

## Respuesta a Requerimientos

|   |                                                                                                                                                                                                                                                                                                 |                                                            |                                                                                  |                            |                                           |
|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------|-------------------------------------------|
| 1 | <b>Datos del Solicitante / Titular</b>                                                                                                                                                                                                                                                          |                                                            |                                                                                  |                            |                                           |
|   | <b>Nombre:</b>                                                                                                                                                                                                                                                                                  | CONNEXIOS LIFE SCIENCE PVT LTD                             | <b>Dirección Electrónica:</b>                                                    | tobos@tobos.com.co         |                                           |
|   | <b>Dirección:</b>                                                                                                                                                                                                                                                                               | No. 49, Shilpa Vidya, First Main Road, J P Nagar 3rd Phase | <b>Domicilio/País de constitución:</b>                                           | INDIA - BANGLA - BANGALORE |                                           |
|   | <b>Identificación:</b><br><br><input type="checkbox"/> CEDULA DE CIUDADANIA<br><input checked="" type="checkbox"/> EMPRESA EXTRANJERA<br><input type="checkbox"/> PASAPORTE<br><br><input type="checkbox"/> CEDULA DE EXTRANJERIA<br><input type="checkbox"/> NIT<br><br><b>Número:</b> 936438- |                                                            |                                                                                  |                            |                                           |
| 2 | <b>Dato de la Creación</b>                                                                                                                                                                                                                                                                      |                                                            |                                                                                  |                            |                                           |
|   | <b>Identificación de la Creación</b>                                                                                                                                                                                                                                                            | <b>No. de Certificado</b>                                  | <b>Vigencia</b>                                                                  | <b>No. de Expediente</b>   | <b>Tipo Trámite</b>                       |
|   | DERIVADOS DE AMIDA CÍCLICA COMO INHIBIDORES DE 11-BETA-HIDROXIESTEROIDE DESHIDROGENASA Y LOS USOS DE LOS MISMOS                                                                                                                                                                                 | 000000                                                     |                                                                                  | 14158010                   | PCT-PATENTE DE INVENCION CAPITULOS I Y II |
| 3 | <b>Texto de la Comunicación</b>                                                                                                                                                                                                                                                                 |                                                            | Adjunto respuesta a examen contenido en el oficio 11066 y anexos a la respuesta. |                            |                                           |

|                                            |               |
|--------------------------------------------|---------------|
| 4                                          | <b>Anexos</b> |
| <input checked="" type="checkbox"/> Anexos |               |

Doctor

JOSE LUIS SALAZAR LÓPEZ

Director Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO -SIC-

E.

S.

D.

TOBOS ABOGADOS S.A.S.

Calle 151 No. 18A-34

Oficina 409 Bogotá D.C.

C.P. 110131166 - Colombia

NIT 900.367.556-3

Tel +57 1 812 3335

Cel +57 320 334 0887

Fax +57 1 812 3335

<http://www.tobos.com.co>

[tobos@tobos.com.co](mailto:tobos@tobos.com.co)

Referencia: Solicitud de patente de invención No. 14-158010

Solicitante: Connexios Life Science PVT. LTD.

Título del Invento: “Derivados de amida cíclica como inhibidores

de 11-beta-hidroxiesteroide deshidrogenasa y los usos de los mismos” (antiguo título)

“Derivados de Amida Cíclica como Inhibidores de 11-Beta- Hidroxiesteroide Deshidrogenasa” (nuevo título)

**RESPUESTA AL EXAMEN DE FONDO NOTIFICADO POR FIJACIÓN EN LISTA NO. 38 OFICIO NO.**

**11066**

ANDREA TOBOS MATEUS, mayor de edad y vecina de Bogotá D.C., identificada como aparece al pie de mi firma, en mi condición de apoderada de la sociedad Connexios Life Science PVT. LTD., domiciliada en Bangalore, India, respetuosamente me dirijo a usted con el fin de dar respuesta al examen de fondo dentro del término de plazo.

**1. EXCEPCIÓN A LA PATENTABILIDAD**

1.1. El Examinador considera que las reivindicaciones 11 a 18 no son patentables porque se refieren a un método de tratamiento.

1.2. Las reivindicaciones 11 a 18 se han eliminado de la solicitud.

**2. REIVINDICACIONES RELATIVAS A UN USO O AUN SEGUNDO USO**

2.1. El Examinador considera que las reivindicaciones 19 a 26 no son patentables porque se refieren a un uso.

2.2. Las reivindicaciones 19 a 26 se han eliminado de la solicitud.

### **3. TITULO**

3.1. El Examinador considera que el título de la invención es ambiguo y no refleja la materia que se pretende proteger.

3.2. Se propone un nuevo título como sigue:

“Derivados de Amida Cíclica como Inhibidores de 11-Beta- Hidroxiesteroide Deshidrogenasa”

En caso de que este título no sea aceptado por el Examinador, le agradezco cambiar el título al que el Examinador considere debe ser el título de la invención.

### **4. REIVINDICACIÓN 1**

4.1. El Examinador objeta la claridad y concisión de la reivindicación 1 por cuanto incluye el término “opcionalmente sustituido”.

4.2. En respuesta a la observación del Examinador, aunque la solicitante no está necesariamente de acuerdo con el Examinador, con el fin de agilizar el examen, el término “opcionalmente sustituido” se ha suprimido en la mayoría de ocurrencias en las reivindicaciones. Sin embargo, este término se ha mantenido en relación con C6-C18 aril opcionalmente sustituido, C1-C18 heteroaril opcionalmente sustituido, pero los posibles sustituyentes opcionales han sido definidos claramente en la reivindicación como sigue:

“en donde cada sustituyente opcional es independientemente seleccionado del grupo que consiste de Cl, Br, F, OH, CO<sub>2</sub>H, CN y C1-C6 alquilo;”

Se aprovecha la oportunidad para corregir la traducción del sustituyente Ar en la reivindicación 1, en donde hizo falta en la traducción la frase “seleccionado del grupo que consiste de:” y para introducir una limitante así:

“A es -CR<sup>a</sup>R<sup>b</sup>- en donde R<sup>a</sup> y R<sup>b</sup> son diferentes” en la reivindicación 1.

4.3. Adicionalmente, el solicitante desea eliminar la reivindicación 4 de la solicitud.

4.4. De igual manera, el solicitante desea eliminar varios de los compuestos reclamados en la reivindicación 9 (ahora reivindicación 8).

4.5. Para atender estas modificaciones se presenta junto con este escrito un juego de reivindicaciones modificado que consta de 9 reivindicaciones y que reemplaza a las reivindicaciones originalmente presentadas, en donde se incorporan los cambios anteriormente señalados. Para facilitar la revisión, también se aporta una copia de trabajo en la que se muestran las modificaciones introducidas (el texto añadido aparece subrayado y el texto eliminado aparece tachado).

4.6. Con base a estas modificaciones y restricciones, se afirma que las reivindicaciones actuales son claras y se encuentran debidamente soportadas en la descripción.

5. EXAMEN DE PATENTABILIDAD – NIVEL INVENTIVO

5.1. El Examinador informa que después de realizada la búsqueda de anterioridades en este caso, concluye que las reivindicaciones 1 a10 no cuentan con nivel inventivo debido a la divulgación contenida en el documento:

| Ítem | Documento    | Título                                                              | Fecha de presentación |
|------|--------------|---------------------------------------------------------------------|-----------------------|
| D1   | WO2010139827 | “Inhibitor compounds of 11-betahydroxysteroid dehydrogenase type 1” | 09/Diciembre/2010     |

En cuanto a la reivindicación 1, el Examinador considera que:

*“El documento D1 es considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, ya que divulga compuestos derivados de perhidroquinolina y erhidroisoquinolina, como inhibidores de 11-β-hidroxiesteroide deshidrogenasa tipo 1 (11β-HSD1) y por tanto adecuados contra patologías tales como trastornos metabólicos, obesidad e inflamación, entre otras.*

*La diferencia entre los compuestos de la invención y los revelados en D1 consiste en el enlazador del anillo principal y en el sustituyente Ar que se selecciona de 7 diferentes anillos heteroarilos, opcionalmente sustituidos, diferentes a los que se observan en la posición del sustituyente V de D1.*

*Sin embargo, esta diferencia no concede un efecto técnico inesperado o una ventaja a los compuestos de la presente invención, ya que no existe soporte comparativo que permita reconocer una mejoría técnica o superior de los compuestos de la presente invención con los que ya se revelan en el estado del arte, que además también actúan como inhibidores de 11-β-hidroxiesteroide deshidrogenasa tipo 1. Al revisar los ensayos que demuestran actividad de la presente invención, no se encuentra un efecto técnico atribuible a los compuestos de la presente invención, porque la solicitante no comparó tales compuestos con los estructuralmente*

*cercanos de D1, en donde dicho documento del estado del arte ya reportaba datos de porcentaje de inhibición (10µM) del orden del 100%, es decir que mostraban ya datos de actividad muy alta de inhibición sobre dicha enzima y por tanto no es posible reconocer que los de la presente invención puedan ser superiores a los ya conocidos en D1. En este punto vale la pena anotar, que las modificaciones en los sustituyentes de compuestos conocidos son posibilidades plenamente conocidas para la persona del oficio normalmente versada en la materia, quien con sus conocimientos en química orgánica heterocíclica y a partir de la bibliografía básica puede realizar cambios en cualquiera de sus sustituyentes o en los heteroátomos de anillos conocidos, como ocurre con los isómeros clásicos en donde los grupos y átomos univalentes pueden ser reemplazados como una opción alternativa de modificación de sustituyentes funcionales 2, es decir, que se sabe que con algunas modificaciones en los sustituyentes, se pueden lograr cambios en las propiedades del compuesto íntimamente relacionadas con su actividad o con el efecto técnico a esperar como es, por ejemplo, incrementar la potencia o el índice (relación) terapéutica como el LD 50, ED50 o el EC90 a partir de algunas modificaciones en la posición de los heteroátomos del anillo principal o en la posición de sus sustituyentes. Lo anterior es importante, porque en la presente invención simplemente se propone una modificación en los sustituyentes de anillos conocidos, pero que como se vio anteriormente, dicha modificación no demostró un efecto técnico inesperado o una ventaja técnica real y por tanto se consideran variaciones estructurales de rutina que no sustentan el requisito evaluado.”*

## 5.2. Argumentos a favor del nivel inventivo de la invención.

5.2.1 La presente invención cuenta con nivel inventivo frente a las enseñanzas divulgadas en D1 debido a que dichas enseñanzas no llevan de forma inmediata a la solución propuesta por la solicitud y mucho menos se puede prever su resultado.

5.2.2 La Guía para Examen de Solicitudes de Patente de Invención y Modelo de Utilidad emitido por la Superintendencia de Industria y Comercio, Delegatura para la Propiedad Industrial, Dirección de Nuevas Creaciones, establece con respecto al requisito de nivel inventivo, lo siguiente:

*“Si el estado de la técnica provee las enseñanzas para derivar la solución, revisar si el conjunto de enseñanzas del estado de la técnica lo llevarían de forma inmediata a la solución propuesta por la solicitud. Si se requiere de pasos adicionales o de corroboración o de superar obstáculos revelados por las propias enseñanzas entonces el estado de la técnica no revela la solución al problema.”* (Subrayado fuera de texto)<sup>1</sup>

5.2.3. El documento citado por el Examinador D1 (WO2010 / 139827) ya había sido citado en el informe de búsqueda internacional en la fase internacional y fue analizado durante la tramitación de la solicitud internacional. Como resultado de los argumentos presentados durante la fase internacional de la solicitud PCT correspondiente, se emitió una opinión escrita sin objeciones

<sup>1</sup> Guía para Examen de Solicitudes de Patente de Invención y Modelo de Utilidad emitido por la Superintendencia de Industria y Comercio, Delegatura para la Propiedad Industrial, Dirección de Nuevas Creaciones. Año 2012. Página 119.

por la Oficina Europea de Patentes. Adjunto una copia de esta opinión escrita para revisión del Examinador.

5.2.4. Sin embargo, la solicitante considera que no hay ninguna enseñanza o sugerencia en el arte previo citado (D1) que pudiera llevar a un experto a la presente invención, partiendo de la técnica anterior citada. Como fue correctamente señalado por el examinador, la presente solicitud enseña ciertos grupos Ar que son patentablemente distintos de los grupos Ar en la técnica anterior citada.

5.2.5. Cabe destacar que el documento D1 enseña unos sustituyentes en la posición correspondiente a Ar el cual no se solapa con la presente invención. De acuerdo con ello, en la presente invención, el grupo Ar se selecciona a partir de 7 estructuras distintas ninguna de las cuales son enseñadas o sugeridas en el documento del arte previo citado. En consecuencia, la invención es inventiva sobre D1.

5.2.6. Además, la solicitante ha modificado las reivindicaciones para indicar que en el grupo de enlace A, A es un grupo de fórmula  $-CR^aR^b-$  en donde  $R^a$  y  $R^b$  son diferentes. Con referencia a la especificación, la solicitante ha encontrado que con compuestos de este tipo la actividad es mayor.

5.2.7. En consecuencia, se afirma respetuosamente que, tras la modificación de las reivindicaciones por las razones expuestas anteriormente, los compuestos reivindicados son inventivos con respecto a lo divulgado por la técnica anterior citada. De hecho, a fin de llegar a la presente invención a partir de lo divulgado en la técnica anterior, una persona experta en la técnica tendría que hacer una serie de modificaciones a los compuestos que se enseñan en la técnica anterior para llegar a la presente invención. Específicamente la persona experta en la técnica tendría que modificar el grupo Ar enseñado en la técnica anterior y, además tendría que modificar la naturaleza de la fracción de enlace. Simplemente no hay indicación o sugerencia en la técnica anterior que pudiera llevar a un experto a llevar a cabo estos dos cambios significativos con alguna expectativa de éxito.

5.2.8. De hecho, los solicitantes señalan que existe evidencia de que los compuestos de la presente invención son mejores que los compuestos divulgados en la técnica anterior citada. El documento D1 tiene inhibición en el intervalo de 10 micro-molar mientras que los compuestos de la presente invención son activos típicamente por debajo de 250 nano-molar lo cual es un orden de magnitud más activo, como el examinador lo puede apreciar.

5.2.9 Por tanto, el solicitante considera que se ha demostrado que los compuestos reivindicados cumple con los requisitos de patentabilidad exigidos por la Superintendencia de Industria y Comercio, y solicita que se le conceda el derecho de patente atendiendo a sus esfuerzos en la investigación y desarrollo de medicamentos innovadores para la gestión de enfermedades.

Atentamente,

A handwritten signature in blue ink, appearing to read 'Andrea Tobos Mateus', is written over a horizontal line.

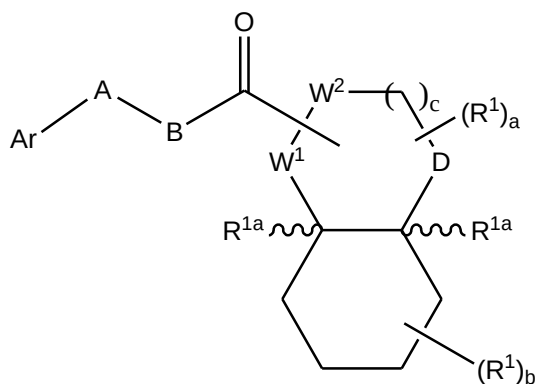
ANDREA TOBOS MATEUS

C.C. 52.223.325 de Bogotá

T.P. 148648

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



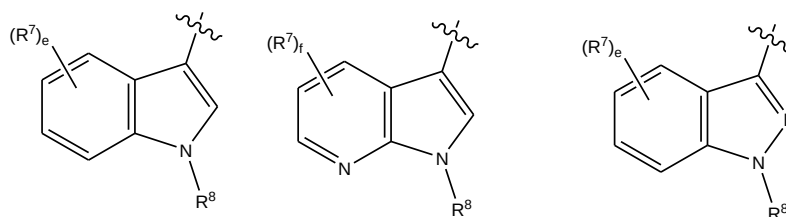
Fórmula (I)

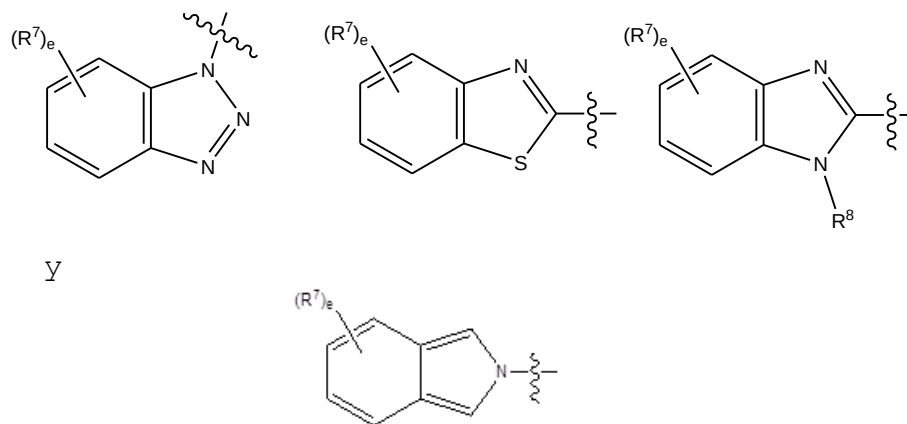
caracterizado porque:

10 cada  $R^1$  y  $R^{1a}$  es independientemente seleccionado del grupo que consiste de H, metilo,  $CONHC(CH_3)_3$ , OH,  $CO_2H$ ,  $CO_2CH_3$ ,  $CO_2CH_2CH_3$ , fenilo,  $CH_2OH$ , CN y  $OCH_3$ ;

o cualquiera dos  $R^1$  en átomos de carbono adyacentes se puede unir para formar una fracción cíclica, o cualquiera dos  $R^1$  en el mismo carbono cuando se toman juntos pueden  
15 formar un grupo de la fórmula  $=O$ .

Ar es una opcionalmente sustituida por grupo  $c1-C_{18}$  heteroarilo;





Y

en donde cada R<sup>7</sup> es independientemente seleccionado  
 del grupo que consiste H, halógeno, OH, NO<sub>2</sub>, CN, SH, NH<sub>2</sub>, CF<sub>3</sub>,  
 OCF<sub>3</sub>, C<sub>1</sub>-C<sub>12</sub>alquilo, C<sub>1</sub>-C<sub>12</sub>haloalquilo, C<sub>2</sub>-C<sub>12</sub>alquenilo, C<sub>2</sub>-  
 C<sub>12</sub>alquinilo, C<sub>2</sub>-C<sub>12</sub>heteroalquilo, C<sub>3</sub>-C<sub>12</sub>cicloalquilo, C<sub>3</sub>-  
 C<sub>12</sub>cicloalquenilo, C<sub>2</sub>-C<sub>12</sub>heterocicloalquilo, C<sub>2</sub>-  
 C<sub>12</sub>heterocicloalquenilo, opcionalmente sustituido C<sub>6</sub>-  
 C<sub>18</sub>arilo, opcionalmente sustituido C<sub>1</sub>-C<sub>18</sub>heteroarilo, C<sub>1</sub>-  
 C<sub>12</sub>alquiloxi, C<sub>2</sub>-C<sub>12</sub>alquenilooxi, C<sub>2</sub>-C<sub>12</sub>alquinilooxi, C<sub>2</sub>-  
 C<sub>10</sub>heteroalquiloxi, C<sub>3</sub>-C<sub>12</sub>cicloalquiloxi, C<sub>3</sub>-  
 C<sub>12</sub>cicloalquenilooxi, C<sub>2</sub>-C<sub>12</sub>heterocicloalquiloxi, C<sub>2</sub>-C<sub>12</sub>  
 heterocicloalquenilooxi, C<sub>6</sub>-C<sub>18</sub>arilooxi, C<sub>1</sub>-C<sub>1</sub>  
 heteroarilooxi, C<sub>1</sub>-C<sub>12</sub>alquiloamino, SR<sup>9</sup>, SO<sub>3</sub>H, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>R<sup>9</sup>,  
 SONR<sup>9</sup>R<sup>10</sup>, SOR<sup>9</sup>, COR<sup>9</sup>, COOH, COOR<sup>9</sup>, CONR<sup>9</sup>R<sup>10</sup>, NR<sup>9</sup>COR<sup>10</sup>, NR<sup>9</sup>COOR<sup>10</sup>,  
 NR<sup>9</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>9</sup>CONR<sup>9</sup>R<sup>10</sup>, NR<sup>9</sup>R<sup>10</sup>, y acil;

en donde cada sustituyente opcional es independientemente seleccionado del grupo que consiste de Cl, Br, F, OH, CO<sub>2</sub>H, CN y C<sub>1</sub>-C<sub>6</sub> alquilo;

5

en donde R<sup>8</sup> es seleccionado del grupo que consiste en H, C<sub>1</sub>-C<sub>12</sub>alquilo, C<sub>2</sub>-C<sub>12</sub>alquenilo, C<sub>2</sub>-C<sub>12</sub>alquinilo, C<sub>2</sub>-C<sub>12</sub>heteroalquilo, C<sub>3</sub>-C<sub>12</sub>cicloalquilo, C<sub>2</sub>-C<sub>12</sub>heterocicloalquilo, C<sub>6</sub>-C<sub>18</sub>arilo, C<sub>1</sub>-C<sub>18</sub>heteroarilo, SO<sub>3</sub>H, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>R<sup>9</sup>, SONR<sup>9</sup>R<sup>10</sup>, SOR<sup>9</sup>, COR<sup>9</sup>, COOH, COOR<sup>9</sup>, y CONR<sup>9</sup>R<sup>10</sup>;

10

en donde cada R<sup>9</sup> y R<sup>10</sup> es independientemente seleccionado del grupo que consiste en H, C<sub>1</sub>-C<sub>12</sub>alquilo, C<sub>2</sub>-C<sub>10</sub>heteroalquilo, C<sub>1</sub>-C<sub>12</sub>haloalquilo, C<sub>3</sub>-C<sub>12</sub>cicloalquilo, C<sub>6</sub>-C<sub>18</sub>arilo, y C<sub>1</sub>-C<sub>18</sub>heteroarilo.

15

e es un entero seleccionado del grupo que consiste de 0, 1, 2, 3 y 4;

f es un entero seleccionado del grupo que consiste de 0, 1, 2, y 3;

20

A es -CR<sup>a</sup>R<sup>b</sup>- en donde R<sup>a</sup> y R<sup>b</sup> son diferentes;

B es un grupo de la fórmula-(CR<sup>c</sup>R<sup>d</sup>)<sub>n</sub>-;

25

en donde cada R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup> y R<sup>d</sup> es independientemente seleccionado del grupo que consiste en H, halógeno, OH, NO<sub>2</sub>, CN, SH, NH<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, C<sub>1</sub>-C<sub>12</sub>alquilo, C<sub>2</sub>-C<sub>10</sub>heteroalquilo, C<sub>1</sub>-C<sub>12</sub>haloalquilo, C<sub>3</sub>-C<sub>12</sub>cicloalquilo, C<sub>6</sub>-C<sub>18</sub>arilo, C<sub>1</sub>-C<sub>18</sub>heteroarilo; SR<sup>2</sup>, SO<sub>3</sub>H, SO<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, SO<sub>2</sub>R<sup>2</sup>, SONR<sup>2</sup>R<sup>3</sup>, SOR<sup>2</sup>, COR<sup>2</sup>,

COOH, COOR<sup>2</sup>, CONR<sup>2</sup>R<sup>3</sup>, NR<sup>2</sup>COR<sup>3</sup>, NR<sup>2</sup>COOR<sup>3</sup>, NR<sup>2</sup>SO<sub>2</sub>R<sup>3</sup>, NR<sup>2</sup>CONR<sup>2</sup>R<sup>3</sup>,  
NR<sup>2</sup>R<sup>3</sup>, y acil,

5 en donde cada R<sup>2</sup> y R<sup>3</sup> es independientemente  
seleccionado del grupo que consiste en H, C<sub>1</sub>-C<sub>12</sub>alquilo, C<sub>2</sub>-  
C<sub>10</sub>heteroalquilo, C<sub>1</sub>-C<sub>12</sub>haloalquilo, C<sub>3</sub>-C<sub>12</sub>cicloalquilo, C<sub>6</sub>-  
C<sub>18</sub>arilo, y C<sub>1</sub>-C<sub>18</sub>heteroarilo;

W<sup>1</sup> y W<sup>2</sup> están seleccionados de tal forma que uno es  
N y el otro es (CR<sup>1</sup><sub>2</sub>),

10 el enlace del carbono carbonil se une a cualquiera  
de W<sup>1</sup> o W<sup>2</sup> es N;

D es O o (CR<sup>1</sup><sub>2</sub>);

n es un entero seleccionado del grupo que consiste  
de 0, 1, 2, 3, y 4;

15 a es un entero seleccionado del grupo que consiste  
de 0, 1, y 2;

b es un entero seleccionado del grupo que consiste  
de 0, 1, 2, 3, 4, 5, 6, 7, y 8,

c es 1;

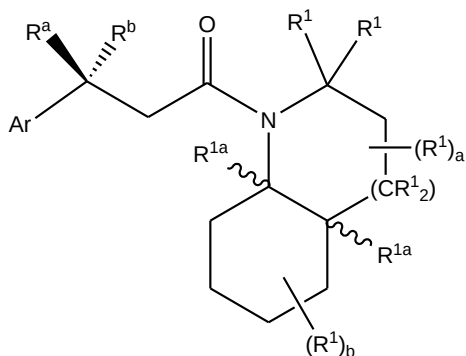
20 o una sal farmacéuticamente aceptable de los  
mismos.

2. Un compuesto de conformidad con la  
reivindicación 1, caracterizado porque D es (CR<sup>1</sup><sub>2</sub>).

25 3. Un compuesto de conformidad con la  
reivindicación 1, caracterizado porque B es CH<sub>2</sub>.

4. Un compuesto de conformidad con la reivindicación 1 que tiene la fórmula:

5



en donde Ar, Ra, Rb, R<sup>1</sup>, R<sup>1a</sup>, a y b son como se definen en la reivindicación 1.

10

5. Un compuesto de conformidad con la reivindicación 1, en donde uno de Ra y Rb es H y el otro es alquilo opcionalmente sustituido.

15

6. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el sustituyente R<sup>7</sup> está ubicado en la posición 4 o en la posición 5 del anillo de seis miembros.

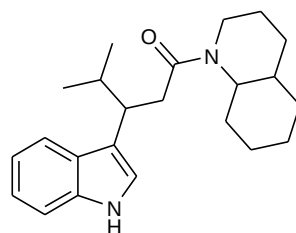
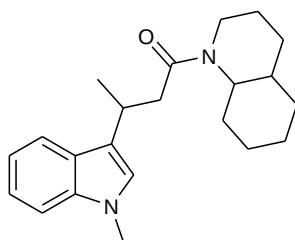
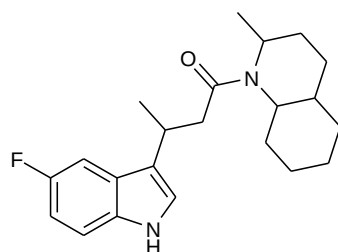
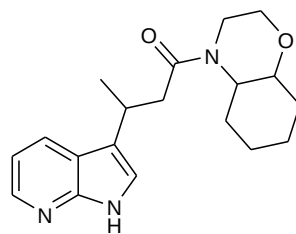
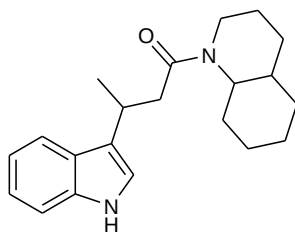
20

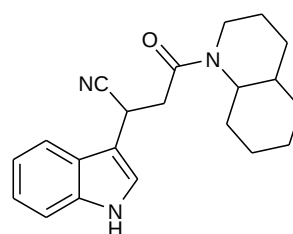
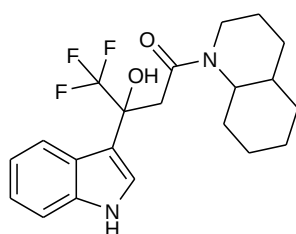
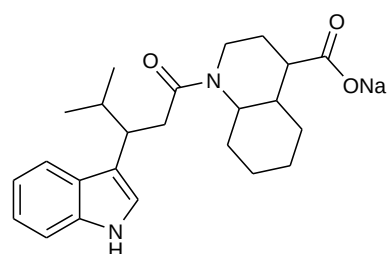
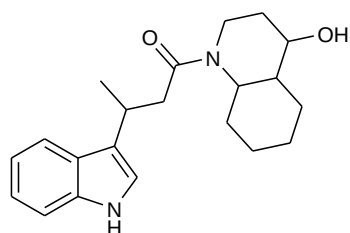
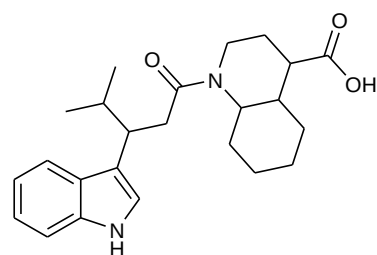
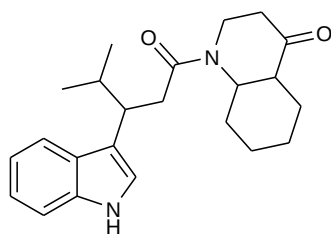
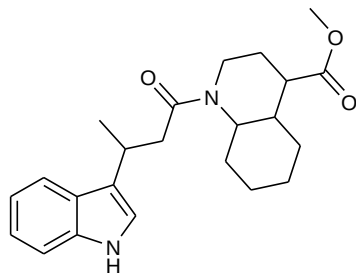
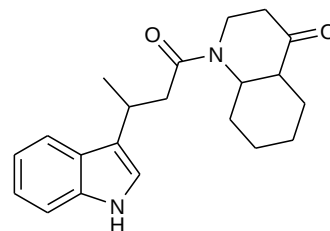
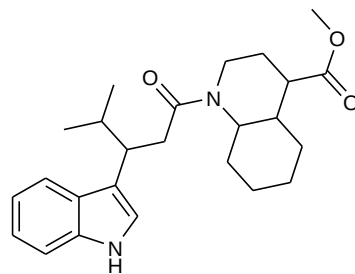
7. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R<sup>7</sup> se selecciona del grupo que consiste de CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, Cl, Br, F, I OH, NO<sub>2</sub>, NH<sub>2</sub>, CN, SO<sub>3</sub>H, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,

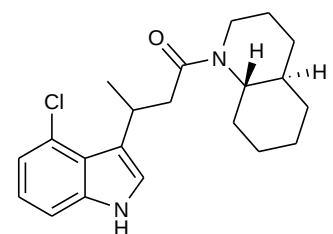
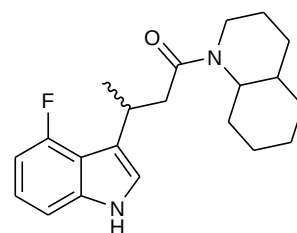
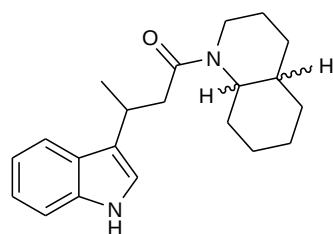
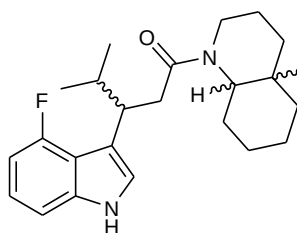
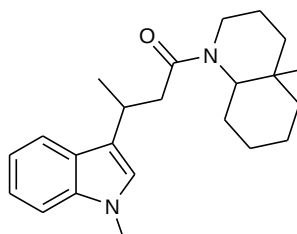
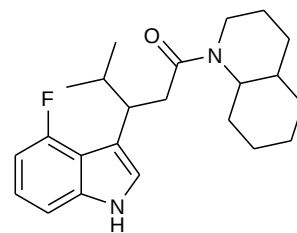
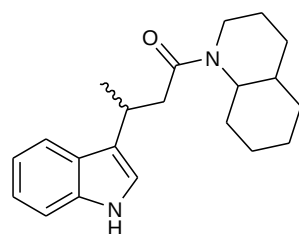
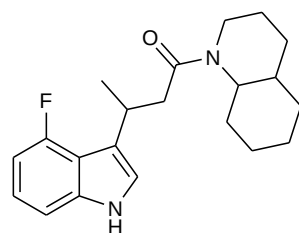
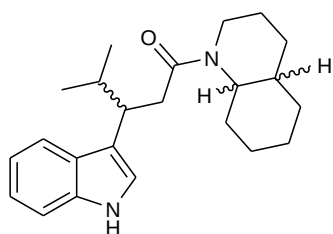
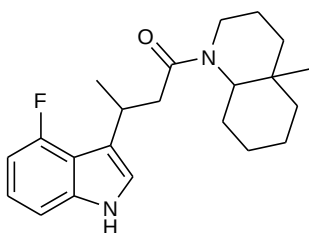
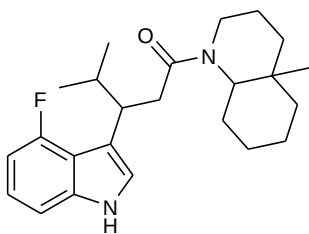
$\text{CF}_3$  y  $\text{OCF}_3$ .

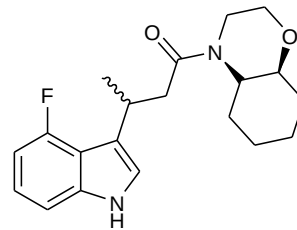
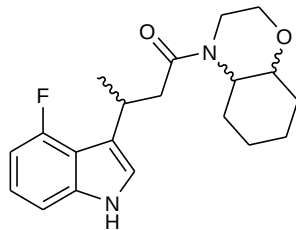
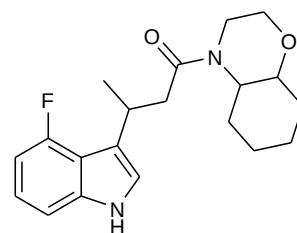
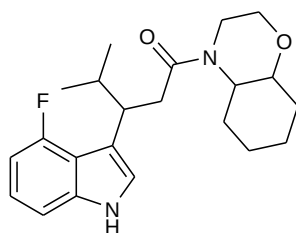
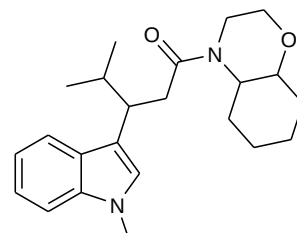
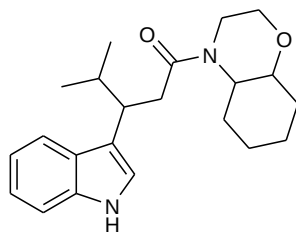
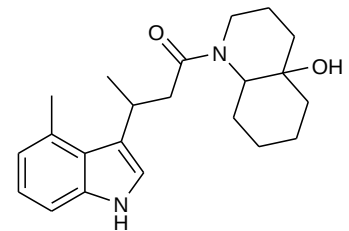
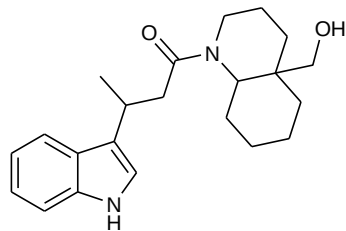
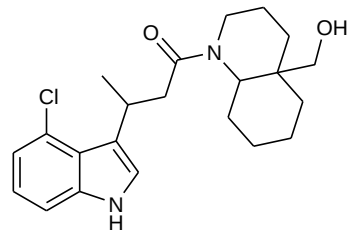
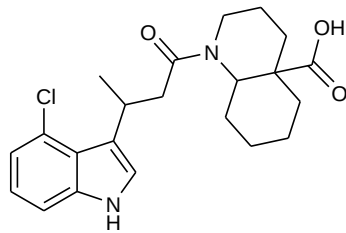
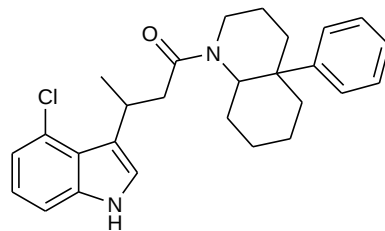
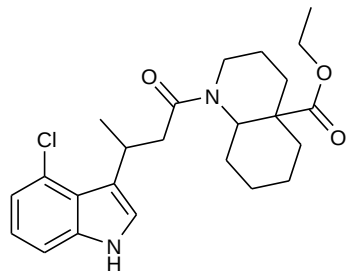
8. Un compuesto de conformidad con la reivindicación 1, seleccionado del grupo que consiste en:

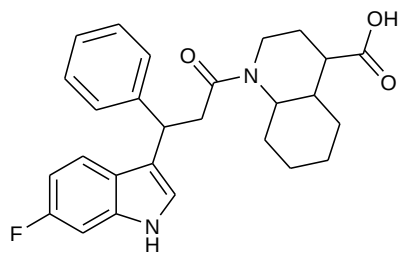
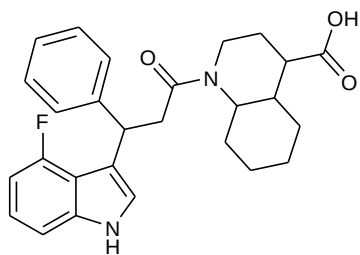
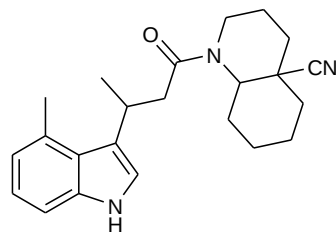
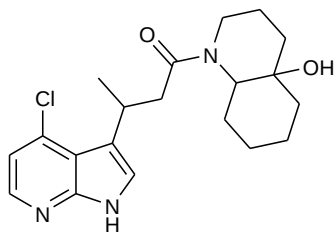
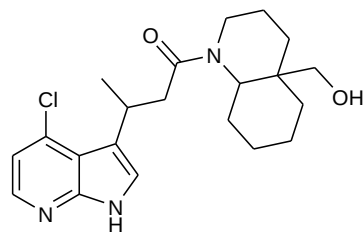
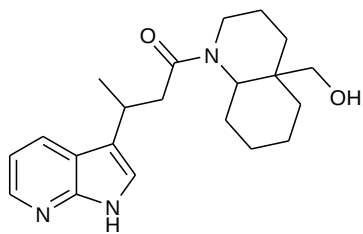
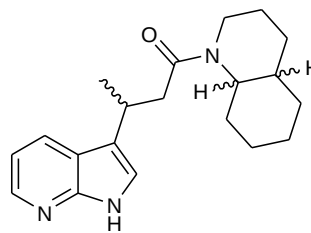
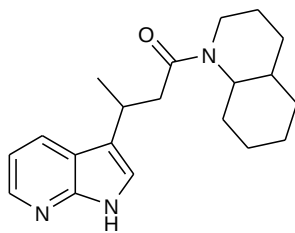
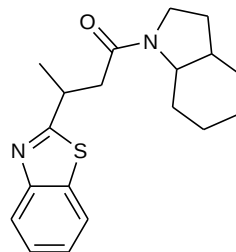
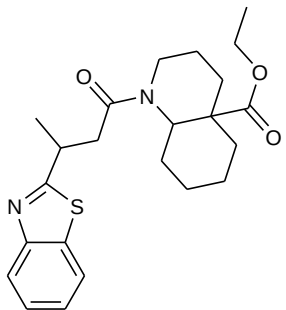
5

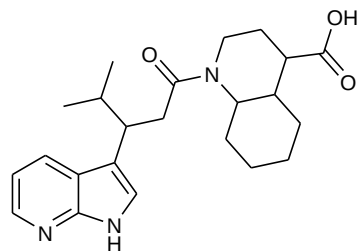
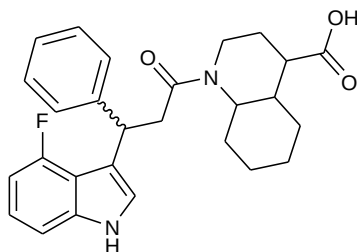
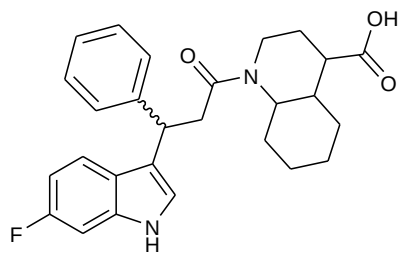
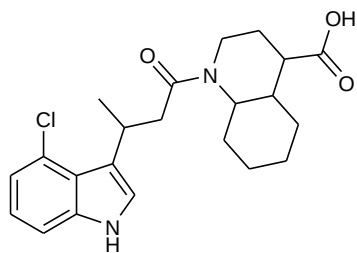
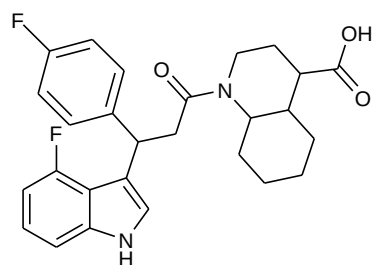
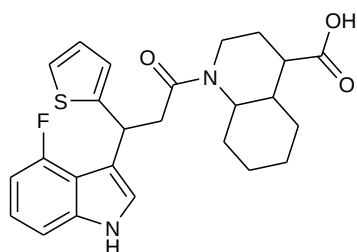
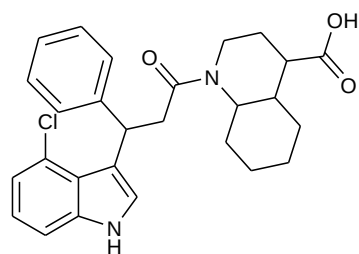
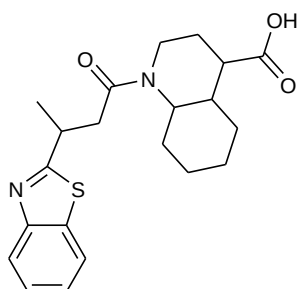
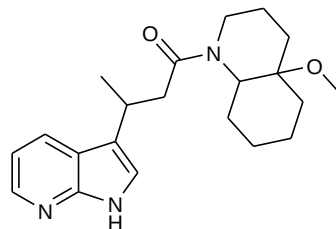
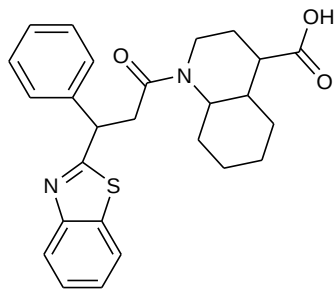


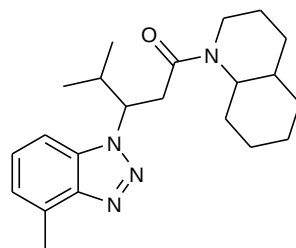
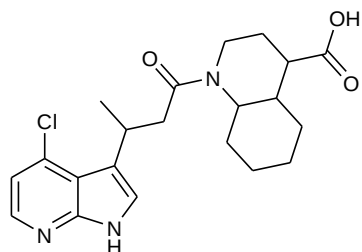
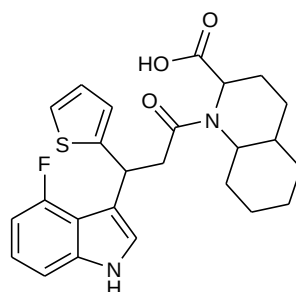
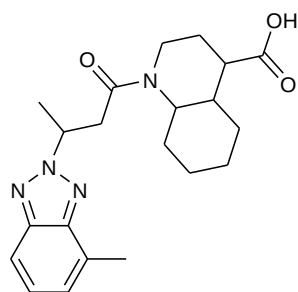
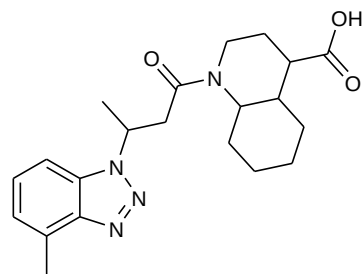
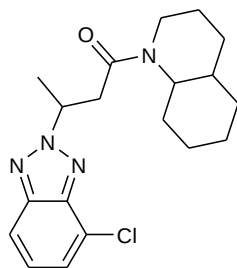
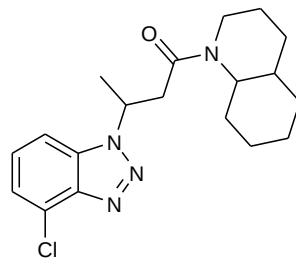
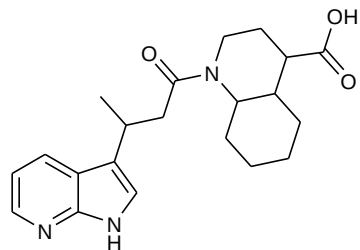
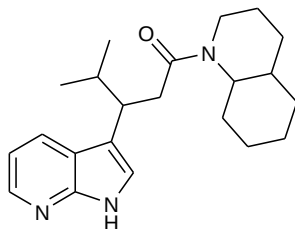


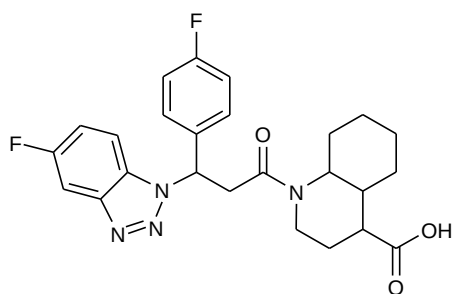
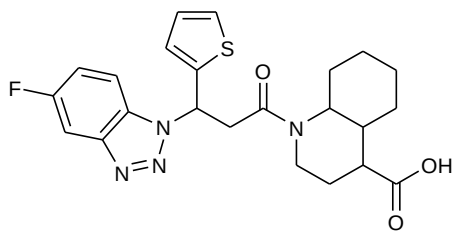
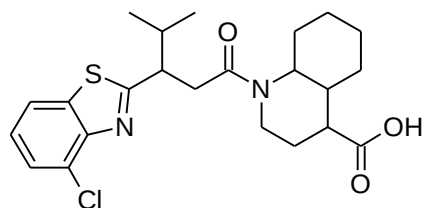
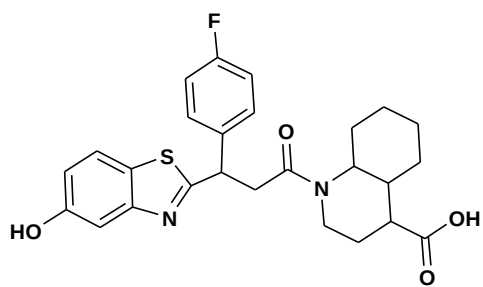
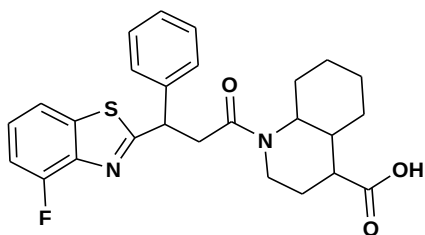
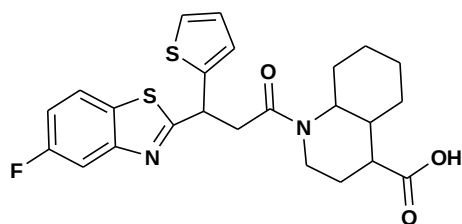
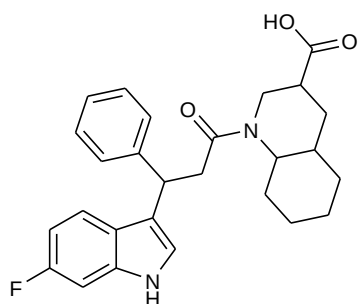
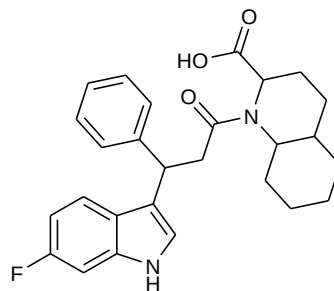
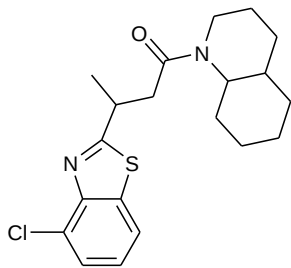


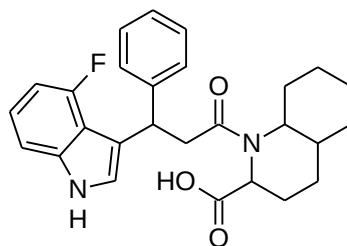
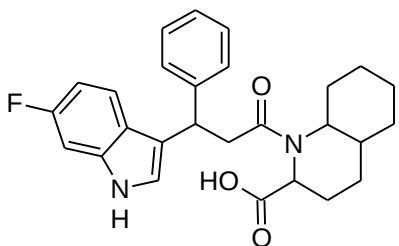
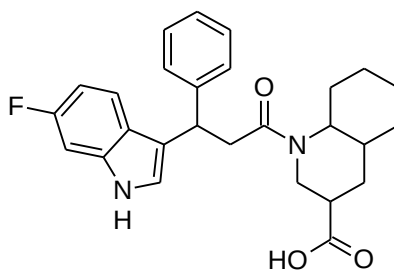
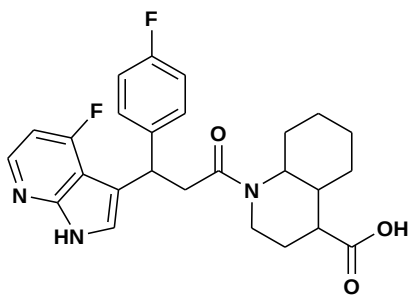
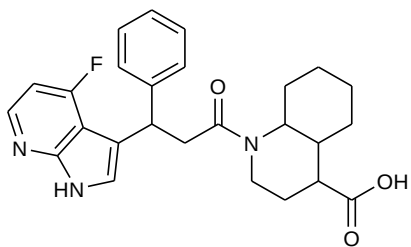
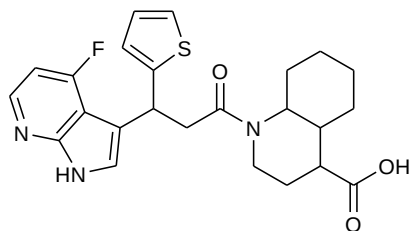
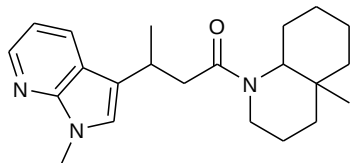
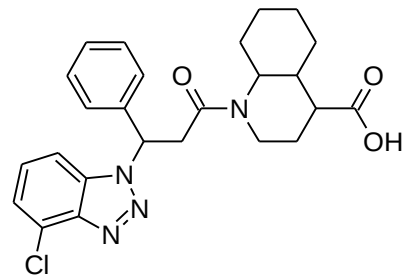
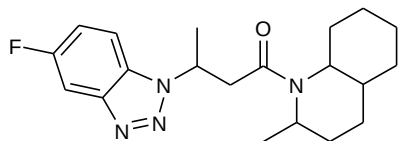


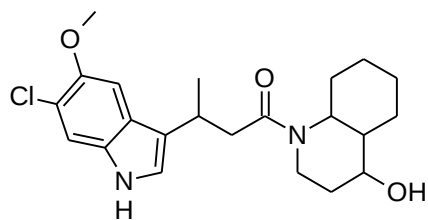
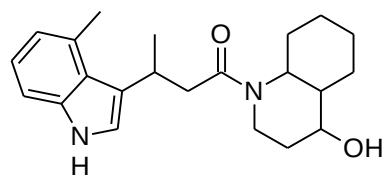
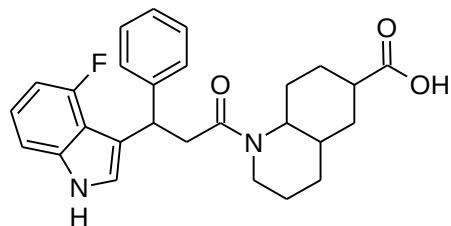
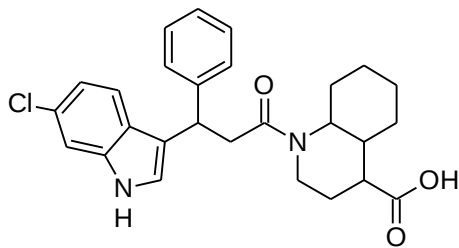
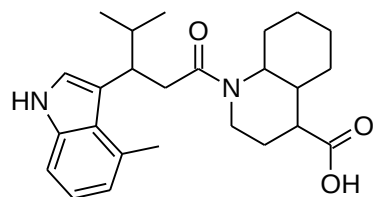
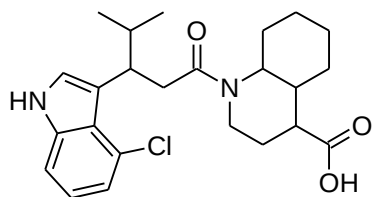
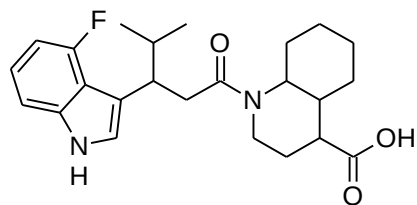
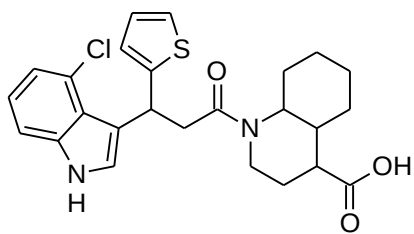
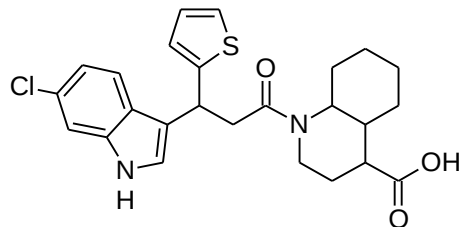
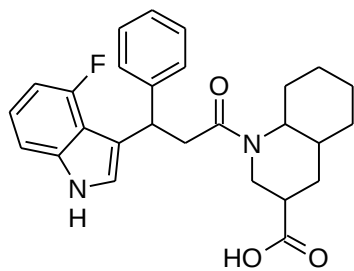
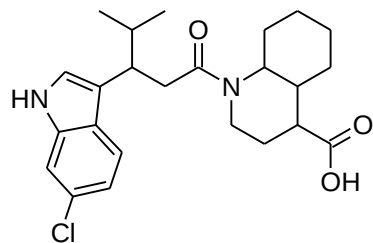
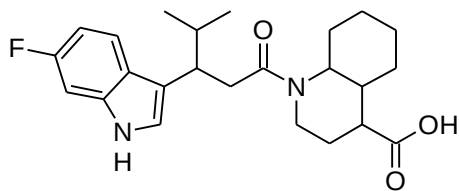


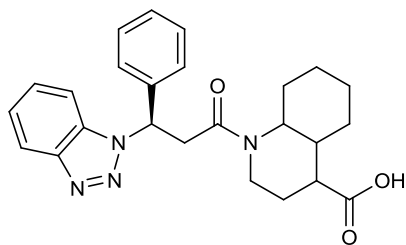
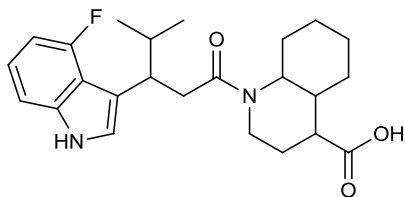
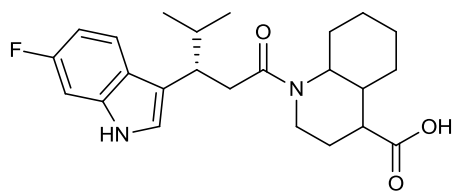
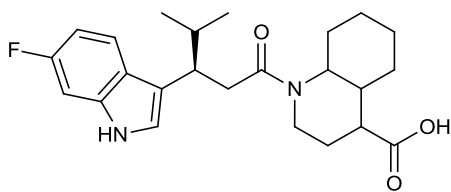
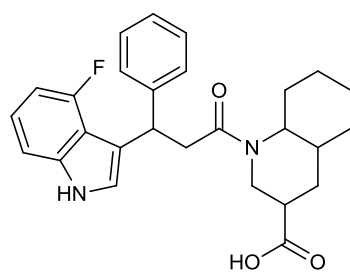
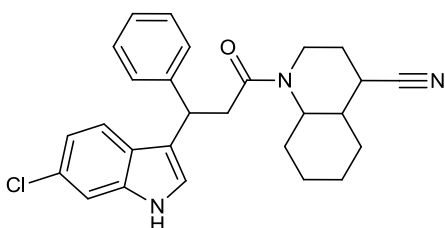
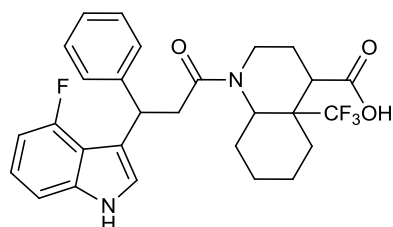
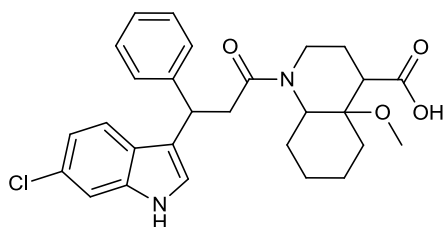
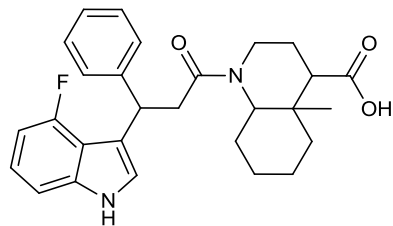
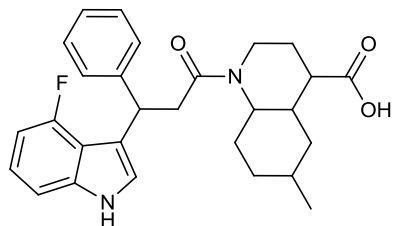
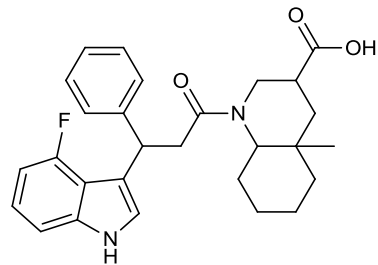
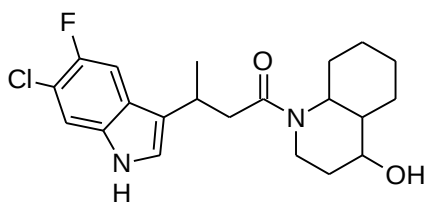


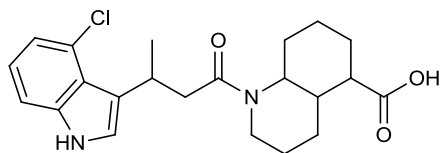
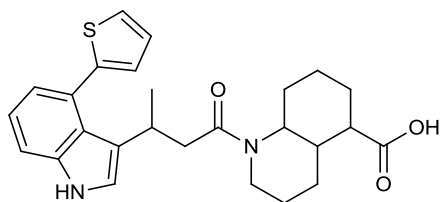
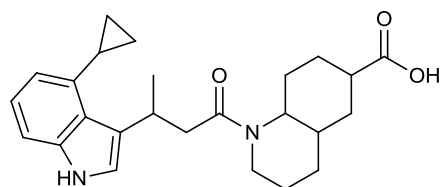
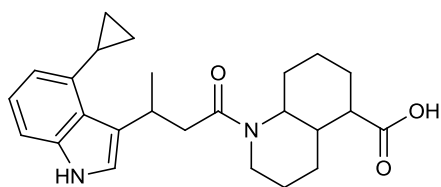
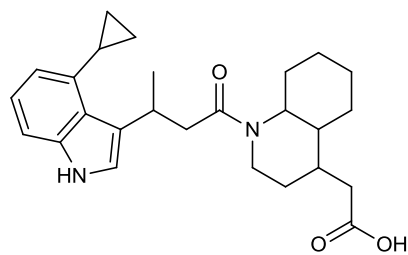
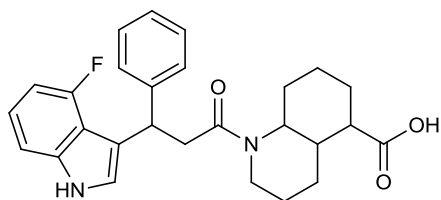
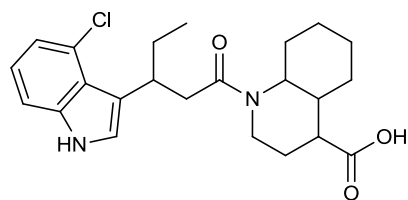
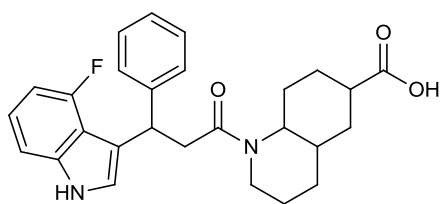
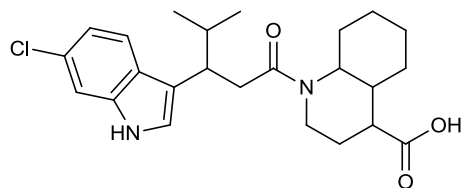
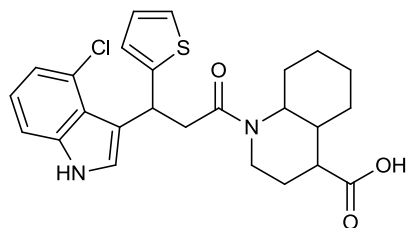
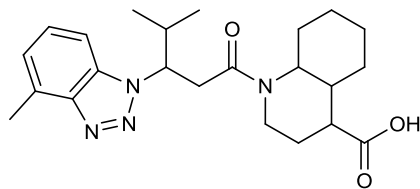
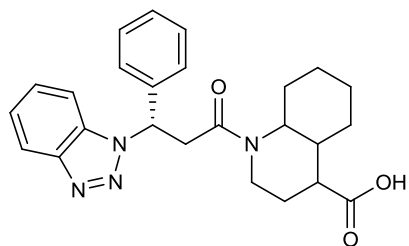


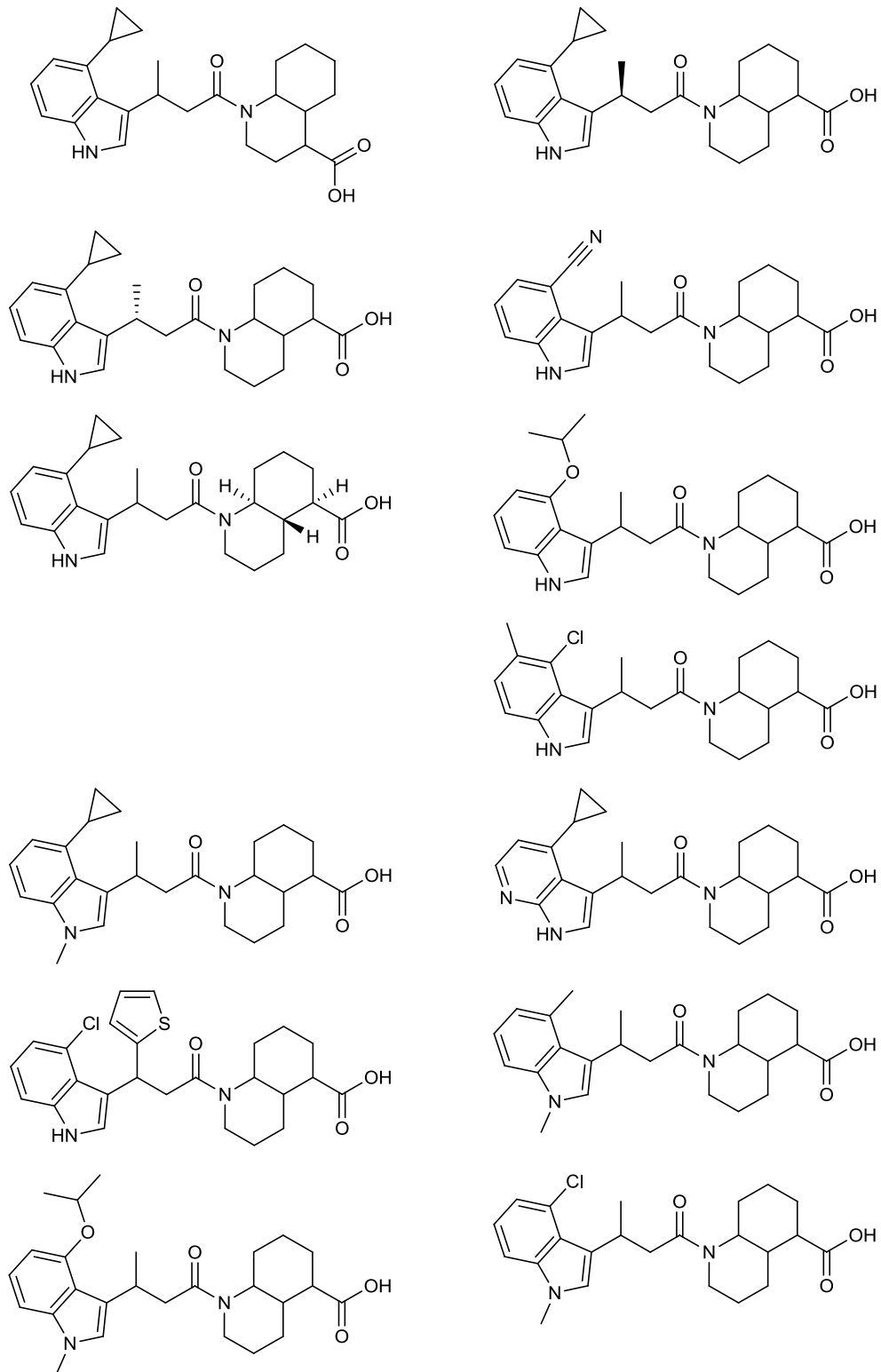


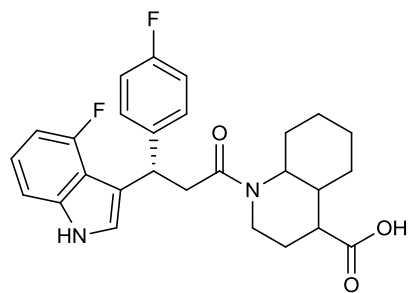
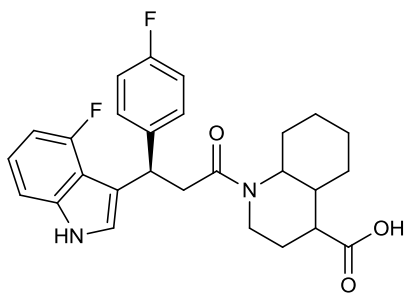
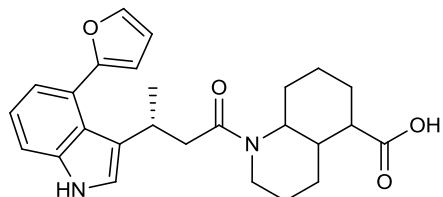
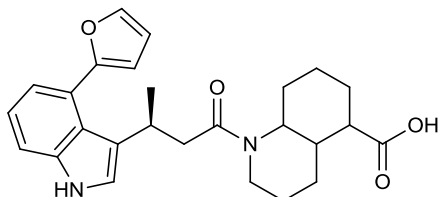
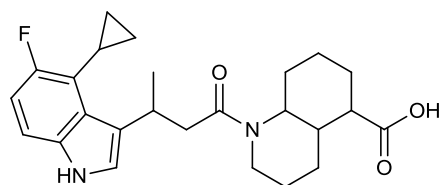
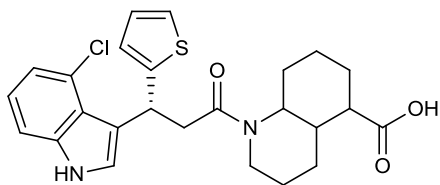
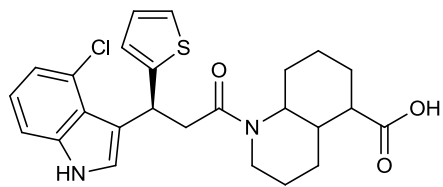
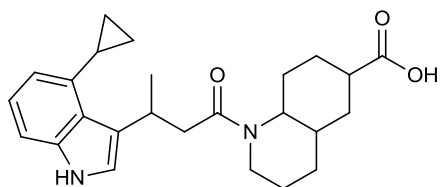
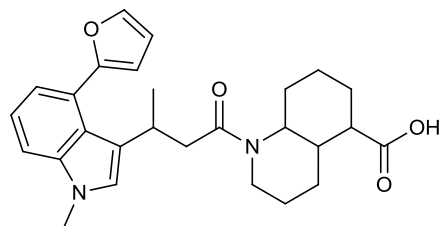
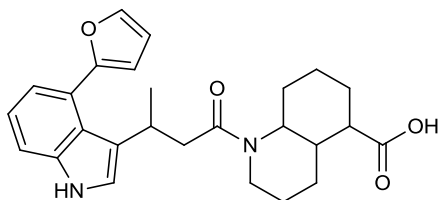
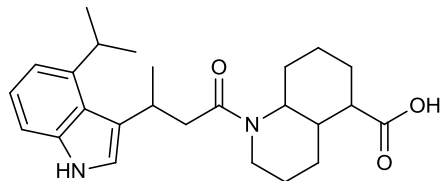
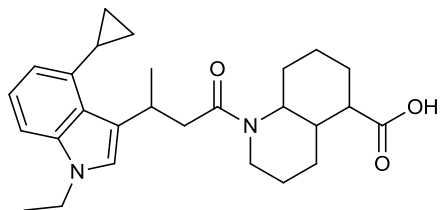


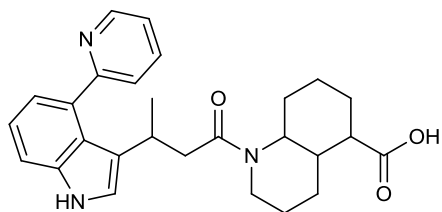
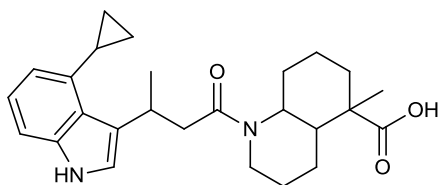
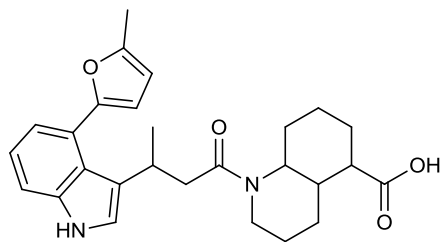
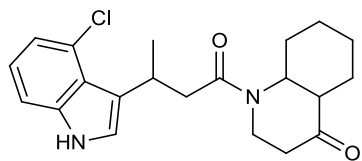
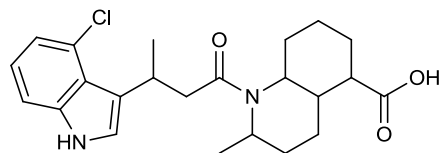
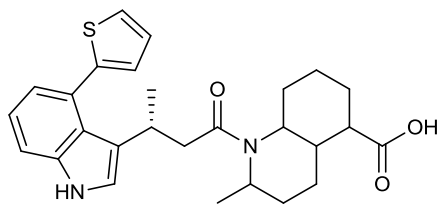
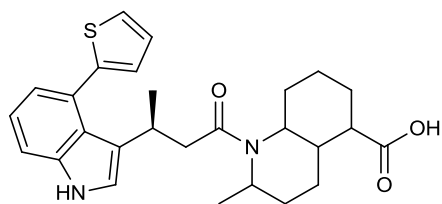
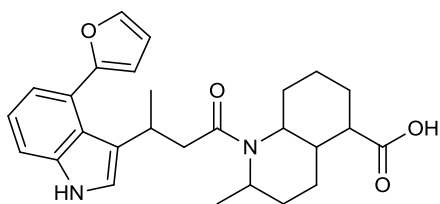
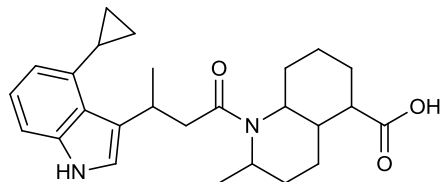
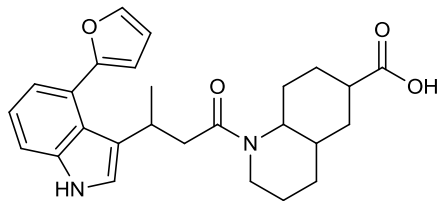
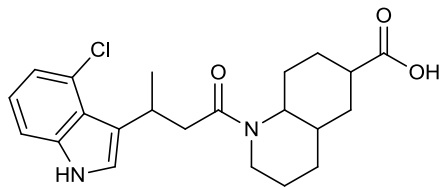
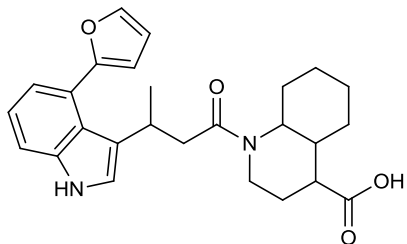


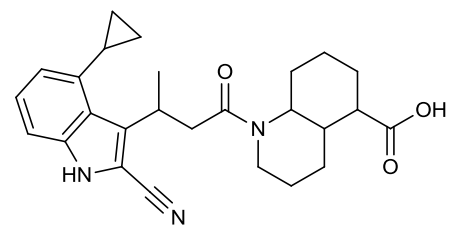
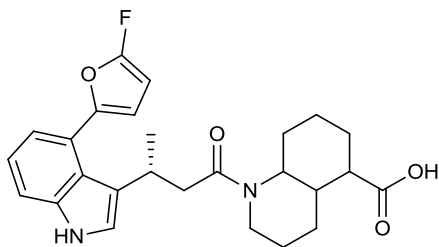
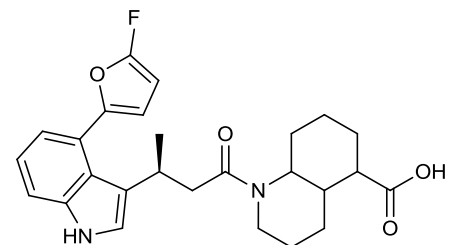
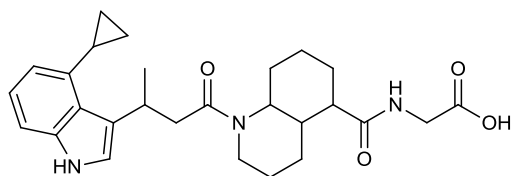
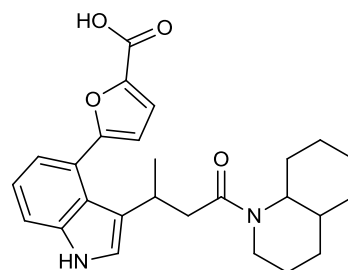
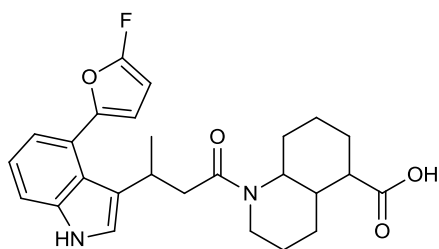
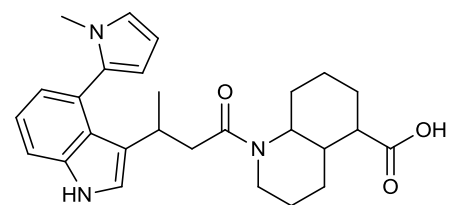
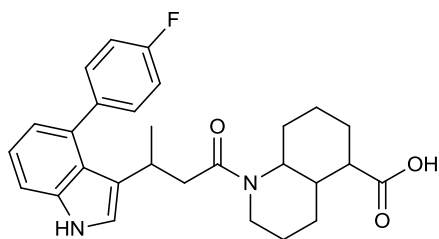
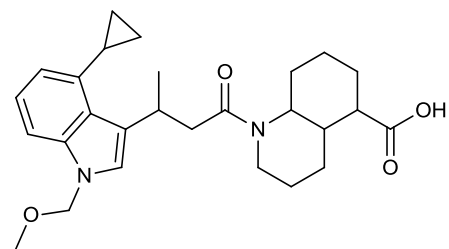
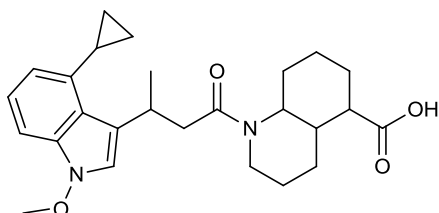
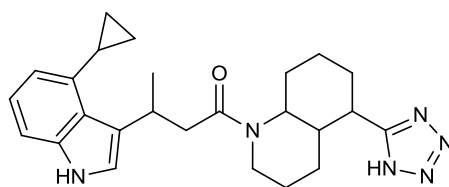
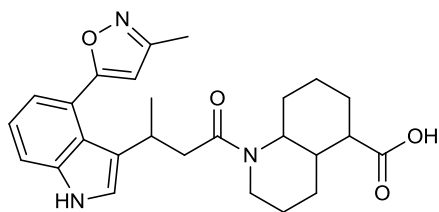


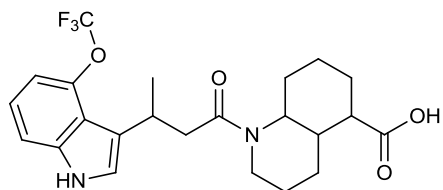
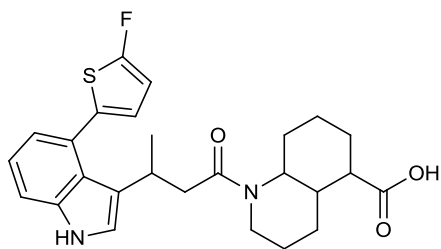
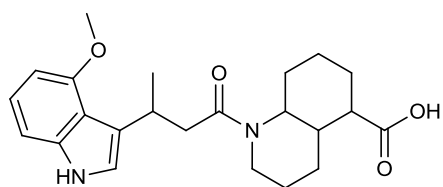
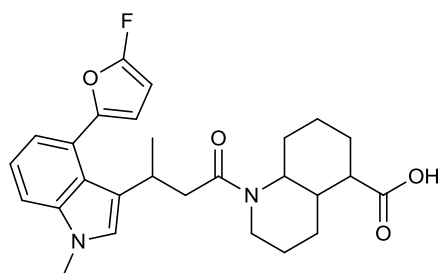
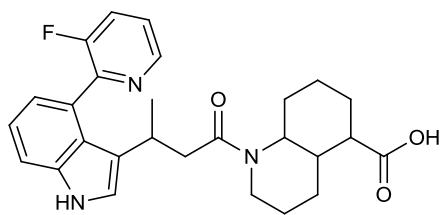
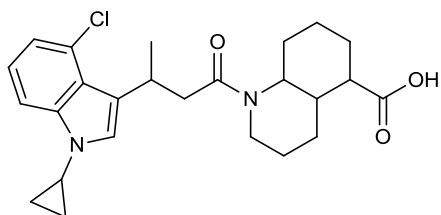
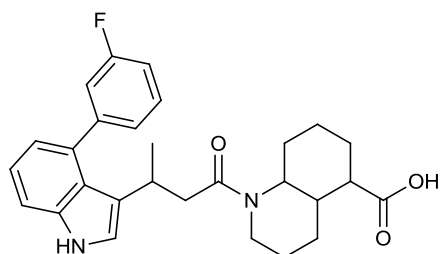
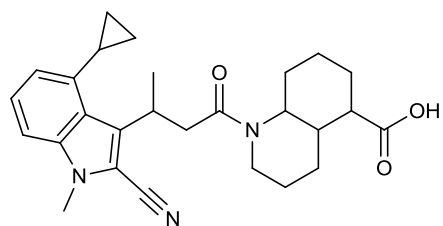
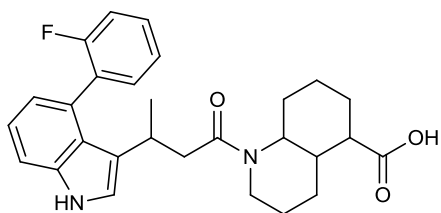
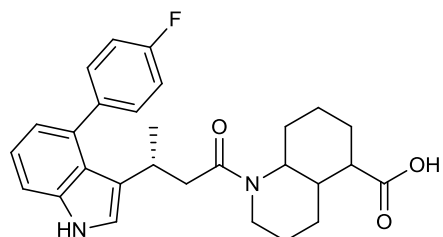
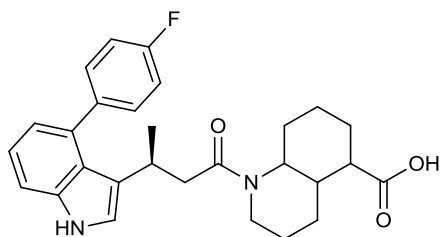


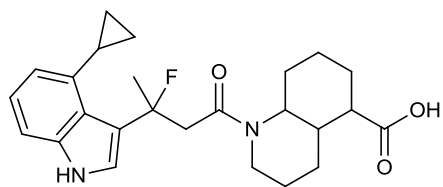
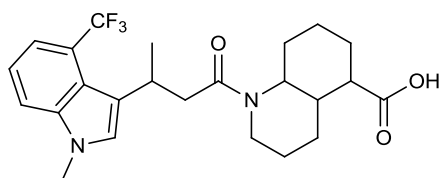
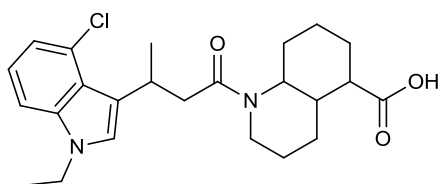
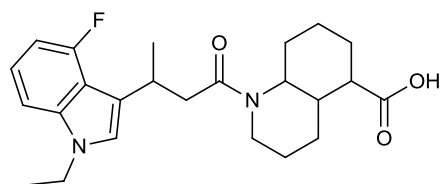
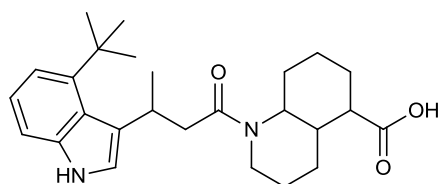
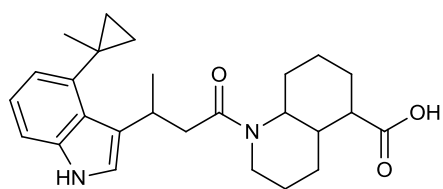
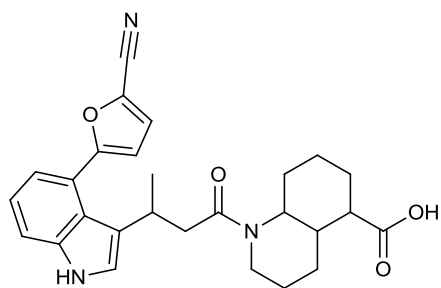
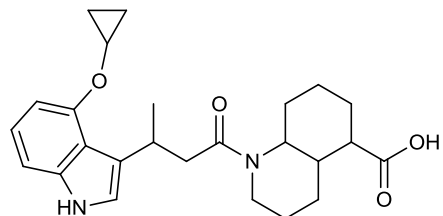
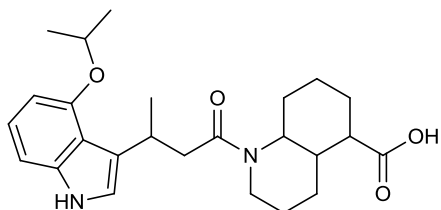
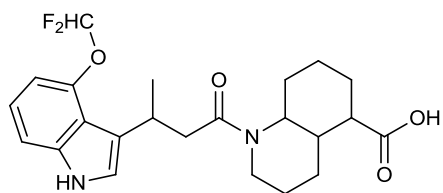
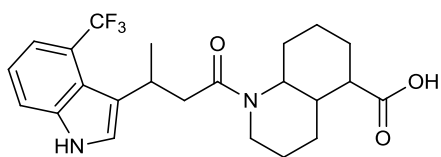


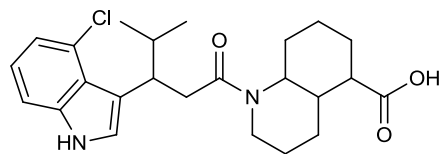
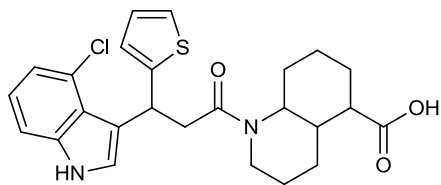
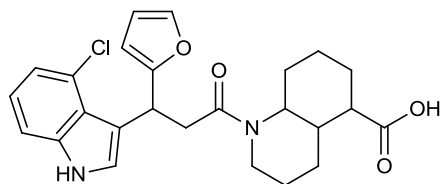
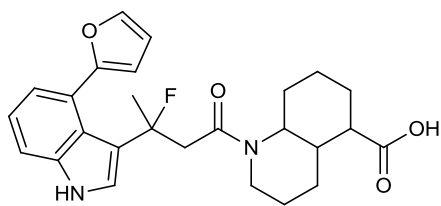
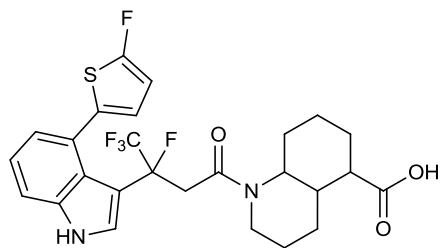
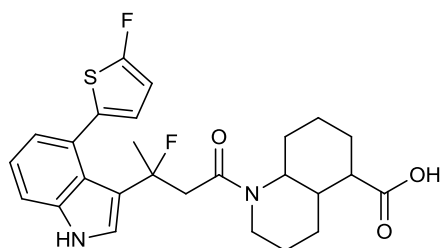
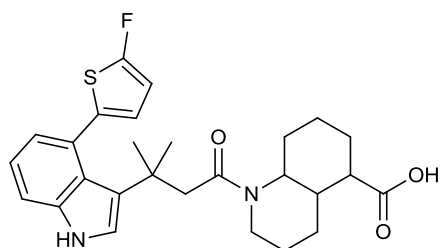
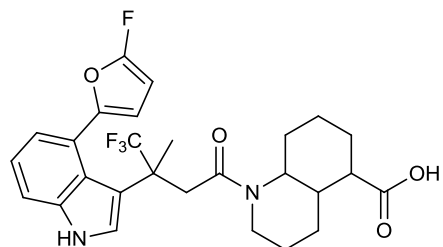
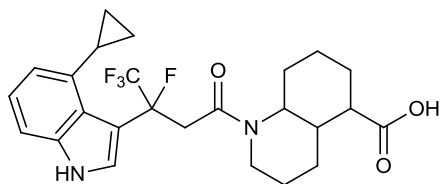
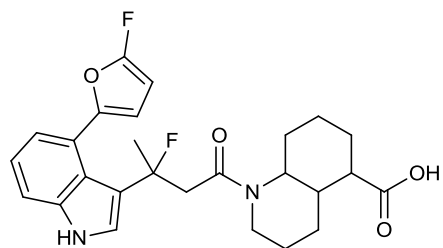


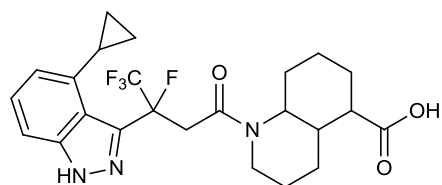
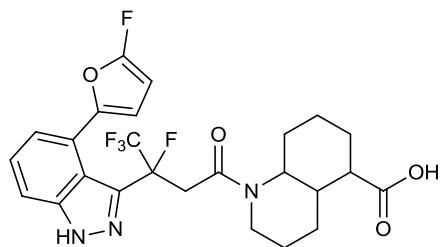
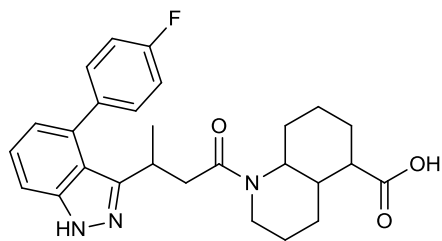
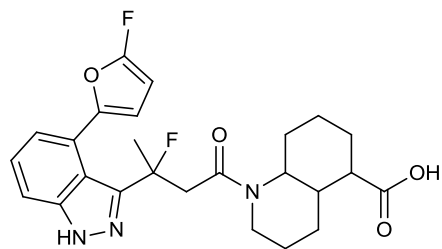
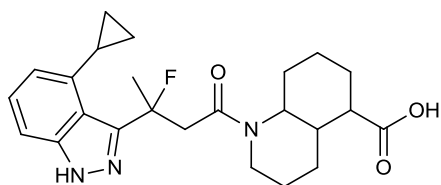
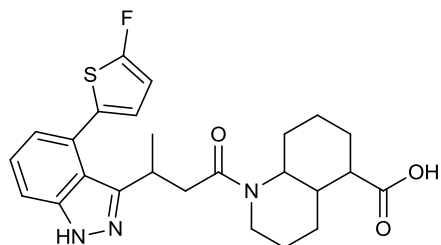
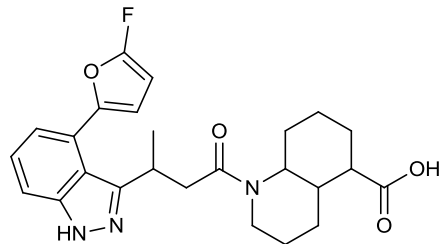
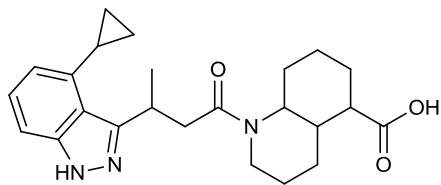


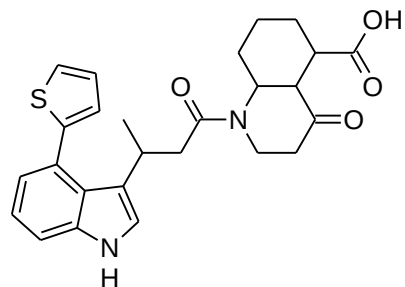
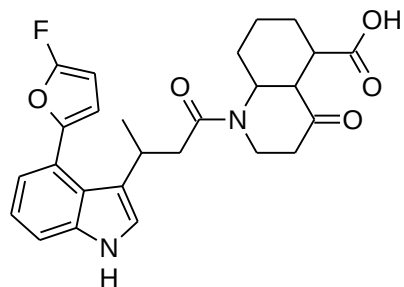
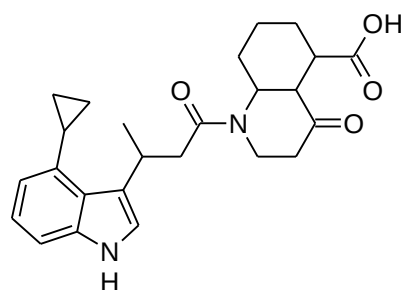
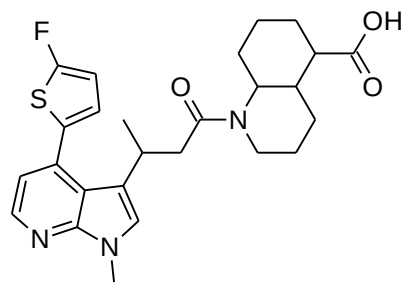
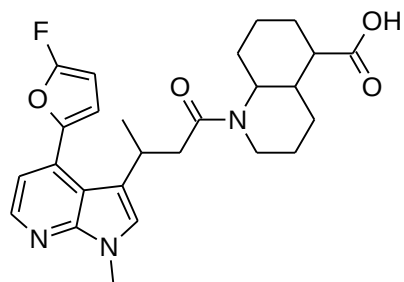
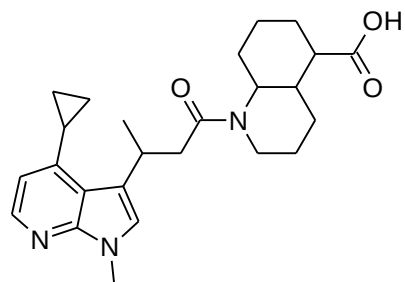
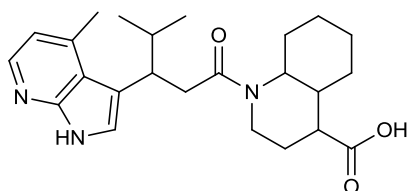
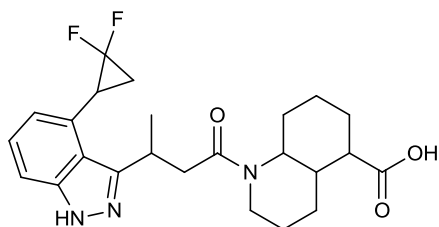


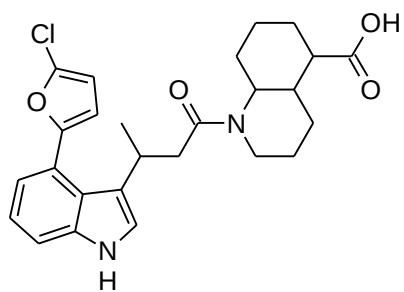
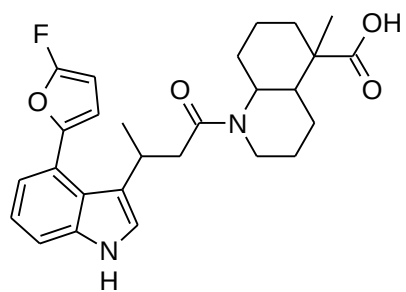
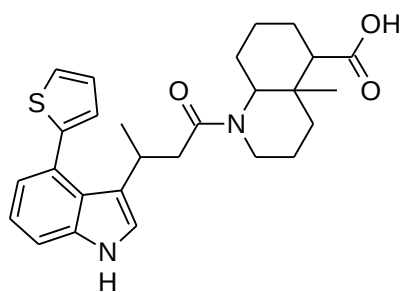
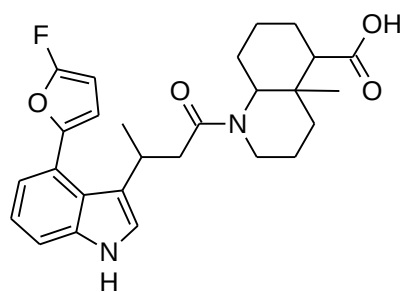
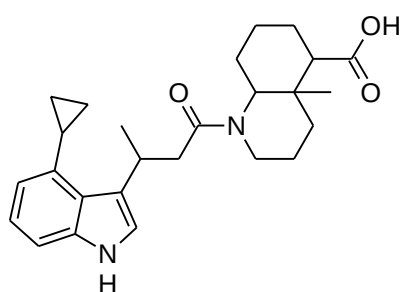
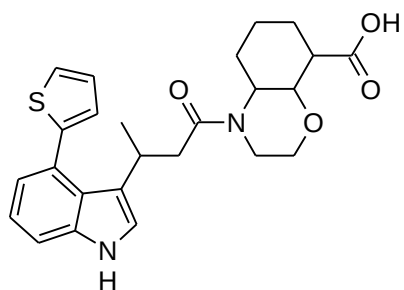
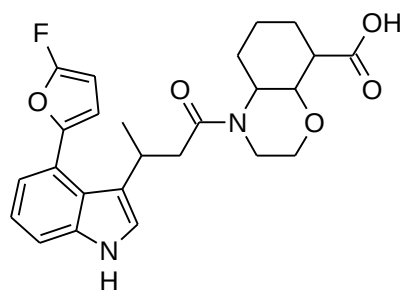
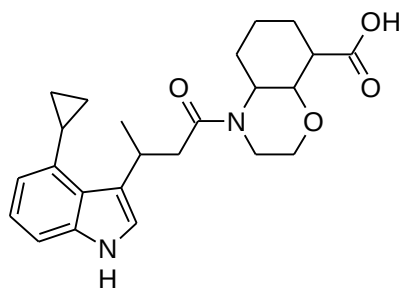


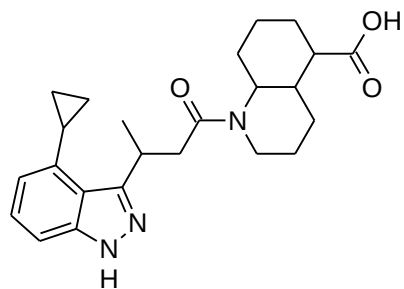
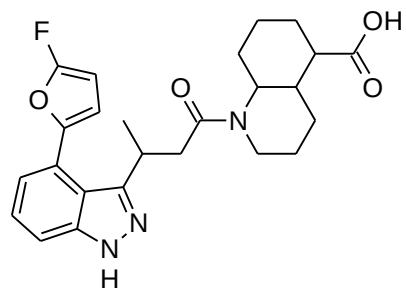
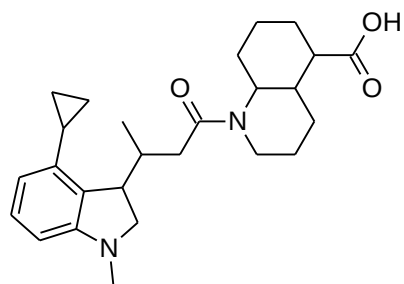
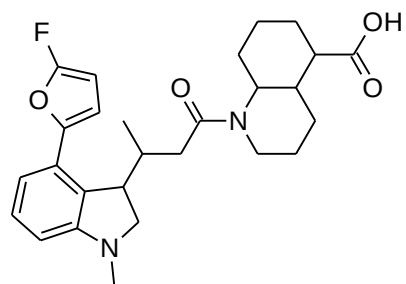
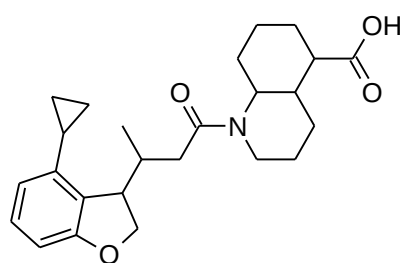
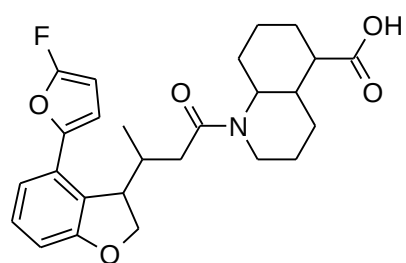
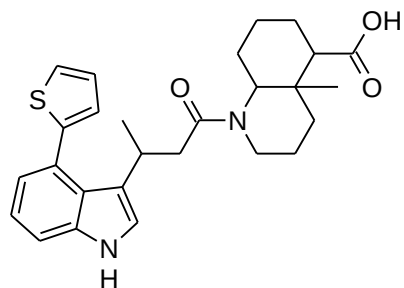
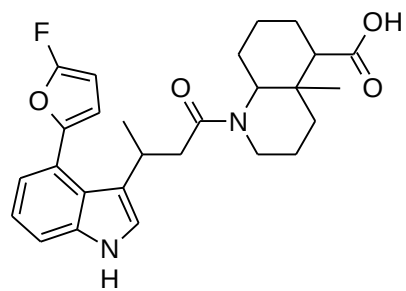
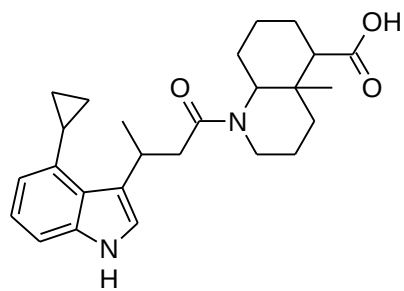


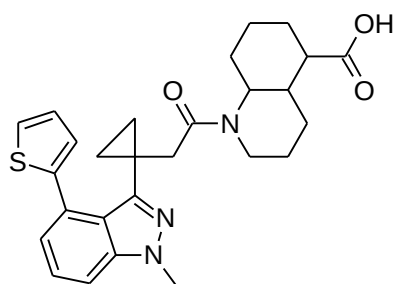
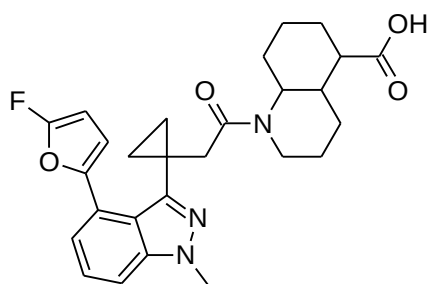
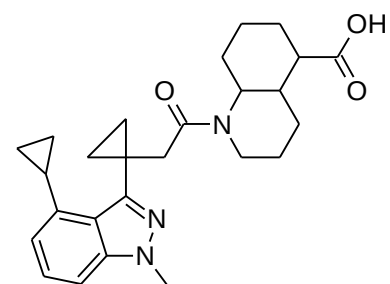
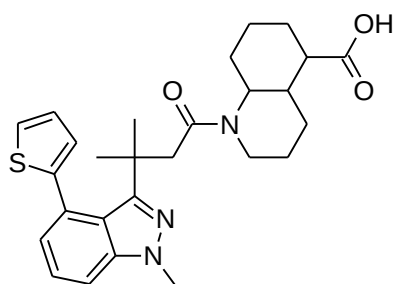
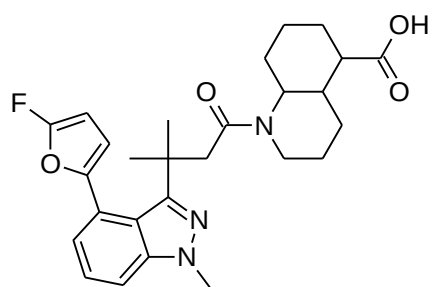
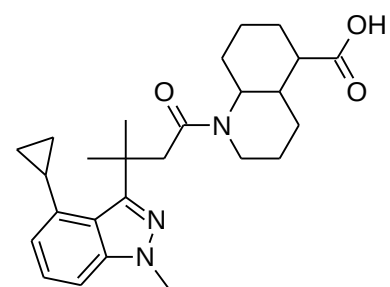
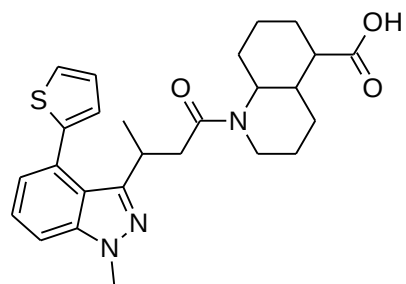
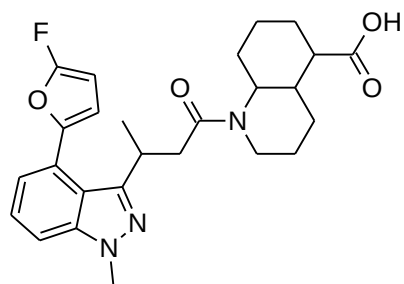
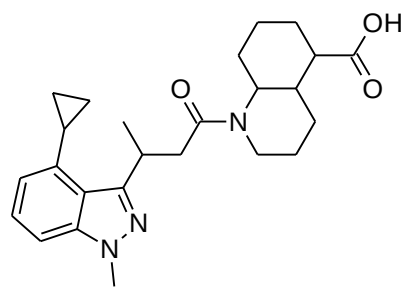
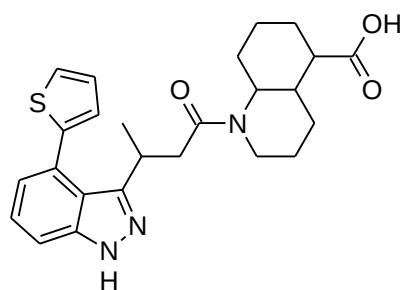


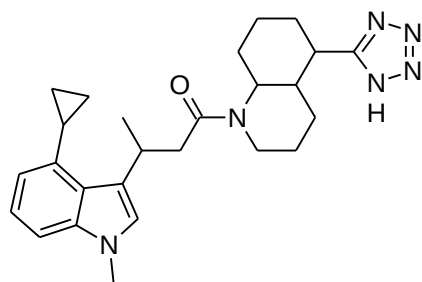
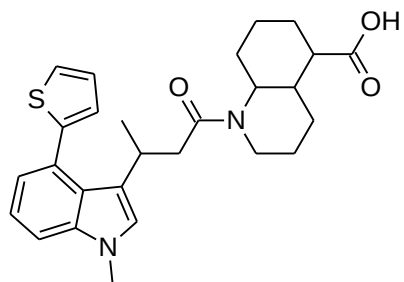
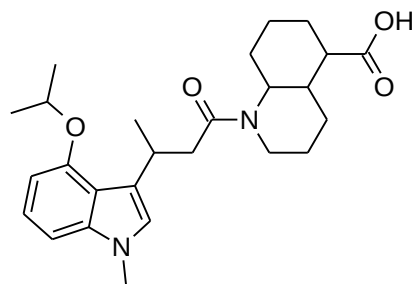
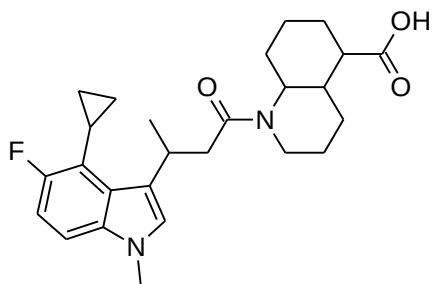
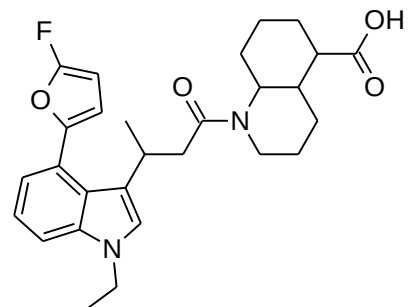
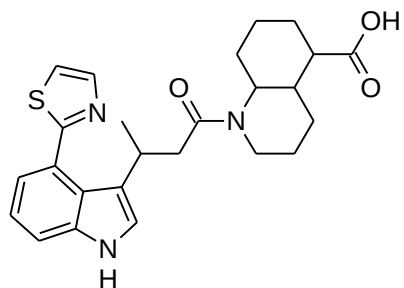
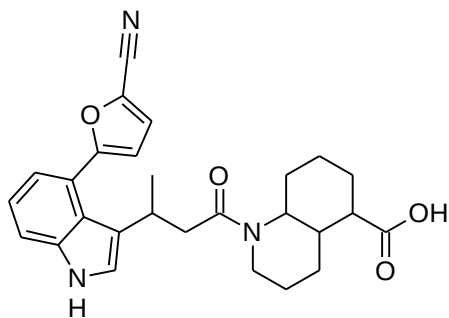
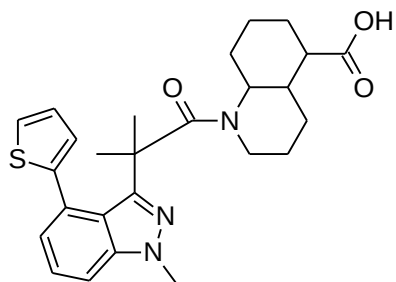
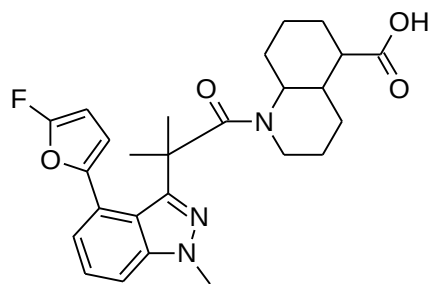
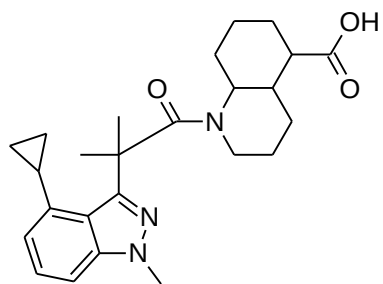


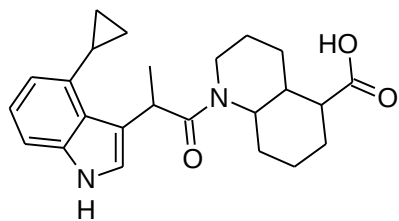
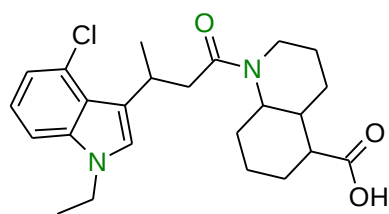
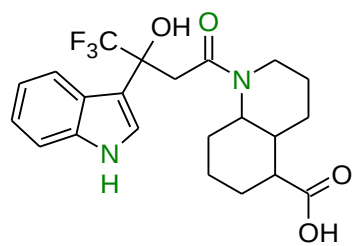
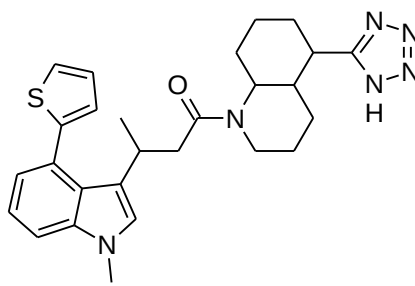
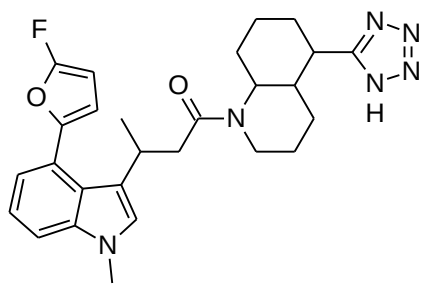
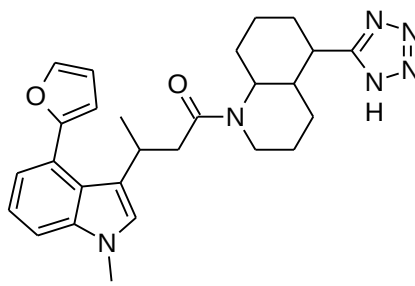
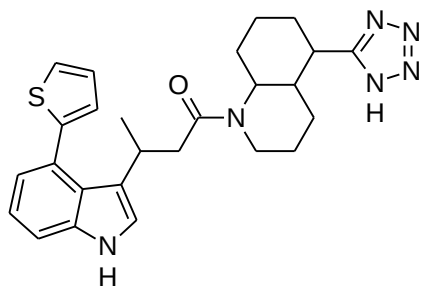
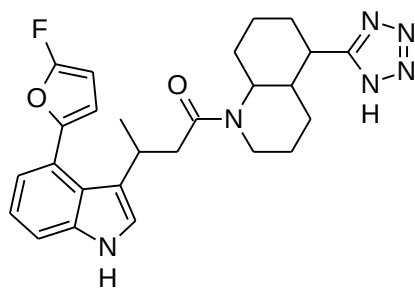
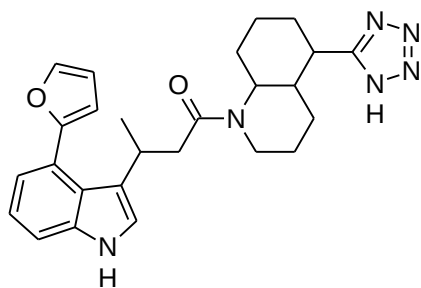










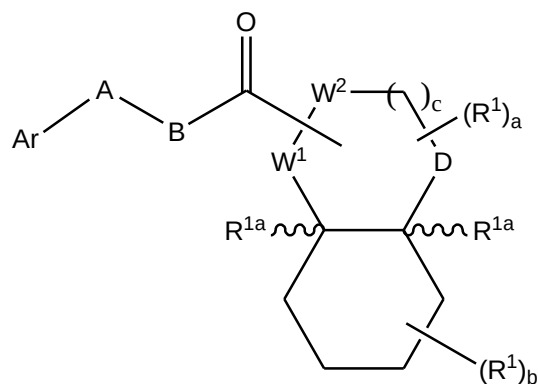


o su sal farmacéuticamente aceptable.

9. Una composición farmacéutica que incluye un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8 y un diluyente, excipiente o vehículo farmacéuticamente aceptable.

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



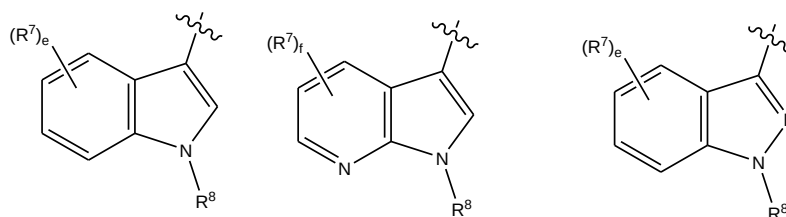
Fórmula (I)

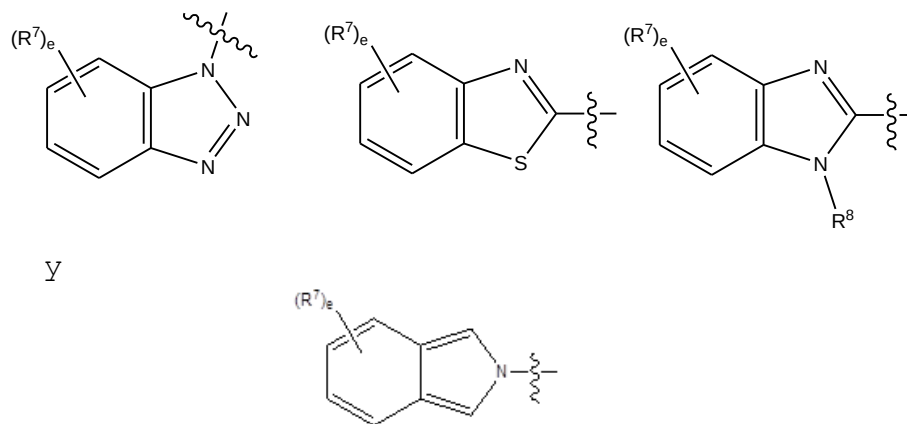
caracterizado porque:

cada  $R^1$  y  $R^{1a}$  es independientemente seleccionado del grupo que consiste de H, metilo,  $CONHC(CH_3)_3$ , OH,  $CO_2H$ ,  $CO_2CH_3$ ,  $CO_2CH_2CH_3$ , fenilo,  $CH_2OH$ , CN y  $OCH_3$ ;

o cualquiera dos  $R^1$  en átomos de carbono adyacentes se puede unir para formar una fracción cíclica, o cualquiera dos  $R^1$  en el mismo carbono cuando se toman juntos pueden formar un grupo de la fórmula  $=O$ .

Ar es una opcionalmente sustituida por grupo  $c1-C_{18}$  heteroarilo;





en donde cada  $R^7$  es independientemente seleccionado  
 del grupo que consiste H, halógeno, OH,  $\text{NO}_2$ , CN, SH,  $\text{NH}_2$ ,  $\text{CF}_3$ ,  
 $\text{OCF}_3$ , ~~opcionalmente sustituido~~  $\text{C}_1\text{-C}_{12}$ alquilo, ~~opcionalmente~~  
~~sustituido~~  $\text{C}_1\text{-C}_{12}$ haloalquilo, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$   
 $\text{C}_{12}$ alquenilo, ~~opcionalmente sustituido~~  $\text{C}_2\text{-C}_{12}$ alquinilo,  
~~opcionalmente sustituido~~  $\text{C}_2\text{-C}_{12}$ heteroalquilo, ~~opcionalmente~~  
~~sustituido~~  $\text{C}_3\text{-C}_{12}$ cicloalquilo, ~~opcionalmente sustituido~~  $\text{C}_3\text{-}$   
 $\text{C}_{12}$ cicloalquenilo, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$   
 $\text{C}_{12}$ heterocicloalquilo, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$   
 $\text{C}_{12}$ heterocicloalquenilo, opcionalmente sustituido  $\text{C}_6\text{-}$   
 $\text{C}_{18}$ arilo, opcionalmente sustituido  $\text{C}_1\text{-C}_{18}$ heteroarilo,  
~~opcionalmente sustituido~~  $\text{C}_1\text{-C}_{12}$ alquiloxi, ~~opcionalmente~~  
~~sustituido~~  $\text{C}_2\text{-C}_{12}$ alqueniloxi, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$   
 $\text{C}_{12}$ alquiniloxi, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$   
 $\text{C}_{10}$ heteroalquiloxi, ~~opcionalmente sustituido~~  $\text{C}_3\text{-}$   
 $\text{C}_{12}$ cicloalquiloxi, ~~opcionalmente sustituido~~  $\text{C}_3\text{-}$   
 $\text{C}_{12}$ cicloalqueniloxi, ~~opcionalmente sustituido~~  $\text{C}_2\text{-}$

C<sub>12</sub>heterocicloalquiloxi, ~~opcionalmente sustituido~~ C<sub>2</sub>-C<sub>12</sub>  
heterocicloalquenilo, ~~opcionalmente sustituido~~ C<sub>6</sub>-  
C<sub>18</sub>arilo, ~~opcionalmente sustituido~~ C<sub>1</sub>-C<sub>1</sub> heteroarilo, ~~opcionalmente sustituido~~ C<sub>1</sub>-C<sub>12</sub>alquiloamino, SR<sup>9</sup>, SO<sub>3</sub>H,  
5 SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>R<sup>9</sup>, SONR<sup>9</sup>R<sup>10</sup>, SOR<sup>9</sup>, COR<sup>9</sup>, COOH, COOR<sup>9</sup>, CONR<sup>9</sup>R<sup>10</sup>,  
NR<sup>9</sup>COR<sup>10</sup>, NR<sup>9</sup>COOR<sup>10</sup>, NR<sup>9</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>9</sup>CONR<sup>9</sup>R<sup>10</sup>, NR<sup>9</sup>R<sup>10</sup>, y acil;

en donde cada sustituyente opcional es independientemente  
seleccionado del grupo que consiste de Cl, Br, F, OH, CO<sub>2</sub>H,  
10 CN y C<sub>1</sub>-C<sub>6</sub> alquilo;

en donde R<sup>8</sup> es seleccionado del grupo que consiste  
en H, ~~opcionalmente sustituido~~ C<sub>1</sub>- C<sub>12</sub>alquilo, ~~opcionalmente  
sustituido~~ C<sub>2</sub>-C<sub>12</sub>alqueno, ~~opcionalmente sustituido~~ C<sub>2</sub>-  
15 C<sub>12</sub>alquino, ~~opcionalmente sustituido~~ C<sub>2</sub>-C<sub>12</sub>heteroalquilo,  
~~opcionalmente sustituido~~ C<sub>3</sub>-C<sub>12</sub>cicloalquilo, ~~opcionalmente  
sustituido~~ C<sub>2</sub>-C<sub>12</sub>heterocicloalquilo, ~~opcionalmente sustituido~~  
C<sub>6</sub>-C<sub>18</sub>arilo, ~~opcionalmente sustituido~~ C<sub>1</sub>- C<sub>18</sub>heteroarilo,  
20 SO<sub>3</sub>H, SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup>, SO<sub>2</sub>R<sup>9</sup>, SONR<sup>9</sup>R<sup>10</sup>, SOR<sup>9</sup>, COR<sup>9</sup>, COOH, COOR<sup>9</sup>, y  
CONR<sup>9</sup>R<sup>10</sup>;

en donde cada R<sup>9</sup> y R<sup>10</sup> es independientemente  
seleccionado del grupo que consiste en H, ~~opcionalmente  
sustituido~~ C<sub>1</sub>-C<sub>12</sub>alquilo, ~~opcionalmente sustituido~~ C<sub>2</sub>-  
25 C<sub>10</sub>heteroalquilo, ~~opcionalmente sustituido~~ C<sub>1</sub>-C<sub>12</sub>haloalquilo,  
~~opcionalmente sustituido~~ C<sub>3</sub>-C<sub>12</sub>cicloalquilo, ~~opcionalmente~~

~~sustituido~~-C<sub>6</sub>-C<sub>18</sub>arilo, y ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>18</sub>heteroarilo.

e es un entero seleccionado del grupo que consiste de 0, 1, 2, 3 y 4;

5 f es un entero seleccionado del grupo que consiste de 0, 1, 2, y 3;

10 A es -CR<sup>a</sup>R<sup>b</sup>- en donde R<sup>a</sup> y R<sup>b</sup> son diferentes;

B es un grupo de la fórmula-(CR<sup>c</sup>R<sup>d</sup>)<sub>n</sub>-;

15 en donde cada R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup> y R<sup>d</sup> es independientemente seleccionado del grupo que consiste en H, halógeno, OH, NO<sub>2</sub>, CN, SH, NH<sub>2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>12</sub>alquilo, ~~opcionalmente sustituido~~-C<sub>2</sub>-C<sub>10</sub>heteroalquilo, ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>12</sub>haloalquilo, ~~opcionalmente sustituido~~-C<sub>3</sub>-C<sub>12</sub>cicloalquilo, ~~opcionalmente sustituido~~-C<sub>6</sub>-C<sub>18</sub>arilo, ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>18</sub>heteroarilo; SR<sup>2</sup>, SO<sub>3</sub>H, SO<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, SO<sub>2</sub>R<sup>2</sup>, SONR<sup>2</sup>R<sup>3</sup>, SOR<sup>2</sup>, COR<sup>2</sup>, COOH, COOR<sup>2</sup>, CONR<sup>2</sup>R<sup>3</sup>, NR<sup>2</sup>COR<sup>3</sup>, NR<sup>2</sup>COOR<sup>3</sup>, NR<sup>2</sup>SO<sub>2</sub>R<sup>3</sup>, NR<sup>2</sup>CONR<sup>2</sup>R<sup>3</sup>, NR<sup>2</sup>R<sup>3</sup>, y acil,

20 en donde cada R<sup>2</sup> y R<sup>3</sup> es independientemente seleccionado del grupo que consiste en H, ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>12</sub>alquilo, ~~opcionalmente sustituido~~-C<sub>2</sub>-C<sub>10</sub>heteroalquilo, ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>12</sub>haloalquilo, ~~opcionalmente sustituido~~-C<sub>3</sub>-C<sub>12</sub>cicloalquilo, ~~opcionalmente~~

~~sustituido~~-C<sub>6</sub>-C<sub>18</sub>arilo, y ~~opcionalmente sustituido~~-C<sub>1</sub>-C<sub>18</sub>heteroarilo;

W<sup>1</sup> y W<sup>2</sup> están seleccionados de tal forma que uno es N y el otro es (CR<sup>1</sup><sub>2</sub>),

el enlace del carbono carbonil se une a cualquiera de W<sup>1</sup> o W<sup>2</sup> es N;

D es O o (CR<sup>1</sup><sub>2</sub>);

n es un entero seleccionado del grupo que consiste de 0, 1, 2, 3, y 4;

a es un entero seleccionado del grupo que consiste de 0, 1, y 2;

b es un entero seleccionado del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7, y 8,

c es 1;

o una sal farmacéuticamente aceptable de los mismos.

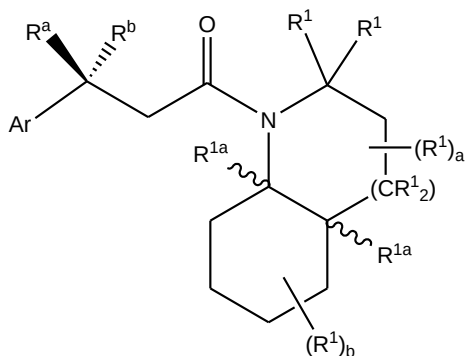
2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque D es (CR<sup>1</sup><sub>2</sub>).

3. Un compuesto de conformidad con la reivindicación 1, caracterizado porque B es CH<sub>2</sub>.

~~4. Un compuesto de conformidad con la reivindicación 1 a 3, caracterizado porque R<sup>a</sup> y R<sup>b</sup> son diferentes.~~

~~54.~~ Un compuesto de conformidad con la

reivindicación 1 que tiene la fórmula:



5

en donde Ar, R<sup>a</sup>, R<sup>b</sup>, R<sup>1</sup>, R<sup>1a</sup>, a y b son como se definen en la reivindicación 1.

10

65. Un compuesto de conformidad con la reivindicación 15, en donde uno de R<sup>a</sup> y R<sup>b</sup> es H y el otro es alquilo opcionalmente sustituido.

15

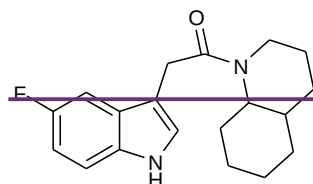
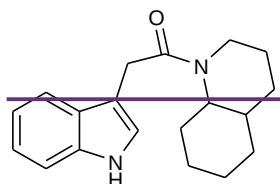
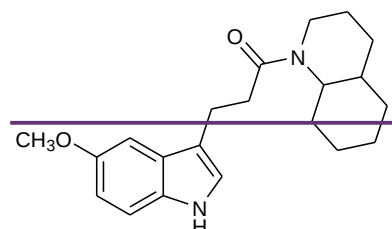
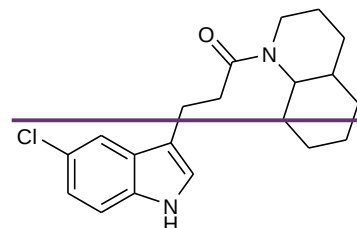
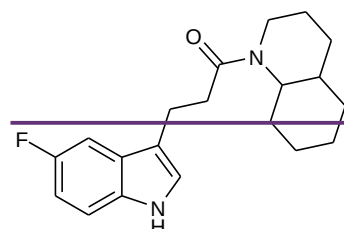
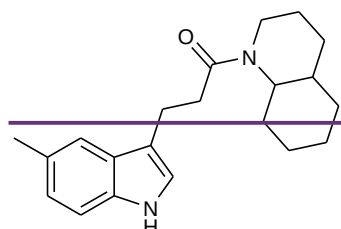
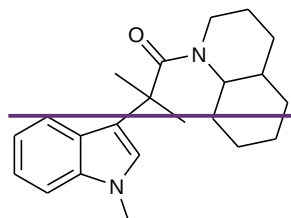
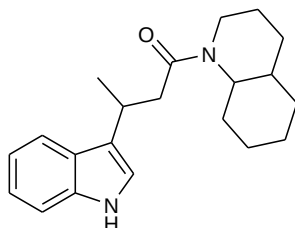
76. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el sustituyente R<sup>7</sup> está ubicado en la posición 4 o en la posición 5 del anillo de seis miembros.

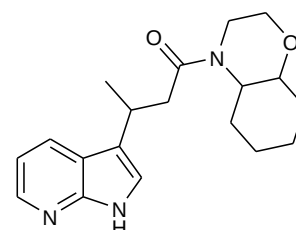
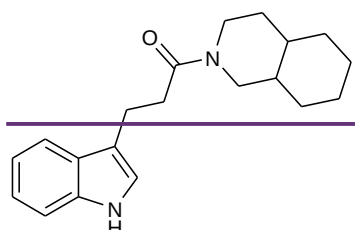
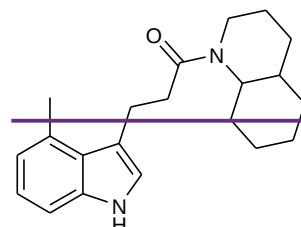
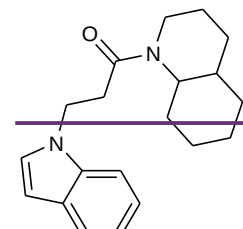
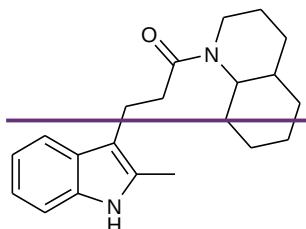
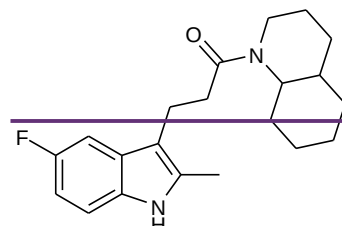
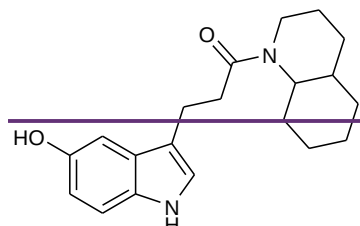
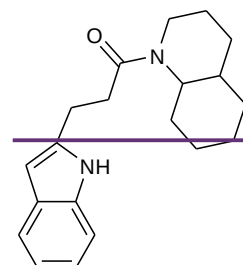
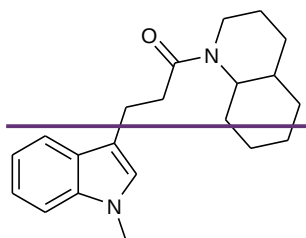
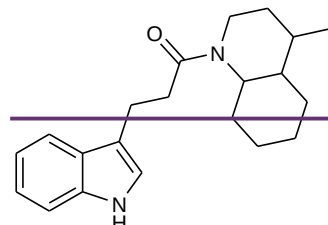
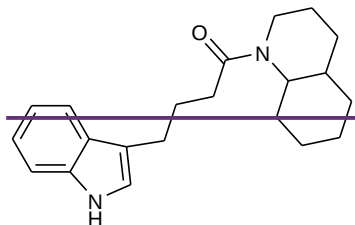
87. Un compuesto de conformidad con la reivindicación 1, caracterizado porque R<sup>7</sup> se selecciona del grupo que consiste de CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, Cl, Br, F, I OH, NO<sub>2</sub>, NH<sub>2</sub>, CN, SO<sub>3</sub>H, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub> y OCF<sub>3</sub>.

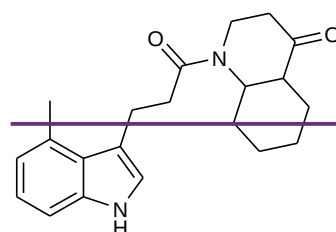
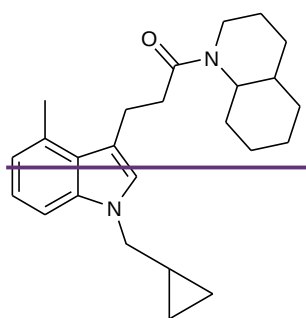
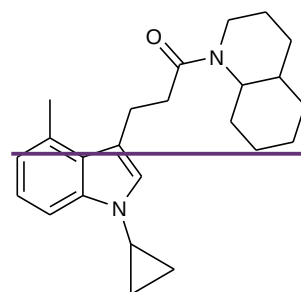
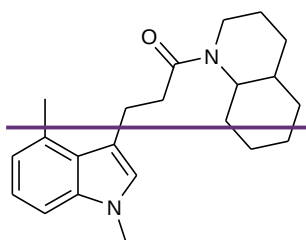
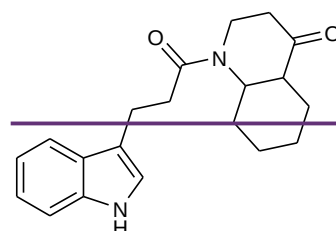
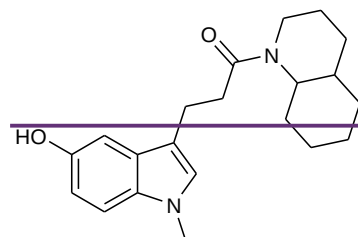
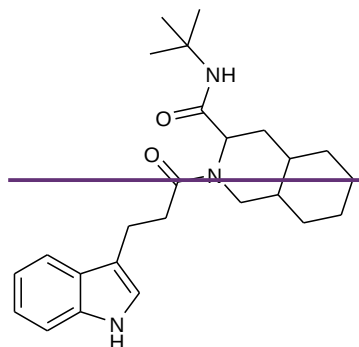
20

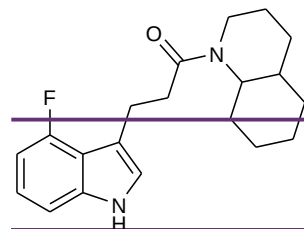
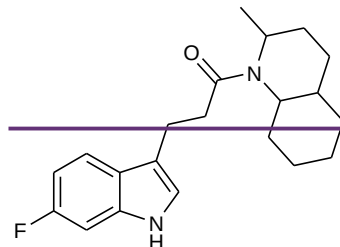
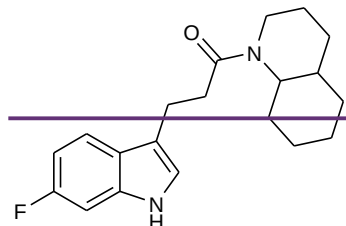
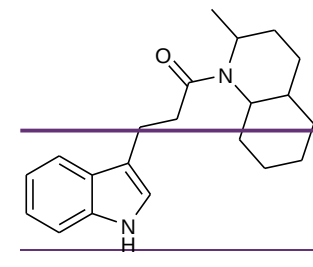
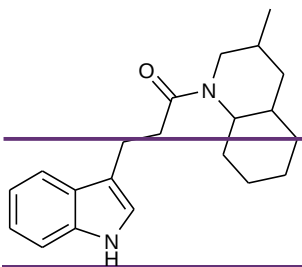
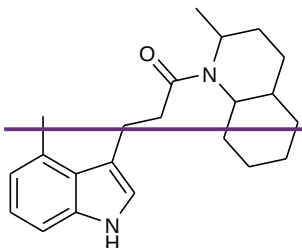
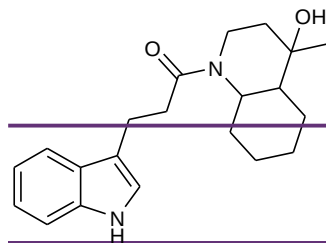
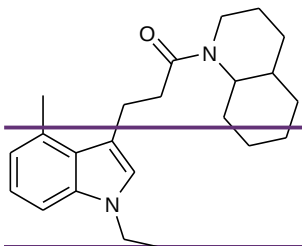
98. Un compuesto de conformidad con la

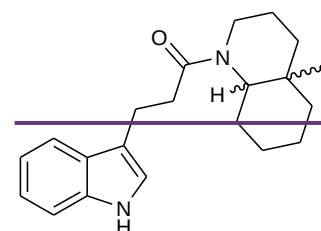
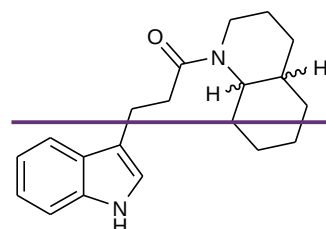
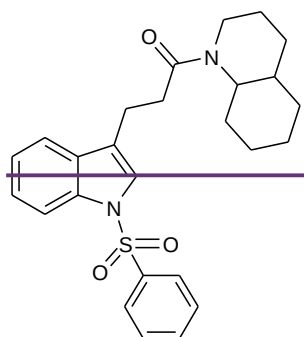
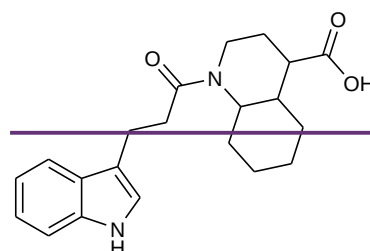
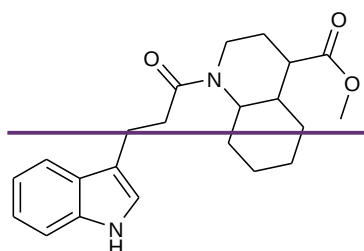
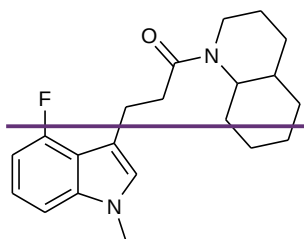
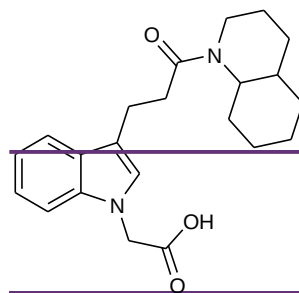
reivindicación 1, seleccionado del grupo que consiste en:

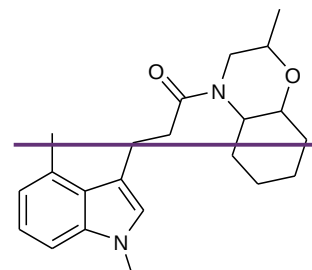
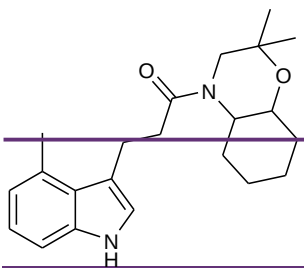
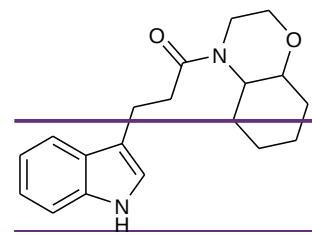
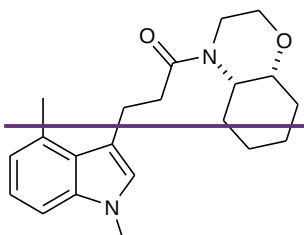
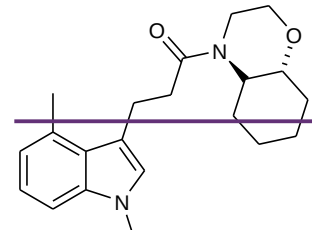
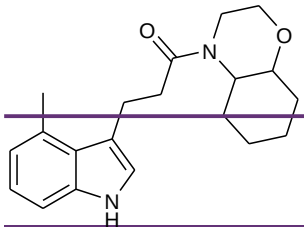
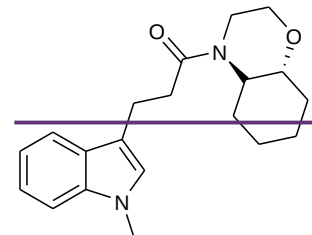
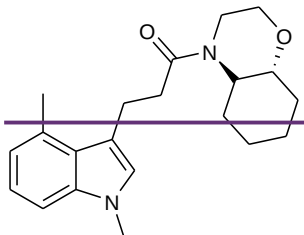
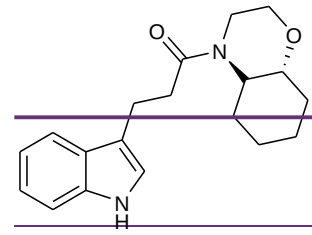
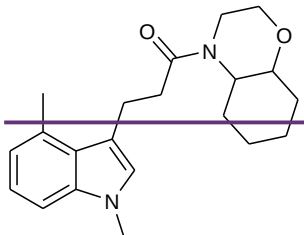
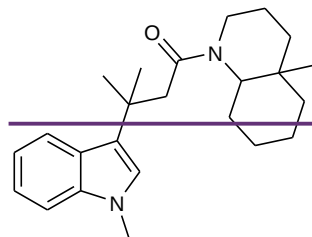
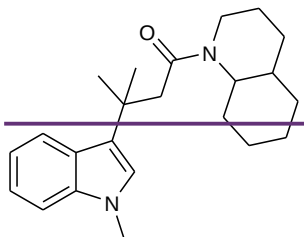


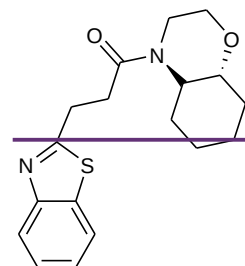
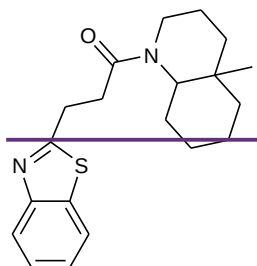
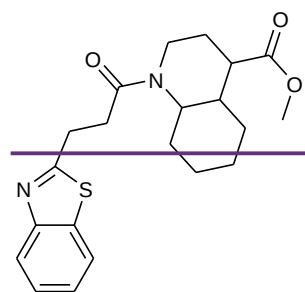
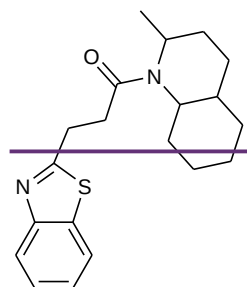
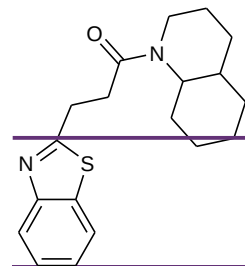
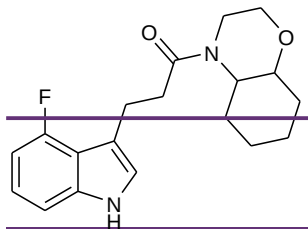
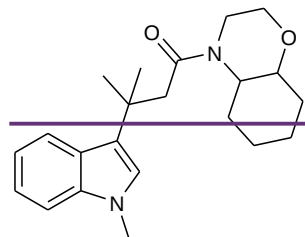
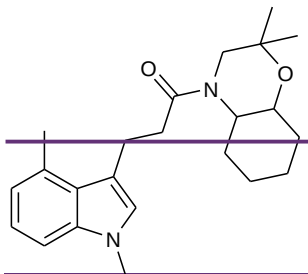


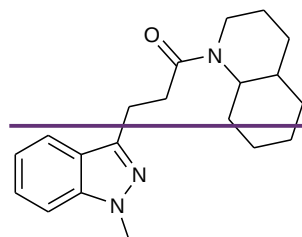
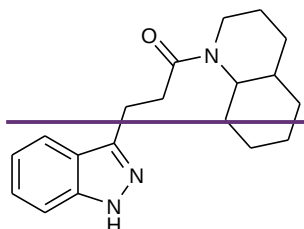
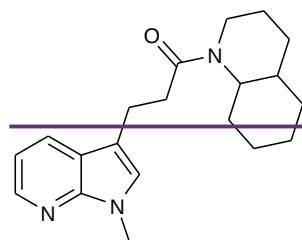
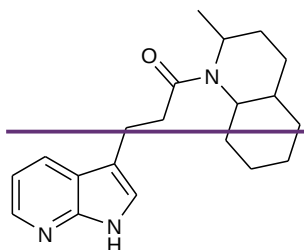
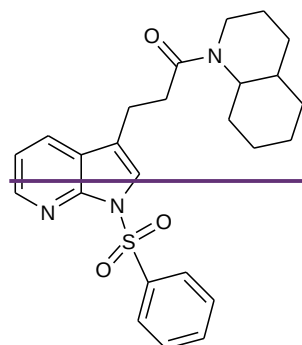
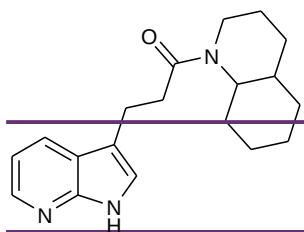
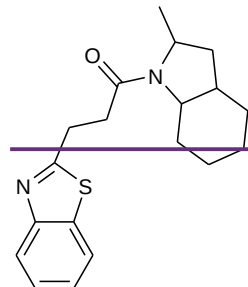
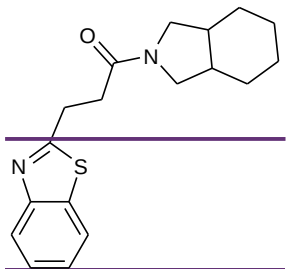
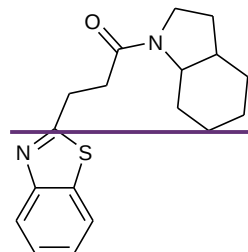
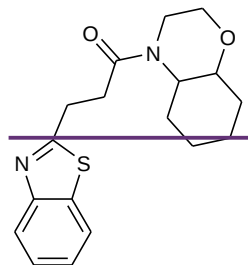


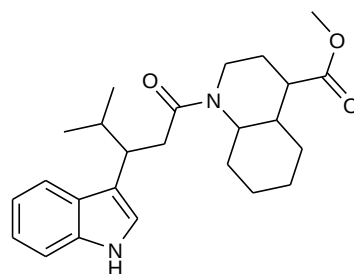
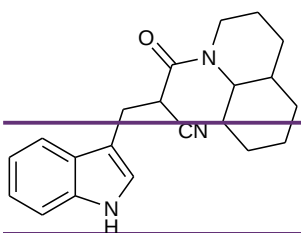
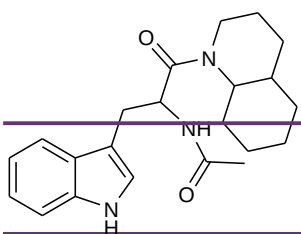
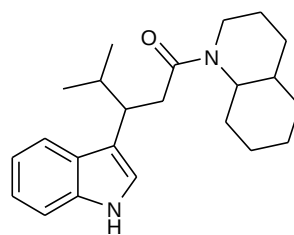
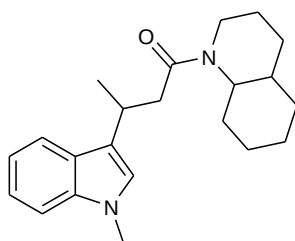
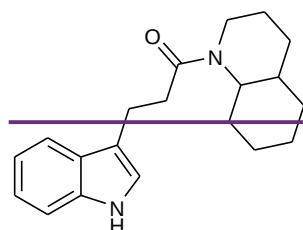
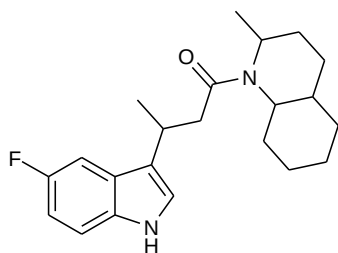
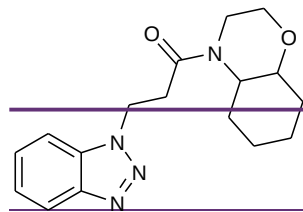
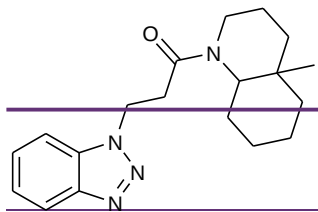


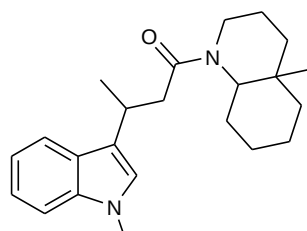
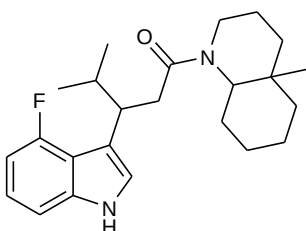
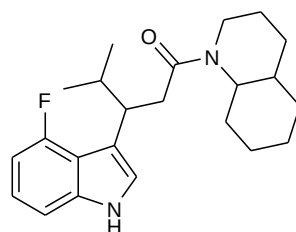
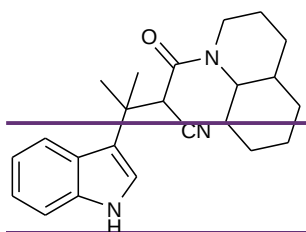
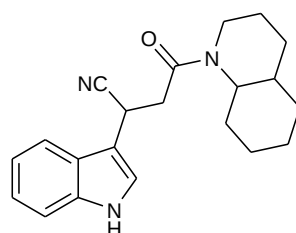
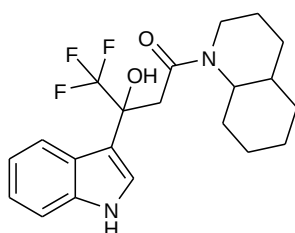
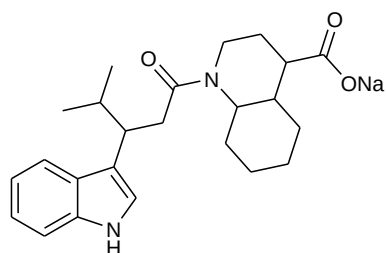
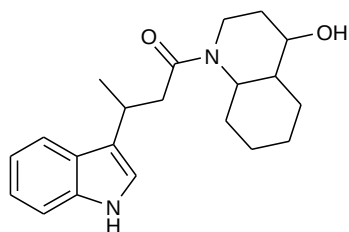
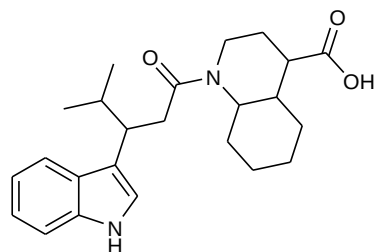
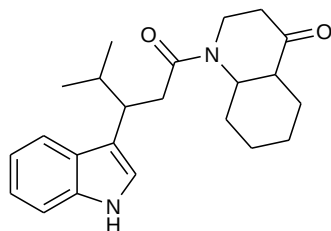
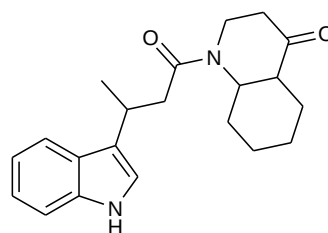
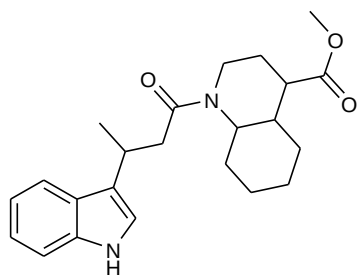


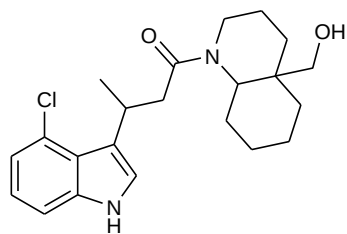
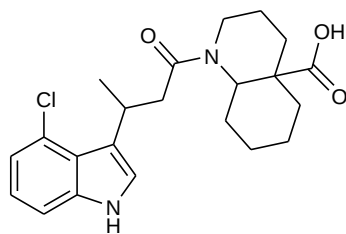
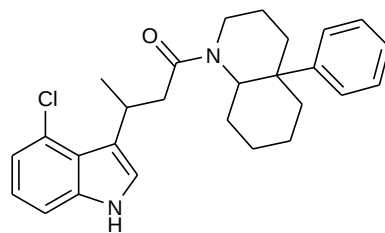
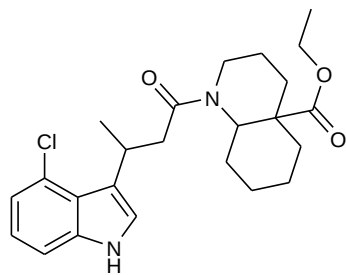
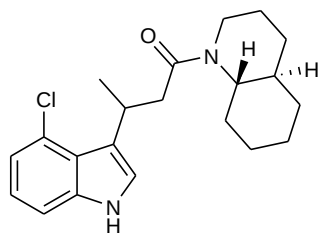
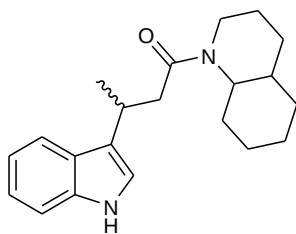
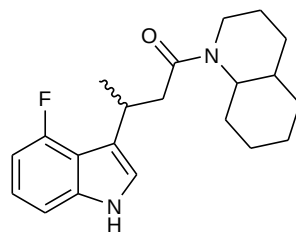
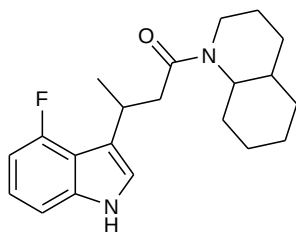
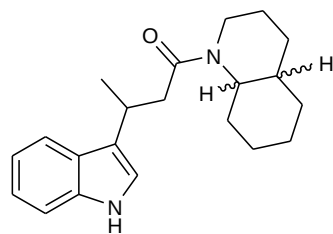
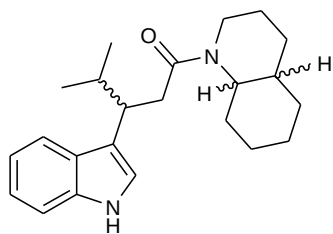
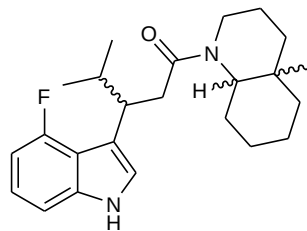
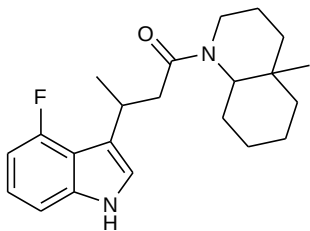


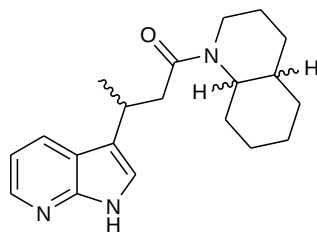
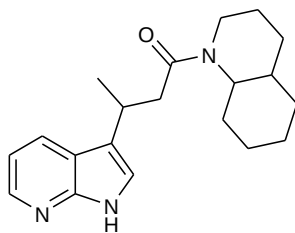
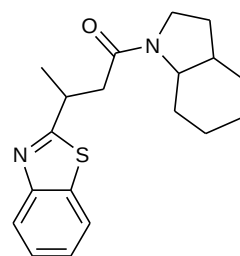
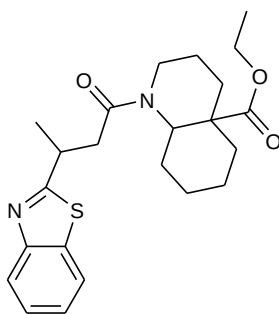
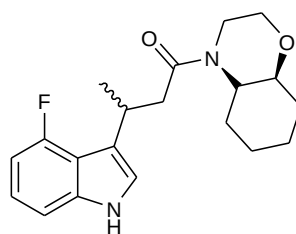
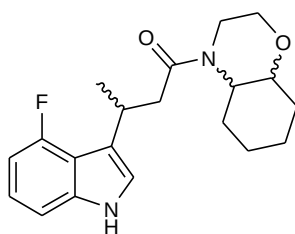
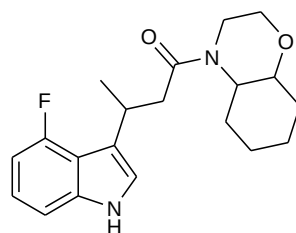
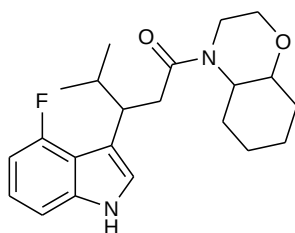
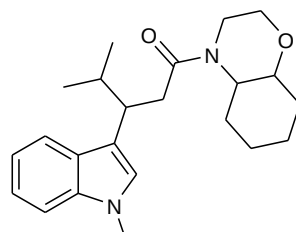
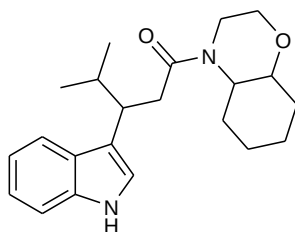
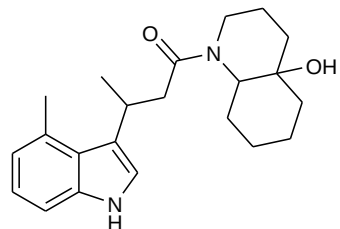
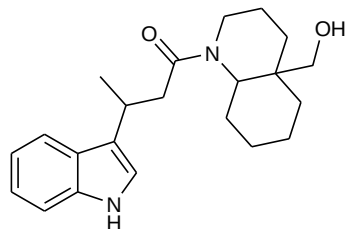


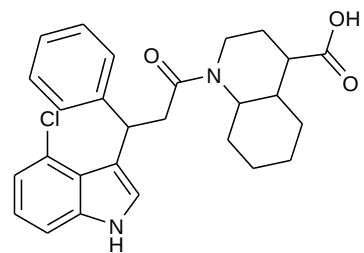
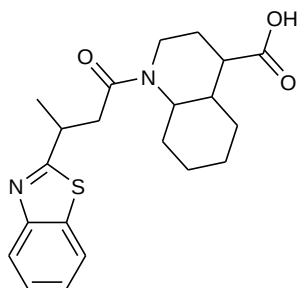
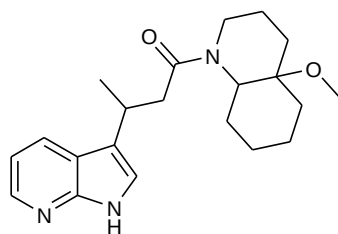
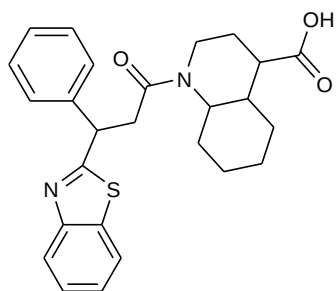
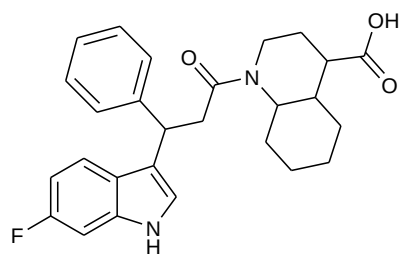
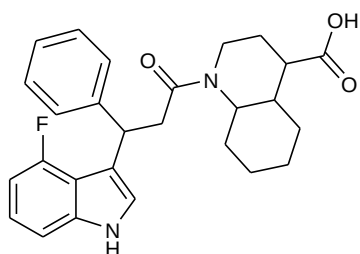
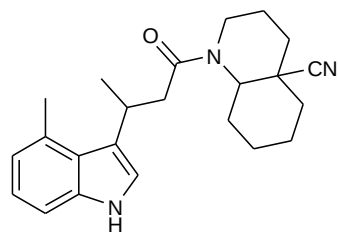
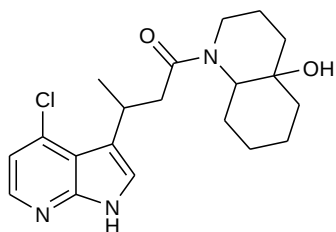
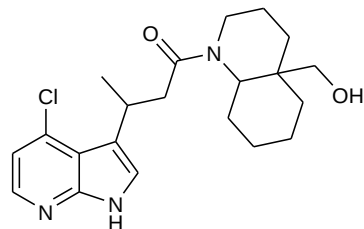
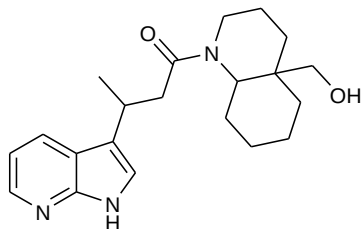


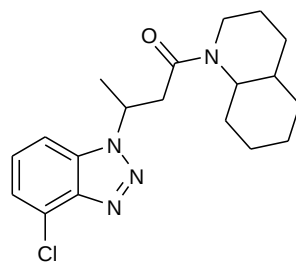
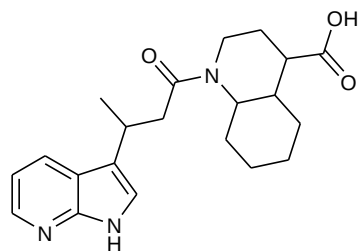
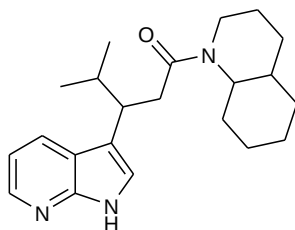
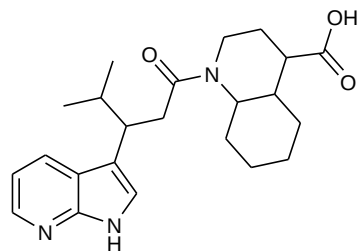
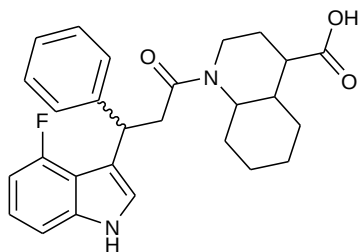
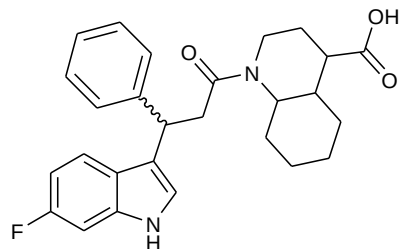
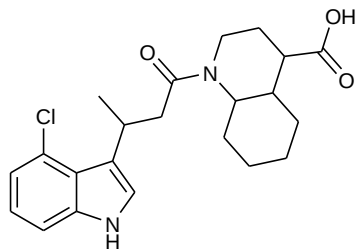
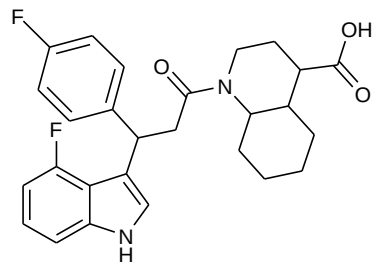
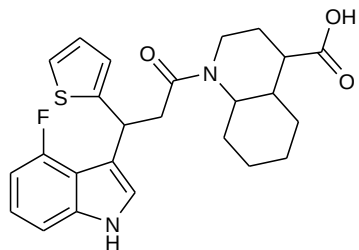


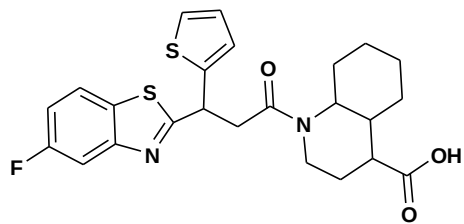
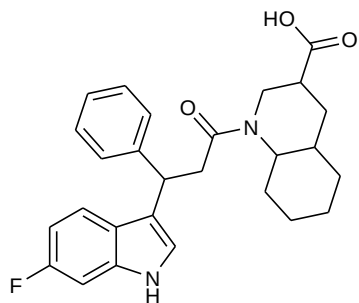
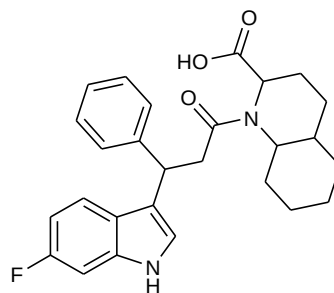
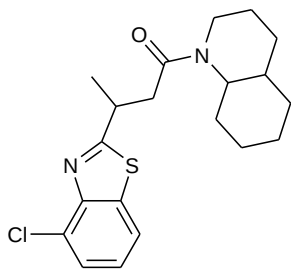
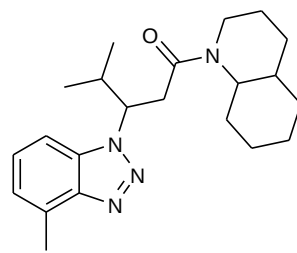
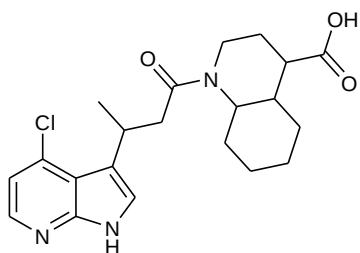
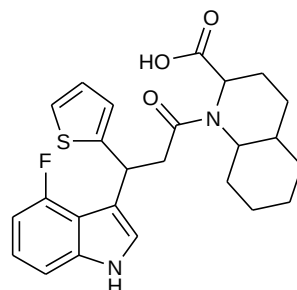
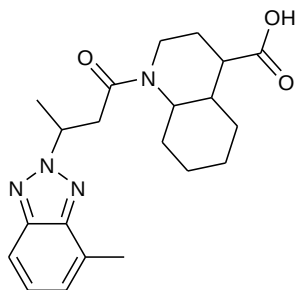
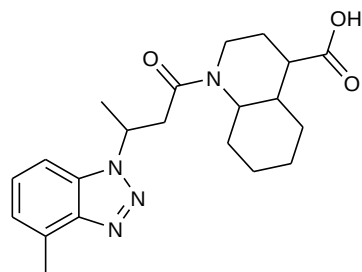
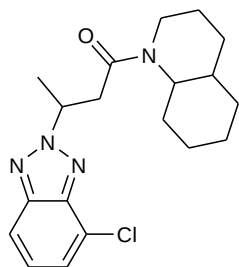


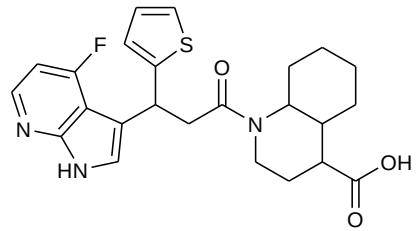
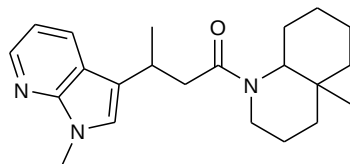
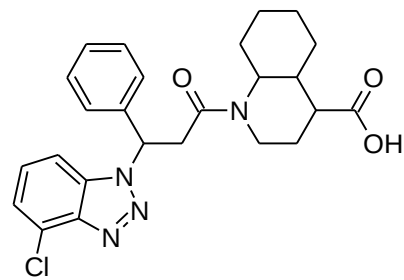
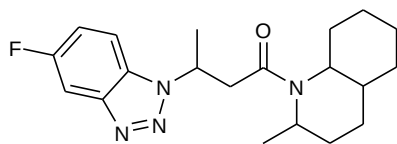
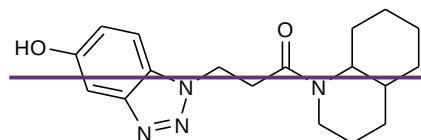
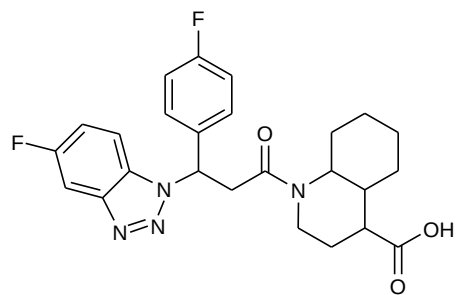
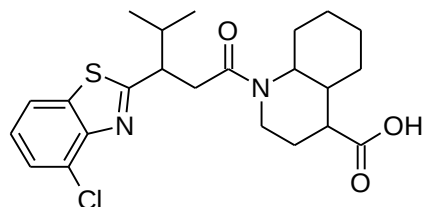
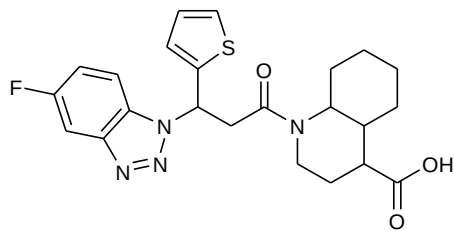
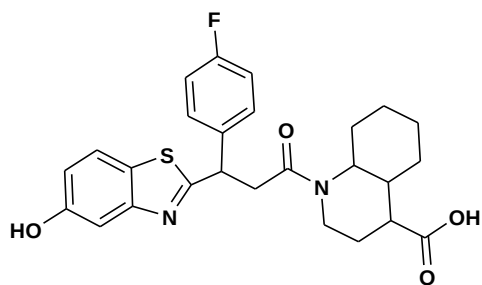
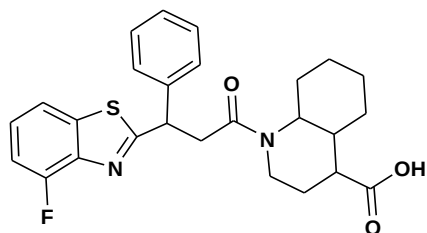


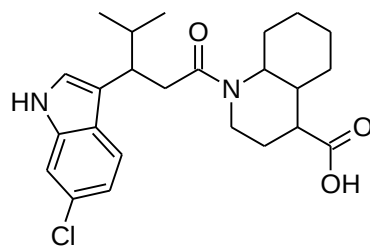
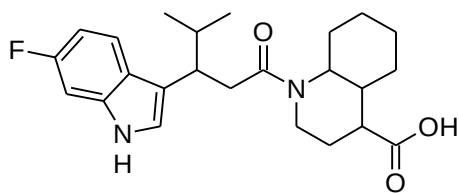
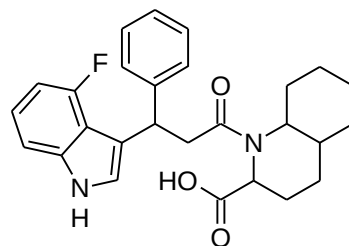
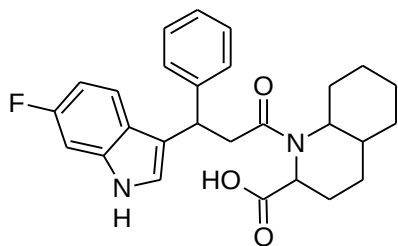
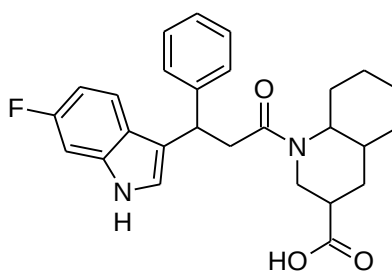
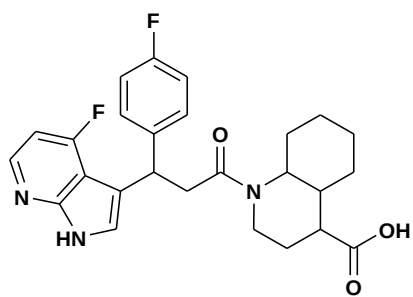
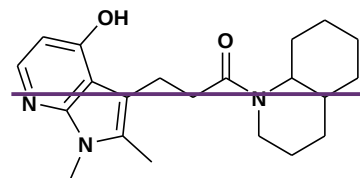
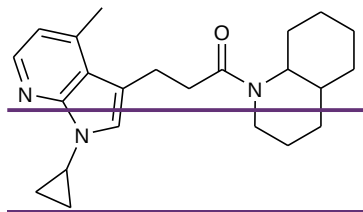
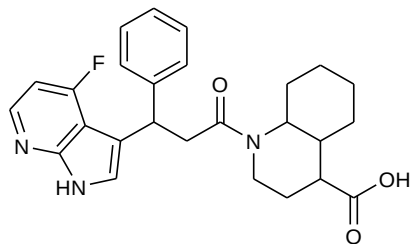


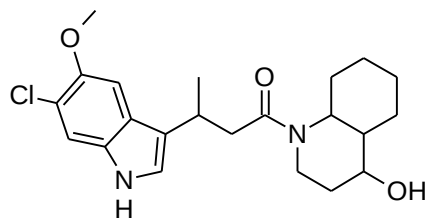
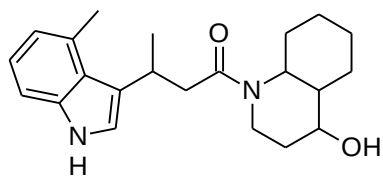
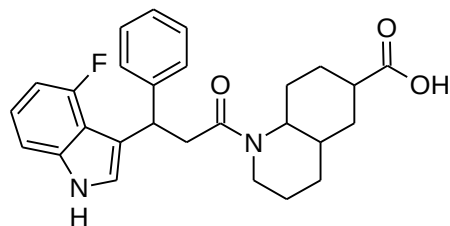
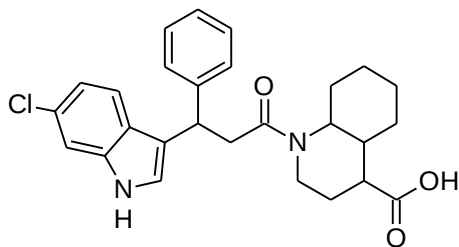
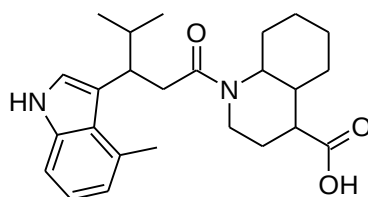
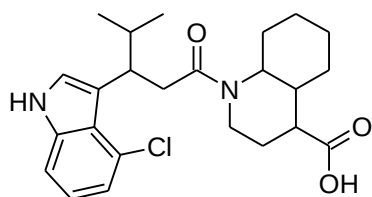
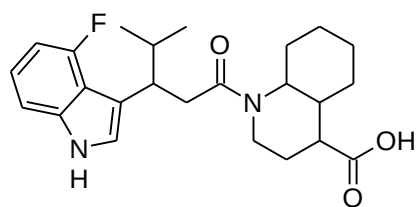
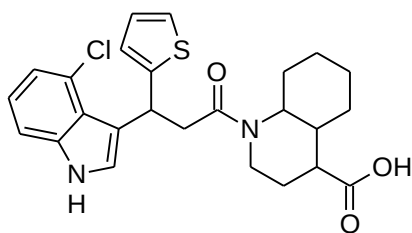
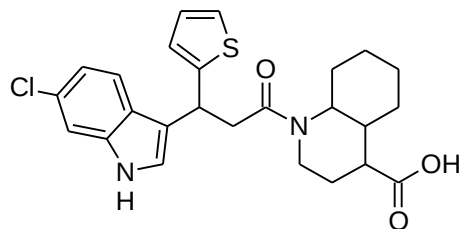
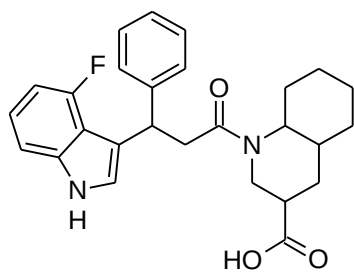


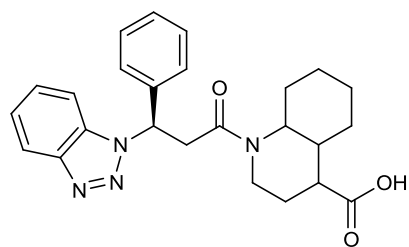
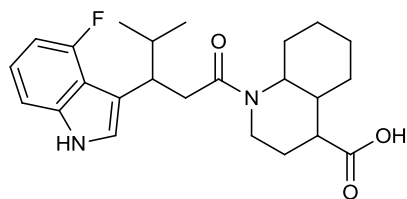
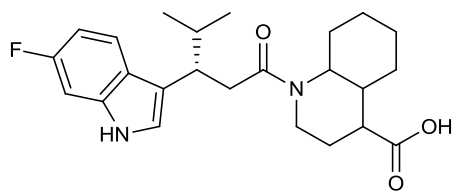
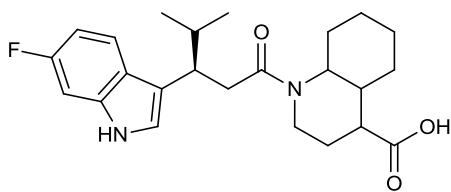
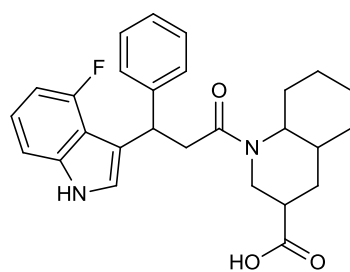
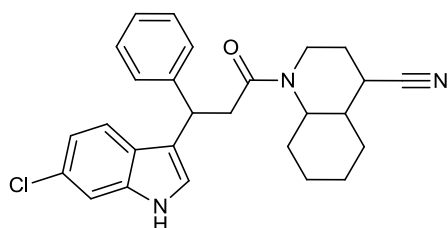
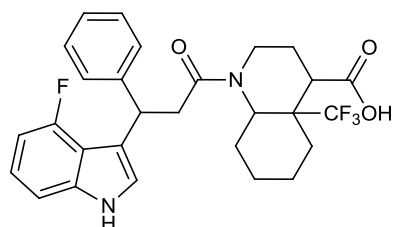
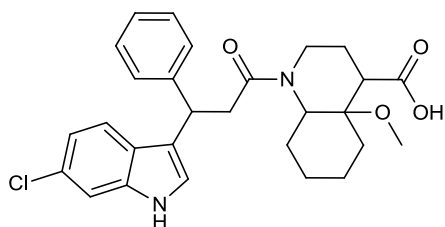
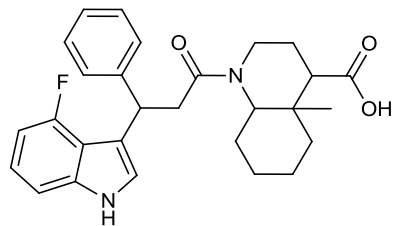
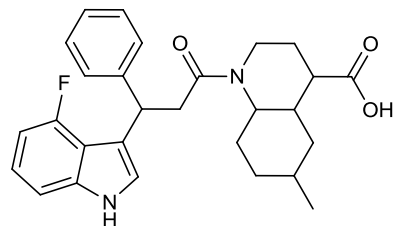
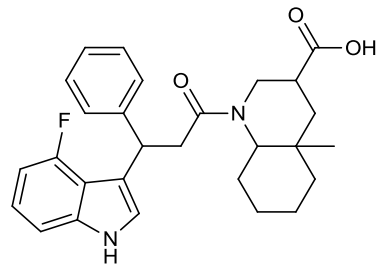
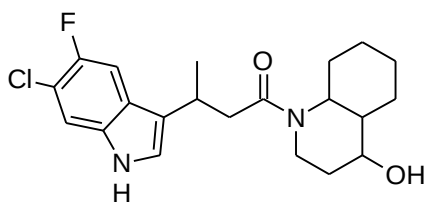


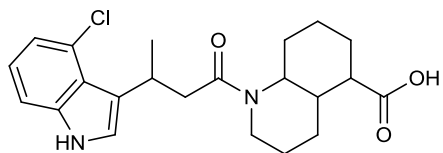
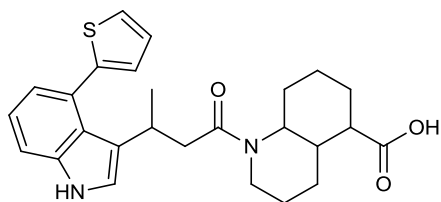
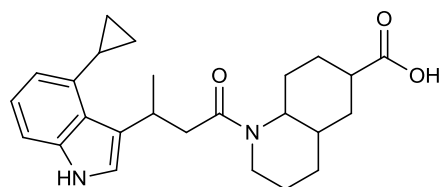
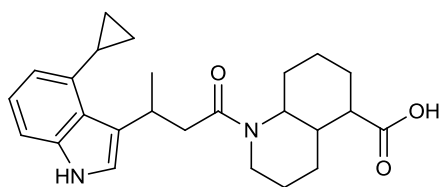
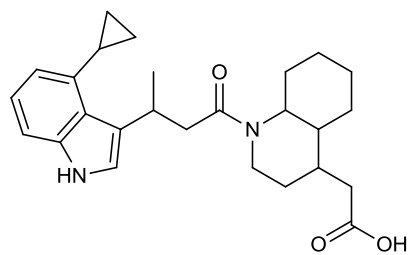
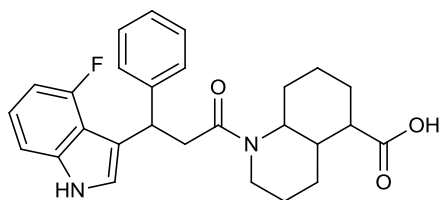
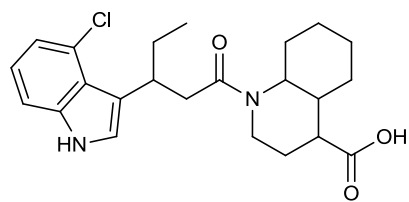
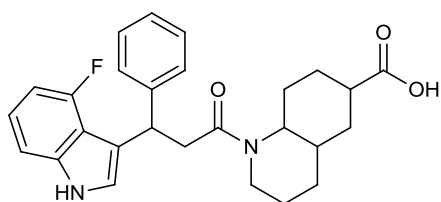
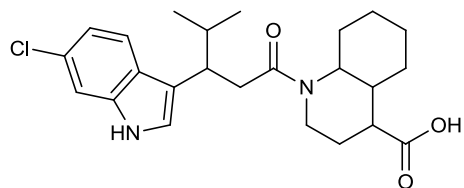
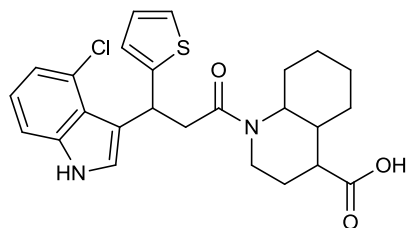
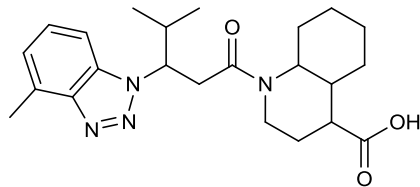
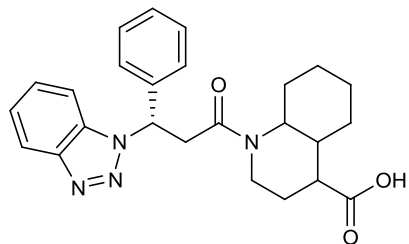


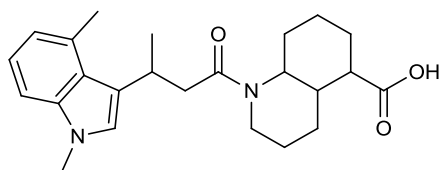
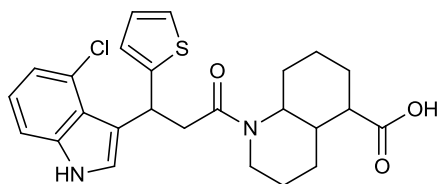
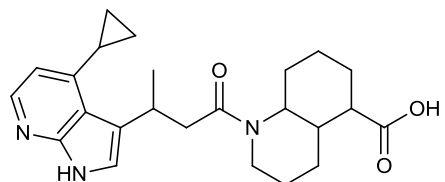
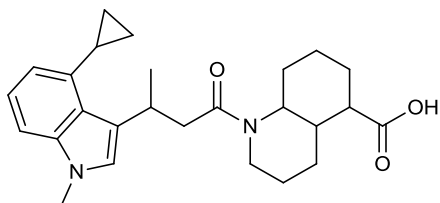
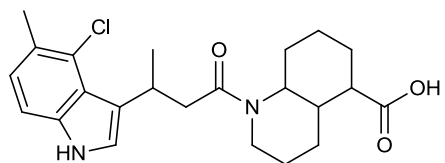
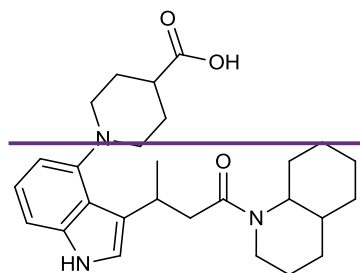
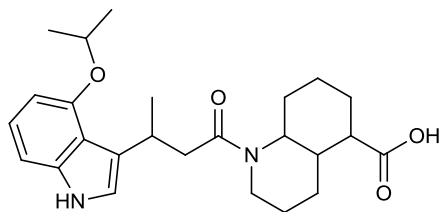
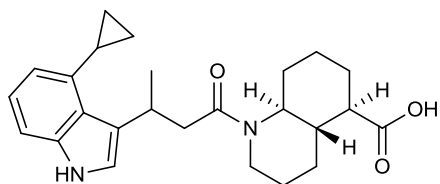
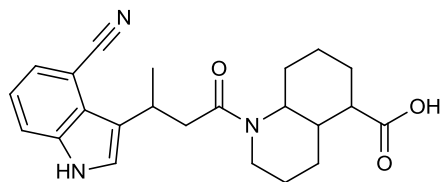
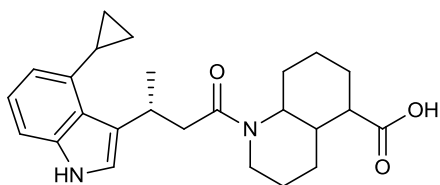
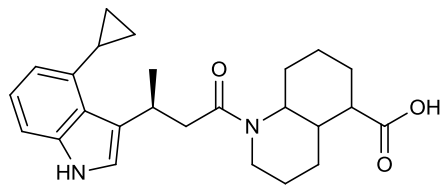
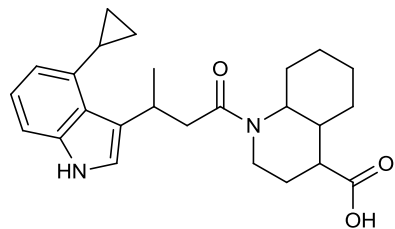


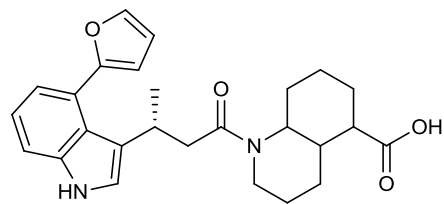
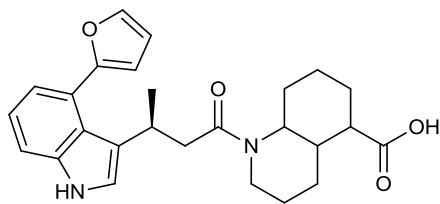
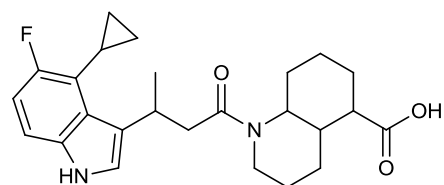
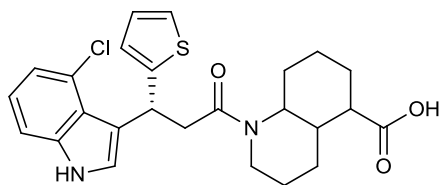
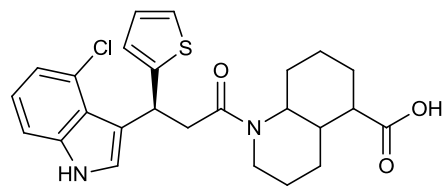
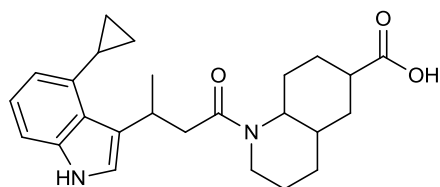
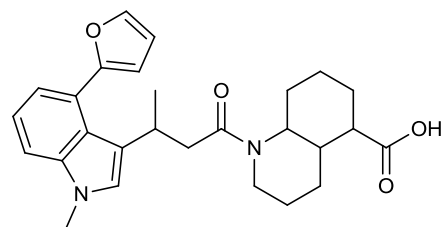
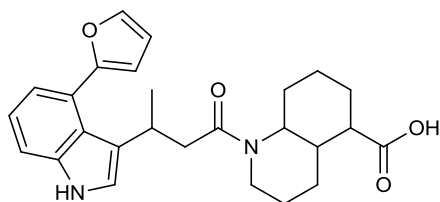
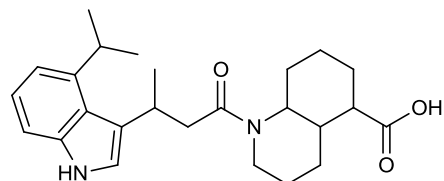
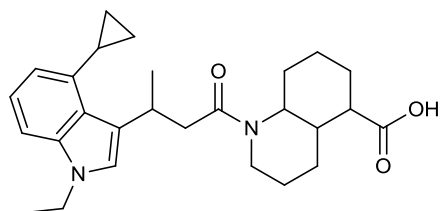
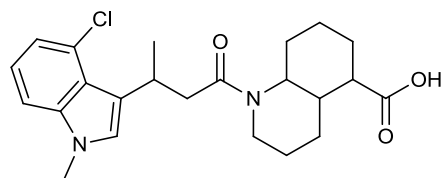
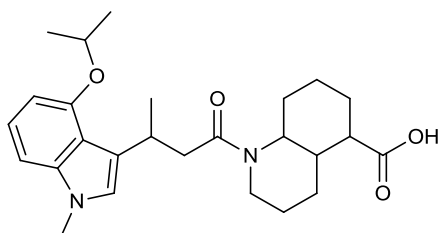


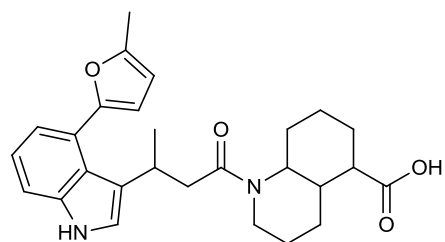
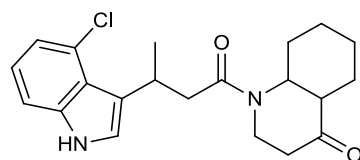
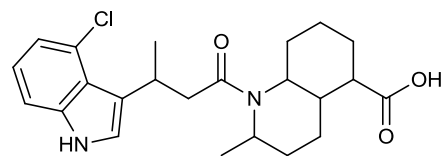
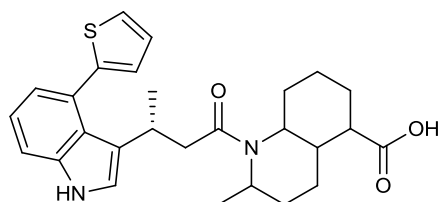
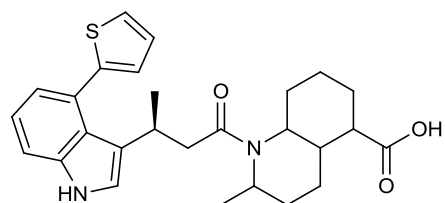
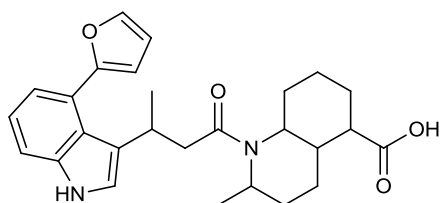
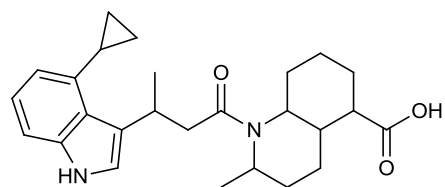
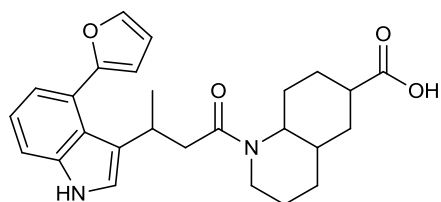
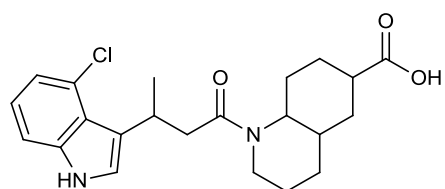
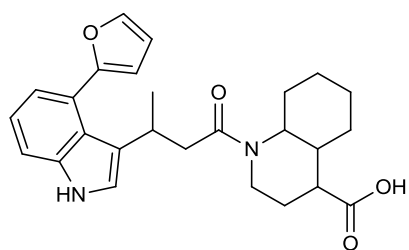
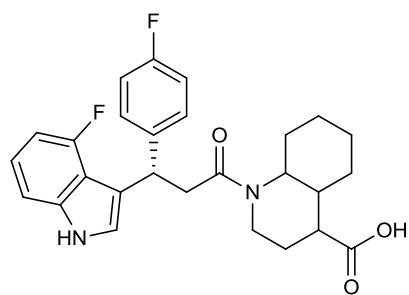
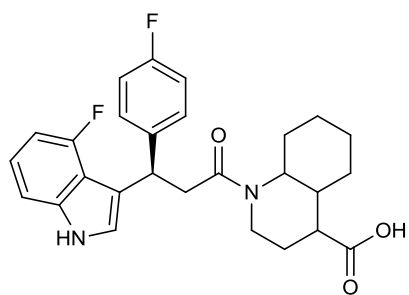


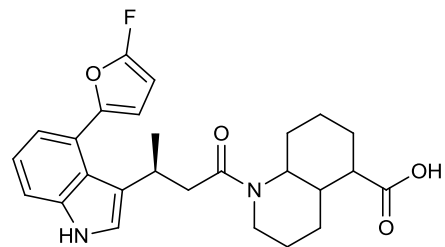
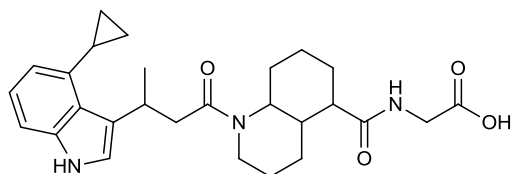
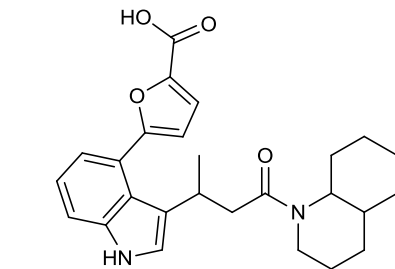
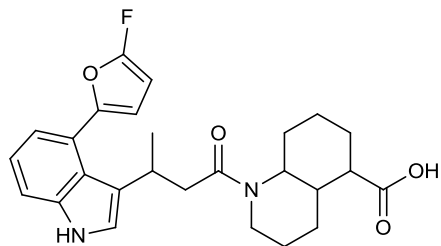
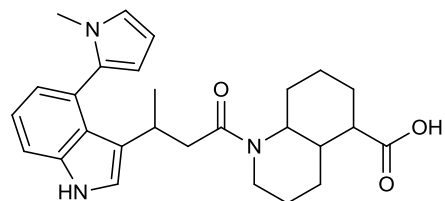
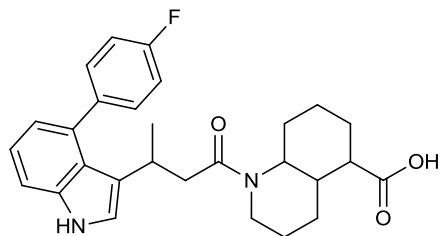
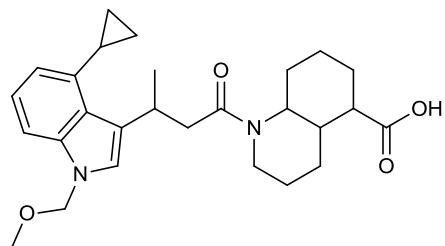
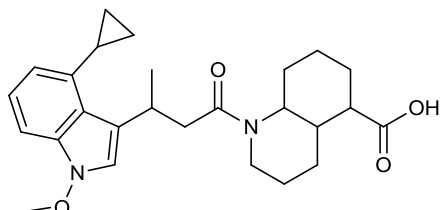
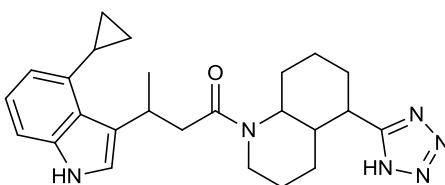
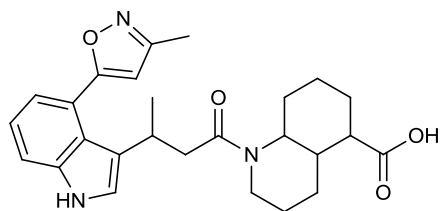
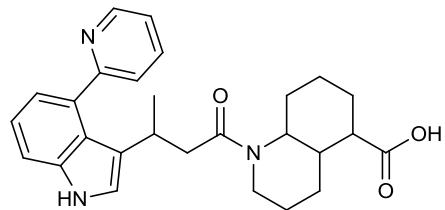
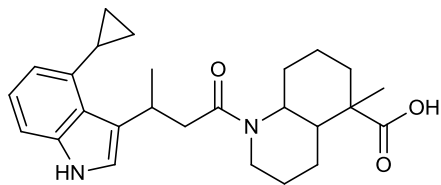


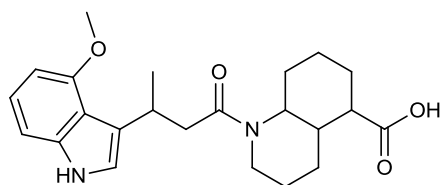
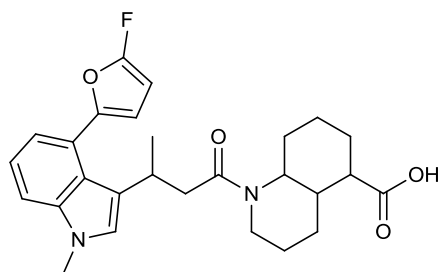
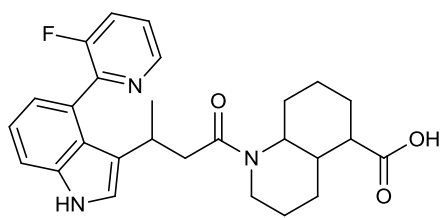
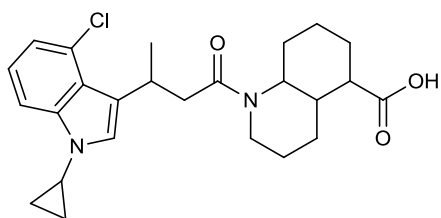
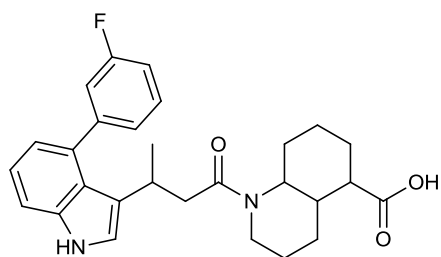
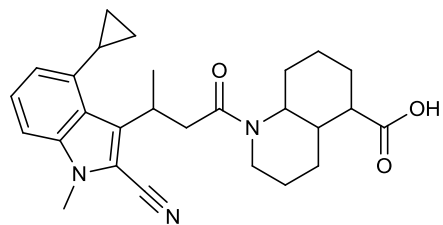
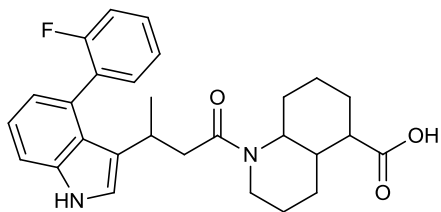
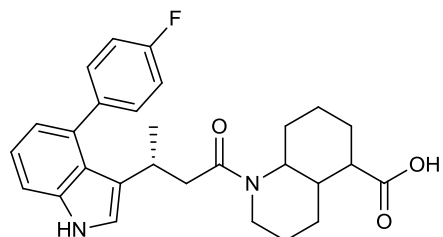
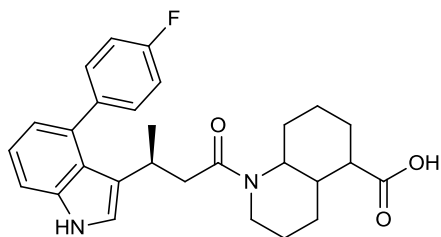
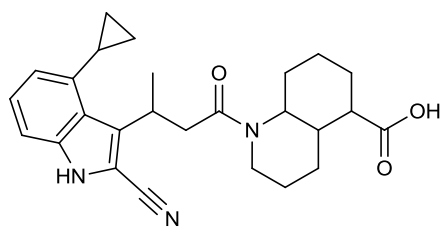
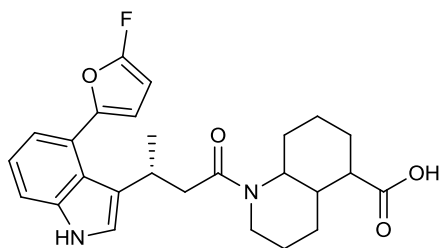


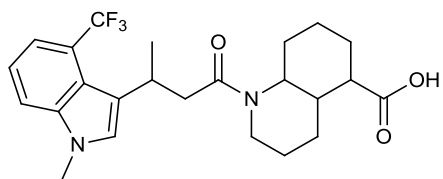
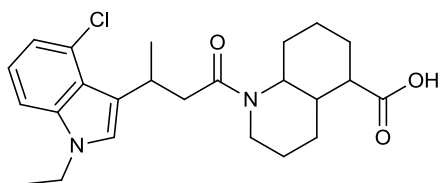
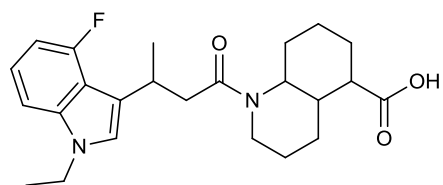
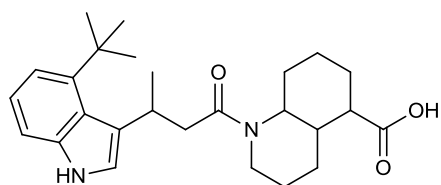
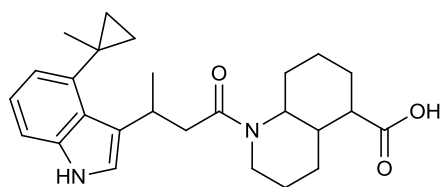
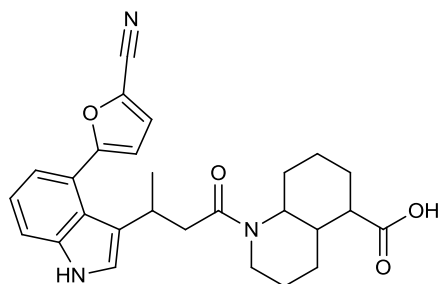
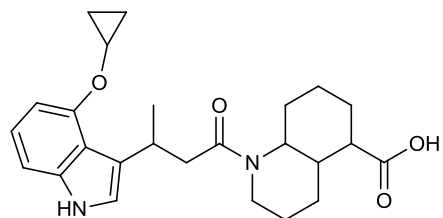
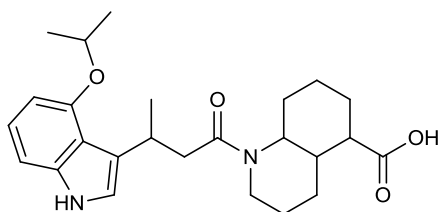
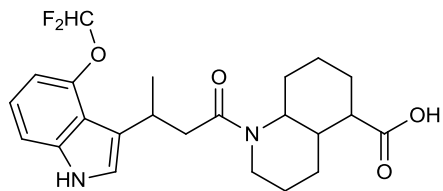
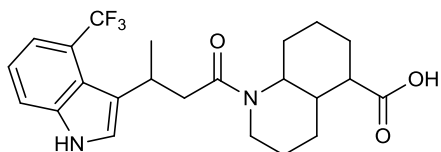
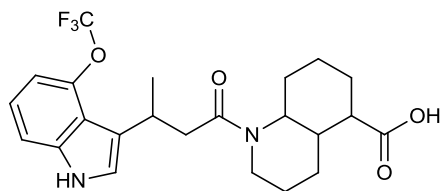
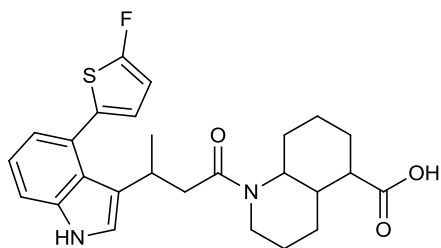


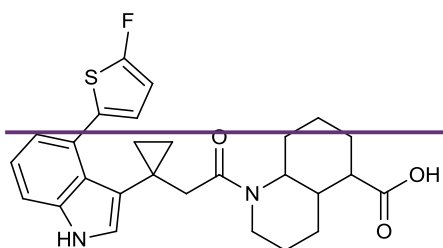
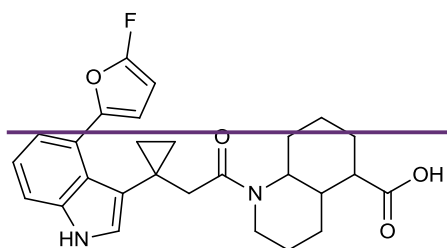
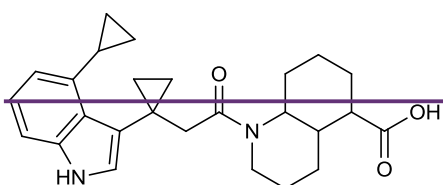
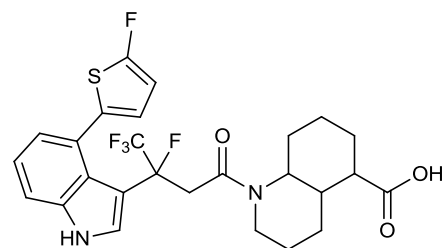
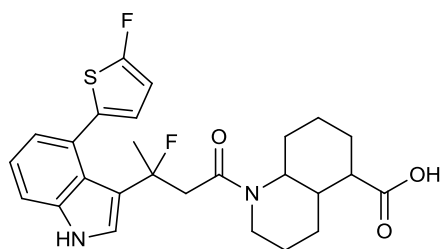
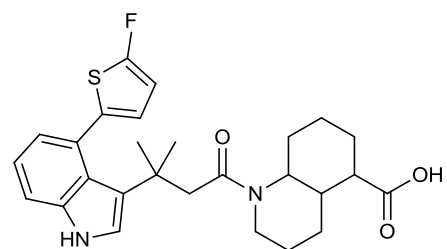
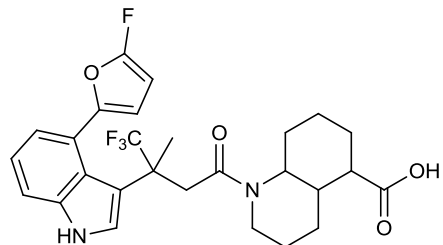
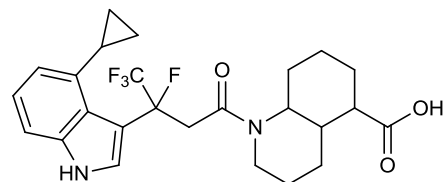
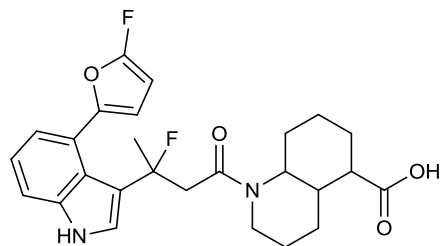
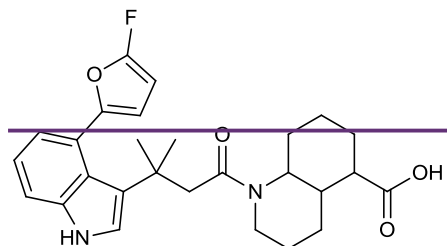
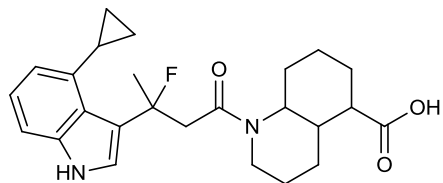
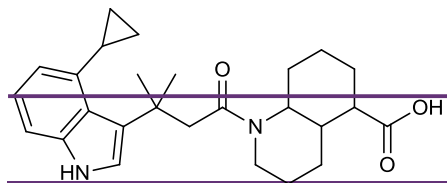


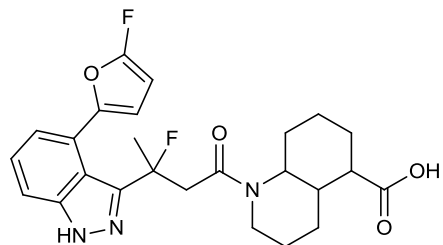
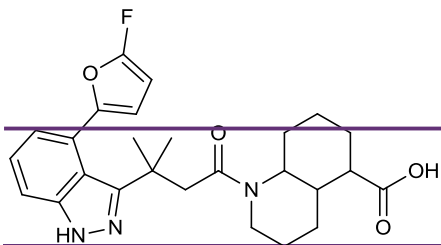
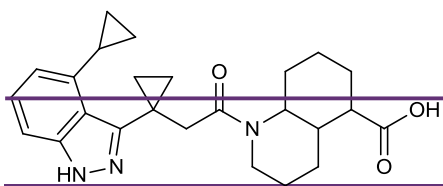
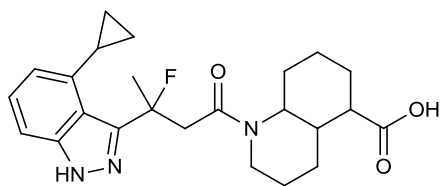
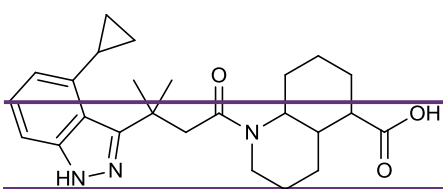
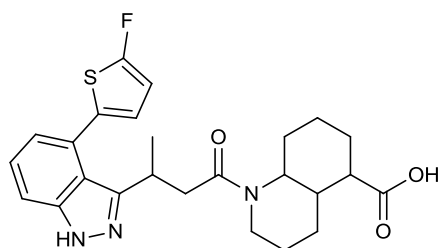
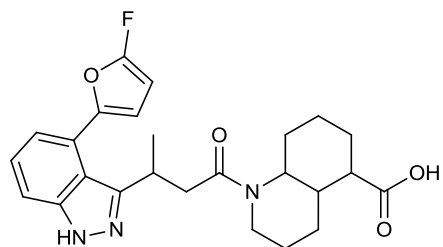
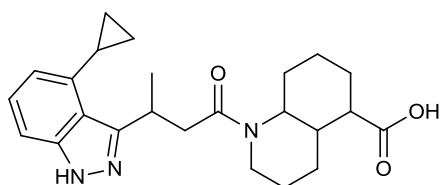
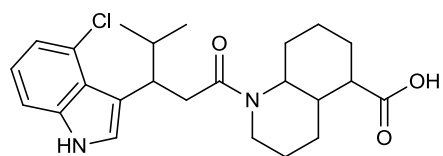
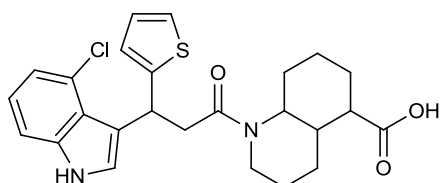
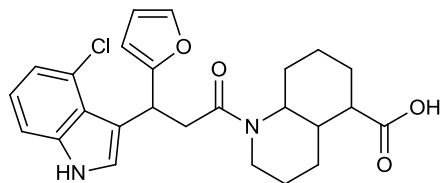
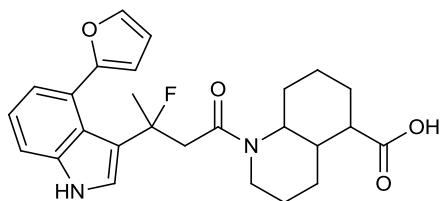


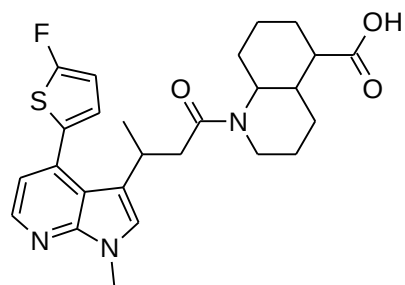
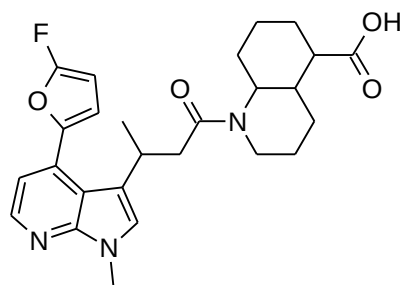
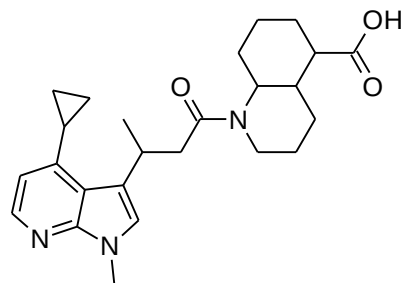
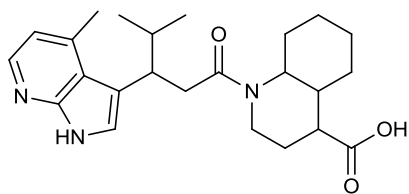
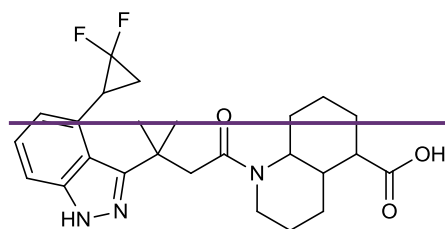
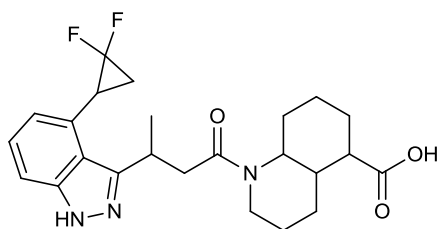
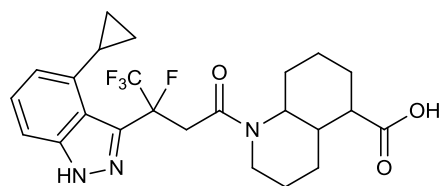
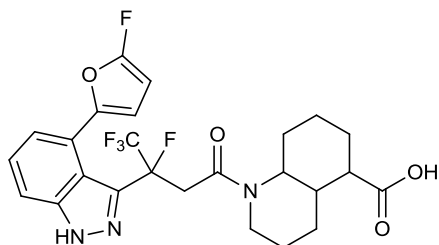
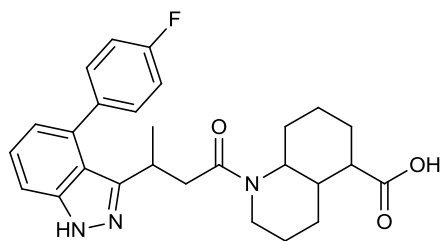
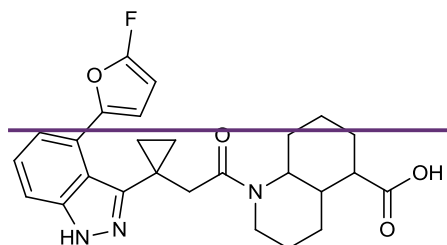


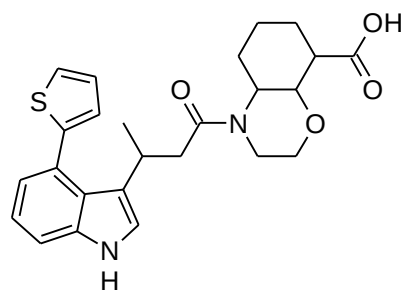
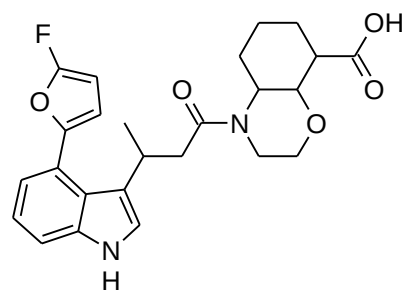
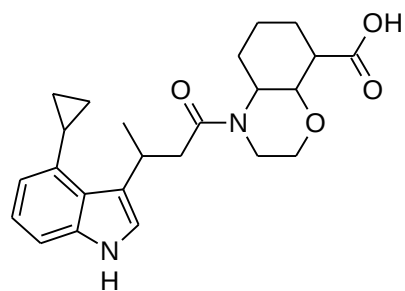
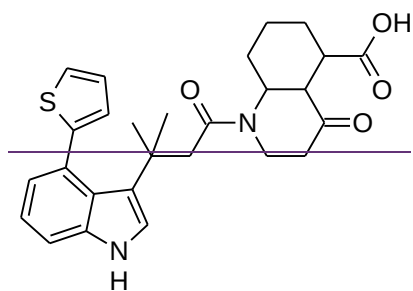
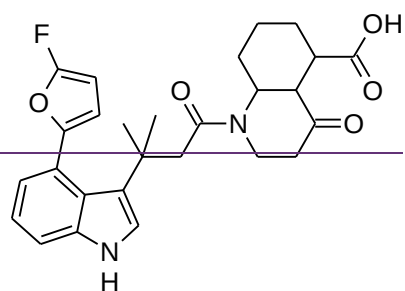
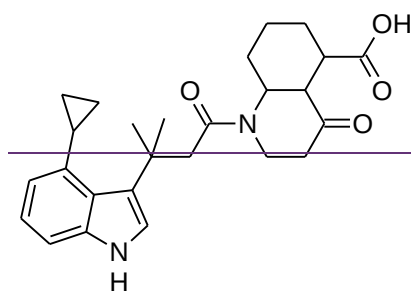
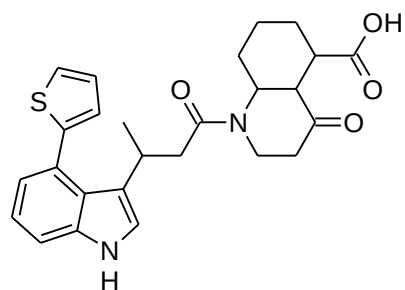
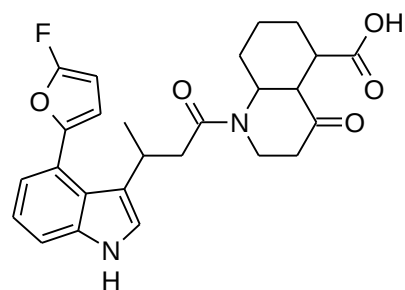
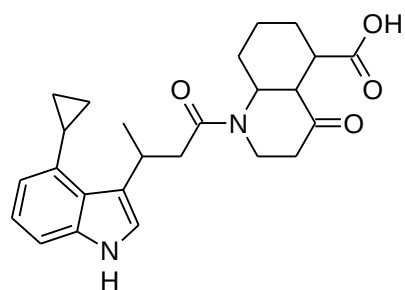
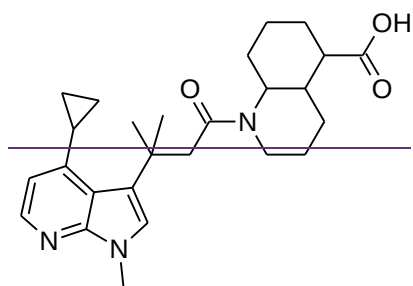


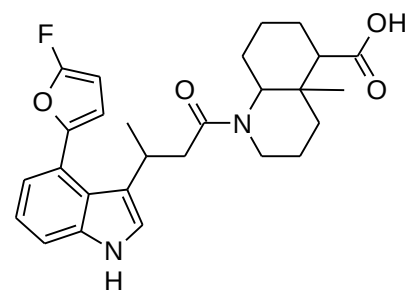
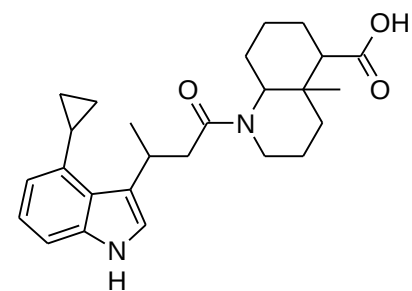
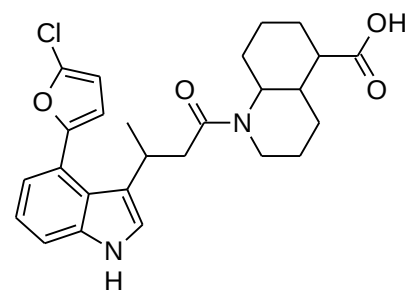
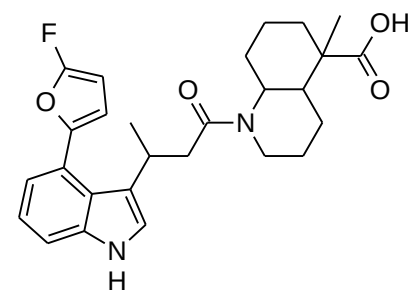
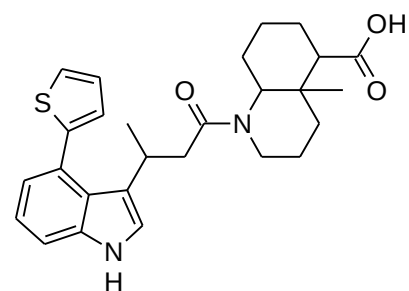
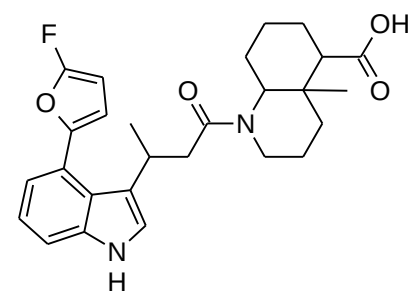
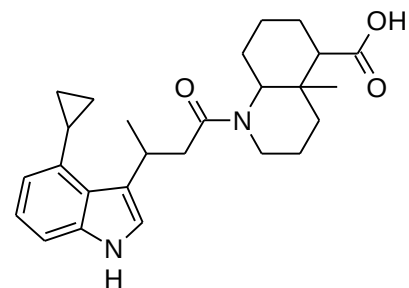
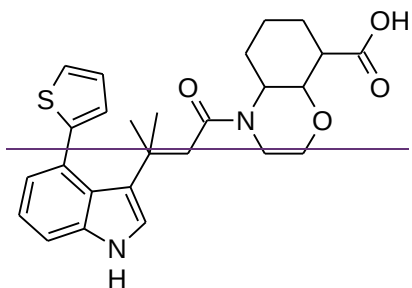
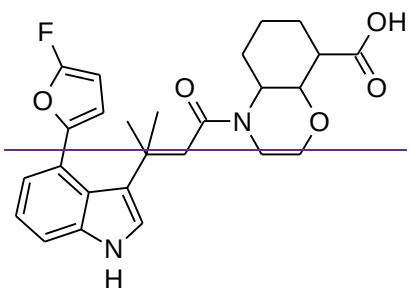
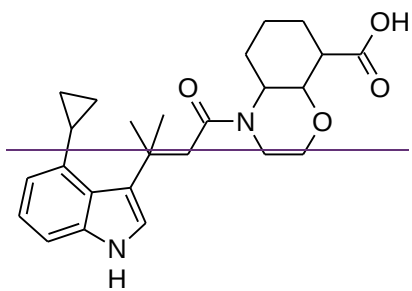


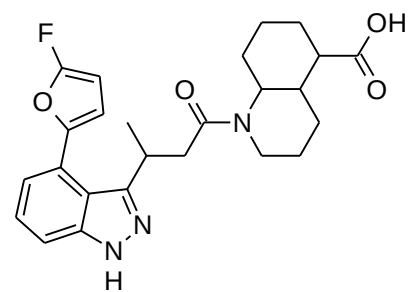
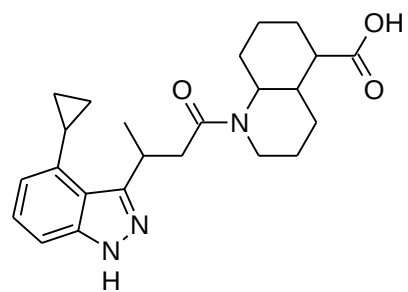
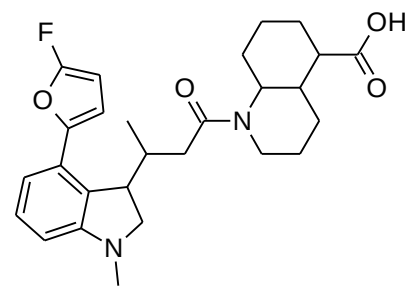
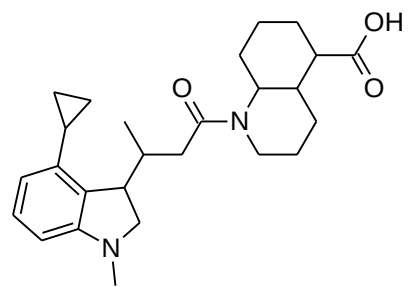
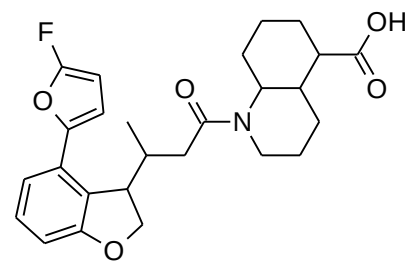
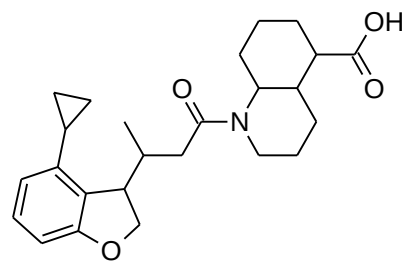
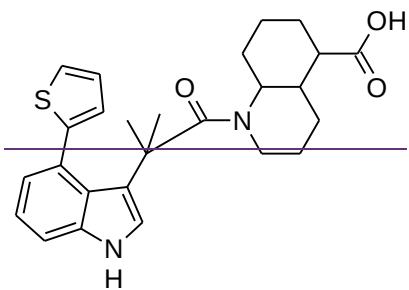
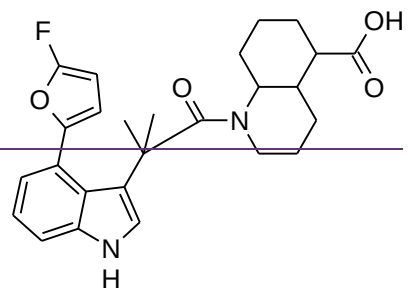
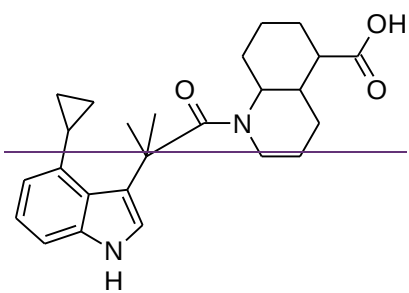
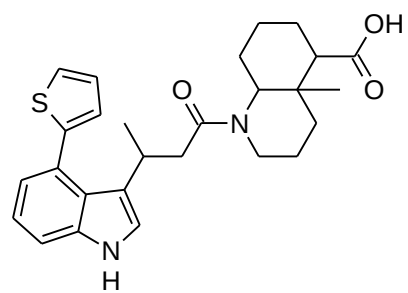


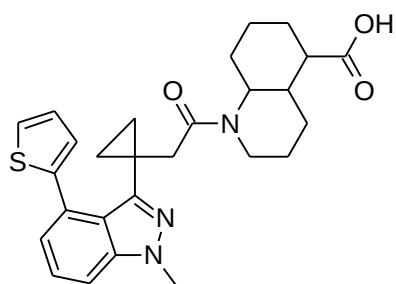
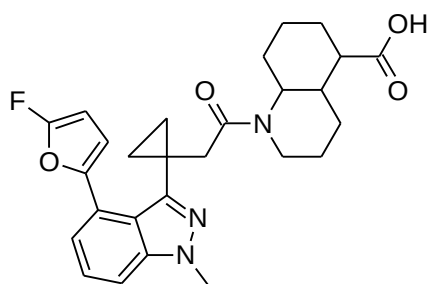
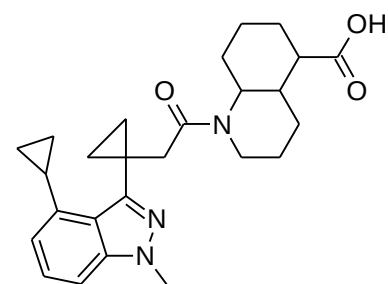
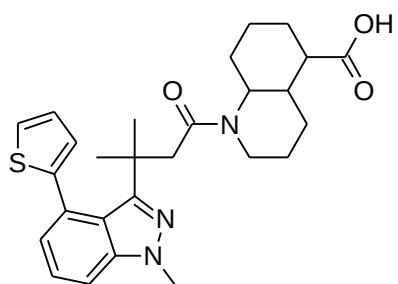
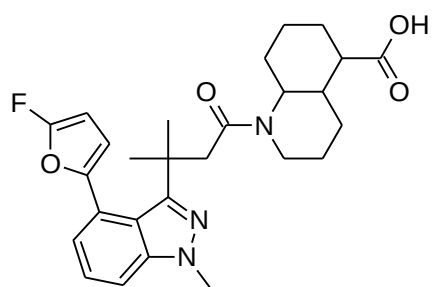
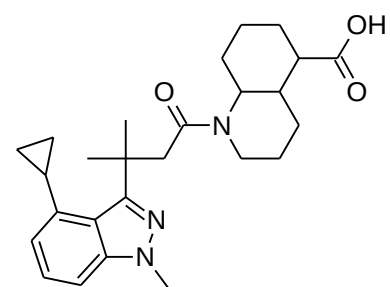
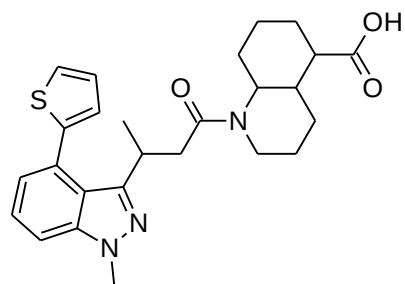
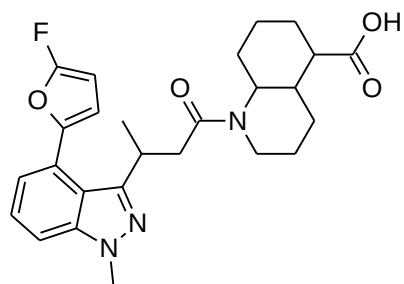
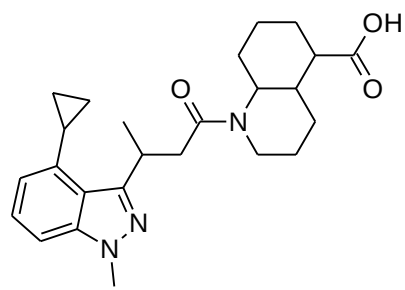
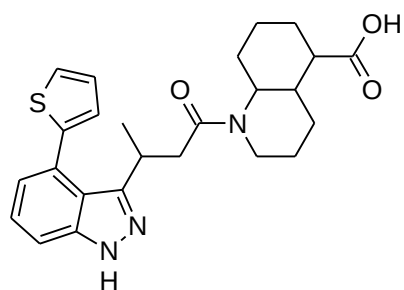


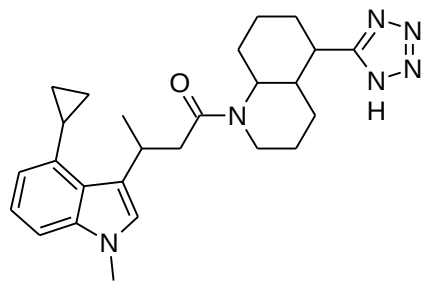
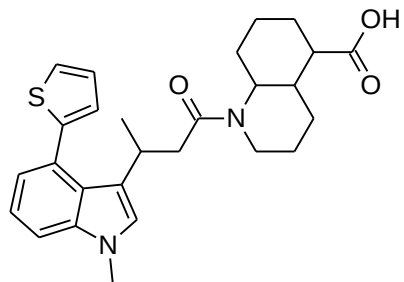
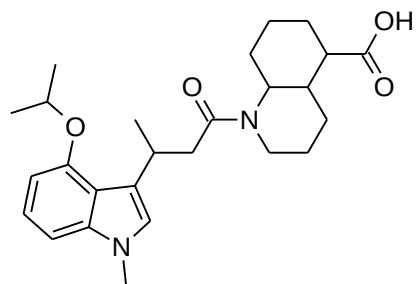
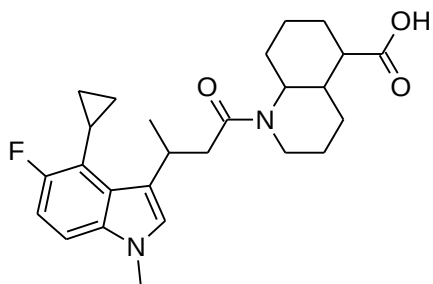
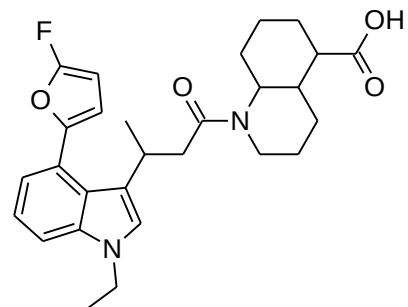
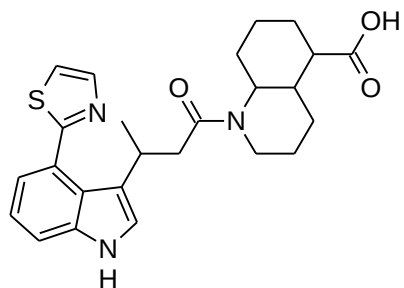
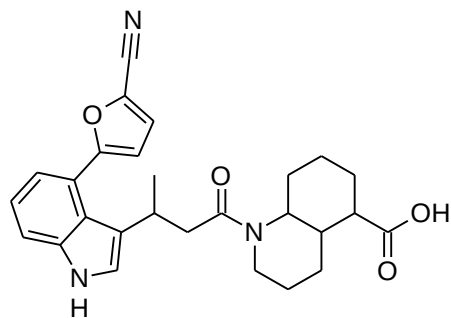
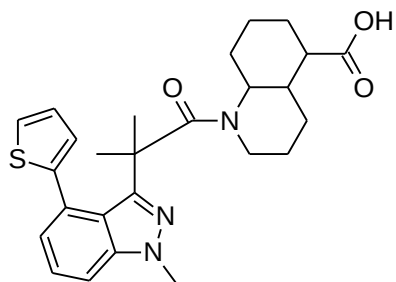
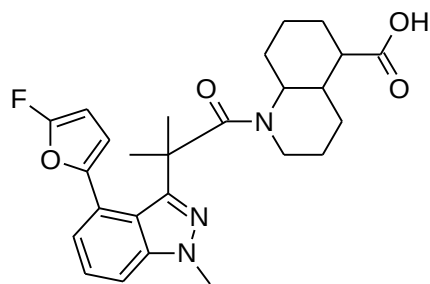
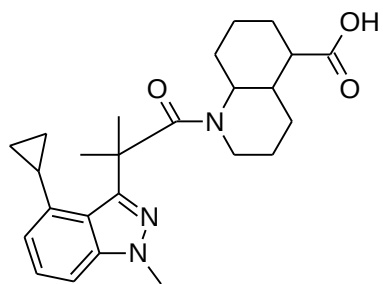


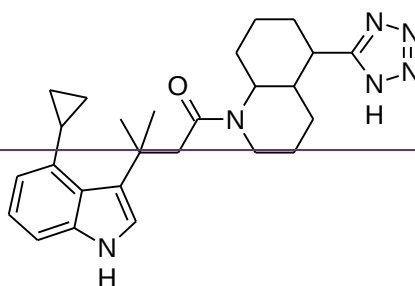
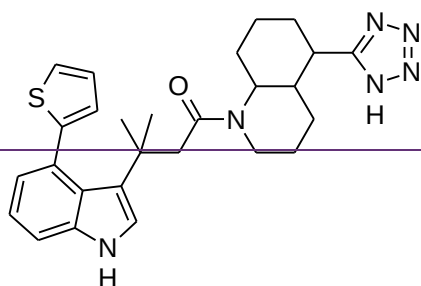
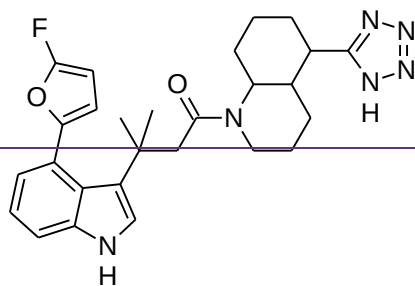
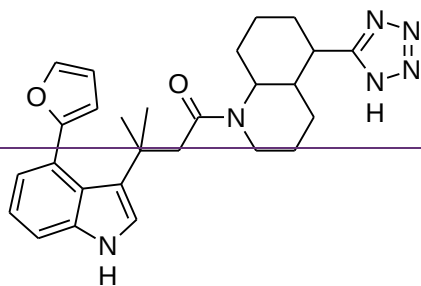
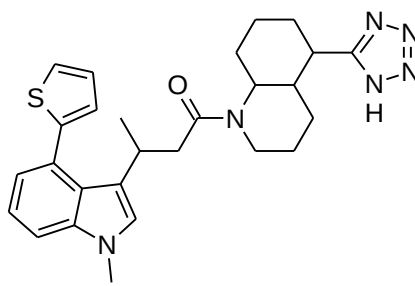
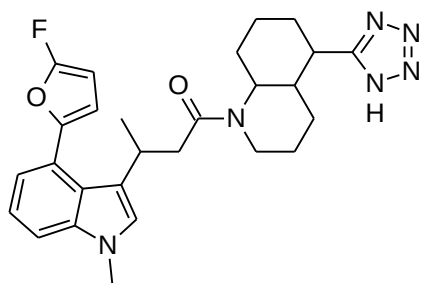
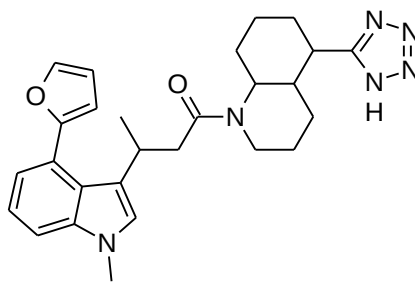
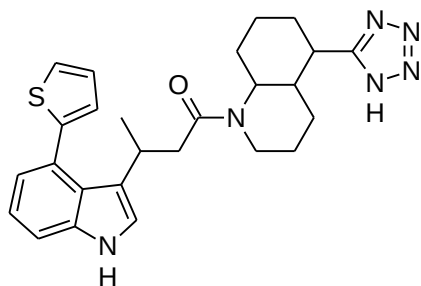
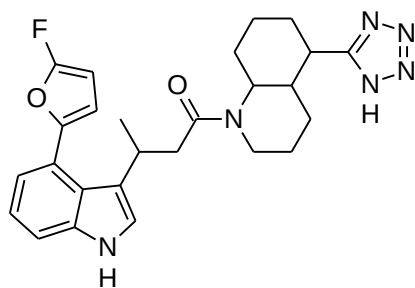
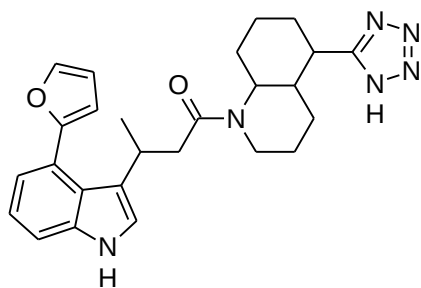


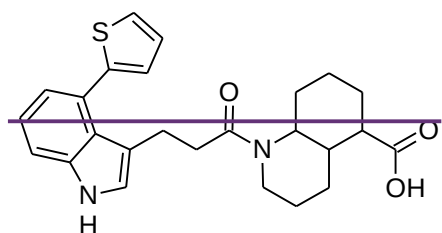
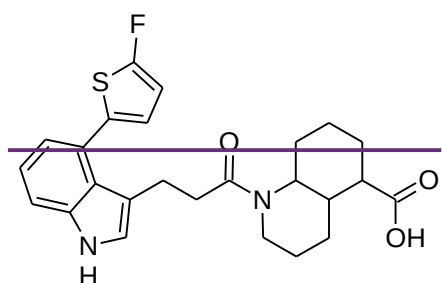
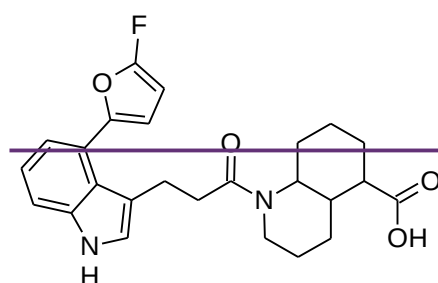
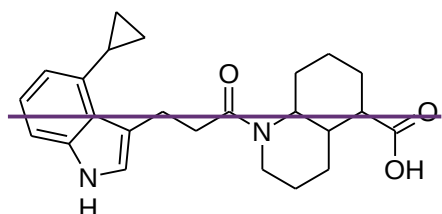
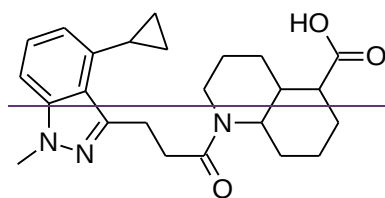
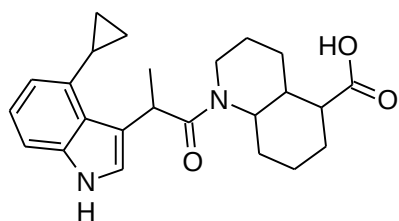
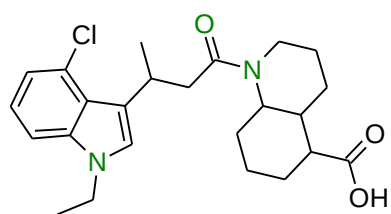
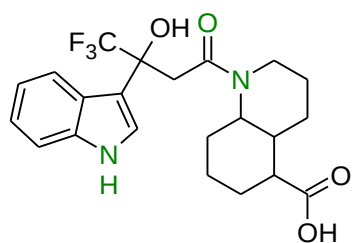












o su sal farmacéuticamente aceptable.

5                    ~~109.~~ Una composición farmacéutica que incluye un compuesto de conformidad con cualquiera de las reivindicaciones 1 a ~~98~~ y un diluyente, excipiente o vehículo farmacéuticamente aceptable.

10                    ~~11. Un método para la prevención o tratamiento de una condición en un mamífero, el método comprendiendo la administración de una cantidad efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9.~~

15                    ~~12. Un método de conformidad con la reivindicación 11, caracterizado porque la condición puede ser prevenida o tratada por la inhibición de 11 $\beta$ -HSD1.~~

20                    ~~13. Un método de conformidad con la reivindicación 12, caracterizado porque la condición se selecciona del grupo que consiste de diabetes, hiperglucemia, baja tolerancia a la glucosa, hiperinsulinemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, dislipidemia, obesidad, obesidad abdominal, glaucoma, hipertensión, aterosclerosis y sus secuelas, retinopatía, nefropatía, neuropatía, miopatía, osteoporosis, osteoartritis, demencia, depresión, enfermedades neurodegenerativas, trastornos~~

~~psiquiátricos, Enfermedad de Cushing, síndrome de Cushing, enfermedades virales, y enfermedades inflamatorias.~~

~~14. Un método de conformidad con la reivindicación 13, caracterizado porque la condición es diabetes.~~

~~15. Un método de conformidad con la reivindicación 14, caracterizado porque la condición es diabetes tipo II.~~

~~16. El método de conformidad con la reivindicación 12, caracterizado porque el compuesto se administra en combinación con un adyuvante.~~

~~17. El método de conformidad con la reivindicación 16, caracterizado porque el adyuvante es seleccionado del grupo que consiste de dipeptidil peptidasa-IV (DP-IV); (b) agentes sensibilizantes de insulina; (c) insulina y miméticos de insulina; (d) sulfonilureas y otros secretagogos de insulina; (e) inhibidores alfa-glucosidasa; (f) GLP-1, análogos GLP-1, y agonistas receptores de GLP-1; y las combinaciones de los mismos.~~

~~18. El método de conformidad con la reivindicación 17, caracterizado porque los agentes sensibilizantes de insulina son seleccionados del grupo que consiste en (i) PPAR-gamma-agonistas, (ii) PPAR-alfa-agonistas, (iii) PPAR-alfa/gamma-dual agonistas, (iv) biguanidas, y combinaciones de los mismos.~~

~~19. El uso de un compuesto de conformidad con la reivindicación 1 en la preparación de un medicamento.~~

~~20. El uso de conformidad con la reivindicación 19, caracterizado porque el medicamento es para el tratamiento de una condición que se puede prevenir o tratar por la inhibición de 11 $\beta$ -HSD1.~~

~~21. El uso de conformidad con la reivindicación 20, caracterizado porque la condición se selecciona del grupo que consiste de diabetes, hiperglucemia, baja tolerancia a la glucosa, hiperinsulinemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, dislipidemia, obesidad, obesidad abdominal, glaucoma, hipertensión, aterosclerosis y sus secuelas, retinopatía, nefropatía, neuropatía, miopatía, osteoporosis, osteoartritis, demencia, depresión, enfermedades neurodegenerativa, trastornos psiquiátricos, Enfermedad de Cushing, síndrome de Cushing, enfermedades virales, y enfermedades inflamatorias.~~

~~22. Un uso de conformidad con la reivindicación 21, caracterizado porque la condición es diabetes.~~

~~23. Un uso de conformidad con la reivindicación 22, caracterizado porque la condición es diabetes tipo II.~~

~~24. Un uso de conformidad con la reivindicación 22 ó 23, caracterizado porque el medicamento contiene un adyuvante.~~

~~25. Un uso de conformidad con la reivindicación 24, caracterizado porque el adyuvante es seleccionado del grupo que consiste de dipeptidil peptidasa IV (DP-IV); (b)~~

5

~~agentes sensibilizantes de insulina; (c) insulina y miméticos de insulina; (d) sulfonilureas y otros secretagogos de insulina; (e) inhibidores alfa-glucosidasa; (f) GLP-1, análogos GLP-1, y agonistas receptores de GLP-1; y las combinaciones de los mismos.~~

10

~~26. El uso de conformidad con la reivindicación 25, caracterizado porque los agentes sensibilizantes de insulina son seleccionados del grupo que consiste en (i) PPAR-gamma-agonistas, (ii) PPAR-alfa-agonistas, (iii) PPAR-alfa/gamma-dual agonistas, (iv) biguanidas, y combinaciones de los mismos.~~

# PATENT COOPERATION TREATY

from the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Kewalramani, Nishant  
No. 40, 1st Floor  
3rd Main Road  
J.C Industrial Estate  
Kanakpura Main Road  
Bangalore 560062  
INDE

## PCT

WRITTEN OPINION OF THE  
INTERNATIONAL PRELIMINARY  
EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing  
(day/month/year)

20.11.2013

Applicant's or agent's file reference  
BLPCT384016

**REPLY DUE** within 2 month(s)  
from the above date of mailing

International application No.  
PCT/IN2012/000841

International filing date (day/month/year)  
21.12.2012

Priority date (day/month/year)  
22.12.2011

International Patent Classification (IPC) or both national classification and IPC  
INV. C07D401/12

Applicant  
Connexios Life Sciences Pvt. Ltd.

1. ☒ The written opinion established by the International Searching Authority:  
☒ is ☐ is not  
considered to be a written opinion of the International Preliminary Examining Authority.
2. This second opinion contains indications relating to the following items:
  - ☒ Box No. I Basis of the opinion
  - ☐ Box No. II Priority
  - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☐ Box No. IV Lack of unity of invention
  - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Box No. VI Certain documents cited
  - ☒ Box No. VII Certain defects in the international application
  - ☐ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).  
**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 55.3 and 66.8.  
**Also:** For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.  
**If no reply is filed,** the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 22.04.2014

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0  
Fax: +49 89 2399 - 4465

Authorized Officer

Traegler-Goeldel, M

Telephone No. +49 89 2399-8278



**WRITTEN OPINION OF THE INTERNATIONAL  
PRELIMINARY EXAMINING AUTHORITY**

International application No.  
PCT/N2012/000841

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into ,  
which is the language of a translation furnished for the purposes of:
    - ☐ international search (under Rules 12.3(a) and 23.1(b))
    - ☐ publication of the international application (under Rule 12.4(a))
    - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the elements of the international application, this opinion has been established on the basis of  
*(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article  
14 are referred to in this opinion as "originally filed")*:

**Description, Pages**

1-252 as originally filed

**Claims, Numbers**

1-26 filed with the letter of

20-09-2013

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
4. ☐ This opinion has been established as if (some of) the amendments listed below had not been made, since  
either they are considered to go beyond the disclosure as filed, or they were not accompanied by a  
letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental  
Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
5. ☐ This opinion has been established:
- ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority  
under Rule 91 (Rule 66.1(d-bis)).
  - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this  
Authority under Rule 91 (Rule 66.4bis).
6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into  
account in drawing up this opinion (Rule 45bis.8(b) and (c)).

---

**Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

---

1. Statement

|                               |     |        |
|-------------------------------|-----|--------|
| Novelty (N)                   | No: | Claims |
| Inventive step (IS)           | No: | Claims |
| Industrial applicability (IA) | No: | Claims |

2. Citations and explanations:

see separate sheet

---

**Box No. VII Certain defects in the international application**

---

The following defects in the form or contents of the international application have been noted:

see separate sheet

re item V:

1. Amendments

The as filed with letter of 20.09.13 are admissible : The definitions of  $R^1$  and  $R^{1a}$  have been limited according to the description as originally filed, p. 22, l.11 to 13 and p. 23, l. 10 to 12. The definition of the term Ar has been limited by insertion of the subject matter of original claim 9 into claim I. As a result claims 8 and 8 have been deleted. The definition of A has been limited to the subject matter of original claim 4 which has been deleted. The limitation of n has its basis on p. 11, l. 17-18, the limitation of c has its basis on the specific embodiments of the compounds of formulas (II), (IIIa), (IIIb), (IVa), (IVb), (Va) to (Vd) and (VI) in the description as originally filed. Thus only minor amendments have been made to the definitions of  $R^a$ ,  $R^b$ ,  $R^c$  and  $R^d$ .

2. Novelty

The subject matter of present claim 1 has been searched completely. Its subject matter is novel with respect to documents D1 to D5 due to the restricted definition of the linking moiety A. Its novel with respect to documents D4 to D6 due to the restriction of the definition of integer c as 1 and is novel with respect to documents D7 to D9 due to the restriction of residue Ar. Thus the subject matter of present claims 1 to 26 is considered to fulfil the requirements of Art. 33 (2) PCT.

3. Inventive step

The closest prior art for the consideration of inventive step of claim 1 is to be seen in document D9, since this document is concerned with perhydroquinoline- and perhydroisoquinoline derivatives which are potent inhibitors of 11- $\beta$ -hydroxysteroid dehydrogenase type 1 as are those of the present claim 1. The structural difference between the claimed compounds and the structural closest ones according to D9 is to be seen in the heteroaryl residue connected to residue A of the bridging moiety -A-B-CO-: in the present case it is an indole, benzothiazole, benzotriazole or benzofuran residue whereas in the compounds according to D9 it is always an isoindol-1,4-dione moiety connected to the bridging moiety via the nitrogen atom. From this document it is clear that in the structural closest compounds an essential technical features is this specific heteroaryl bearing the 2 oxo groups. Thus, the skilled person in order to solve the problem of providing further inhibitors of 11- $\beta$ -hydroxysteroid dehydrogenase type 1 could not have been taught by document D9 to replace the essential isoindol-1,4-dione moiety of D9 by any of the above specified benzocondensed heteroaryl

residues according to claim 1 lacking the 2 oxo groups. Thus the subject matter of present claim 1 is considered to fulfil the requirement of Art. 33 (3) PCT. The same applies to claims 2 to 26.

#### 4. Industrial applicability

Claims 11 to 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment or method of treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### re item VII:

Claims 12 and 20 are still defined in functional terms that are not considered to be clear in the sense of Art. 6 PCT. The therapeutic application is defined by means of a mechanism of action which does not allow for a practical application in the treatment of a specific pathological condition (disease). The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.