

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-000580- -00002-0000

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Doctora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Referencia: Expediente No. 10 000.580

Solicitud de Patente PCT ENTRADA EN FASE NACIONAL

Titulada: "ANTAGONISTAS NO BASICOS DEL RECEPTOR DE LA HORMONA
CONCENTRADORA DE MELANINA 1 Y PROCEDIMIENTOS

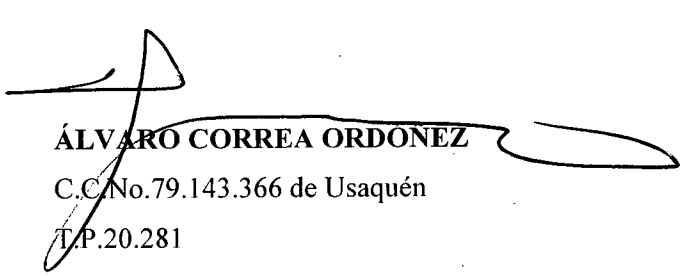
Solicitante: BRISTOL – MYERS SQUIBB COMPANY

MEMORIAL DE COMPLEMENTACIÓN

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad en referencia, manifiesto lo siguiente:

Estamos presentando nuevo capítulo reivindicatorio, modificado de acuerdo con el Artículo 19 del PCT, el cual fue modificado en la fase Internacional.

Atentamente,


ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

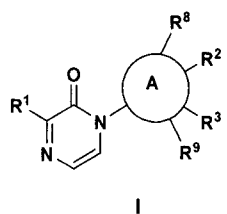
Anexo: Capítulo Reivindicatorio

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REIVINDICACIONES

Habiéndose descrito la invención como antecede se reclama como propiedad lo contenido en las siguientes reivindicaciones:

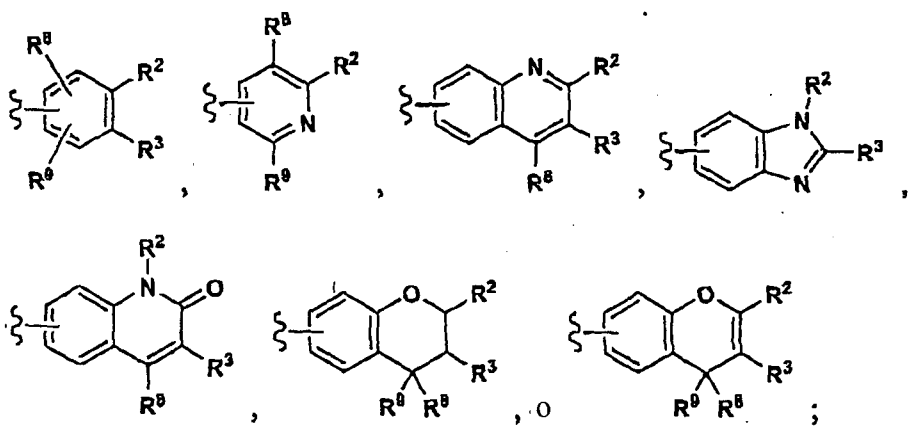
1. Compuesto de Fórmula I o una sal farmacéuticamente aceptable del mismo



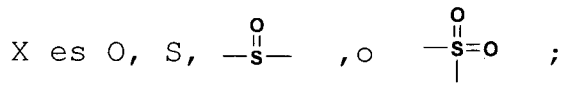
caracterizado porque



es



R¹ es Z-Y-X-, donde



Y es un enlace, un cicloalquilo de 3 a 6 miembros, una

cadena alquilo; y

Z es opcionalmente fenil sustituido o naftilo, piridinilo, pirazinilo, pirimidinilo, piridinonilo, benzotiazolilo, benzoxalilo, benzimidazolilo, quinolinilo, tiazolilo, indanilo, imidazolinilo;

R^2 es $-E-G-(J)_m$, donde m es un número entero de 1 a 3;

E es O, S o un enlace;

G es alquilo inferior, fenilalquilo, cicloalquilo, cicloalquilalquilo, alquilocicloalquilo, cicloalcoxi, alquilocicloalcoxi o cicloalcoxialquilo, y

cada J es independientemente hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3 , CF_3O- , $-COOR^5$ o $-CO-NR^{5a}R^6$, donde cada uno de R^{5a} y R^6 se selecciona independientemente entre el grupo que consiste en H, alquilo C_{1-3} y cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser propanodiilo, butanodiilo o pentanodiilo con el átomo de N al que están unidos para formar una amina cíclica de 4, 5 ó 6 miembros que puede estar opcionalmente sustituida;

R^5 es H, alquilo C_{1-6} o cicloalquilo;

R^7 es alquilo inferior; y

R^3 es alquilo C_{1-6} , cicloalquilo, alcoxi C_{1-6} , halógeno, hidrógeno, $-S$ -alquilo C_{1-6} , CN, CF_3O o CF_3 ;

con la condición de que cuando A es un grupo fenileno, E-G y R^3 no sean grupos alcoxi inferior no

sustituidos iguales, y cuando G es alquilo inferior y J es H, R³ no sea hidrógeno; y

cada uno de R⁸ y R⁹ es independientemente hidrógeno, halógeno o alquilo inferior;

5 incluyendo ésteres de los mismos, profármacos de los mismos, solvatos de los mismos y todos los estereoisómeros de los mismos.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque

10 X es O o S; y/o

R¹ es Z-Y-X,

donde Y es un enlace o una cadena alquilenos de 1 a 3 átomos;

15 Z es fenilo, o piridinilo, pirazinilo, pirimidinilo, piridinonilo, benzotiazolilo, benzoxalilo, benzimidazolilo, quinolinilo, tiazolilo, indanilo, o imidazolinilo;

R² es -E-G-J;

E es O o S;

G es una cadena alquilenos o alquilocicloalquilo;

20 J es H, OH, SO₂R⁷, alquilo inferior, alcoxi inferior o CF₃;

R³ es alquilo C₁₋₆, alcoxi C₁₋₆, H o halo;

R⁸ es H o alquilo; y

R⁹ es H.

25 3. Compuesto de conformidad con la reivindicación 1,

caracterizado porque

R^1 es Z-Y-X;

X es S;

Y es un enlace o una cadena alquilenos;

5 Z es fenilo o piridilo;

E es O;

G es una cadena alquilenos o alquilcicloalquilo;

J es H o OH;

R^3 es H, alcoxi, alquilo o halo;

10 R^8 es H o CH_3 ; y

R^9 es H.

4. Compuesto de conformidad con la reivindicación 1, caracterizado porque

fenilo, piridinilo, pirazinilo, pirimidinilo, piridinonilo,
15 benzotiazolilo, benzoxazolilo, benzimidazolilo, quinolinilo, tiazolilo, indanilo o imidazolinilo; cualquiera de los cuales puede ser insustituido o sustituido con 1, 2 ó 3 de amino, halo, alquilo C_{1-6} , alquilamino C_{1-3} , di-alquilamino C_{1-3} , alcoxi C_{1-3} , tioalquilo C_{1-3} , trifluoroalcoxi C_{1-3} , trifluorometilo, cicloalquilo, cicloalcoxi o
20 heteroarilo; y

J es hidrógeno, hidroxilo, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, alquilo inferior, alcoxi inferior, CF_3 , CF_3O- , $-COOR^5$ o $-CO-NR^{5a}R^6$, donde cada uno de R^{5a} y R^6 se selecciona independientemente entre el grupo que consiste en H, alquilo C_{1-3} y cicloalquilo, o R^{5a} y R^6 tomados juntos pueden ser
25 propanodiilo, butanodiilo o pentanodiilo con el átomo de N al que están

unidos para formar una amina cíclica de 4, 5 ó 6 miembros opcionalmente sustituida con alquilo inferior, alcoxi inferior, hidroxilo, CF_3 o CF_3O .

5. Compuesto de conformidad con la reivindicación 1, caracterizado porque:

5 Z es

(1) fenilo, que está opcionalmente sustituido con:

a) halógeno,

b) alquilo,

c) alcoxi,

10 d) polihaloalquilo,

e) polihaloalcoxi,

f) amino, alquilamino o dialquilamino,

g) alquiltio,

h) OH,

15 i) un éster, o

j) arilo,

(2) heteroarilo, que es:

a) piridinilo,

b) pirazinilo, o

20 c) pirimidinilo,

estando cada uno de a), b) o c) opcionalmente sustituido con alquilo, polihaloalquilo, alcoxi o halógeno,

(3) benzotiazolilo opcionalmente sustituido con halo o alcoxi,

(4) benzoxazolilo opcionalmente sustituido con halo,

25 (5) bencimidazolilo,

- (6) tiazol opcionalmente sustituido con arilo o alquilo,
- (7) indanilo,
- (8) quinolinilo opcionalmente sustituido con CF_3 , o
- (9) imidazolidinilo;

5 Y es un enlace o alquilenos;

X es S, O, SO o SO_2 ;

J es

(1) H,

(2) $-\text{CO}-\text{NR}^{5a}\text{R}^6$, donde R^{5a} y R^6 junto con el N al que están
10 unidos forman un anillo pirrolidinilo,

(3) OH,

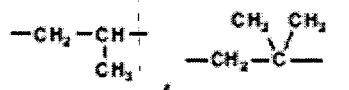
(4) COOH ,

(5) COO -alquilo, o

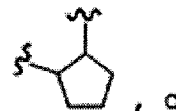
(6) SO_2R^7 ,

15 m es 1 ó 2; y/o

G es un enlace o CH_2 , $(\text{CH}_2)_2$, $(\text{CH}_2)_3$,



$-\text{CH}_2-\text{CH}(\text{w})-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2-\text{CH}(\text{w})-\text{CF}_3$, cicloalquilo que es



20 cicloalcoxi que es ;

E es O; y/o

R^3 es H, alcoxi, hidroxialquilo, alquilo, halo o
hidroxialcoxi;

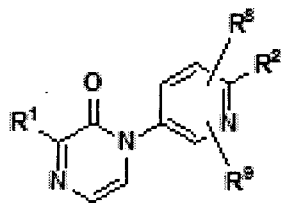
R^8 es H, halo o alquilo; y

25 R^9 es H.

6. Compuesto de conformidad con la reivindicación 1, caracterizado porque R^3 es alcoxi C_1-C_6 o alquilo C_1-6 .

7. Compuesto de Fórmula IB o una sal farmacéuticamente aceptable del mismo, que tiene la estructura

5



IB

10 8. Compuesto de conformidad con la reivindicación 7, caracterizado porque

R^1 es Z-Y-X- donde

X es S,

Y es una cadena alquilo de 1 a 3 carbonos o un enlace,

15 Z es piridinilo, pirazinilo, pirimidinilo, piridinonilo, benzotiazolilo, benzoxalilo, benzimidazolilo, quinolinilo, tiazolilo, indanilo, imidazolinilo o fenilo;

cada uno de Z está opcionalmente sustituido con CF_3 , CF_3O o halo;

20 R^2 es -E-G-J, donde

E es O,

G es alquilo inferior o alquilcicloalquilo, y

J es OH;

R^3 es alcoxi, alquilo o halo;

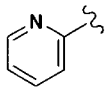
25 R^4 es H o alquilo; y

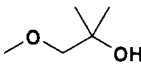
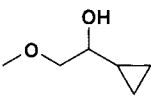
R⁹ es H.

9. Compuesto de conformidad con la reivindicación 7, caracterizado porque

X es S;

5 Y es un enlace o (CH₂)₂;

Z es  o  ;

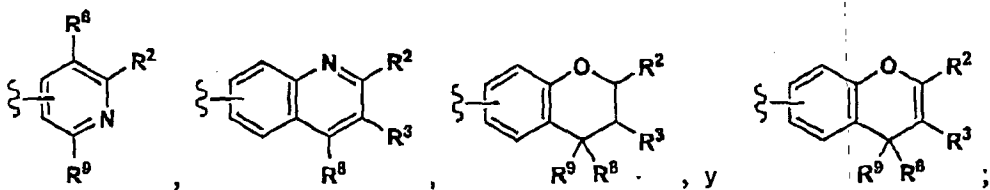
R² es E-G-J que es  o  ;

10 R³ es H, Cl, CH₃, o CH₃O; y
cada uno de R⁸ y R⁹ es H.

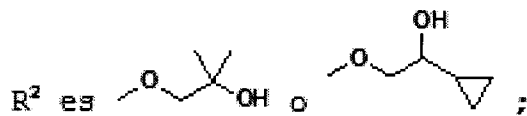
10. Compuesto de conformidad con la reivindicación 1, caracterizado porque

(A)

15 se selecciona entre el grupo que consiste en:



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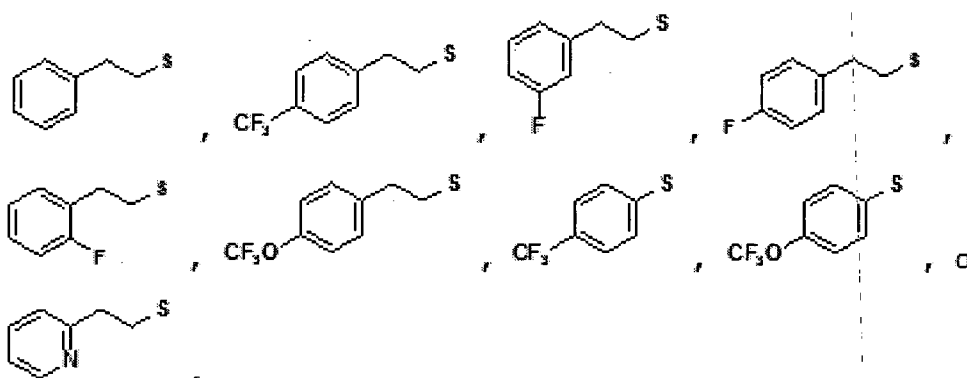


R³ es metoxi, Cl, H o metilo; y

R¹ se selecciona entre el grupo que consiste en:

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11. Composición farmacéutica caracterizada porque comprende una cantidad terapéuticamente eficaz de un compuesto de conformidad con la reivindicación 1, solo o en combinación con al menos un agente terapéutico adicional, junto con un vehículo o diluyente farmacéuticamente aceptable donde el agente terapéutico adicional es un inhibidor de acetil-colinesterasa, un agonista del receptor-1 muscarínico, un agonista nicotínico, un modulador del receptor de ácido glutámico (AMPA y NMDA), un agente nootrópico, un agente para la enfermedad de Alzheimer, un agente para el tratamiento de la enfermedad de Parkinson, un agente hipolipidémico, un agente anti-obesidad; agente antidiabético, un supresor del apetito; agente hipocolesterolémico/hipolipidémico, agente de aumento de HDL, agente potenciador de la cognición, un agente usado para tratar neurodegeneración, un agente usado para tratar afecciones respiratorias, un agente usado para tratar trastornos intestinales, un agente antiinflamatorio; un agente ansiolítico; un antidepresivo; un agente antihipertensivo; un agente anti-trastorno del sueño; un glicósido cardíaco; o un agente antitumoral.

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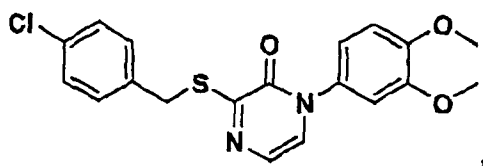
12. Combinación farmacéutica caracterizada porque comprende: al

menos un compuesto de conformidad con la reivindicación 1 y al menos un agente terapéutico adicional donde el agente terapéutico adicional es un inhibidor de acetil-colinasterasa, un agonista del receptor-1 muscarínico, un agonista nicotínico, un modulador del receptor de ácido glutámico (AMPA y NMDA), un agente nootrópico, un agente para la enfermedad de Alzheimer, un agente para el tratamiento de la enfermedad de Parkinson, un agente hipolipidémico, un agente anti-obesidad; agente antidiabético, un supresor del apetito; agente hipocolesterolémico/hipolipidémico, agente de aumento de HDL, agente potenciador de la cognición, un agente usado para tratar neurodegeneración, un agente usado para tratar afecciones respiratorias, un agente usado para tratar trastornos intestinales, un agente antiinflamatorio; un agente ansiolítico; un antidepresivo; un agente antihipertensivo; un agente anti-trastorno del sueño; un glicósido cardiaco; o un agente antitumoral.

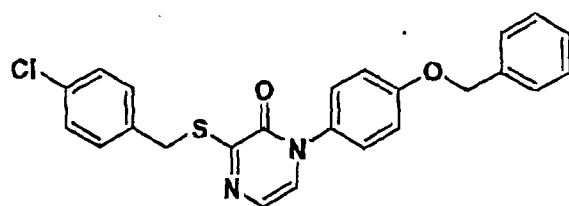
13. Uso de un compuesto de conformidad con la reivindicación 1 en la preparación de un medicamento para el tratamiento de la obesidad.

14. Uso de un compuesto de conformidad con la reivindicación 1 en la preparación de un medicamento para el tratamiento de la diabetes.

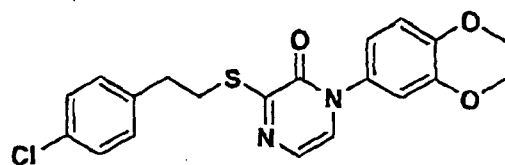
20 15. Compuesto de conformidad con la reivindicación 1 caracterizado por es seleccionado del grupo que consiste de:



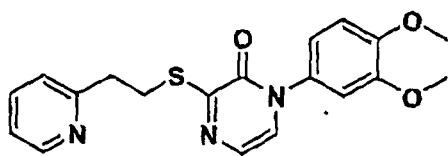
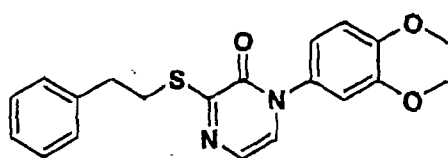
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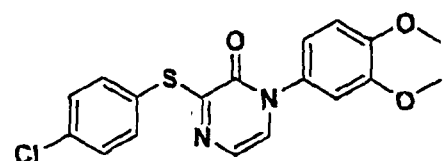
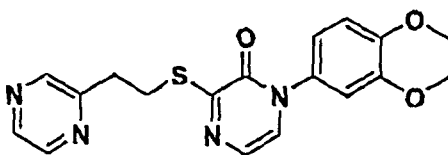
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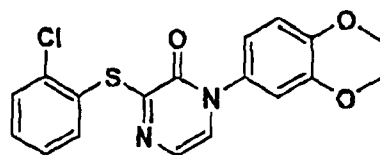
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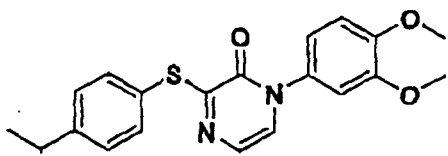
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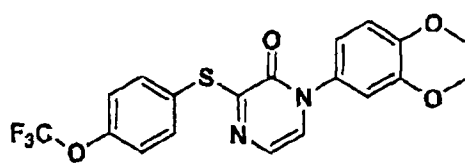


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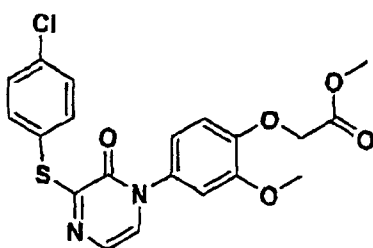


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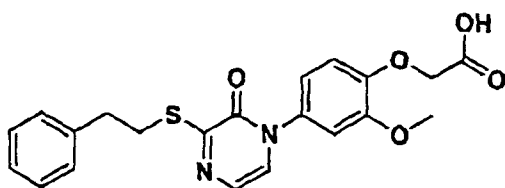




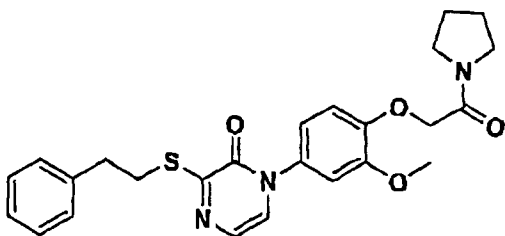
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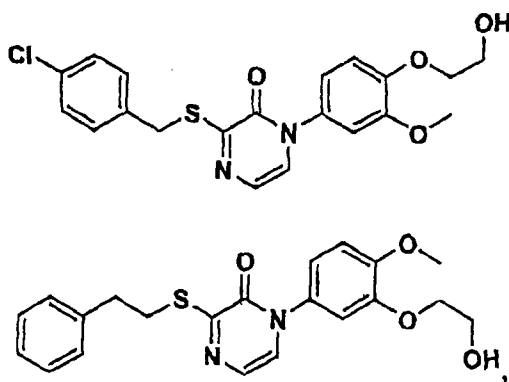
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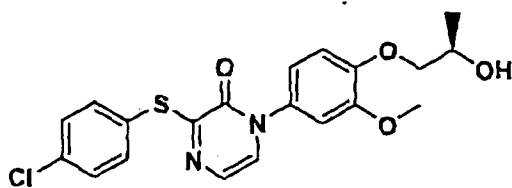
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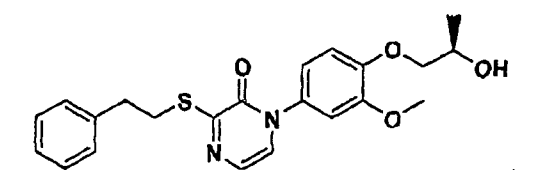
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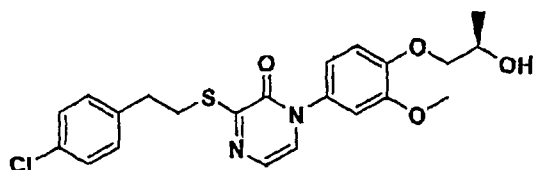
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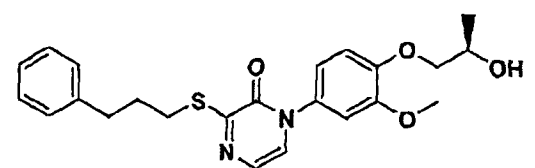
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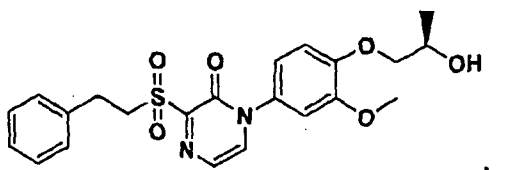
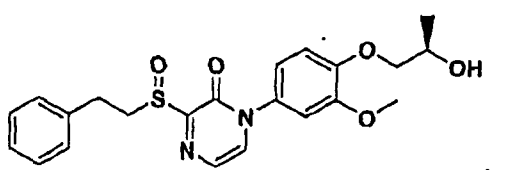
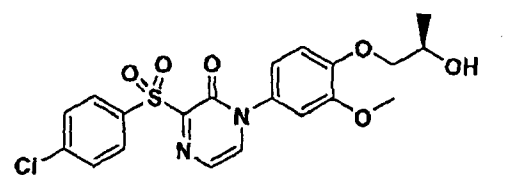
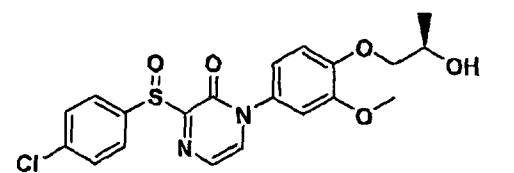
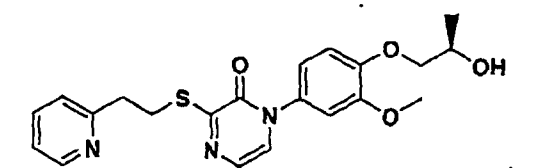
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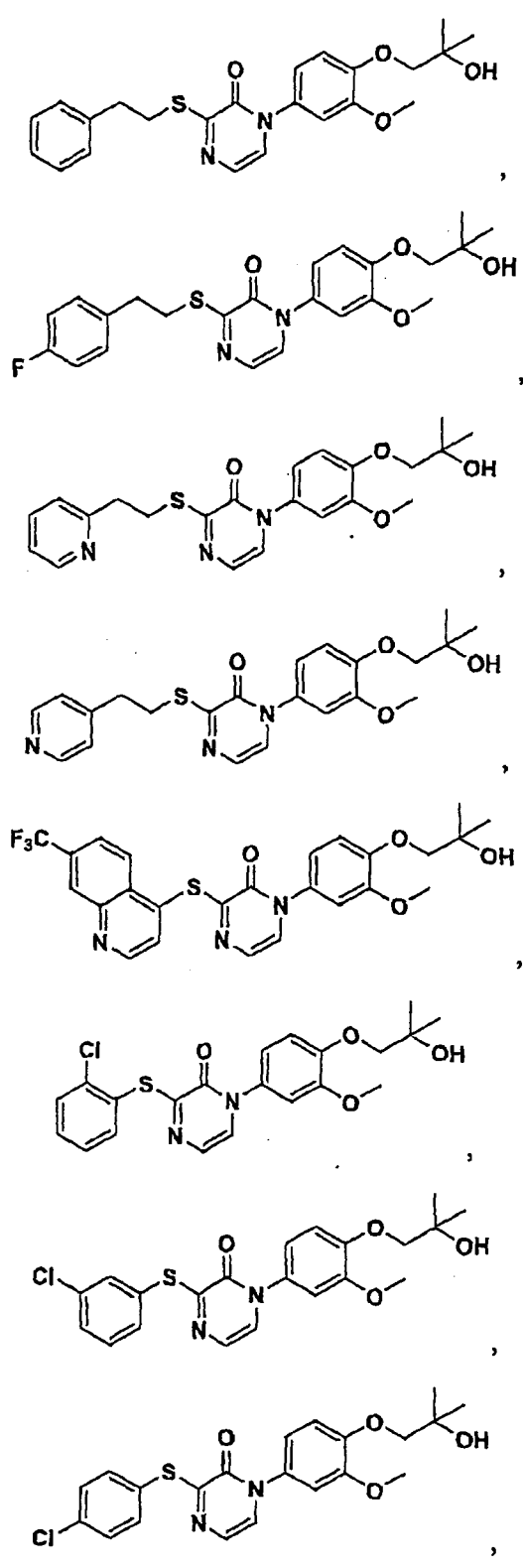
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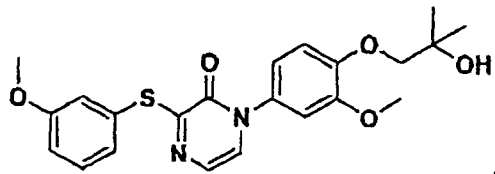
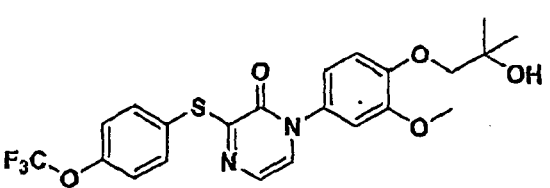
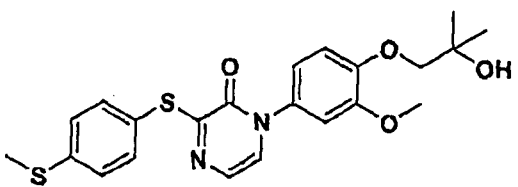
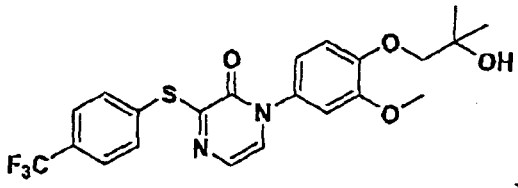
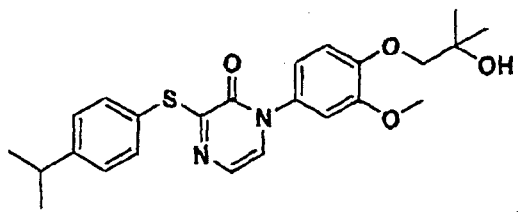
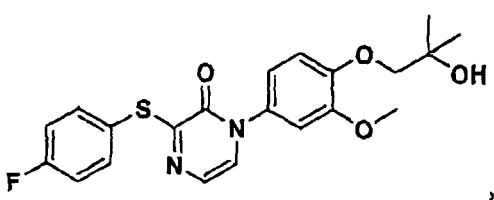
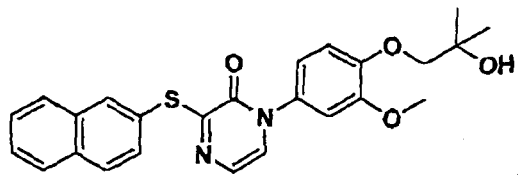
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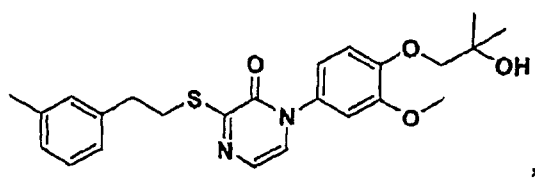
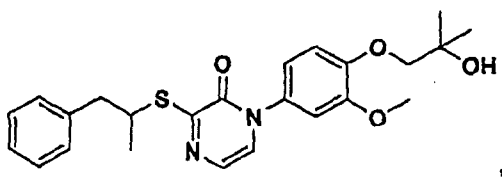
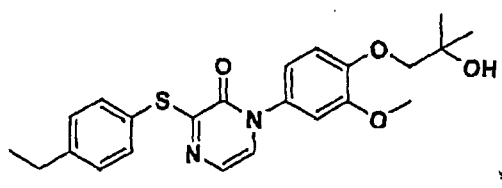
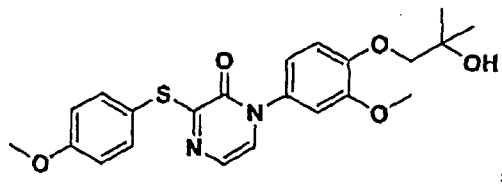
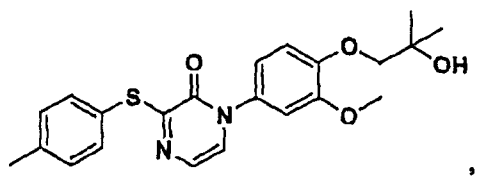
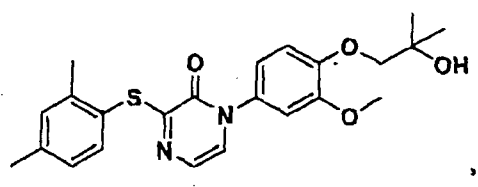
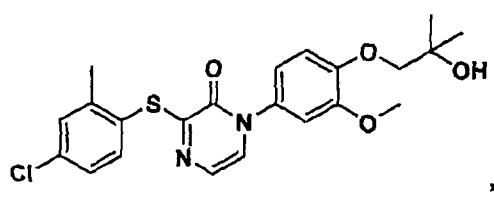
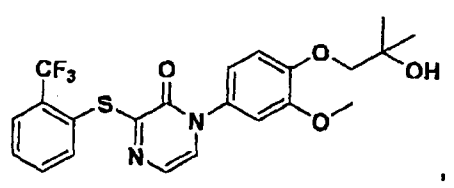
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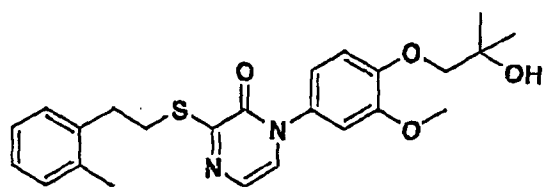
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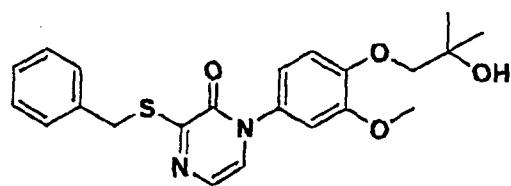
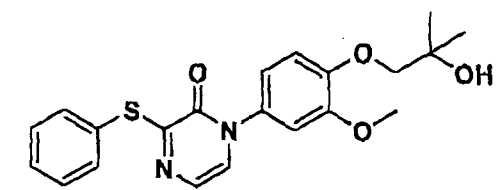
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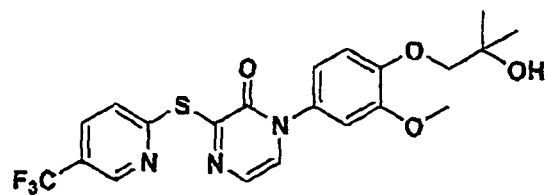
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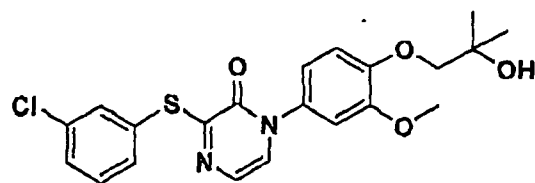
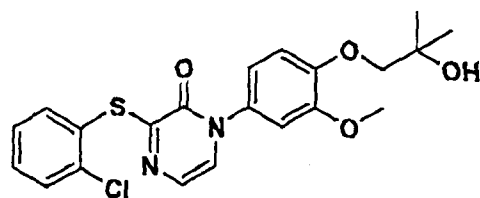
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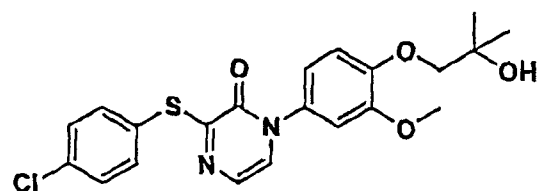
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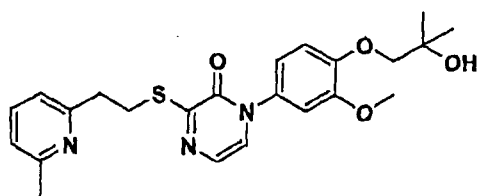
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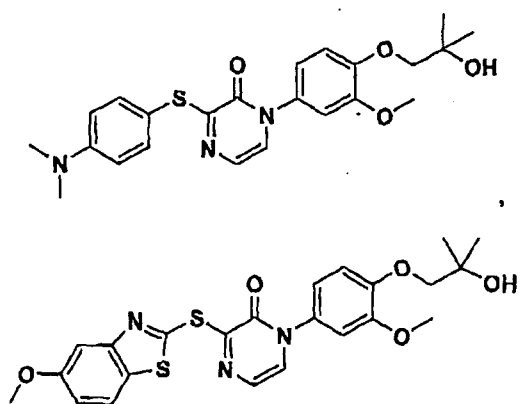
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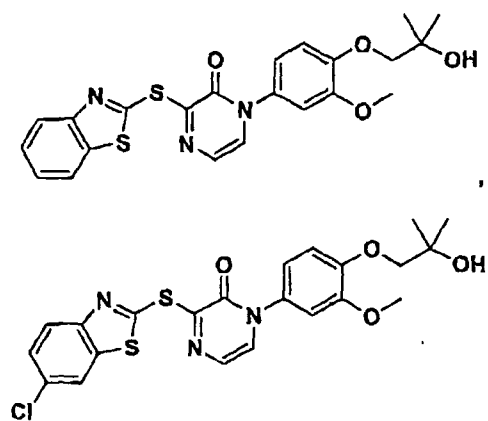
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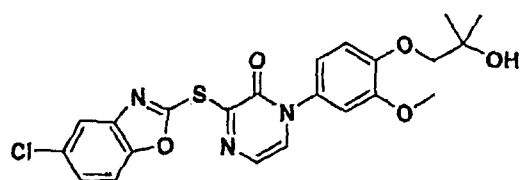
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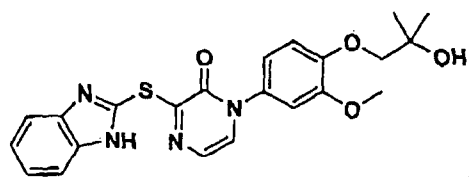
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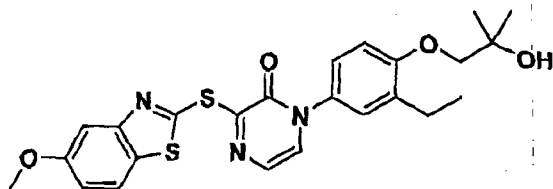


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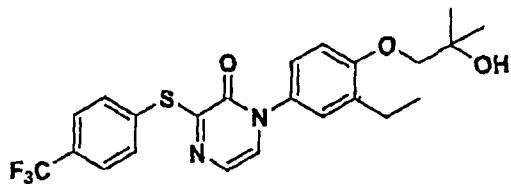


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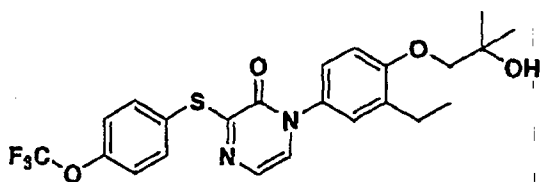




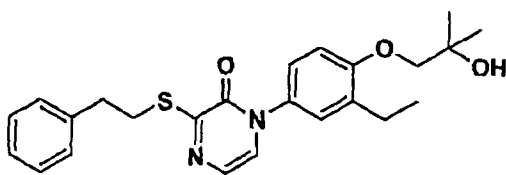
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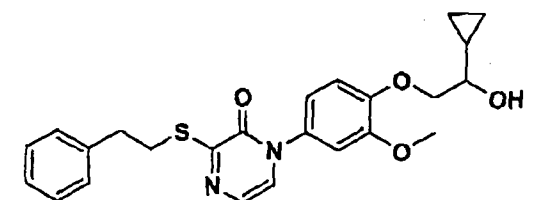
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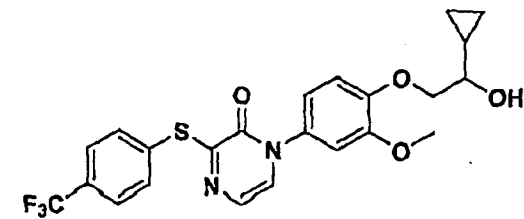
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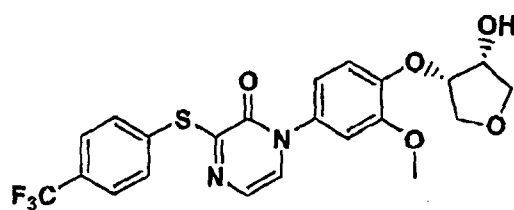


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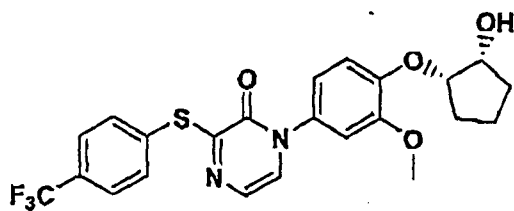


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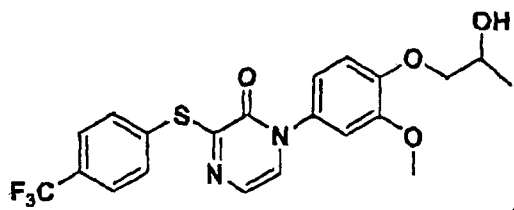




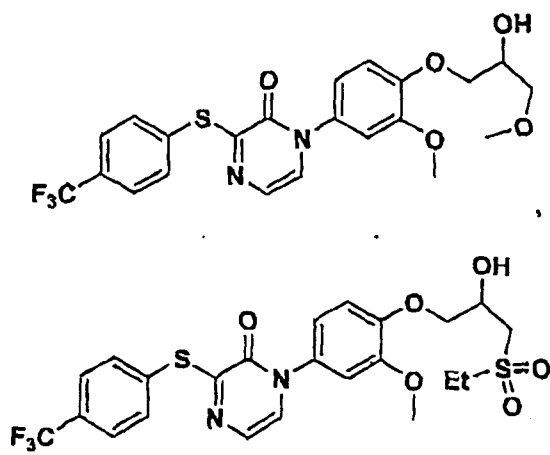
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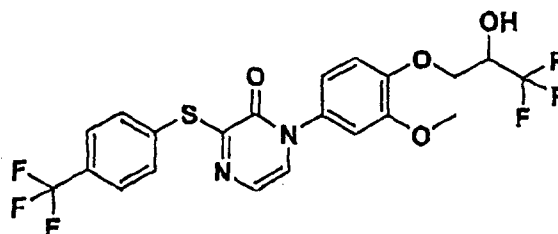
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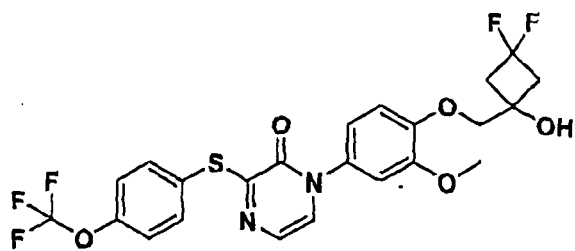


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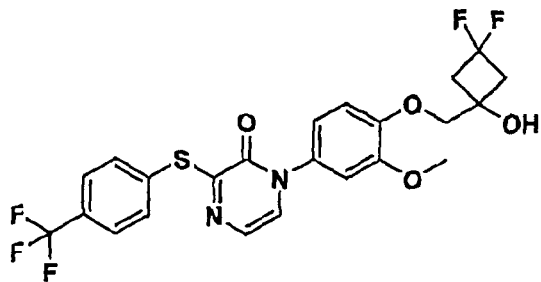


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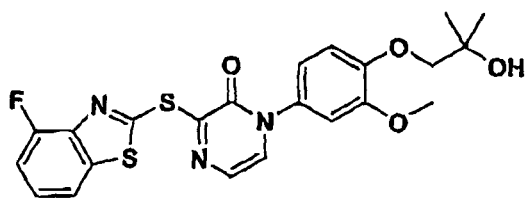
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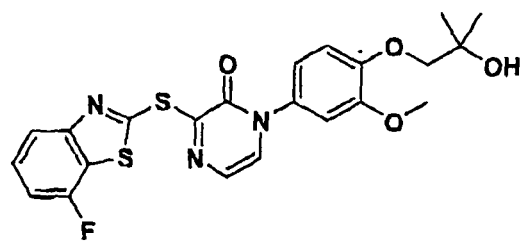
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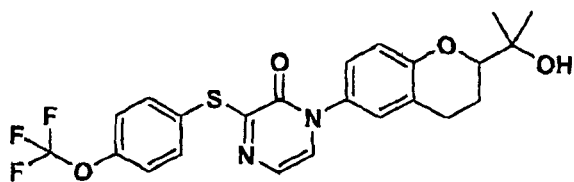
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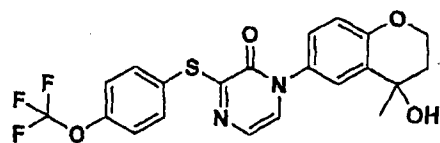
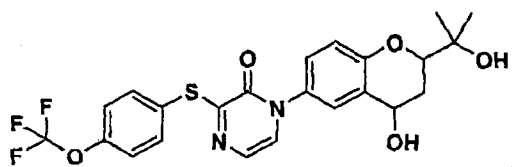
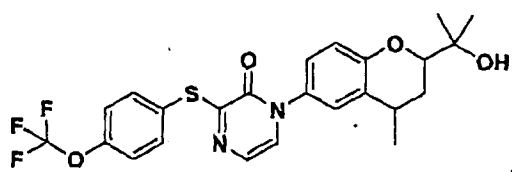
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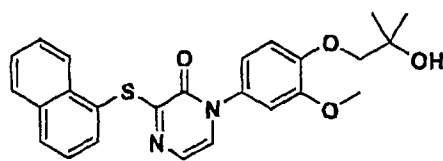
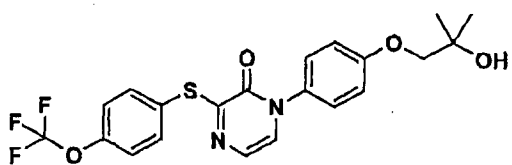
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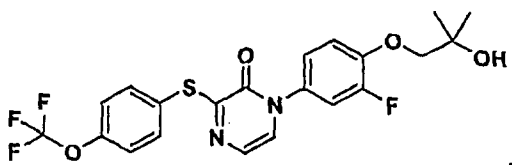
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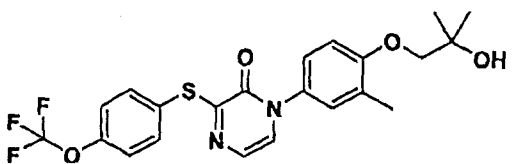
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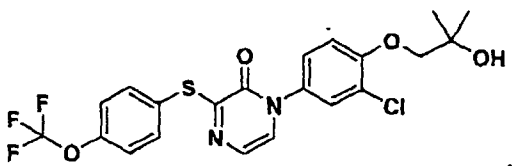
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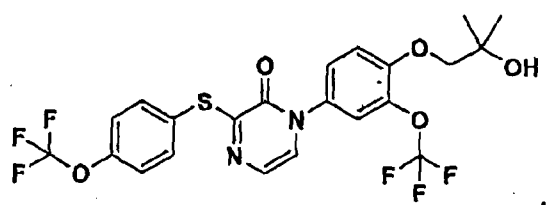
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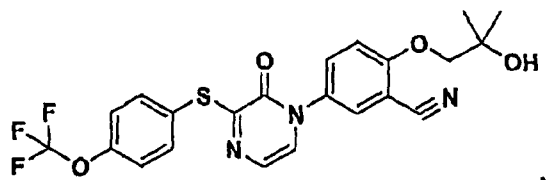
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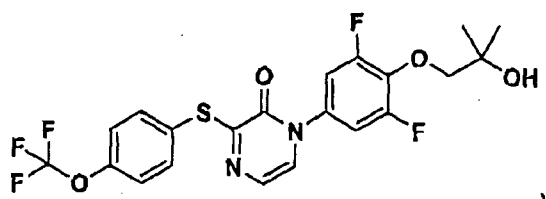
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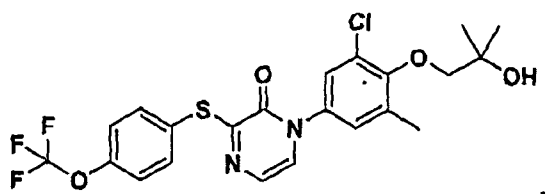
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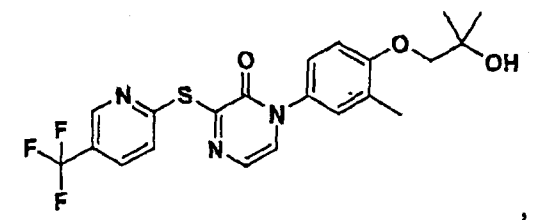
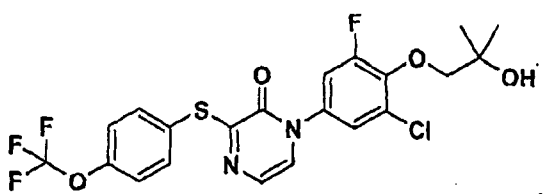
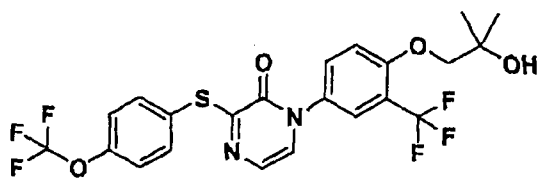
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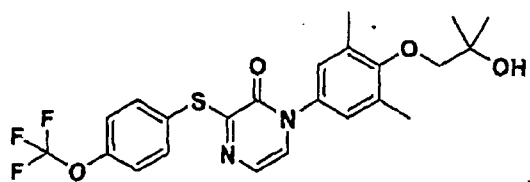


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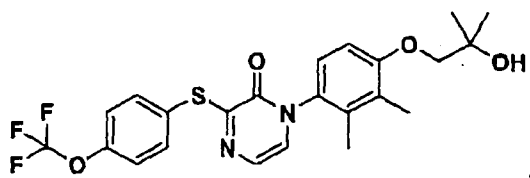


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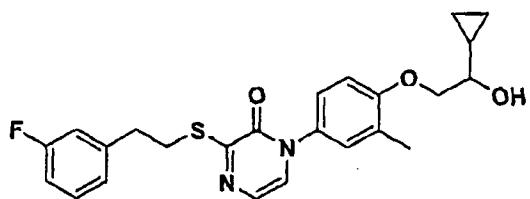




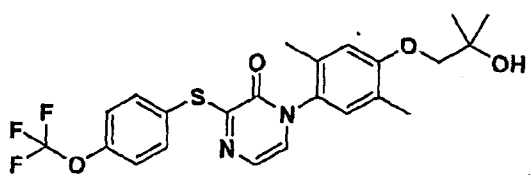
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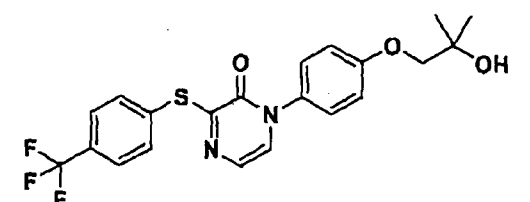
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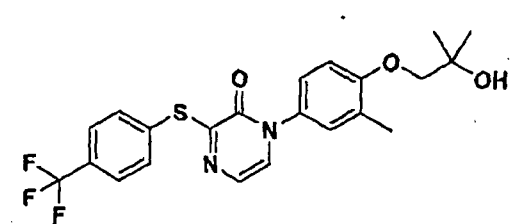
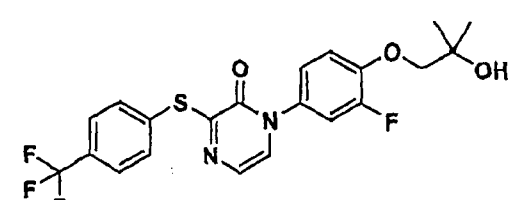
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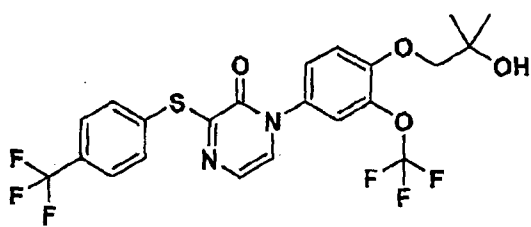


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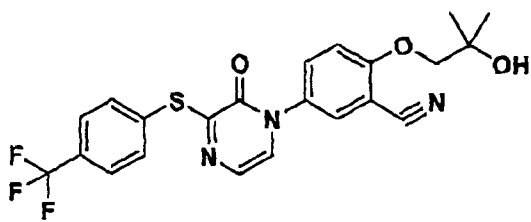


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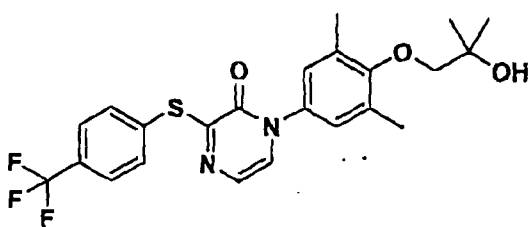




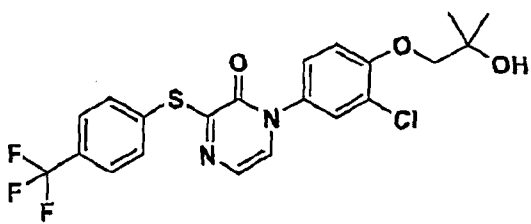
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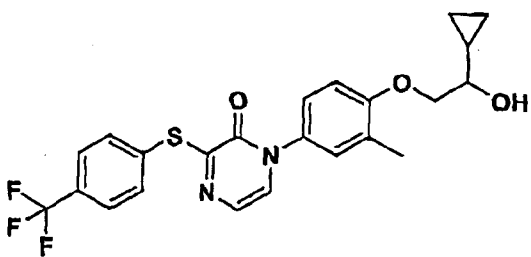
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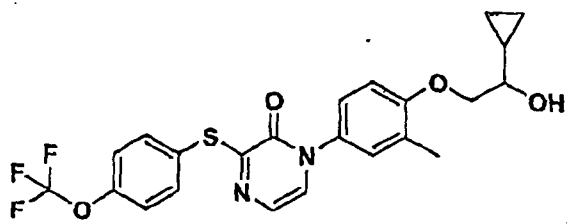
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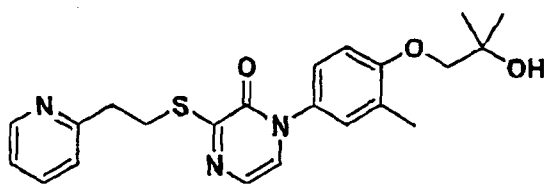
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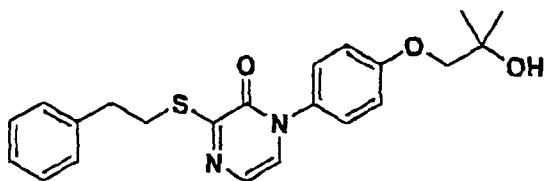
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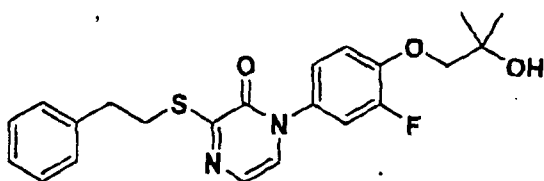
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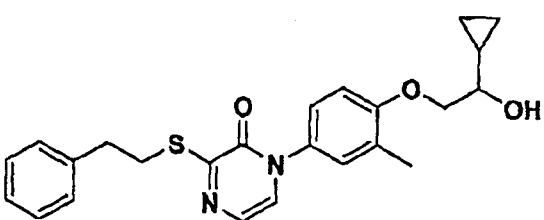
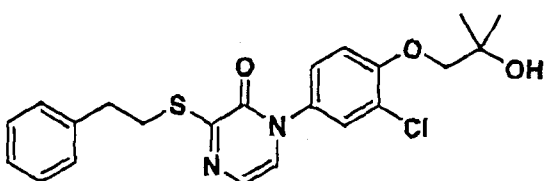
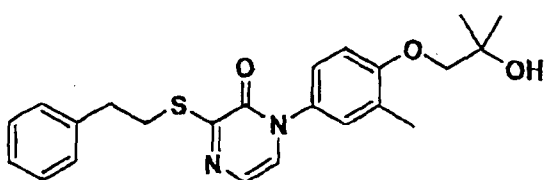
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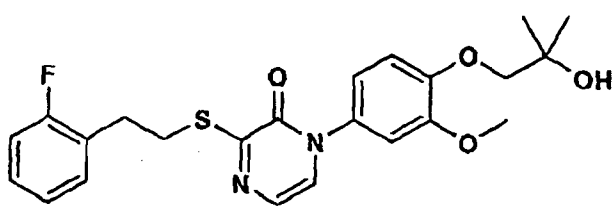
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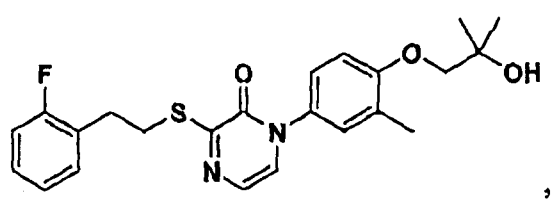
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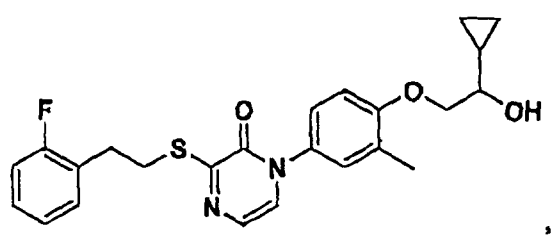
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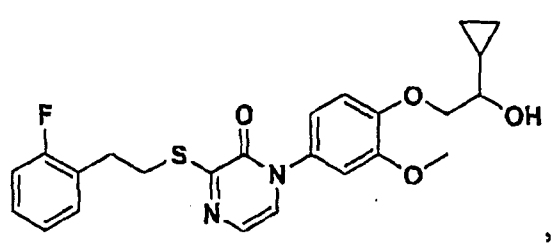
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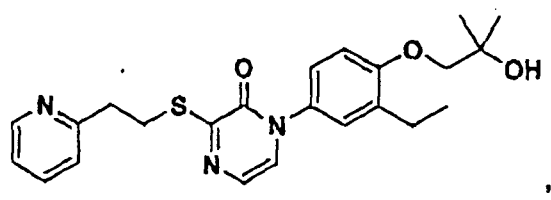
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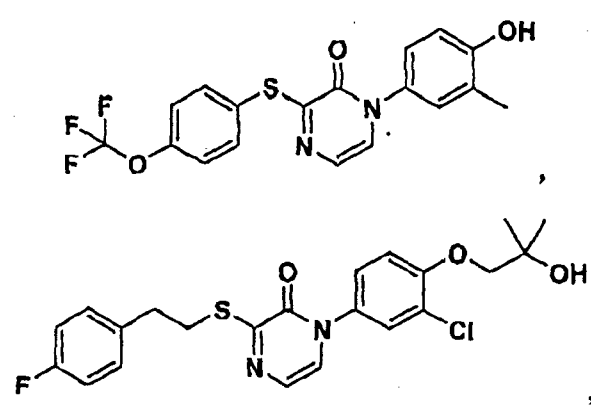
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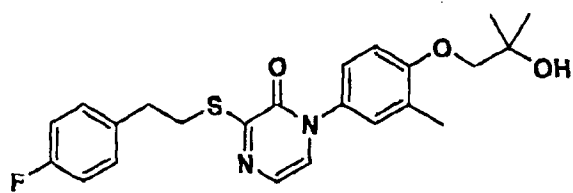


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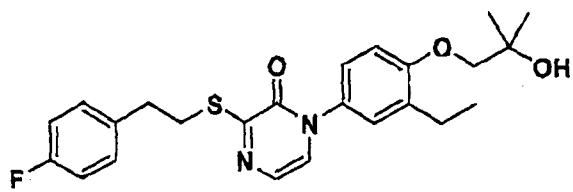


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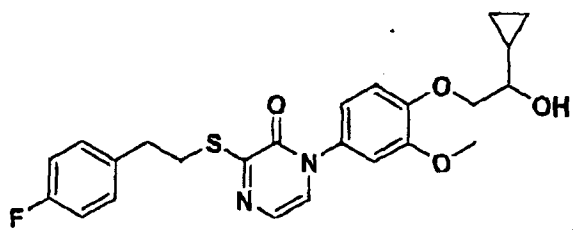




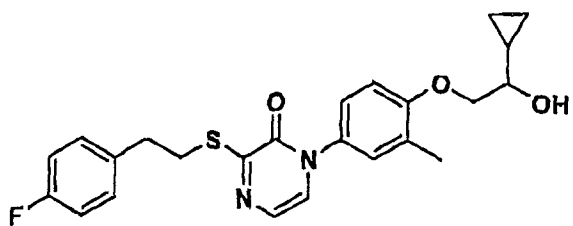
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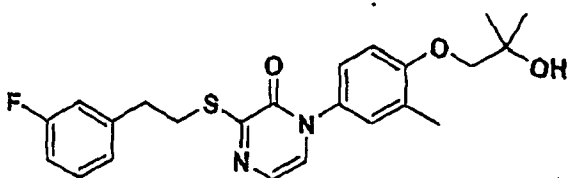
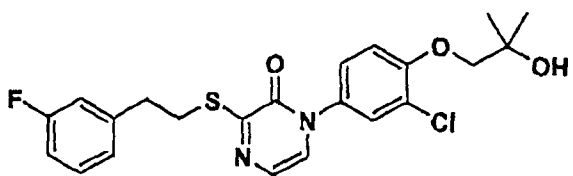
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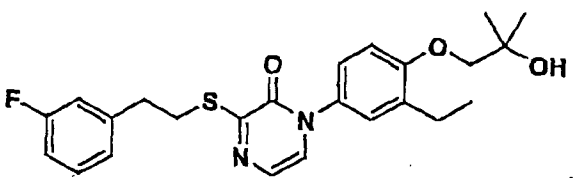
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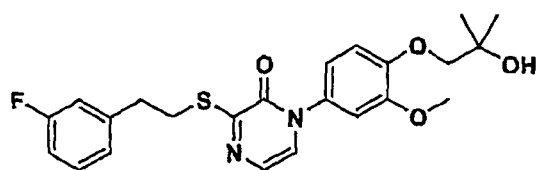
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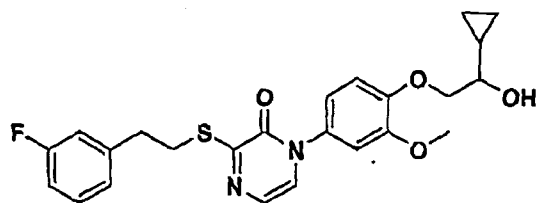
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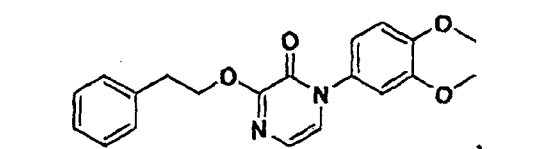
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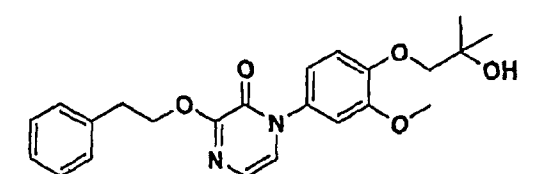
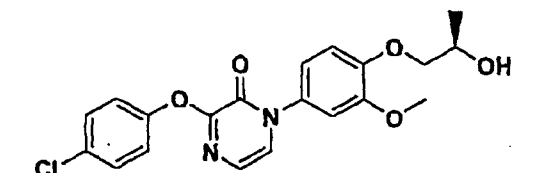
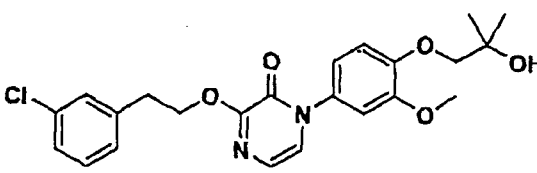
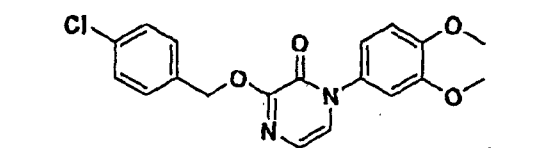
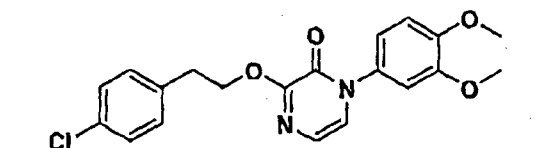
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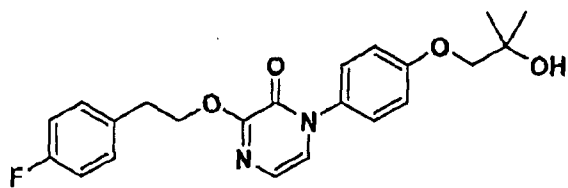
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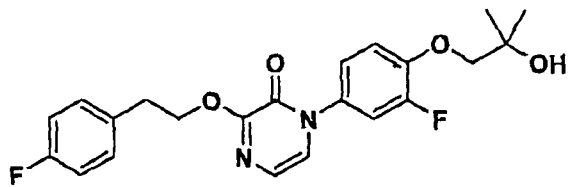
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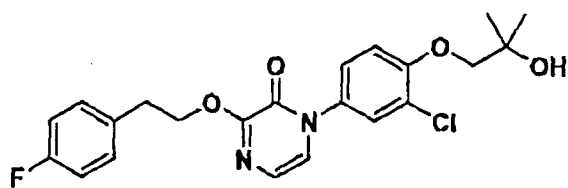
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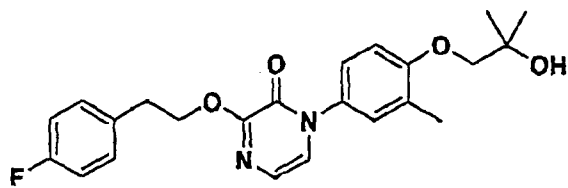
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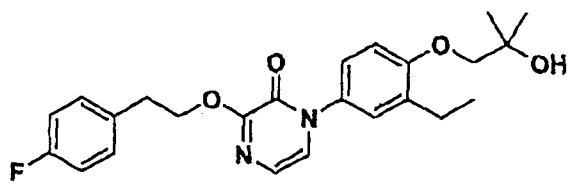
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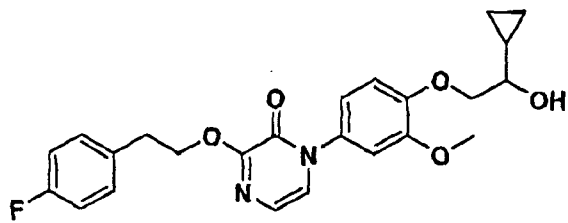
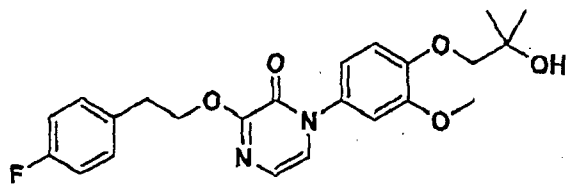
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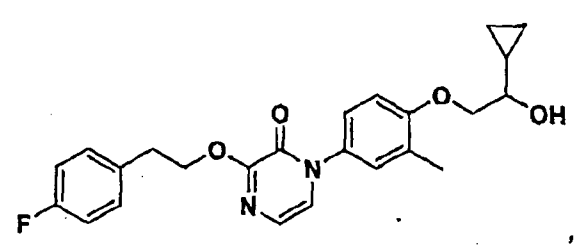
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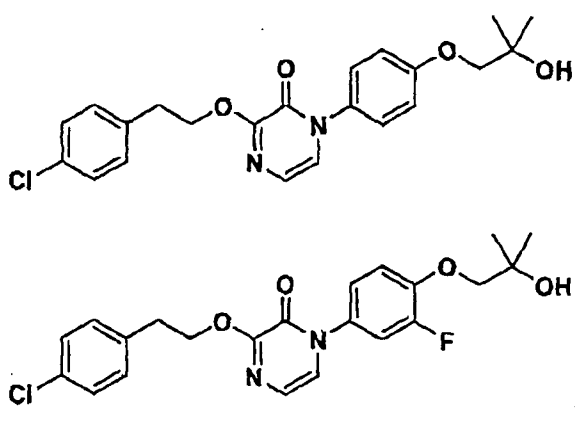
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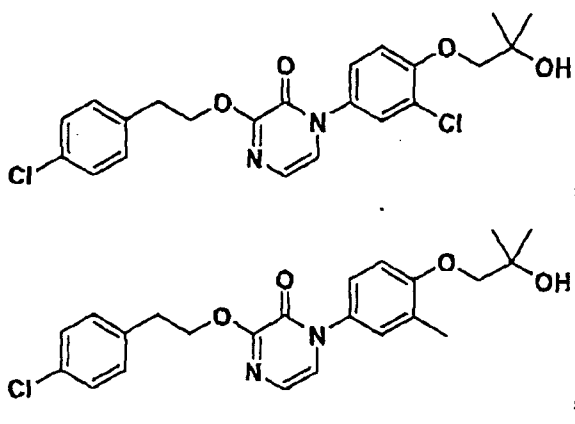
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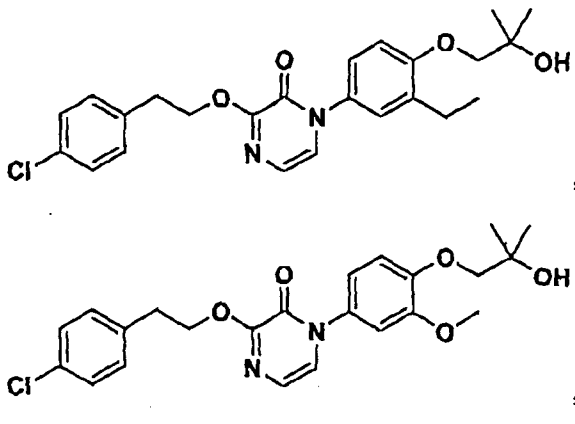
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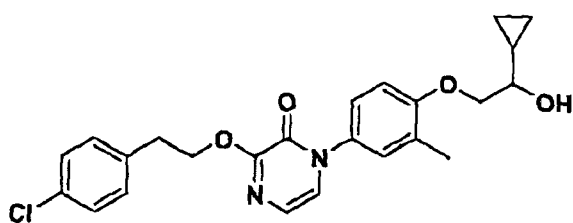


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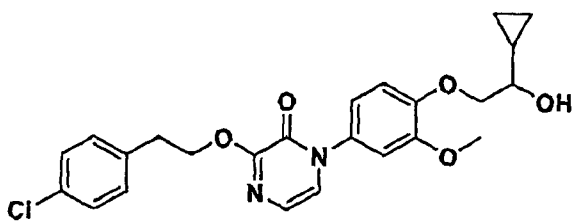


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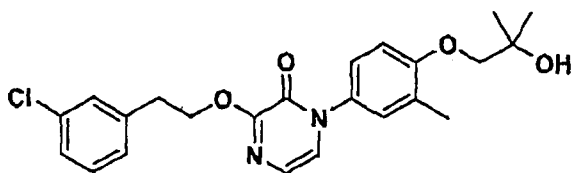
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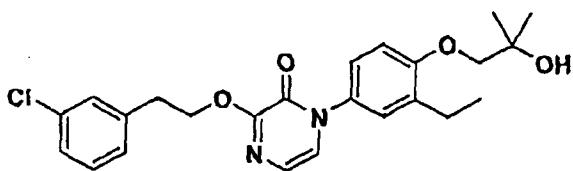
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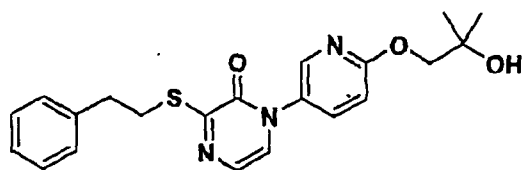
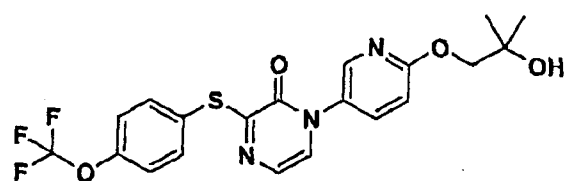
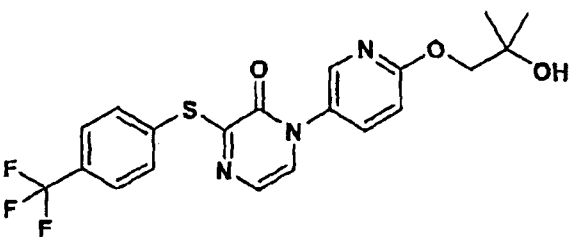
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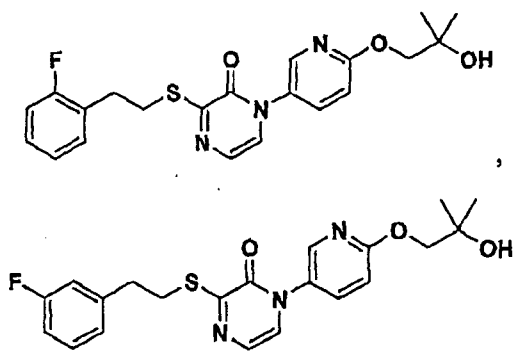
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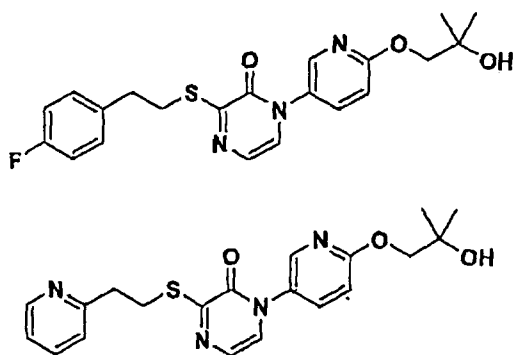
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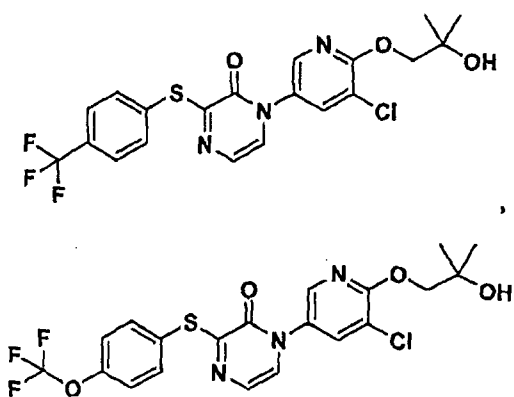
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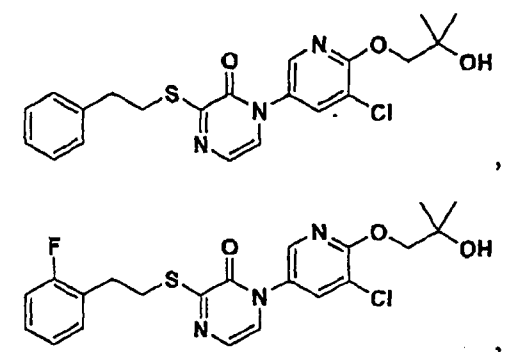
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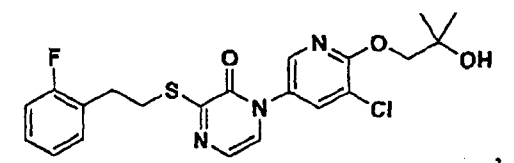
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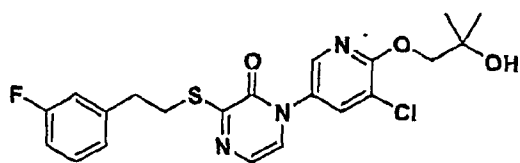
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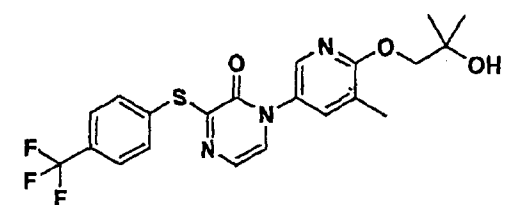
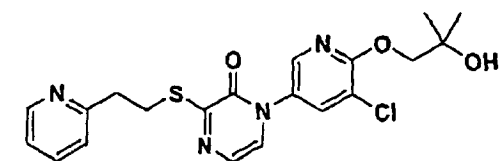
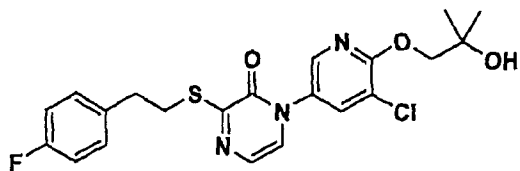
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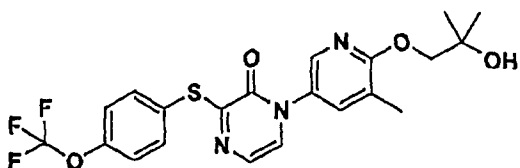
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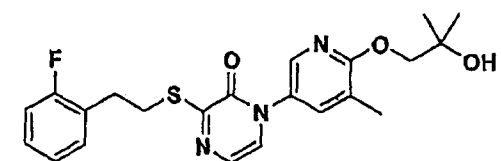
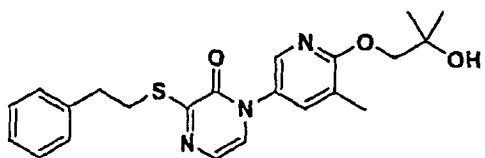
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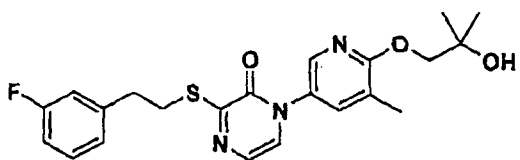
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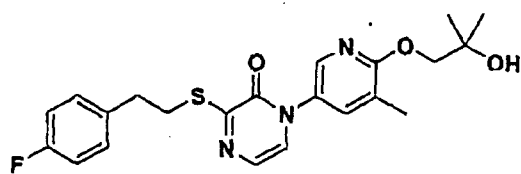


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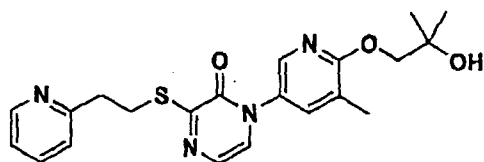


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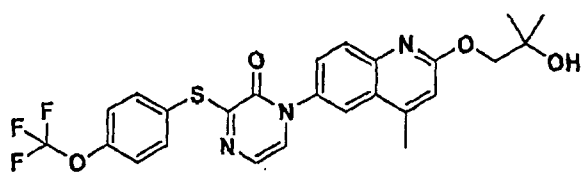




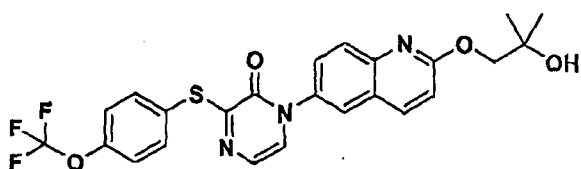
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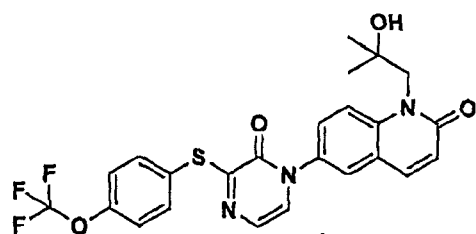
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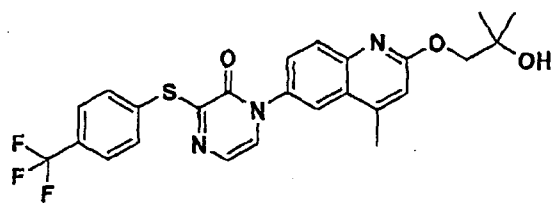
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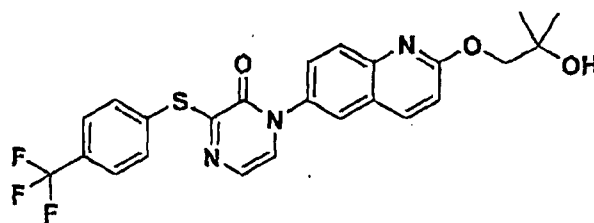
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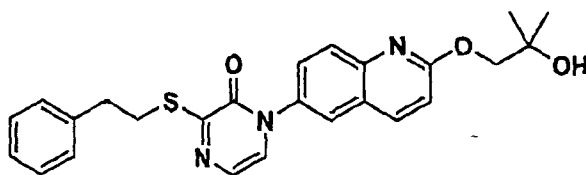
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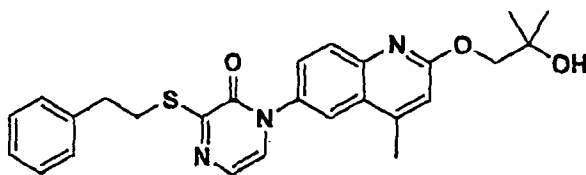
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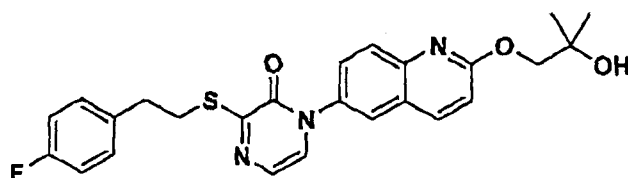
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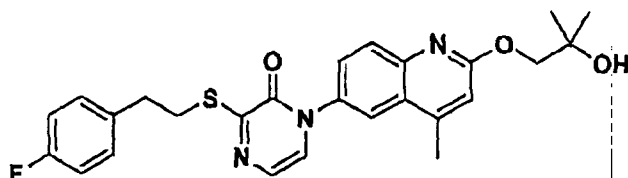
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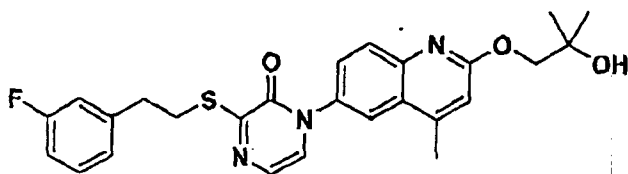
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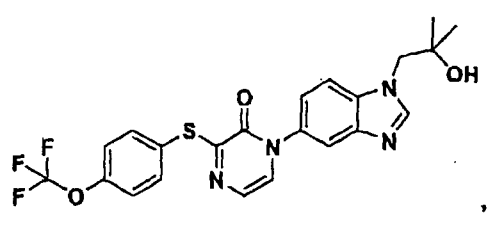
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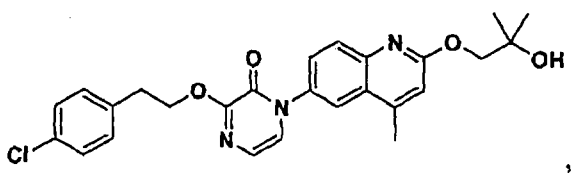
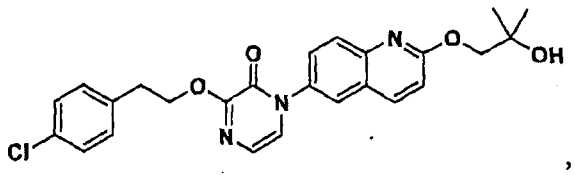
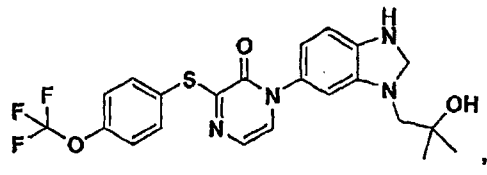
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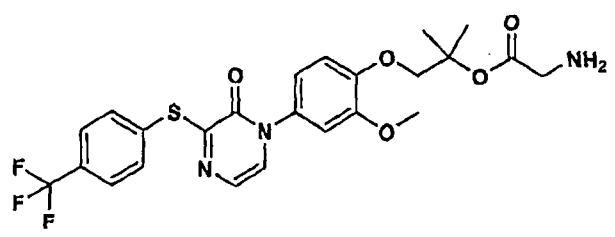
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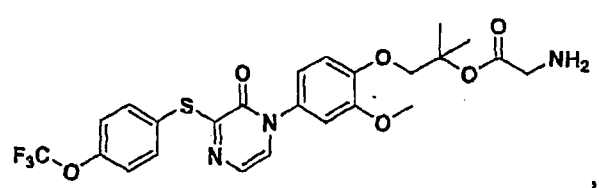
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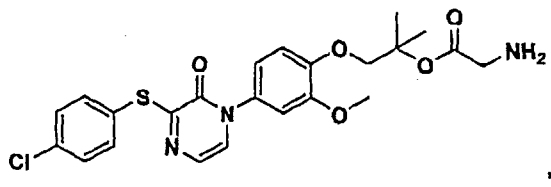
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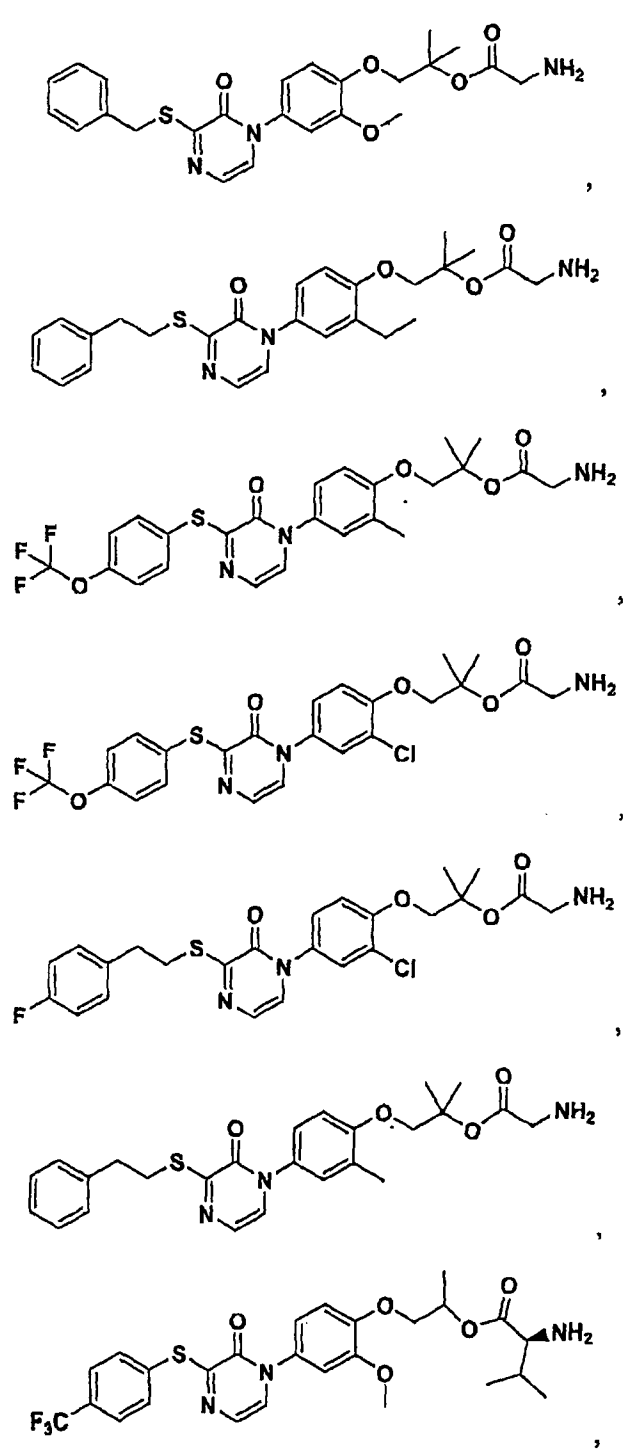
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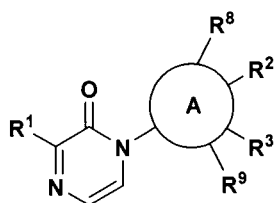
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RESUMEN DE LA INVENCIÓN

La presente solicitud proporciona compuestos, incluyendo todos los estereoisómeros, solvatos, profármacos y formas farmacéuticamente aceptables de los mismos de acuerdo con la

5 Fórmula I



10

en la que $\textcircled{A}$, R^1 , R^2 , R^3 , R^8 , y R^9 se definen en la presente.

Además, la presente solicitud proporciona composiciones farmacéuticas que contienen al menos un compuesto de acuerdo con la Fórmula I y opcionalmente al menos un agente
15 terapéutico adicional. Finalmente, la presente solicitud proporciona métodos para tratar a un paciente que padece de una enfermedad o trastorno modulado por MCHR-1 tal como, por ejemplo, obesidad, diabetes, depresión o ansiedad, mediante la administración de una dosis terapéuticamente eficaz de un
20 compuesto de acuerdo con la Fórmula I.

Docket No.: 10899 PCT

PATENT COOPERATION TREATY

International Filing No: PCT/US2008/069361

International Filing Date: 07 July 2008

Priority Date: 06 July 2007

Applicant: **BRISTOL-MYERS SQUIBB COMPANY****For: NON-BASIC MELANIN CONCENTRATING HORMONE RECEPTOR-1
ANTAGONISTS AND METHODS**International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. 41 22 338 82 70**AMENDMENT UNDER ARTICLE 19**

Applicants wish to make amendments to the claims. Please enter the amendments made to claims 1, 6, 8, 9, 10, 19, 21, 22, 23, 29, and 30 by replacing originally filed pages 115 to 131 with substituted pages 115 to 151. Support for these amendments can be found in the specification and claims as originally filed. No new matter has been added. Claims 2 to 5, 7, 11, 13 to 17, 24 to 28 and 31 are canceled. Claims 12, 18, and 20 remain unchanged. Claim 32 is new. Substitute Pages 115 to 151 are enclosed herewith. A marked up version of the Claims showing the changes to the originally filed claims is also included.

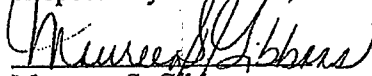
Remarks

The claims have been amended in response to the Written Opinion of the International Searching Authority to distinguish the claims over the references cited therein, D1 to D9. New claim 32 is directed to the compounds exemplified in the specification as originally filed.

Acceptance of the enclosed Substitute Pages is respectfully requested.

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
April 16, 2009

Respectfully submitted,

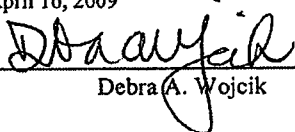


Maureen S. Gibbons
Agent for Applicant
Reg. No. 44,121
Phone: 609-252-3453
Fax: 609-252-4526

CERTIFICATE OF FACSIMILE

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being facsimile transmitted to the International Bureau of WIPO, Fax No. 41 22 338 82 70 on the date shown below.

Date of Deposit: April 16, 2009

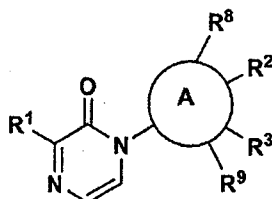


Debra A. Wojcik

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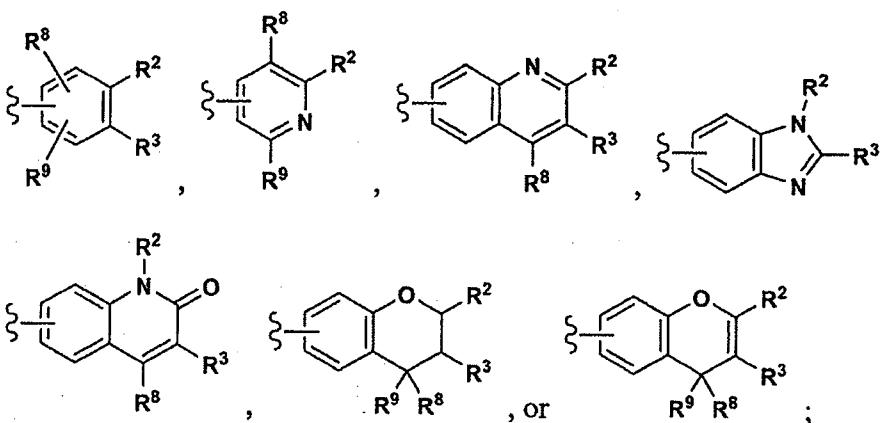
WHAT IS CLAIMED IS:

1. A compound of Formula I or a pharmaceutically acceptable salt thereof

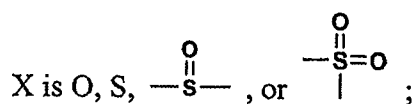


I

wherein



R^1 is Z-Y-X-, wherein



Y is a bond, a 3- to 6-membered cycloalkyl, an alkylene chain; and

Z is optionally substituted phenyl or naphthyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolyl;

R^2 is -E-G-(J)_m, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

each J is independently hydrogen, hydroxyl, CN, -SO₂R⁷, -SR⁷, -SOR⁷, lower alkyl, lower alkoxy, CF₃, CF₃O-, -COOR⁵, or -CO-NR^{5a}R⁶, wherein R^{5a} and R⁶ are

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R⁹ is H.

7. Cancel.

8. The compound as defined in Claim 1 wherein

R¹ is Z-Y-X-;

X is S;

Y is a bond or alkylene chain;

Z is phenyl or pyridyl;

E is O;

G is an alkylene chain or alkylcycloalkyl;

J is H or OH;

R³ is H, alkoxy, alkyl, or halo;

R⁸ is H or CH₃; and

R⁹ is H.

4

9. The compound as defined in Claim 1 wherein

Z is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolyl; any of which may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C₁₋₆ alkyl, C₁₋₃ alkylamino, di-C₁₋₃ alkylamino, C₁₋₃ alkoxy, C₁₋₃ thioalkyl, C₁₋₃ trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and

J is hydrogen, hydroxyl, CN, -SO₂R⁷, -SR⁷, -SOR⁷, lower alkyl, lower alkoxy, CF₃, CF₃O-, -COOR⁵, or -CO-NR^{5a}R⁶, wherein R^{5a} and R⁶ are each independently selected from the group consisting of H, C₁₋₃ alkyl, and cycloalkyl, or R^{5a} and R⁶ taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF₃, or CF₃O.

10. The compound of Claim 1 wherein:

Z is

(1) phenyl which is optionally substituted with:

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each independently selected from the group consisting of H, C₁₋₃ alkyl, and cycloalkyl, or R^{5a} and R⁶ taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R⁵ is H, C₁₋₆ alkyl, or cycloalkyl;

R⁷ is lower alkyl; and

R³ is C₁₋₆ alkyl, cycloalkyl, C₁₋₆ alkoxy, halogen, hydrogen, -S-C₁₋₆ alkyl, CN, CF₃O, or CF₃;

with the proviso that where $\textcircled{\text{A}}$ is a phenylene group, E is O or S, and further providing that E-G and R³ are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R³ is not hydrogen; and

R⁸ and R⁹ are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. Cancel.

3. Cancel.

4. Cancel.

5. Cancel.

6. The compound as defined in Claim 1 wherein

X is O or S;

R¹ is Z-Y-X-;

wherein Y is a bond or an alkylene chain of 1 to 3 atoms;

Z is phenyl, or pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazoliny;

R² is -E-G-J;

E is O or S;

G is an alkylene chain or alkylcycloalkyl;

J is H, OH, SO₂R⁷, lower alkyl, lower alkoxy, or CF₃;

R³ is C₁₋₆ alkyl, C₁₋₆ alkoxy, H, or halo;

R⁸ is H or alkyl; and

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- a) halogen,
- b) alkyl,
- c) alkoxy,
- d) polyhaloalkyl,
- e) polyhaloalkoxy,
- f) amino, alkylamino or dialkylamino,
- g) alkylthio,
- h) OH,
- i) an ester, or
- j) aryl,
- (2) heteroaryl which is:
 - a) pyridinyl,
 - b) pyrazinyl, or
 - c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

- (3) benzothiazolyl optionally substituted with halo or alkoxy,
- (4) benzoxazolyl optionally substituted with halo,
- (5) benzimidazolyl,
- (6) thiazolyl optionally substituted with aryl or alkyl,
- (7) indanyl,
- (8) quinolinyl optionally substituted with CF_3 , or
- (9) imidazolidinyl;

Y is a bond or alkylene;

X is S, O, SO, or SO_2 ;

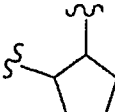
J is

- (1) H,
- (2) $-\text{CO}-\text{NR}^{5a}\text{R}^6$ wherein R^{5a} and R^6 together with the N to which they are attached form a pyrrolidinyl ring,
- (3) OH,
- (4) COOH ,
- (5) COOalkyl , or

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(6) SO_2R^7 ,

m is 1 or 2;

G is a bond or CH_2 , $(\text{CH}_2)_2$, $(\text{CH}_2)_3$, $\text{—CH}_2\text{—CH—}$
 CH_3 , $\text{—CH}_2\text{—C—}$
 $\text{CH}_3 \text{ CH}_3$, $\text{—CH}_2\text{—CH—CH}_2\text{OCH}_3$, $\text{—CH}_2\text{—CH—CF}_3$, cycloalkyl which is , orcycloalkoxy which is ;

E is O;

 R^3 is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy; R^8 is H, halo or alkyl; and R^9 is H

or a prodrug ester of said compound selected from the group consisting of glycine prodrug esters, valine prodrug esters, and phosphate prodrug esters.

11. Cancel.

6 12. The compound of Claim 7, wherein R^3 is $\text{C}_1\text{—C}_6$ alkoxy or $\text{C}_1\text{—C}_6$ alkyl.

13. Cancel.

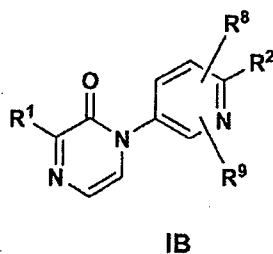
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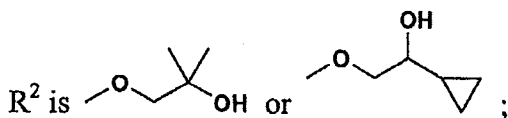
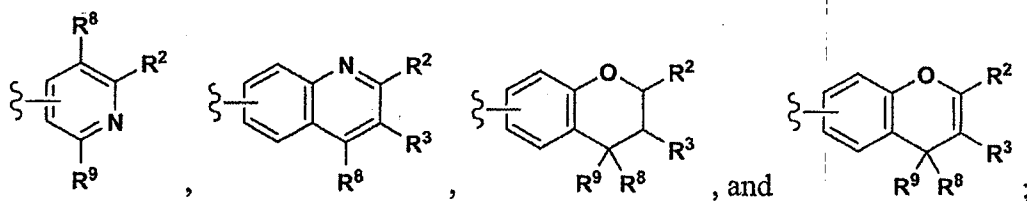
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18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure



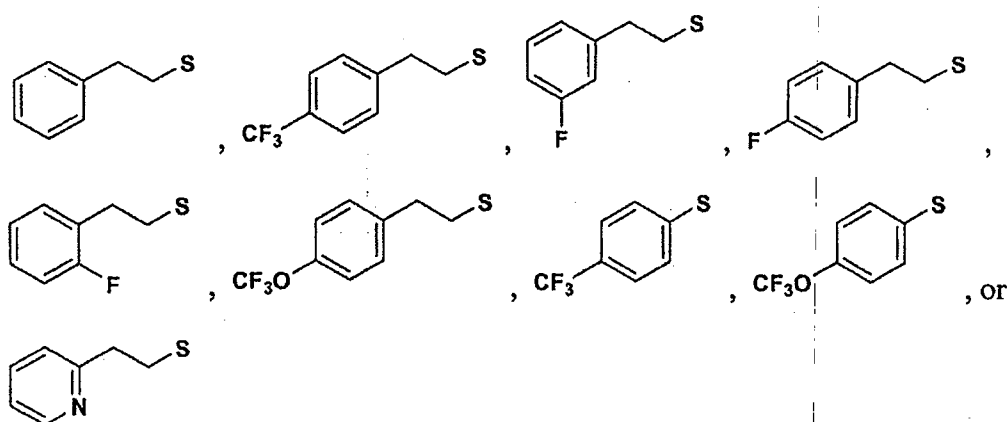
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R^3 is methoxy, Cl, H, or methyl; and

R^1 is selected from the group consisting of:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent wherein said additional therapeutic agent is selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

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19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolinyll or phenyl,

each of which Z is optionally substituted with CF_3 , CF_3O , or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

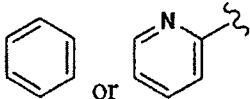
R^8 is H or alkyl; and

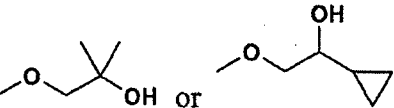
R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is  ;

R^2 is E-G-J which is  ;

R^3 is H, Cl, CH_3 , or CH_3O ; and

R^8 and R^9 are each H.

21. The compound of Claim 1 wherein

(A) is selected from the group consisting of;

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18 23. A pharmaceutical combination comprising: at least one compound according to claim 1, and at least one additional therapeutic agent selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

24. Cancel.

25. Cancel.

26. Cancel.

27. Cancel.

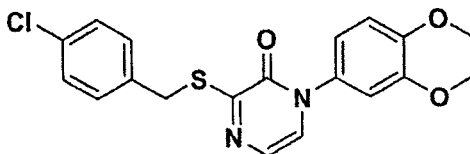
28. Cancel.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of obesity.

30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes.

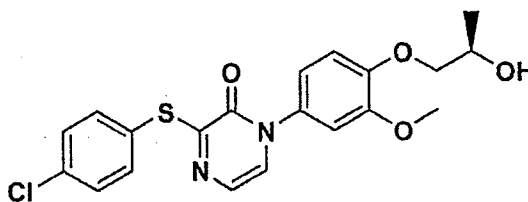
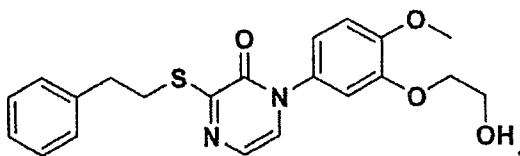
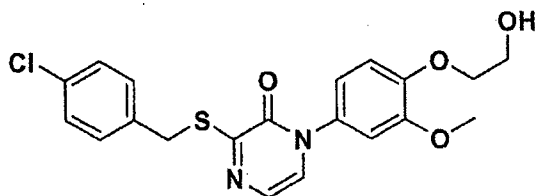
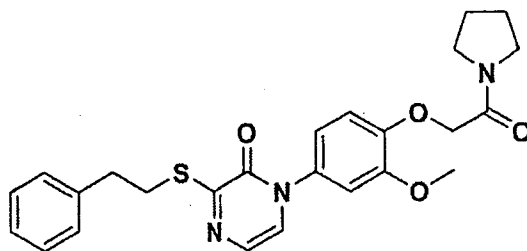
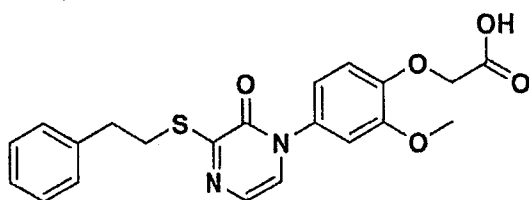
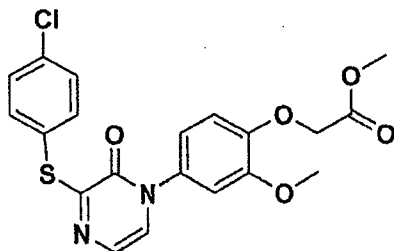
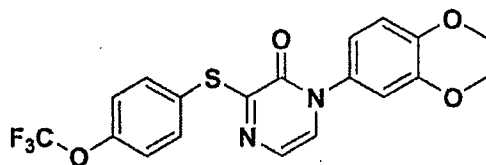
31. Cancel.

32. New. The compound according to claim 1 selected from the group consisting of:

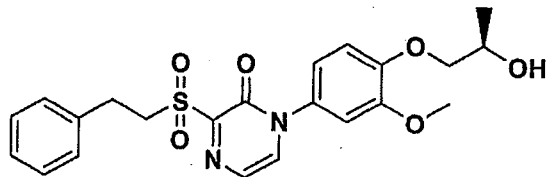
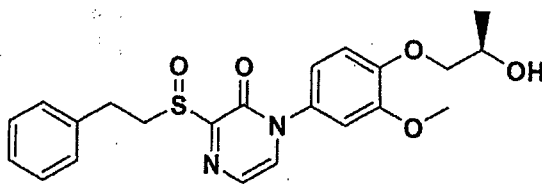
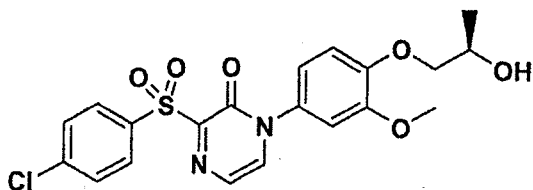
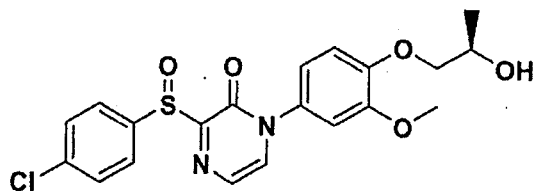
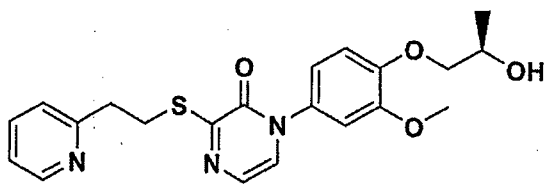
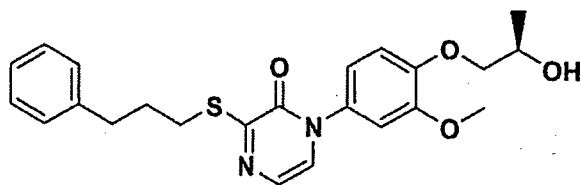
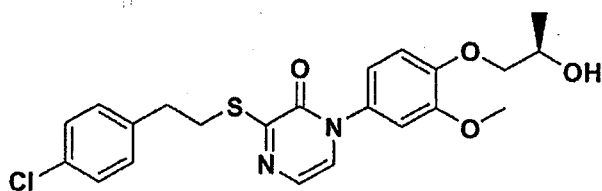
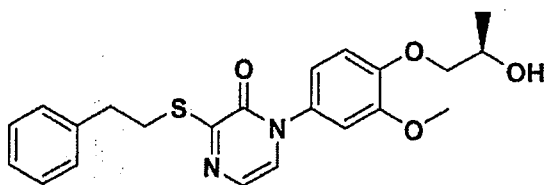


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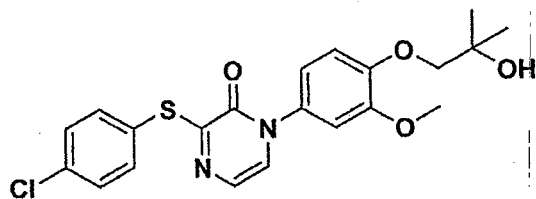
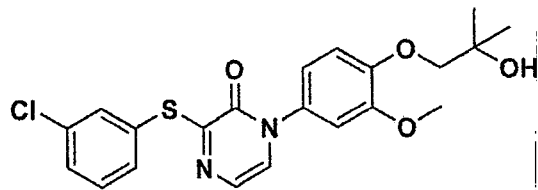
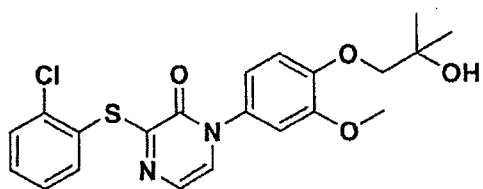
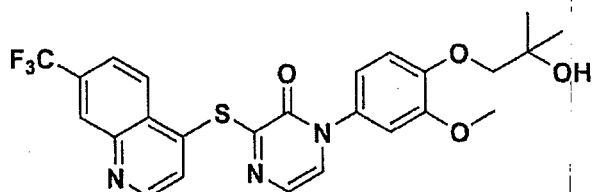
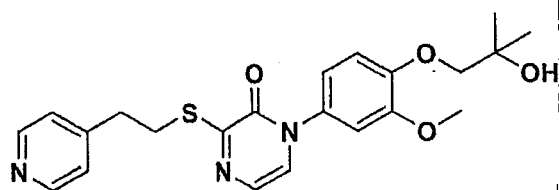
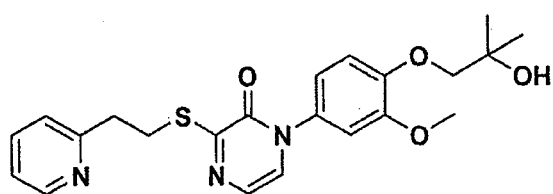
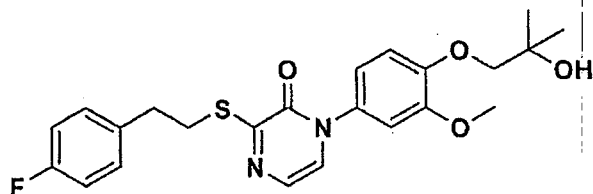
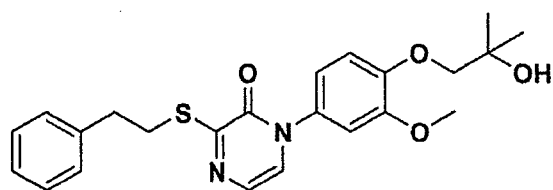


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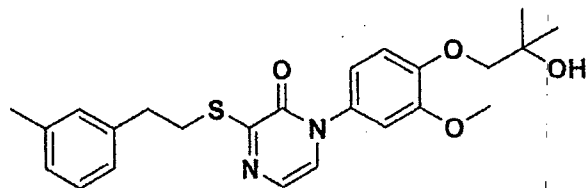
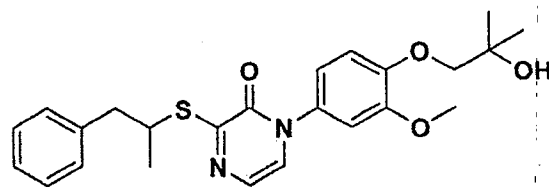
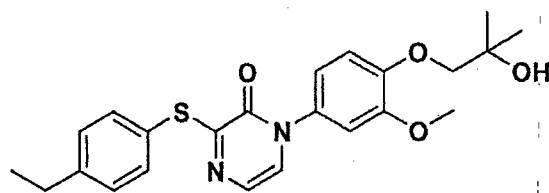
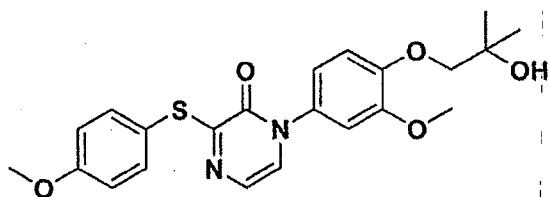
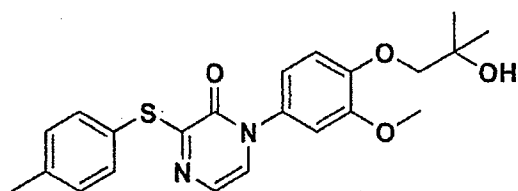
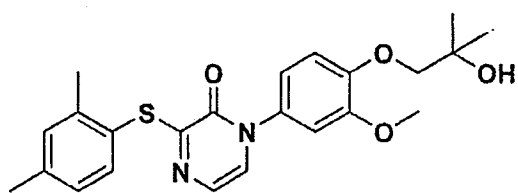
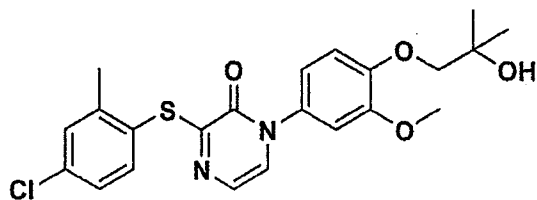
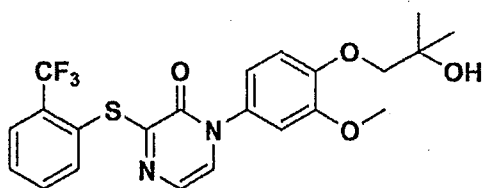
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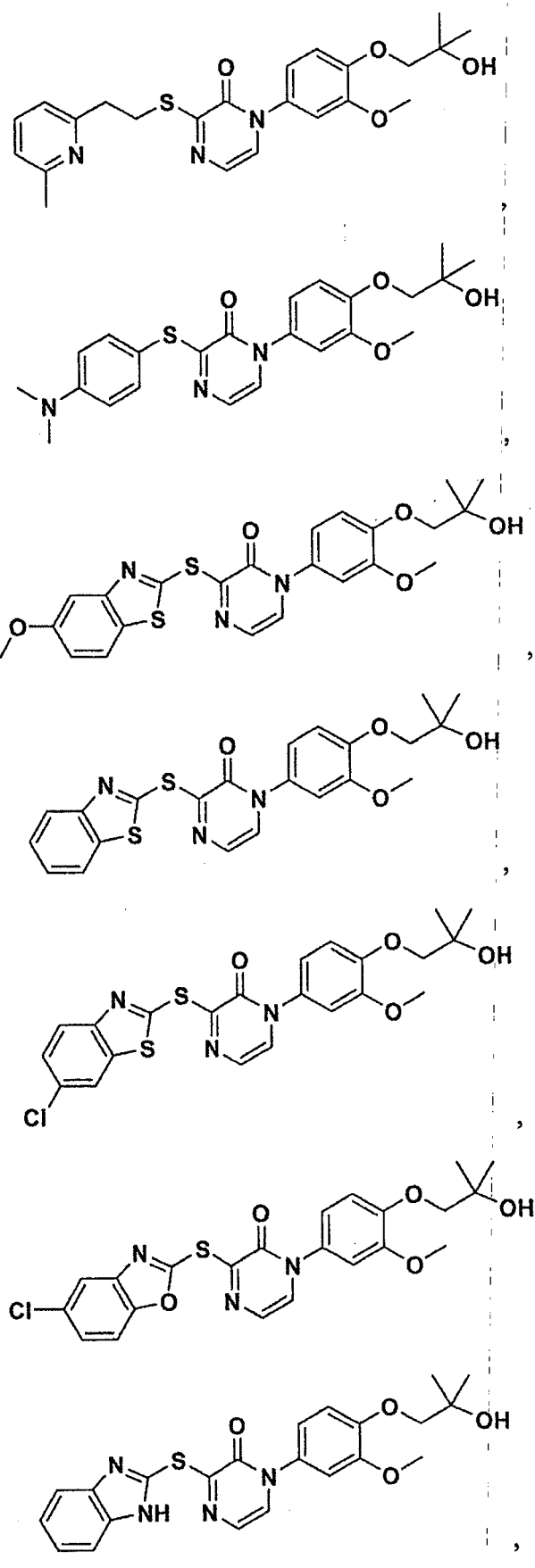
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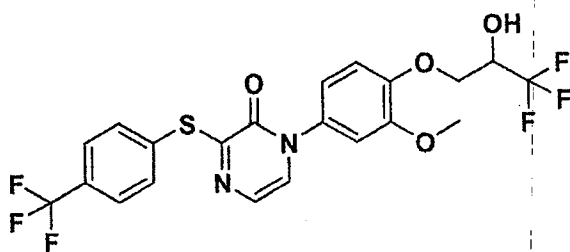
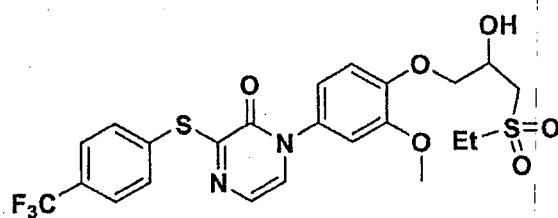
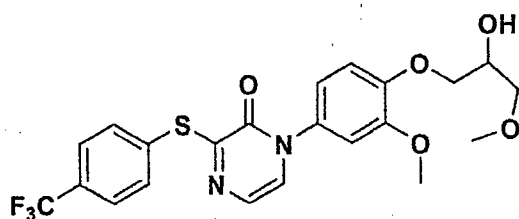
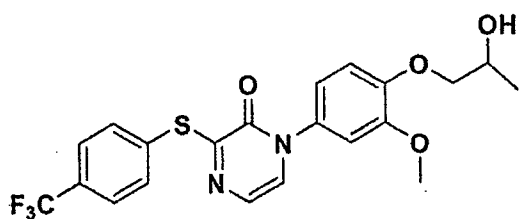
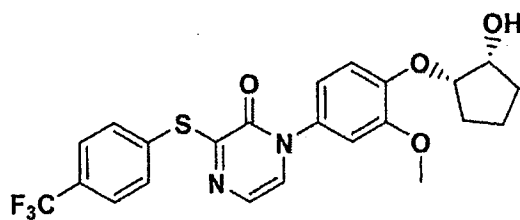
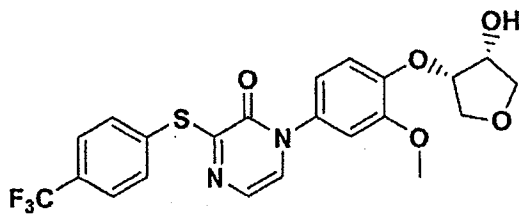
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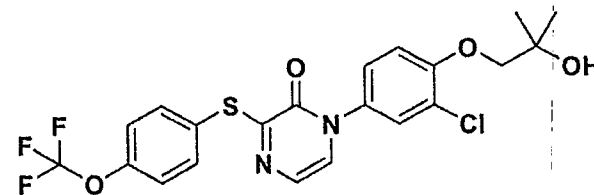
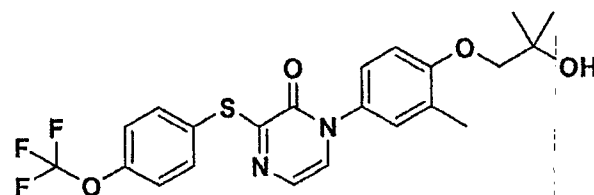
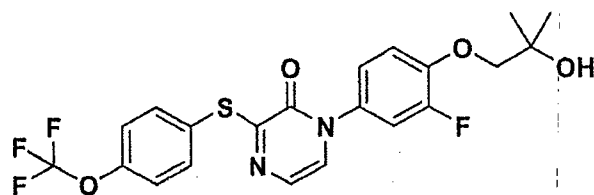
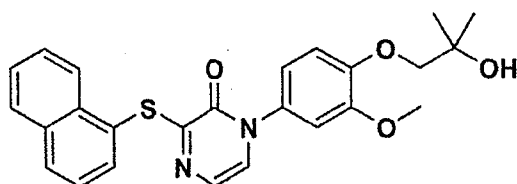
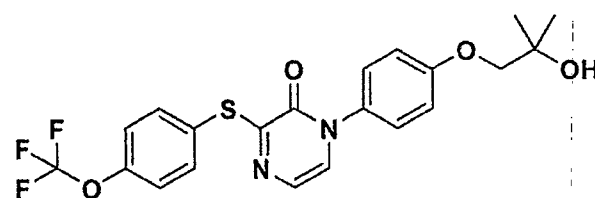
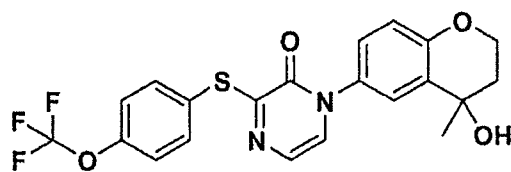
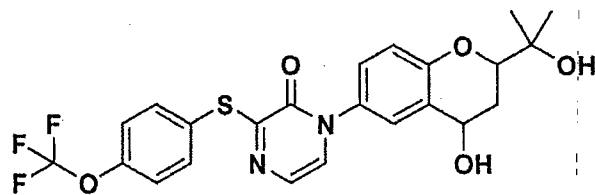
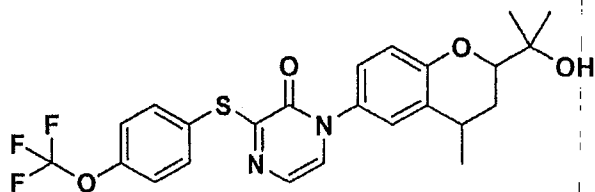
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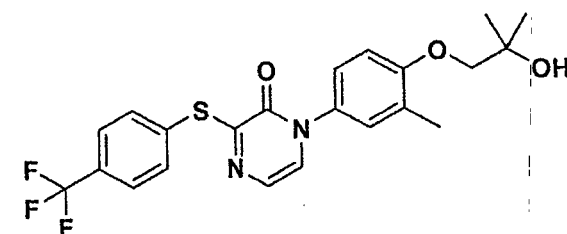
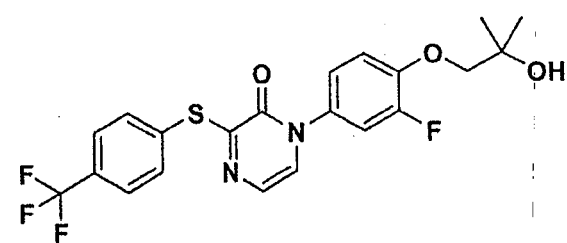
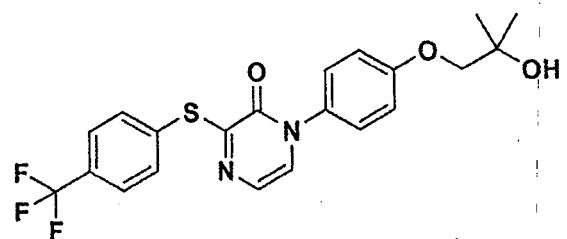
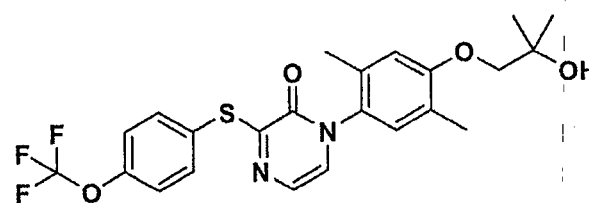
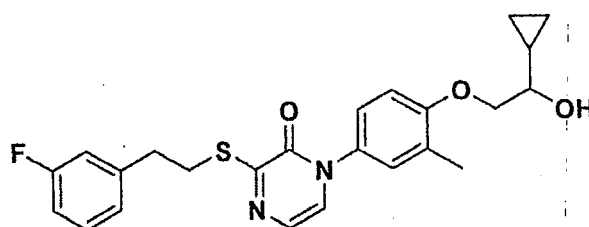
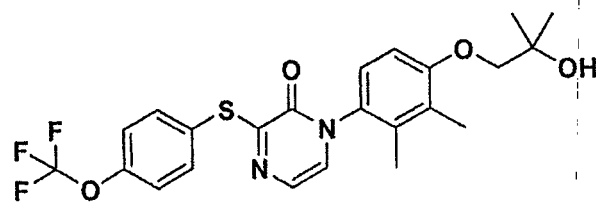
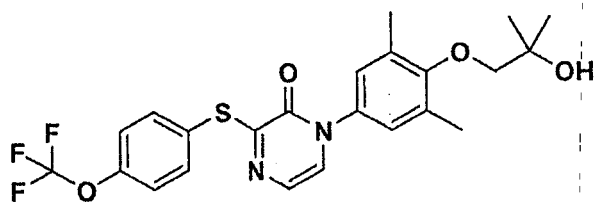
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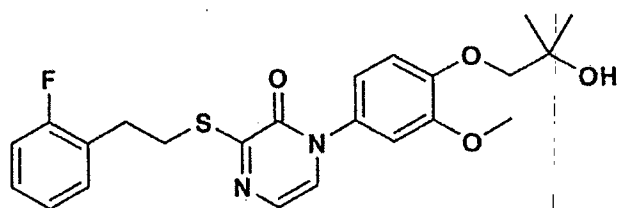
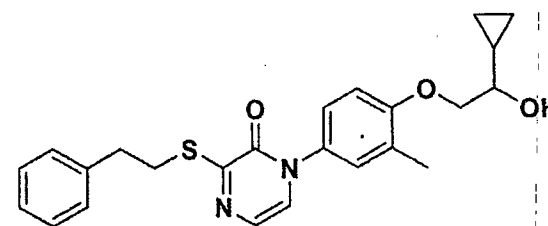
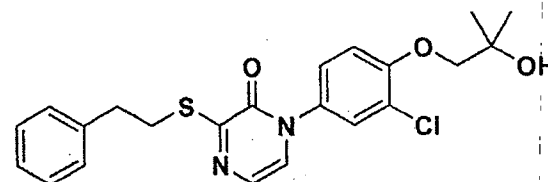
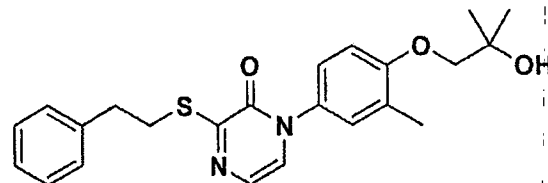
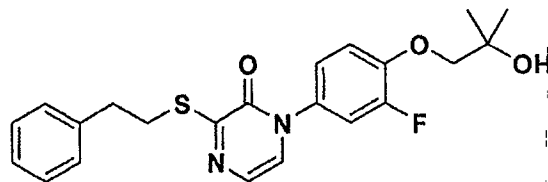
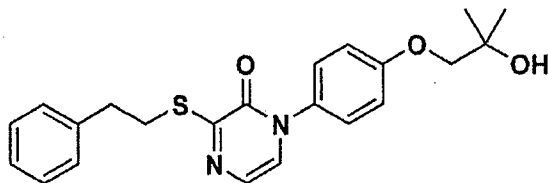
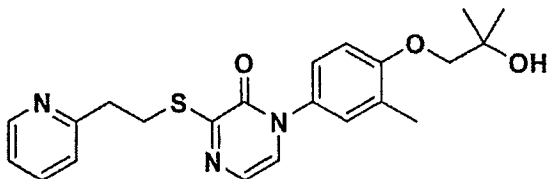
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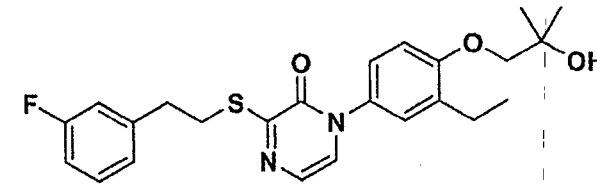
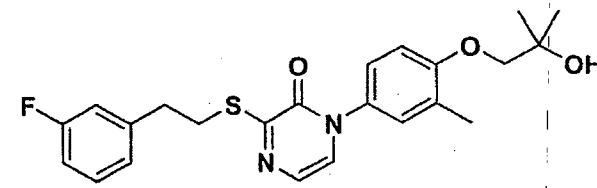
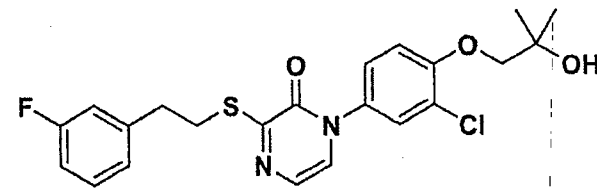
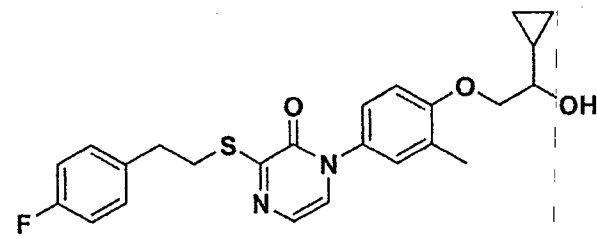
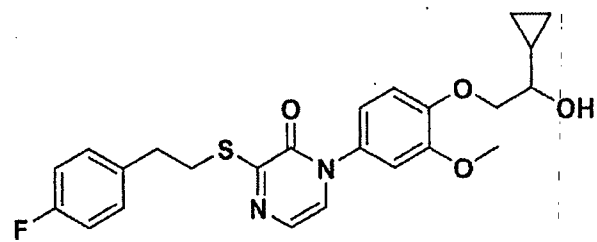
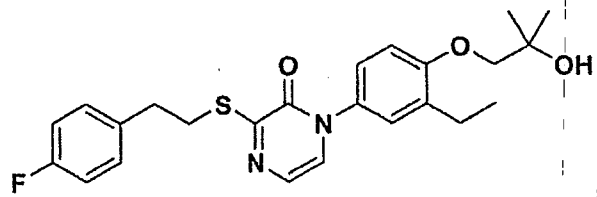
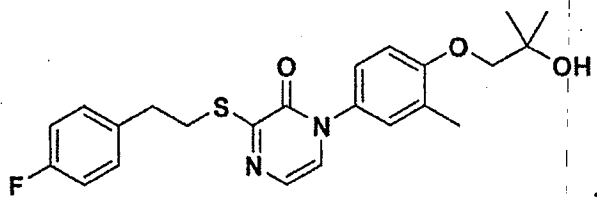
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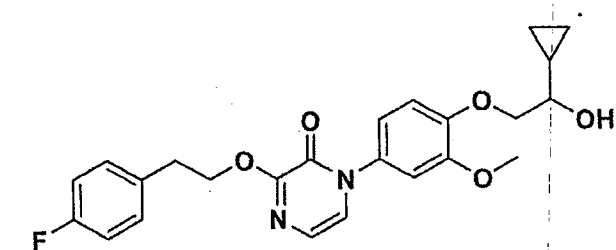
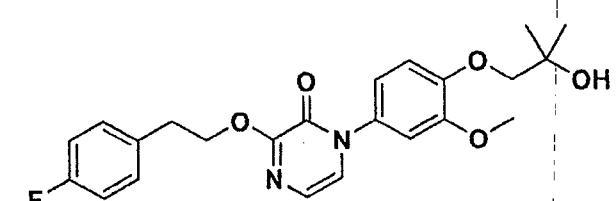
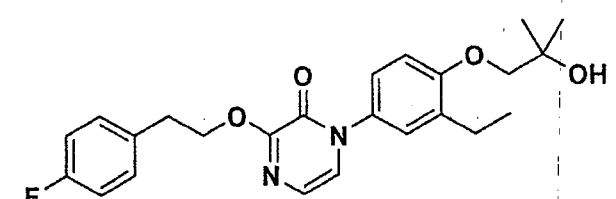
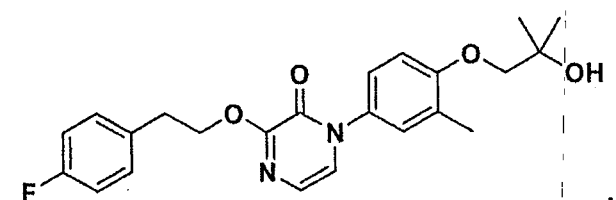
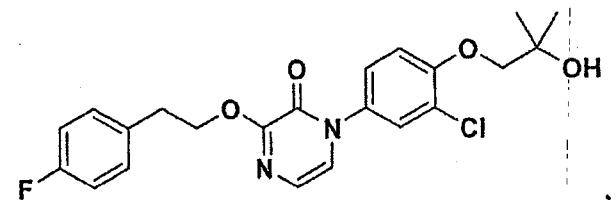
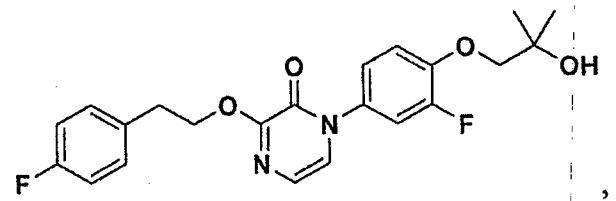
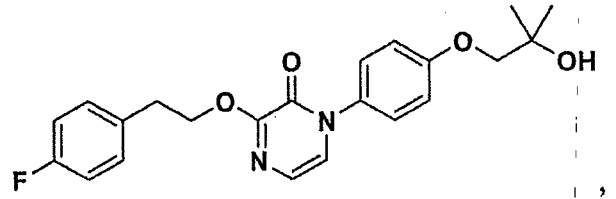
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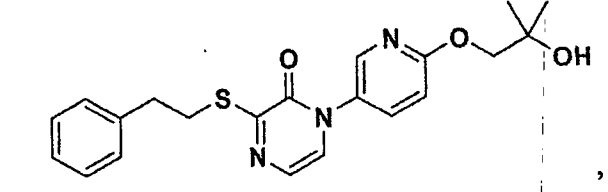
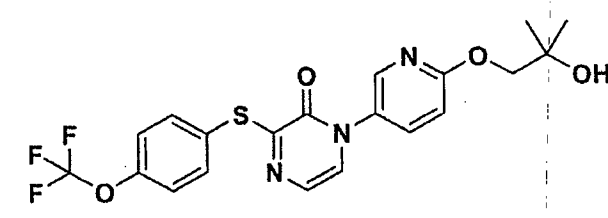
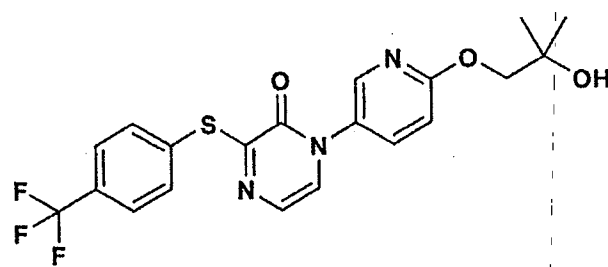
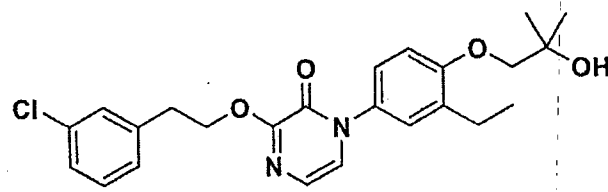
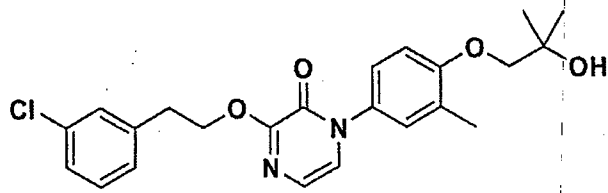
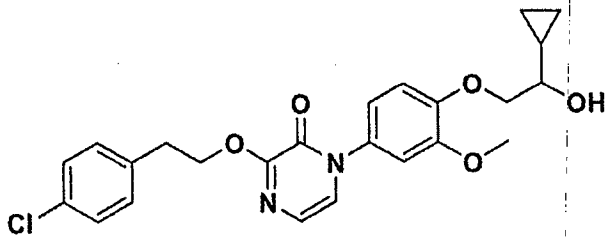
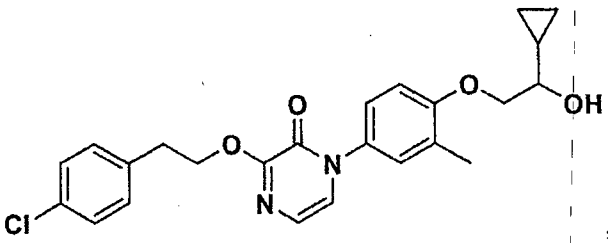
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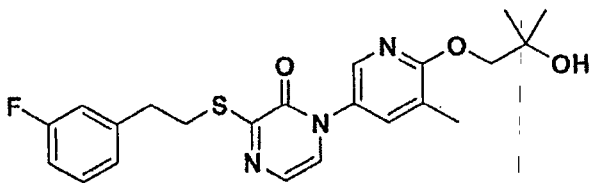
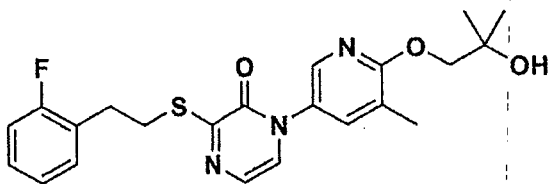
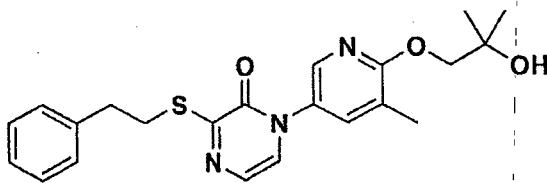
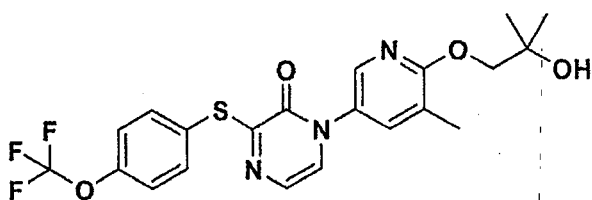
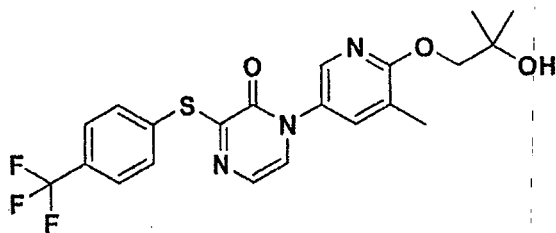
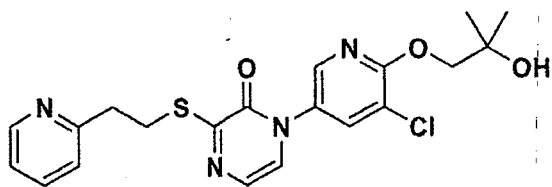
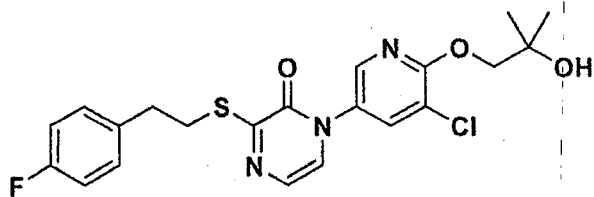
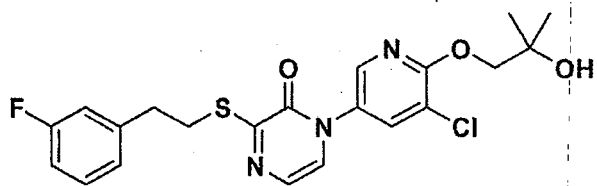
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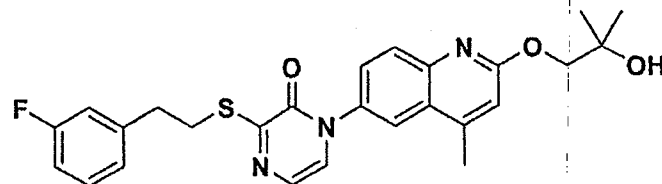
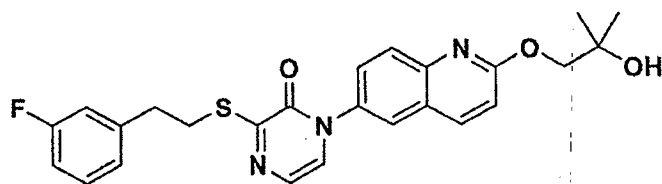
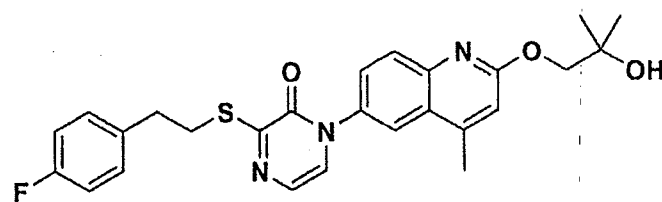
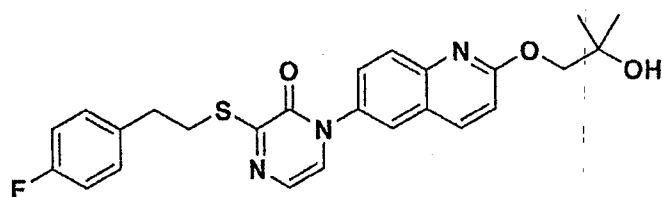
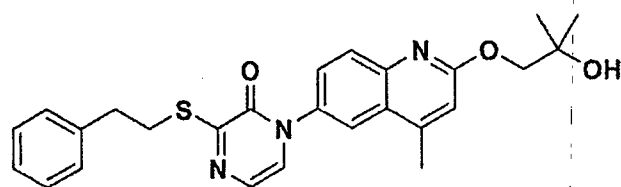
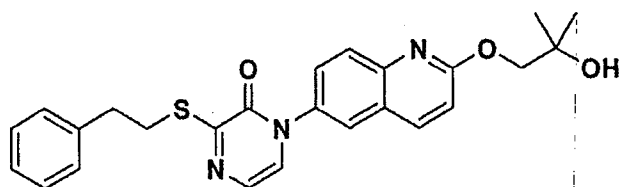
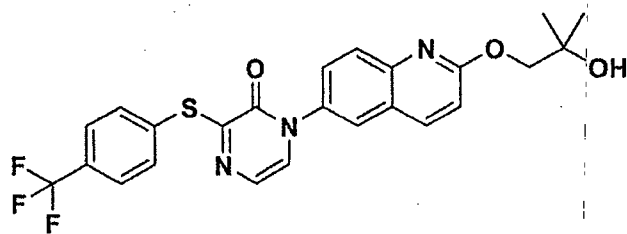
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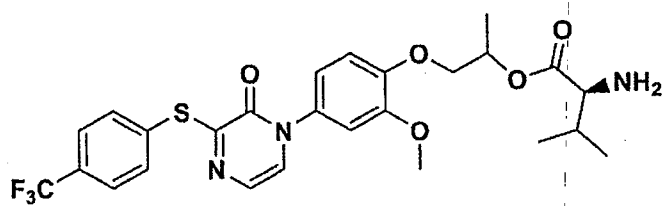
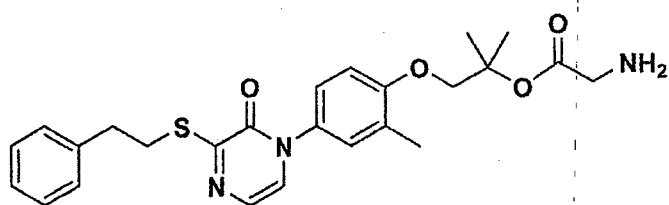
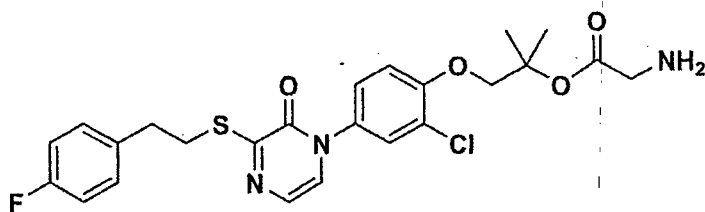
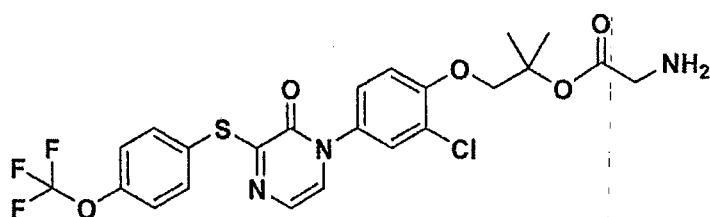
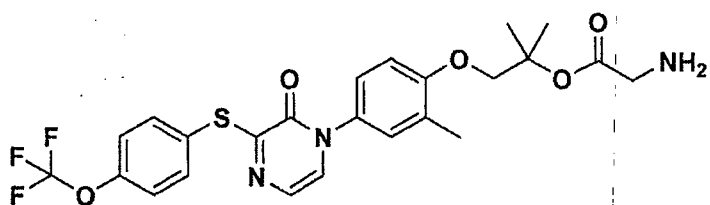
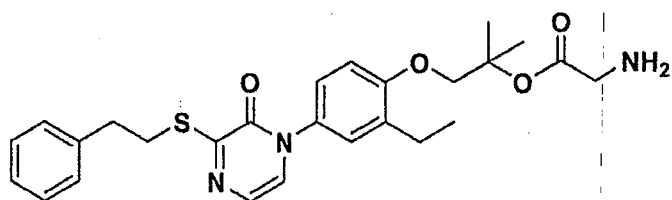
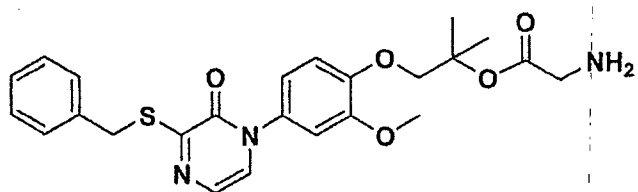
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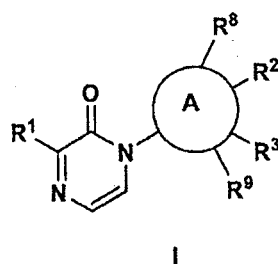


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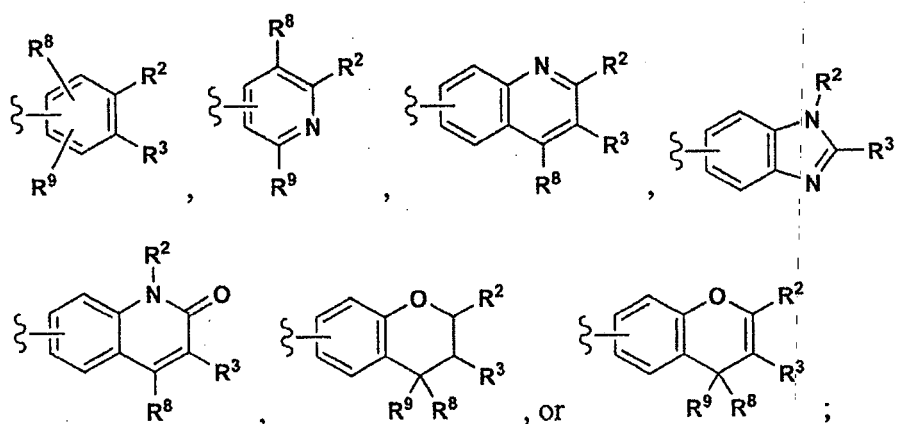
MARKED-UP CLAIMS

WHAT IS CLAIMED IS:

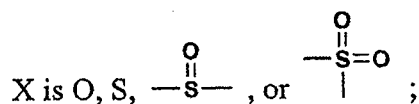
1. A compound of Formula I or a pharmaceutically acceptable salt thereof



wherein



R¹ is Z-Y-X-, wherein



Y is a bond, a 3- to 6-membered cycloalkyl, an alkyl alkylene chain;

and

Z is ~~aryl~~ optionally substituted phenyl or heteroaryl naphthyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolyl;

R² is -E-G-(J)_m, with m being an integer from 1 to 3;

E is O, S or a bond;

G is lower alkyl, phenylalkyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, cycloalkoxy, alkylcycloalkoxy, or cycloalkoxyalkyl, and

MARKED-UP CLAIMS

each J is independently hydrogen, hydroxyl, CN, $-\text{SO}_2\text{R}^7$, $-\text{SR}^7$, $-\text{SOR}^7$, lower alkyl, lower alkoxy, CF_3 , $\text{CF}_3\text{O}-$, $-\text{COOR}^5$, or $-\text{CO-NR}^{5a}\text{R}^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine which may be optionally substituted;

R^5 is H, C_{1-6} alkyl, or cycloalkyl;

R^7 is lower alkyl; and

R^3 is C_{1-6} alkyl, cycloalkyl, C_{1-6} alkoxy, halogen, hydrogen, $-\text{S-C}_{1-6}$ alkyl, CN, CF_3O , or CF_3 ;

with the proviso that where $\textcircled{\text{A}}$ is a phenylene group, E is O or S, and further providing that E-G and R^3 are not identical unsubstituted lower alkoxy groups, and when G is lower alkyl and J is H, R^3 is not hydrogen; and

R^8 and R^9 are each independently hydrogen, halogen, or lower alkyl;

including esters thereof, prodrugs thereof, solvates thereof, and all stereoisomers thereof.

2. Cancel.

3. Cancel.

4. Cancel.

5. Cancel.

6. The compound as defined in Claim 1 wherein

X is O or S;

R^1 is Z-Y-X-;

wherein Y is a bond or an alkylene chain of 1 to 3 atoms;

Z is phenyl, or pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazoliny;

R^2 is -E-G-J;

E is O or S;

G is an alkylene chain or alkylcycloalkyl;

J is H, OH, SO_2R^7 , lower alkyl, lower alkoxy, or CF_3 ;

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MARKED-UP CLAIMS

R^3 is C_{1-6} alkyl, C_{1-6} alkoxy, H, or halo;

R^8 is H or alkyl; and

R^9 is H.

7. Cancel.

8. The compound as defined in Claim 7 1 wherein

R^1 is Z-Y-X-;

X is S;

Y is a bond or alkylene chain;

Z is phenyl or pyridyl;

E is O;

G is an alkylene chain or alkylcycloalkyl;

J is H or OH;

R^3 is H, alkoxy, alkyl, or halo;

R^8 is H or CH_3 ; and

R^9 is H.

9. The compound as defined in Claim 1 wherein

Z is phenyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, or imidazolyl; any of which may either be unsubstituted or substituted with 1, 2 or 3 of amino, halo, C_{1-6} alkyl, C_{1-3} alkylamino, di- C_{1-3} alkylamino, C_{1-3} alkoxy, C_{1-3} thioalkyl, C_{1-3} trifluoroalkoxy, trifluoromethyl, cycloalkyl, cycloalkoxy, or heteroaryl; and

J is hydrogen, hydroxyl, CN, $-SO_2R^7$, $-SR^7$, $-SOR^7$, lower alkyl, lower alkoxy, CF_3 , CF_3O- , $-COOR^5$, or $-CO-NR^{5a}R^6$, wherein R^{5a} and R^6 are each independently selected from the group consisting of H, C_{1-3} alkyl, and cycloalkyl, or R^{5a} and R^6 taken together can be propanediyl, butanediyl or pentanediyl with the N atom to which they are attached to form a 4-, 5- or 6-membered cyclic amine optionally substituted with lower alkyl, lower alkoxy, hydroxyl, CF_3 , or CF_3O .

10. The compound of Claim 1 wherein:

MARKED-UP CLAIMS

Z is

(1) phenyl which is optionally substituted with:

- a) halogen,
- b) alkyl,
- c) alkoxy,
- d) polyhaloalkyl,
- e) polyhaloalkoxy,
- f) amino, alkylamino or dialkylamino,
- g) alkylthio,
- h) OH,
- i) an ester, or
- j) aryl,

(2) heteroaryl which is:

- a) pyridinyl,
- b) pyrazinyl, or
- c) pyrimidinyl,

each of a), b) or c) being optionally substituted with alkyl, polyhaloalkyl, alkoxy, or halogen,

- (3) benzothiazolyl optionally substituted with halo or alkoxy,
- (4) benzoxazolyl optionally substituted with halo,
- (5) benzimidazolyl,
- (6) thiazolyl optionally substituted with aryl or alkyl,
- (7) indanyl,
- (8) quinolinyl optionally substituted with CF₃, or
- (9) imidazolidinyl;

Y is a bond or alkylene;

X is S, O, SO, or SO₂;

J is

- (1) H,
- (2) -CO-NR^{5a}R⁶ wherein R^{5a} and R⁶ together with the N to which they are attached form a pyrrolidinyl ring,
- (3) OH,

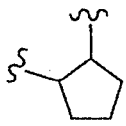
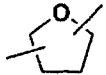
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MARKED-UP CLAIMS

- (4) COOH,
- (5) COOalkyl, or
- (6) SO₂R⁷,

m is 1 or 2;

G is a bond or CH₂, (CH₂)₂, (CH₂)₃, $\begin{array}{c} -CH_2-CH- \\ | \\ CH_3 \end{array}$, $\begin{array}{c} CH_3 \quad CH_3 \\ | \quad | \\ -CH_2-C- \end{array}$,

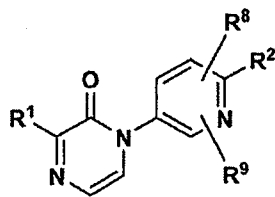
$\begin{array}{c} \sim \\ | \\ -CH_2-CH-CH_2OCH_3 \end{array}$, $\begin{array}{c} | \\ -CH_2-CH-CF_3 \end{array}$, cycloalkyl which is , or
cycloalkoxy which is ;

- E is O;
- R³ is H, alkoxy, hydroxyalkyl, alkyl, halo, or hydroxyalkoxy;
- R⁸ is H, halo or alkyl; and
- R⁹ is H

or a prodrug ester of said compound selected from the group consisting of glycine prodrug esters, valine prodrug esters, and phosphate prodrug esters.

- 11. Cancel.
- 12. The compound of Claim 7, wherein R³ is C₁-C₆ alkoxy or C₁-6 alkyl.
- 13. Cancel.
- 14. Cancel.
- 15. Cancel.
- 16. Cancel.
- 17. Cancel.
- 18. A compound of Formula IB or a pharmaceutically acceptable salt thereof having the structure

MARKED-UP CLAIMS



IB

19. The compound as defined in Claim 18 wherein

R^1 is Z-Y-X- wherein

X is S,

Y is an alkyl chain of 1 to 3 carbons or a bond,

Z is ~~heteroaryl~~ ~~heteroaryl~~ pyridinyl, pyrazinyl, pyrimidinyl, pyridinonyl, benzothiazolyl, benzoxalyl, benzimidazolyl, quinolinyl, thiazolyl, indanyl, imidazolyl or phenyl,

each of which Z is optionally substituted with CF_3 , CF_3O , or halo;

R^2 is -E-G-J wherein

E is O,

G is lower alkyl or alkylcycloalkyl, and

J is OH;

R^3 is alkoxy, alkyl or halo;

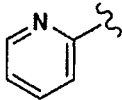
R^8 is H or alkyl; and

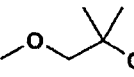
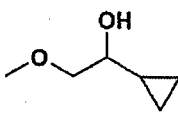
R^9 is H.

20. The compound as defined in Claim 18 wherein

X is S;

Y is a bond or $(CH_2)_2$;

Z is  or  ;

R^2 is E-G-J which is  or  ;

R^3 is H, Cl, CH_3 , or CH_3O ; and

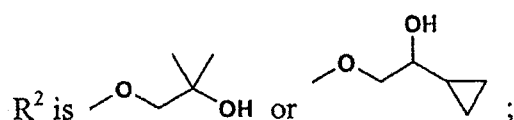
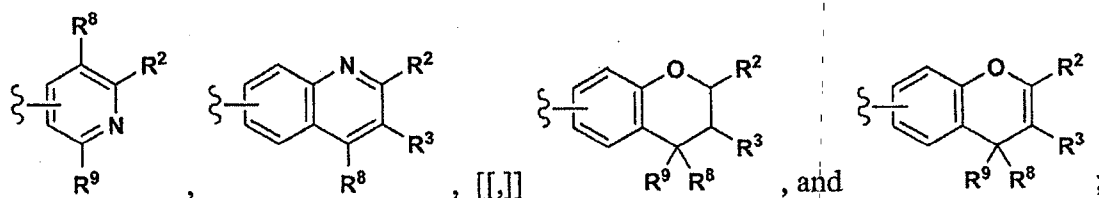
R^8 and R^9 are each H.

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MARKED-UP CLAIMS

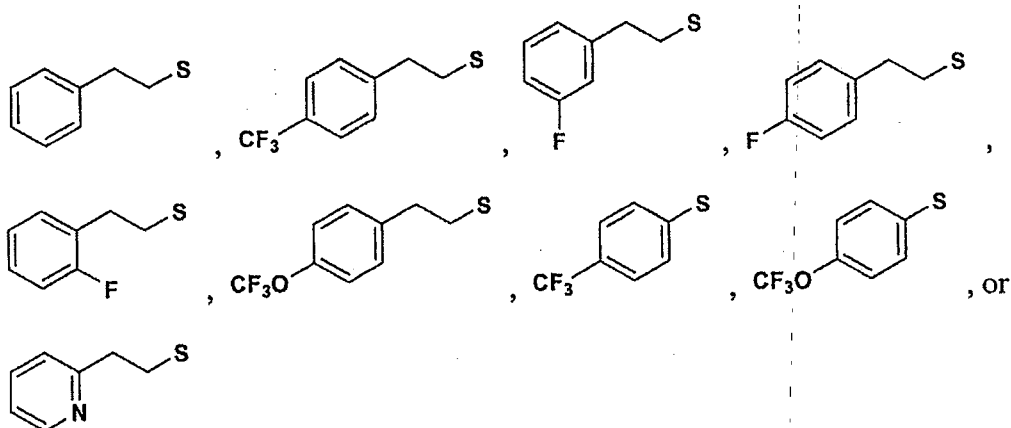
21. The compound of Claim 1 wherein

(A) is selected from the group consisting of;



R³ is methoxy, Cl, H, or methyl; and

R¹ is selected from the group consisting of:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in Claim 1, alone or in combination with at least one additional therapeutic agent, in association with a pharmaceutically acceptable carrier or diluent wherein said additional therapeutic agent is selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to

MARKED-UP CLAIMS

treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; and an anti-tumor agent.

23. A pharmaceutical combination comprising: at least one compound according to claim 1, and at least one additional therapeutic agent selected from the group consisting of an acetyl-cholinesterase inhibitor, a muscarinic receptor-1 agonist, a nicotinic agonist, a glutamic acid receptor (AMPA and NMDA) modulator, a nootropic agent, an agent for Alzheimer's disease, an agent for treatment of Parkinson's disease, anti-hyperlipidemia agent, an anti-obesity agent; anti-diabetic agent, appetite suppressant; cholesterol/lipid-lowering agent, HDL-raising agent, cognition enhancing agent, an agent used to treat neurodegeneration, an agent used to treat respiratory conditions, an agent used to treat bowel disorders, an anti-inflammatory agent; anti-anxiety agent; an anti-depressant; an anti-hypertensive agent; an anti-sleep disorder agent; a cardiac glycoside; or and an anti-tumor agent.

24. Cancel.

25. Cancel.

26. Cancel.

27. Cancel.

28. Cancel.

29. Use of a compound as defined in Claim 1 in the manufacture of a medicament for the treatment of diabetes obesity.

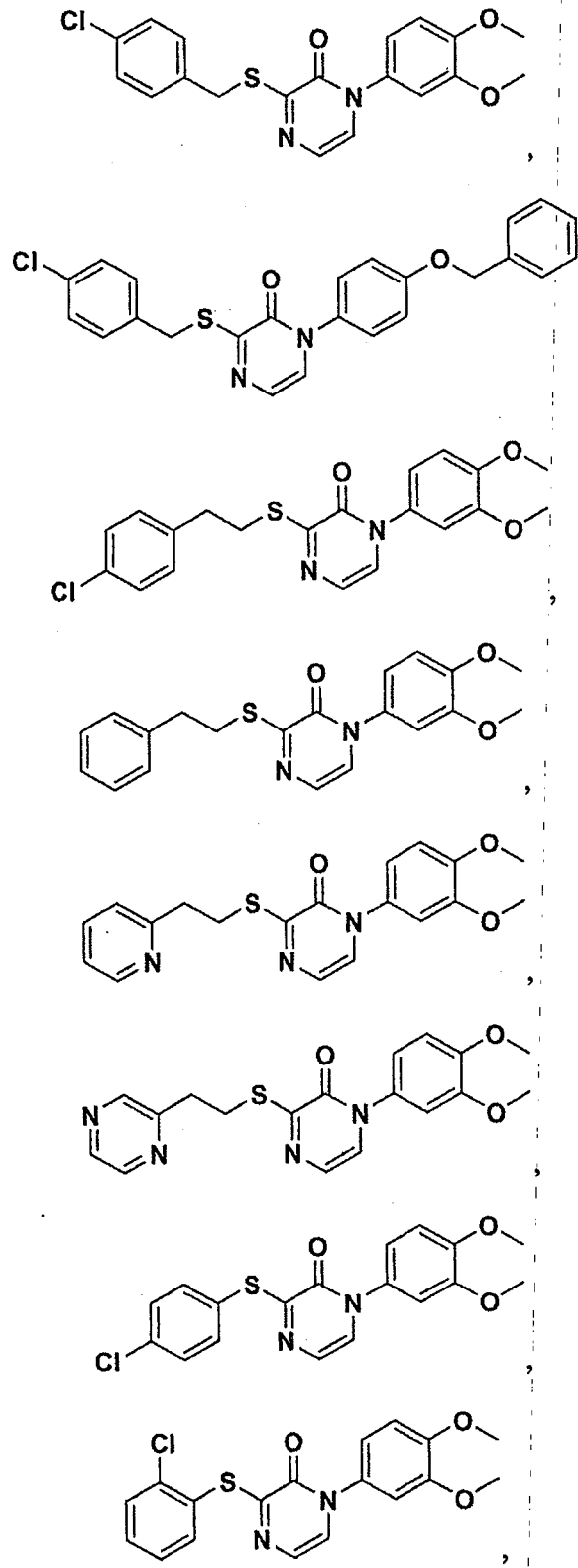
30. Use of a compound as defined in Claim 1 in the manufacture of a medicament for treatment of diabetes., ~~in which such treatment comprises a combination with another therapeutic agent, for concurrent or sequential use, in any order.~~

31. Cancel.

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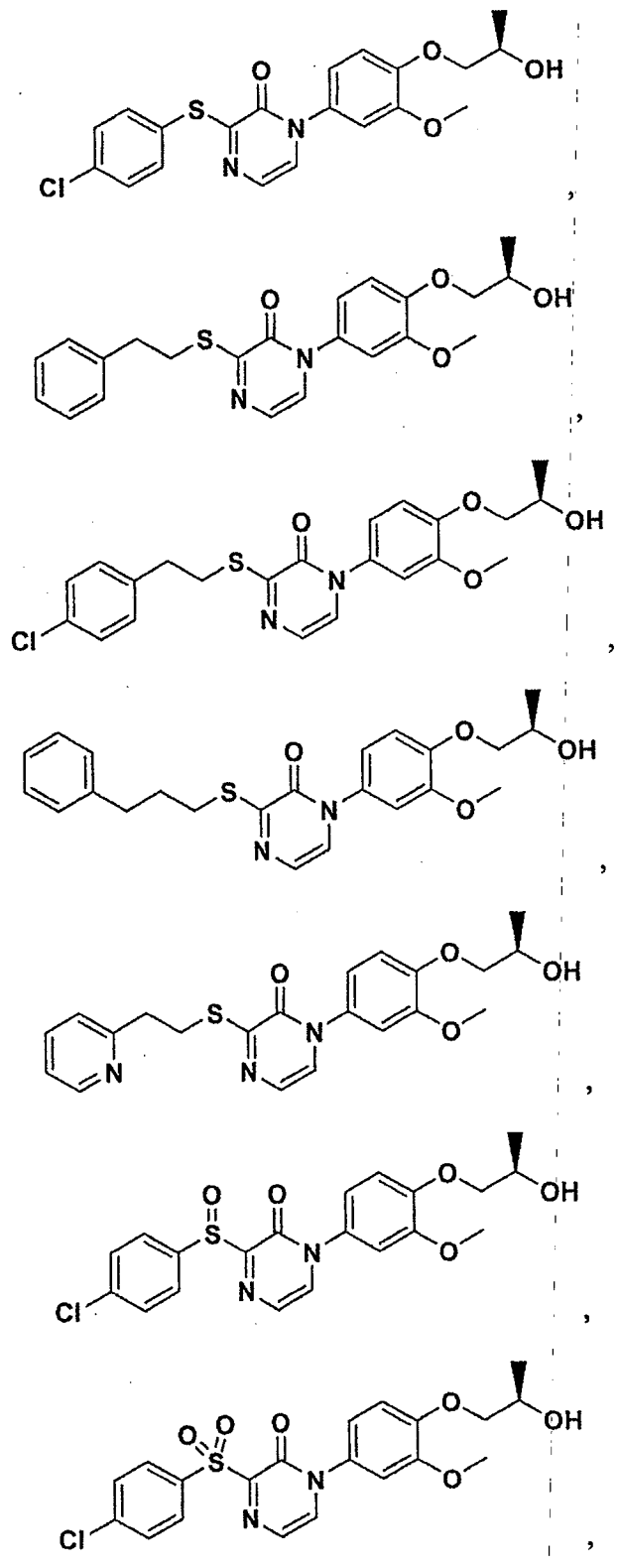
MARKED-UP CLAIMS

32. New. The compound according to claim 1 selected from the group consisting of:



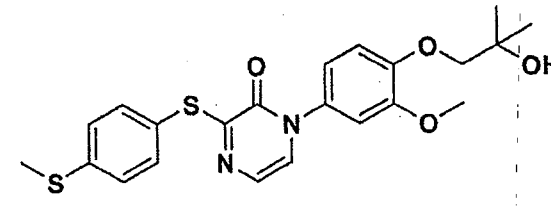
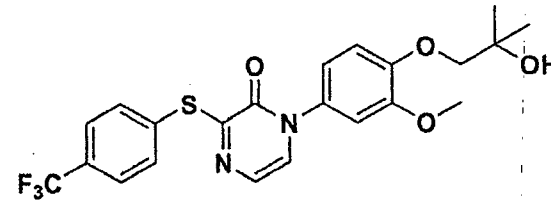
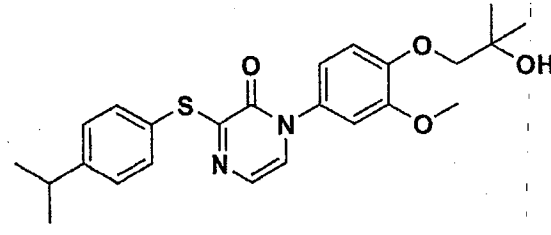
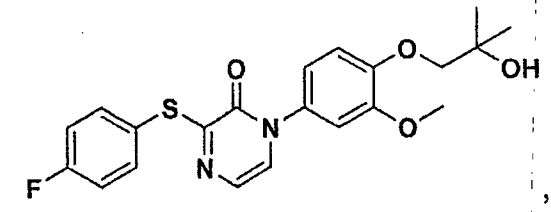
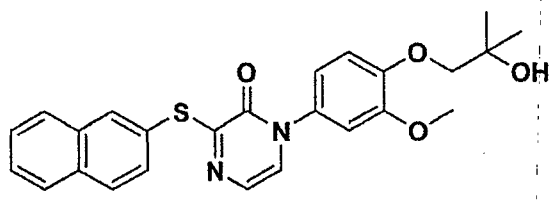
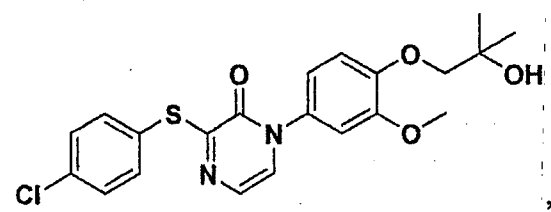
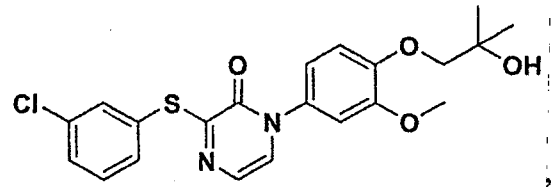
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MARKED-UP CLAIMS

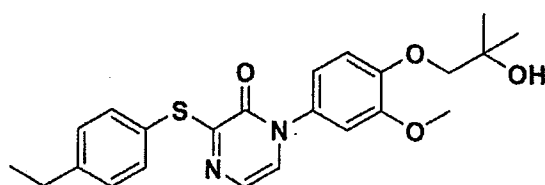
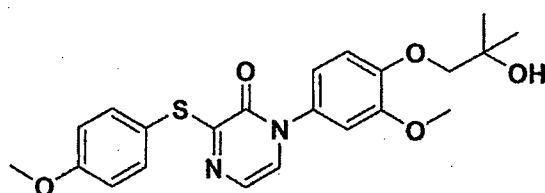
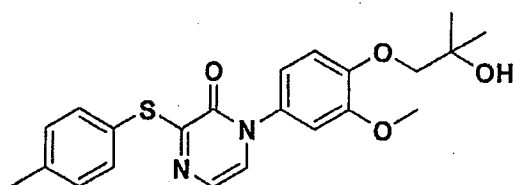
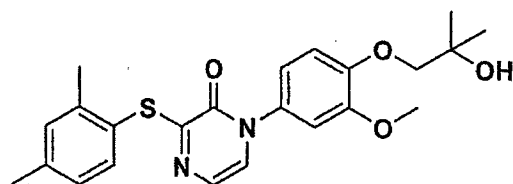
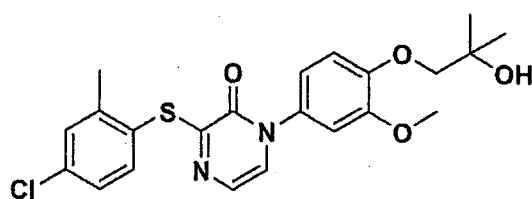
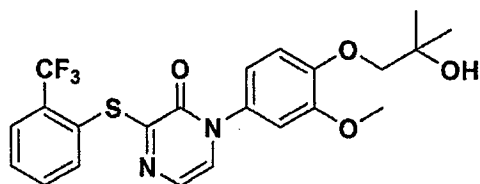
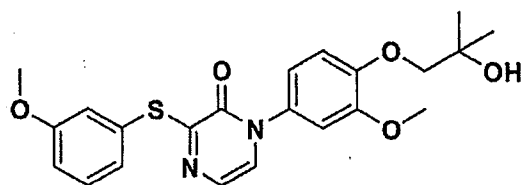
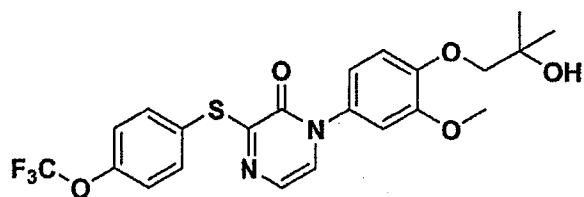


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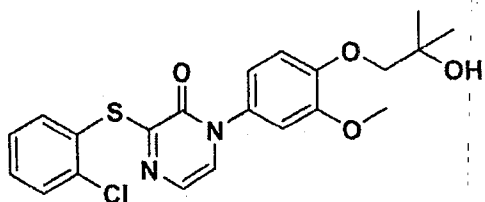
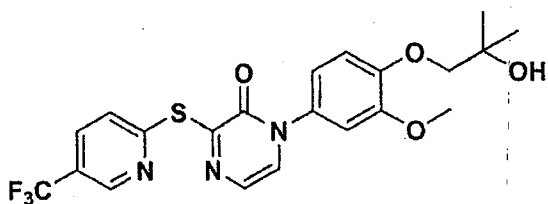
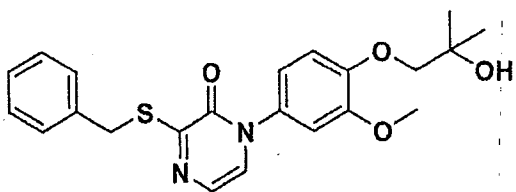
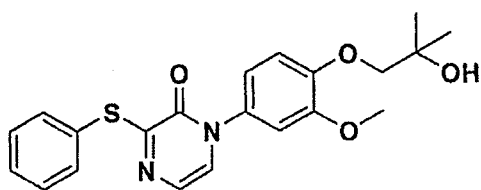
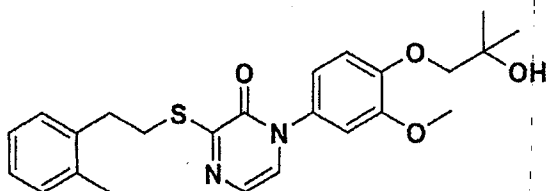
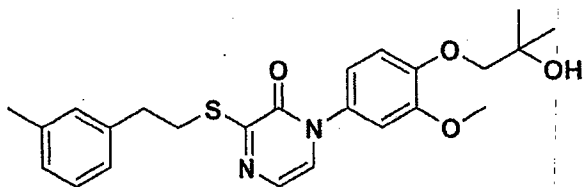
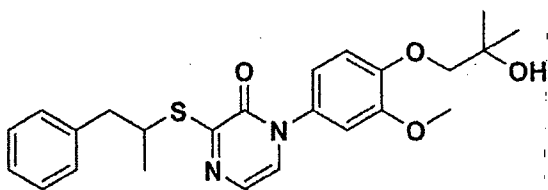


MARKED-UP CLAIMS



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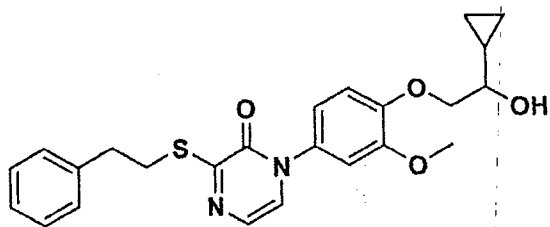
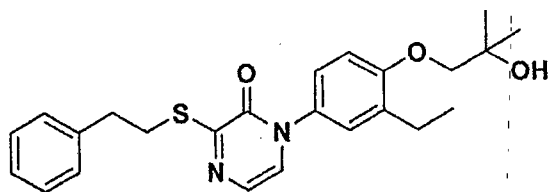
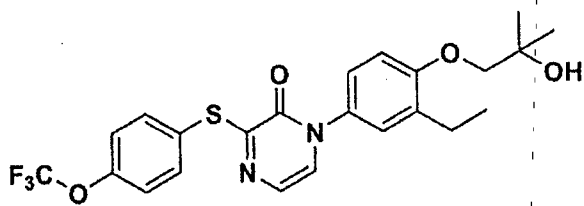
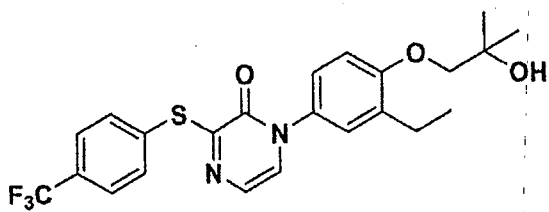
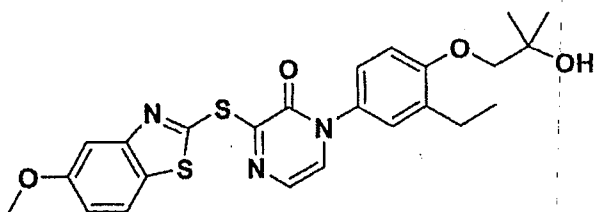
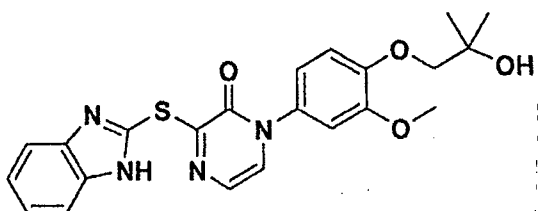
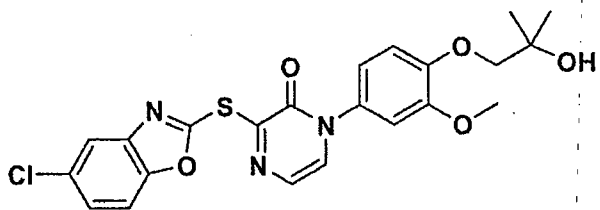
MARKED-UP CLAIMS



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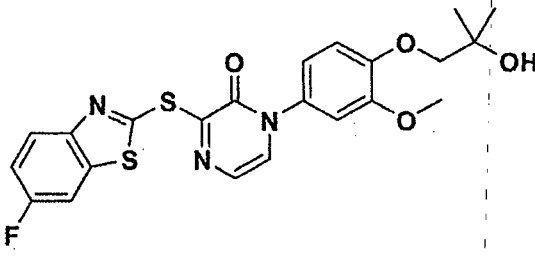
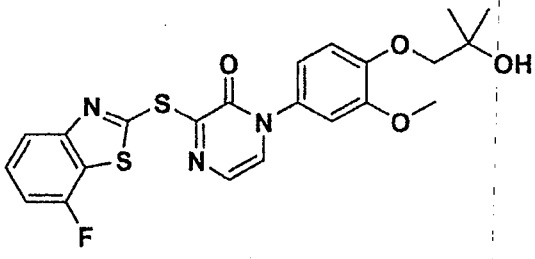
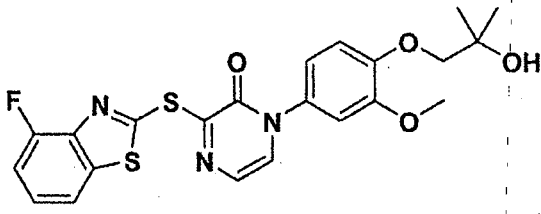
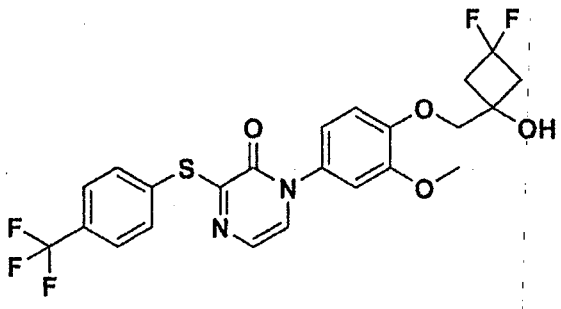
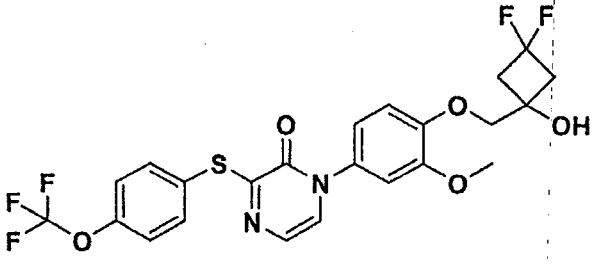
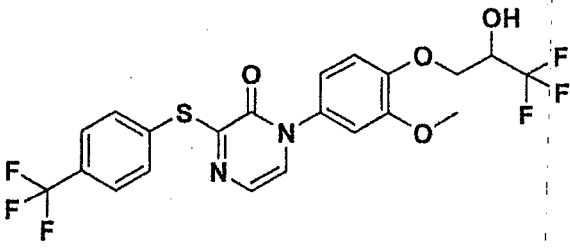
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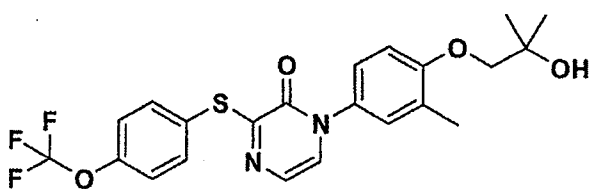
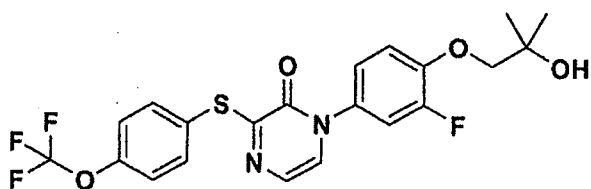
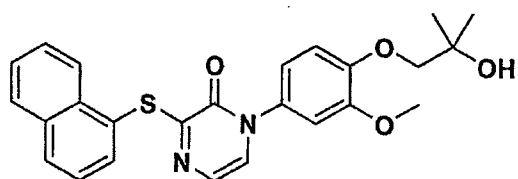
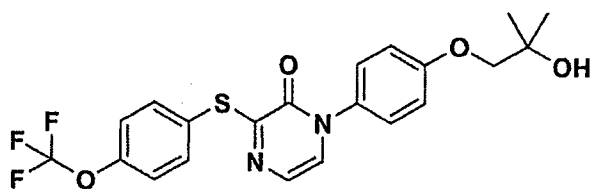
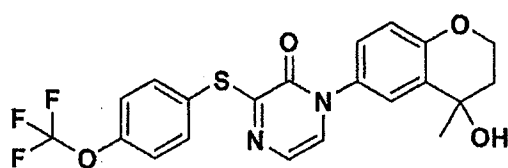
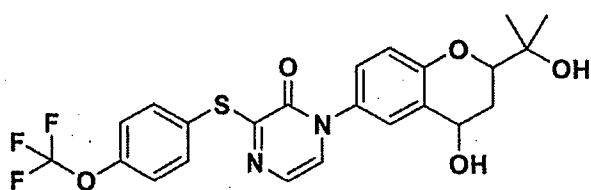
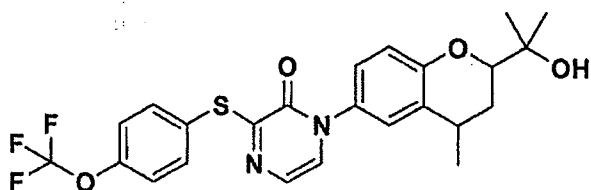
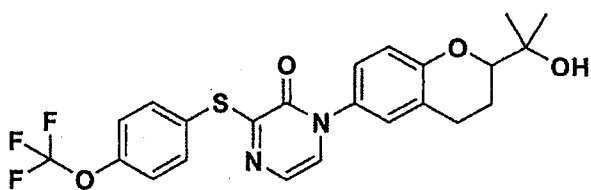


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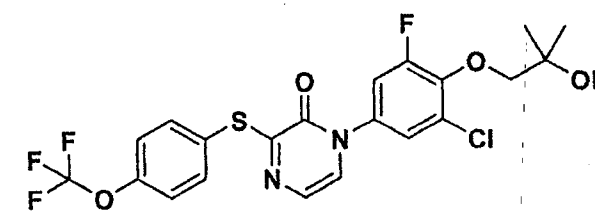
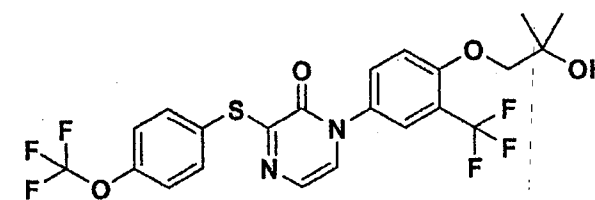
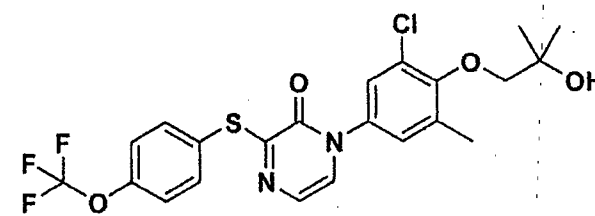
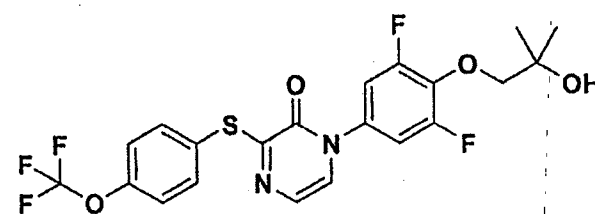
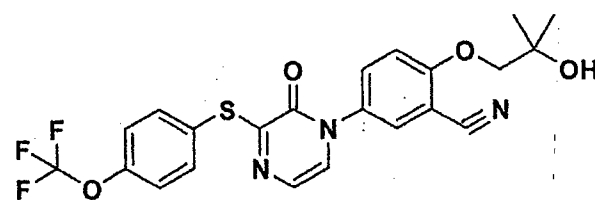
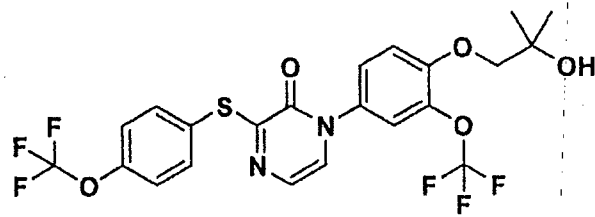
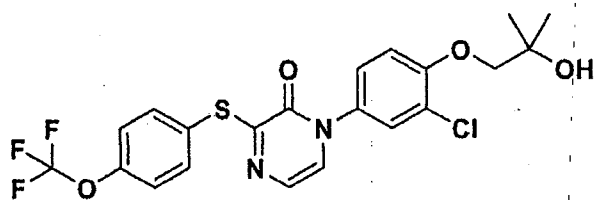


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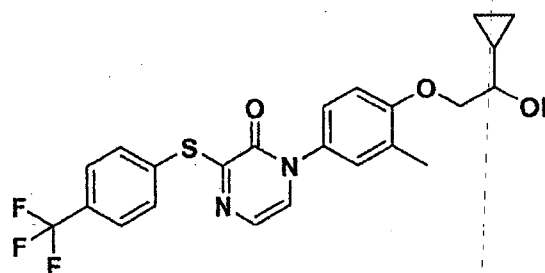
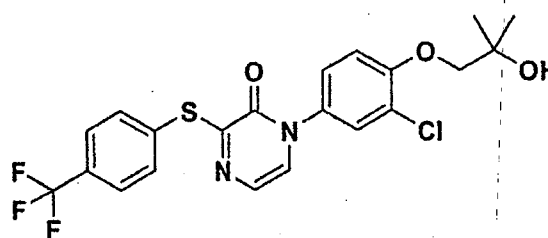
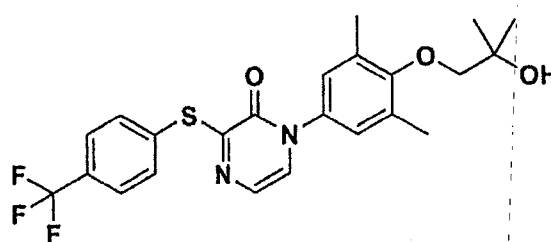
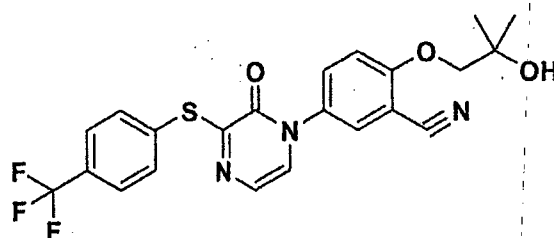
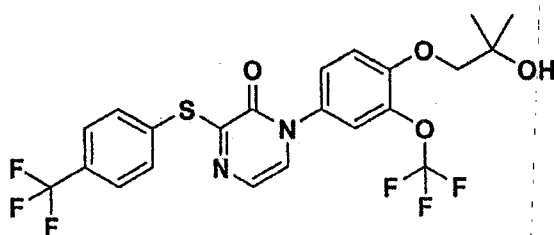
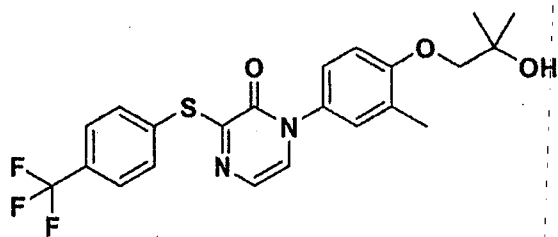
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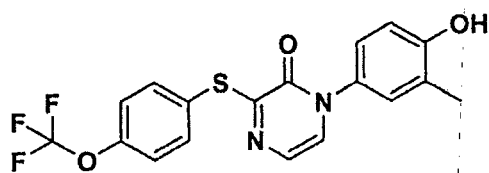
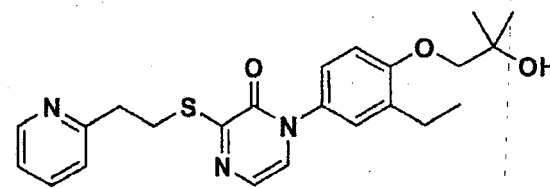
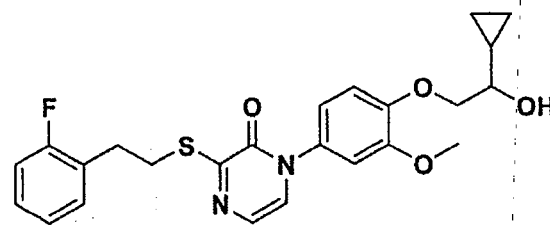
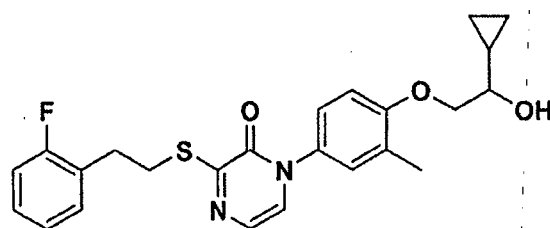
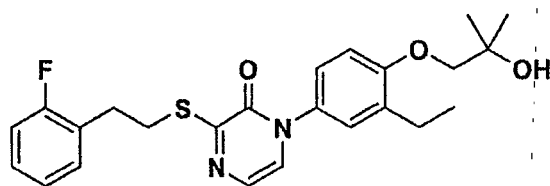
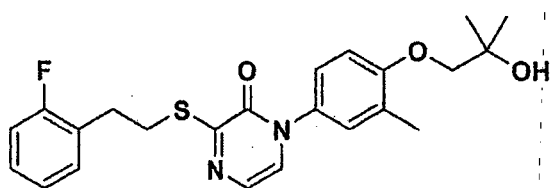
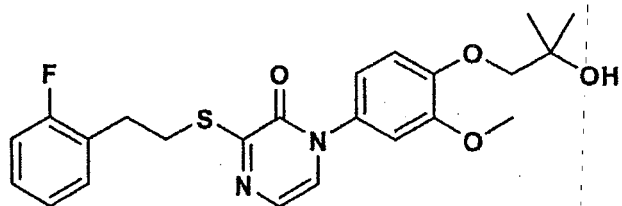
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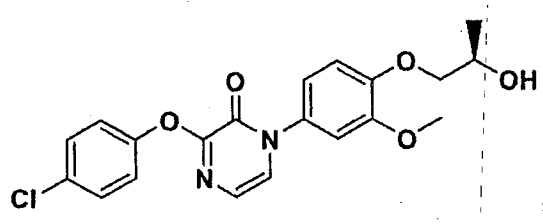
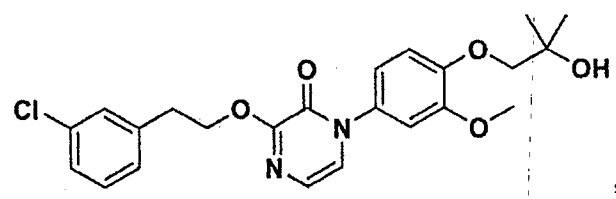
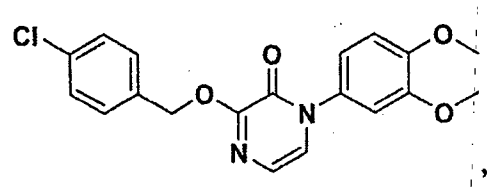
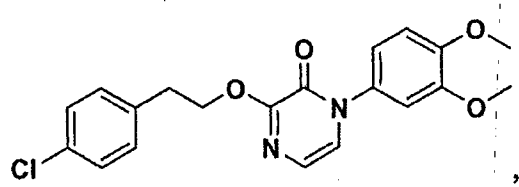
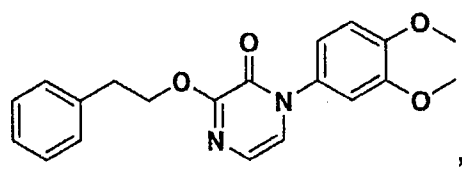
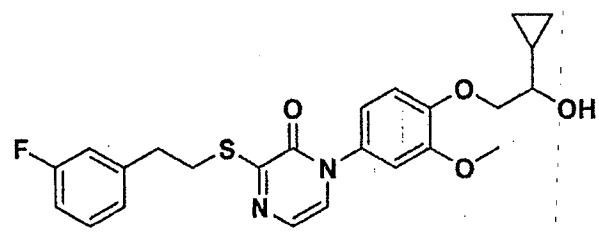
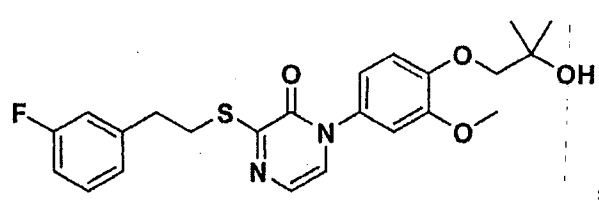
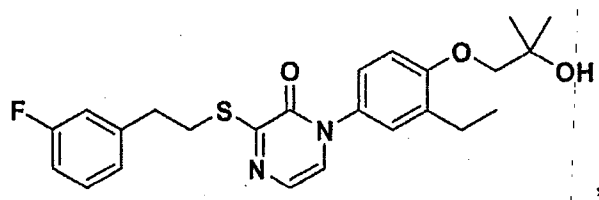
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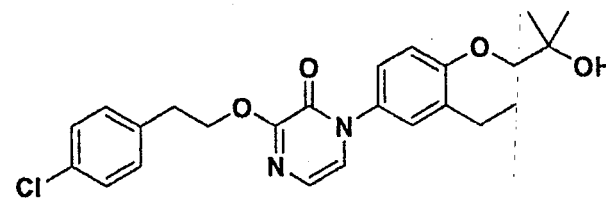
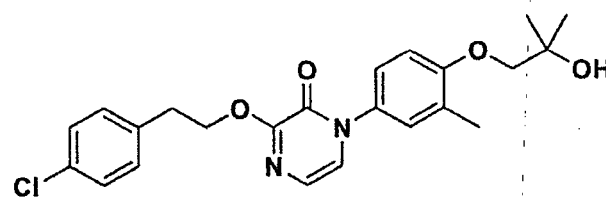
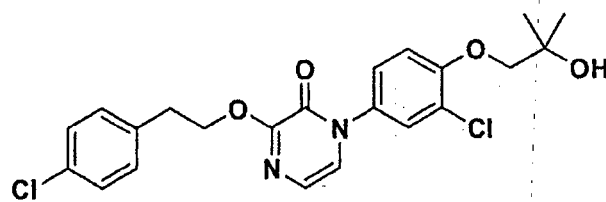
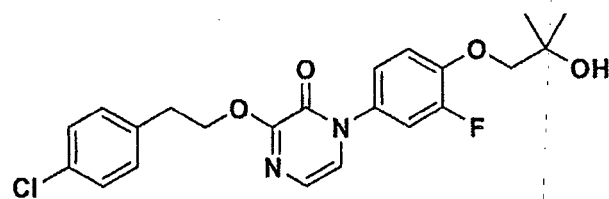
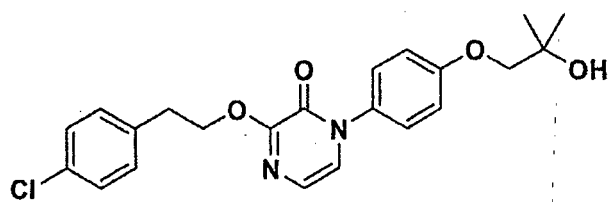
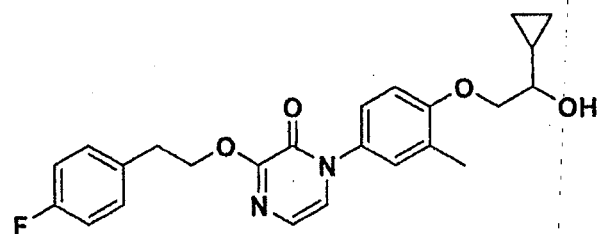
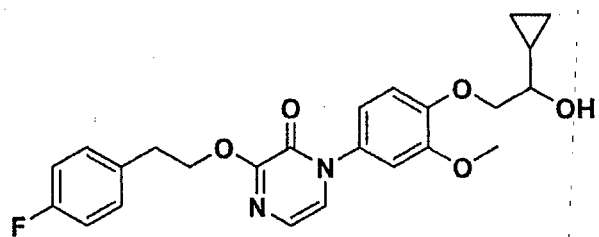


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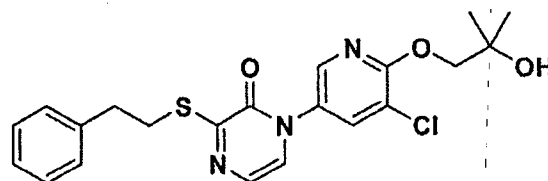
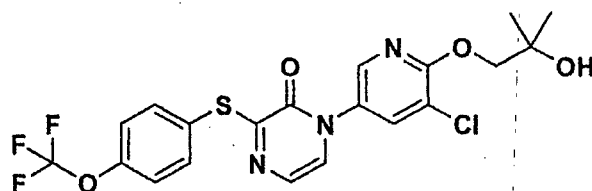
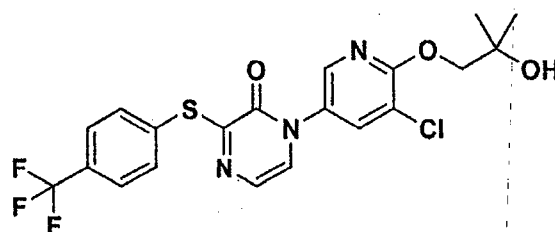
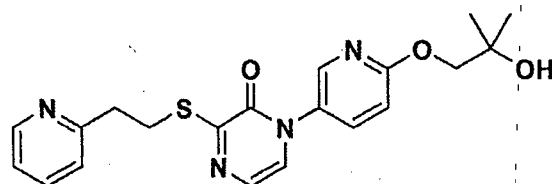
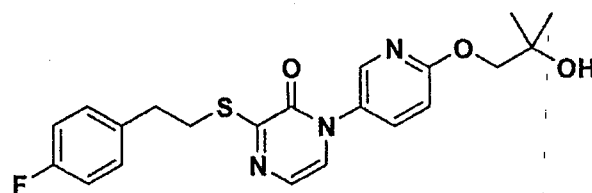
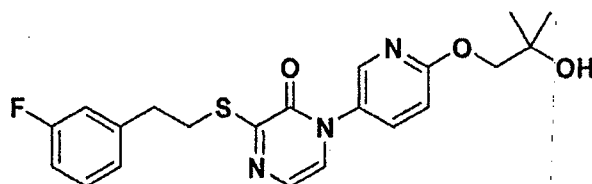
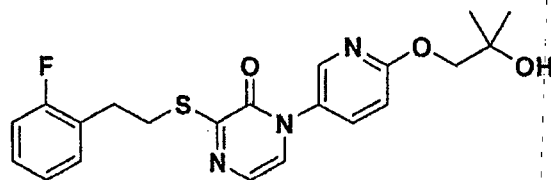
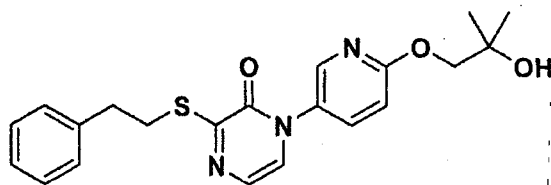
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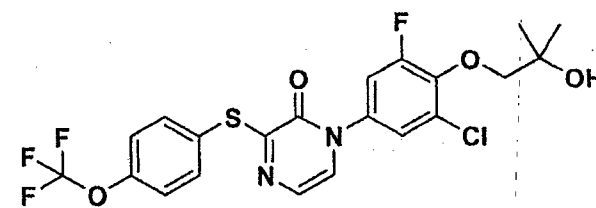
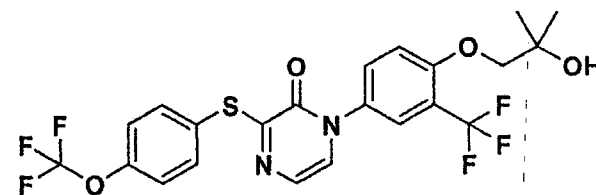
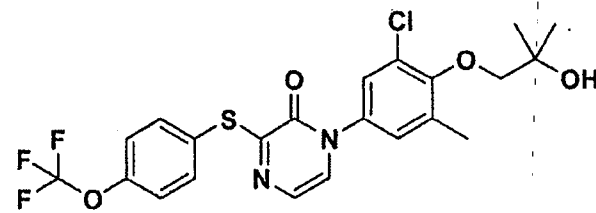
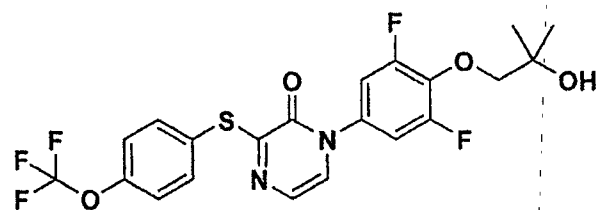
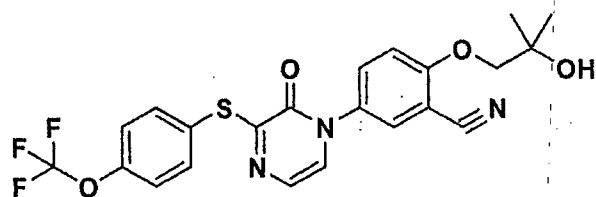
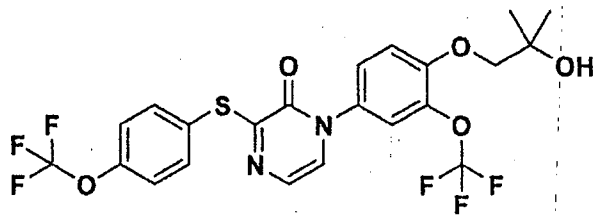
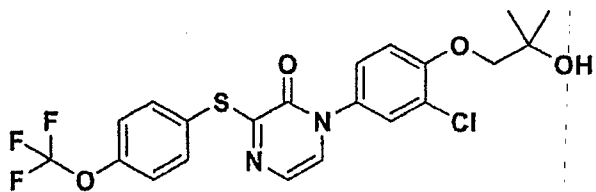
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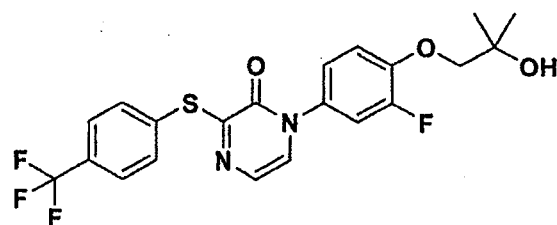
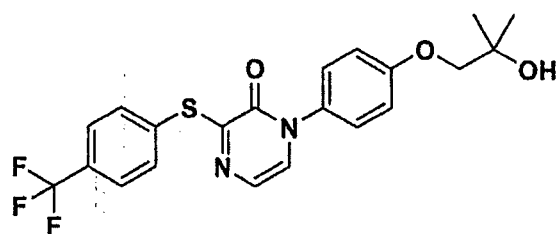
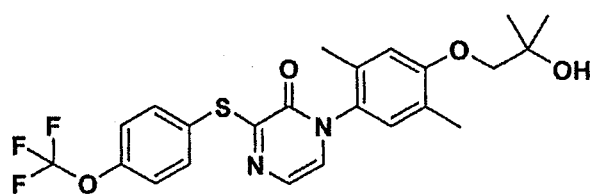
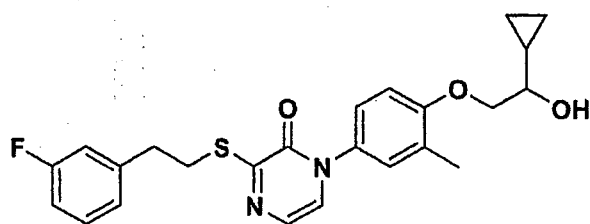
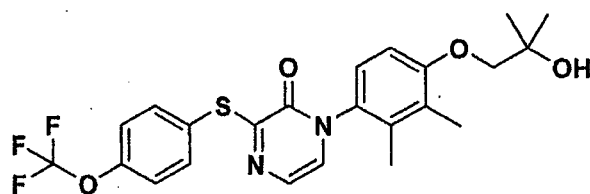
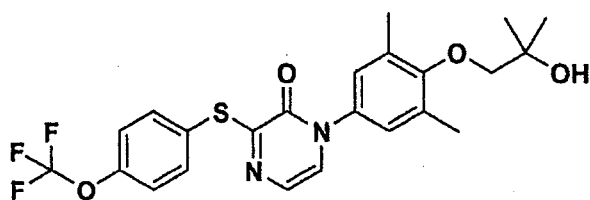
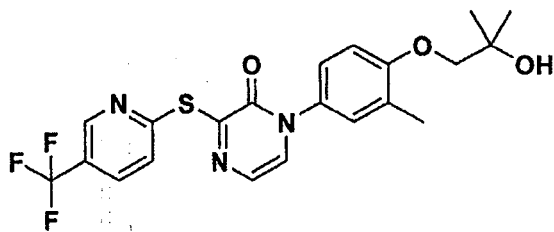


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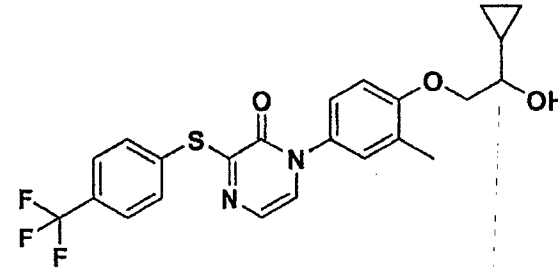
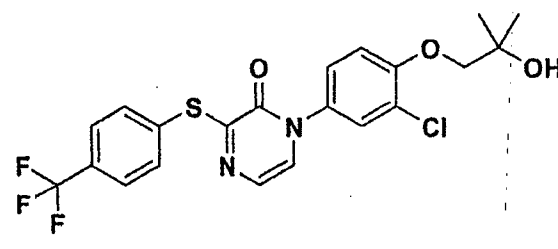
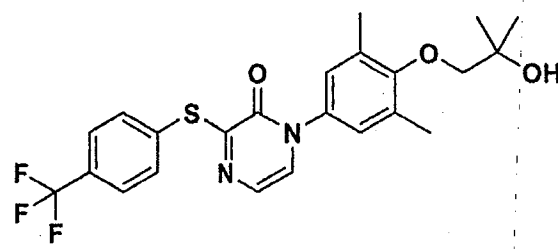
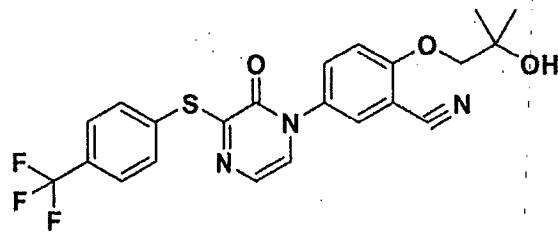
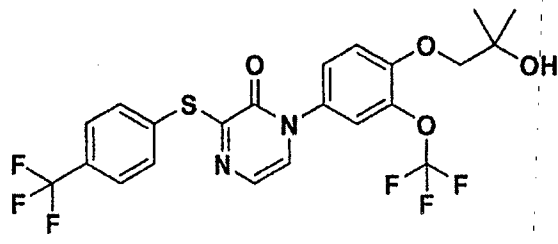
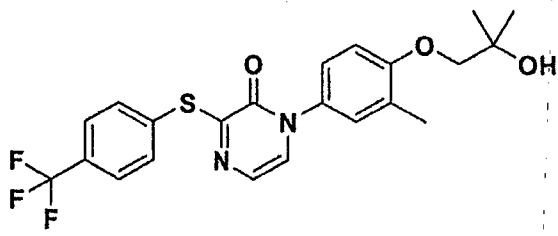


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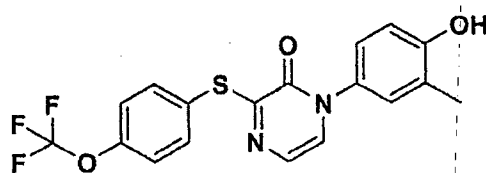
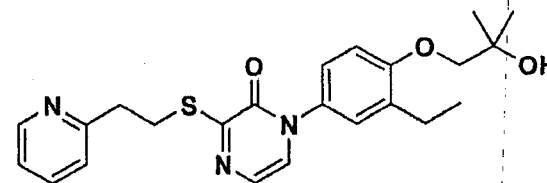
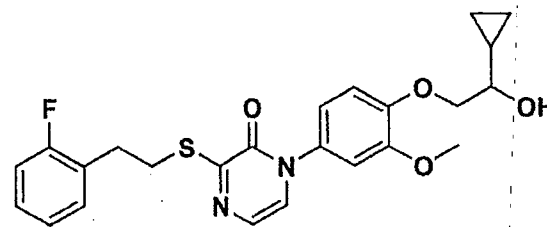
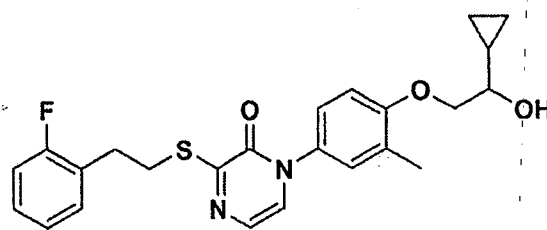
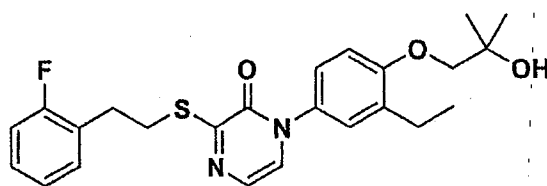
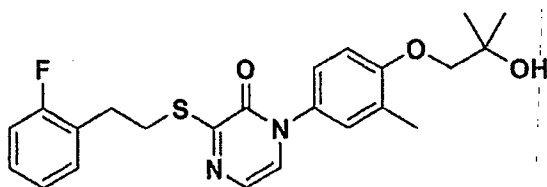
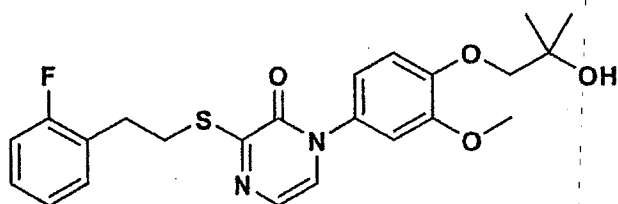
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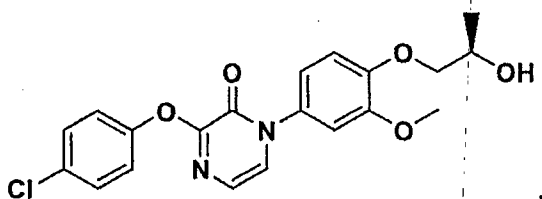
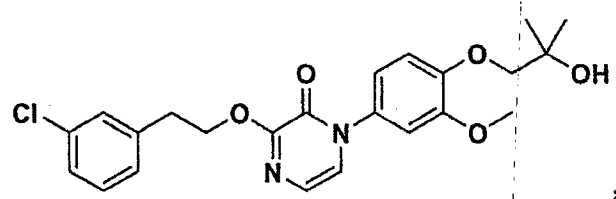
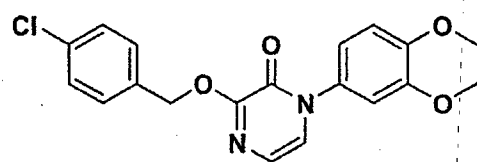
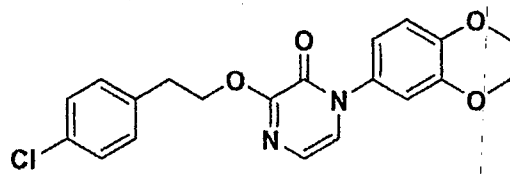
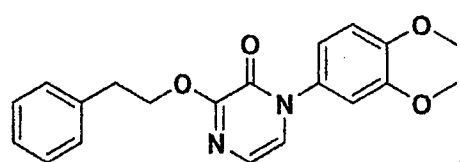
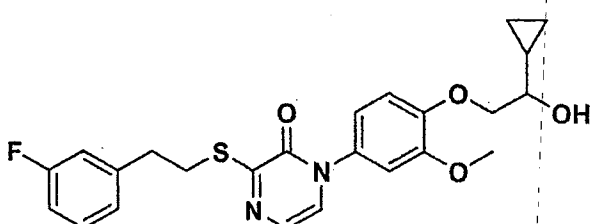
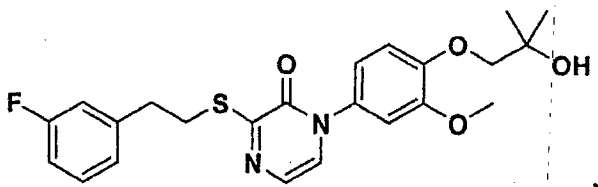
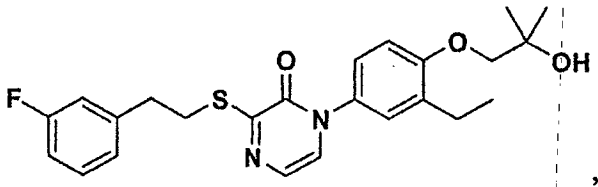


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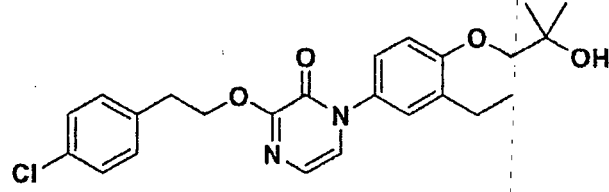
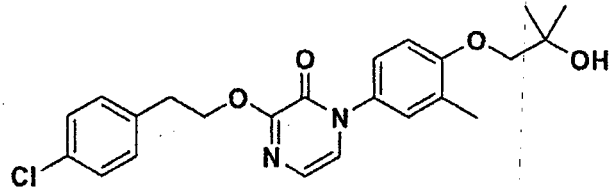
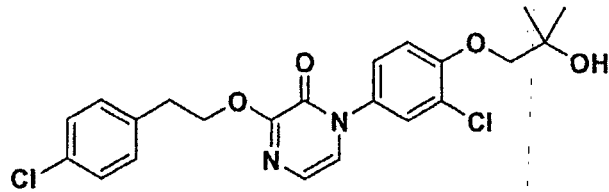
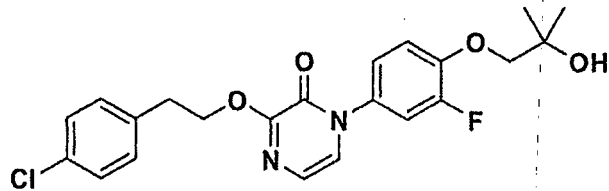
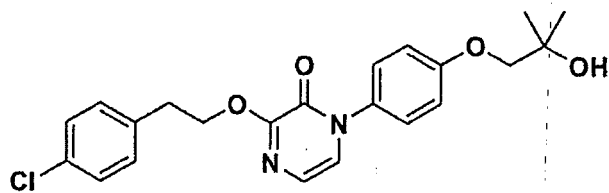
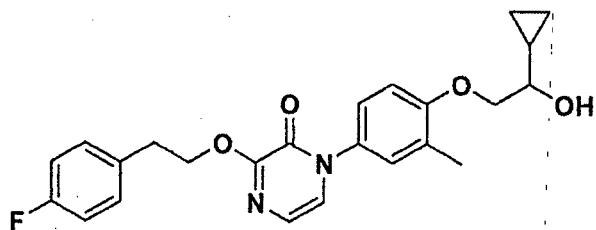
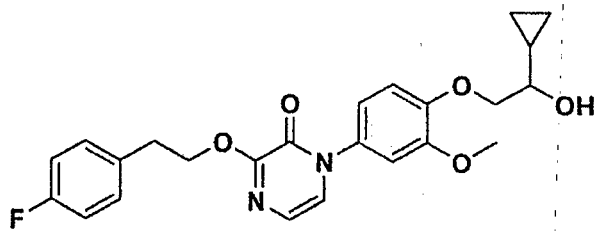
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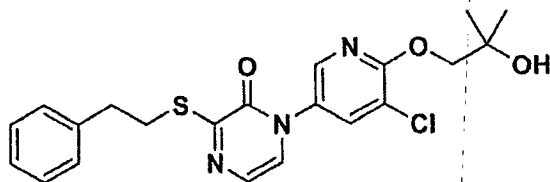
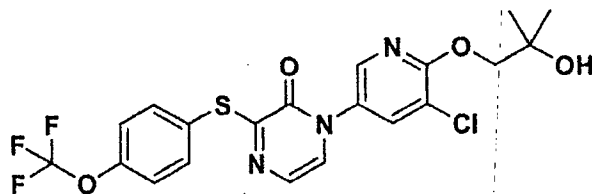
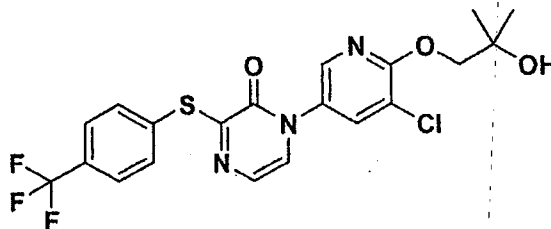
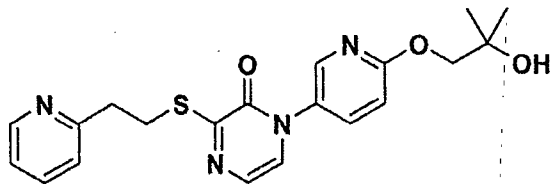
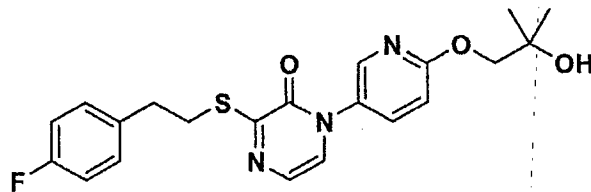
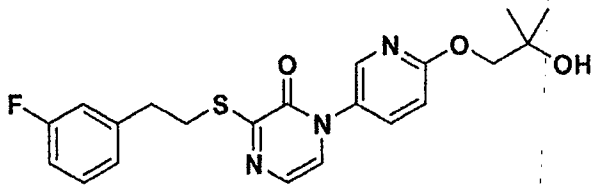
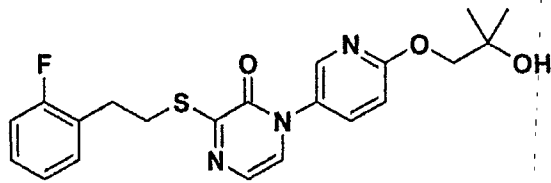
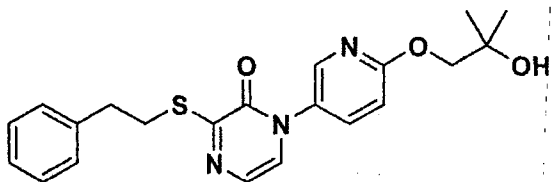
MARKED-UP CLAIMS



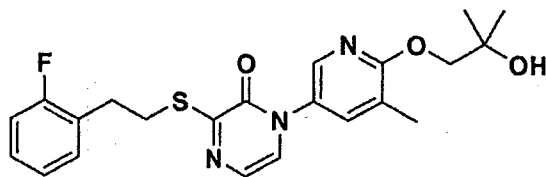
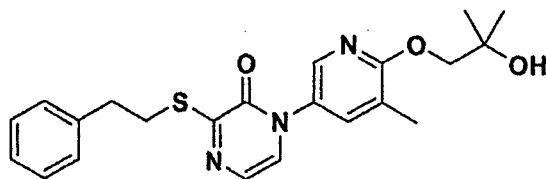
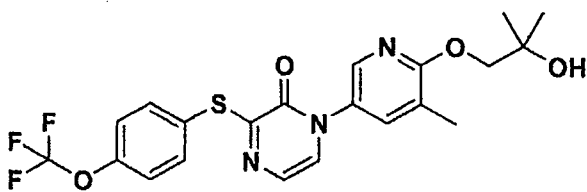
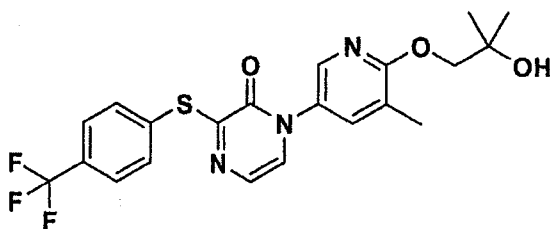
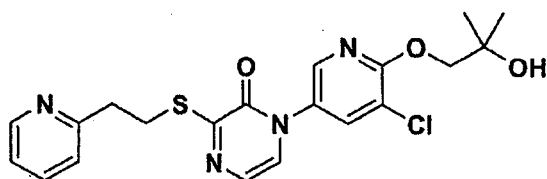
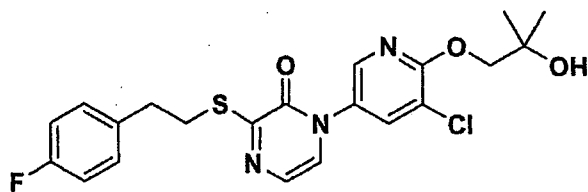
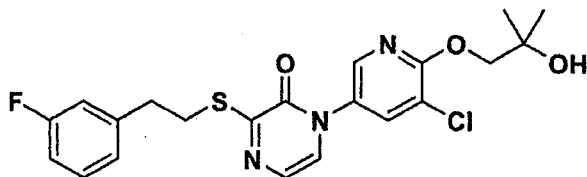
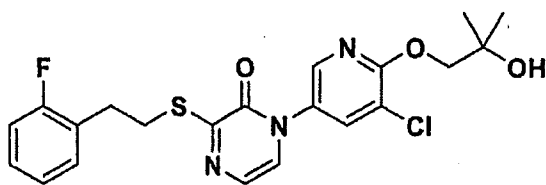
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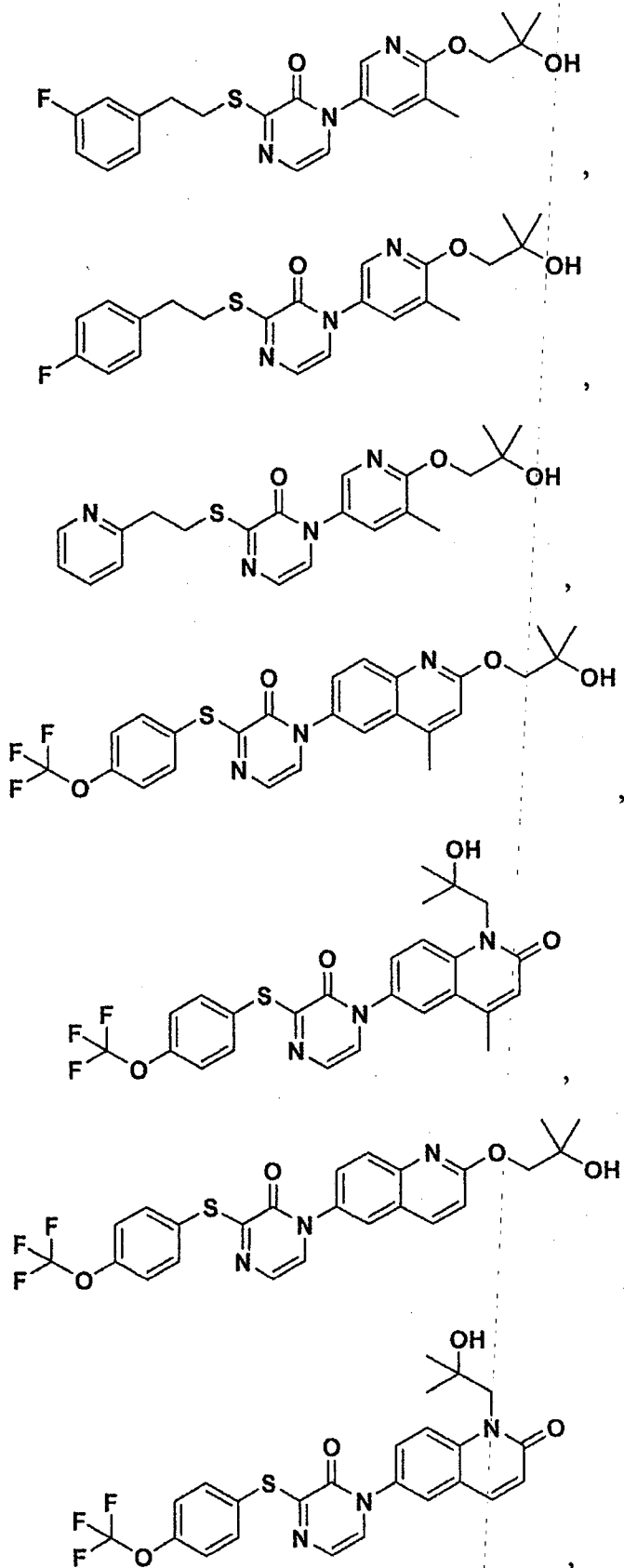


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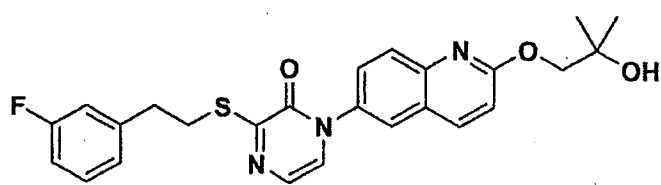
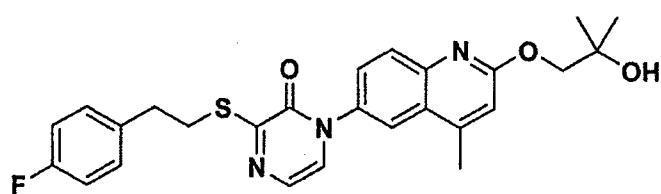
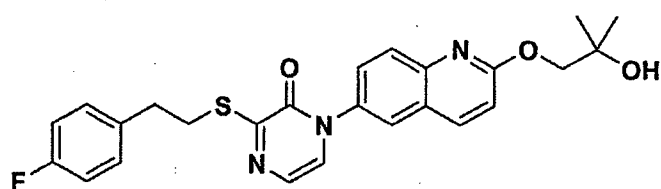
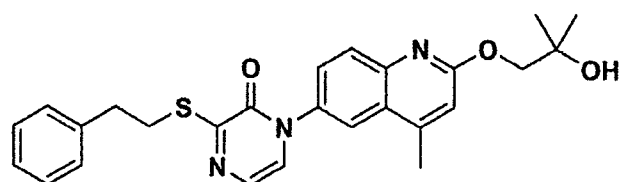
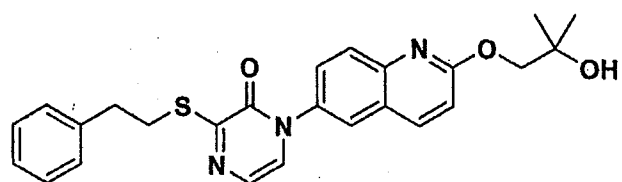
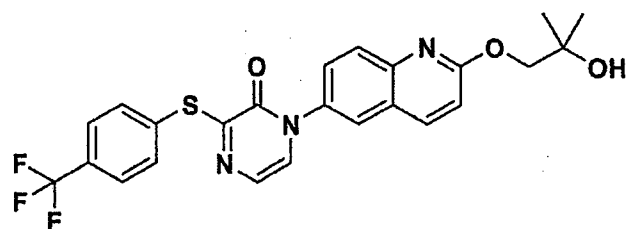
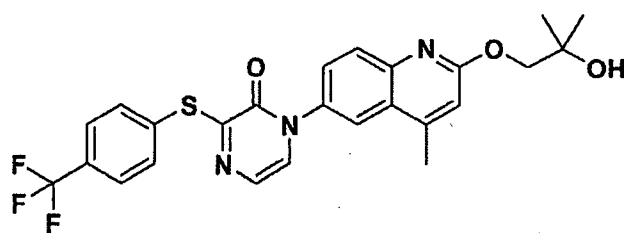


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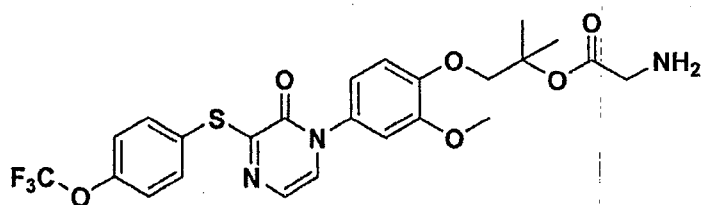
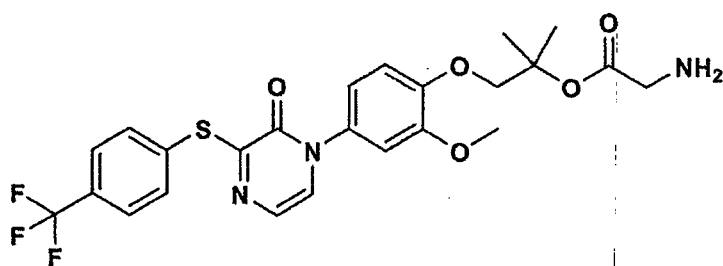
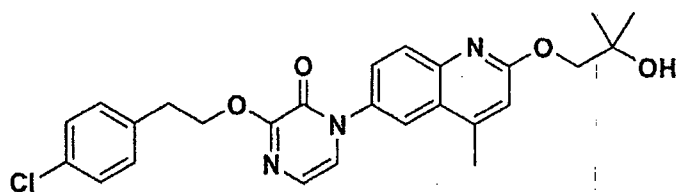
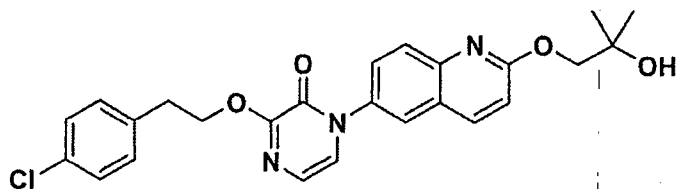
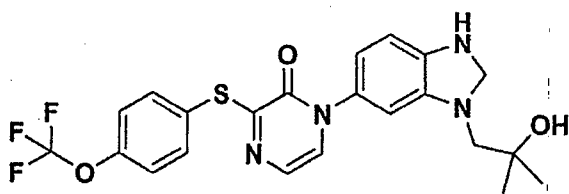
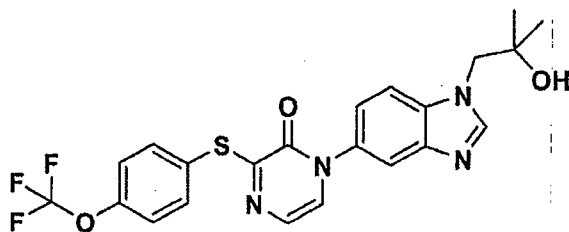
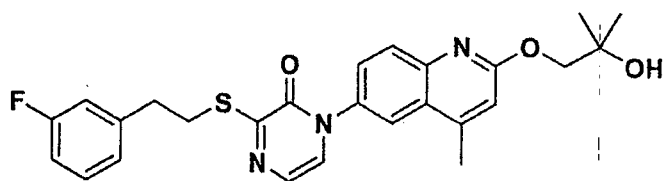


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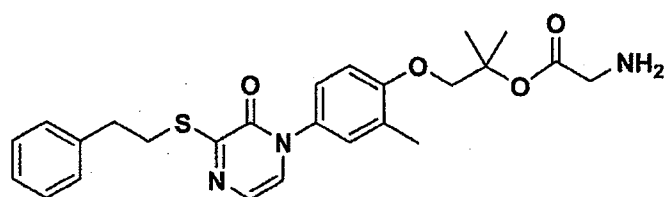
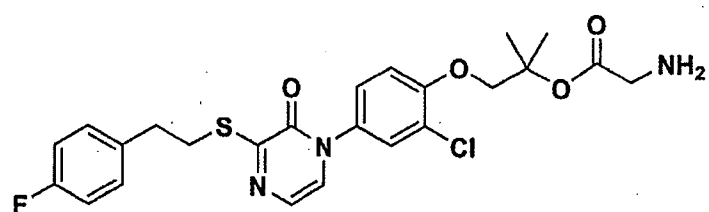
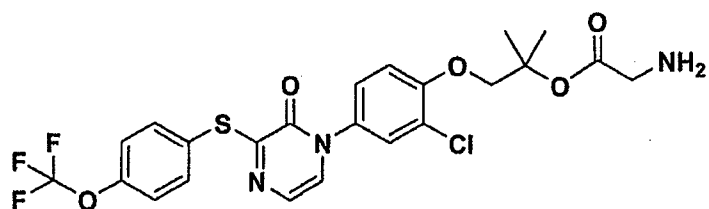
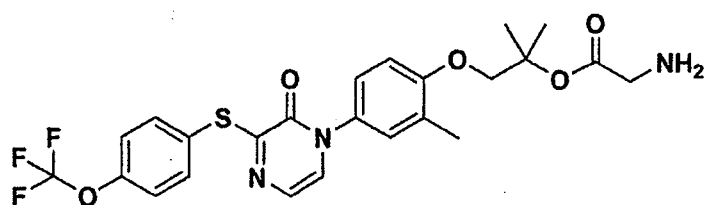
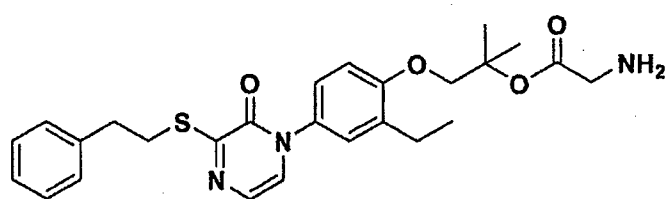
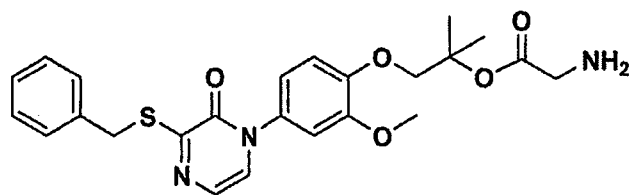
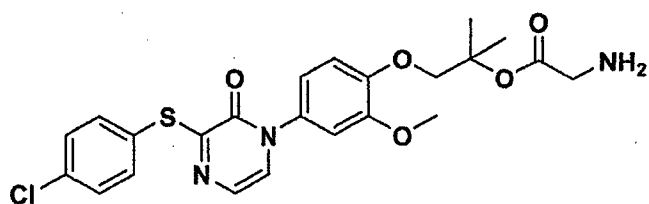


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