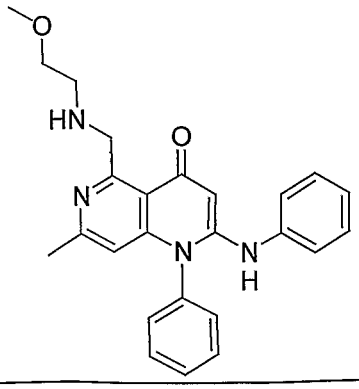
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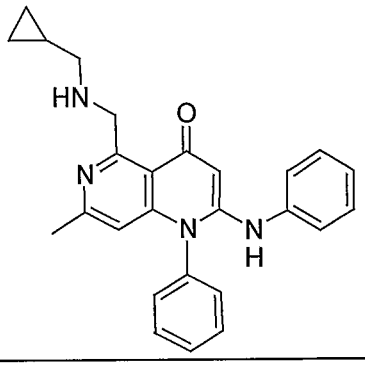
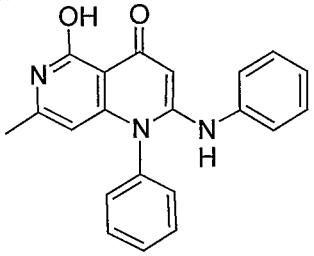
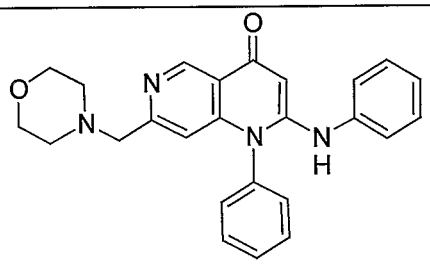
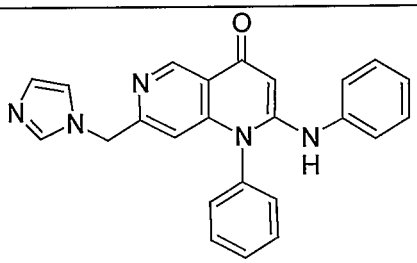
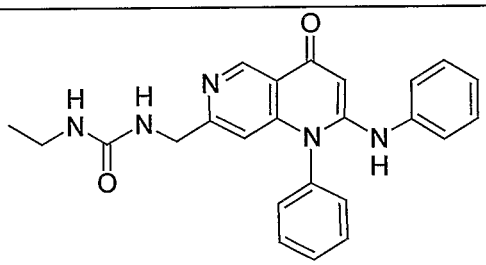
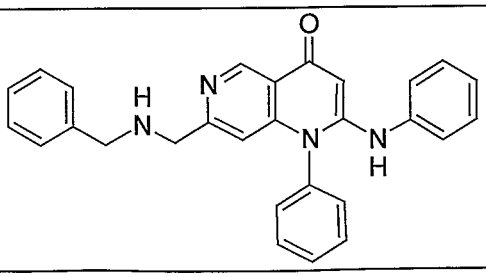
Example	Structure
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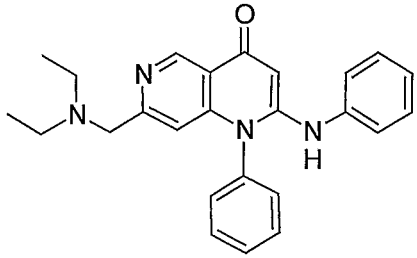
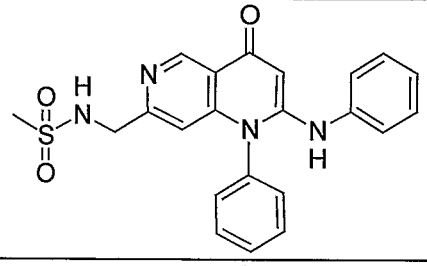
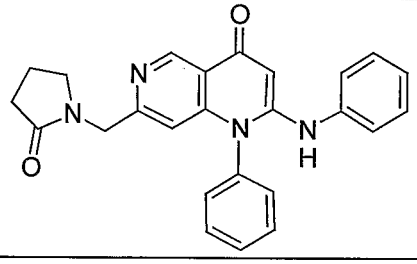
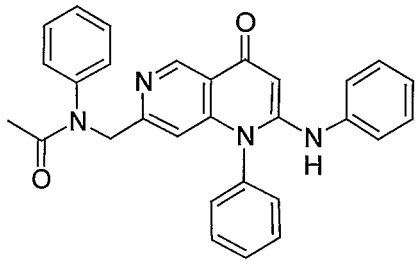
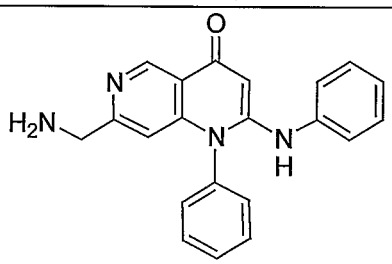
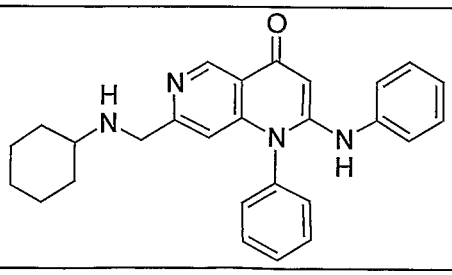
Example	Structure
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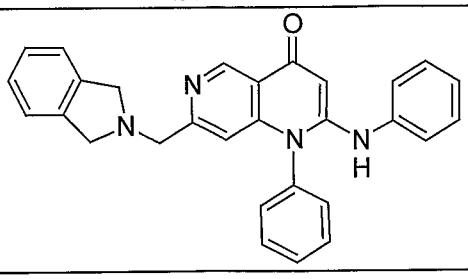
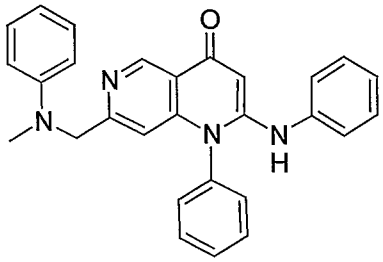
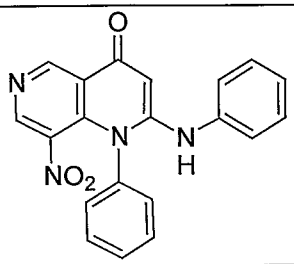
Example	Structure
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Example	Structure
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984	

Example	Structure
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987	
988	
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Example	Structure
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991	
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993	
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Example	Structure
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998	
999	
1000	
1001	

Example	Structure
1002	
1003	
1004	

Biological Evaluation

Demonstration of the activity of the compounds of this invention is accomplished through *in vitro, ex vivo* and *in vivo* assays that are well known in the art.

***in vivo* test procedure:**

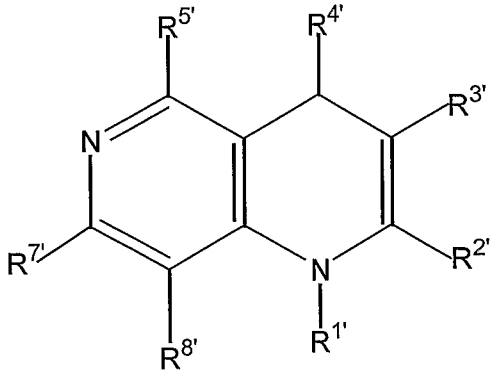
Male Wistar rats (270-330g) were fasted overnight and then given either vehicle or compound by oral gavage. Two or three hours later, the rats were given an intraperitoneal dose of glucose (2g/kg). The rats were tail-bled for glucose using a Glucometer (Bayer Corporation, Mishawaka, IN) just prior to the glucose dose and 15, 30 and 60 minutes afterward. The area under the glucose curve was calculated by the trapezoidal method for both the vehicle and treated animals, and the percent reduction in the glucose AUC by the compound calculated. A typical positive effect of the compound results in a 12-20% reduction in the AUC relative to the AUC of the vehicle-treated group. Compounds of present invention were found to have a blood glucose lowering effect in this *in vivo* assay.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing examples are included by way of illustration only. Accordingly, the scope of the invention is limited only by the scope of the appended claims.

CLAIMS

What is claimed is:

1. A compound of the formula II



(II)

wherein

$R^{1'}$ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

$R^{1'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{10} is selected from nitro, nitrile, hydroxy, halogen, acyl of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4

heteroatoms selected from N, $S(=O)_{0-2}$ and O, $NR^{11}R^{12}$, $C(=O)OR^{11}$, $C(=O)NHR^{11}$, $NHC(=O)R^{13}$, $NHS(=O)_2R^{13}$, $S(=O)_{0-2}R^{13}$, $S(=O)_2NHR^{11}$, cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O);

R^{13} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

R^{11} and R^{12} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

A is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and haloalkyl of 1-8 carbon atoms;

R^9 is selected from hydroxy, alkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, O-A-R^{14}, $NR^{11}R^{12}$; or

R^9 is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, all of which may be substituted with 1-3 of R^{10}, or

R^9 is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said

heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{14} is selected from cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

with the proviso for $R^{1'}$ that when A is CH_2, R^9 is not optionally substituted biphenyl;

$R^{2'}$ is selected from $NR^{15}R^{16}$, $S(O)_{0-2}R^{17}$, and OR^{17};

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, $S(=O)_2NHR^{18}$;

R^{18} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, and alkynyl of 2-6 carbon atoms, all of which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9;

R^{16} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

R^{16} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{17} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms, A-R^9, or

R^{17} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N,

$S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{3'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$, and O, cycloalkenyl of 4-8 carbon atoms, and heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$, and A-R^{20};

R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^9, or

R^{19} and R^{20} are independently selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{4'}$ is selected from =O, =S, and OR^{21};

R^{21} is hydrogen, or

R^{21} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, or A-C(=O)$NR^{24}R^{25}$, or

$R^{5'}$, $R^{7'}$, and $R^{8'}$ are independently selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, haloalkyl of 1-8 carbon atoms, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, cycloalkoxy of 3-8 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$;

Q is selected from O and $S(=O)_{0-2}$;

R^{22} is selected from hydrogen, alkyl of 1-8 carbon atoms, haloalkyl of 1-8 carbon atoms, and cycloalkyl of 3-8 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, and cycloalkoxy of 3-8 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

with the proviso for $A(OR^{22})$-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-8 carbon atoms, haloalkoxy of 1-8 carbon atoms, and cycloalkoxy of 3-8 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said

heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or

heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, C(=O)R^{24}, C(=O)OR^{26}, C(=O)N$R^{25}R^{30}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)N$R^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered

heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, and heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms, all of which may be substituted with 1-3 of R^{10};

R^{29} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein $R^{4'}$ is =O.

3. The compound of claim 1, wherein $R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, N$R^{19}R^{20}$, A-OR^{19}, A-N$R^{19}R^{20}$ and A-R^{20}.

4. The compound of claim 3, wherein R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms and A-R^{9}, or wherein R^{19} and R^{20} are independently selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(O)_{0-2}$ and O, cycloalkyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon

atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}.

5. The compound of claim 1, wherein $R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$ and A-R^{20}; and

$R^{4'}$ is =O.

6. The compound of claim 5, wherein R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms and A-R^9, or wherein R^{19} and R^{20} are independently selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(O)_{0-2}$ and O, cycloalkyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}.

7. The compound of claim 1, wherein $R^{2'}$ is $NR^{15}R^{16}$.

8. The compound of claim 7, wherein

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, and $S(=O)_2NHR^{18}$;

R^{18} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-6 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is alkyl of 1-6 carbon atoms, which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9; and

R^{16} is selected from alkyl of 1-6 carbon atoms and A-R^9, or

R^{16} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}.

9. The compound of claim 1, wherein $R^{2'}$ is $NR^{15}R^{16}$;

$R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$ and A-R^{20}; and

$R^{4'}$ is =O.

10. The compound of claim 9, wherein

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, and $S(=O)_2NHR^{18}$;

R^{18} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-6 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is alkyl of 1-6 carbon atoms, which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

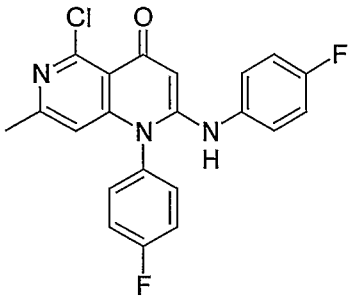
R^{18} is A-R^9; and

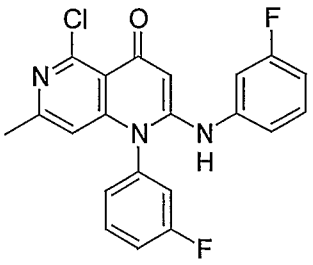
R^{16} is selected from alkyl of 1-6 carbon atoms and A-R^9, or

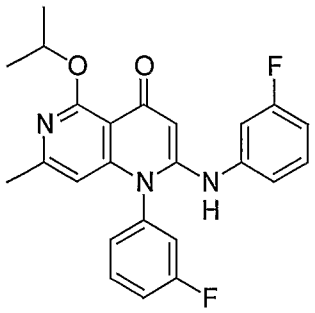
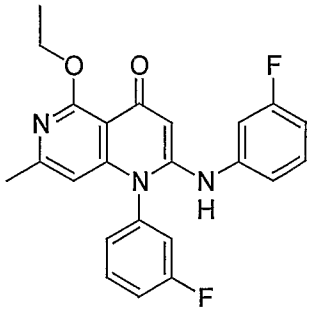
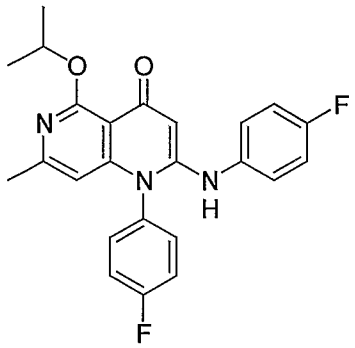
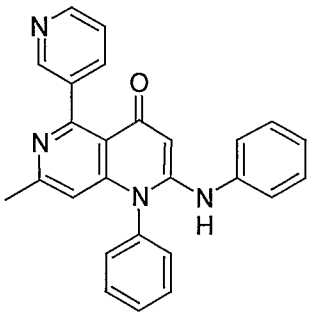
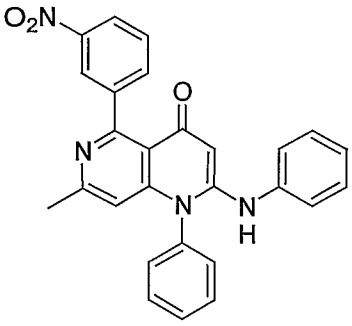
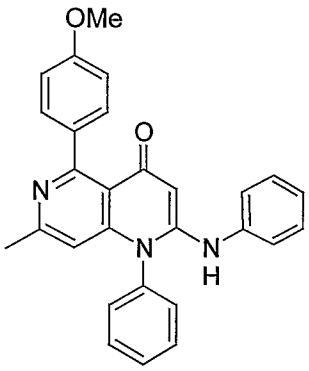
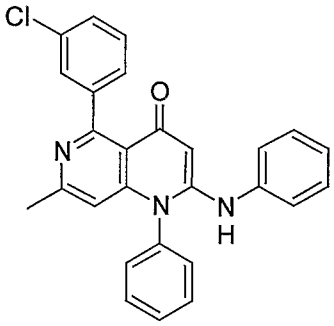
R^{16} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}.

11. The compound of claim 10, selected from the group consisting of:





and .

12. The compound of claim 9, wherein R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms and A-R^9, or wherein R^{19} and R^{20} are independently selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(O)_{0-2}$ and O, cycloalkyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon

atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}.

13. The compound of claim 1 or 9, wherein $R^{5'}$ is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{5'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

with the proviso for $A(OR^{22})$-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, wherein one or more of the carbon atoms in said

heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, C(=O)R^{24}, C(=O)OR^{26}, C(=O)N$R^{25}R^{30}$, S(=O)$_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)N$R^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, S(=O)$_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, S(=O)$_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, S(=O)$_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A(OR^{22})-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, S(=O)$_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, S(=O)$_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, S(=O)$_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}; and

R^{29} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, A-$C(=O)NR^{24}R^{25}$, A-$NR^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}.

14. The compound of claim 13, wherein $R^{5'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$ is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{5'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of

1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, and A-C(=O)R^{24};

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, wherein one or more

of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $C(=O)R^{24}$, $C(=O)OR^{26}$, $C(=O)NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms

in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

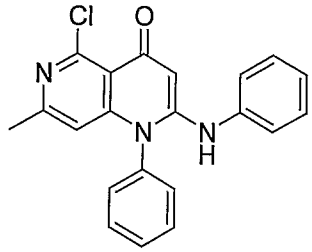
R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}; and

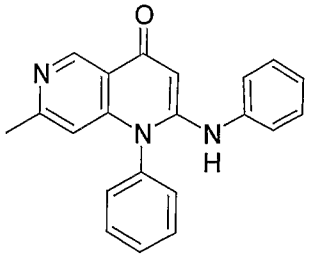
R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

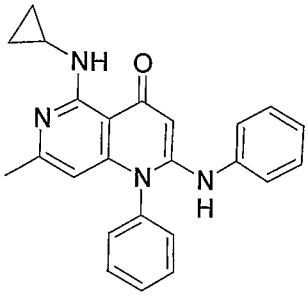
R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

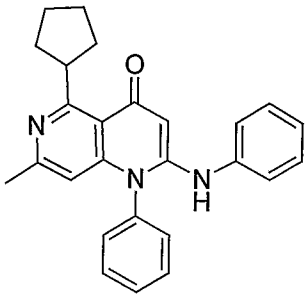
R^{29} is 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}.

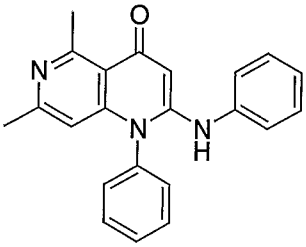
15. The compound of claim 14 selected from the group consisting of:

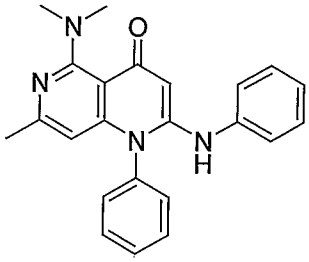


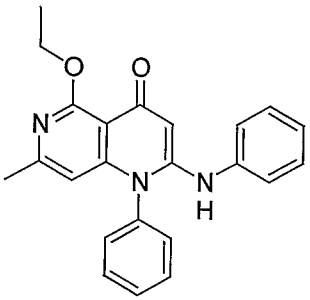


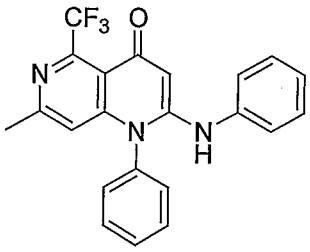


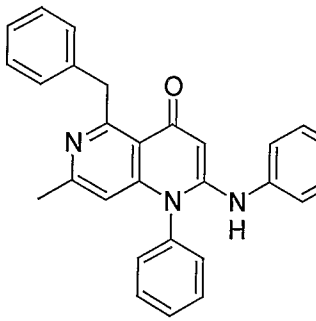


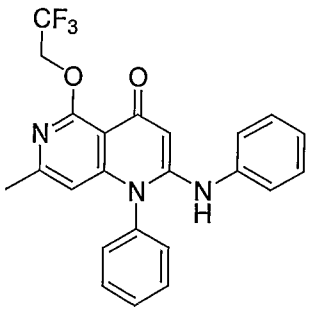


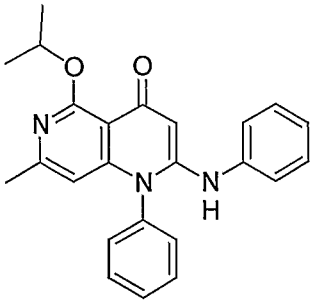


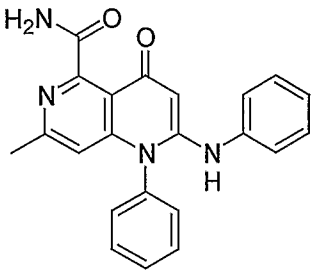


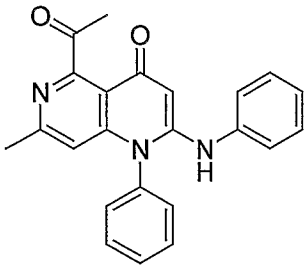












and .

16. The compound of claim 1 or 9, wherein $R^{7'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{7'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, or A-C(=O)$NR^{24}R^{25}$, or

$R^{7'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

with the proviso for $A(OR^{22})$-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $C(=O)R^{24}$, $C(=O)OR^{26}$, $C(=O)NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A(OR^{22})-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10};

R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}.

17. The compound of claim 16, wherein $R^{7'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{7'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl

may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, or $S(=O)_2R^{26}$, , or

$R^{7'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)R^{24}$, and A-$C(=O)NR^{24}R^{25}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said

heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)N$R^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

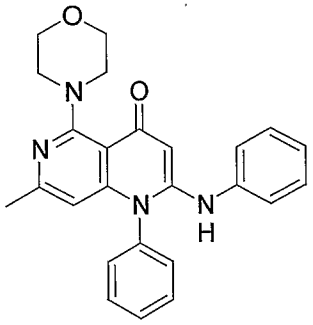
R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10};

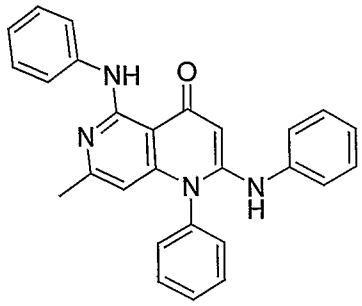
R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

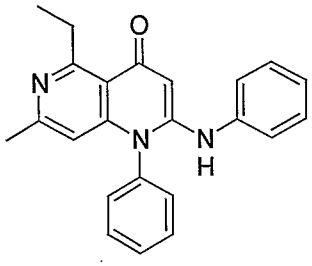
R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

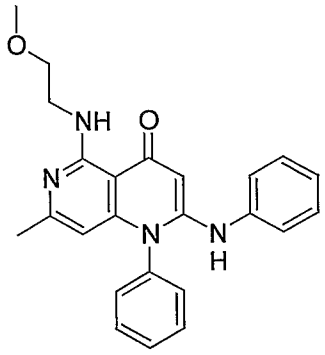
R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}.

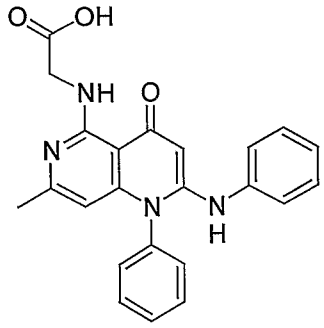
18. The compound of claim 17 selected from the group consisting of:

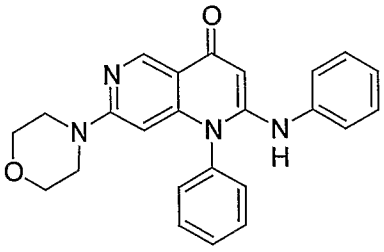


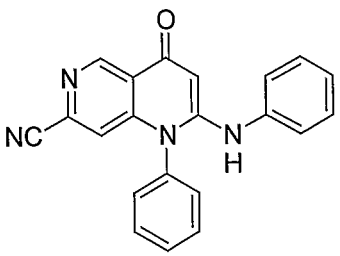


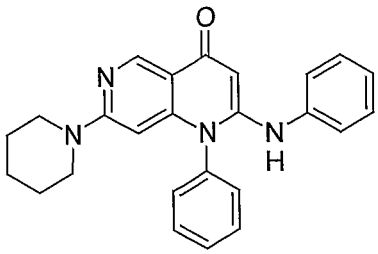


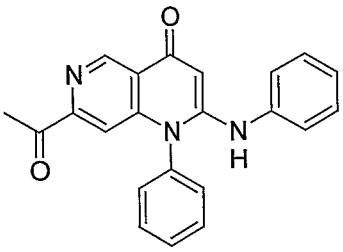


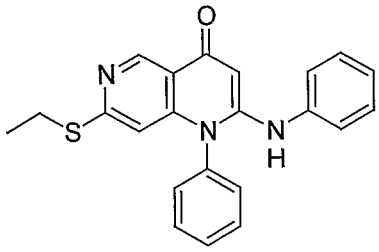


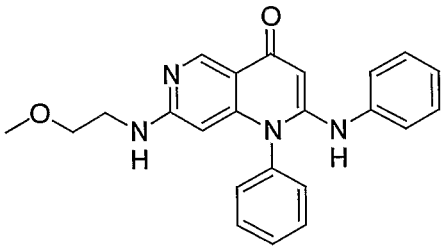


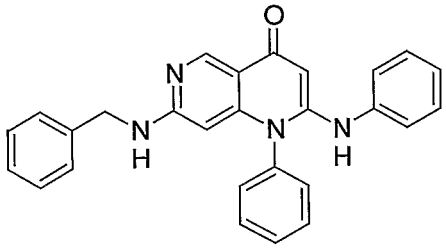


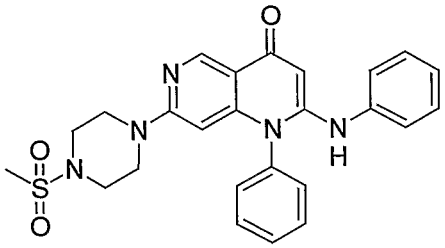


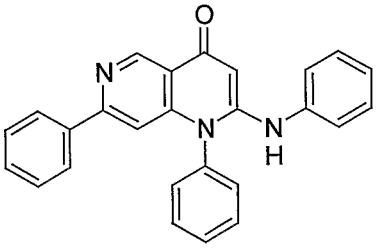


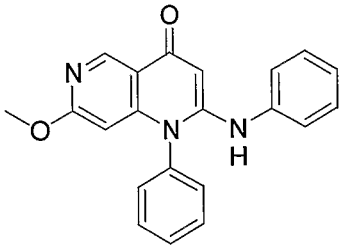


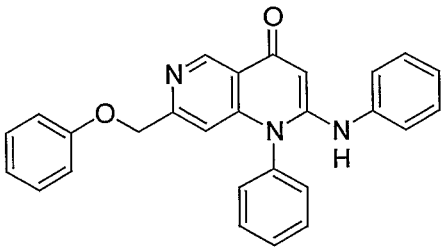


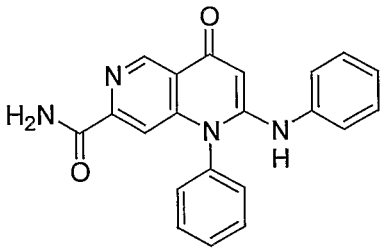


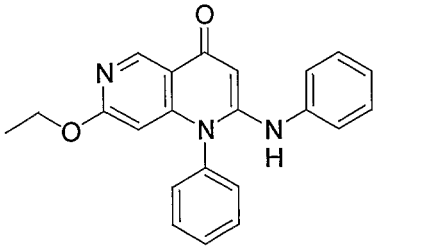


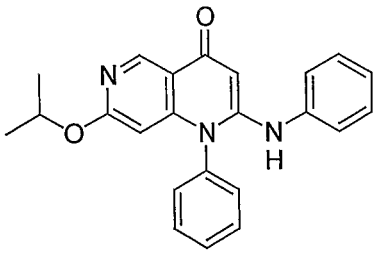


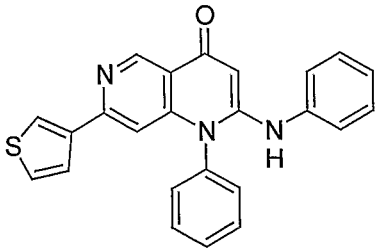


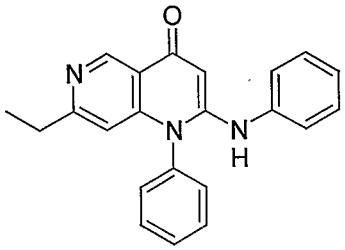


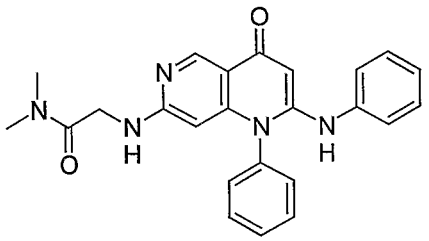












and .

19. The compound of claim 1 or 9, wherein $R^{8'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{8'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, or A-C(=O)$NR^{24}R^{25}$, or

$R^{8'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

with the proviso for $A(OR^{22})$-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $C(=O)R^{24}$, $C(=O)OR^{26}$, $C(=O)NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A(OR^{22})-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10};

R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}.

20. The compound of claim 1 or 9, wherein $R^{8'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{8'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said

heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, or $S(=O)_2R^{26}$, , or

$R^{8'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, $S(=O)_{0-2}$-R^{29}, $S(=O)_{0-2}$-A-$NR^{24}R^{25}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, monocyclic heteroaryland/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

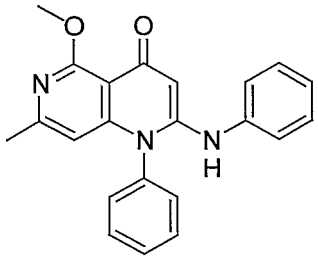
R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10};

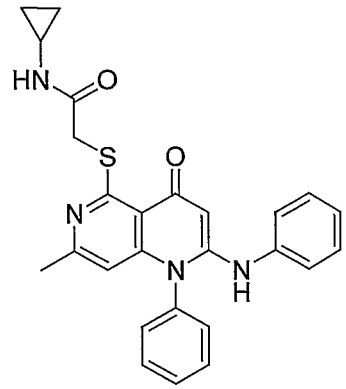
R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, , A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

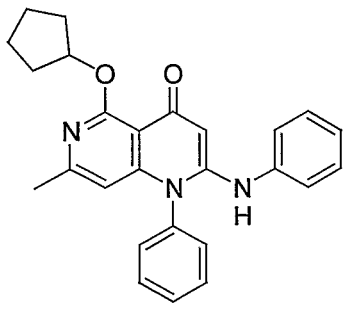
R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

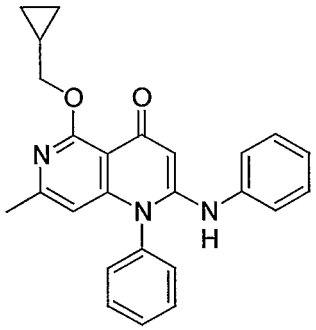
R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}.

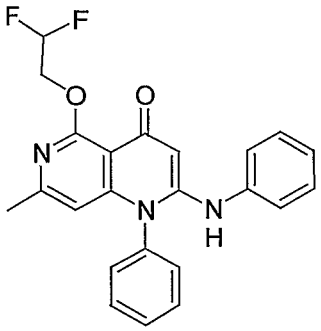
21. The compound of claim 20 selected from the group consisting of:

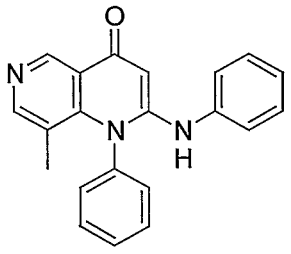


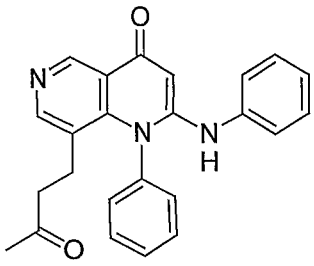


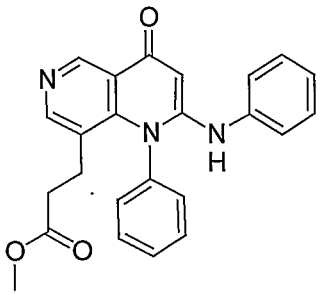


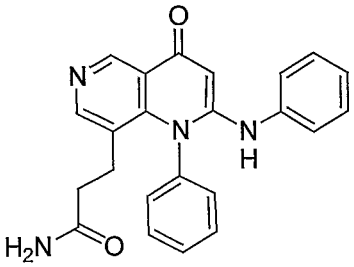


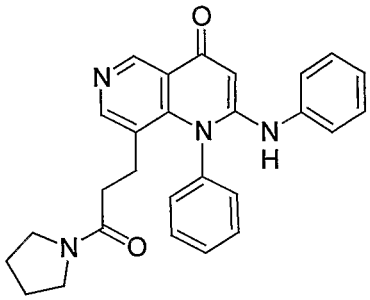


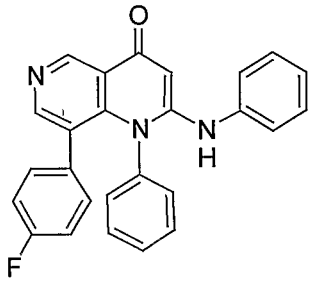


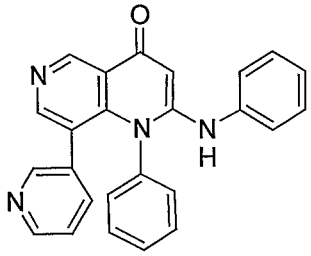


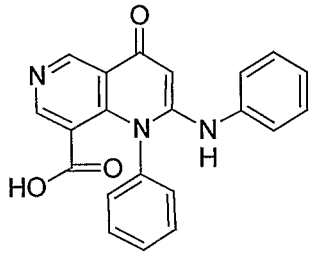


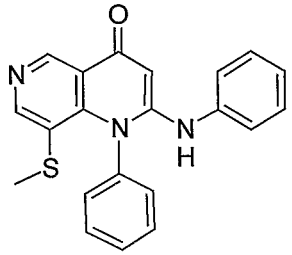


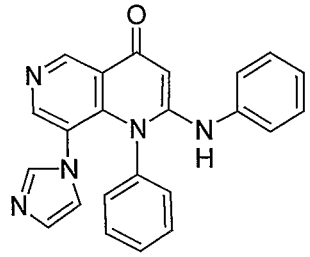


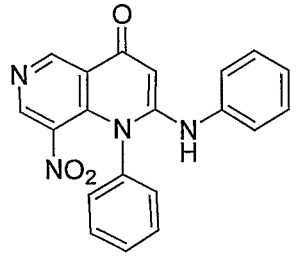






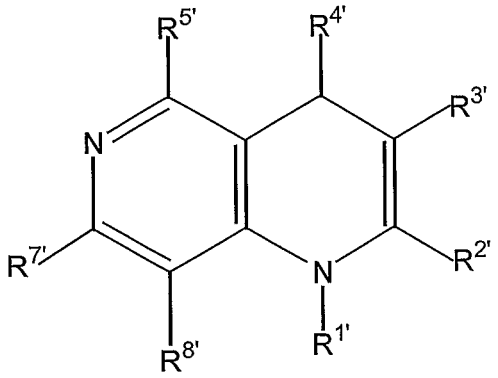






and

22. A compound of the formula II



(II)

wherein

$R^{1'}$ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

$R^{1'}$ is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{10} is selected from nitro, nitrile, hydroxy, halogen, acyl of 1-6 carbon atoms, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, $NR^{11}R^{12}$, $C(=O)OR^{11}$, $C(=O)NHR^{11}$, $NHC(=O)R^{13}$, $NHS(=O)_2R^{13}$, $S(=O)_{0-2}R^{13}$, $S(=O)_2NHR^{11}$, cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, 5-7

membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O);

R^{13} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

R^{11} and R^{12} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, and cycloalkenyl of 4-6 carbon atoms;

A is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and haloalkyl of 1-8 carbon atoms;

R^9 is selected from hydroxy, alkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, O-A-R^{14}, $NR^{11}R^{12}$; or

R^9 is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, all of which may be substituted with 1-3 of R^{10}, or

R^9 is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said

heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{14} is selected from cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

with the proviso for $R^{1'}$ that when A is CH_2, R^9 is not optionally substituted biphenyl;

$R^{2'}$ is $NR^{15}R^{16}$;

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, $S(=O)_2NHR^{18}$;

R^{18} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, and alkynyl of 2-6 carbon atoms, all of which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9;

R^{16} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, and A-R^9, or

R^{16} is selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{3'}$ is selected from cycloalkyl of 3-6 carbon atoms, heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, both of which may be substituted with 1-3 of R^{10}, or

$R^{3'}$ is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, hydrogen, nitro, halogen, $NR^{19}R^{20}$, A-OR^{19}, A-$NR^{19}R^{20}$ and A-R^{20};

R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^9, or

R^{19} and R^{20} are independently selected from aryl of 6-10 carbon atoms, heteroaryl of 2-9 carbon atoms and 1-4 heteroatoms selected from N, $S(O)_{0-}$

$_2$ and O, cylcoalkyl of 3-8 carbon atoms, cycloalkenyl of 5-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein said heterocycloalkyl and said heterocycloakenyl may further be fused with phenyl or a 5-6 membered heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

$R^{4'}$ is selected from =O, =S, and OR^{21};

R^{21} is hydrogen, or

R^{21} is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-8 carbon atoms, cycloalkenyl of 4-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10};

$R^{5'}$ is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, or A-C(=O)$NR^{24}R^{25}$, or

$R^{5'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6

carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)$NR^{24}R^{25}$, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)$NR^{24}R^{25}$;

Q is selected from O and $S(=O)_{0-2}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 4-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

with the proviso for A(OR^{22})-R^{23} that when R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, A is not CH;

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic

heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein

said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $C(=O)R^{24}$, $C(=O)OR^{26}$, $C(=O)NR^{25}R^{30}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein

said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, $A(OR^{22})$-R^{23}, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, a 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}; and

R^{29} is selected from alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, A-$C(=O)NR^{24}R^{25}$, A-$NR^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, cycloalkenyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and 5-7 membered heterocycloalkenyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, wherein one or more of the carbon atoms in said heterocycloalkyl or heterocycloalkenyl may be oxidized to C(=O), wherein said heterocycloalkyl or said heterocycloalkenyl may be substituted with 1-3 of R^{10}.

$R^{7'}$ and $R^{8'}$ are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{7'}$ and $R^{8'}$ are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{7'}$ and $R^{8'}$ are independently selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, A(OR^{22})-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$;

and pharmaceutically acceptable salts thereof.

23. The compound of claim 22, wherein

$R^{4'}$ is =O;

R^{15} is selected from hydrogen, alkyl of 1-6 carbon atoms, cylcoalkyl of 3-8 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, A-R^9, $C(=O)R^{18}$, $C(=O)NHR^{18}$, and $S(=O)_2NHR^{18}$;

R^{18} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-6 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{18} is alkyl of 1-6 carbon atoms, which may be substituted with 1-3 of halogen or alkoxy of 1-6 carbon atoms, or

R^{18} is A-R^9; and

R^{16} is selected from alkyl of 1-6 carbon atoms and A-R^9, or

R^{16} is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-8 carbon atoms, and 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, all of which may be substituted with 1-3 of R^{10}, or

R^{15} and R^{16} combine, together with the nitrogen atom to which they are attached, to form a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, or a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{19} and R^{20} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms and A-R^9, or wherein R^{19} and R^{20} are independently selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(O)_{0-2}$ and O, cycloalkyl of 3-6 carbon atoms, 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(O)_{0-2}$ and O, wherein one or more of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10}; and

$R^{5'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{5'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, $S(=O)_2R^{26}$, A-$C(=O)R^{24}$, A-$C(=O)OR^{24}$, or A-$C(=O)NR^{24}R^{25}$, or

$R^{5'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-$NR^{24}R^{25}$, $C(=O)R^{24}$, and A-$C(=O)R^{24}$;

R^{22} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and cycloalkyl of 3-6 carbon atoms;

R^{23} is selected from hydroxy, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, and cycloalkoxy of 3-6 carbon atoms, or

R^{23} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{23} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{24} and R^{25} are independently selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{24} and R^{25} are independently selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3

heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} are independently selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{24} and R^{25} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), all of which may be substituted with 1-3 of R^{10};

R^{26} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{26} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{26} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{27} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{27} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{27} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{28} is selected from hydrogen, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, and A-C(=O)N$R^{24}R^{25}$, or

R^{28} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{28} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

R^{30} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, and A-R^{23}, or

R^{30} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{30} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, or

R^{25} and R^{30} combine, together with the nitrogen atom to which they are attached, to form a 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and O, or a monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10};

R^{29} is selected from alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, A-C(=O)R^{24}, A-C(=O)OR^{24}, A-C(=O)N$R^{24}R^{25}$, A-N$R^{27}R^{28}$, or

R^{29} is selected from cycloalkyl of 3-6 carbon atoms, phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$, and O, all of which may be substituted with 1-3 of R^{10}, or

R^{29} is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, O, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10};

$R^{7'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{7'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-N$R^{24}R^{25}$, C(=O)R^{24}, C(=O)OR^{24}, C(=O)N$R^{24}R^{25}$, or $S(=O)_2R^{26}$, , or

$R^{7'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, A-R^{23}, N$R^{27}R^{28}$, A-N$R^{27}R^{28}$, A-Q-R^{29}, Q-R^{29}, Q-A-N$R^{24}R^{25}$, C(=O)R^{24}, C(=O)N$R^{24}R^{25}$, A-C(=O)R^{24}, and A-C(=O)N$R^{24}R^{25}$;

$R^{8'}$ is selected from cycloalkyl of 3-6 carbon atoms, phenyl, and monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms, all of which may be substituted with 1-3 of R^{10}, or

$R^{8'}$ is selected from 5-7 membered heterocycloalkyl of 3-6 carbon atoms and 1-2 heteroatoms selected from N, $S(=O)_{0-2}$ and O, and/or wherein one of the carbon atoms in said heterocycloalkyl may be oxidized to C(=O), wherein said

heterocycloalkyl may be substituted with 1-3 of R^{10}, A-R^{23}, A-$NR^{24}R^{25}$, $C(=O)R^{24}$, $C(=O)OR^{24}$, $C(=O)NR^{24}R^{25}$, or $S(=O)_2R^{26}$, , or

$R^{8'}$ is selected from hydrogen, halogen, nitrile, nitro, hydroxy, alkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, A-R^{23}, $NR^{27}R^{28}$, A-$NR^{27}R^{28}$, A-Q-R^{29}, $S(=O)_{0-2}$-R^{29}, $S(=O)_{0-2}$-A-$NR^{24}R^{25}$, $C(=O)NR^{24}R^{25}$, A-$C(=O)OR^{24}$, and A-$C(=O)NR^{24}R^{25}$.

24. The compound of claim 23, wherein $R^{1'}$ is selected from alkyl of 1-8 carbon atoms, and A-R^9, or

$R^{1'}$ is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cycloalkyl of 3-6 carbon atoms, all of which may be substituted with 1-3 of R^{10};

A is selected from alkyl of 1-6 carbon atoms, and haloalkyl of 1-8 carbon atoms;

R^9 is selected from hydroxy, alkoxy of 1-6 carbon atoms, cycloalkoxy of 3-6 carbon atoms, O-A-R^{14}, $NR^{11}R^{12}$; or

R^9 is selected from phenyl, monocyclic heteroaryl of 2-5 carbon atoms and 1-3 heteroatoms selected from N, $S(=O)_{0-2}$ and O, cylcoalkyl of 3-6 carbon atoms, all of which may be substituted with 1-3 of R^{10}.

25. The compound of claim 24, wherein $R^{1'}$ is phenyl, which may be substituted with 1-3 of R^{10}.

26. A method of treating or preventing a disease or condition selected from the group consisting of diabetes (Type 1 or Type 2), maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), gestational diabetes, and metabolic syndrome X, comprising administering to a mammal an effective amount of a compound of claim 1 or 22.

27. The method of claim 26, wherein said disease or condition is diabetes (Type 1 or Type 2).

28. The method of claim 27, wherein said disease or condition is Type 2 diabetes.

29. The method of claim 26, further comprising administering a PPAR-agonist, an insulin sensitizer, a sulfonylurea, an insulin secretagogue, a hepatic glucose output lowering compound, an α-glucosidase inhibitor or insulin in combination with said compound of claim 1 or 22.

30. The method of claim 29, wherein said PPAR-agonist is selected from rosiglitazone and pioglitazone.

31. The method of claim 29, wherein said sulfonylurea is selected from glibenclamide, glimepiride, chlorpropamide, and glipizide.

32. The method of claim 29, wherein said insulin secretagogue is selected from GLP-1, GIP, PAC/VPAC receptor agonists, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, and glipizide.

33. The method of claim 29, wherein said α-glucosidase inhibitor is selected from acarbose, miglitol and voglibose.

34. The method of claim 29, wherein said hepatic glucose output lowering compound is metformin.

35. The method of claim 26, further comprising administering an HMG-CoA reductase inhibitor, nicotinic acid, a bile acid sequestrant, a fibric acid derivative, antihypertensive drug, or an anti-obesity drug in combination with said compound of claim 1 or 22.

36. The method of claim 35, wherein said anti-obesity drug is selected from a β-3 agonist, a CB-1 antagonist, and a lipase inhibitor.

37. A method of treating or preventing secondary causes of diabetes selected from glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes, comprising administering to a mammal an effective amount of a compound of claim 1 or 22.

38. A method of increasing the sensitivity of pancreatic beta cells to an insulin secretagogue, comprising administering to a mammal an effective amount of a compound of claim 1 or 22.

39. The method of claim 38, wherein said insulin secretagogue is selected from GLP-1, GIP, PAC/VPAC receptor agonists, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, and glipizide.

40. A pharmaceutical composition, comprising a compound according to claim 1 or 22 and a pharmaceutically acceptable carrier.