HCl hydrochloric acid

HOAT 1-hydroxy-7-azabenzotriazole

HOBt 1-hydroxybenzotriazole hydrate

H_2 hydrogen

H_2O water

H_2O_2 hydrogen peroxide

H_3PO_4 orthophosphoric acid

H_2SO_4 sulphuric acid

HNO_3 nitric acid

HCOOK potassium formate

$HCOONH_4$ ammonium formate

HMDS hexamethyldisilazane

HPLC high performance liquid chromatography or high pressure liquid chromatography

I_2 iodine

LiHMDS lithium bis(trimethylsilyl)-amide

LDA lithium diisopropylamide

MBP myelin basic protein

MCPBA meta-chloroperbenzoic acid

MeCN, CH_3CN acetonitrile

$MgSO_4$ magnesium sulfate

MeOH, CH_3OH methanol

MeI methyl iodide

MOPS 3-(*N*-morpholino)propanesulfonic acid

2-MeTHF 2-methyl tetrahydrofuran

mL, ml milliliter

min minute

N_2 nitrogen

NMP *N*-methylpyrrolidinone

$NaHCO_3$ sodium bicarbonate

$NaBH_4$ sodium borohydride

$NaBH_3CN$ sodium cyanoborohydride

NaO*t*Bu sodium *tert*-butoxide

NaOMe, CH_3ONa, $NaOCH_3$ sodium methoxide

NaOH sodium hydroxide

$NaClO_2$ sodium chlorite

NaClO sodium hypochlorite

NaCl sodium chloride

NaH_2PO_4 sodium biphosphate

NaH sodium hydride

NaI sodium iodide

Na_2SO_4 sodium sulfate

$Na_2S_2O_3$ sodium thiosulfate

NBS *N*-bromosuccinimide

NIS *N*-iodosuccinimide

NCS *N*-chlorosuccinimide

NEt_3 triethylamine

NH_3 ammonia

NH_4Cl ammonium chloride

$NH_2OH{\cdot}HCl$ hydroxylamine hydrochloride

$(NH_4)_2Ce(NO_3)_6$ ceric ammonium nitrate

Pd/C palladium on carbon

$Pd_2(dba)_3$ bis(dibenzylideneacetone) palladium

$Pd(OAc)_2$ palladium acetate

$Pd(OH)_2$ palladium hydroxide

$Pd(PPh_3)_4$ palladium tetrakis triphenylphosphine

$Pd(PPh_3)_2Cl_2$ bis(triphenylphosphine)palladium(II) chloride

$Pd(dppf)Cl_2$ 1,1-bis(diphenylphosphino)ferrocene palladium chloride

P(*t*-Bu)$_3$ tri(*tert*-butyl)phosphine

PE petroleum ether (60-90 °C)

PBS phosphate buffered saline

$POCl_3$ phosphorous oxychloride

$PhI(OAc)_2$ iodobenzene diacetate

K_2CO_3 potassium carbonate

KOH potassium hydroxide

RT rt r.t. room temperature

Rt retention time

$SOCl_2$ thionyl chloride

SO_2Cl_2 sulfuryl chloride

t-BuOK Potassium *tert*-butanolate

TBTU *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

TBS tris buffered saline

THF tetrahydrofuran

TFA trifluoroacetic acid

TEAC bis(*tetra*-ethylammonium)carbonate

Tris trihydroxymethyl aminomethane

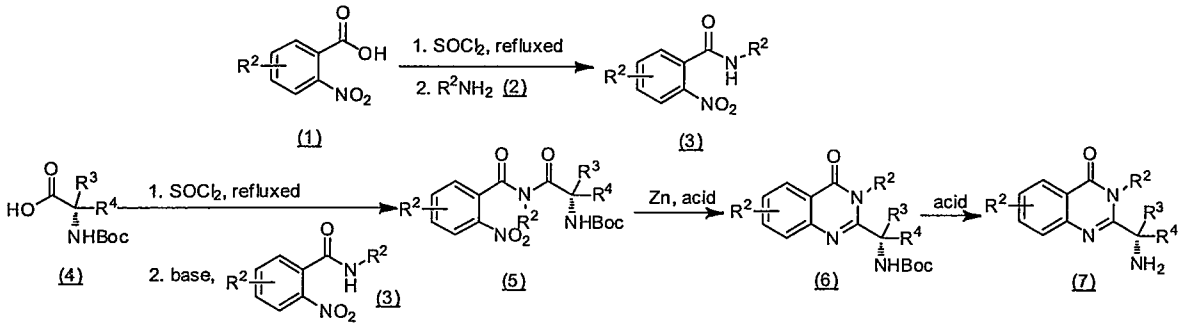
TsCl 4-toluene sulfonyl chloride

μL microliter

Zn zinc

[347] Representative synthetic procedures for the preparation of compounds of the disclosure are outlined below in following schemes. Unless otherwise indicated, each R^1, R^2, R^3, R^4 and X carry the definitions set forth above in connection with formula (I). "PG" is a suitable alkyne protecting group.

Scheme 1



[348] The intermediate (7) can be prepared in a general method illustrated in Scheme 1. Benzoic acid (1) is first reacted with $SOCl_2$ at refluxed temperature in a nonpolar solvent such as toluene, followed by treating with amino compound (2) to provide amide (3). Compound (4) is first reacted with $SOCl_2$ at refluxed temperature in a nonpolar solvent such as toluene, followed by treating with compound (3) to provide compound (5). The reduction and cyclization of the nitro compound (5) in the presence of Zn powder and an acid (such as acetic acid) provides compound (6). Deprotection of the amino group of compound (6) under standard conditions known to those skilled in the art such as, but not limited to, treatment with an acid to give the intermediate (7).

Scheme 2

mmol) and DIPEA (5.71 g, 44.2 mmol) in 100 mL of anhydrous DCM was added the above pale yellow solution slowly at 0 °C. The resulted mixture was stirred at room temperature for 24 hours, then washed with water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 7/1) to give the title compound as a yellow solid (6.58 g, 72.4%).

MS (ESI, neg. ion.) m/z: 410.0 $[M-H]^-$.

Step 3) (*S*)-*tert*-butyl (1-(5-chloro-3-cyclopropyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-carbamate

[473] To a solution of (*S*)-*tert*-butyl (1-(2-chloro-*N*-cyclopropyl-6-nitrobenzamido)-1-oxopropan-2-yl)carbamate (6.58 g, 16.0 mmol) in acetic acid (32 mL) was added zinc powder (4.16 g, 63.6 mmol) in one portion. The reaction mixture was stirred at 35 °C for 24 hours and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and the resulted mixture was washed with saturated $NaHCO_3$ aqueous solution (100 mL x 2) and brine (200 mL). The separated organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 8/1) to give the title compound as a pale yellow solid (4.74 g, 81.25%).

MS (ESI, pos. ion.) m/z: 364.2 $[M+H]^+$.

Step 4) (*S*)-2-(1-aminoethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one

[474] To a solution of (*S*)-*tert*-butyl (1-(5-chloro-3-cyclopropyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (4.7 g, 12.9 mmol) in EtOAc (10 mL) was added a solution of HCl in EtOAc (10 mL, 3.5 M) in one portion at room temperature. The mixture was stirred at room temperature overnight. The resulted suspension was dissolved in 150 mL of water. The aqueous phase was extracted with EtOAc (30 mL x 3), neutralized to pH = 8 with Na_2CO_3 powder, and extracted with EtOAc (100 mL x 4) again. The combined organic phases were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the title compound as a pale yellow solid (2.57 g, 75.6%).

MS (ESI, pos. ion.) m/z: 264.2 $[M+H]^+$;

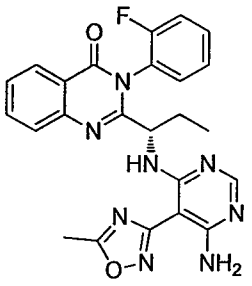
^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (m, 2H), 7.43 (m, 1H), 4.87 (dd, J = 13.0, 6.4 Hz, 1H), 2.94 (m, 1H), 1.52 (d, J = 6.6 Hz, 3H), 1.38 (m, 2H), 0.95 (m, 2H).

dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 2/1) to give the title compound as an off-white solid (39 mg, 58.8%).

MS (ESI, pos. ion) m/z: 453.2 $[M+H]^+$; HPLC: 98.3%;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.02 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 7.57-7.48 (m, 2H), 7.42 (dd, J = 6.4, 2.6 Hz, 1H), 6.34 (td, J = 7.7, 5.3 Hz, 1H), 4.52 (s, 3H), 3.17-3.05 (m, 1H), 2.20-2.08 (m, 1H), 2.06-1.97 (m, 1H), 1.48-1.40 (m, 2H), 1.27-1.21 (m, 1H), 1.08 (t, J = 7.4 Hz, 3H), 0.91-0.86 (m, 1H).

Example 55 (*S*)-2-(1-((6-amino-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-yl)amino)-propyl)-3-cyclopropyl-5-fluoroquinazolin-4(3*H*)-one



[530] A mixture of 6-chloro-5-(5-methyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-amine (23.0 mg, 0.11 mmol), (*S*)-2-(1-aminopropyl)-3-(2-fluorophenyl)quinazolin-4(3*H*)-one (38.8 mg, 0.13 mmol) and *N,N*-diisopropylethylamine (42.3 mg, 0.33 mmol) in *n*-buthanol (2.0 mL) was heated to 125 °C and stirred further for 24 hours. After completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by a preparative TLC (DCM/MeOH, v/v, 50/1) to give the title compound as a light yellow solid (20 mg, 39%), which composed of two isomers (A and B) with a ratio of 3/4 (isomer A/isomer B).

MS (ESI, pos. ion) m/z: 473.2 $[M+H]^+$; HPLC: 99.1% (total purity of isomer A and B);

Isomer A: ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.76 (d, J = 7.3 Hz, 1H), 7.88 (s, 1H), 7.84-7.69 (m, 2H), 7.60-7.44 (m, 3H), 7.41-7.30 (m, 2H), 7.20 (t, J = 8.8 Hz, 1H), 5.80 (br s, 1H), 5.32-5.26 (m, 1H), 2.71 (s, 3H), 2.16-2.08 (m, 1H), 2.02-1.88 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H).

Isomer B: ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.31 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 7.84-7.69 (m, 3H), 7.60-7.44 (m, 3H), 7.41-7.30 (m, 2H), 5.18 (td, J = 7.7, 5.0 Hz, 1H), 2.74 (s, 3H), 2.45 (br s, 1H), 2.02-1.88 (m, 1H), 1.81 (tt, J = 14.9, 7.4 Hz, 1H), 0.91 (t, J = 7.3 Hz, 3H).

Example 56 (*S*)-2-(1-((6-amino-5-(3-ethyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)-propyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one

with a mixture of THF (2 mL) and water (50 mL). The resulted mixture was stirred at rt for 1 hour and filtered to give the title compound as a white solid (9.8 g, 85%).

MS (ESI, pos. ion) m/z: 258.1 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.27 (s, 1H), 7.55 (s, 2H), 6.32 (s, 2H), 2.40 (m, 1H), 1.13 (d, J = 7.0 Hz, 6H).

Step 4) 6-chloro-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine

[539] To a suspension of *N*'-((4-amino-6-chloropyrimidine-5-carbonyl)oxy)isobutyrimid amide (7.5g, 29.1 mmol) in DMSO (20 mL) was added Bu_4NF (1 M in THF, 60 mL, 60.0 mmol) and the resulted mixture was stirred at rt overnight. The reaction was monitored by TLC (PE/EtOAc, v/v, 1/1). After the completion, the reaction was diluted with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL). The separated organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) =7/1) to give the title compound as a white solid (0.9 g, 14 %).

MS (ESI, pos. ion) m/z: 240.1 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.47 (s, 1H), 8.43 (s, 1H), 8.10 (s, 1H), 3.18 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H).

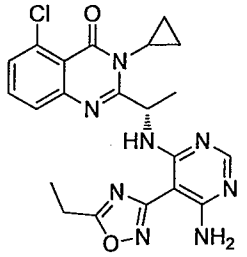
Step 5) (*S*)-2-(1-((6-amino-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one

[540] To a suspension of (*S*)-2-(1-aminoethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one (70 mg, 0.27mmol) and 6-chloro-5-(3-isopropyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (65 mg, 0.28 mmol) in *n*-BuOH (4 mL) was added DIPEA (75 mg, 0.58 mmol). The resulted mixture was heated at reflux for 20 hours. The reaction was monitored by TLC (PE/EtOAc, v/v, 1/1). After the completion, the mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a white solid (82 mg, 65%).

MS (ESI, pos. ion) m/v: 467.1 $[M+H]^+$; HPLC: 99.2%;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.24 (d, J = 7.1 Hz, 1H), 8.12 (s, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.52 (m, 4H), 6.19 (m, 1H), 3.20 (m, 1H), 3.13 (m, 1H), 1.59 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.9 Hz, 6H), 1.26 (m, 1H), 1.03 (m, 1H), 0.91-0.78 (m, 2H).

Example 61 (*S*)-2-(1-((6-amino-5-(5-ethyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-yl)amino)-ethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one



Step 1) 4,6-dimethoxypyrimidine-5-carbaldehyde

[550] To a suspension of 4,6-dichloropyrimidine-5-carbaldehyde (5 g, 28.25 mmol) in dried MeOH (100 mL) was added K_2CO_3 (7.8 g, 56.5 mmol). The reaction was heated to 90 °C and stirred further for 1 hour, then concentrated *in vacuo*. The residue was dissolved in a mixed solvent of water (100 mL) and DCM (100 mL), and the mixture was extracted with DCM (50 mL x 3). The combined organic phases were concentrated *in vacuo*. The residue was stirred with DCM/PE (10 mL, v/v, 1/20) at rt for 3 hours, and filtered to give the crude compound as a yellow solid. The crude compound was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 5/1) to give the title compound as a white solid (2.2 g, 46.3%).

MS (ESI, pos. ion) m/z: 169.1 $[M+H]^+$.

Step 2) 4,6-dimethoxypyrimidine-5-carbaldehyde oxime

[551] To a solution of 4,6-dimethoxypyrimidine-5-carbaldehyde (2.2 g, 13.08 mmol) in ethyl acetate (45 mL) was added a solution of $NH_2OH{\cdot}HCl$ (910 g, 13.08 mmol) in water (18 mL), followed by the addition of sodium acetate (1.07 g, 13.08 mmol) at room temperature. After stirring at 28 °C for 3 hours, the reaction mixture was filtered and the filter cake was washed with 30 mL of water, dried at 60 °C in a vacuum dryer to give the title compound as a white solid (2.2 g, yield 91.8%).

MS (ESI, pos. ion) m/z: 184.1 $[M+H]^+$;

^1H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (s, 1H), 8.47 (s, 1H), 8.08 (s, 1H), 3.96 (s, 6H).

Step 3) 3-(4,6-dimethoxypyrimidin-5-yl)-5-ethyl-1,2,4-oxadiazole

[552] To a three-neck flask charged with 4,6-dimethoxypyrimidine-5-carbaldehyde oxime (2.0 g, 10.93 mmol) and $(NH_4)_2Ce(NO_3)_6$ (12.0 g, 21.86 mmol) was added CH_3CHCN (37 mL) at rt under N_2 protection. Then the reaction mixture was heated to 70 °C and stirred

further for 6 hours, then filtered and the filtrate was *in vacuo*. The residue was dissolved in EtOAc (50 mL), and the resulted mixture was washed with saturated Na_2CO_3 aqueous solution (50 mL x 2) and brine (50 mL x 2). The separated organic phase was concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) =10/1) to give the title compound as a yellow solid (805 mg, 31.0%).

MS (ESI, pos. ion) m/z: 237.2 $[M+H]^+$.

Step 4) 3-(4,6-dichloropyrimidin-5-yl)-5-ethyl-1,2,4-oxadiazole

[553] To a suspension of 3-(4,6-dimethoxypyrimidin-5-yl)-5-ethyl-1,2,4-oxadiazole (650 mg, 2.75 mmol) and DMF (6.0 mL) in toluene (14 mL) was added $POCl_3$ (6 mL, 62.75 mmol). Then the reaction was heated to 120 °C and stirred further for 10 hours, then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the title compound as yellow syrup (320 mg, yield 51.4%).

MS (ESI, pos. ion) m/z: 245.1 $[M+H]^+$.

Step 5) 6-chloro-5-(5-ethyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-amine

[554] To a solution of 3-(4,6-dichloropyrimidin-5-yl)-5-ethyl-1,2,4-oxadiazole (320 mg, 1.31 mmol) in THF (10 mL) was bubbled through NH_3 (gas) at rt for 1 hour, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound as a pale yellow solid (330 mg, yield 100%).

MS (ESI, pos. ion) m/z: 226.1 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.35 (s, 1H), 7.85 (s, 1H), 7.07 (s, 1H), 3.05-2.99 (q, J = 7.6 Hz, 2H), 1.36-1.32 (t, J = 7.6 Hz, 3H).

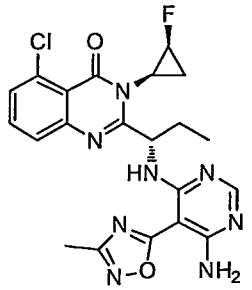
Step 6) (*S*)-2-(1-((6-amino-5-(5-ethyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-yl)amino)-ethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one

[555] To a mixture of (*S*)-2-(1-aminoethyl)-5-chloro-3-cyclopropylquinazolin-4(3*H*)-one (50 mg, 0.19 mmol) and 6-chloro-5-(5-ethyl-1,2,4-oxadiazol-3-yl)pyrimidin-4-amine (43 mg, 0.19 mmol) in 4 mL of *n*-BuOH was added DIPEA (49.1 mg, 0.38 mmol). The mixture was heated to 120 °C and stirred overnight, then concentrated in *vacuo*. The residue was dissolved in EtOAc (15 mL), and the resulted mixture was washed with water (10 mL x 2). The separated organic phase was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/EtOAc (v/v) = 1/3) to give the title compound as a yellow solid (31 mg, yield 36%).

MS (ESI, pos. ion) m/z: 453.3 $[M+H]^+$;

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.01 (d, J = 7.4 Hz, 1H), 8.14 (s, 1H), 7.53 (m, 2H), 7.46-7.39 (m, 1H), 6.33 (m, 1H), 6.01-5.39 (s, 2H), 3.12 (m,1H), 3.04 (q, J = 7.6 Hz, 2H), 1.65 (d, J = 9.6 Hz, 3H), 1.50 (t, J = 7.6 Hz, 3H), 1.46-1.39 (m, 2H), 0.90 (m, 2H).

Example 62 2-((*S*)-1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)propyl)-5-chloro-3-((1*R*,2*S*)-2-fluorocyclopropyl)quinazolin-4(3*H*)-one



Step 1) 2-chloro-*N*-((1*R*,2*S*)-2-fluorocyclopropyl)-6-nitrobenzamide

[556] To a suspension of 2-chloro-6-nitrobenzoic acid (806 mg, 4.0 mmol) in toluene (10 mL) was added $SOCl_2$ (952 mg, 8.0 mmol) in one portion at room temperature. After addition, the reaction mixture was stirred at 110 °C for 9 hours and concentrated *in vacuo* to give yellow oil which was dissolved in 1,4-dioxane (10 mL) to give a pale yellow suspension. The pale yellow suspension was added dropwise to a suspension of (1*R*,2*S*)-2-fluorocyclopropylamine tosylate (1.0 g, 4.0 mmol) and $NaHCO_3$ (1.34 g, 16.0 mmol) in 1,4-dioxane (10 mL) at 5 °C. The reaction mixture was stirred at room temperature overnight, and diluted with 100 mL of water. The resulted mixture was extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound as a pale yellow solid (940 mg, yield 90.86%).

MS (ESI, pos. ion) m/z: 259.0 $[M+H]^+$;

^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.12 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 6.08 (s, 1H), 4.80 (ddd, J = 63.6, 8.8, 5.7 Hz, 1H), 3.08 (td, J = 9.4, 5.3 Hz, 1H), 1.32 (dt, J = 14.9, 8.3 Hz, 1H), 1.24 (m, 1H).

Step 2) *tert*-butyl ((*S*)-1-(2-chloro-*N*-((1*R*,2*S*)-2-fluorocyclopropyl)-6-nitrobenzamido)-1-oxobutan-2-yl)carbamate

$NaHCO_3$ aqueous solution. The resulted mixture was concentrated *in vacuo*, and the residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 10/1) to give the title compound as a yellowish solid (253 mg, 66%).

MS (ESI, pos. ion) m/z: 400.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63-7.61 (m, 2H), 7.59-7.57 (m,1H), 7.55-7.51 (m, 2H), 7.48-7.46 (dd, J = 6.4, 3.6 Hz, 1H), 7.39-7.37 (d, J = 7.2 Hz, 1H), 7.29-7.27 (m, 1H), 5.59-5.57 (d, J = 7.2 Hz, 1H), 4.52-4.49 (m, 1H), 1.42 (s, 9H), 1.26-1.26 (d, J = 6.8 Hz, 3H).

Step 5) (*S*)-2-(1-aminoethyl)-5-chloro-3-phenylquinazolin-4(3*H*)-one

[569] To a solution of (*S*)-*tert*-butyl (1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (367 mg, 0.92 mmol) in EtOAc (10 mL) was added a solution of HCl in EtOAc (8 mL, 24 mmol, 3 M) at rt. The reaction was stirred at rt for 40 hours, and concentrated in *vacuo*. The residue was dissolved in 26 mL of H_2O, and the resulted mixture was extracted with EtOAc/PE (10 mL/5 mL). The aqueous phase was basified to pH = 8.5 with $NaHCO_3$ powder, and extracted with DCM (75 mL x 2). The combined organic phase was washed with 50 mL of saturated brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the title compound as a yellowish solid (253 mg, 92%).

MS (ESI, pos. ion) m/z: 300.0 $[M+H]^+$;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63-7.61 (m, 2H), 7.59-7.51 (m, 3H), 7.47-7.45 (dd, J = 6.6, 2.5 Hz, 1H), 7.28-7.26 (m, 2H), 3.68 (q, J = 6.6 Hz, 1H), 1.28-1.26 (d, J = 6.6 Hz, 3H).

Step 6) (*S*)-2-(1-((6-amino-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)amino)ethyl)-5-chloro-3-phenylquinazolin-4(3*H*)-one

[570] A mixture of (*S*)-2-(1-aminoethyl)-5-chloro-3-phenylquinazolin-4(3*H*)-one (35 mg, 0.116 mmol), 6-chloro-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyrimidin-4-amine (24.7 mg, 0.116 mmol) and DIPEA (30 mg, 0.233 mmol) in *n*-BuOH (1 mL) was heated to 125 °C and stirred further for 4 hours, then cooled to rt, and concentrated *in vacuo*. The residue was suspended with EtOAc (2 mL) and H_2O (2 mL), the title compound was collected through filtration as a white solid (42 mg, 76%).

MS (ESI, pos. ion) m/z: 475.0 $[M+H]^+$; HPLC: 99%;

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.54 (m, 1H), 8.01 (s, 1H), 7.59-7.45 (m, 6H), 7.33-7.26 (m, 1H), 6.40 (br s, 2H), 5.13 (m, 1H), 2.71 (s, 3H), 1.46 (m, 3H).

filtered over a pad of CELITE®, and the filtrate was extracted with EtOAc (20 mL x 3). The combined organic phases was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as pale yellow oil (507 mg, 90.0%).

MS (ESI, pos. ion) m/z: 410.3 $[M+H]^+$;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.85 (s, 1 H), 7.69-7.65 (t, J = 7.8 Hz, 1 H), 7.54 (s, 1 H), 7.46-7.44 (dd, J = 8.0, 0.9 Hz, 1 H), 7.34-7.29 (t, J = 8.8 Hz, 2 H), 3.88 (s, 3 H), 2.98-2.91 (m, 1 H), 1.99-1.96 (m, 1 H), 1.49-1.30 (m, 12 H), 0.99-0.91 (m, 2H), 0.86-0.84 (m, 2 H).

Step 2) (*S*)-2-(1-aminoethyl)-3-cyclopropyl-5-(1-methyl-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one

[573] To a solution of (*S*)-*tert*-butyl (1-(5-chloro-3-cyclopropyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (507 mg, 1.24 mmol) in EtOAc (6 mL) was added a solution of HCl in EtOAc (3.0 M, 4.0 mL), the mixture was stirred at rt for 5 hours, and then concentrated *in vacuo*. The residue was suspended in DCM (20 mL), and the resulted suspension was neutralized with saturated $NaHCO_3$ aqueous solution. The water phase was extracted with DCM (10 mL x 2). The combined organic phase were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the title compound as pale brown oil (322 mg, 84.0%).

MS (ESI, pos. ion) m/z: 310.2 $[M+H]^+$.

Step 3) (*S*)-2-(1-((6-amino-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-yl)amino)ethyl)-3-cyclopropyl-5-(1-methyl-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one

[574] To a mixture of (*S*)-2-(1-aminoethyl)-3-cyclopropyl-5-(1-methyl-1*H*-pyrazol-4-yl)quinazolin-4(3*H*)-one (113 mg, 0.36 mmol) and 6-chloro-5-(3-methyl-1,2,4-oxadiazol-5-yl)pyrimidin-4-amine (81.1 mg, 0.38 mmol) in *n*-BuOH (1.5 mL) was added *N,N*-diisopropylethylamine (0.15 mL, 0.85 mmol), the mixture was then heated at 120 °C for 3 hours, then cooled down to rt and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as a pale yellow solid (150 mg, 84.7%).

MS (ESI, pos. ion) m/z: 485.8 $[M+H]^+$; HPLC: 98.2 %;

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.37-9.36 (d, J = 6.8 Hz, 1 H), 8.13 (s, 1 H), 7.87 (s, 1 H), 7.75-7.72 (t, J = 7.8 Hz, 1 H), 7.63 (s, 2H), 7.55 (s, 1 H), 7.53-7.51 (m, 1 H) 7.36-7.31

Ex. 51	22.61	76.88	18.25	136.09
Ex. 52	7.72	321.85	6.71	370.21
Ex. 53	27.98	62.13	34.06	72.92
Ex. 54	42.76	40.65	99.13	25.06
Ex. 55	10.96	226.62	2.69	922.97
Ex. 56	19.98	87.00	20.35	122.05
Ex. 57	18.25	95.25	10.41	238.59
Ex. 58	61.84	28.11	121.5	20.44
Ex. 59	6.66	261.01	3.36	739.20
Ex. 61	6.07	286.47	3.29	755.39
Ex. 62	50.38	34.50	46.24	53.71
Ex. 63	47.88	36.31	17.92	138.60
Ex. 64	55.81	31.15	49.60	50.07
Ex. 65	33.14	52.45	32.64	76.09

Example B: Evaluation of Pharmacokinetics After Intravenous and Oral Administration of The Compounds Disclosed Herein In Mice, Rats, Dogs And Monkeys

[589] The compounds disclosed herein are assessed in pharmacokinetic studies in mice, rats, dogs or monkeys. The compounds are administered as a water solution, 2% HPMC + 1% TWEEN®80 in water solution, 5% DMSO + 5% solutol in saline, 4% MC suspension or capsule. For the intravenous administration, the animals are generally given at 1 or 2 mg/kg dose. For the oral (p.o.) dosing, mice and rats are generally given 5 or 10 mg/kg dose, and dogs and monkeys are generally given 10 mg/kg dose. The blood samples (0.3 mL) are drawn at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12 and 24 h time points or 0.083, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h time points and centrifuged at 3,000 or 4000 rpm for 2 to 10 min. The plasma solutions are collected, stored at -20 °C or -70 °C until analyzed by LC/MS/MS as described above.

Table 3 Pharmacokinetic profiles in Rats

Example #	**iv dosing**					**F (%)**
	dose (mg/kg)	**$T_{1/2}$** (h)	**AUC_{last}** (ng.h/mL)	**CL/F** (L/h/kg)	**Vss** (L/kg)	
Ex. 1	0.5	0.78	355	2.84	3.68	32.28
Ex. 2	1	1.26	405	2.47	3.93	63.9
Ex. 3	1	1.19	237	4.25	6.23	64.49

Ex. 43	1	1.52	452	2.21	3.41	90.04
Ex. 44	1	0.57	231	4.42	2.51	13.97
Ex. 45	1	0.97	278	3.71	4.61	70.25
Ex. 46	1	0.71	300	3.35	3.65	20.20
Ex. 47	1	0.94	271	366	3.16	23.58
Ex. 48	1	0.68	254	4.04	2.42	32.74
Ex. 49	1	0.66	196	5.12	4.10	4.37
Ex. 50	1	1.14	192	5.20	3.96	28.29
Ex. 51	1	1.91	609	1.64	1.64	59.81
Ex. 52	1	1.22	194	5.14	6.07	21.29
Ex. 53	1	1.62	429	2.29	3.88	97.32
Ex. 55	1	1.05	143	7.07	7.21	8.88
Ex. 56	1	1.73	217	4.48	8.12	60.92
Ex. 57	1	0.99	199	4.98	5.84	12.14
Ex. 58	1	2.38	580	1.57	5.03	106.15
Ex. 59	1	1.92	229	4.42	7.32	3.27
Ex. 61	1	1.00	169	5.85	7.07	NA
Ex. 62	1	1.35	238	4.31	6.11	27.69
Ex. 64	1	0.777	596	1.70	1.69	111.3
Ex. 65	1	0.904	260	7.74	9.09	88.73

Table 4 Pharmacokinetic profiles in Mice, Dogs and Monkeys

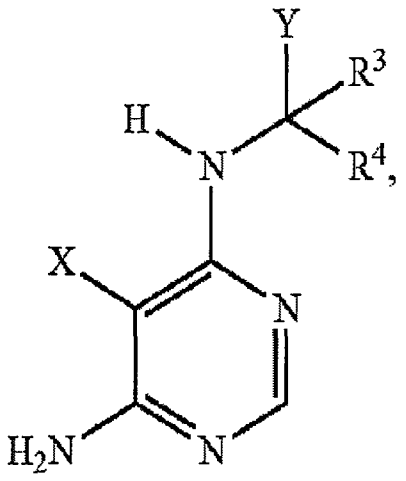
Example #	**Species**	**iv dosing**					**F** (%)
		dose (mg/kg)	**$T_{1/2}$** (h)	**AUC_{last}** (ng.h/mL)	**CL/F** (L/h/kg)	**Vss** (L/kg)	
Ex. 4	Mouse	1	1.48	651	15.3	3.80	11.0
	Dog	1	11.4	1580	0.58	6.01	34.1
	Monkey	1	3.09	1520	0.696	1.92	55.35
Ex. 64	Mouse	1	0.56	883	1.13	0.41	78.7
	Dog	1	3.63	10000	0.11	0.48	76.3
	Monkey	1	3.49	2340	0.43	1.40	133.9
Ex. 65	Mouse	1	0.79	527	1.90	0.84	33.3
	Dog	1	10.6	2690	0.37	4.25	24.84
	Monkey	1	6.71	1060	0.92	4.20	10.0

Example C: Kinase Activity Assay

CLAIMS

1. A compound having Formula (I):

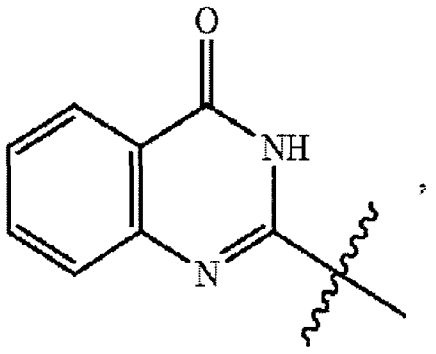
(I)



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, or a pharmaceutically acceptable salt thereof, wherein:

X is C_3-heterocyclyl or 5-6 membered heteroaryl, wherein X is optionally substituted by 1, 2, 3, 4, or 5 R^1 groups;

Y is



wherein Y is optionally substituted by 1, 2, or 3 R^2 groups;

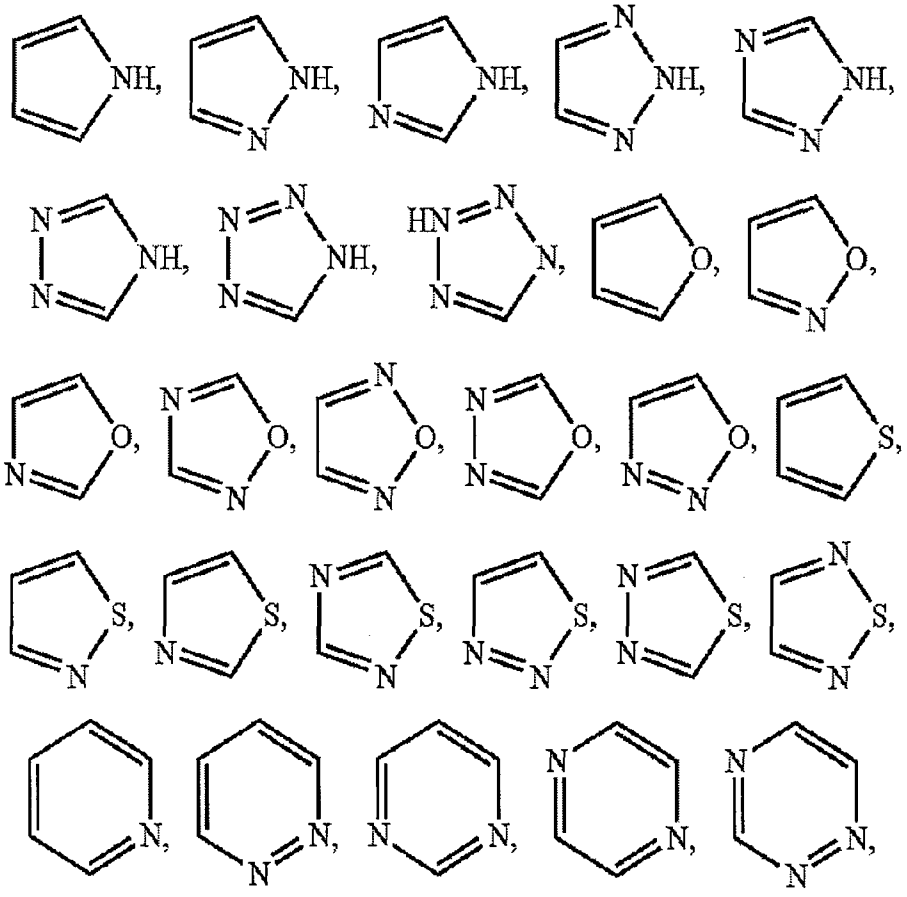
each R^1 is independently H, —C(=O)NH_2, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl or -(C_1-C_4)alkylene-OR^a;

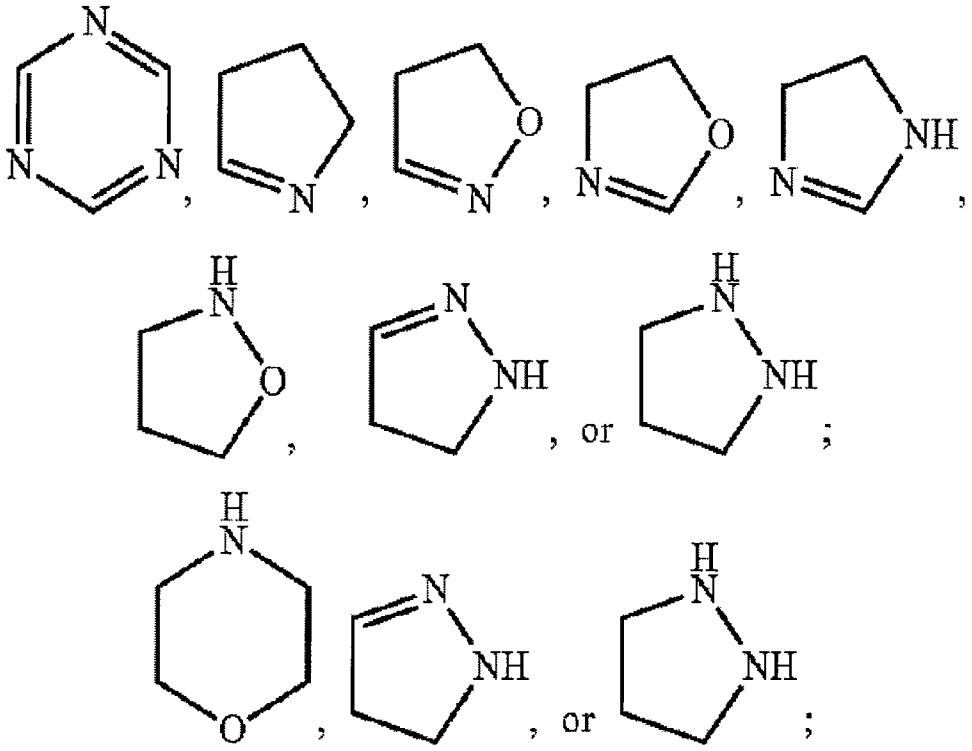
each R^2 is independently H, F, Cl, Br, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, phenyl, or 5-membered heteroaryl, wherein each of the (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, phenyl, and 5 membered heteroaryl is optionally substituted with 1, 2, 3, or 4 substitutents independently selected from F, Cl, Br, —OR^a, or (C_1-C_6)alkyl;

each R^3 and R^4 is independently H or (C_1-C_4)alkyl; and

each R^a and R^b is independently H or (C_1-C_6)alkyl.

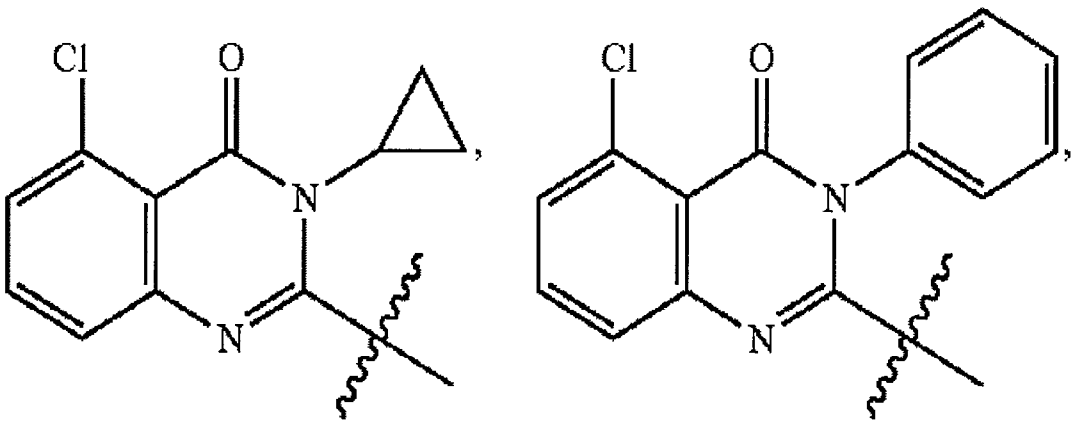
2. The compound according to claim **1**, wherein X is a monovalent heterocyclyl or heteroaryl group derived from one of the following structures:

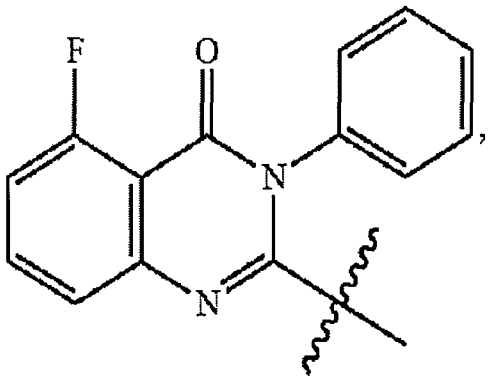


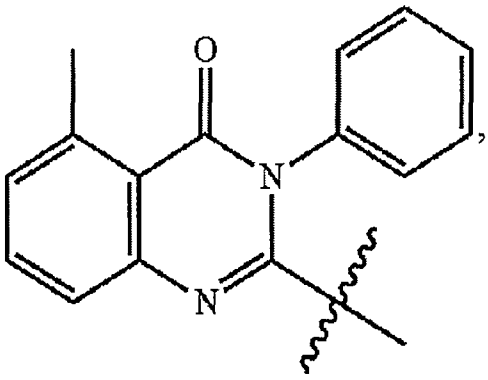


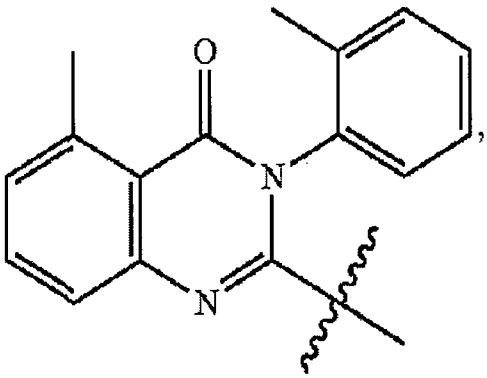
and wherein X is optionally substituted by 1, 2, or 3 R^1 groups.

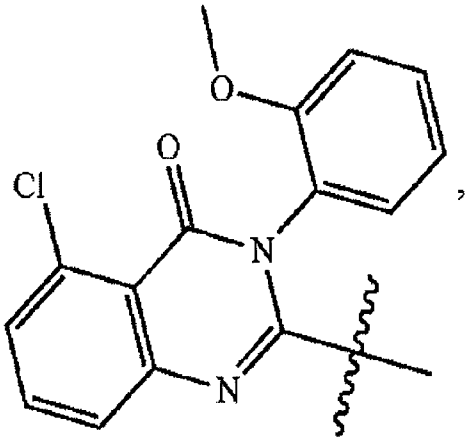
3. The compound according to claim **1**, wherein Y is

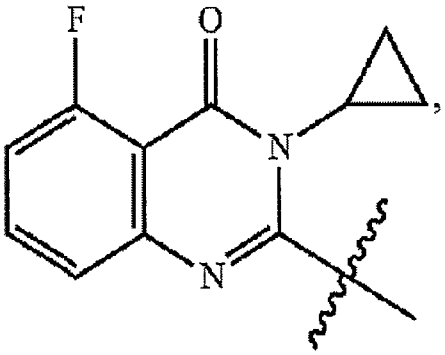


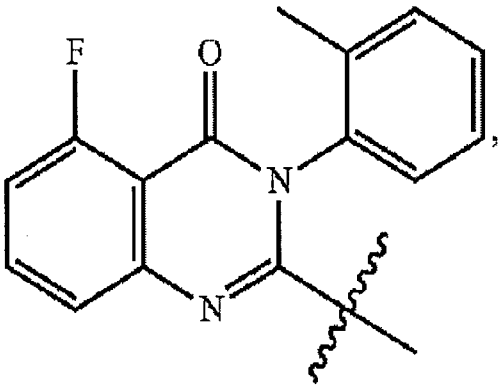


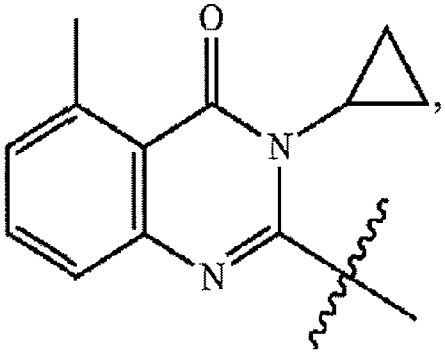


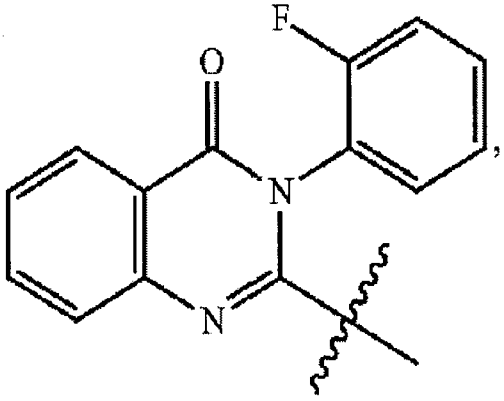


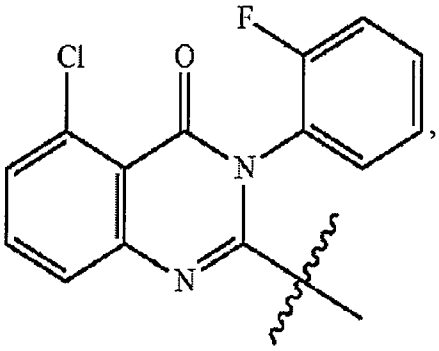


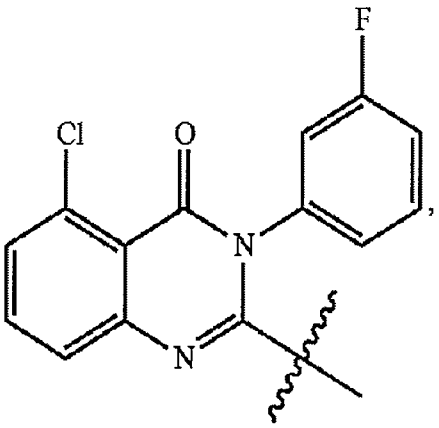


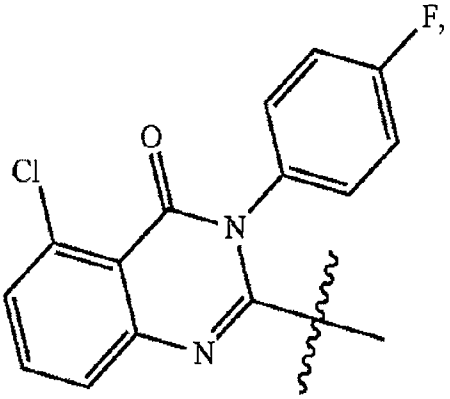


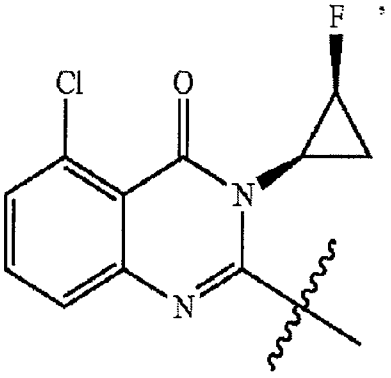


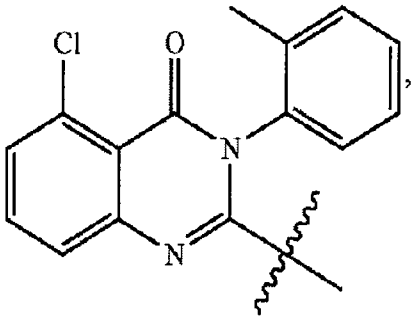


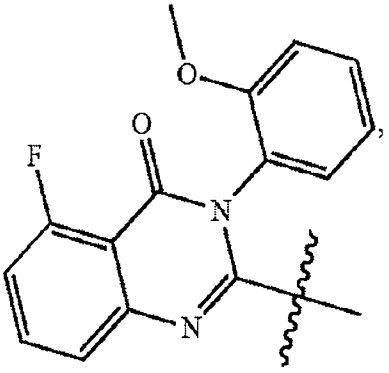


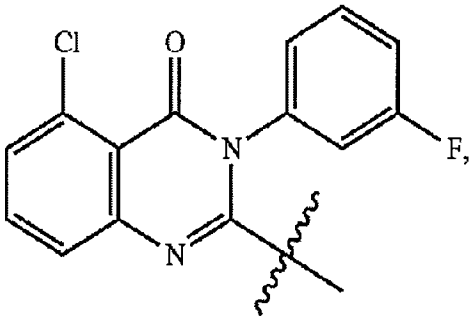


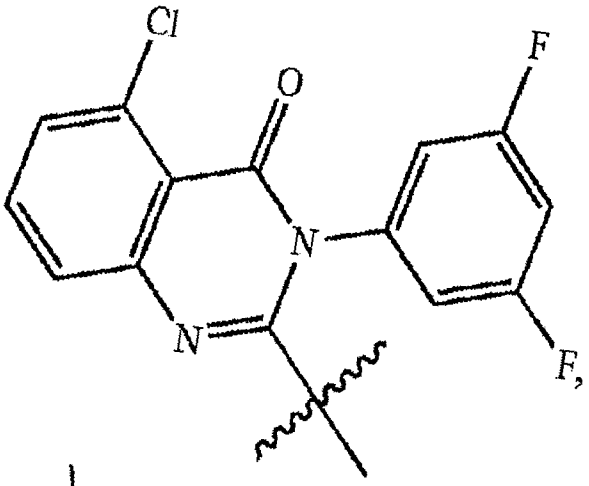








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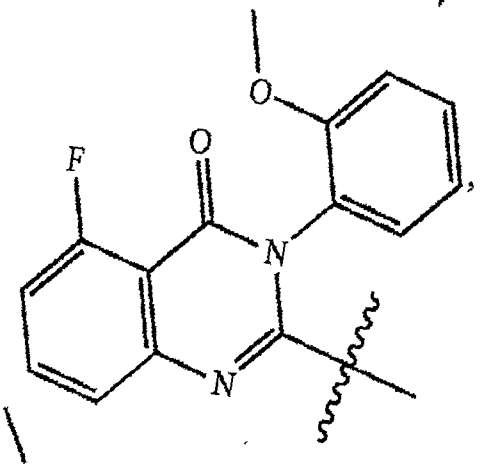
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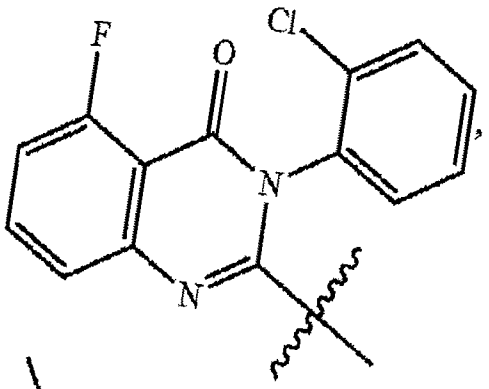
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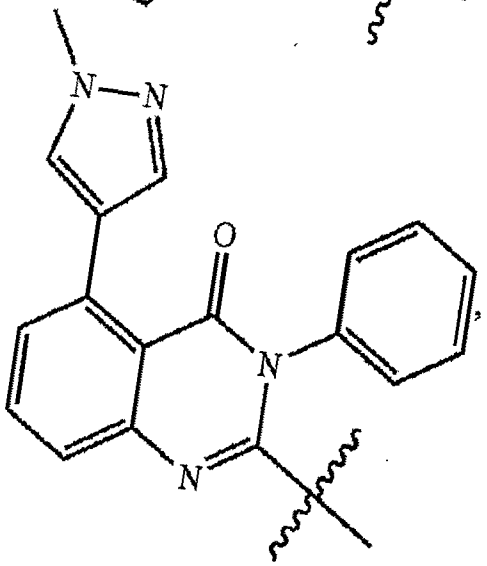
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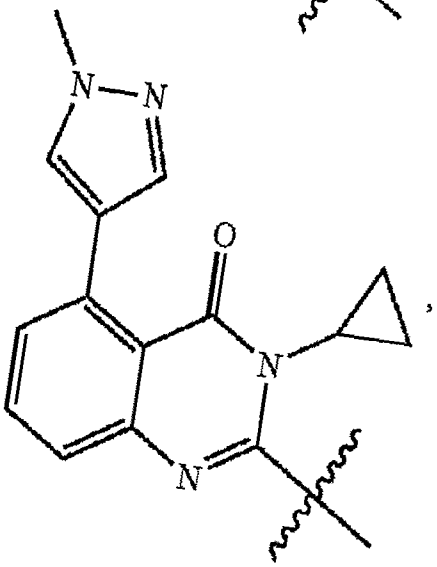
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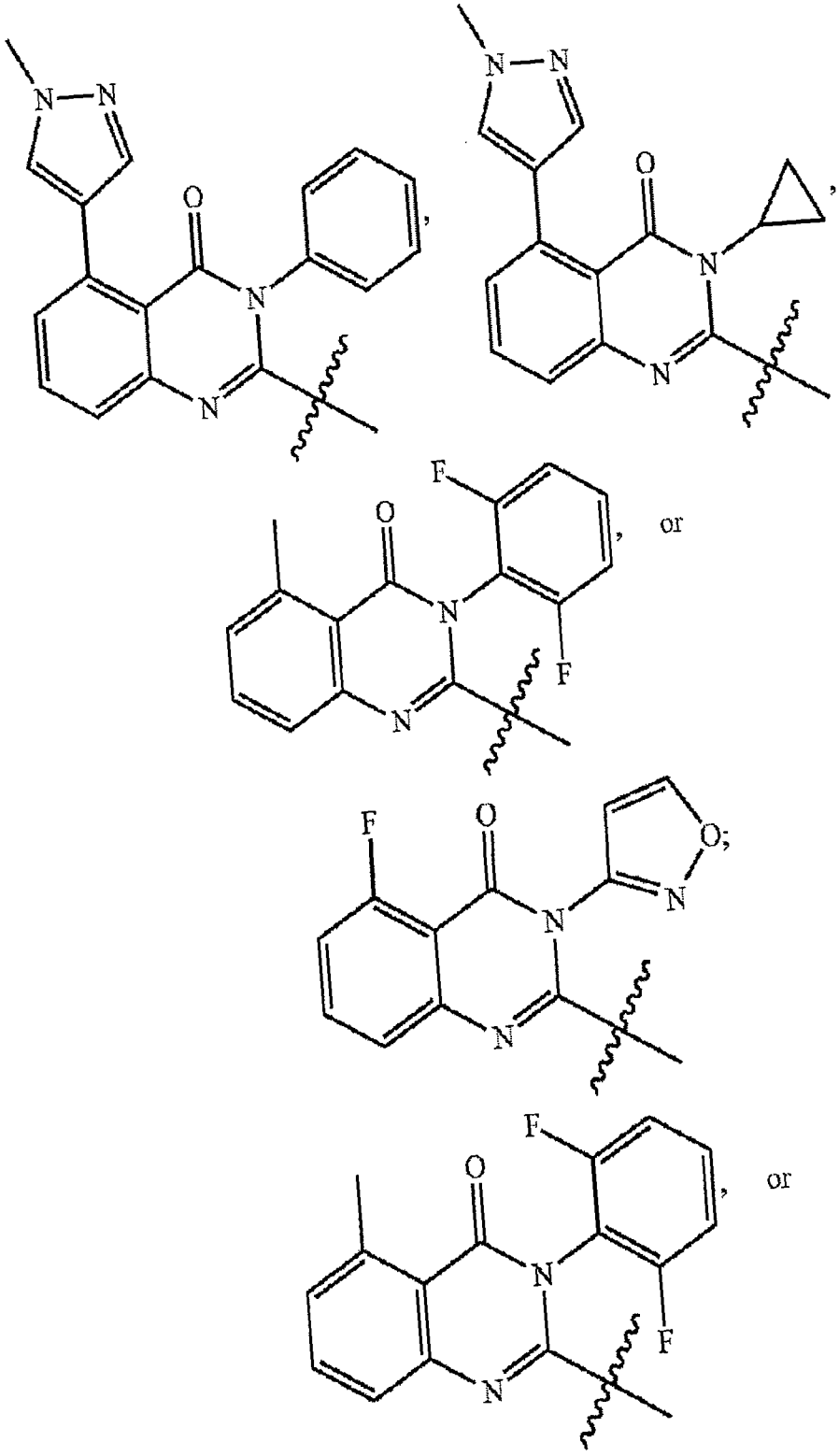


and wherein Y is optionally substituted by 1 or 2 R^2 groups.

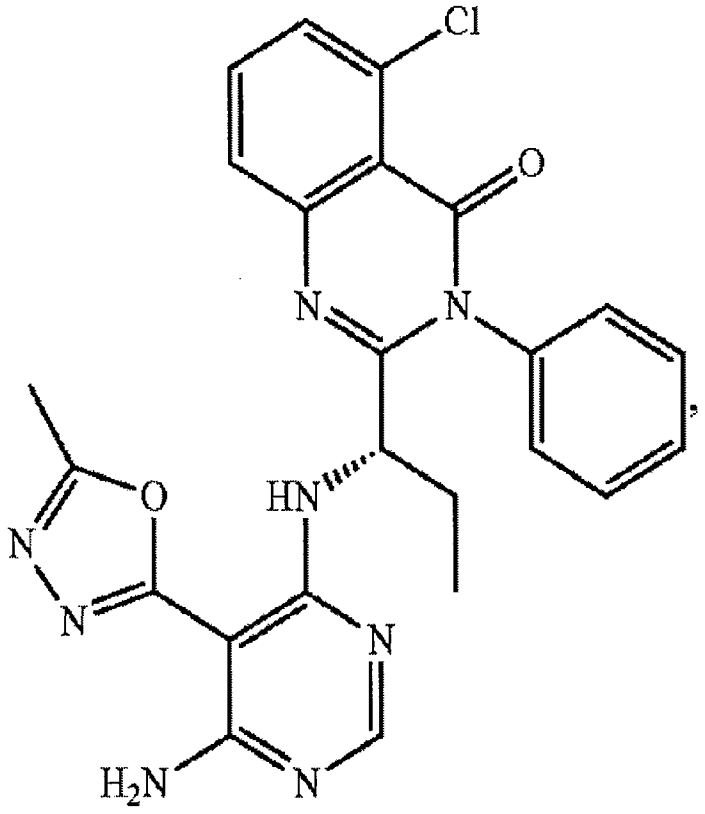
4. The compound according to claim **1**, wherein each R^1 is independently H, —C(=O)NH_2, (C_1-C_3)alkyl or (C_3-C_6) cycloalkyl; and each R^2 is independently H, F, Cl, (C_1-C_3) alkyl, (C_3-C_6)cycloalkyl, or phenyl, wherein each of the (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, and phenyl is optionally substituted with 1, 2, 3, or 4 substitutents independently selected from F, OR^a, and (C_1-C_3)alkyl.

5. The compound according to claim **1**, wherein each R^3 and R^4 is independently H or (C_1-C_3)alkyl.

6. The compound according to claim **1**, wherein each R^a and R^b is independently H or (C_1-C_3)alkyl.

7. A compound having one of the following structures:

(1)



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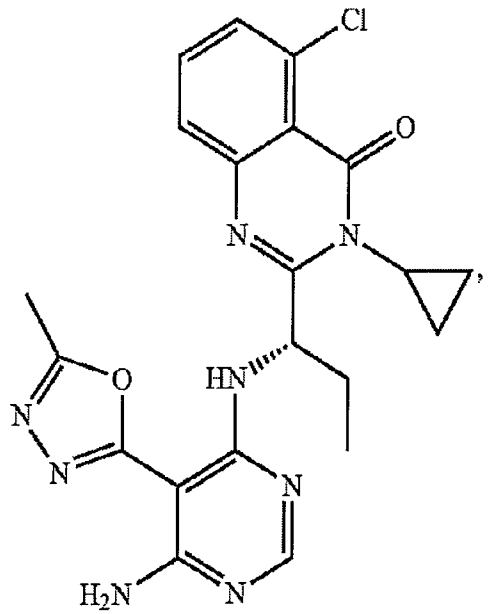

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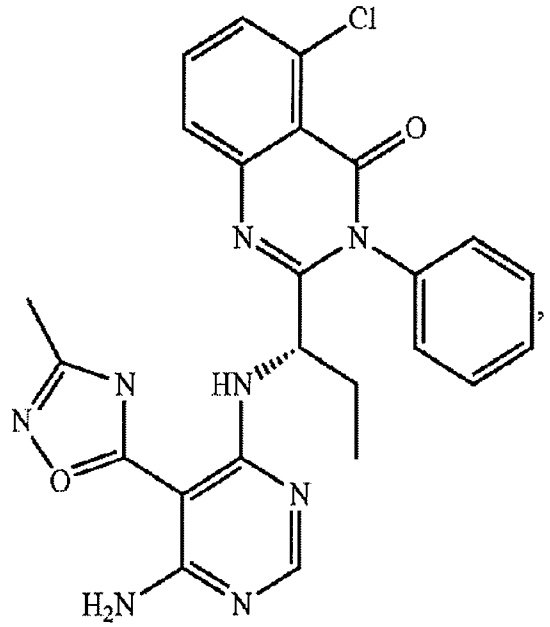

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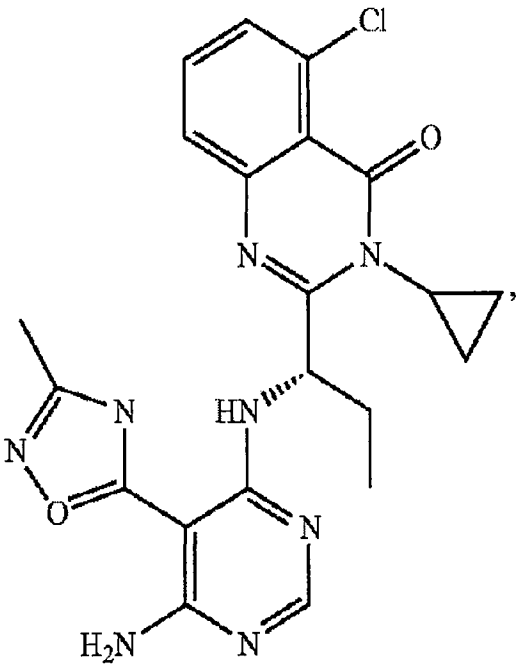

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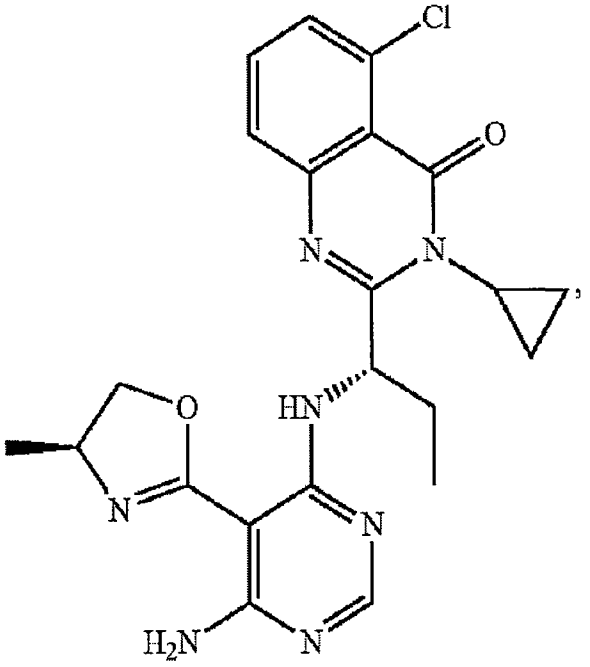

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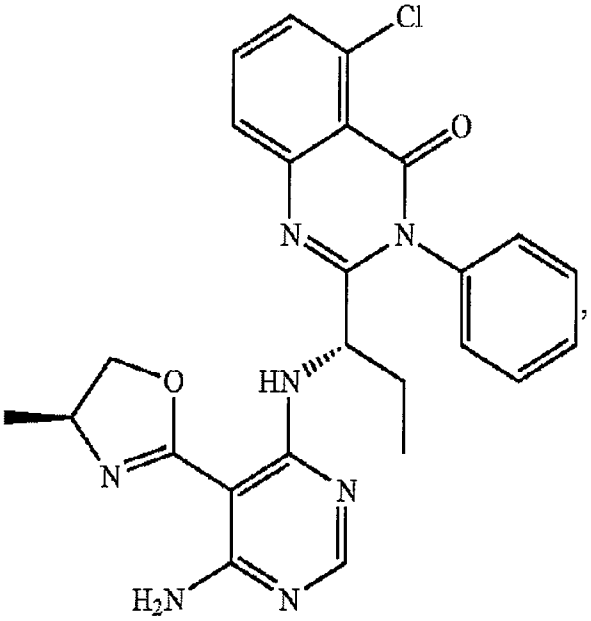

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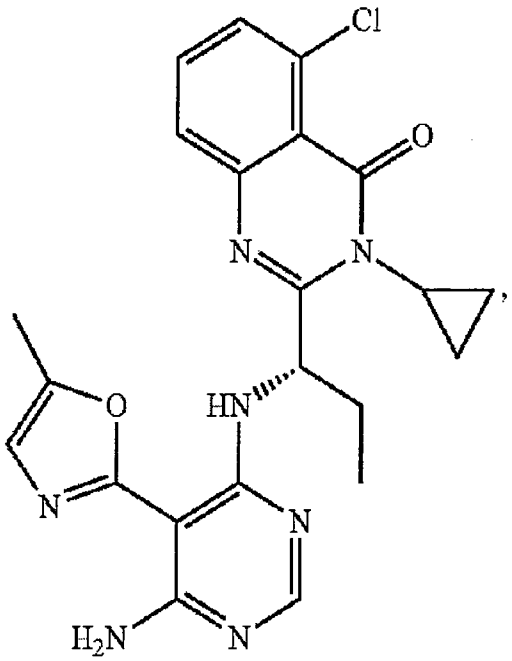

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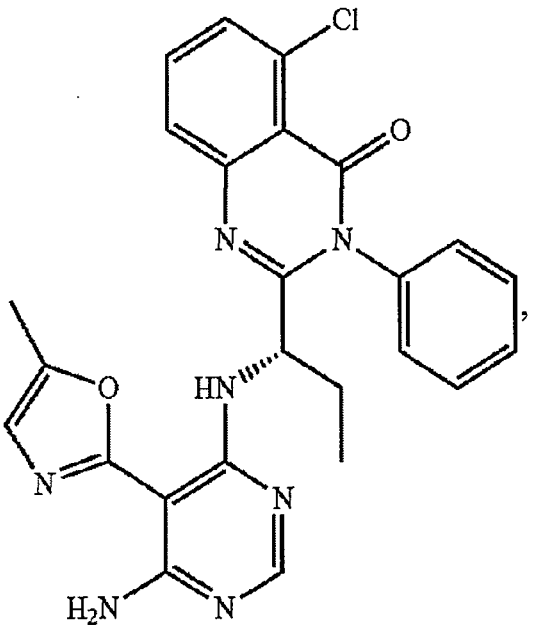

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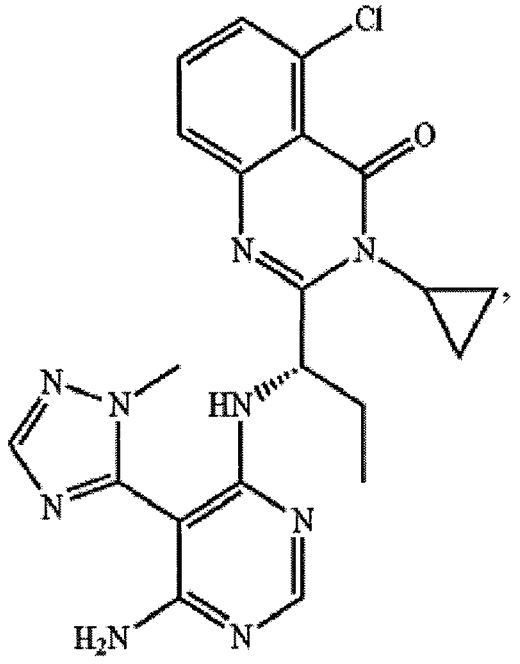

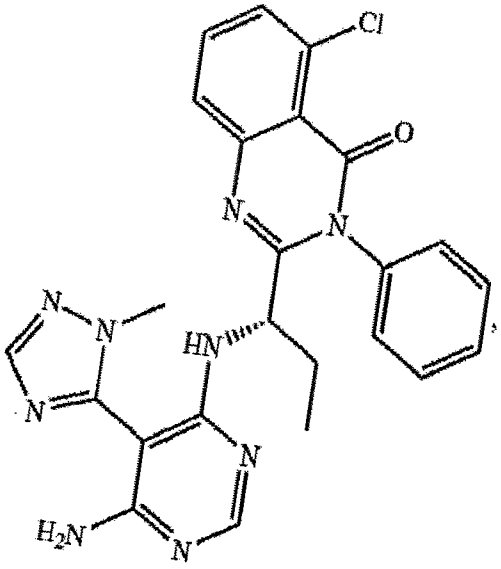

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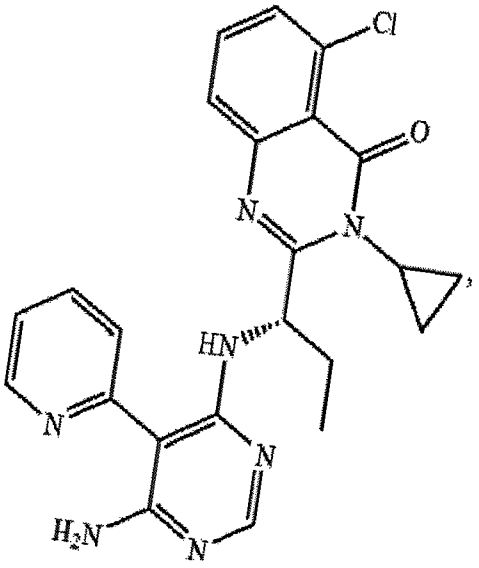

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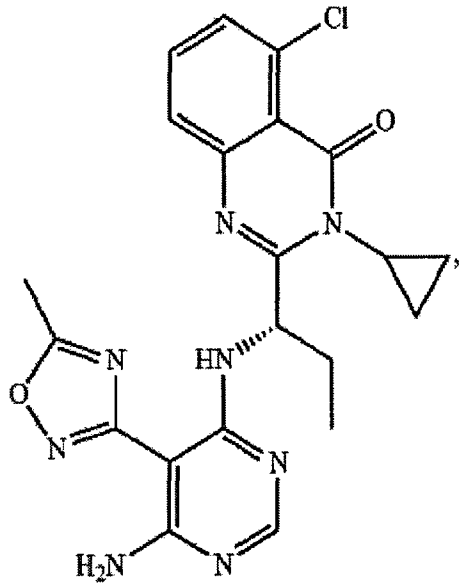

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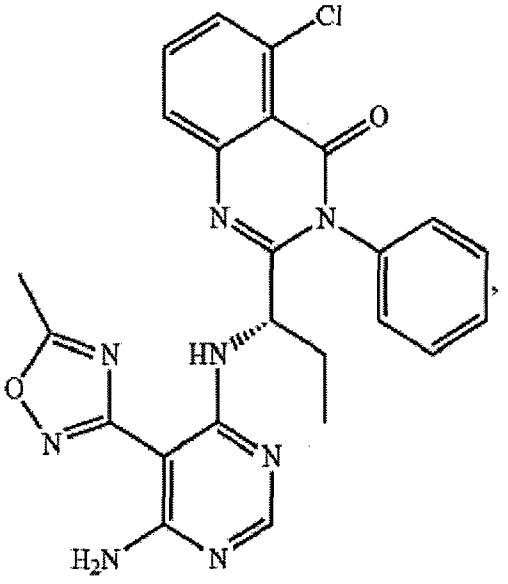

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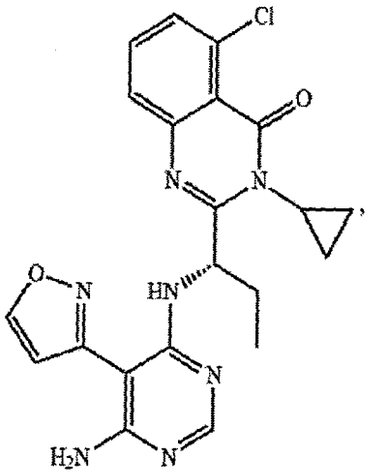

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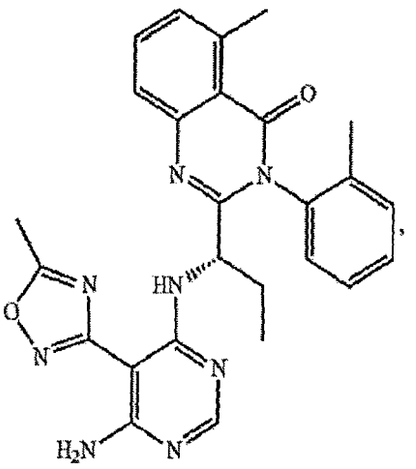

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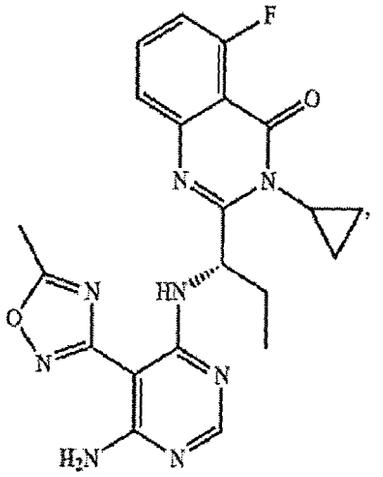

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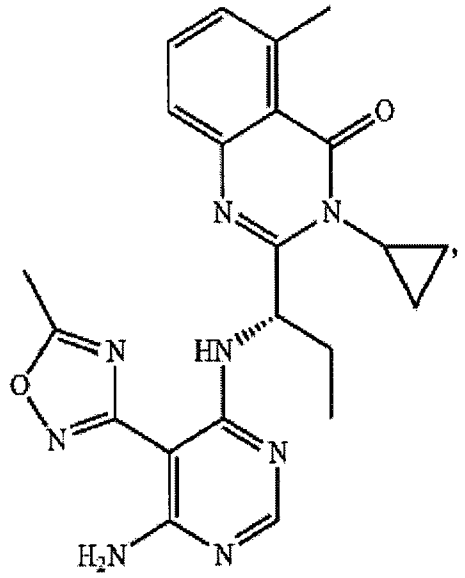

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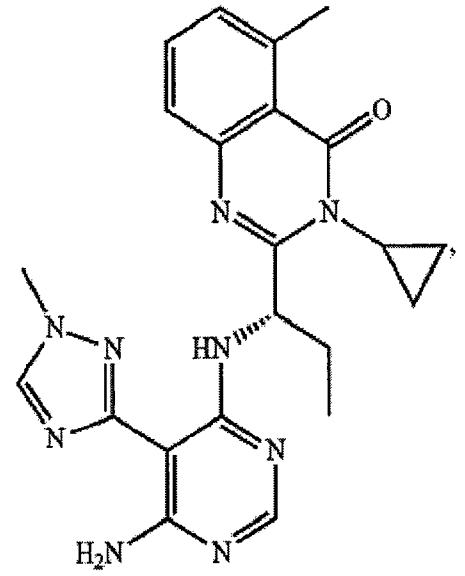

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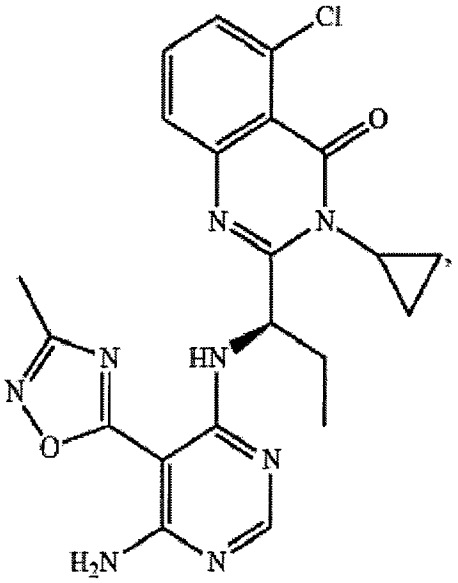

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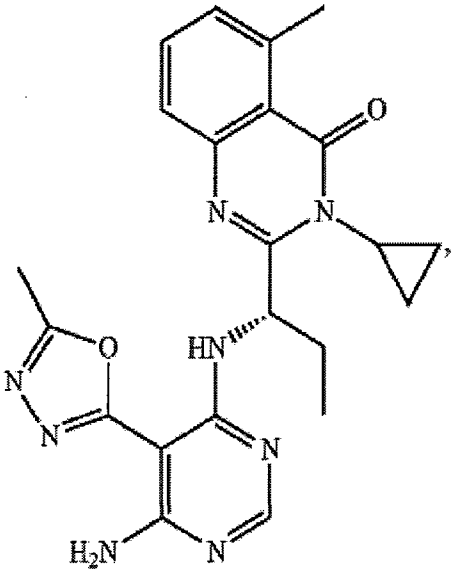

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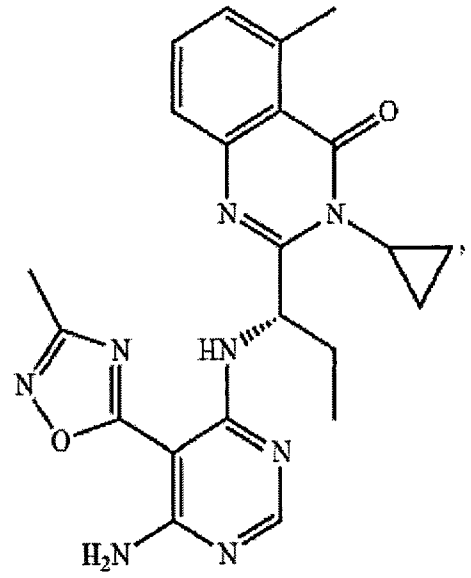

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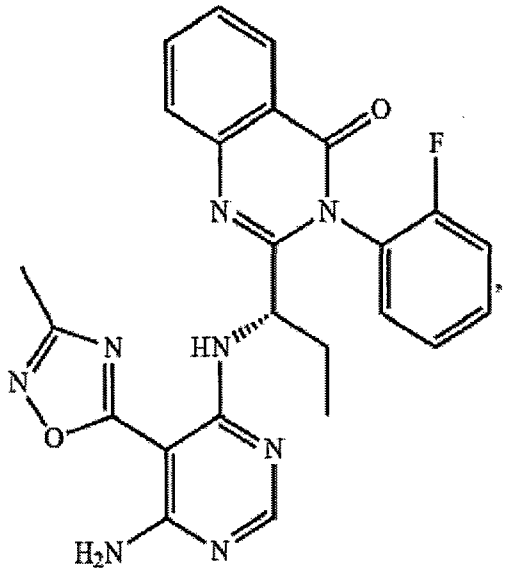

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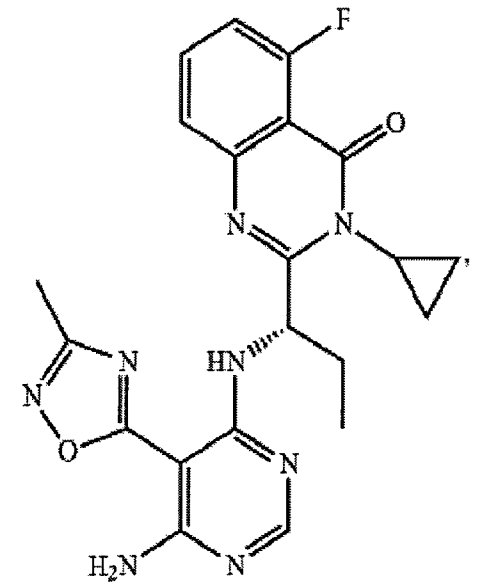

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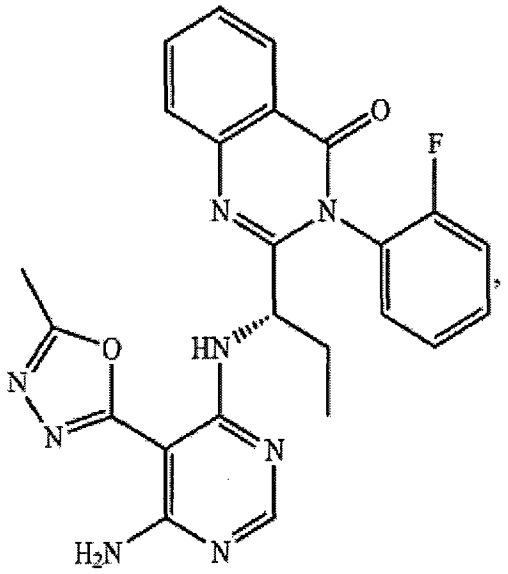

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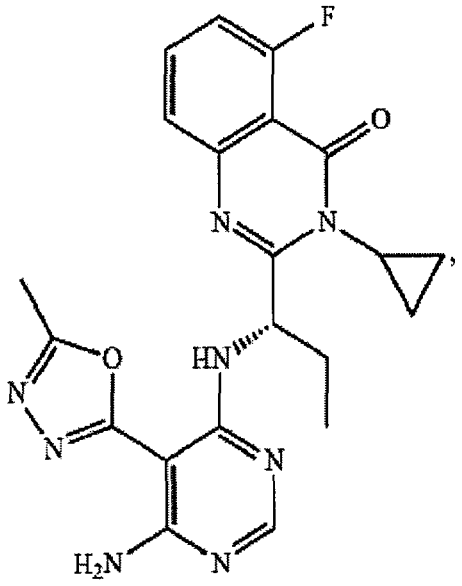

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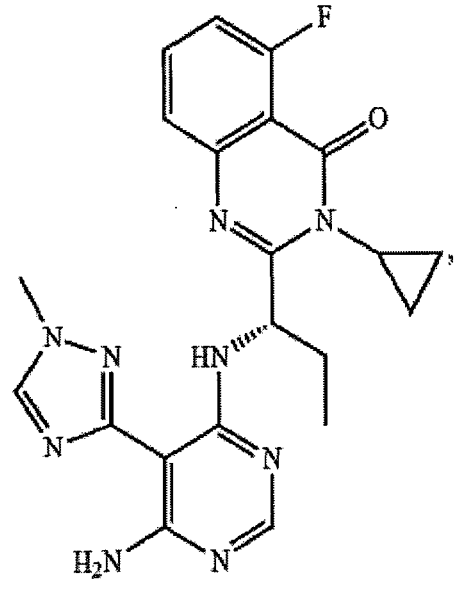

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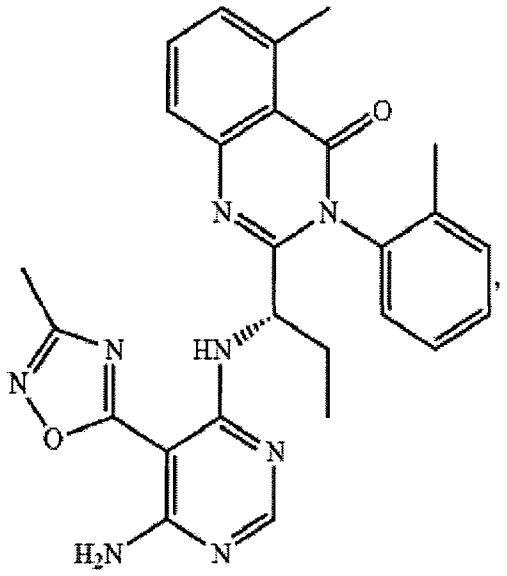

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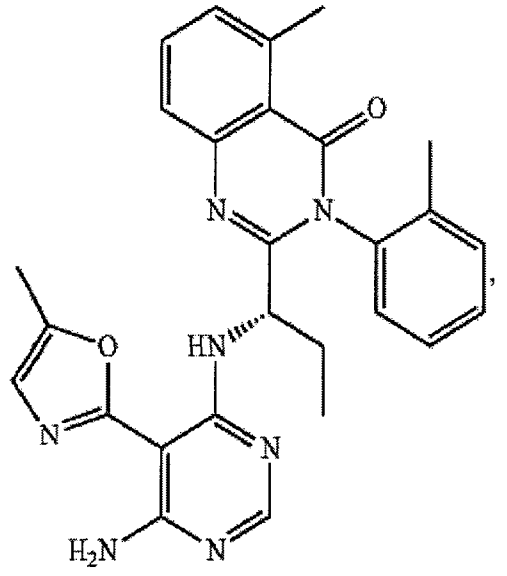

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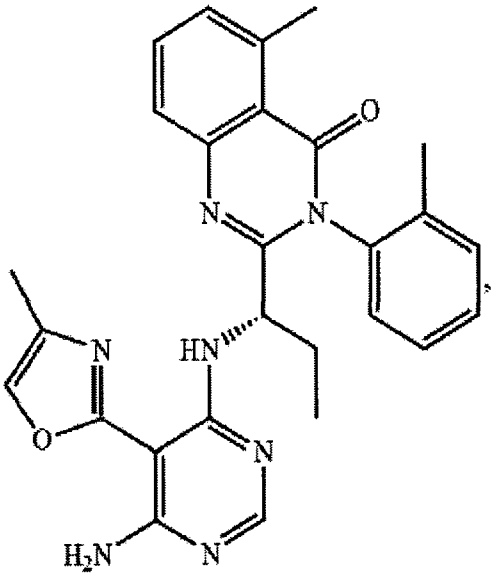

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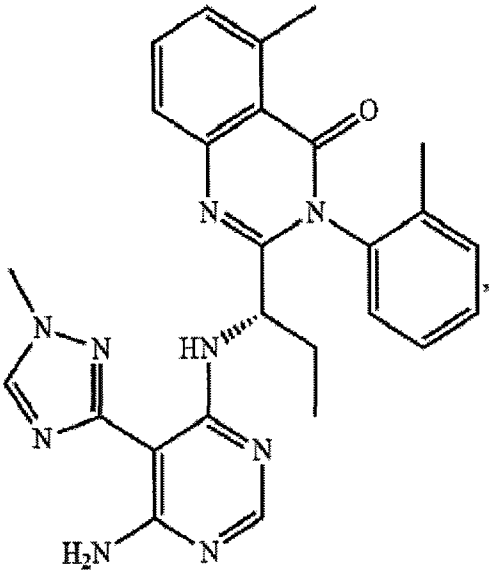

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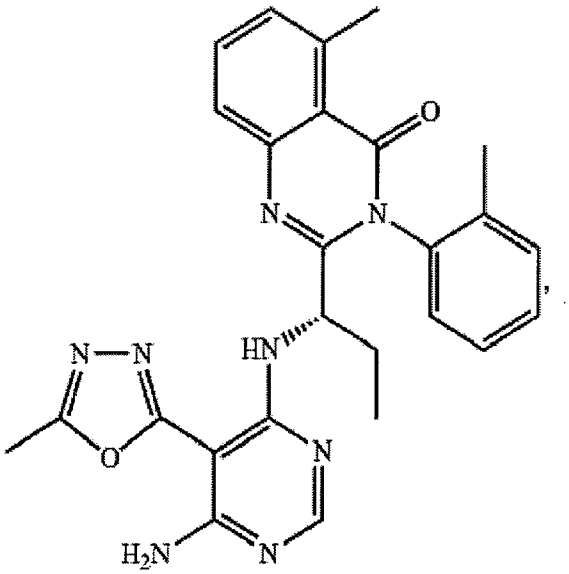

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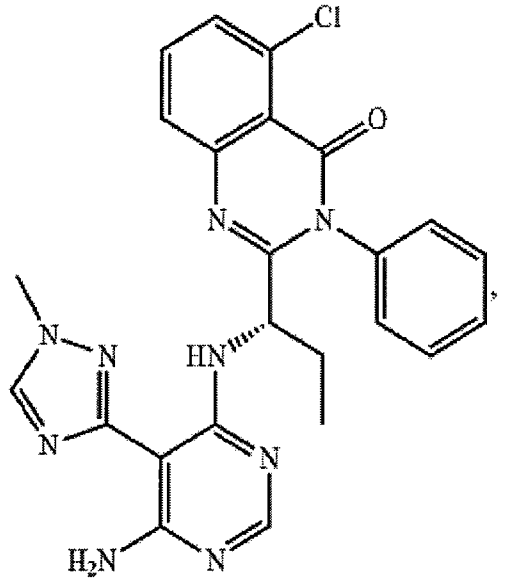

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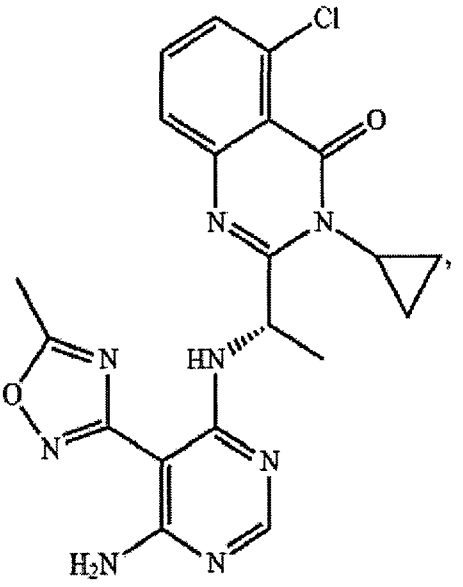

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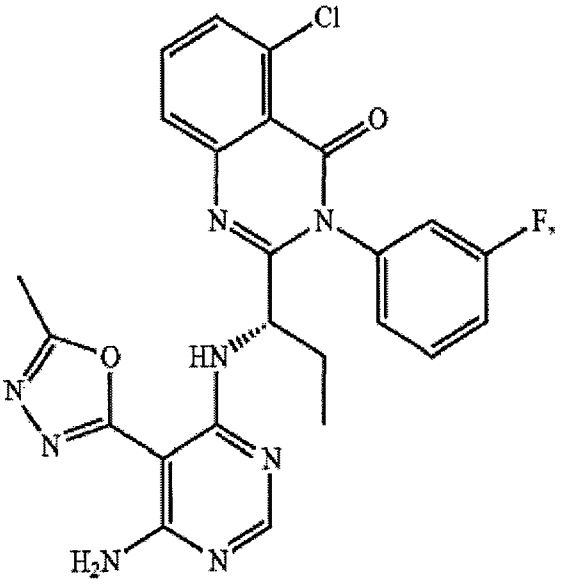

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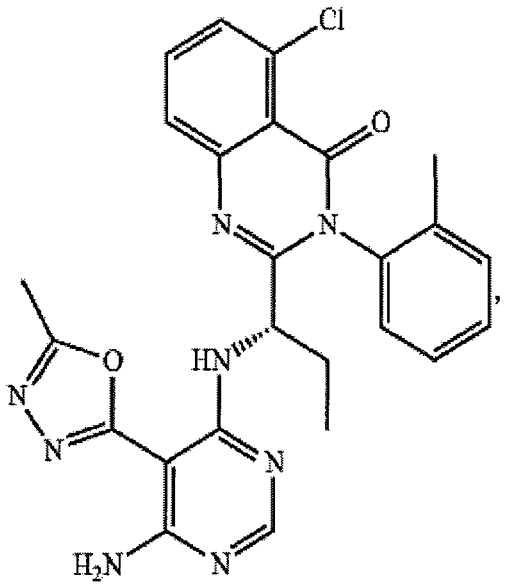

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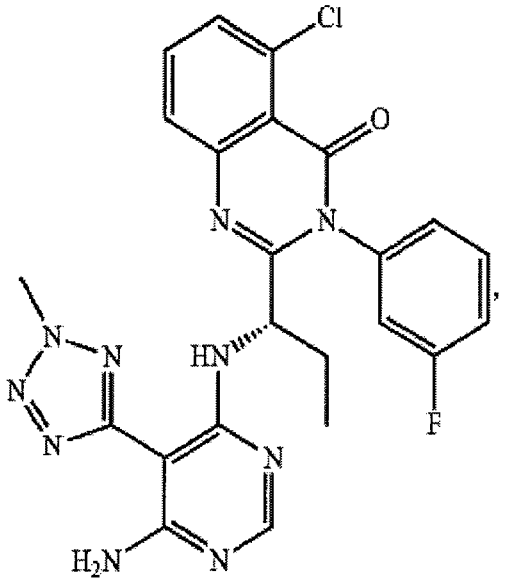

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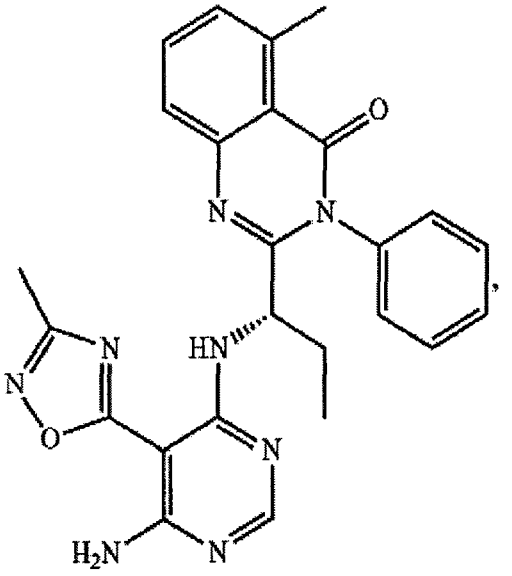

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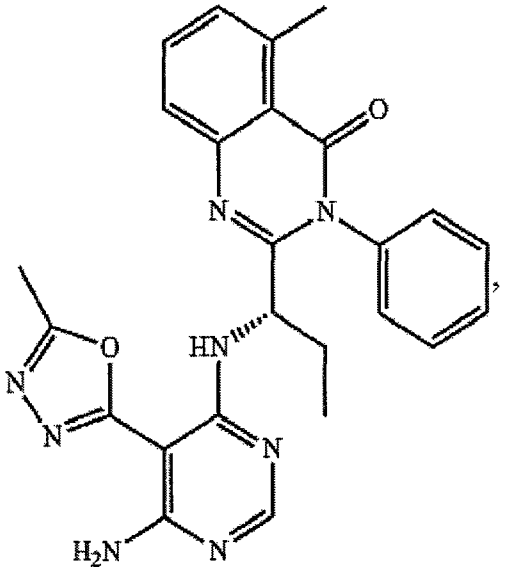

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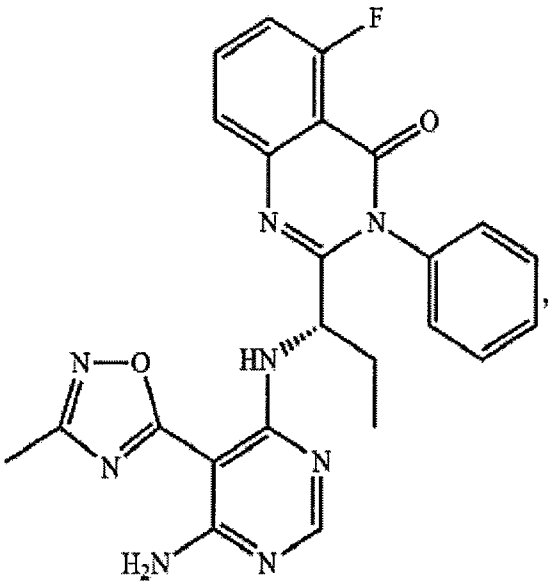

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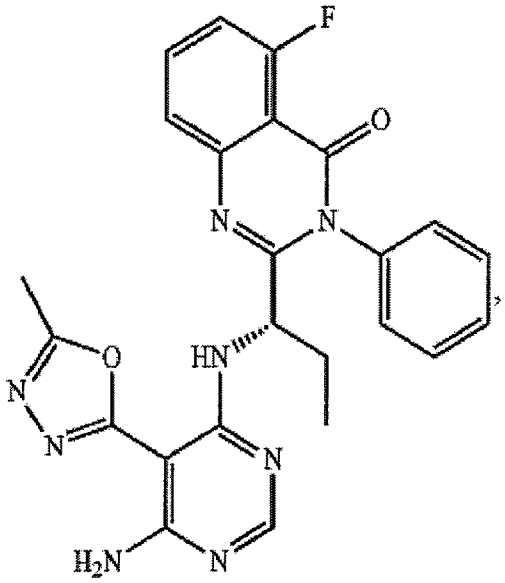

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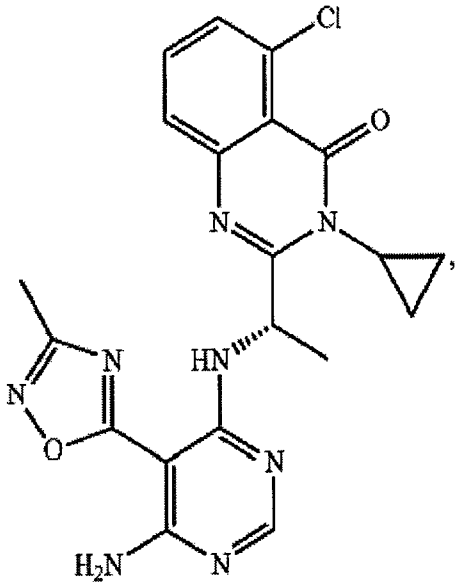

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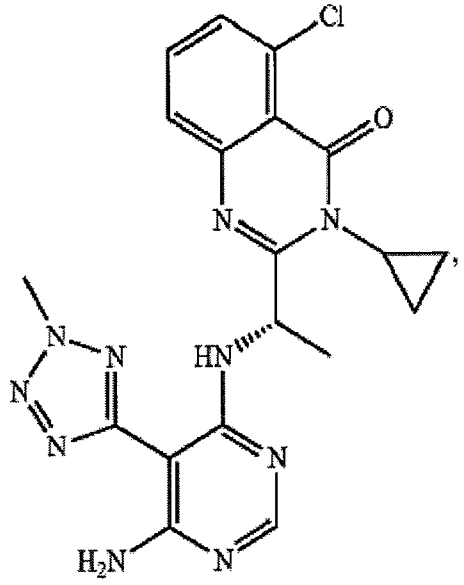

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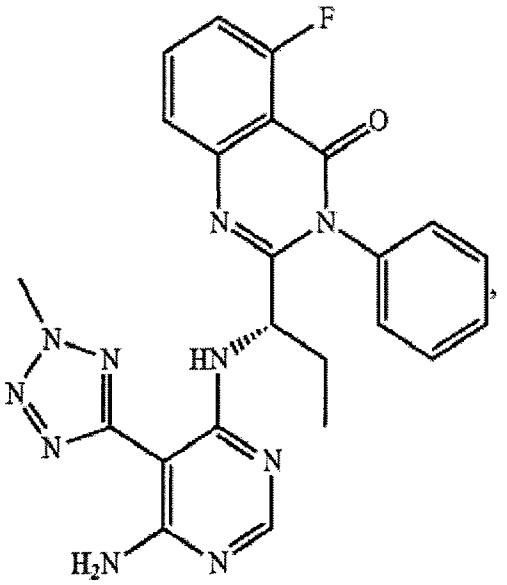

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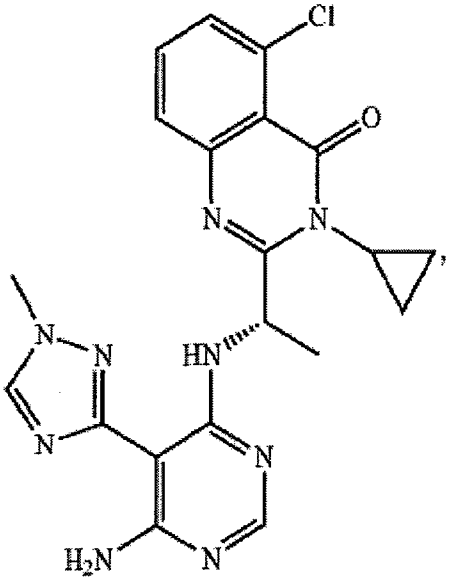

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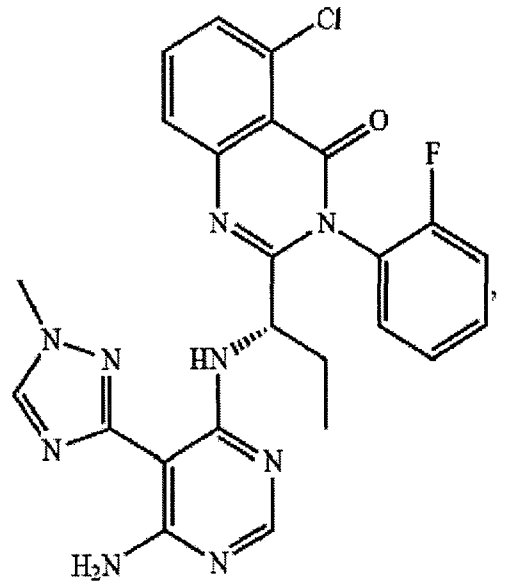

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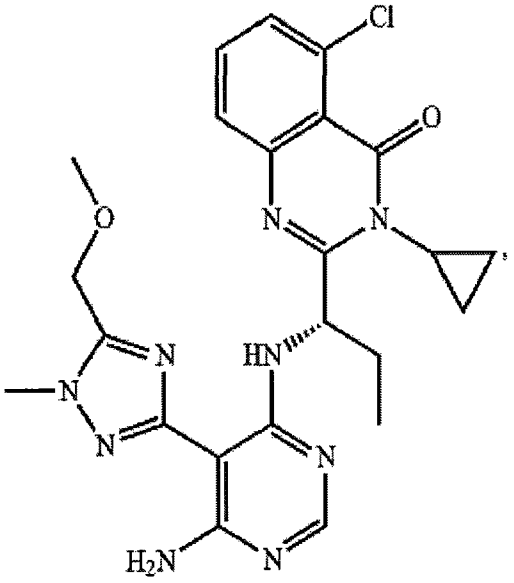

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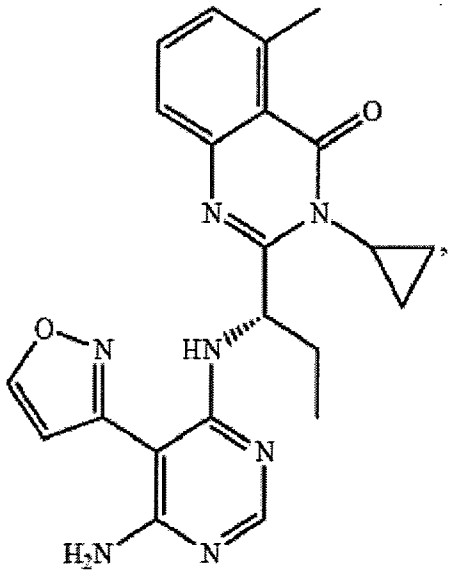

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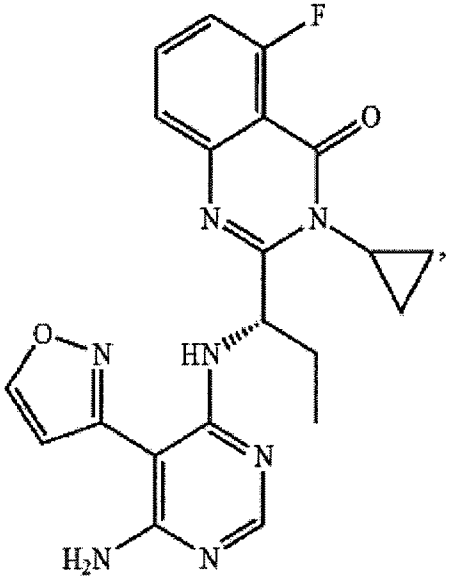

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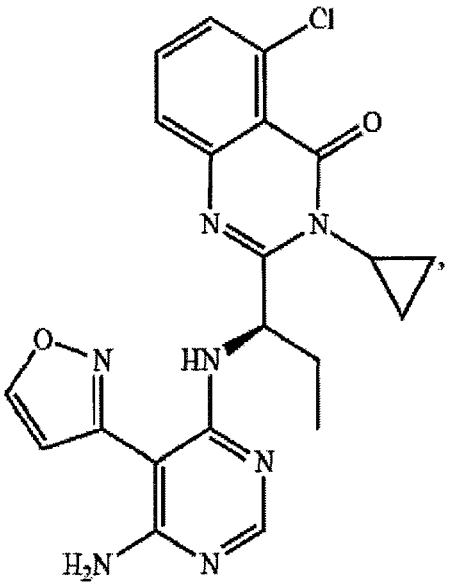

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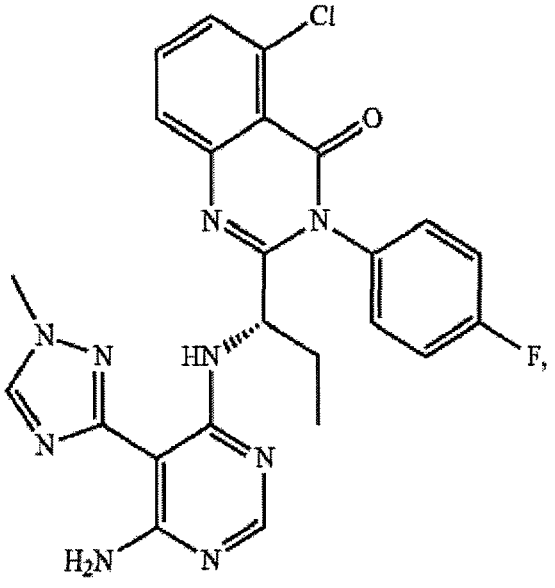

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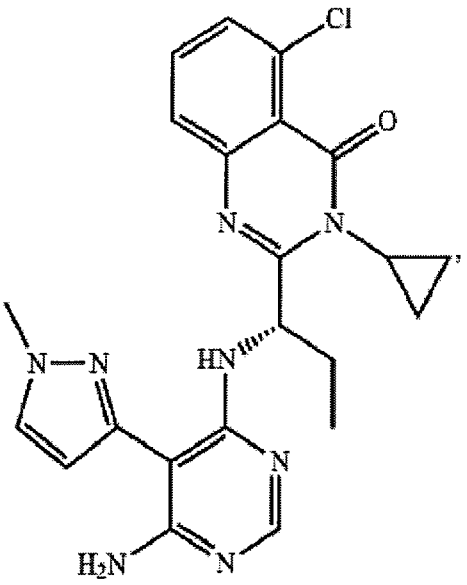

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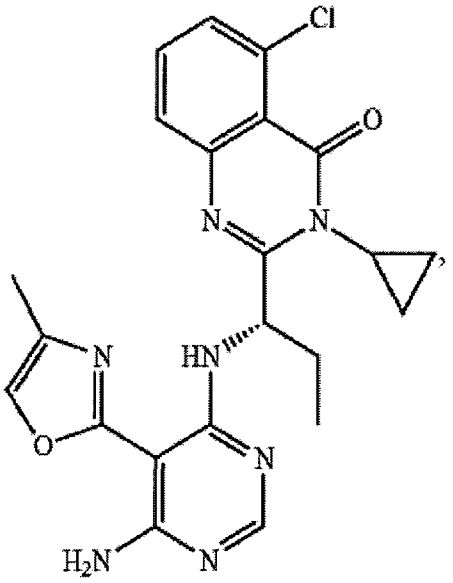

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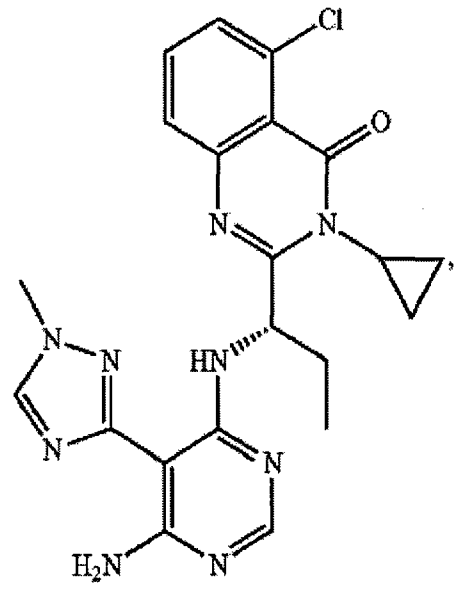

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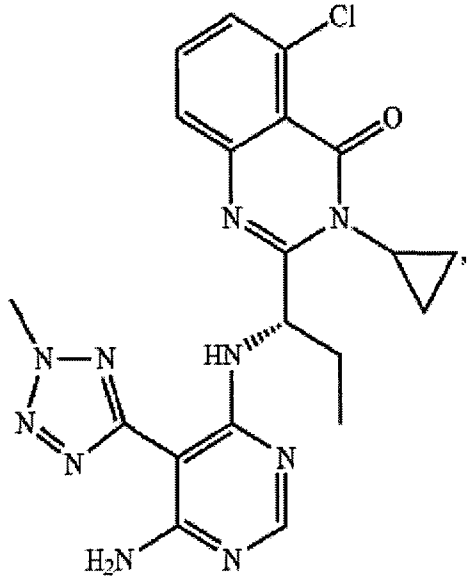

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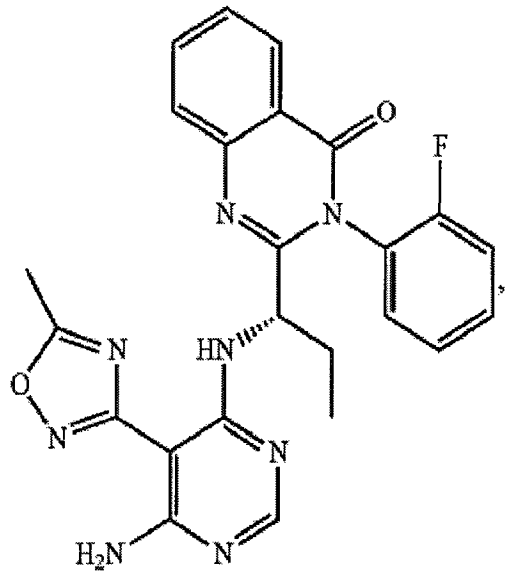

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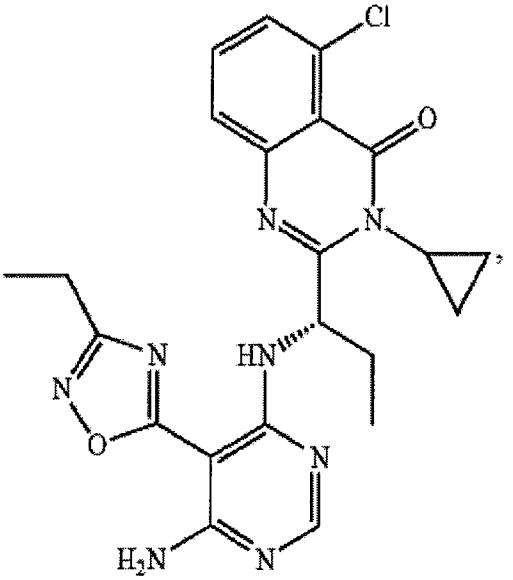

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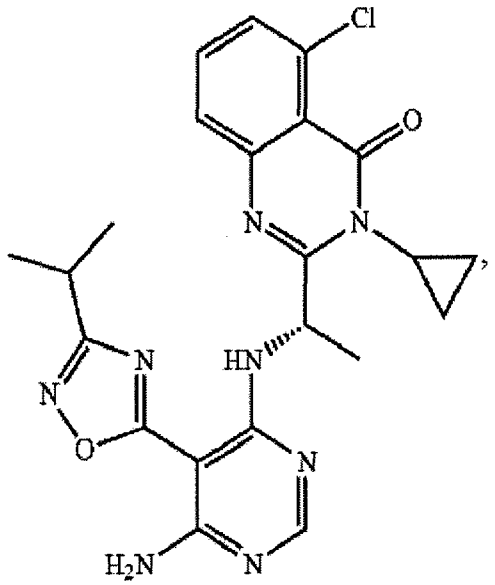

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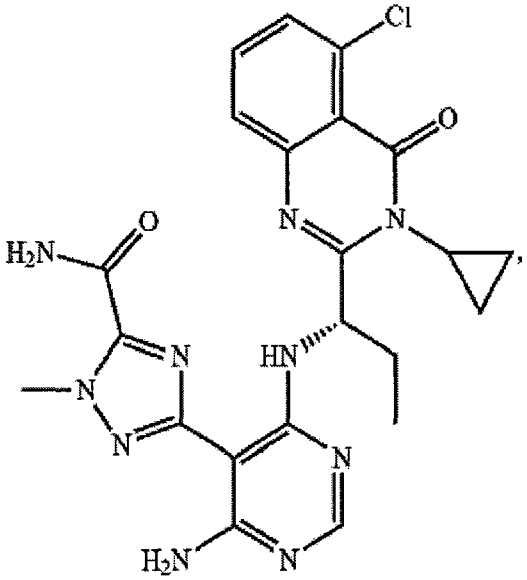

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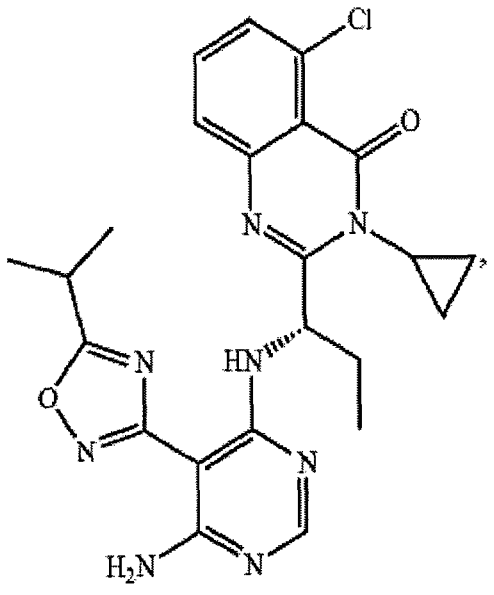

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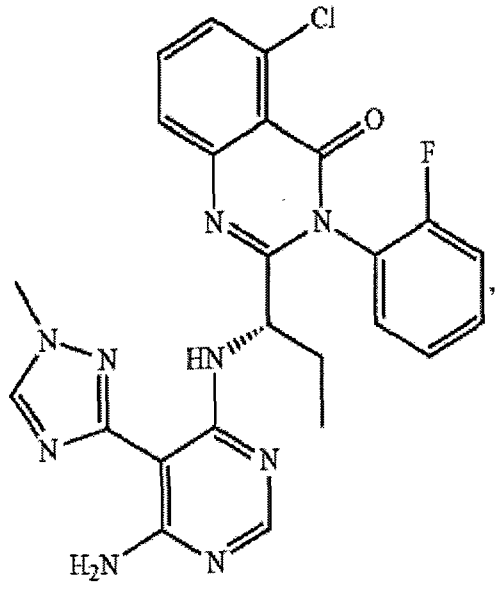

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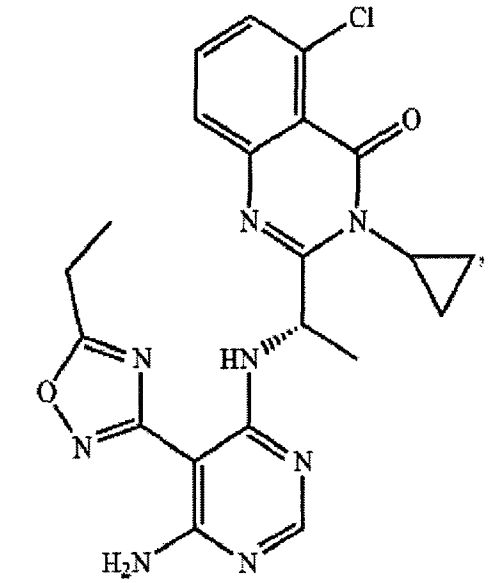

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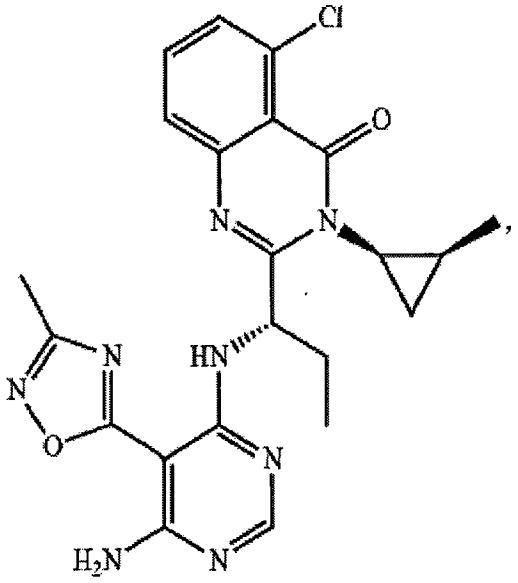

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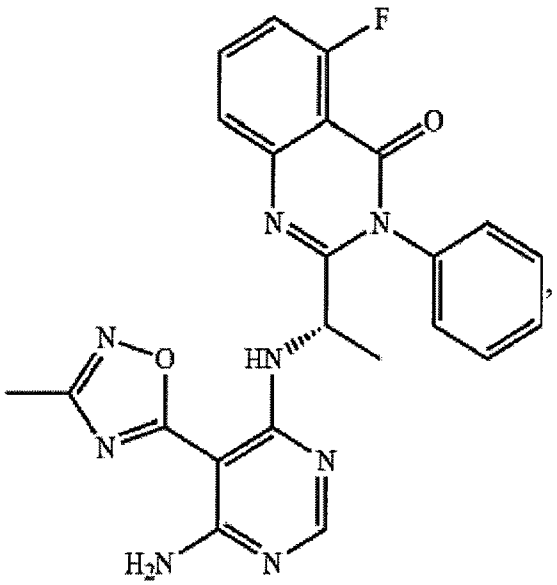

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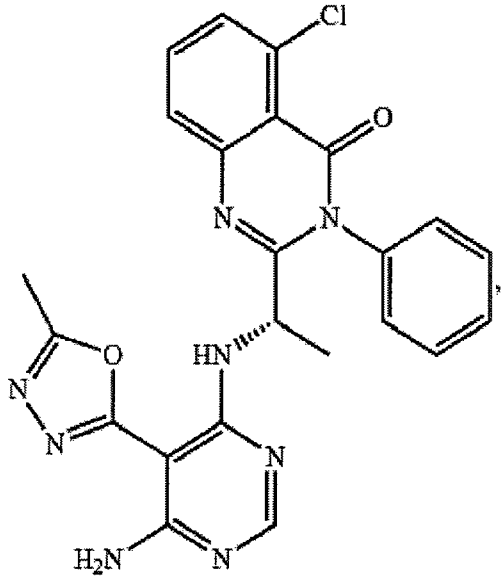

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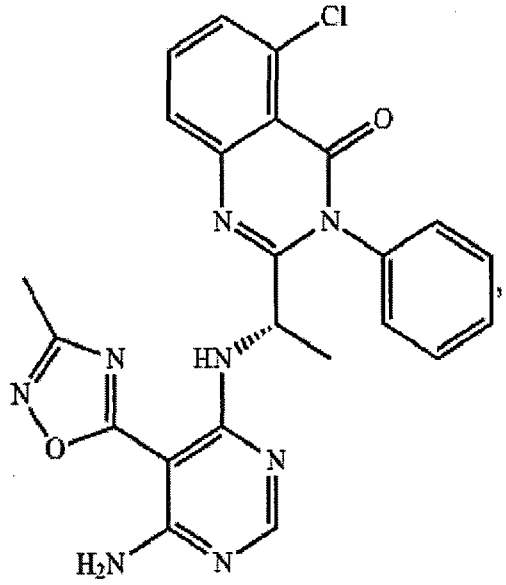

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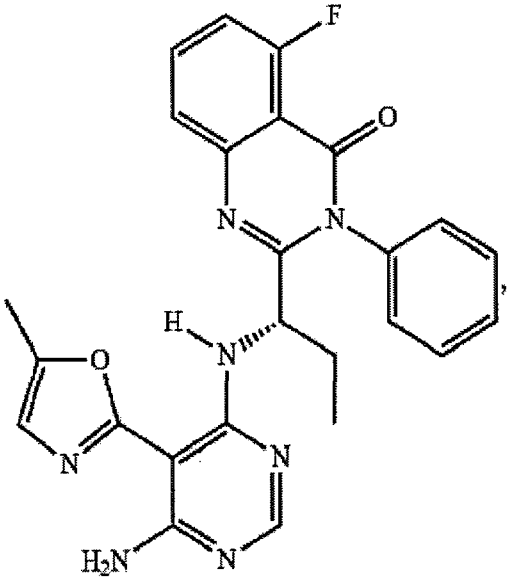

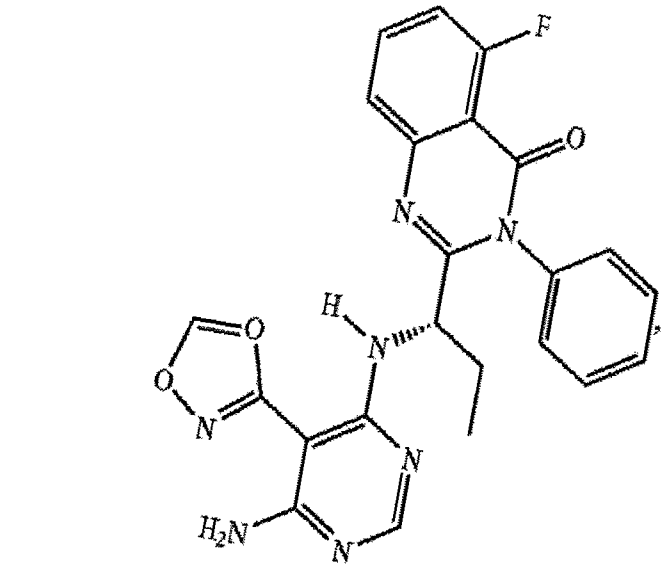

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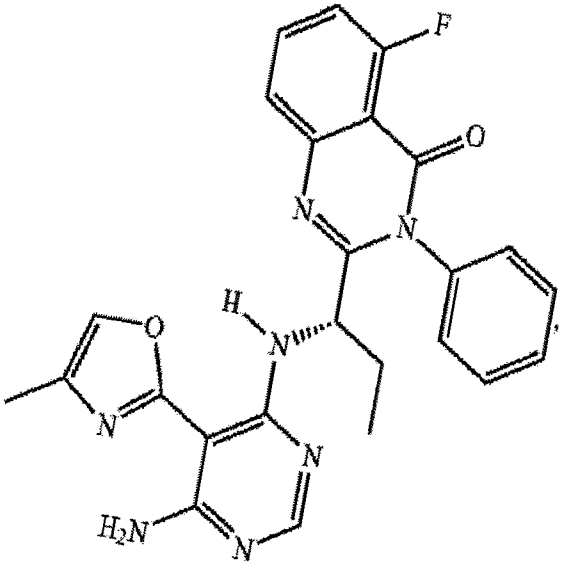

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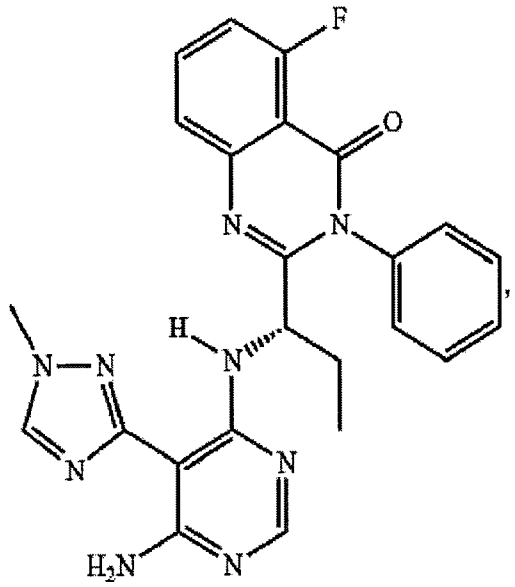

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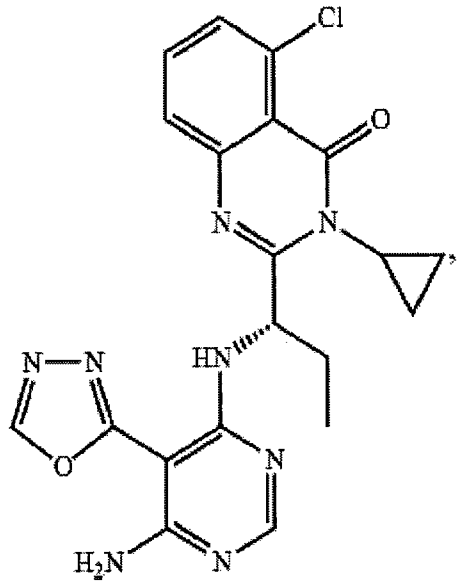

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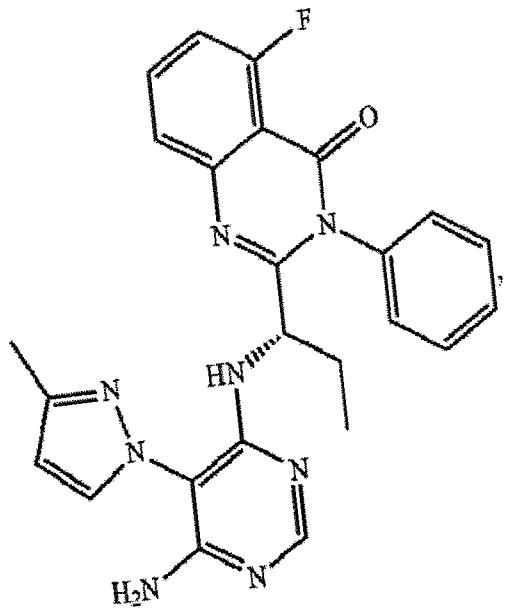

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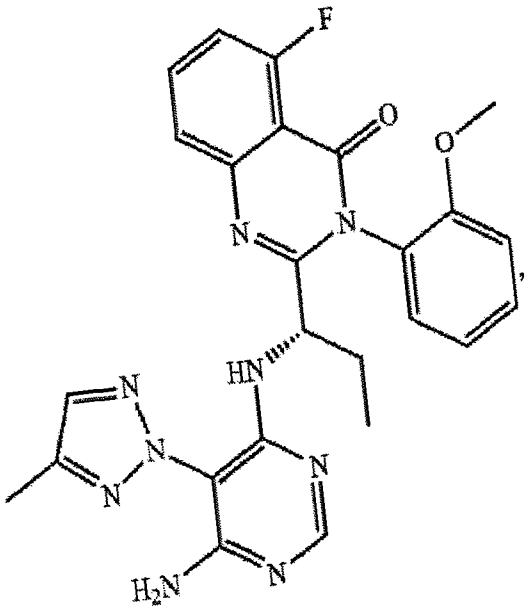

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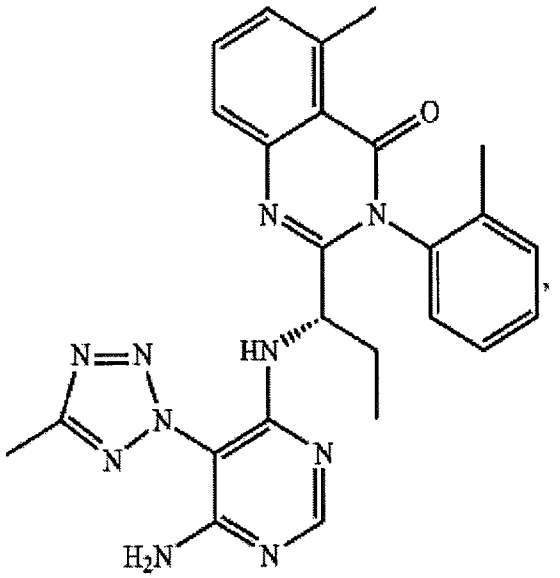

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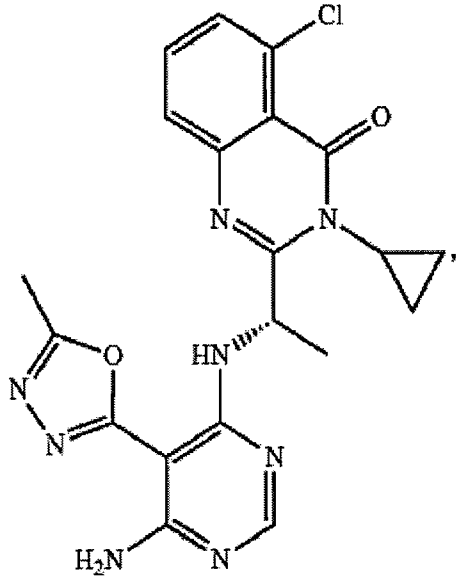

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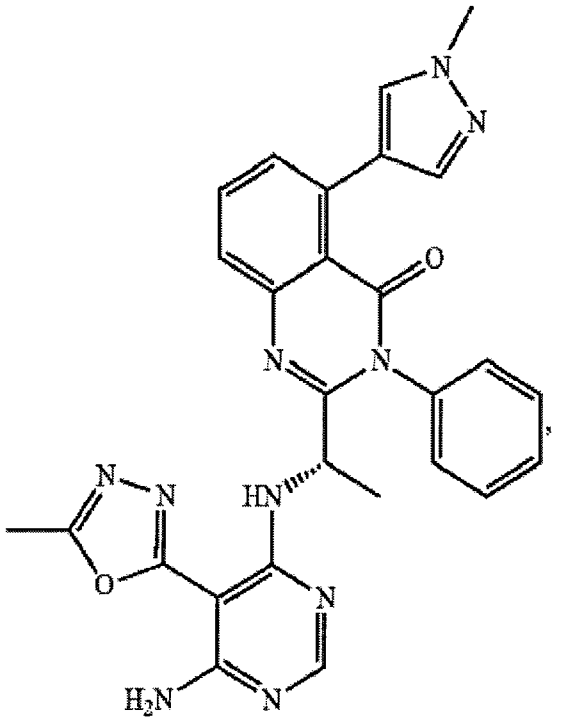

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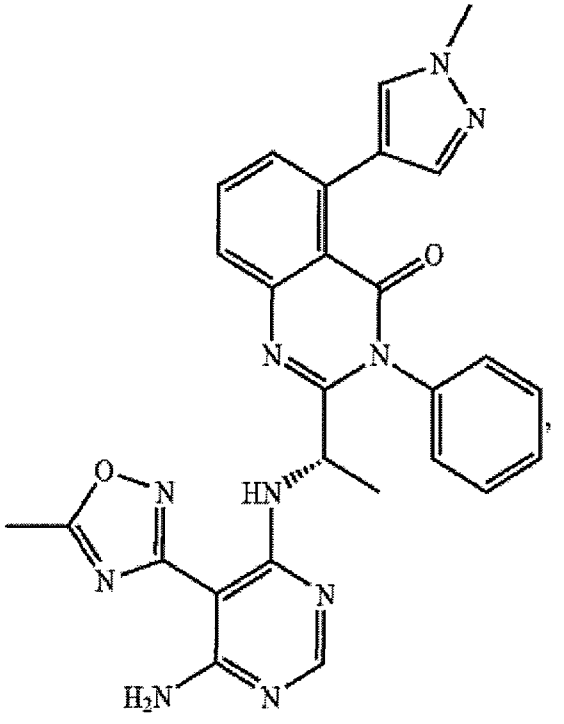

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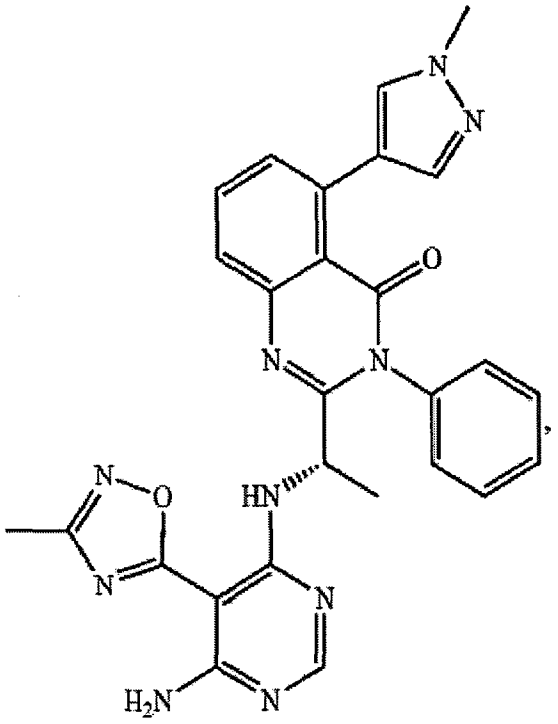

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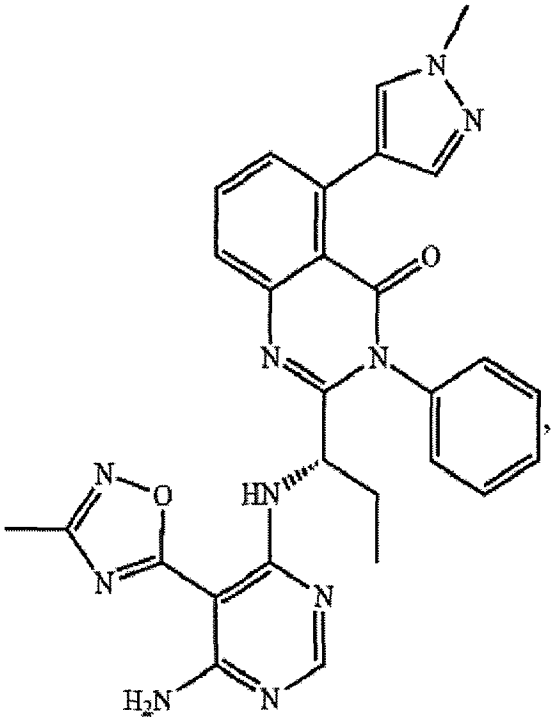

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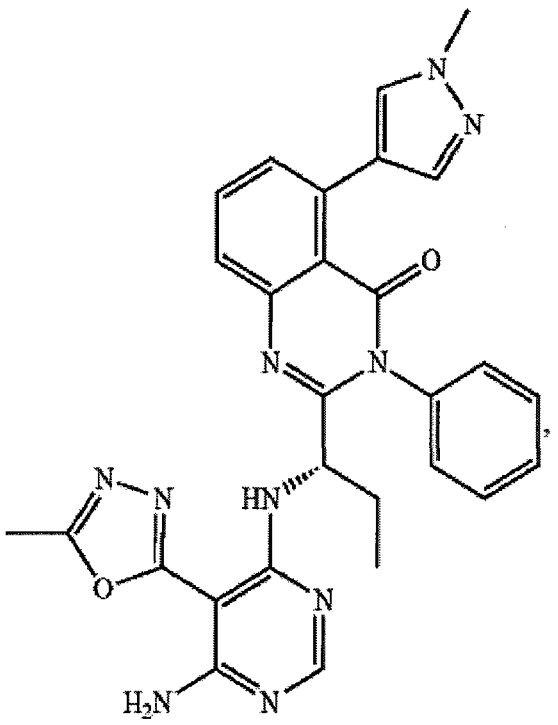

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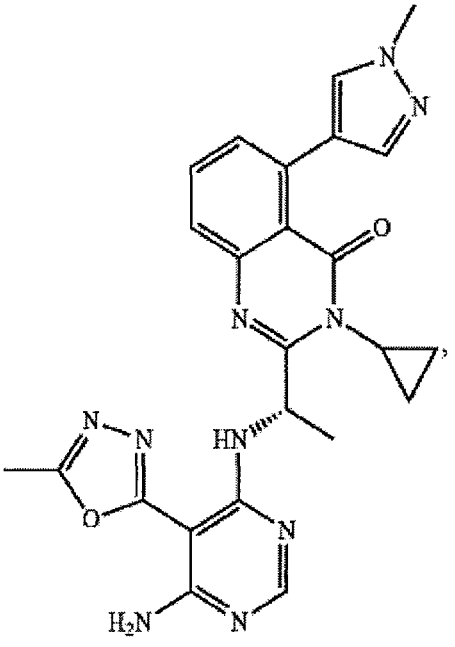

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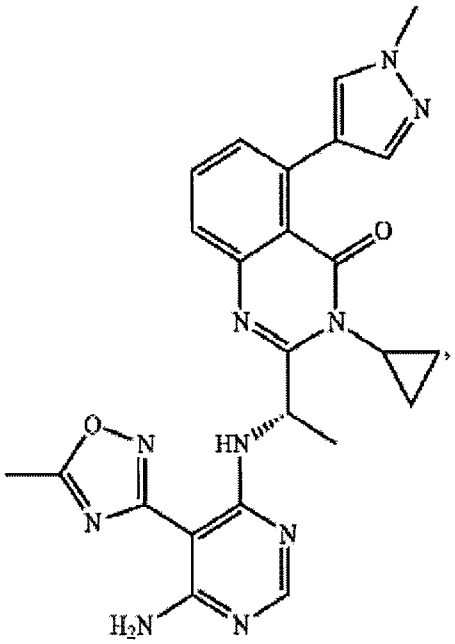

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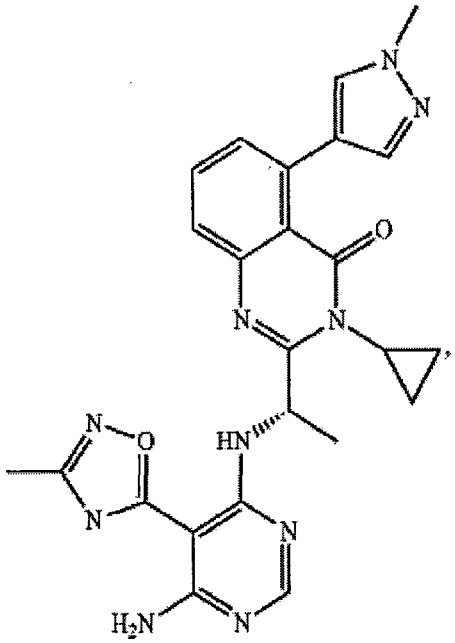

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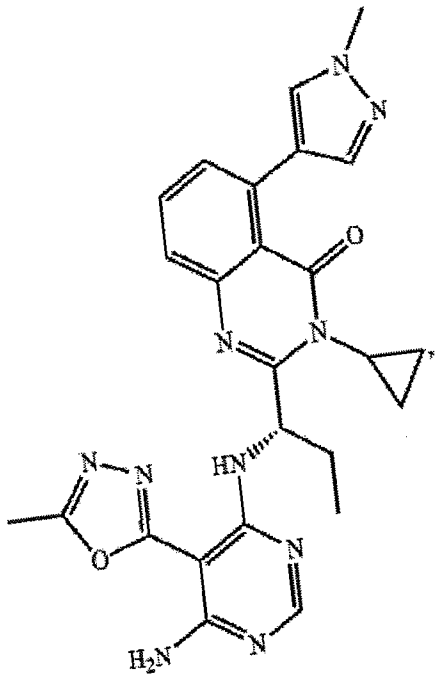

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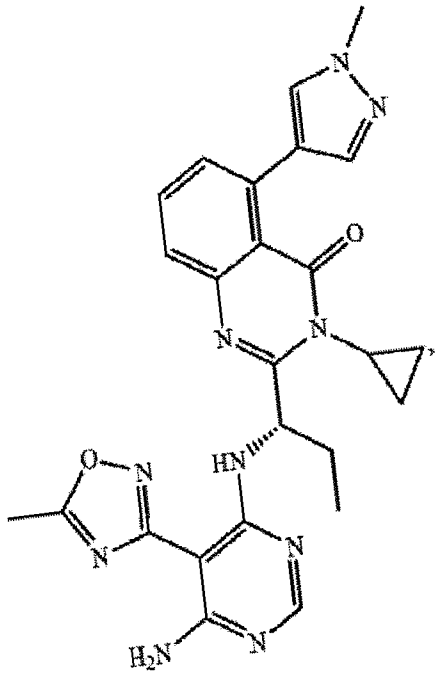

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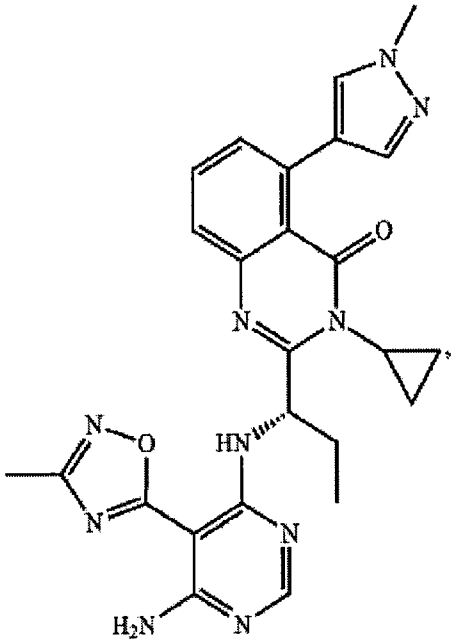

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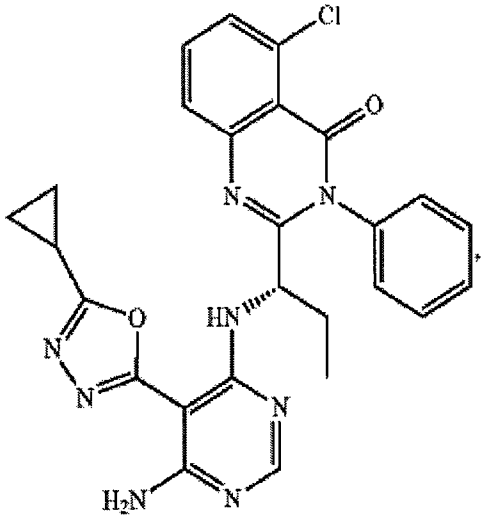

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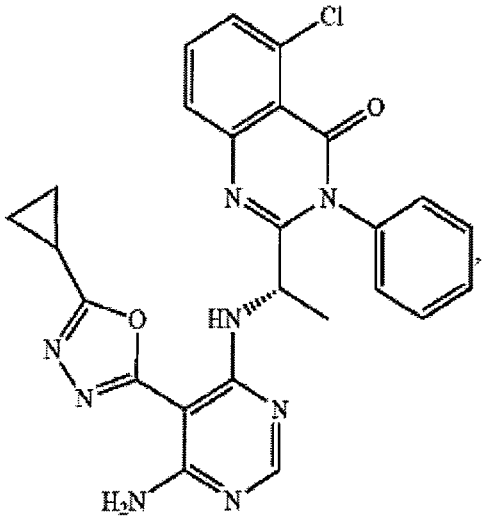

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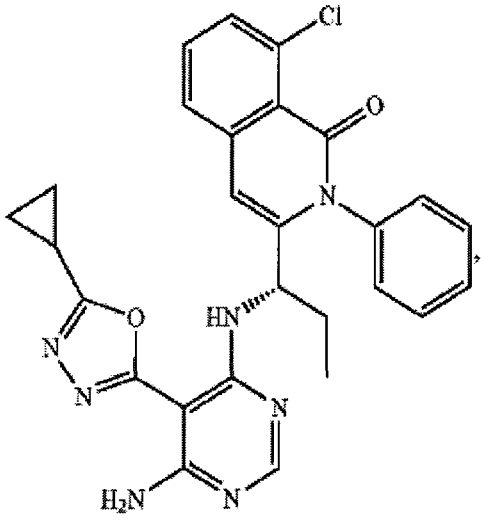

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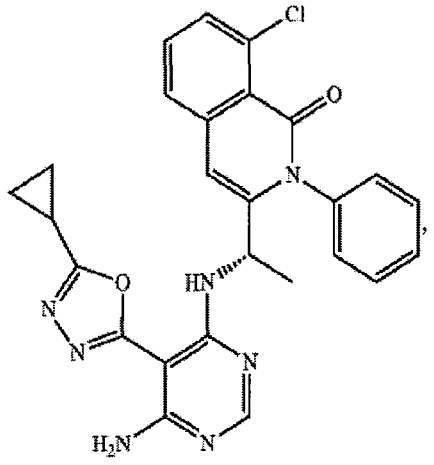

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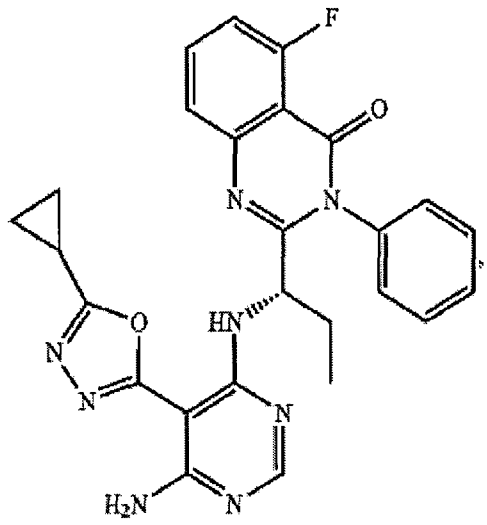

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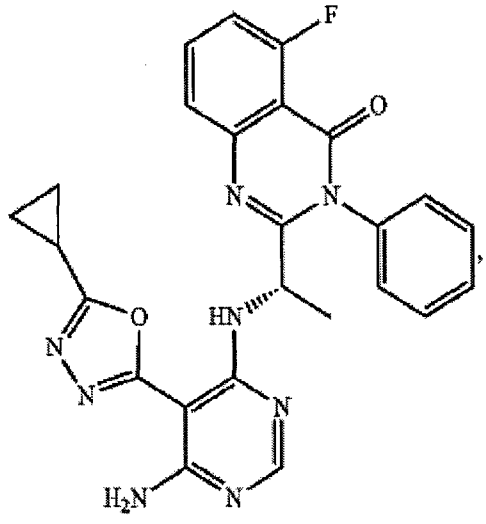

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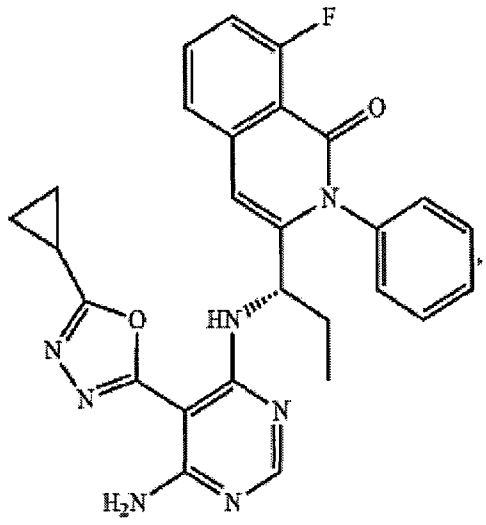

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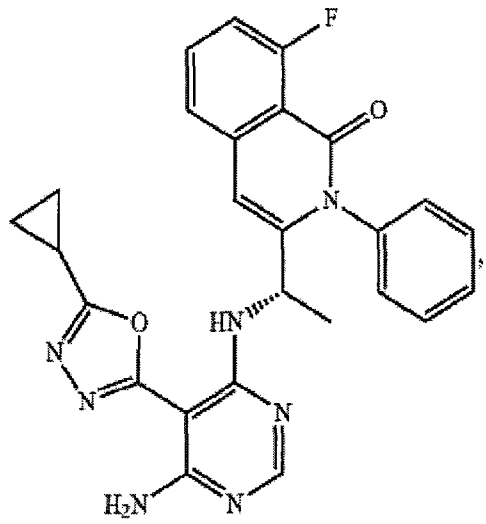

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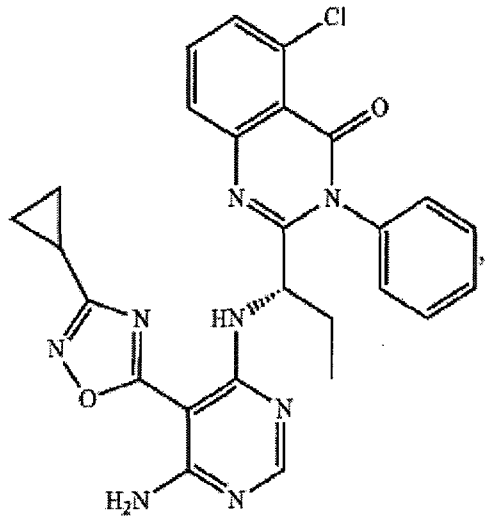

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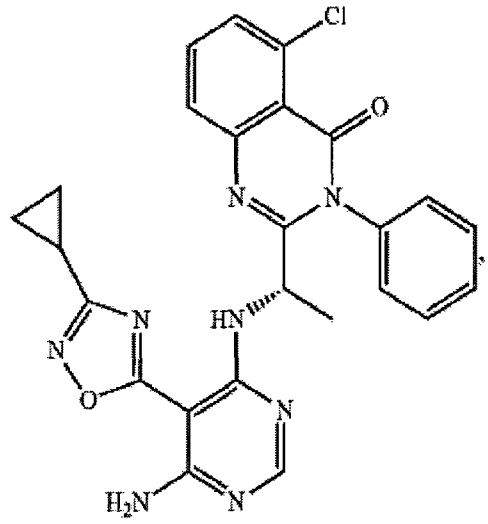

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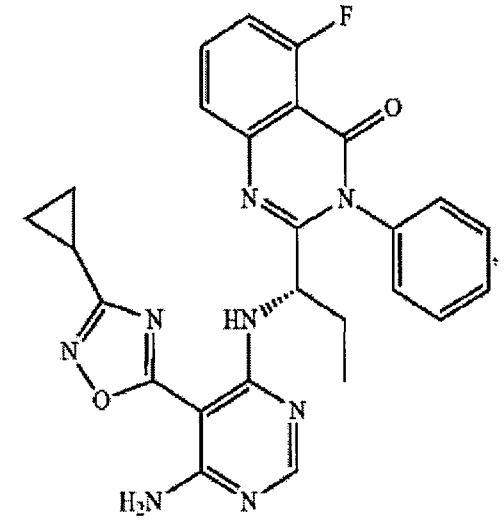

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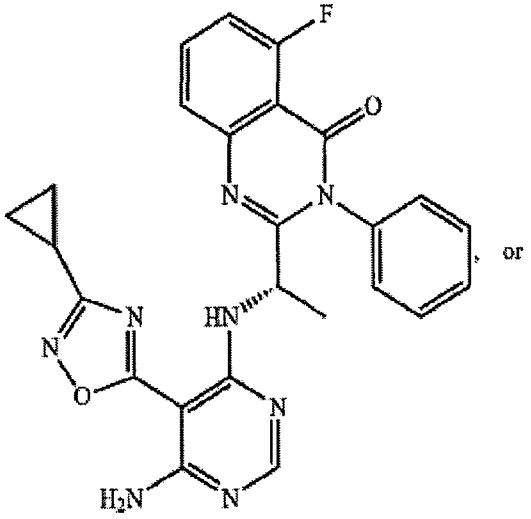

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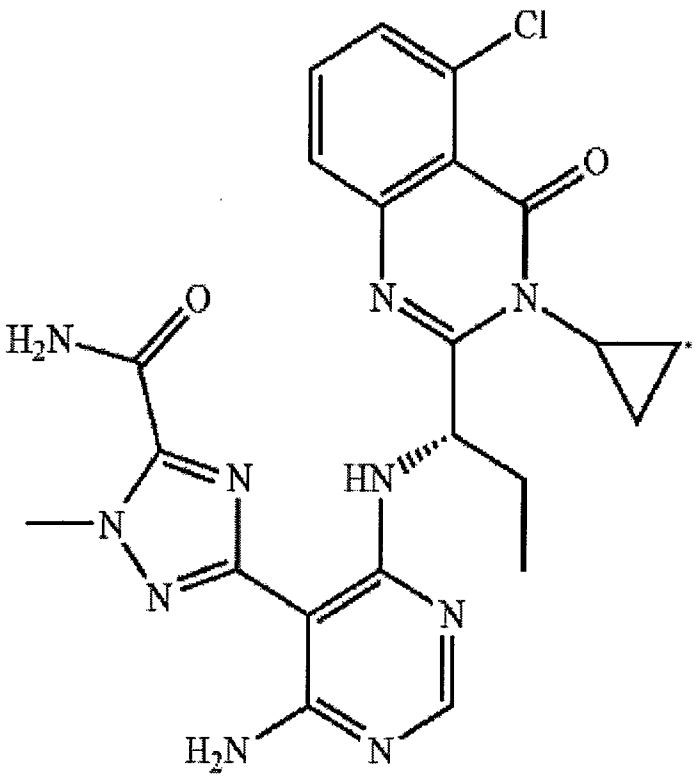
(98)



or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, or a pharmaceutically acceptable salt or a prodrug thereof.

8. A pharmaceutical composition comprising the compound according to claim **1**, and one or more pharmaceutically acceptable carriers, excipients, diluents, adjuvants, vehicles or a combination thereof.

9. The pharmaceutical composition according to claim **8** further comprising one or more therapeutic agents.

10. A pharmaceutical composition comprising the compound according to claim **7**, and one or more pharmaceutically acceptable carriers, excipients, diluents, adjuvants, vehicles or a combination thereof.

11. The pharmaceutical composition according to claim **10** further comprising one or more therapeutic agents.