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(54) **Title:** THIAZOLIDINONES, OXAZOLIDINONES, AND PYRROLIDINONES FOR HBV

(57) **Abstract:** The present invention relates to certain single-enantiomer pyrrazol-4-yl derivatives of thiazolidinones, oxazolidinones, and pyrrolidinones which are useful in the treatment of Hepatitis B virus.

THIAZOLIDINONES, OXAZOLIDINONES, AND PYRROLIDINONES FOR HBV

Cross Reference to Related Applications

This application claims priority to U.S. Provisional Application Ser. No. 60/701,819, filed July 21, 2005, and to U.S. Provisional Application Ser. No. 60/706,602, filed August 8, 2005, both of which are hereby incorporated herein by reference in their entirety.

Field of the Invention

The present invention relates to pyrrazol-4-yl derivatives of thiazolidinones, oxazolidinones, and pyrrolidinones which are useful in the treatment of Hepatitis B virus.

Background of the Invention

Despite various treatment options available for patients infected with Hepatitis B virus (hereafter "HBV"), sustained treatment success as evidenced by decrease of HBV DNA in serum and anti-HBe or HBs seroconversion is frequently limited to a relatively small patient population.

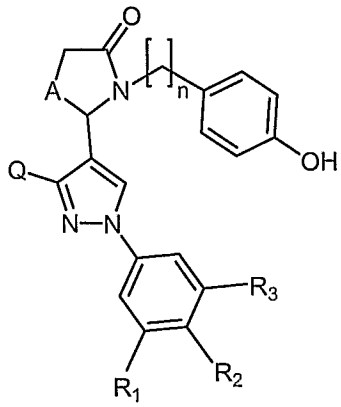
For example, for several years interferon alpha has been widely used for the treatment of chronic HBV infection. However, interferon is effective only in certain subpopulations of chronic hepatitis B patients, and even in such patients it is poorly tolerated. Similarly, lamivudine (3'-thia-2',3'-dideoxycytidine), a particularly strong inhibitor of HBV replication, is used to treat HBV infection. However, resistance to lamivudine is increasingly common and has limited its efficacy in a high proportion of patients. The most recently-approved treatment for HBV is adefovir dipivoxil (9-(2-((-bis((pivaloyloxy)methoxy)phosphinyl) methoxy)ethyl)adenine). Although this nucleoside analog is active against the lamivudine-resistant viruses, its sustained viral response rate is poor (below 20%), and its maximum tolerated dose and treatment duration are often limited by nephrotoxicity.

More recent developments in HBV research have led to clinical trials for several compounds with promising antiviral activity. For example, certain nucleoside analogs have been reported to exhibit significant anti-HBV activity (*e.g.*, 2'-fluoro-5-methyl-beta-L-arabinofuranosyluracil (Bukwang) and 2'-deoxy-5-fluoro-3'-thiacytidine (Gilead); 2'-deoxy-L-thymidine and 2'-deoxy-L-cytidine (both Idenix)). Similarly, carbocyclic nucleoside analogs (6H-purin-6-one, 2-amino-1,9-dihydro-9-((1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl) monohydrate (Bristol-Myers Squibb), as well as acyclic nucleoside analogs with liver targeting properties (Remofovir; Ribapharm), were reported as having anti-HBV activity in clinical trials.).

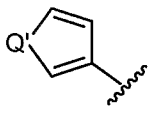
However, while most of the recently discovered drugs with anti-HBV activity exhibited promising *in vitro* antiviral activity, low response rates and the emergence of resistance limit the efficacy of these clinical candidates. Therefore, although various compositions and methods for HBV treatment are known in the art, there is still a need to provide new and improved compositions and methods for treatment of HBV infections in human patients.

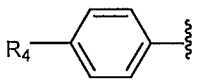
Thus, in light of the limited efficacy, resistance profiles, and toxicity of current anti-HBV drugs, there is a strong need for novel anti-HBV drugs that are more effective and less toxic and that exhibit a different resistance profile.

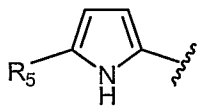
Brief Description of the Invention

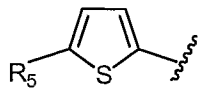


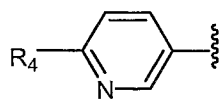
where n is 1 or 2; R_1, R_2, and R_3 are, independently, H, F, Cl, Br, or CF_3 and R_1 may also be methyl; A is O, S, or CH_2; and Q is selected from the following:

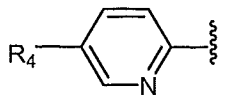
1a  where Q' is O, S, or NH

1b  where R_4 is F or Cl

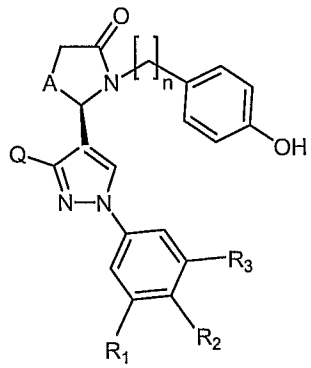
1c  where R_5 is H, F, or Cl

1d  where R_5 is H, F, or Cl

1e  where R_4 is F or Cl

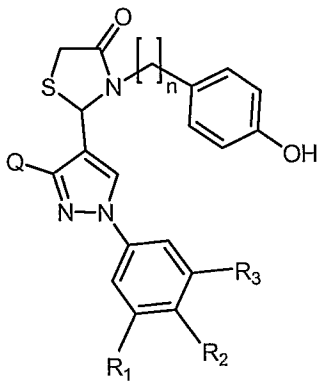
1f  where R_4 is F or Cl

Additionally, this invention provides compounds of formula I-R below, in which the chiral carbon is in the *R* configuration,

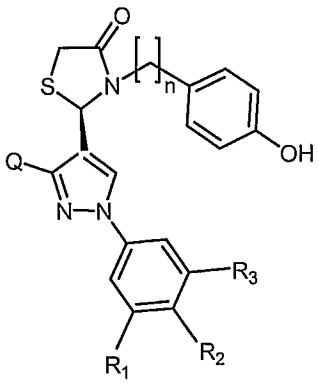


I-R

In one subgeneric embodiment, shown below, the invention provides a compound of formula II, which is a compound of formula I where A is S, n is 1 or 2, and other substituents are as defined above for formula I.

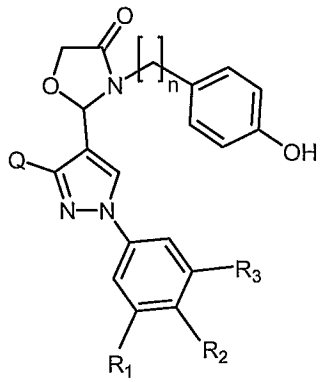


Additionally, this invention provides compounds of formula II-R below, in which the chiral carbon is in the *R* configuration,



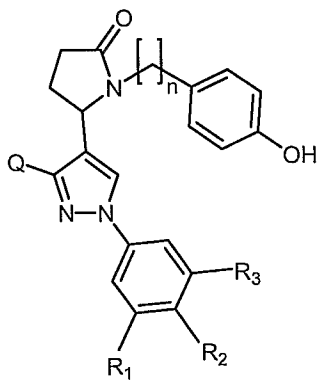
II-R

In another subgeneric embodiment, shown below, the invention provides a compound of formula III, where A is O, n is 1 or 2, and other substituents are as defined above for formula I.



III

In another subgeneric embodiment, the invention provides a compound of formula IV, where A is CH_2, n is 1 or 2, and other substituents are as defined above for formula I.



This invention also provides the R isomers of formulas III and IV.

In another subgeneric embodiment, the invention provides a compound of formula I, where R_2 is F or Cl.

In another subgeneric embodiment, the invention provides a compound of formula I, where R_2 is Cl.

In another subgeneric embodiment, the invention provides a compound of formula I, where R_1 and R_3 are both F.

In another subgeneric embodiment, the invention provides a compound of formula I, where R_1 is methyl and R_2 is F.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2 and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2 and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-furyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-furyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 3-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 4-fluorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 4-fluorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 4-chlorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 4-chlorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-fluoro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-fluoro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-fluoro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-fluoro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-chloro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-chloro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 2-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is S, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-furyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-furyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 3-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 4-fluorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 4-fluorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 4-chlorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 4-chlorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-fluoro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-fluoro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-fluoro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-fluoro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-chloro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-chloro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 2-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is O, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-thienyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-thienyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-furyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-furyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 3-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 4-fluorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 4-fluorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 4-chlorophenyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 4-chlorophenyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-fluoro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-fluoro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-fluoro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-fluoro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-chloro-5-pyridyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-chloro-5-pyridyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-pyrrolyl, and n is 2.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 1.

In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-pyrrolyl or 5-fluoro-2-pyrrolyl, and n is 2.

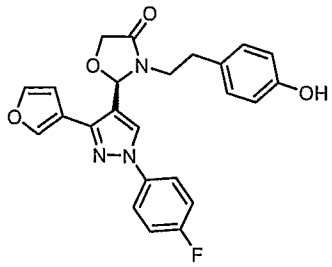
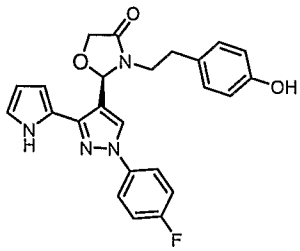
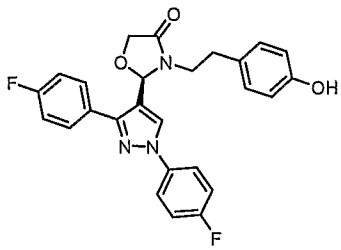
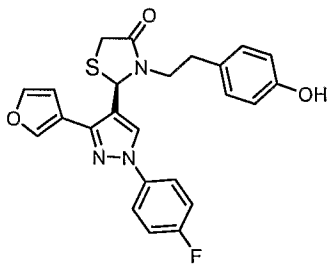
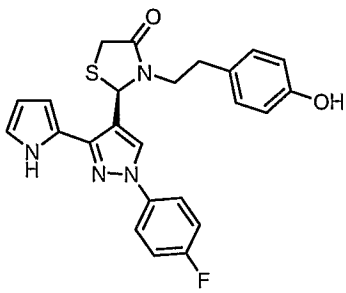
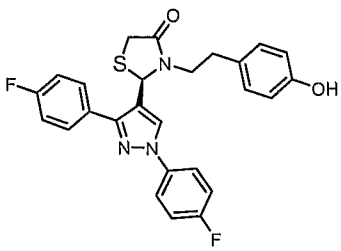
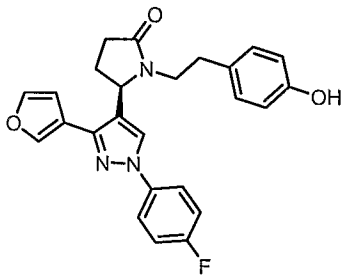
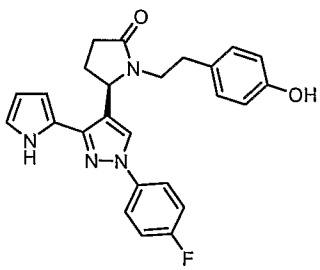
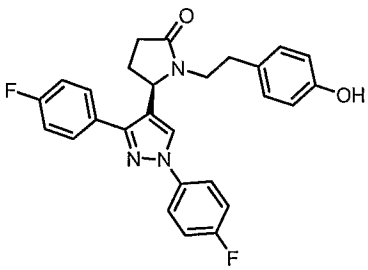
In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-thienyl, and n is 1.

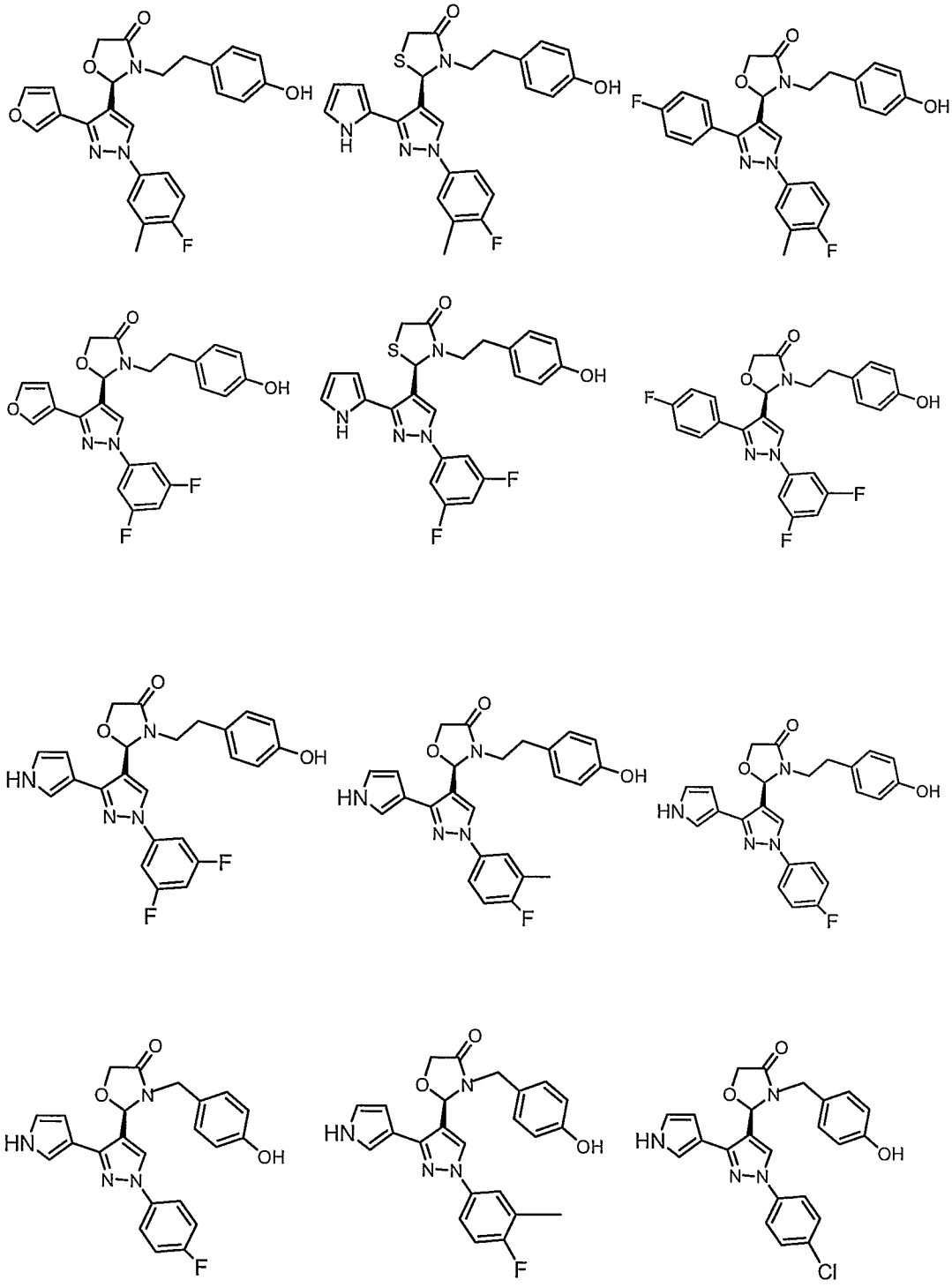
In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 2-thienyl, and n is 2.

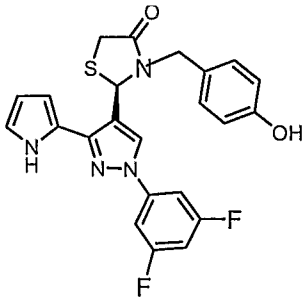
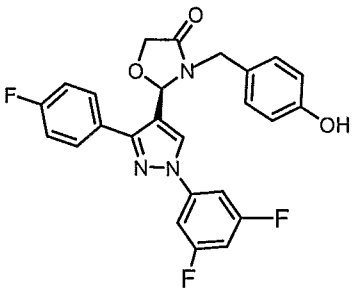
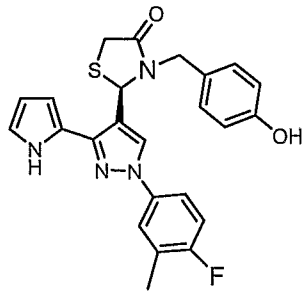
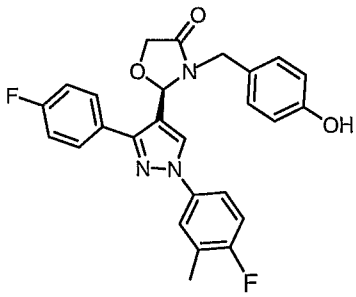
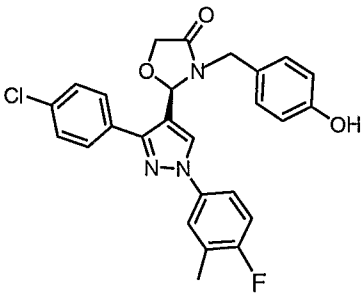
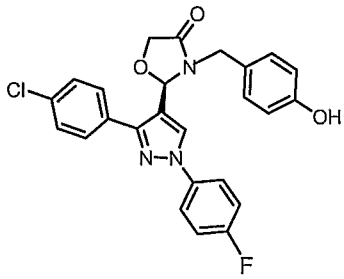
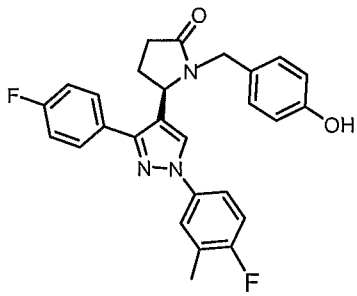
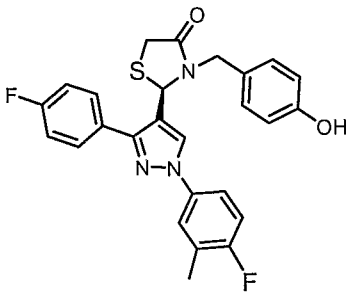
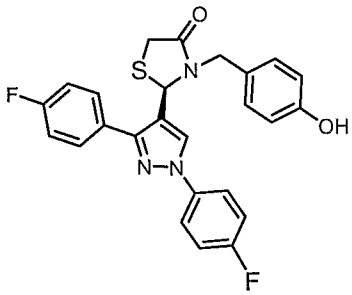
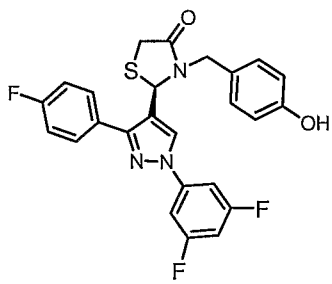
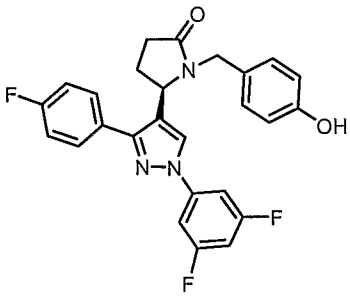
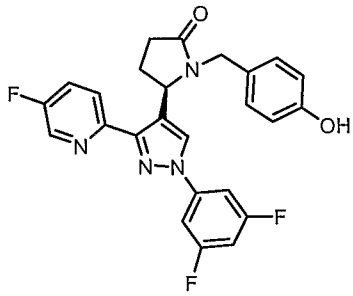
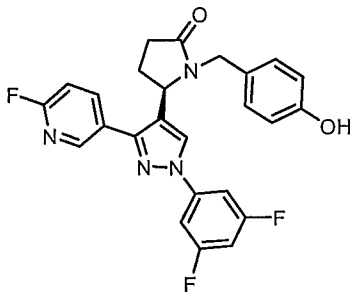
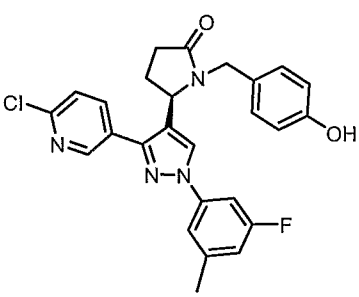
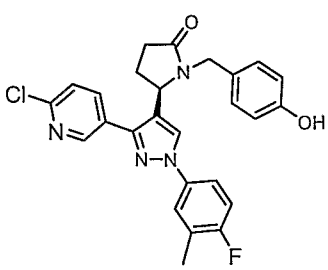
In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 1.

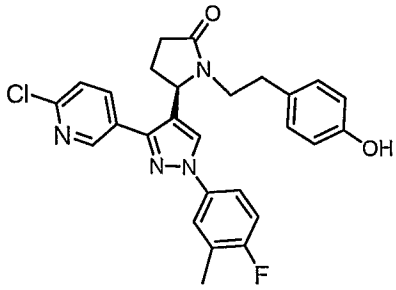
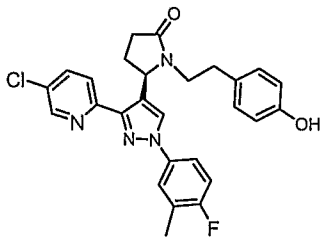
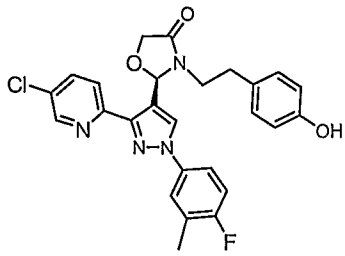
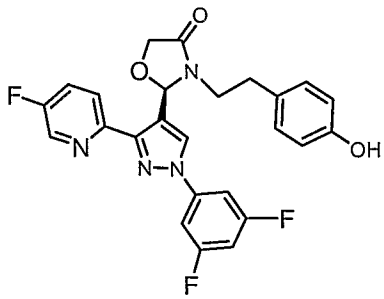
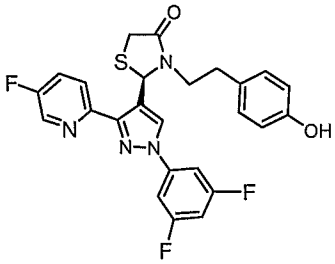
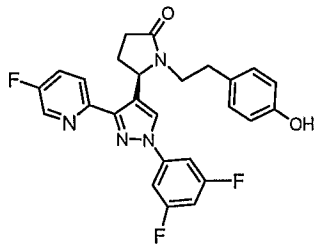
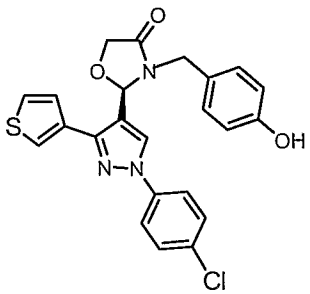
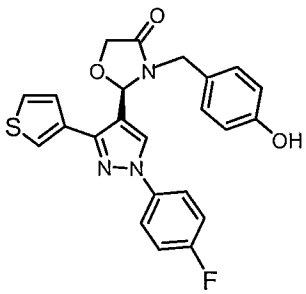
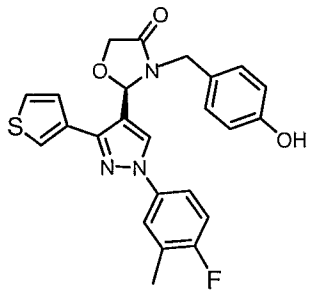
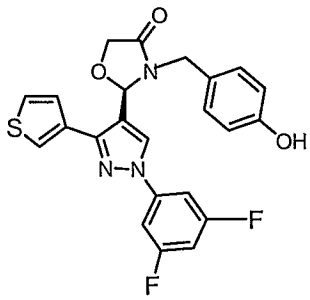
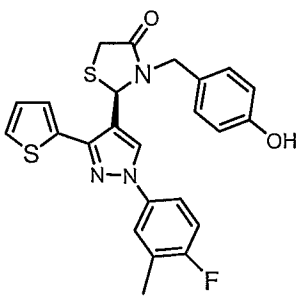
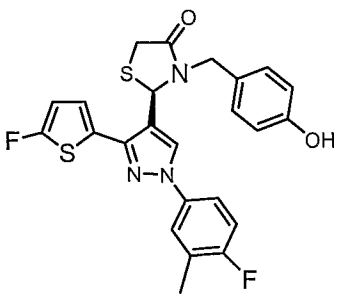
In a further subgeneric embodiment, this invention provides a compound of formula I, where A is CH_2, Q is 5-chloro-2-thienyl or 5-fluoro-2-thienyl, and n is 2.

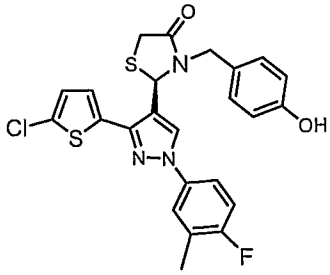
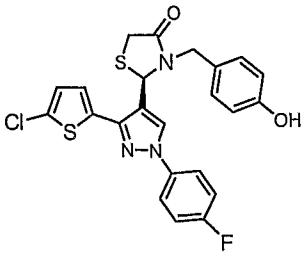
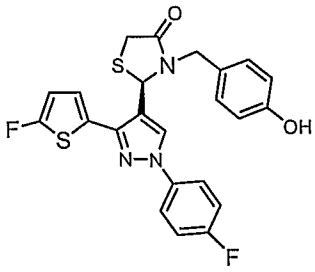
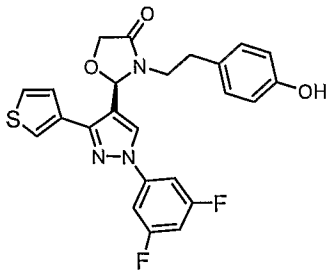
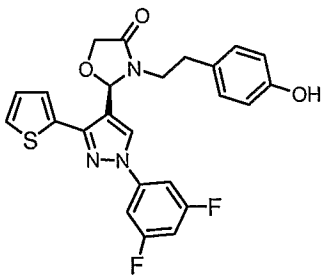
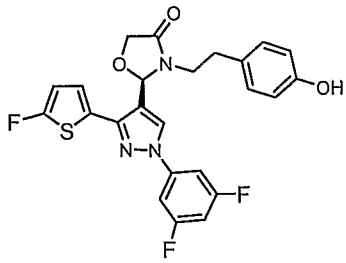
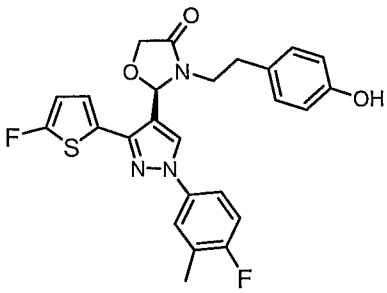
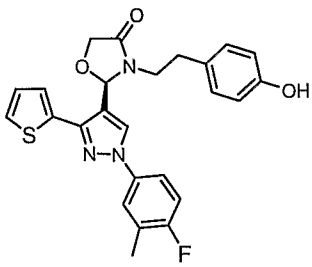
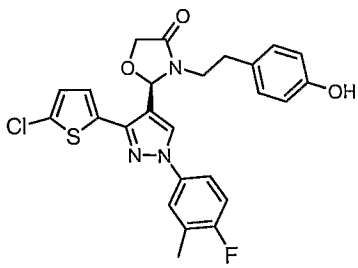
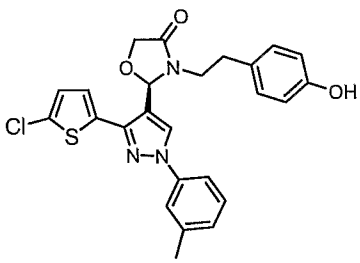
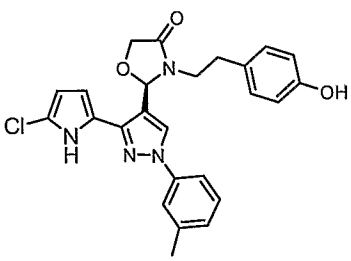
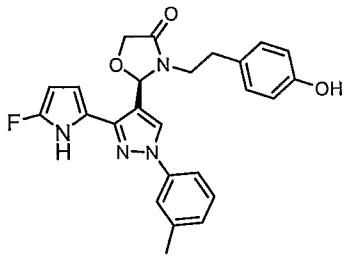
Specific embodiments of the invention include the compounds whose structures are shown below, as well as in the Table 1 in the next section.

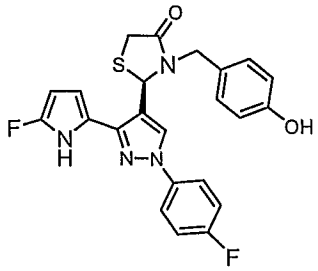
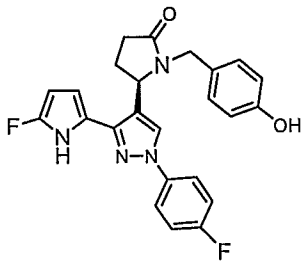
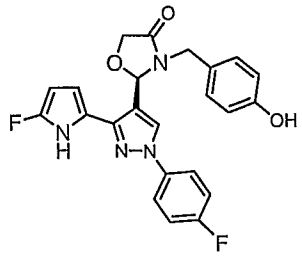
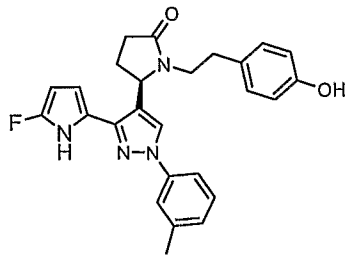
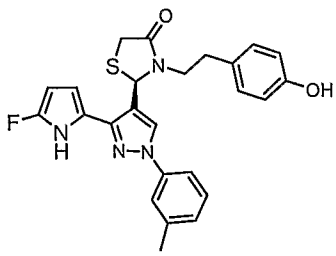
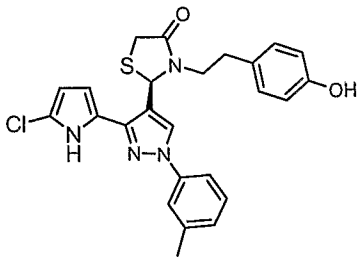
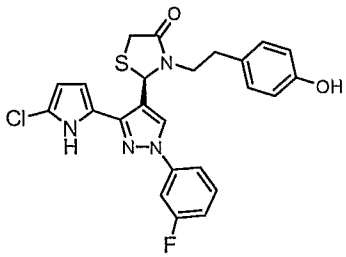
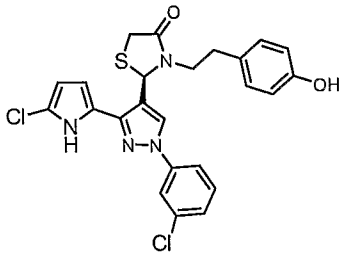
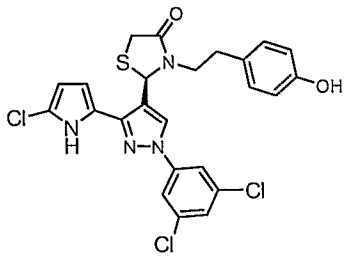
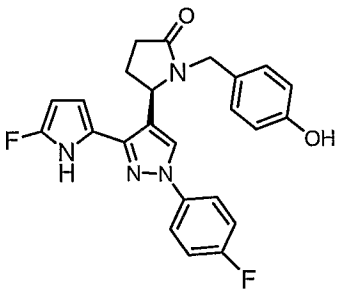
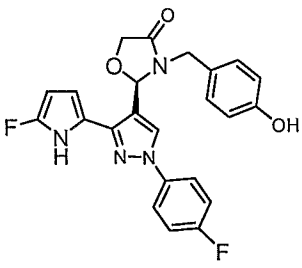
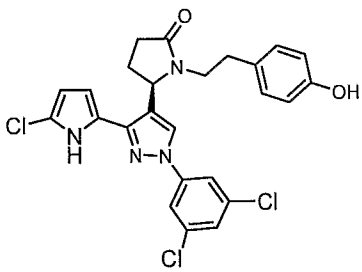










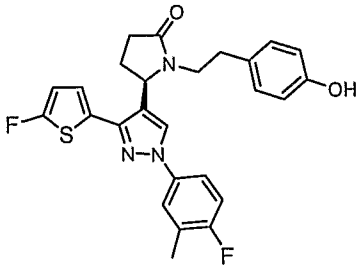


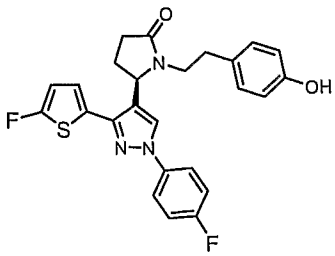
















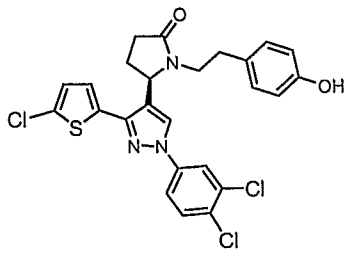














O
N
OH
F
S
N–N
F


O
N
OH
F
S
N–N
F


O
N
OH
Cl
S
N–N
Cl
Cl

Detailed Description of the Invention

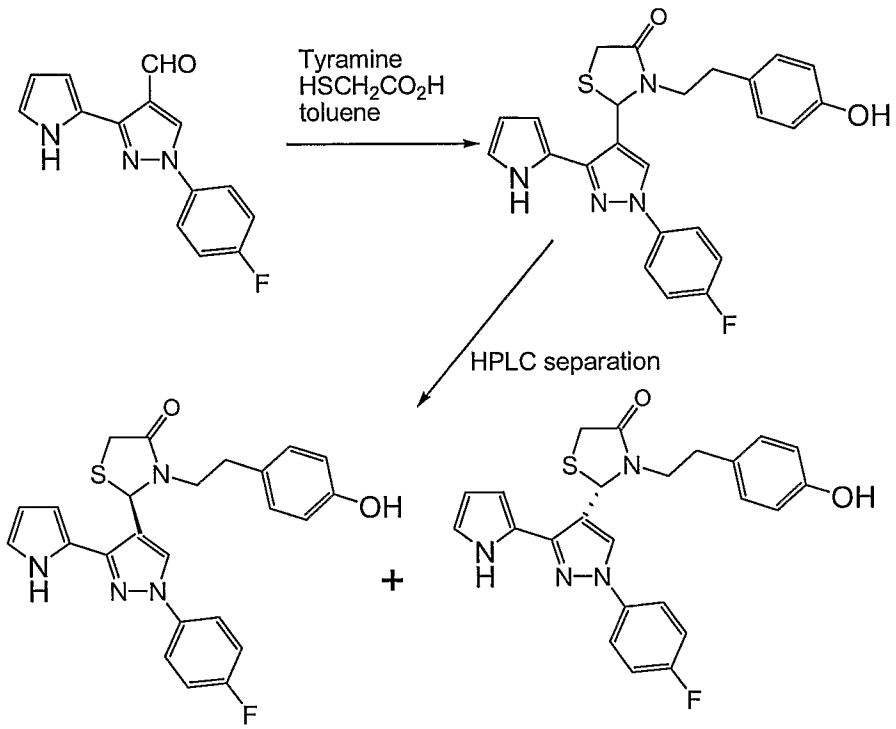
Synthesis

Compounds of this invention can be prepared according to the schemes below. Chiral separations are performed by supercritical fluid chromatography (SFC) according to the method of Berger. Berger, T. A. "Practical advantages of packed column supercritical fluid chromatography in supporting combinatorial chemistry," *ACS Symposium Series* (2000), 748(Unified Chromatography), 203-233. CODEN: ACSMC8 ISSN:0097-6156. CAN 132:216255 AN 2000:154567 CAPLUS; Berger, T. A.; Todd, B. S. "Packed column supercritical fluid chromatography of oligoethers using pure carbon dioxide with flame ionization and ultraviolet detection" *Chromatographia* (2001), 54(11/12), 777-781. CODEN: CHRGB7 ISSN:0009-5893. CAN 136:296563 AN 2002:67904 CAPLUS; Berger, T. A.; Todd, B. S. "Packed column supercritical fluid chromatography of polysiloxanes using pure and hexane modified carbon dioxide with flame ionization and ultraviolet detection," *Chromatographia* (2001), 54(11/12), 771-775. CODEN: CHRGB7 ISSN:0009-5893. CAN 136:295293 AN 2002:67903 CAPLUS

The Berger procedure may be summarized as follows: The racemic mixture (60 mg) is dissolved in methanol (2 ml) and injected into a preparative chiral column (ChiralPak AD-H SFC, i.d. 1cm x 25 cm). The SFC conditions are as follows: mobile phase, 65% CO_2 and 35% methanol: flow rate, 10 ml/min; detection wavelength, 220 nm. Two pools of material were isolated with different retention times. The absolute configuration was assigned by comparison based on the crystallographic results of CP060[1] (CP060-(R)-(+), $[\alpha]_D = +33.3°$; CP060-(S)-(-), $[\alpha]_D = -33.5°$) (Kato, Tatsuya; Ozaki, Tomokazu; Tamura, Kazuhiko; Suzuki, Yoshiyuki; Akima, Michitaka; Ohi, Nobuhiro, "Novel Calcium Antagonists with Both Calcium Overload Inhibition and Antioxidant Activity. 2. Structure-Activity Relationships of Thiazolidinone Derivatives," *Journal of Medicinal Chemistry* (1999), 42(16), 3134-3146. Representations of the ***R*** form are made on that basis.

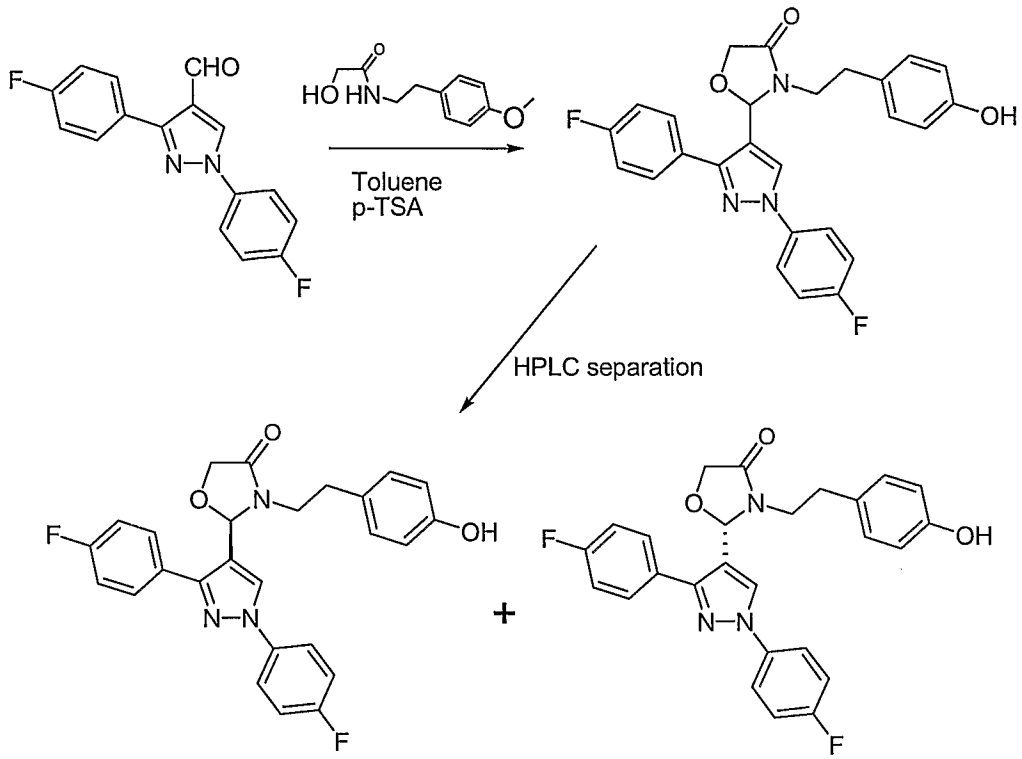
[1] 2-(3, 5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3, 4-(methylenedioxy)phenoxy] ethyl]amino]propyl]-1,3-thiazolidin-4-one.

Synthesis of 2-(3-pyrrolylpyrazol-4-yl)thiazolidinone



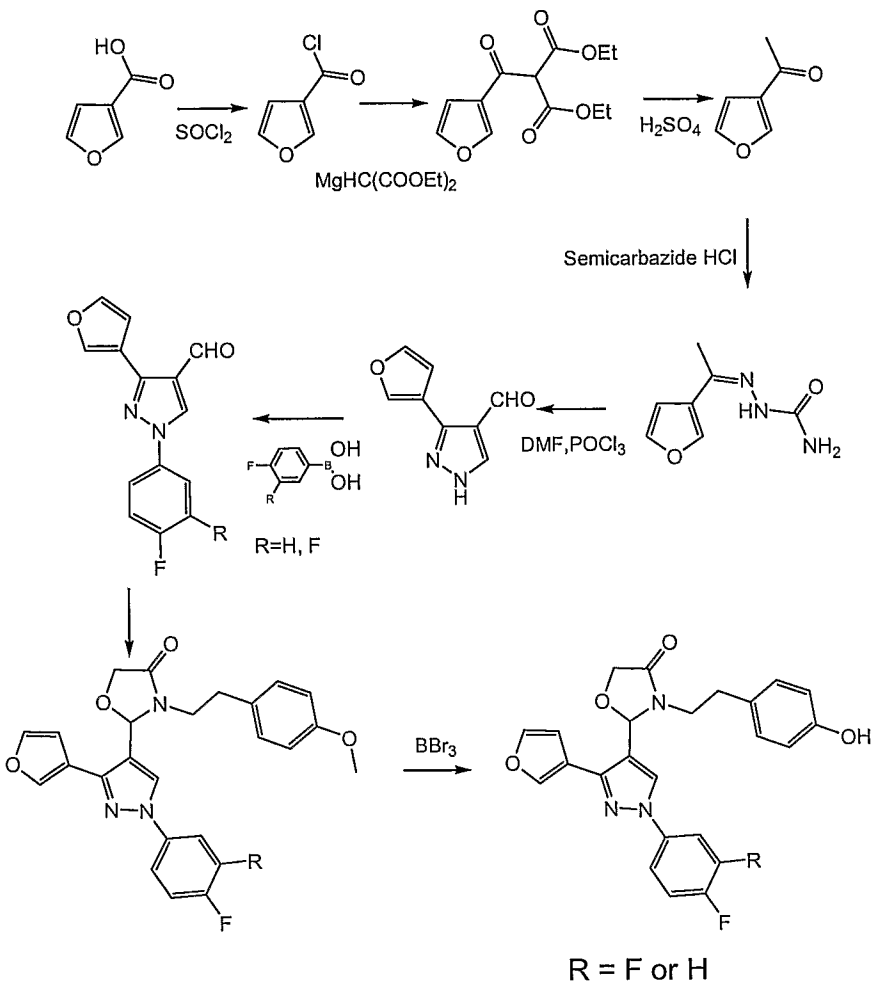
A mixture of 1-(4-fluorophenyl)-3-(1H-pyrrol-2-yl)-1H-pyrazole-4-carbaldehyde (128 mg, 0.5mmol) and tyramine (82 mg, 0.6mmol) in 20 ml of methanol was refluxed for 3 hours, then the solvent was removed *in vacuo* and the residue was dried in oven under reduced pressure. The residue was dissolved in 20 ml of toluene and mercaptoacetic acid (92 mg, 1mmol) was added. The mixture was refluxed with condenser equipped with molecular sieves for 10 hours. The solvent was removed *in vacuo* and the resulting oily residue was dissolved in chloroform and washed with saturated sodium bicarbonate twice and water twice. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column (chloroform) to give a racemic product as white solid.

Synthesis of 2-(3-phenylpyrrazol-4-yl)oxazolidinones



A mixture of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (0.5g, 2mmol), 2-hydroxy-N-[2-(4-methoxy-phenyl)-ethyl]-acetamide (0.46g, 2.2mmol), and p-toluenesulfonic acid (5mg) in 40 ml of toluene was refluxed with condenser equipped with molecular sieves for 24 hours. The solvent was removed *in vacuo* and the resulting residue was dried in vacuo and dissolved in 20 ml of anhydrous dichloromethane under argon. The mixture was cooled to -70°C in a acetone-dry ice bath and 5 ml of 1M boron tribromide in dichloromethane was added dropwise with stirring. The reaction mixture was stirred at room temperature overnight, then 20 ml of water was added with stirring until two clear layer solution formed. The organic layer was separated and the water layer was extracted with dichloromethane twice. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The residue was purified by silica gel column (chloroform/methanol, 40:1) to give pure product as a white solid. The pure isomer was obtained by following the above resolution method with the same conditions.

Synthesis of (2-3-furfurylpyrrazolyl)-4-oxazolidinone



3-Furoyl chloride

A mixture of 25 g of 3-furoic acid and 65 ml of thionyl chloride was heated to reflux for 6 hours. Then excess thionyl chloride was removed, and the residue was distilled under reduced pressure to give 25 g of 3-furoyl chloride as a colorless oil.

3-Acetylfuran

In a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser (protected by a drying tube) is placed 4.4 g of magnesium turnings 4 ml of anhydrous ethanol and 0.6 ml of carbon tetrachloride are added under argon. If the reaction does not start immediately, the flask is heated for a short time at 70°C on an oil bath. After the reaction has proceeded for several minutes, 120 ml of anhydrous ether is added cautiously with stirring. A solution of 30.6 g of diethyl malonate

in16.5 ml of anhydrous ethanol and 20 ml of anhydrous ether is added with stirring at such a rate that rapid boiling is maintained; heat is supplied when necessary. The mixture is heated under reflux at 70°C on an oil bath for 4-5 hours, at which time most of the magnesium has dissolved. To the gray solution is added 21.4 g of furan-3-carbonyl chloride dissolved in 50 ml of ether in a period of 15 minutes. Heating under reflux at 70°C on the oil bath is continued throughout the addition of the furan-3-carbonyl chloride and until the solution becomes too viscous to stir. The reaction mixture is cooled (ice-bath) and shaken with dilute sulfuric acid (20.4 ml of concentrated sulfuric acid in 160 ml of water) until all the solid has dissolved and the reaction mixture become clear solution. The ether phase is separated and the aqueous layer extracted with 60 ml of ether. The ether extracts are combined and washed with water, and the solvent is removed by distillation to give crude intermediates diethyl 2-(Furan-3-carbonyl)-malonate as an yellow oily product.

To the crude oily 2-(Furan-3-carbonyl)-malonic acid diethyl ester is added a solution of 40 ml of glacial acetic acid, 4 ml of concentrated sulfuric acid, and 20 ml of water, and the mixture is heated under reflux for 6 hours or until no more carbon dioxide is evolved. The reaction mixture is chilled in an ice-salt bath (-20°C), made alkaline with cold 20% sodium hydroxide solution, The yellow oil layer was extracted with ether three times, the combined ether solution was washed with brine twice and dried over anhydrous sodium sulfate and evaporated to dryness at about 10°C under reduced pressure to give 13.9g of the crude product as yellow solid.

Semicarbazone

A mixture of 3-acetylfuran (11.0g, 0.1mol) and semicarbazide hydrochloride (11.2g, 0.1mol), and sodium acetate (27.6g, 0.2mol) in 350 ml of methanol was refluxed for 2 hours, then 100 ml of water was added and the mixture was refluxed for another 2 hours. The methanol was removed in vacuo. The solid was filtered and washed with water to give 9.6 g of yellow solid after drying *in vacuo*.

3-(Furan-3-yl)-1H-pyrazole-4-carbaldehyde

$POCl_3$ (3.0ml, 33mmol) was slowly added to anhydrous DMF (7.65ml, 66mmol) at 0°C (ice-bath) with stirring. After stirring for 5 min, the semicarbazone (2.5g, 15mmol) was added portionwise to the above mixture with well-stirring. The mixture was heated to 60 °C

for 5 hours and poured onto 20g of ice. It was neutralized with NaOH (6g in 24 ml of water) and heated at 60 °C for 20 min, then cooled to room temperature and neutralized with 10N HCl to pH 6. The resulting white precipitates were filtered and washed with water. After drying in vacuo at 60 °C, 2 of the aldehyde as yellow solid was obtained.

1-(4-Fluoro-phenyl)-3-furan-3-yl-1H-pyrazole-4-carbaldehyde

To a 25 ml round bottle flask was added in sequence: 4-fluorophenylboronic acid (84mg, 0.6mmol), 3-(furan-3-yl)-1H-pyrazole-4-carbaldehyde (49mg,0.3mmol), copper (II) acetate (81mg, 0.45mmol), 4Å molecular sieves (250mg), pyridine (49μL), and 4 ml of anhydrous dichloromethane. The reaction mixture was stirred at ambient temperature for 2 days. The resulting mixture was filtered through Celite, washed with methanol and purified by silica gel column (hexane/ethyl acetate, 4:1) to give product as white solid.

2-[1-(4-Fluoro-phenyl)-3-furan-3-yl-1H-pyrazol-4-yl]-3-[2-(4-hydroxy-phenyl)-ethyl]-oxazolidin-4-one

A mixture of 1-(4-fluoro-phenyl)-3-furan-3-yl-1H-pyrazole-4-carbaldehyde (0.51g, 2mmol), 2-hydroxy-N-[2-(4-methoxy-phenyl)-ethyl]-acetamide (0.46g, 2.2mmol), and p-toluenesulfonic acid (5mg) in 40 ml of toluene was refluxed with condenser equipped with molecular sieves for 24 hours. The solvent was removed *in vacuo* and the resulting residue was dried in vacuo and dissolved in 20 ml of anhydrous dichloromethane under argon. The mixture was cooled to -70°C in an acetone-dry ice bath and 5 ml of 1M boron tribromide in dichloromethane was added dropwise with stirring. The reaction mixture was stirred at room temperature overnight, then 20 ml of water was added with stirring until two clear layer solution formed. The organic layer was separated and the water layer was extracted with dichloromethane twice. The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The residue was purified by preparative HPLC.

HBV Screening Assay

HepG2 cells are transduced using a baculovirus to deliver the HBV genome essentially as previously described (Delaney, W.E., and Isom, H.C. Hepatitis B virus replication in human HepG2 cells mediated by hepatitis B virus recombinant baculovirus. Hepatology 1998; 28: 1134-1146.). Transduced cells are cultured in supplemented EMEM

media with 10% fetal bovine serum in a 5% CO_2 incubator at 37°C for three days in the presence of test compounds. The cells are lysed in a buffer containing 0.5% NP-40 and 500 microgram/ml proteinase K. A solid-phase hybridization is performed to capture the viral DNA and to label the target DNA with Digoxigenin-labeled DNA probes. The captured viral DNA is detected by ELISA using horseradish peroxidase-conjugated anti-digoxigenin antibodies. The EC_{50} values are determined using ExcelFit software from the inhibition values of a titration curve for each compound.

For CC_{50} determinations, the test compounds are co-cultured with non-transduced HepG2 for three days under the conditions described above. The Promega CellTiter 96 AQ_{ueous} One Solution Cell Proliferation Assay is used to measure cell proliferation/viability. The CC_{50} values are determined using ExcelFit™ software from the inhibition values of the titration curve for each compound.

Three racemates were resolved by chiral chromatography. The activities of the dextro- and levorotatory fractions were determined. The structures and results given as the EC_{50} are presented in the table below.

Activities of Isolated Enantiomers

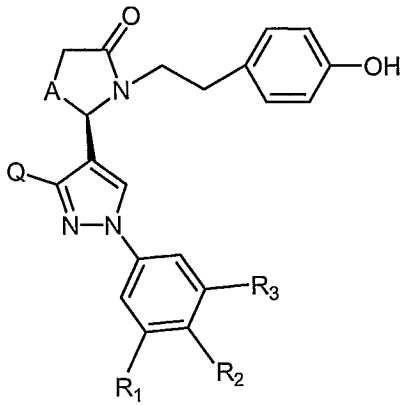


Table 1 Cmpd #	form	$EC_{50}(\mu M)$	$[\alpha]_D$	Q	A	R_2	$R_{1,3}$
15	(+)	0.010	+ 105.2	pyrrol-2-yl	S	F	H
16	(-)	2.6	-105.5				
32	(+)	0.019	+32.35	4-F-phenyl	O	F	H
33	(-)	>10	-33.62				
19	(+)	0.054	+85.5	4-Cl-pyrrol-2-yl	S	F	H
18	(-)	9.22	-81.0				

In each case the dextrorotatory form is more than 250 fold more active than the levorotatory enantiomer. The assignment of absolute configuration is based crystal structure of 2-(3, 5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3, 4-methylenedioxy)phenoxy] ethyl]amino]propyl]-1,3-thiazolidin-4-one. Kato, T., *et al.*, 1999, *J.Med. Chem.* 42, 3134-46. As used herein the R absolute configuration is intended to denote the dextrorotatory form. As used herein the term substantially free of the levorotatory form should be construed by reference to examples 15, 32 and 19, which are substantially free of the levorotatory form. The invention encompasses both mixtures of the dextrorotatory and levorotatory forms and compositions comprising the dextrorotatory form substantially free of the levorotatory form. As used herein, "substantially free" means a greater than 90% enantiomeric excess of one isomer.

Test Results for Selected Compounds

Table 1 below lists selected compounds with their structures and corresponding antiviral activity. For EC_{50} determinations, the following legend applies: A: EC_{50} < 50nM; B: EC_{50} = 50nM – 175 nM; C: EC_{50} = 175 – 750nM; D: > 750 nM). Antiviral activity was determined using assay systems as described above. ND means not determined.

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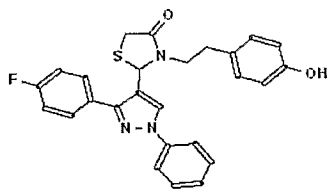
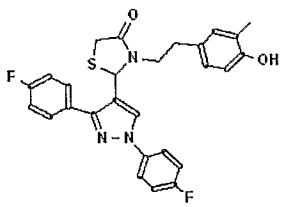
1		C
2		C

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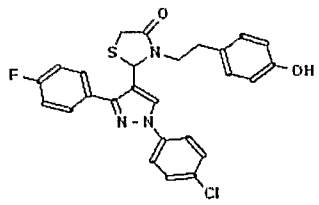
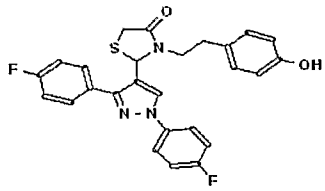
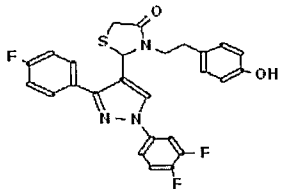
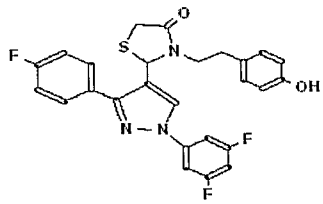
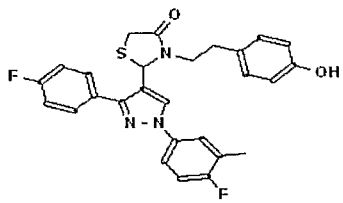
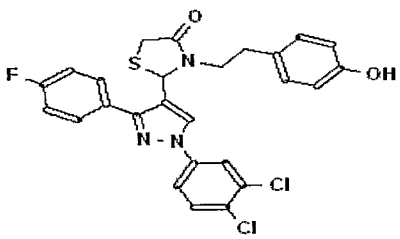
3		B
4		B
5		A
6		B
7		A
8		B

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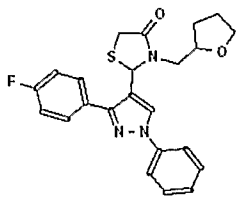
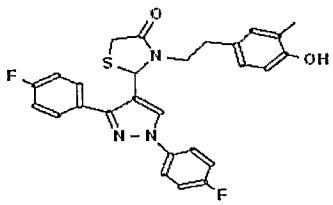
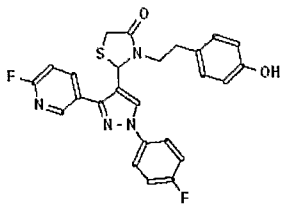
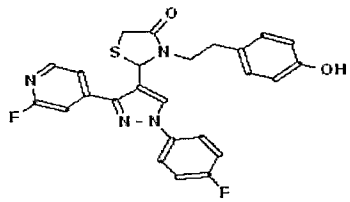
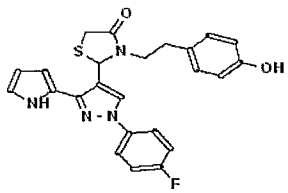
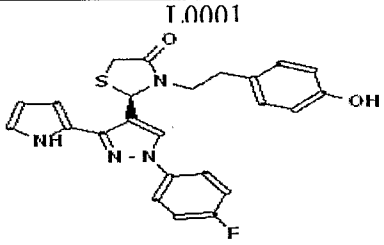
9		D
10		C
11		A
12		D
13		B
15		A

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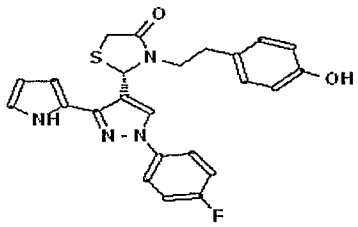
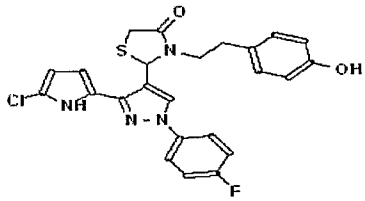
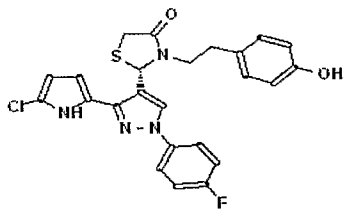
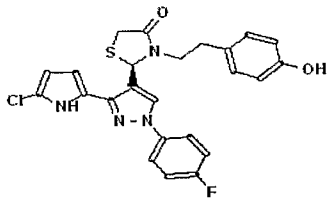
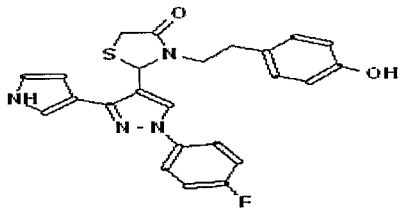
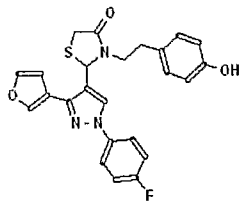
16		D
17		C
18		D
19		B
20		C
21		B

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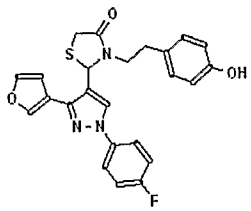
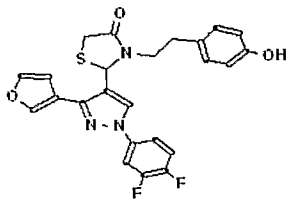
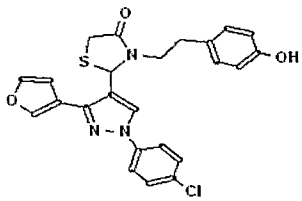
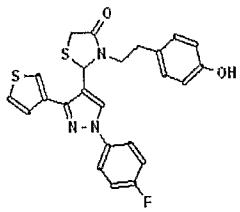
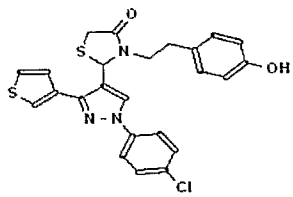
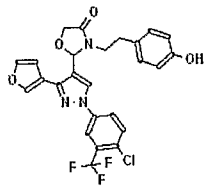
22		B
23		B
24		B
25		B
26		B
26a		A

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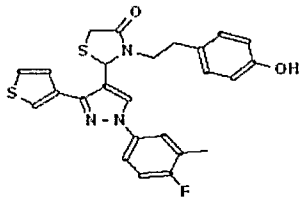
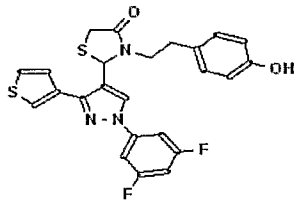
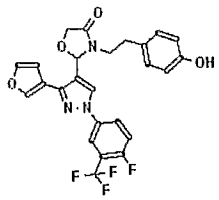
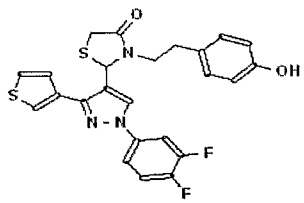
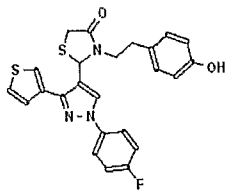
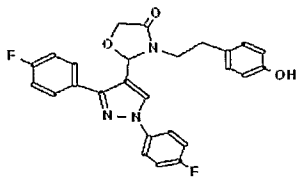
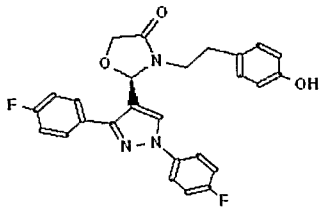
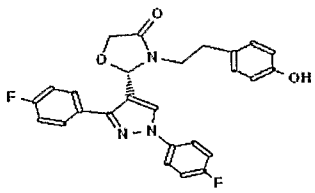
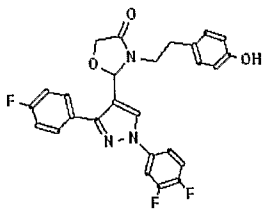
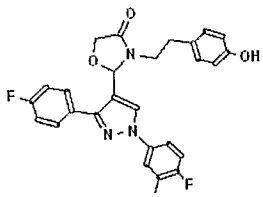
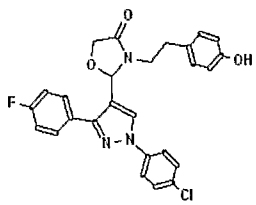
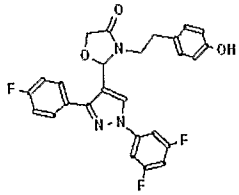
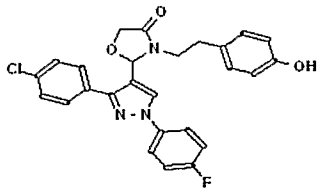
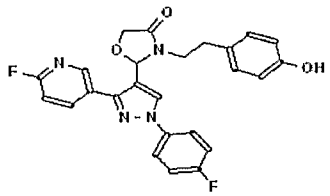
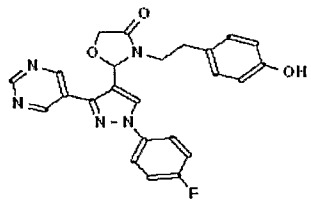
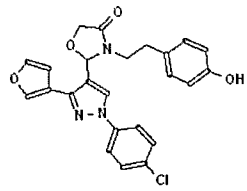
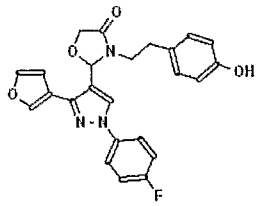
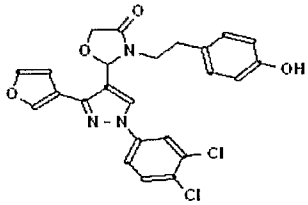
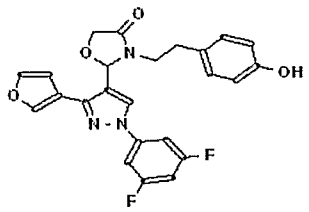
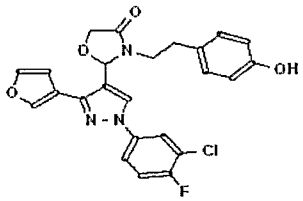
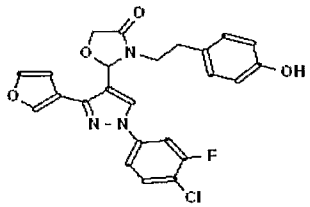
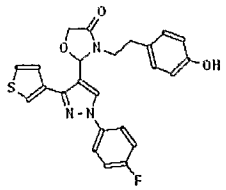
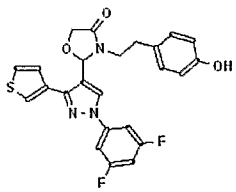
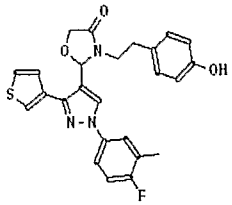
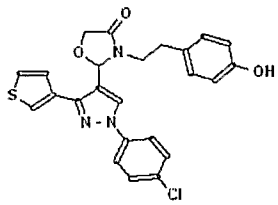
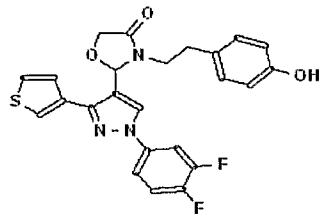
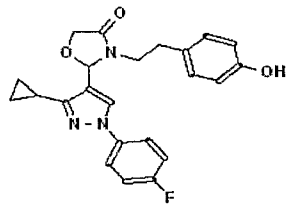
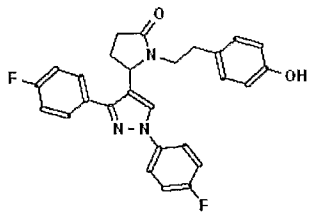
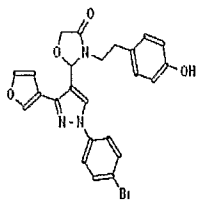
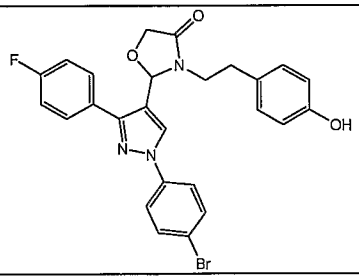
27		B
28		C
28a		
29		B
30		C
31		A

CPD #	Structure	EC50
32		A
33		D
34		A
35		A
36		A
37		A

CPD #	Structure	EC50
38		A
39		A
40		D
41		A
42		A
43		A

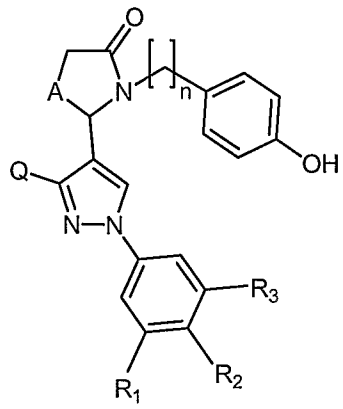
CPD #	Structure	EC50
44		A
45		A
46		A
47		A
48		A
49		B

CPD #	Structure	EC50
50		A
51		A
52		B
53		B
53a		A
54		A

Claims

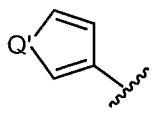
What is claimed is

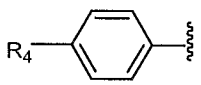
1. A compound of formula I

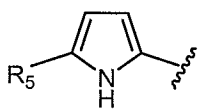


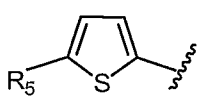
I

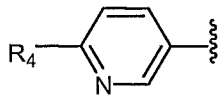
where n is 1 or 2; R_1, R_2, and R_3 are, independently, H, F, Cl, Br or CF_3, and R_1 may also be methyl; A is O, S or CH_2; and Q is selected from the following:

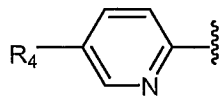
1a  where Q' is O, S or NH

1b  where R_4 is F or Cl

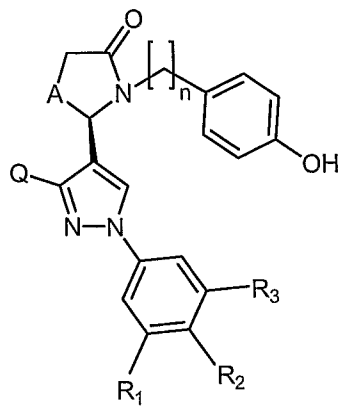
1c  where R_5 is H, F or Cl

1d  where R_5 is H, F or Cl

1e  where R_4 is F or Cl.

1f  where R_4 is F or Cl.

2. A compound of formula IR



IR

where all substituents are defined as for formula I.

3. The compound of claim 1 or claim 2, where R_1 is CF_3.

4. The compound of claim 1 or claim 2, where R_2 is Br.

5. The compound of claim 1 or claim 2, where R_2 is I.

6. The compound of claim 1 or claim 2, where A is O.

7. The compound of claim 6, where Q is furan-3-yl or thiophen-3-yl.

8. The compound of claim 7, where n is 2 and R_1 is H.

9. The compound of claim 7, where R_2 is Br and R_3 is H.

10. The compound of claim 8, where R_2 is Cl or F, and R_3 is CF_3.

11. The compound of claim 6, where R_2 is H, n is 2, and R_1 is not methyl.

12. The compound of claim 1 or claim 2, where A is S.

13. The compound of claim 12, where Q is a furan-3-yl or thiophen-3-yl.

14. The compound of claim 13, where n is 2, and R_1 is H.

15. The compound of claim 14, where R_2 is Br, and R_3 is H.

16. The compound of claim 15, where R_2 is Cl or F, and R_3 is CF_3.

17. The compound of claim 13, where R_2 is H, n is 2, and R1 is not methyl.

18. The compound of claim 1 or claim 2, where A is CH_2.

19. The compound of claim 18, where Q is furan-3-yl or thiophen-3-yl.

20. The compound of claim 19, where n is 2, and R_1 is H.

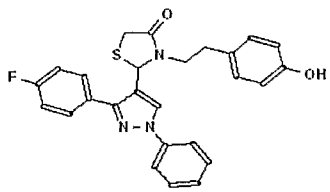
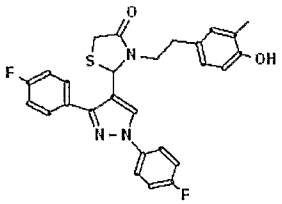
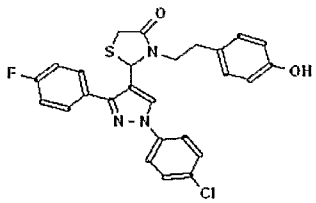
21. The compound of claim 20, where R_2 is Br, and R_3 is H.

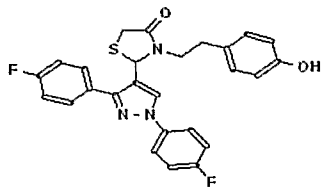
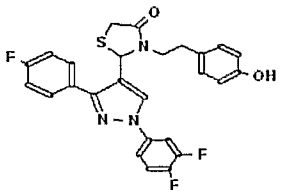
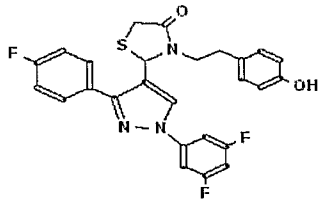
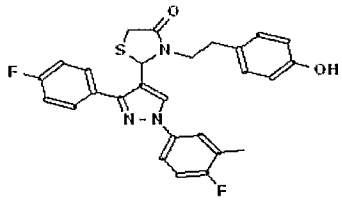
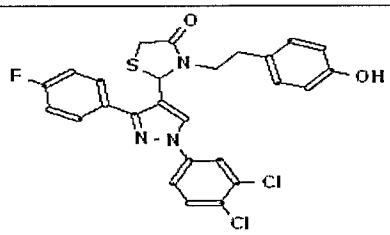
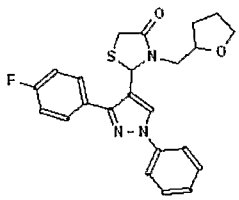
22. The compound of claim 20, where R_2 is Cl or F, and R_3 is CF_3.

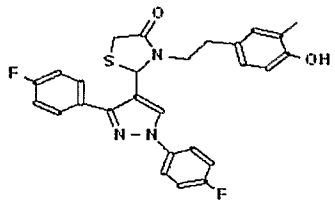
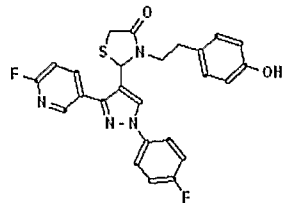
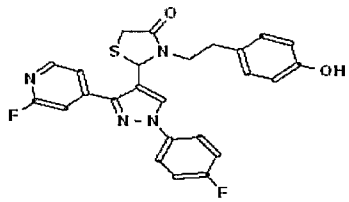
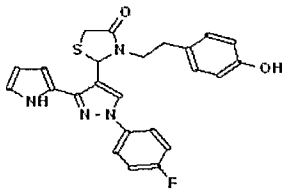
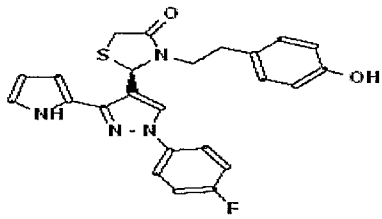
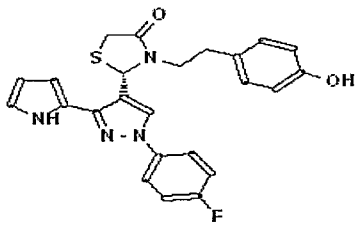
21. The compound of claim 17, where R_2 is H, n is 2, and R_1 is not methyl.

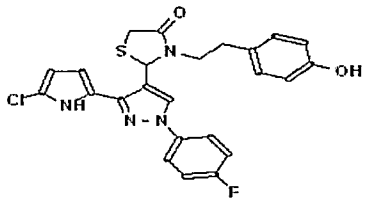
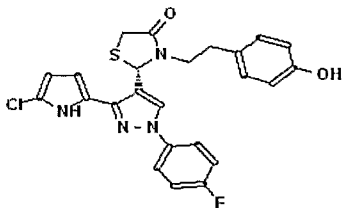
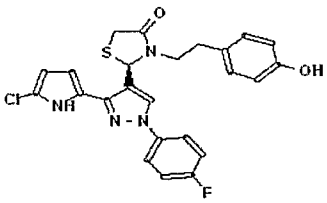
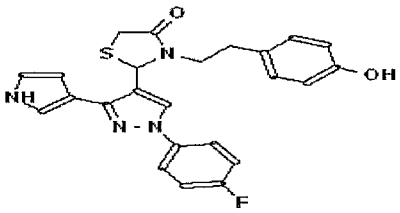
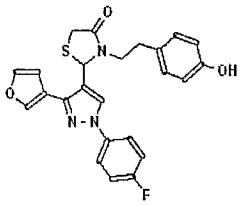
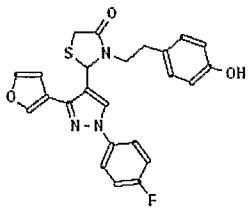
22. A composition comprising a compound of any one of claims 1-21, which composition is substantially free of the levorotatory enantiomer of the compound.

23. A compound selected from those pictured below.

CPD #	Structure
1	
2	
3	

CPD #	Structure
4	
5	
6	
7	
8	
9	

CPD #	Structure
10	
11	
12	
13	
15	
16	

CPD #	Structure
17	
18	
19	
20	
21	
22	

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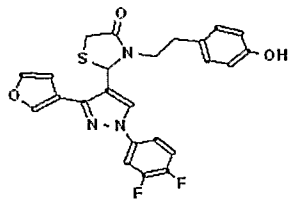
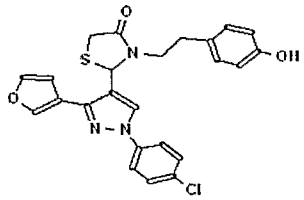
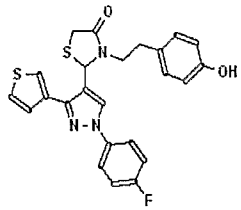
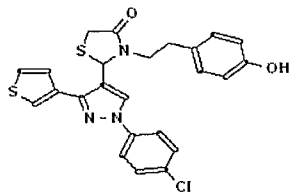
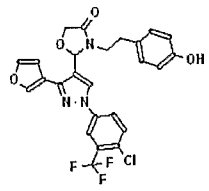
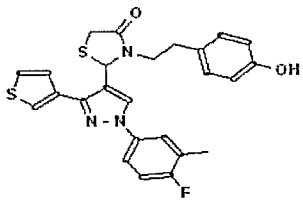
23	
24	
25	
26	
26a	
27	

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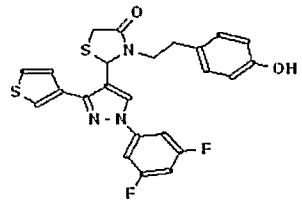
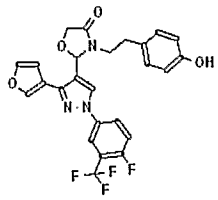
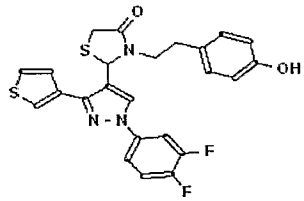
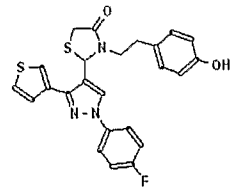
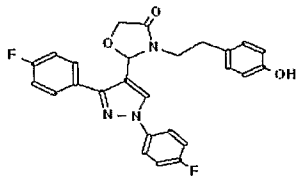
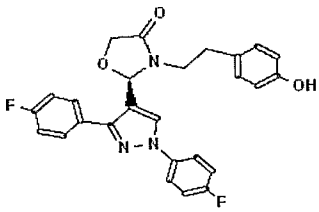
28	
28a	
29	
30	
31	
32	

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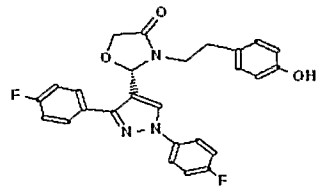
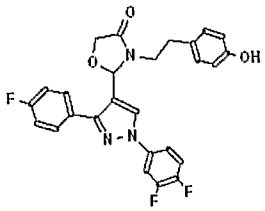
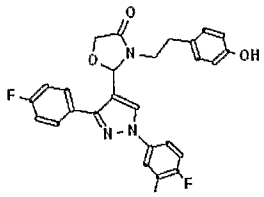
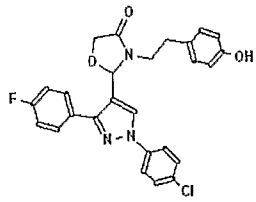
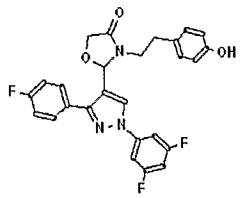
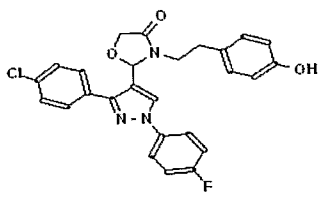
33	
34	
35	
36	
37	
38	

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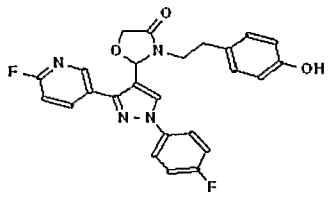
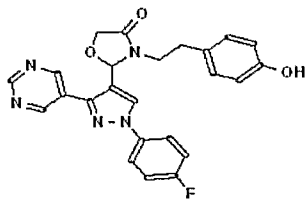
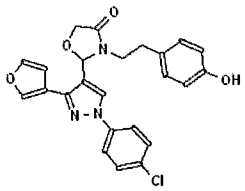
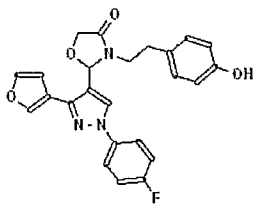
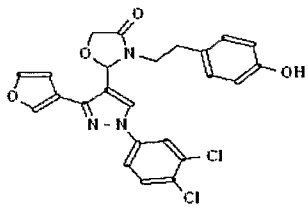
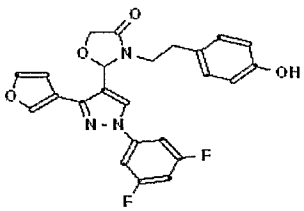
39	
40	
41	
42	
43	
44	

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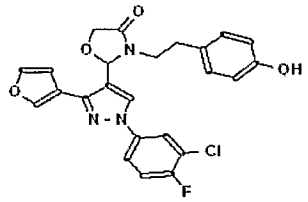
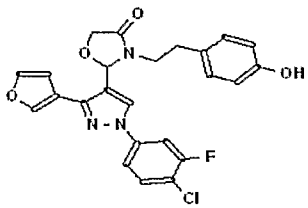
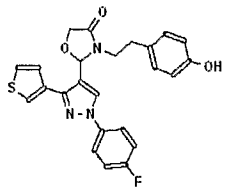
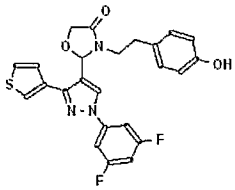
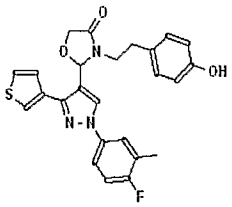
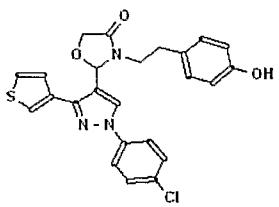
45	
46	
47	
48	
49	
50	

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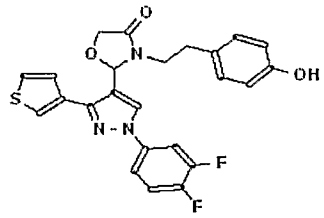
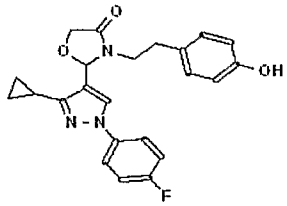
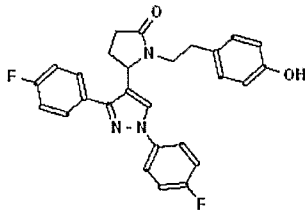
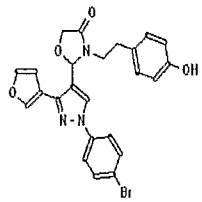
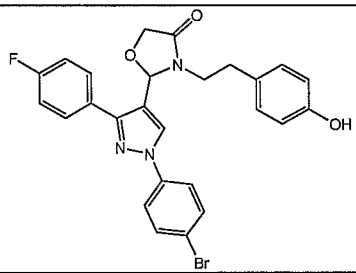
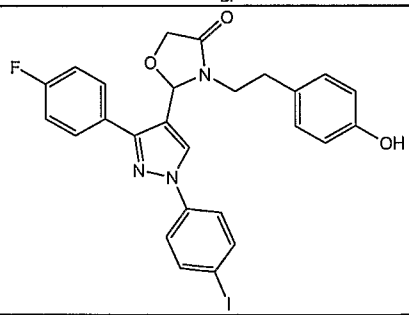
51	
52	
53	
53a	
54	
55	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/28343

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 31/422**(2006.01),**31/427**(2006.01);**C07D 263/18**(2006.01),**277/14**(2006.01)

USPC: 514/369,376,403;548/182,225,364.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/369, 376, 403; 548/182, 225, 364.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,105,556 B2 (CHENG et al) 12 September 2006 (12.09.2006) see entire document.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
14 October 2006 (14.10.2006)

Date of mailing of the international search report
22 NOV 2006

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Form PCT/ISA/210 (second sheet) (April 2005)