

Señores

Superintendencia de Industria y Comercio

Dirección de Nuevas Creaciones

E. S. D.

Ref: Expediente No. NC2020/0013864.

Solicitud de Patente de Invención denominada «MODULADORES DE LA PROTEÓLISIS Y MÉTODOS ASOCIADOS DE USO».

Fase nacional de la solicitud PCT/US2019/025878.

Solicitante: ARVINAS OPERATIONS, INC. y YALE UNIVERSITY.

Luz Helena Adarve, identificada como aparece al pie de mi firma, y obrando en mi condición de apoderada de **ARVINAS OPERATIONS, INC.** y **YALE UNIVERSITY**, solicitante de la patente en referencia, a continuación, doy respuesta al Oficio **No. 10428** del 22 de junio de 2023.

1. Respecto a las Objeciones a la Claridad y Concisión de las reivindicaciones (Artículo 30 de la Decisión 486)

En el numeral 3.1 del Oficio No. **10428**, se presentan las siguientes objeciones a la claridad de las reivindicaciones:

«Esta oficina informa que la reclamada no es concisa, ya que multitud de sustituyentes, así como su gran cantidad de posibles significados, así como sus combinaciones y/o permutaciones, hacen que la materia resultante sea extremadamente amplia, lo que pone en duda que toda ella realmente cumpla con el efecto técnico que se reclama.»

Se sugiere, entonces, restringir el alcance de las reivindicaciones a una generalización razonable de aquéllos compuestos efectivamente sintetizados, y probado su efecto técnico en la descripción»

Sobre estas objeciones, el solicitante no está de acuerdo con ellas, debido a que la materia reivindicada describe compuestos y composiciones que son útiles como moduladores de la ubiquitinación dirigida de una variedad de polipéptidos y otras proteínas que se degradan y/o se inhiben mediante dichos compuestos, que tienen la ventaja de una amplia gama de actividades farmacológicas y que son coherentes con la degradación/inhibición de los polipéptidos diana de básicamente cualquier familia o clase de proteína para el tratamiento o la mejora de una enfermedad, tal como un cáncer (ver párrafo [00012] de la descripción de la presente solicitud). Por lo anterior, los compuestos y composiciones objetados realmente tienen un efecto técnico mejorado frente a lo existente en el estado del arte.

Sin embargo, con el objetivo para acelerar el proceso de esta solicitud, a pesar del desacuerdo del solicitante con las objeciones de claridad a las reivindicaciones planteadas por la examinadora, **es deseo del solicitante presentar un nuevo capítulo reivindicatorio compuesto por 17 reivindicaciones**, que encuentran su debido sustento en las reivindicaciones y la descripción originalmente presentadas, sin que ello conlleve ampliación de la invención como se explica más adelante.

Este nuevo capítulo reivindicatorio restringe el alcance de las reivindicaciones de acuerdo con la sugerencia del examinador.

2. Respecto a la Determinación del Estado de la Técnica y al Examen de Patentabilidad

En los numerales 4, 5 y 6 del oficio citado, ese Despacho concluye que las reivindicaciones de la presente solicitud de patente carecen de novedad y de nivel inventivo frente a las enseñanzas del documento **US2018015087** (D1).

2.1. Novedad y nivel inventivo

Aunque el examinador haya citado el documento D1 para objetar la novedad y la altura inventiva de la presente invención, es posible afirmar que este no enseña las características esenciales de la invención como se explica a continuación.

Con el fin de acelerar el proceso de la presente solicitud y debido a las objeciones presentadas respecto a la novedad y nivel inventivo de las reivindicaciones, **es deseo del solicitante presentar un nuevo capítulo reivindicatorio compuesto por 17 reivindicaciones**, que encuentran su debido sustento en las reivindicaciones y la descripción originalmente presentadas, sin que ello conlleve ampliación de la invención.

La reivindicación enmendada 1 se modifica de la siguiente manera:

- Se reemplaza la definición de la variable W_3 , se agrega una definición para las variables X_3 , R_1 , R_{1a} , R_{1b} , T y n , y se eliminan la definición de las variables R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14a} y R_{14b} . Estas modificaciones están soportadas al menos por la reivindicación 6 de la correspondiente solicitud PCT PCT/US2019/025878 (cuya publicación es WO 2019/195609);
- se eliminan dos estructuras particulares de la definición de la variable W_4 ;
- se eliminan dos definiciones alternativas particulares del ULM;
- se eliminan las Fórmulas PTM-III y PTM-IV de la definición del PTM;
- se añade fenilo a la definición de R_{PTM9} y R_{PTM10} , cuyo soporte se puede encontrar, al menos, por ejemplo, en la estructura de los Ejemplos 482 a 484 de la publicación WO 2019/195609 de la correspondiente solicitud PCT;
- se agrega la frase «*sustituyentes independientemente seleccionados*»¹, a la definición de R_{PTM3} y R_{PTM5} , en donde el respaldo para esta enmienda se puede encontrar, al menos, por ejemplo, en la estructura de los Ejemplos 1, 2, 4, 6, 7, 9, 127–32, 181–254, 330–410, 436–44, 458–65, 469–77, 480, 482–502, 506–13, 524–38 y 571–3 de la publicación WO 2019/195609 de la correspondiente solicitud PCT; y
- se modifican cuestiones formales.

Las anteriores reivindicaciones 4 y 5 se eliminaron. Las reivindicaciones enmendadas 8 y 9, correspondientes a las anteriores reivindicaciones 10 y 11, se modifican para agregar una definición de variable m , cuyo respaldo se puede encontrar, al menos, por ejemplo, en los párrafos [00272] y [00273] en las páginas 284 a 286 de la publicación WO 2019/195609. La reivindicación enmendada 10, correspondiente a la anterior reivindicación 12, se modifica a una forma dependiente

y para eliminar estructuras compuestas particulares para mantener la coherencia con las enmiendas de la reivindicación 1. Las reivindicaciones enmendadas 2 a 14 se modificaron por cuestiones de forma. Las reivindicaciones enmendadas 4 a 14 se modificaron para actualizar su dependencia de forma coherente. Las reivindicaciones 15 a 17 son nuevas reivindicaciones añadidas, cuyo respaldo se puede encontrar, al menos, por ejemplo, en las reivindicaciones 3, 7 y 8 de la publicación WO 2019/195609.

Sobre el nuevo capítulo reivindicatorio modificado que ahora se presenta, se indica que corresponde sustancialmente a las mismas **concedidas** en los Estados Unidos (US) bajo el número de patente 11,161,841, lo que evidencia su novedad y nivel inventivo.

El solicitante respetuosamente indica que la invención de la solicitud es nueva e inventiva al menos por las siguientes razones:

- Las presentes reivindicaciones son nuevas porque especifican compuestos ULM-L-PTM de la forma VLM-L-PTM, donde VLM es un resto basado en tetrahidropirrol, L es un conector y PTM es un resto basado en quinazolinilo con un sustituyente piperazinilo. En contraste con las presentes reivindicaciones, los compuestos divulgados en el documento D1 terminan en un resto de talidomida, que es estructuralmente muy diferente al VLM basado en tetrahidropirrol de las reivindicaciones de la presente solicitud. Como tal, debido a que el documento D1 citado no describe todos y cada uno de los aspectos de los compuestos reivindicados actualmente, el documento D1 no anticipa las reivindicaciones de la solicitud. Por lo tanto, se solicita respetuosamente la reconsideración y el retiro de la objeción por falta de novedad.
- Las presentes reivindicaciones, no solo son nuevas, sino también tienen nivel inventivo, debido a que, aunque este despacho alega que el objeto de la reivindicación 1 se considera obvio porque muchos de los significados de ULM, L y PTM ya se describen en dicho documento D1 y, en consecuencia, la persona del oficio normalmente versada en la materia estaría motivada a elegir significados del documento D1 para el conjugado X-Y-Z del mismo D1 con el fin de alcanzar el objeto de dicha reivindicación 1 y, el solicitante respetuosamente no está de acuerdo al menos porque, como se indicó anteriormente, las reivindicaciones de la presente solicitud especifican

compuestos ULM-L-PTM de la forma VLM-L-PTM, donde VLM es un resto basado en tetrahidropirrol, L es un conector y PTM es un resto basado en quinazolinilo con un sustituyente piperazinilo, en donde, en contraste con las reivindicaciones de la presente solicitud, los compuestos descritos en el documento D1 terminan en un resto talidomida, que son estructuralmente muy diferente al VLM basado en tetrahidropirrol de las presentes reivindicaciones. De hecho, el documento D1 no describe los compuestos VLM-L-PTM.

Por lo tanto, una persona del oficio medianamente versada en la materia se alejaría de la invención de la presente solicitud porque estaría motivada por el documento D1 a buscar compuestos ULM-L-PTM adicionales que terminen en un resto de talidomida, no los compuestos como se reivindican actualmente en la presente solicitud.

Por lo tanto, se solicita respetuosamente la reconsideración y el retiro de la objeción por falta de nivel inventivo.

Por lo anterior, se concluye que las reivindicaciones independientes de la presente solicitud poseen características que no se dan a conocer de manera obvia para una persona versada en la materia por el documento D1, por ende, la presente invención debe ser considerada como novedosa y con nivel inventivo sobre el estado de la técnica presentado por el examinador.

3. Conclusión

Las modificaciones realizadas a las reivindicaciones de la presente solicitud de patente y las aclaraciones presentadas a lo largo del presente escrito permiten superar completamente las objeciones realizadas a la claridad de las reivindicaciones, por lo cual, la presente solicitud cumple a cabalidad las exigencias establecidas por el artículo 30 de la Decisión 486 según los requerimientos del Examinador.

De otra parte, los argumentos expuestos en el numeral 2 del presente escrito ponen de manifiesto de una manera clara y contundente que lo revelado en las nuevas reivindicaciones de la presente solicitud resulta completamente novedoso e inventivo sobre las enseñanzas del estado del arte más cercano representado por

el documento D1, toda vez que nada dentro de dicho documento revela en forma directa o al menos llega a sugerir las características definidas en la invención de la presente solicitud. Por consiguiente, no se puede derivar la inexistencia de los requisitos de ley para la concesión del privilegio de patentabilidad.

En consecuencia, me permito solicitar a ese Despacho, proceder con la revisión de las modificaciones y de los argumentos aquí presentados, para conceder el privilegio de patente solicitado para la materia objeto de las 17 reivindicaciones ahora presentadas en el capítulo reivindicatorio modificado, y que de subsistir alguna duda o inquietud respecto a la patentabilidad de la presente invención, a pesar de las modificaciones y argumentos técnicos ahora presentados, sin apartarse del espíritu inventivo originalmente revelado en la solicitud internacional, se le brinde la oportunidad al solicitante de aclararla o de limitar aún más la invención, mediante la emisión de un segundo examen de fondo, teniendo en cuenta el nuevo capítulo reivindicatorio que se somete a revisión, antes de que se emita una decisión definitiva por parte de ese Despacho, de conformidad con lo dispuesto en 1.2.2.5.1 del artículo primero de la Resolución 54093 de 2012.

4. Anexos

Junto con este escrito se incluye lo siguiente:

- Capítulo reivindicatorio modificado, en donde se han llevado a cabo las modificaciones mencionadas anteriormente.

5. Pagos

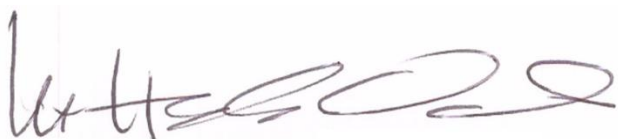
Junto con esta respuesta se paga la tasa correspondiente a la modificación del capítulo reivindicatorio y una reivindicación adicional.

6. Petición

Solicito al Despacho, y en el evento que el examinador considere que pese a las modificaciones presentadas aún existen objeciones, que proceda a emitir un segundo examen de fondo sobre el nuevo capítulo reivindicatorio presentado.

En este sentido requiero se me comunique a través del SIPI o cualquier otro medio la existencia de estas objeciones para, de esta manera, si procede, realizar el nuevo pago del examen de patentabilidad de la solicitud de la referencia.

Atentamente,



LUZ HELENA ADARVE GÓMEZ.

C.C 41.575.435 de Bogotá.

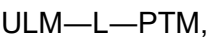
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REIVINDICACIONES (con marcas de modificación)

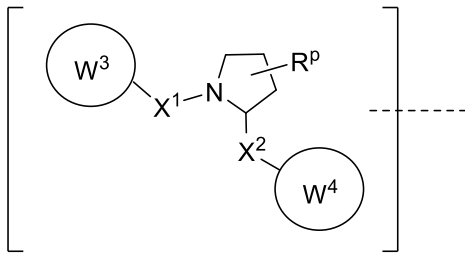
1. Un compuesto ~~bifuncional~~ que tiene la estructura química:



o una sal farmacéuticamente aceptable de este,

donde:

el ULM es:



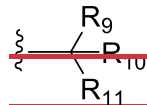
en donde

X¹ y X² se seleccionan cada uno de manera independiente de un enlace, O, NR^{Y3}, CR^{Y3}R^{Y4}, C=O, C=S, SO y SO₂;

R^{Y3} y R^{Y4} se seleccionan cada uno de manera independiente de H, alquilo C₁₋₆ opcionalmente sustituido por 1 o más halo, y alcoxi C₁₋₆ opcionalmente sustituido por 0-3 ~~grupos~~ R^P;

cada R^P es ~~0, 1, 2 o 3 grupos~~, seleccionados de manera independiente de H, halo, -OH, alquilo C₁₋₃, y C=O;

W³ se selecciona de entre ~~fenilo opcionalmente sustituido con alquilo C₁₋₆, un heteroarilo de~~



~~5-10 miembros opcionalmente sustituido con alquilo C₁₋₆, y~~ W³ se selecciona de entre T opcionalmente sustituido, -T-N(R^{1a}R^{1b})X³ opcionalmente sustituido, -T-N(R^{1a}R^{1b}) opcionalmente sustituido, -T-Arilo opcionalmente sustituido, -T-Heteroarilo opcionalmente sustituido, T-biheteroarilo opcionalmente sustituido, -T- heterociclilo opcionalmente sustituido, -T-biheterociclilo opcionalmente sustituido, -NR¹-T-Arilo opcionalmente sustituido, -NR¹-T-Heteroarilo opcionalmente sustituido, y -NR¹-T-Heterociclilo opcionalmente sustituido;

X³ es C=O o R¹;

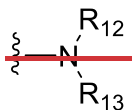
R¹, R^{1a}, y R^{1b} son cada uno independientemente seleccionados de entre H, alquilo C₁₋₆ opcionalmente sustituido por 1 o más halo u -OH, R^{Y3}C=O, R^{Y3}C=S, R^{Y3}SO, R^{Y3}SO₂, N(R^{Y3}R^{Y4})C=O, N(R^{Y3}R^{Y4})C=S, N(R^{Y3}R^{Y4})SO y N(R^{Y3}R^{Y4})SO₂;

T se selecciona de entre alquilo opcionalmente sustituido, -(CH₂)_n-, donde cada uno de los grupos metileno opcionalmente se sustituye con uno o dos sustituyentes seleccionados de entre halógeno, metilo, alcoxi opcionalmente sustituido, alquilo C₁₋₆ opcionalmente sustituido por 1 o más sustituyentes independientemente seleccionados de entre halógeno, C(O) NR¹R^{1a}, y NR¹R^{1a}, o R¹ y R^{1a} se unen para formar un heterociclilo opcionalmente sustituido; y

n es de 0 a 6

~~R₉ y R₁₀ son seleccionados de manera independiente de hidrógeno, alquilo C₁₋₆, alcoxi C₁₋₆, y haloalquilo C₁₋₆;~~

~~R₁₁ se selecciona de entre heterociclilo de 3-11 miembros, alcoxi C₁₋₆, heteroarilo~~

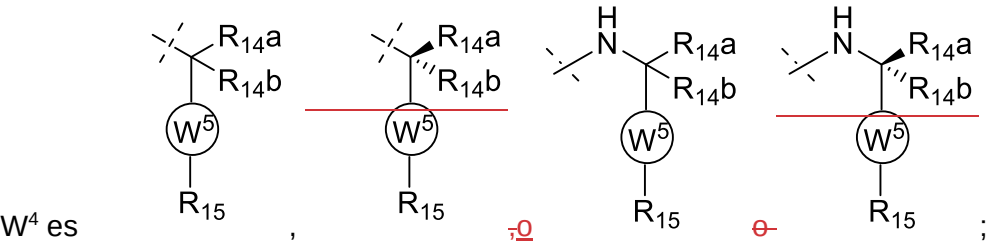


de 5-10 miembros, arilo C₆₋₁₀, y ~~en donde el heterociclilo, heteroarilo, y arilo son opcionalmente sustituidos con alquilo C₁₋₆;~~

~~R₁₂ es H o alquilo C₁₋₆;~~

~~R₁₃ es H, alquilo, alquilcarbonilo C₁₋₆, (cicloalquil de 3-11 miembros)alquilcarbonilo C₁₋₆, aralquilcarbonilo C₆₋₁₀, arilcarbonilo C₆₋₁₀, (heterociclilo de 3-11 miembros)carbonilo o aralquilo C₆₋₁₀;~~

~~R_{14a} y R_{14b} se seleccionan cada uno de manera independiente de H, haloalquilo C₁₋₆, y alquilo C₁₋₆;~~

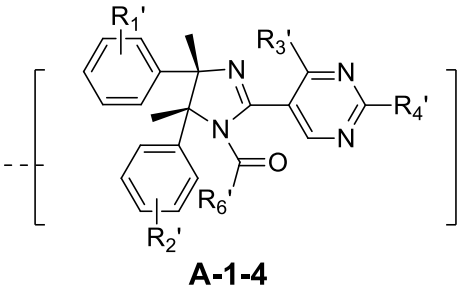
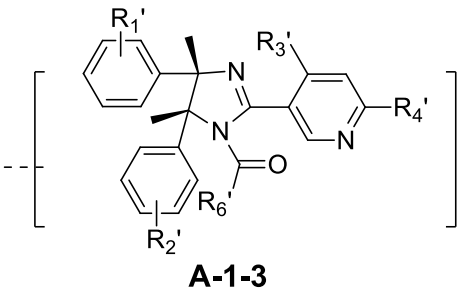
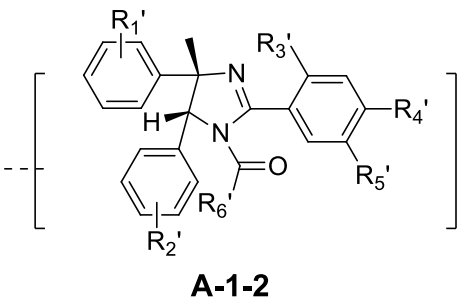
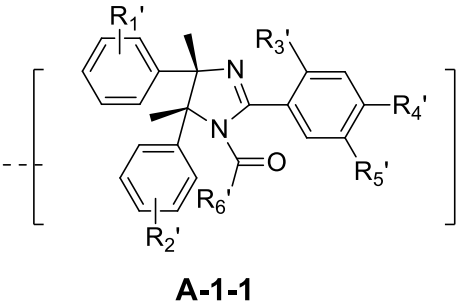


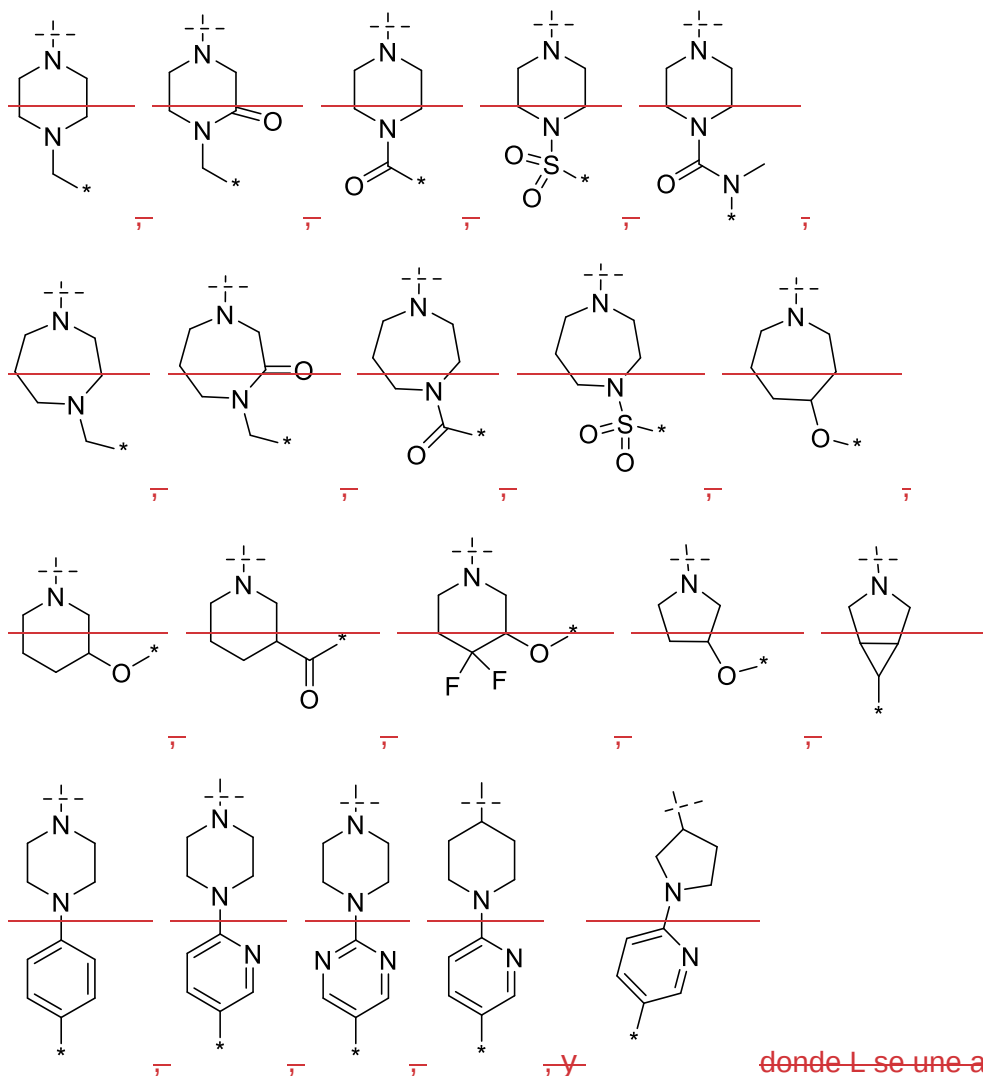
R_{14a} y R_{14b} ~~se seleccionan~~ son cada uno de manera independiente ~~de H, haloalquilo C₁₋₆~~ o alquilo C₁₋₆ opcionalmente sustituido;

W⁵ es ~~un~~ fenilo opcionalmente sustituido o ~~un~~ heteroarilo de 5-10 miembros opcionalmente sustituido;

R₁₅ se selecciona de entre H, halógeno, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a} SO₂R_{14b}, alquilo C₁₋₆ opcionalmente sustituido, haloalquilo C₁₋₆ opcionalmente sustituido, haloalcoxi C₁₋₆ opcionalmente sustituido, arilo C₆₋₁₀ opcionalmente sustituido, heteroarilo de 5-10 miembros opcionalmente sustituido, cicloalquilo C₃₋₁₁ opcionalmente sustituido, ~~o~~ cicloheterocicloalquilo de 3-11 miembros opcionalmente sustituido;

~~o ULM es~~





~~R^{6'} o al átomo del extremo de R^{4'};~~

~~R7' de la Fórmula A-4-1 a A-4-6 es uno o más halógenos;~~

~~R8' de la Fórmula A-4-1 a A-4-6 es uno o más grupos seleccionados de H, F, Cl, Br, I, CN, NO₂, metoxi, etoxi, isopropoxi, y OH, alquilo C₁₋₆, alquenilo C₁₋₆, alquinilo C₁₋₆, metoxi, etoxi, isopropoxi, y OH;~~

~~R9' de la Fórmula A-4-1 a A-4-6 se selecciona de entre alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, hetero arilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, alquenilo y cicloalquenilo sustituido;~~

~~Z de la Fórmula A-4-1 a A-4-6 se selecciona de entre H, OCH₃, OCH₂CH₃ y halógeno;~~

~~R10' y R11' de la Fórmula A-4-1 a A-4-6 se seleccionan cada uno de manera independiente de H, (CH₂)_n-R', (CH₂)_n-NR'R'', (CH₂)_n-NR'COR'', (CH₂)_n-NR'SO₂R'', (CH₂)_n-COOH, (CH₂)_n-COOR', (CH₂)_n-CONR'R'', (CH₂)_n-OR', (CH₂)_n-SR', (CH₂)_n-SOR', (CH₂)_n-CH(OH)-R', (CH₂)_n-COR', (CH₂)_n-SO₂R', (CH₂)_n-SONR'R'', (CH₂)_n-SO₂NR'R'', (CH₂CH₂O)_m-(CH₂)_n-R', (CH₂CH₂O)_m-(CH₂)_n-OH, (CH₂CH₂O)_m-(CH₂)_n-OR', (CH₂CH₂O)_m-(CH₂)_n-NR'R'', (CH₂CH₂O)_m-(CH₂)_n-NR'COR'', (CH₂CH₂O)_m-(CH₂)_n-NR'SO₂R'', (CH₂CH₂O)_m-(CH₂)_n-COOH, (CH₂CH₂O)_m-(CH₂)_n-COOR', (CH₂CH₂O)_m-(CH₂)_n-CONR'R'', (CH₂CH₂O)_m-(CH₂)_n-SO₂R', (CH₂CH₂O)_m-(CH₂)_n-COR', (CH₂CH₂O)_m-(CH₂)_n-SONR'R'', (CH₂CH₂O)_m-(CH₂)_n-SO₂NR'R'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-R', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-OH, (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-OR', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-NR'R'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-NR'COR'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-NR'SO₂R'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-COOH, (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-COOR', (CH₂)_p-(CH₂CH₂O)_m-~~

~~(CH₂)_n-CONR'R'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-SO₂R', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-COR', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-SONR'R'', (CH₂)_p-(CH₂CH₂O)_m-(CH₂)_n-SO₂NR'R'', arilo-(CH₂)_n-COOH y heteroarilo-alquilo-CO-alquilo-NR'R''_m, donde el alquilo es opcionalmente sustituido con OR' y heteroarilo-(CH₂)_n-heterociclo donde el heterociclo es opcionalmente sustituido con alquilo, hidroxilo, COOR' y COR'; donde R' y R'' se seleccionan de entre H, alquilo, alquilo sustituido con halógeno, hidroxilo, NH₂, NH(alquilo), N(alquilo)₂, oxo, carboxi, cicloalquilo y heteroarilo;~~

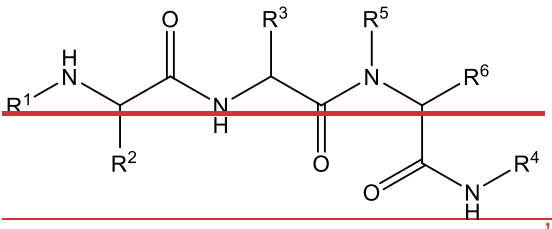
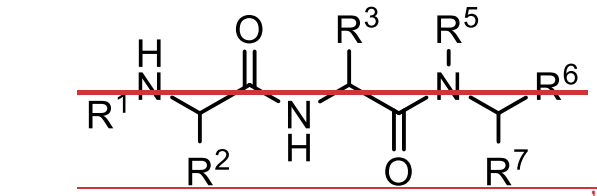
~~m, n y p son de manera independiente de 0 a 6;~~

~~R₁₂' de la Fórmula A-4-1 a A-4-6 se selecciona de entre O-(alquilo), O-(alquilo)-acoxi, C(O)-(alquilo), C(OH)-alquilo-alcoxi, C(O)-NH-(alquilo), C(O)-N-(alquilo)₂, S(O)-(alquilo), S(O)₂-(alquilo), C(O)-(amino cíclico) y O-arilo-(alquilo), O-arilo-(alcoxi);~~

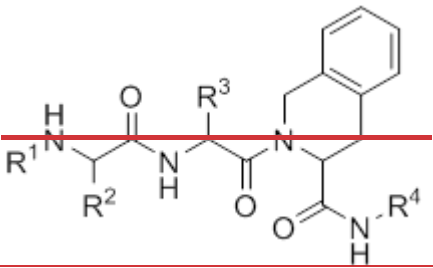
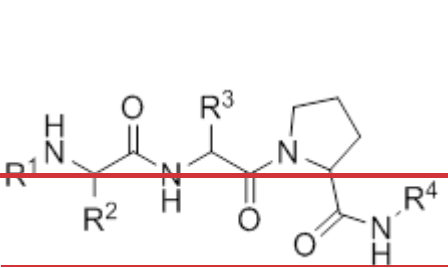
~~R₁' de la Fórmula A-4-1 a A-4-6 se selecciona dentro del grupo que consiste en H, alquilo, alquilo sustituido con arilo, alquilo sustituido con aloci, cicloalquilo, cicloalquilo sustituido con ari, y cicloalquilo sustituido con alcoxi; y~~

~~ indica conexión con L;~~

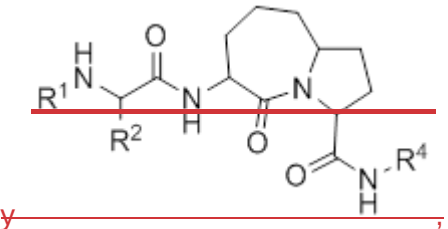
~~o ULM se selecciona de entre:~~



~~(I) (II)~~



~~(III) (IV)~~



~~(V)~~

~~en donde:~~

~~R¹ para las Fórmulas (I), (II), (III), (IV) y (V) es H o alquilo;~~

~~R² para las Fórmulas (I), (II), (III), (IV) y (V) es H o alquilo;~~

~~R³ para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre H, alquilo, cicloalquilo y heterocicloalquilo;~~

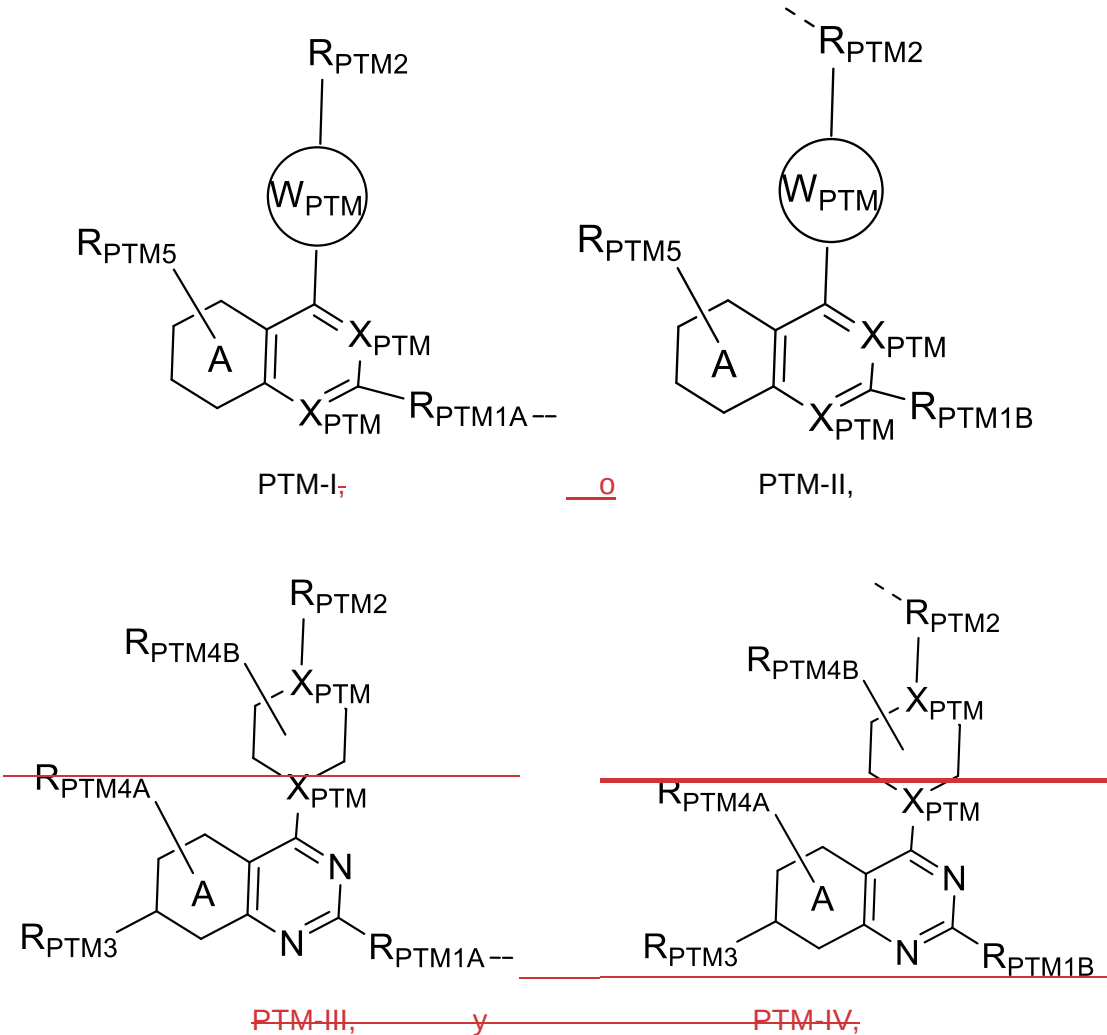
~~R⁵ y R⁶ para las Fórmulas (I), (II), (III), (IV) y (V) se seleccionan de manera independiente de entre H, alquilo, cicloalquilo, heterocicloalquilo, o R⁵ y R⁶ tomados juntos para las Fórmulas (I), (II), (III), (IV) y (V) forman un anillo pirrolidina o piperidina opcionalmente fusionado de manera adicional a 1-2 anillos cicloalquilo, heterocicloalquilo, arilo o heteroarilo, cada uno de los cuales puede fusionarse de manera adicional a otro anillo cicloalquilo, heterocicloalquilo, arilo o heteroarilo;~~

~~R³ y R⁵ para las Fórmulas (I), (II), (III), (IV) y (V) tomados juntos pueden formar un anillo de 5-8 miembros opcionalmente fusionado de manera adicional a 1-2 anillos cicloalquilo, heterocicloalquilo, arilo o heteroarilo;~~

~~R⁷ para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilo-C(O)-R⁴, arilalquilo, heteroarilo, heteroarilo-C(O)-R⁴, heteroarilo-R⁴, heteroarilo-naftaleno, heteroarilalquilo o C(O)NH-R⁴, cada uno de los cuales opcionalmente se sustituye de manera adicional con 1-3 sustituyentes que se seleccionan de entre halógeno, alquilo, haloalquilo, hidroxilo, alcoxi, ciano, (hetero)cicloalquilo, arilo, (hetero)arilo, C(O)NH-R⁴ o C(O)-R⁴; y~~

~~R⁴ se selecciona de entre alquilo, cicloalquilo, heterocicloalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilo o arilo bicíclico, arilalquilo, heteroarilo o heteroarilo bicíclico, heteroarilalquilo, opcionalmente sustituido de manera adicional;~~

el PTM se selecciona de entrees:



en donde:

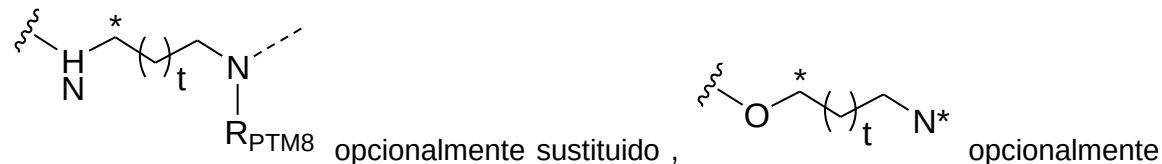
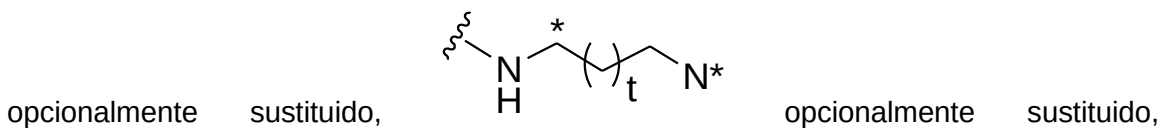
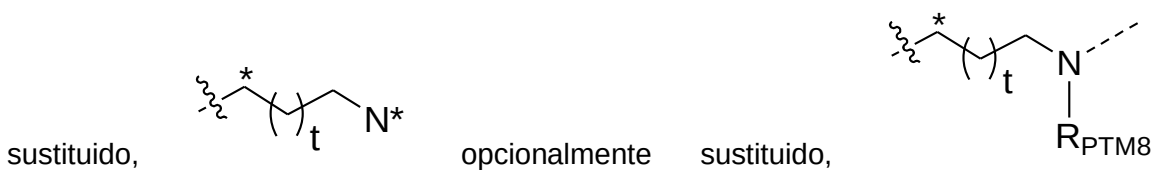
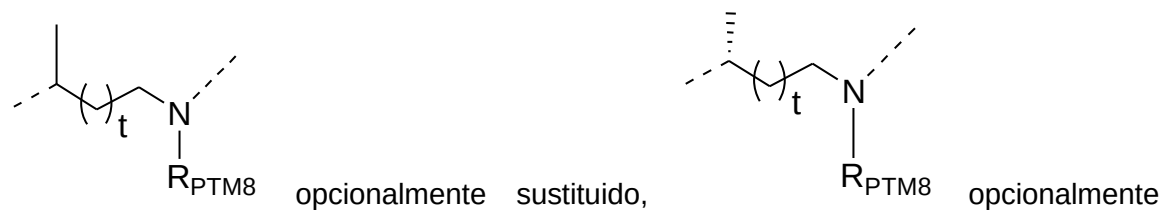
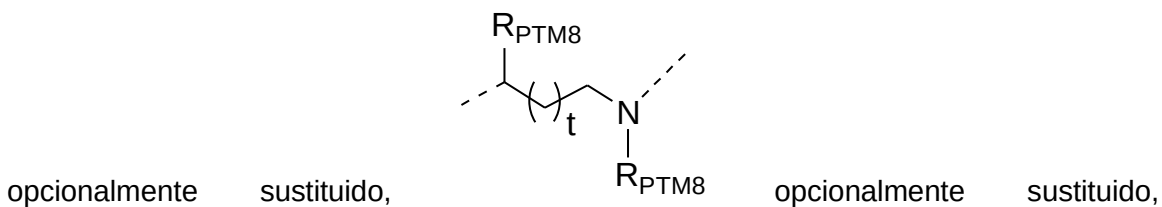
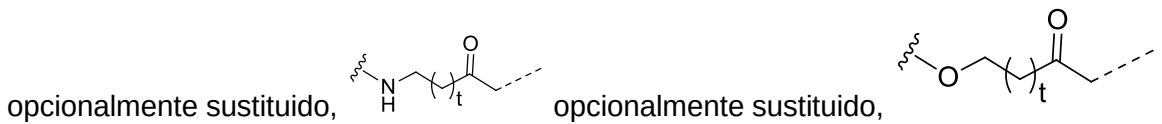
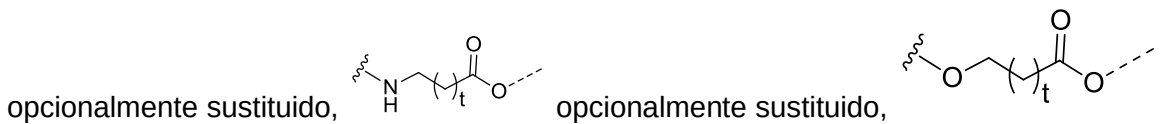
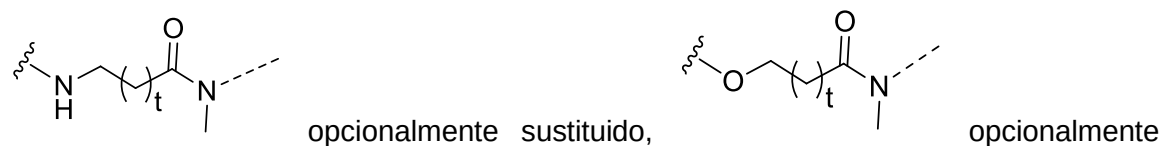
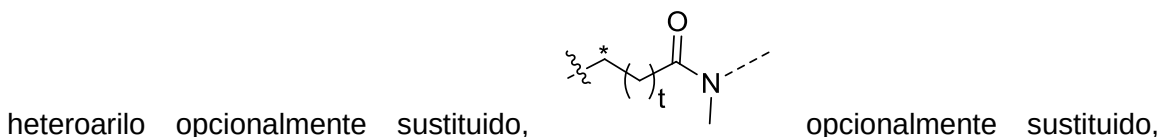


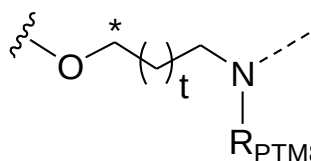
es ~~feniloun arilo~~, heteroarilo de 6 miembros, cicloalquilo de 6 miembros, o heterocicloalquilo de 6 miembros;

X_{PTM} es C o N;

W_{PTM} se selecciona de entre cicloalquilo C₃₋₆ opcionalmente sustituido, heteroalquilo C₃₋₆ opcionalmente sustituido, heterocicloalquilo de 3-6 miembros opcionalmente sustituido, arilo opcionalmente sustituido, y heteroarilo opcionalmente sustituido;

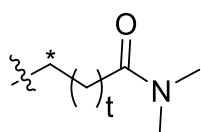
R_{PTM1A} ~~es—se selecciona de entre~~ NR_{PTM9}R_{PTM10}, OR_{PTM9}R_{PTM10}, H, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, cicloalquilo C₃₋₆ opcionalmente sustituido, O-(cicloalquilo C₃₋₆) opcionalmente sustituido, -O-alquilo C₁₋₄ -cicloalquilo C₃₋₆ opcionalmente sustituido, heteroalquilo C₃₋₆ opcionalmente sustituido, O-(heteroalquilo C₃₋₆) opcionalmente sustituido, O-alquilo C₁₋₄-heteroalquilo C₃₋₆opcionalmente sustituido, O-alquilo C₁₋₄-heterocicloalquilo C₃₋₆ opcionalmente sustituido, arilo opcionalmente sustituido, O-arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, , O-



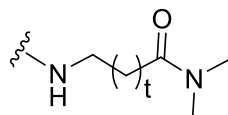


sustituido, y R_{PTM8} opcionalmente sustituido, donde N* es un átomo de N de un heterocicloalquilo del L;

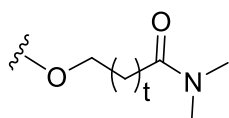
R_{PTM1B} ~~es~~ se selecciona de entre $NR_{PTM9}R_{PTM10}$, $OR_{PTM9}R_{PTM10}$, H, alquilo opcionalmente sustituido, O-alquilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, O-(cicloalquilo C_{3-6}) opcionalmente sustituido, -O-alquilo C_{1-4} -cicloalquilo C_{3-6} opcionalmente sustituido, heteroalquilo C_{3-6} opcionalmente sustituido, O-(heteroalquilo C_{3-6}) opcionalmente sustituido, O-alquilo C_{1-4} -heteroalquilo C_{3-6} opcionalmente sustituido, arilo opcionalmente sustituido, O-arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, O-heteroarilo opcionalmente sustituido,



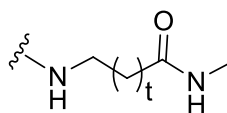
opcionalmente sustituido,



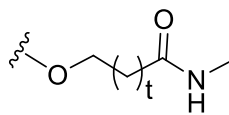
opcionalmente sustituido,



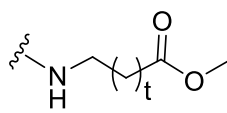
opcionalmente sustituido,



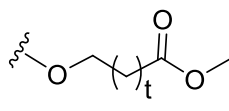
opcionalmente sustituido,



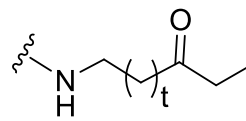
opcionalmente sustituido,



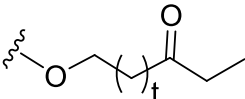
opcionalmente sustituido,



opcionalmente sustituido,



opcionalmente

sustituido,  opcionalmente sustituido;

R_{PTM9} y R_{PTM10} son cada uno seleccionado de manera independiente de entre H, alquilo C_{1-6} opcionalmente sustituido, amino alifático opcionalmente sustituido, amido alifático opcionalmente sustituido y fenilo;

R_{PTM2} es H, $(C=O)R_{PTM2'}$, o alquilo opcionalmente sustituido;

$R_{PTM2'}$ es alquilo opcionalmente sustituido, alqueno o opcionalmente sustituido, -N $(R_{PTM8})_2$ o $-C(OH)_2$;

R_{PTM3} es alquilo, alcoxi, fenilo o naftaleno o, cada uno opcionalmente sustituido ~~de manera independiente~~ con 1, 2, o 3 sustituyentes independientemente seleccionados de entre OH, H, ~~o~~ y halógeno;

R_{PTM4A} es OH, H, halógeno, o alquilo C_{1-6} opcionalmente sustituido;

R_{PTM4B} es OH, H, $-CH_2CN$, halógeno, o alquilo C_{1-6} opcionalmente sustituido;

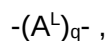
R_{PTM5} es 1, 2, o 3 sustituyentes independientemente seleccionados de entre arilo opcionalmente sustituido, biarilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, biheteroarilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, ~~ciclo~~heterocicloalquilo de 3-6 miembros opcionalmente sustituido, halógeno, H, alquilo opcionalmente sustituido, OH y alcoxi;

R_{PTM8} es ~~un~~ H o alquilo;

t es 0, 1, 2, 3, 4, 5, o 6; y

 indica el sitio de unión de **L**; y

L es:



donde:

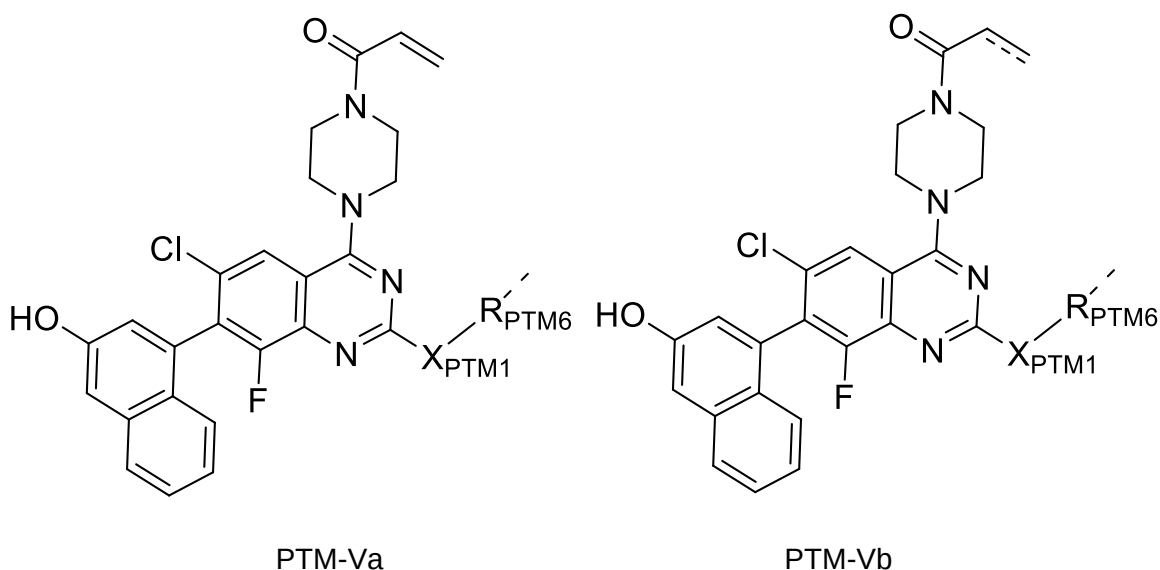
~~$(A^L)_q$ es un grupo que se conecta con al menos uno de un ULM, PTM, o ambos;~~

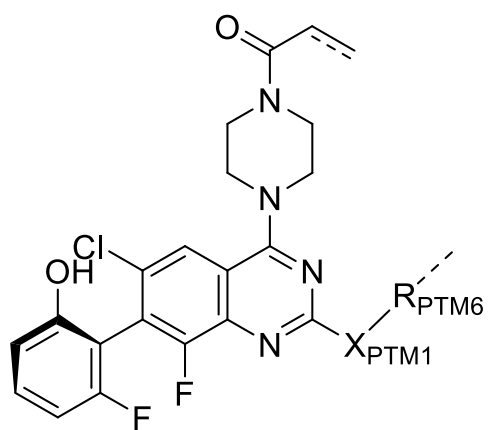
q es un número entero mayor o igual que 1;

cada A^L se selecciona de manera independiente de entre un enlace, $CR^{L1}R^{L2}$, O, S, SO, SO₂, NR^{L3}, SO₂NR^{L3}, SONR^{L3}, CONR^{L3}, NR^{L3}CONR^{L4}, NR^{L3}SO₂NR^{L4}, CO, $CR^{L1}=CR^{L2}$, $C\equiv C$, SiR^{L1}R^{L2}, P(O)R^{L1}, P(O)OR^{L1}, NR^{L3}C(=NCN)NR^{L4}, NR^{L3}C(=NCN), NR^{L3}C(=CNO₂)NR^{L4}, cicloalquilo C₃₋₁₁ opcionalmente sustituido con 0-6 ~~grupos~~-R^{L1} y/o R^{L2}, heterociclilo C₃₋₁₁ opcionalmente sustituido con 0-6 ~~grupos~~-R^{L1} y/o R^{L2}, arilo opcionalmente sustituido con 0-6 ~~grupos~~-R^{L1} y/o R^{L2}, y heteroarilo opcionalmente sustituido con 0-6 ~~grupos~~-R^{L1} y/o R^{L2}, donde R^{L1} o R^{L2}, cada uno de manera independiente se enlaza opcionalmente a otros grupos para formar ~~un resto~~-cicloalquilo ~~y/o~~ heterociclilo, cada uno opcionalmente sustituido con 0-4 ~~grupos~~-R^{L5}; y

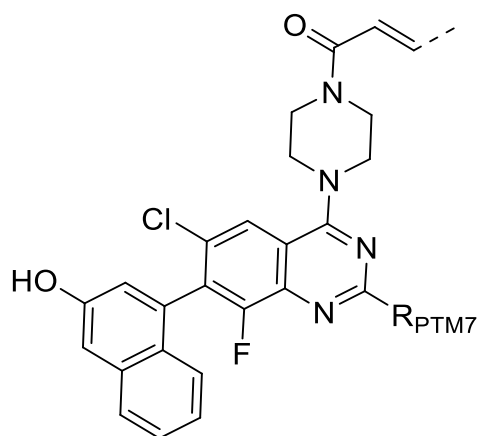
R^{L1}, R^{L2}, R^{L3}, R^{L4} y R^{L5} son, cada uno de manera independiente, seleccionados de entre H, halo, alquilo C₁₋₈, Oalquilo C₁₋₈, Salquilo C₁₋₈, NHalquilo C₁₋₈, N(alquilo C₁₋₈)₂, cicloalquilo C₃₋₁₁, arilo, heteroarilo, heterociclilo C₃₋₁₁, Ocicloalquilo C₁₋₈, Scicloalquilo C₁₋₈, NHcicloalquilo C₁₋₈, N(cicloalquilo C₁₋₈)₂, N(cicloalquilo C₁₋₈)(alquilo C₁₋₈), OH, NH₂, SH, SO₂alquilo C₁₋₈, P(O)(Oalquilo C₁₋₈)(alquilo C₁₋₈), P(O)(Oalquilo C₁₋₈)₂, CC-alquilo C₁₋₈, CCH, CH=CH(alquilo C₁₋₈), C(alquilo C₁₋₈)=CH(alquilo C₁₋₈), C(alquilo C₁₋₈)=C(alquilo C₁₋₈)₂, Si(OH)₃, Si(alquilo C₁₋₈)₃, Si(OH)(alquilo C₁₋₈)₂, COalquilo C₁₋₈, CO₂H, halógeno, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO₂NHalquilo C₁₋₈, SO₂N(alquilo C₁₋₈)₂, SONHalquilo C₁₋₈, SON(alquilo C₁₋₈)₂, CONHalquilo C₁₋₈, CON(alquilo C₁₋₈)₂, N(alquilo C₁₋₈)CONH(alquilo C₁₋₈), N(alquilo C₁₋₈)CON(alquilo C₁₋₈)₂, NHCONH(alquilo C₁₋₈), NHCON(alquilo C₁₋₈)₂, NHCONH₂, N(alquilo C₁₋₈)SO₂NH(alquilo C₁₋₈), N(alquilo C₁₋₈) SO₂N(alquilo C₁₋₈)₂, NH SO₂NH(alquilo C₁₋₈), NH SO₂N(alquilo C₁₋₈)₂, y NH SO₂NH₂.

2. El compuesto ~~bifuncional~~ de acuerdo con la reivindicación 1, donde el PTM **es representado porse selecciona de entre:**

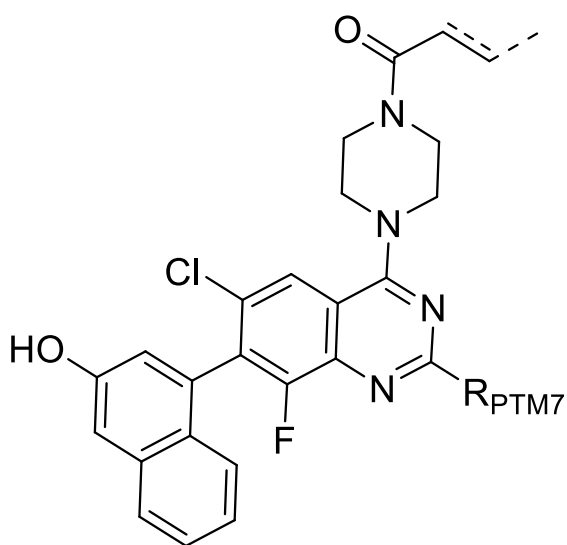




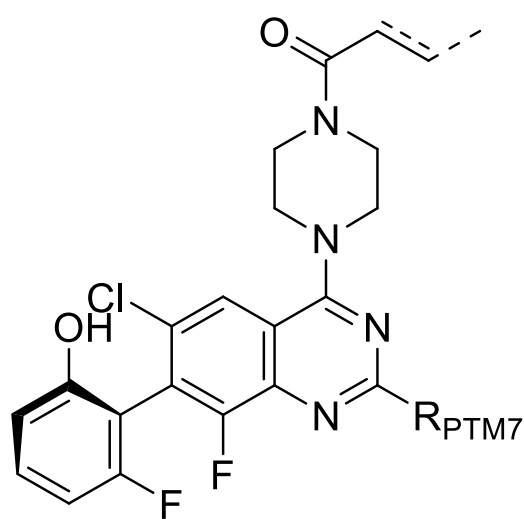
PTM-VI



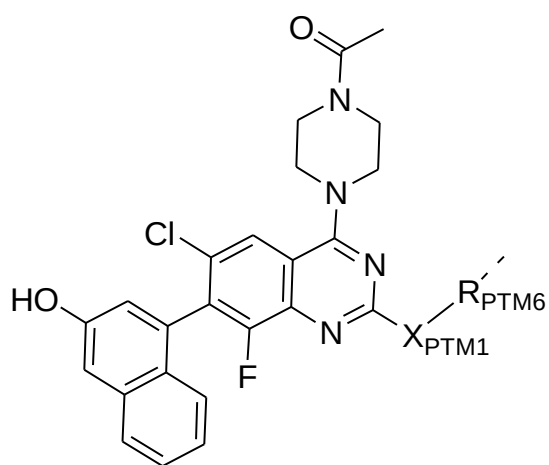
PTM-VIIa



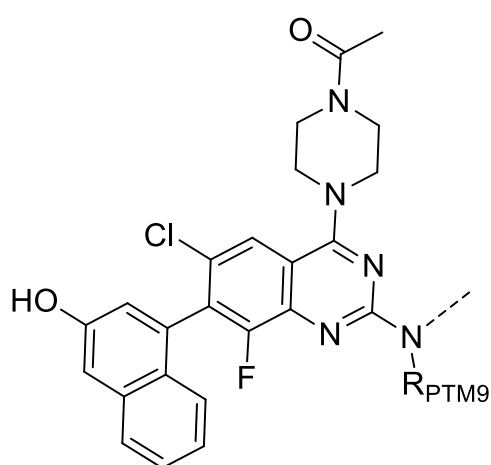
PTM-VIIb



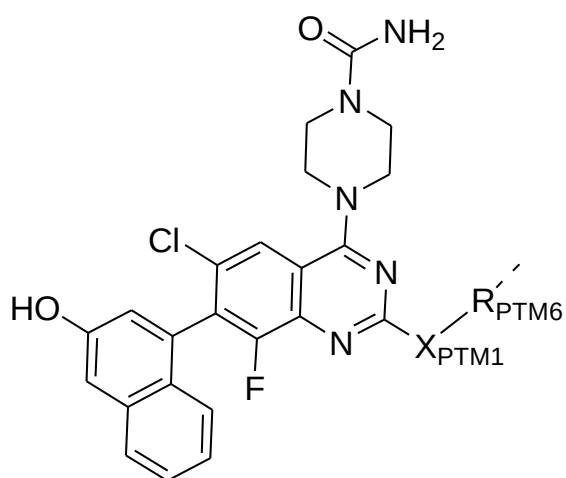
PTM-VIII



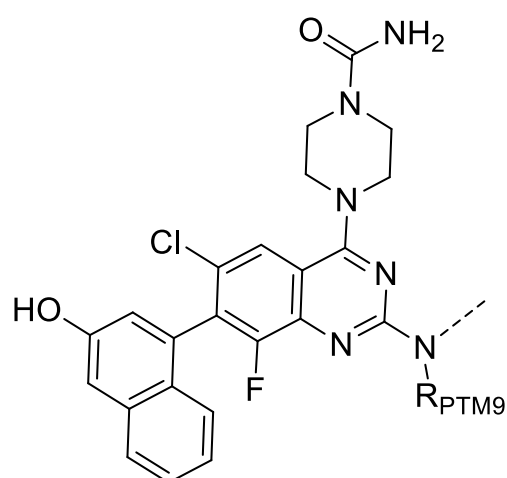
PTM-IXa



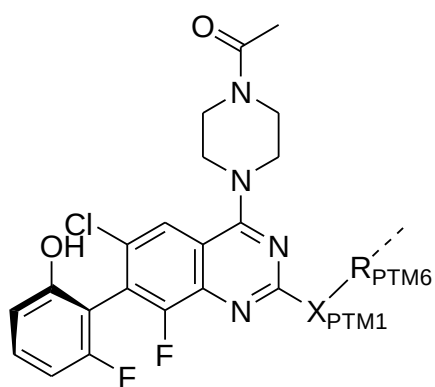
PTM-I-Xb



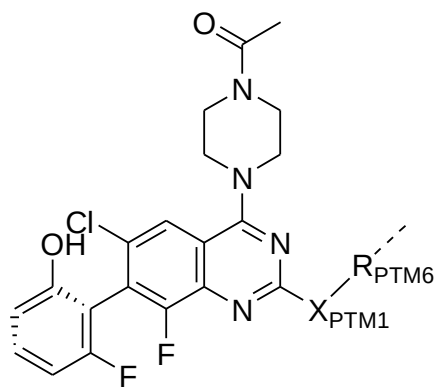
PTM-Xa



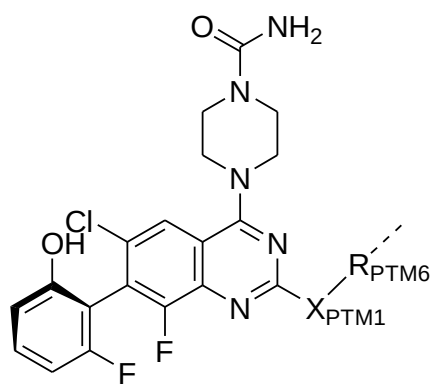
PTM-Xb



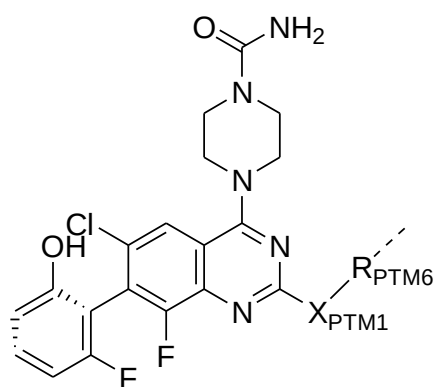
PTM-XI



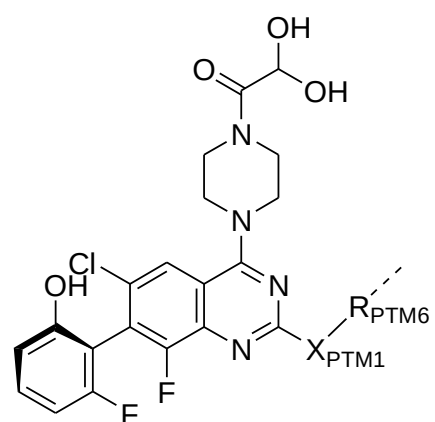
PTM-XII



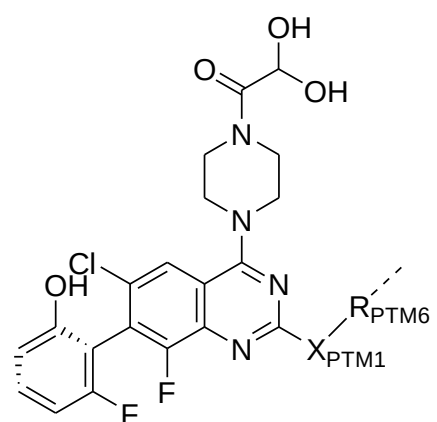
PTM-XIII



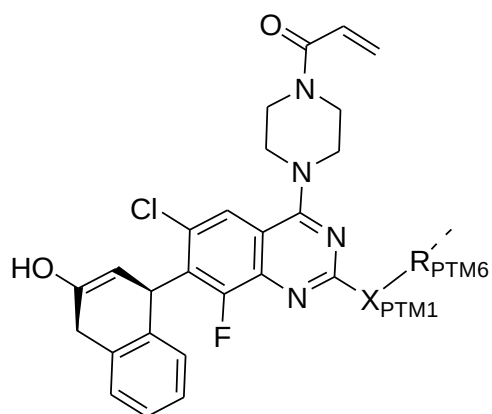
PTM-XIV



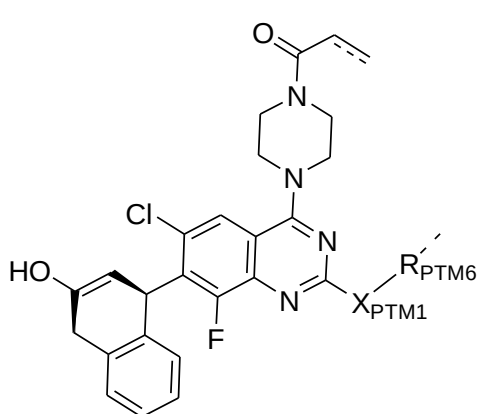
PTM-XV



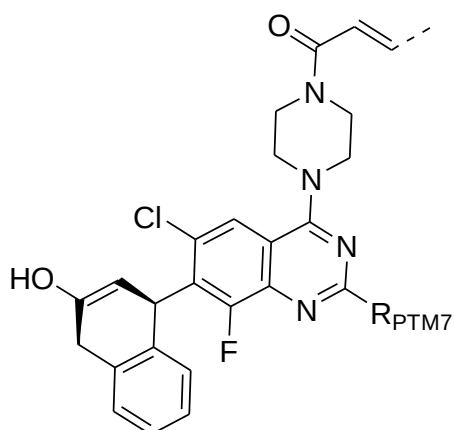
PTM-XVI



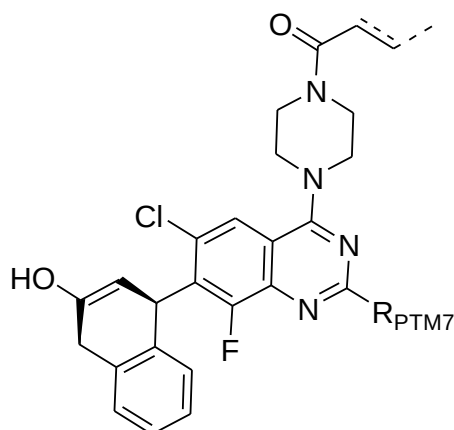
PTM-XVIIa



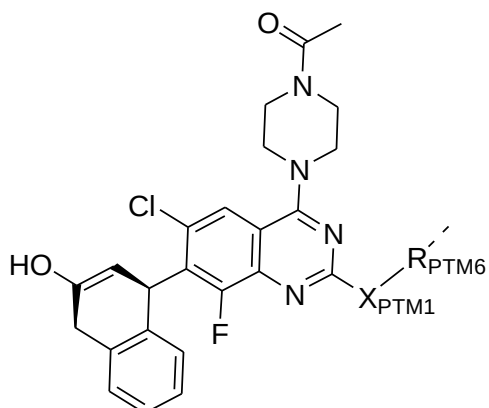
PTM-XVIIb



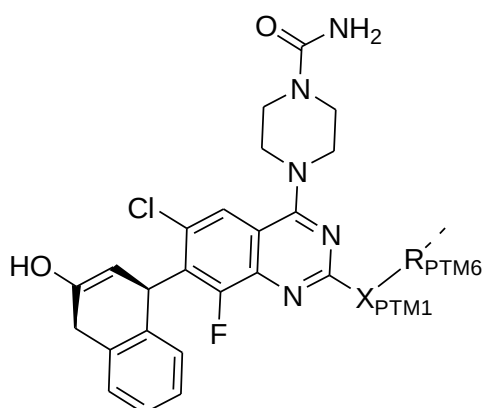
PTM-XVIII



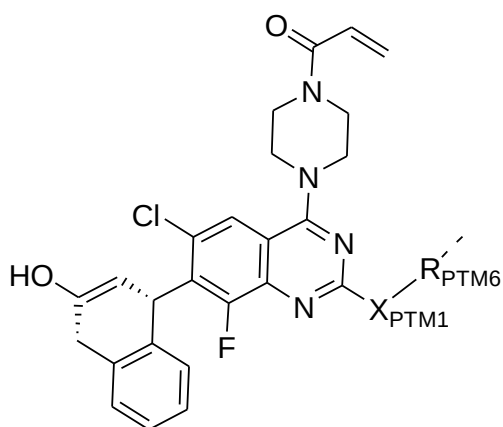
PTM-XIV



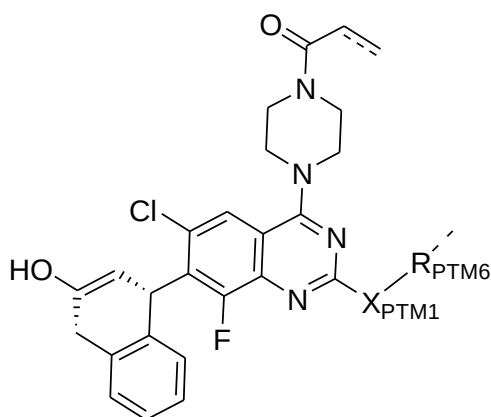
PTM-XV



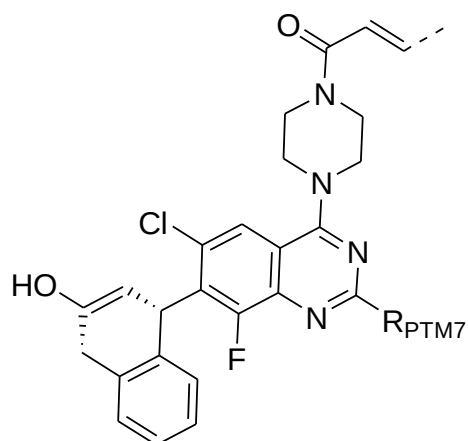
PTM-XVI



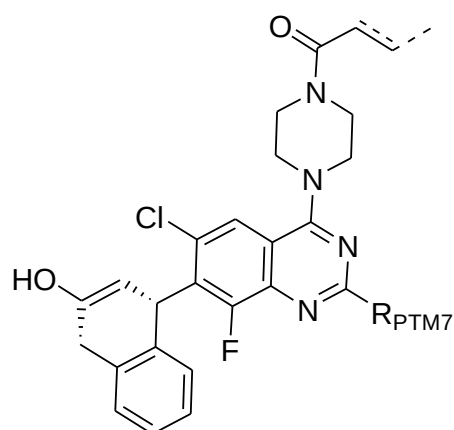
PTM-XVIIa



PTM-XVIIb



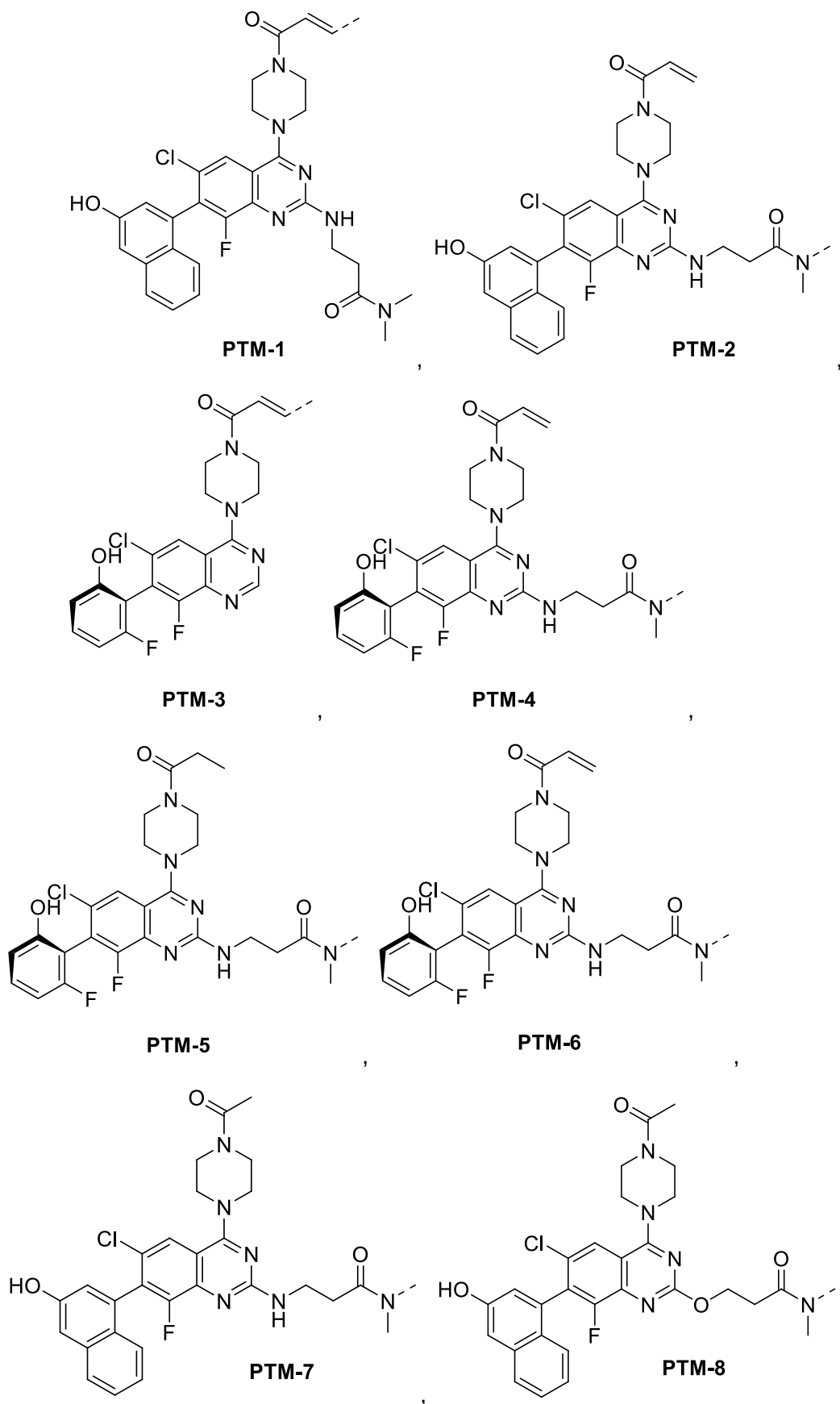
PTM-XVIII

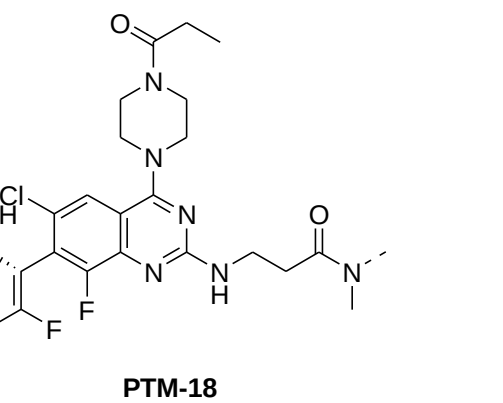
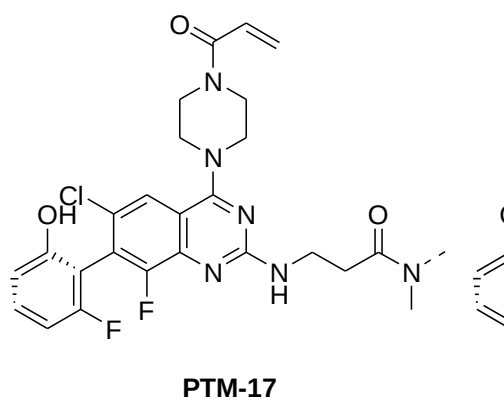
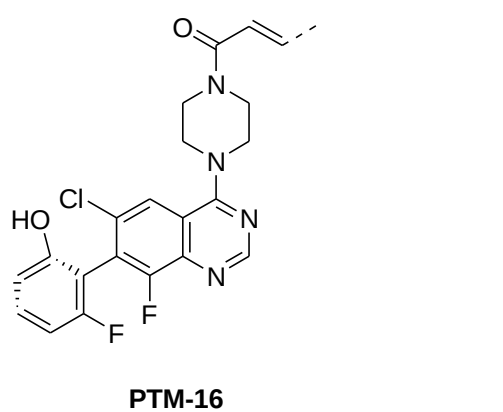
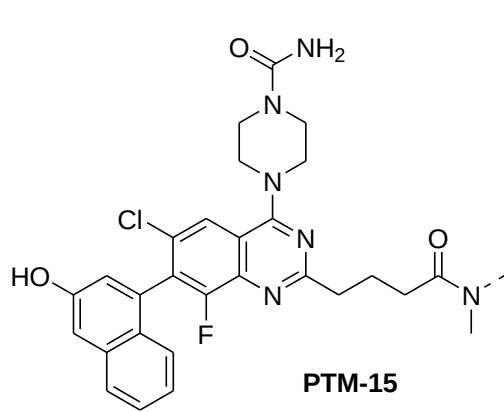
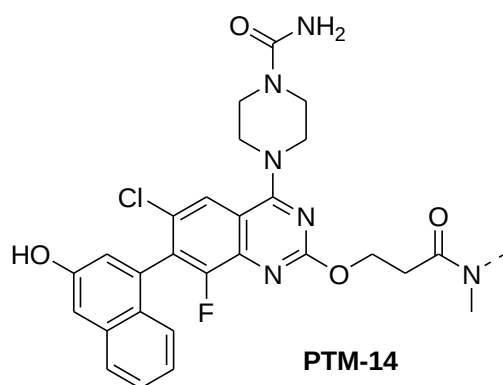
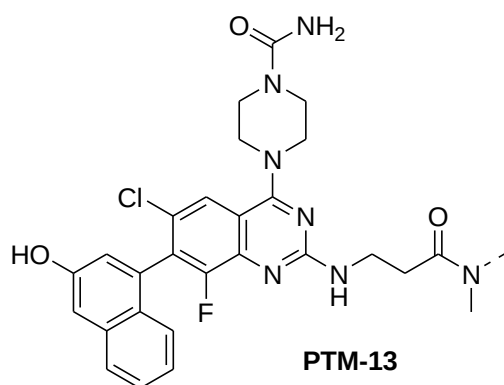
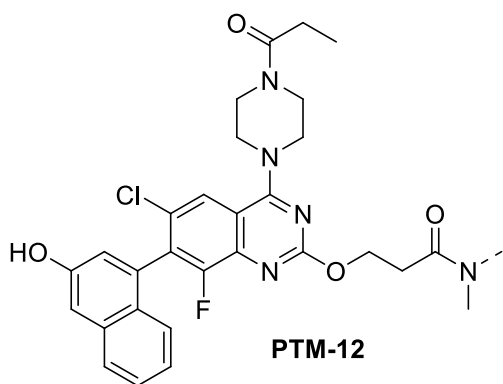
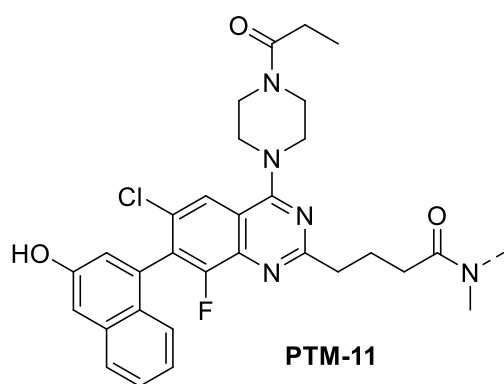
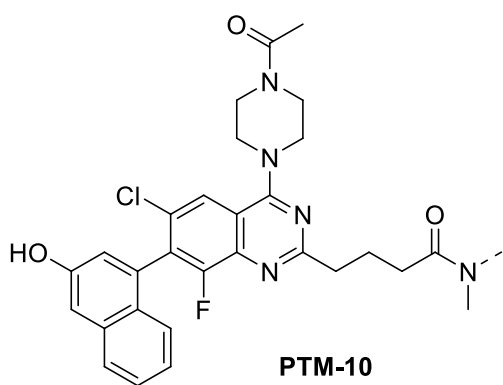
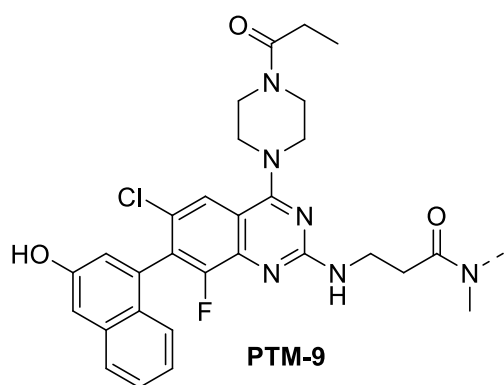


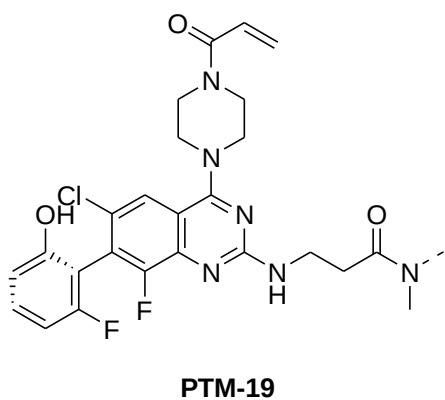
PTM-XIX


puede ser un enlace simple o un enlace doble; y
 indica el sitio de unión del L.

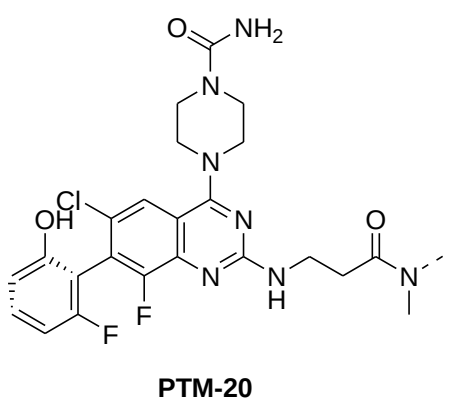
3. El compuesto ~~bifuncional~~ de acuerdo con cualquiera de la reivindicación 1 o reivindicación 2, donde el PTM es representado por la estructura química seleccionada de entre:



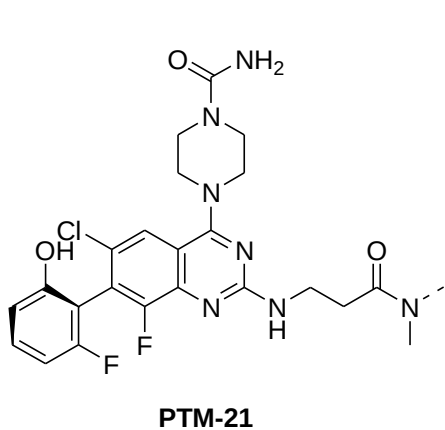




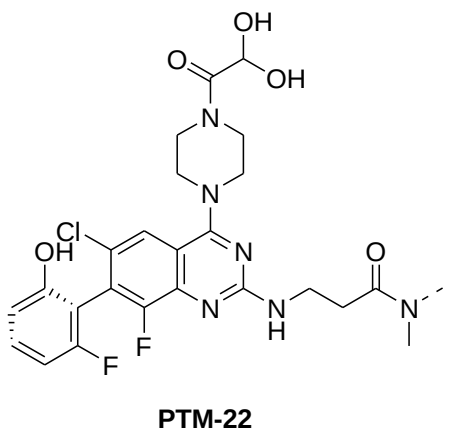
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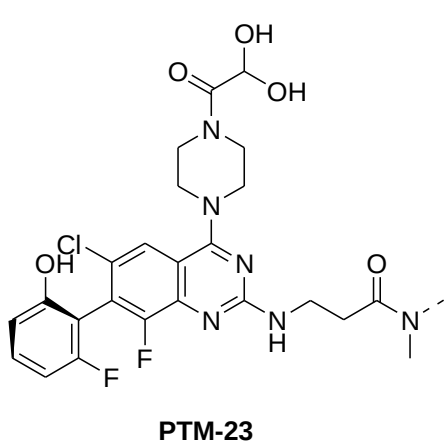
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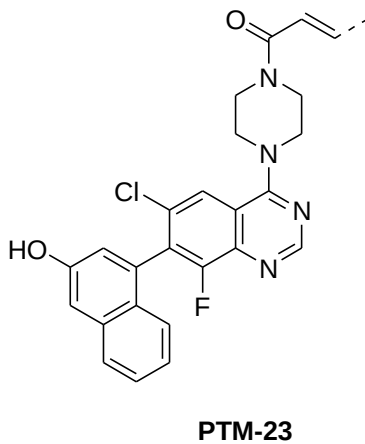
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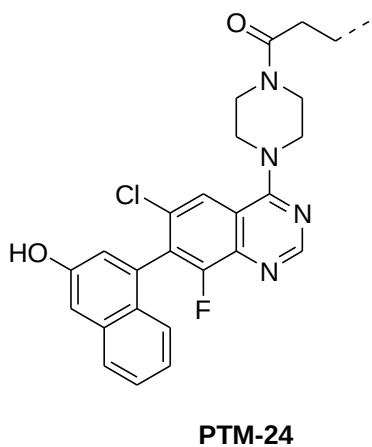
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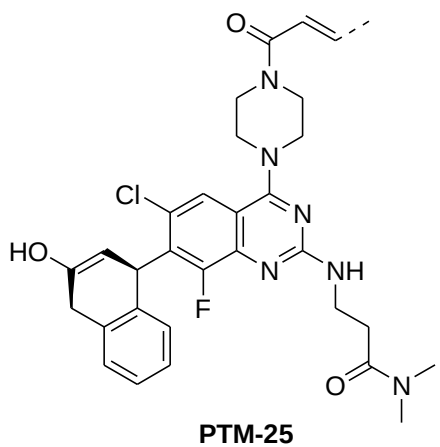
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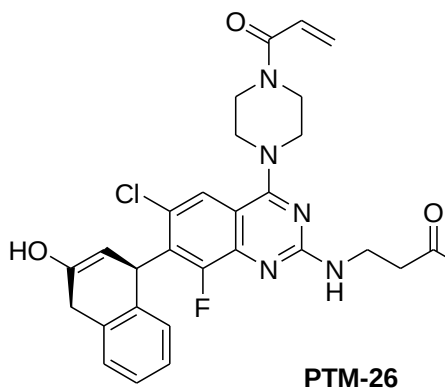
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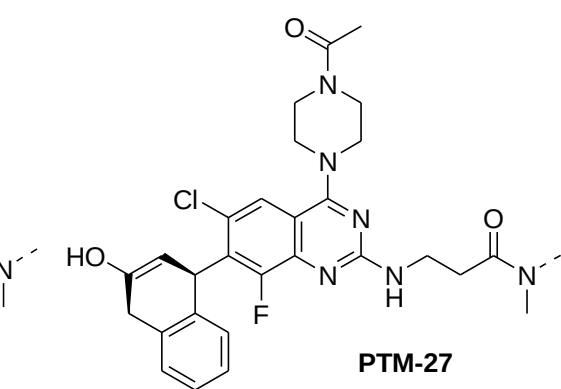
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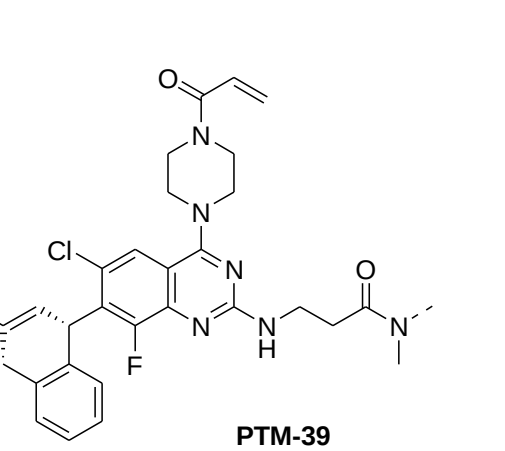
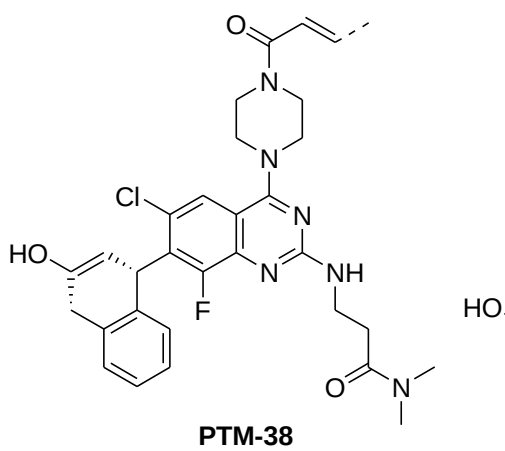
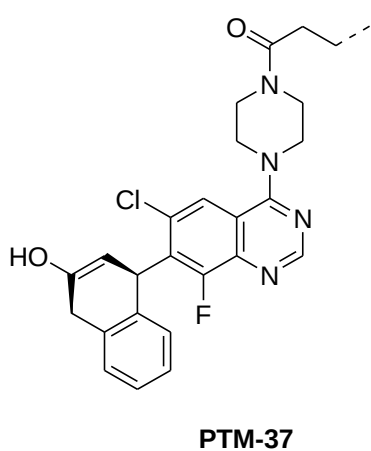
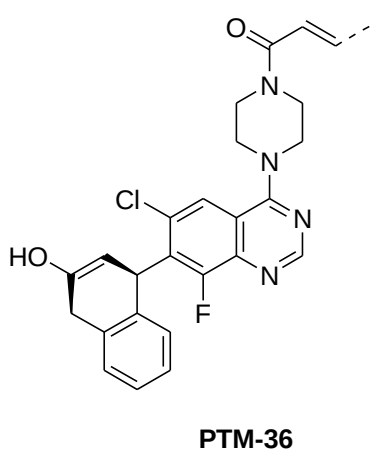
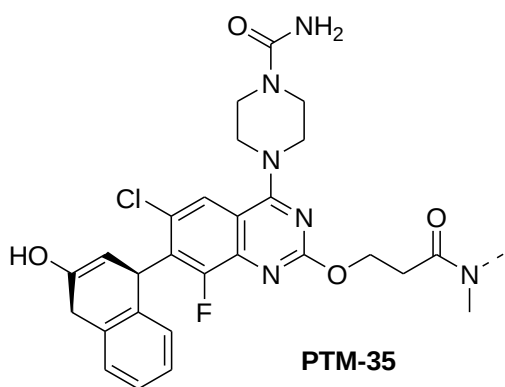
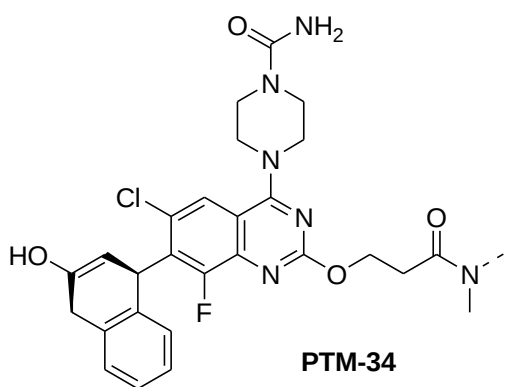
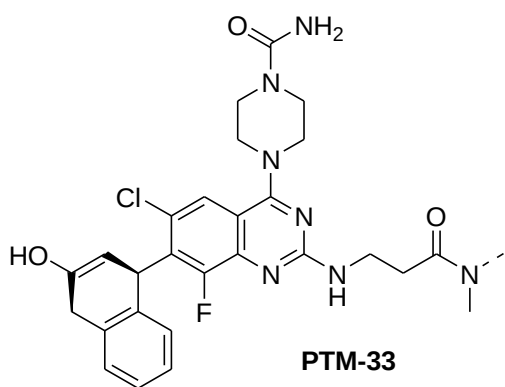
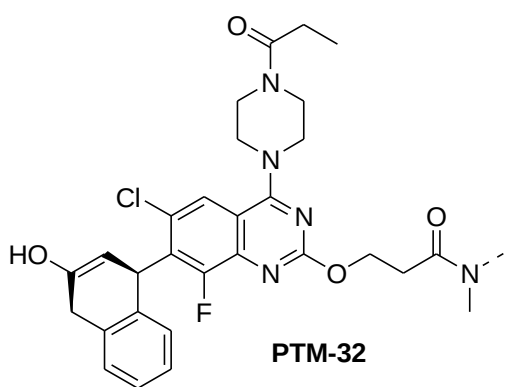
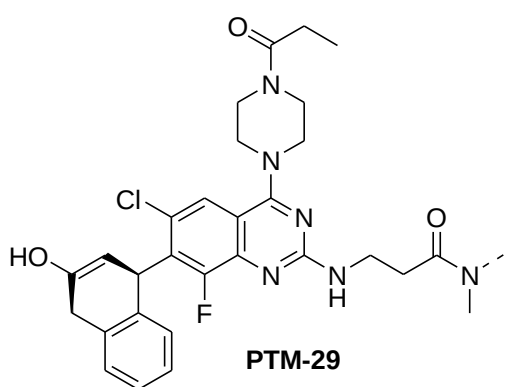
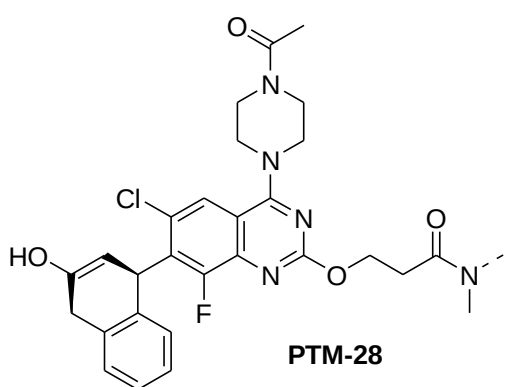
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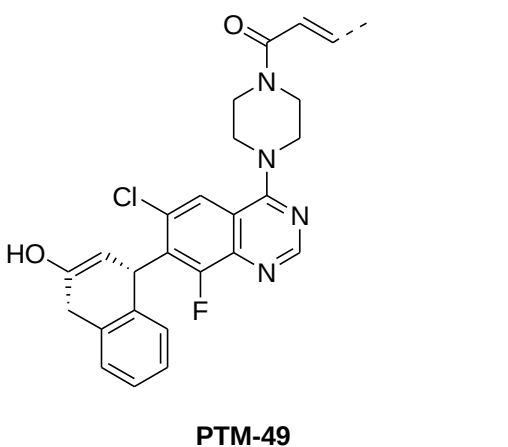
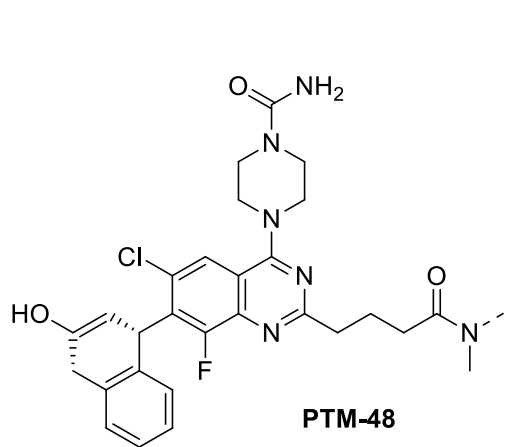
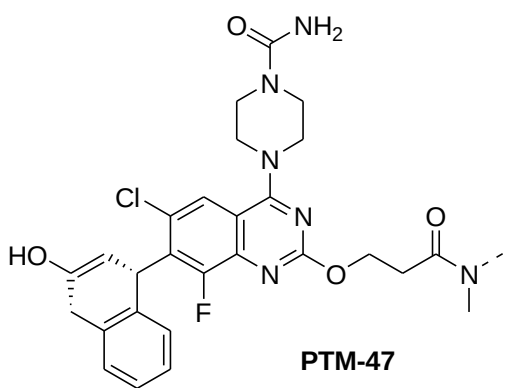
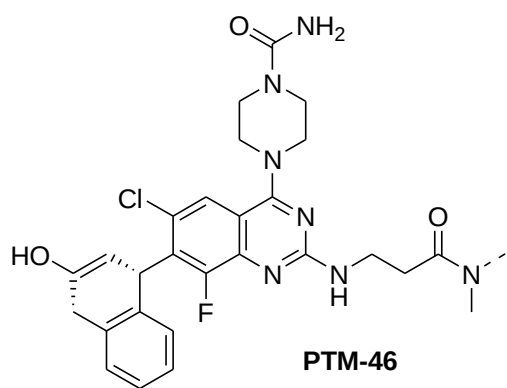
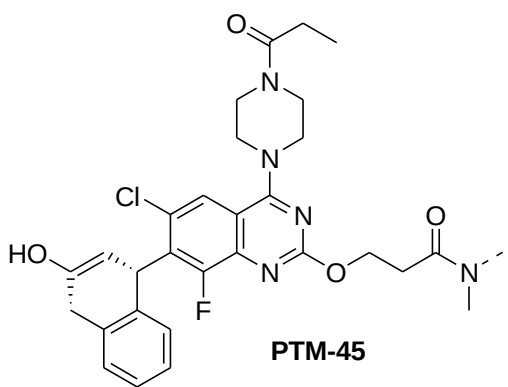
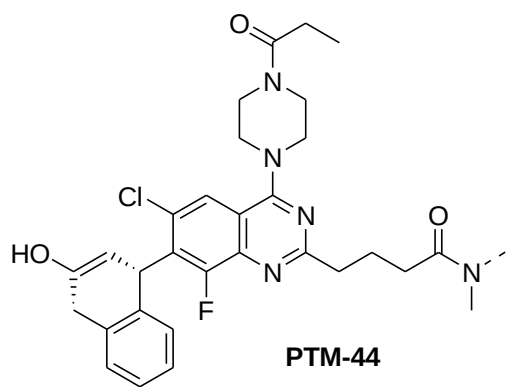
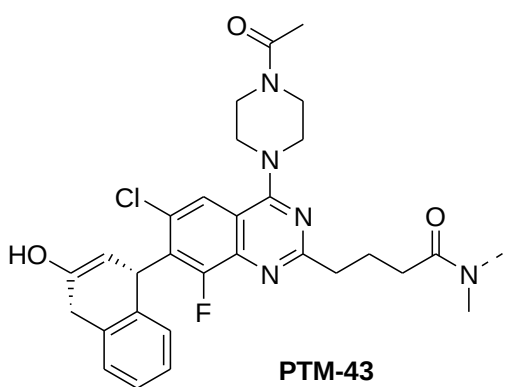
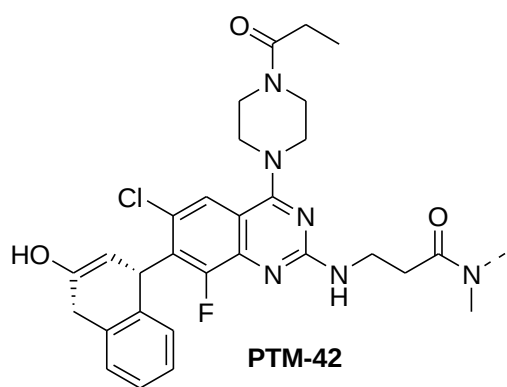
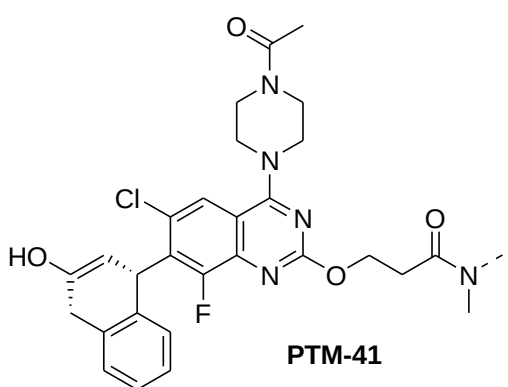
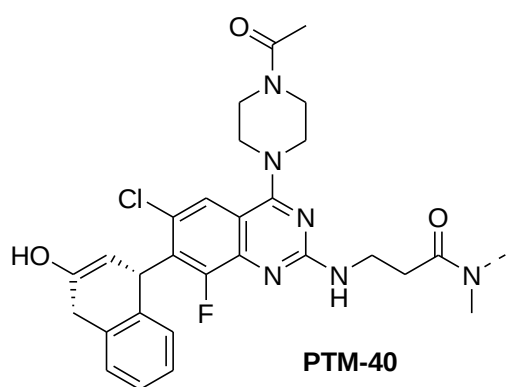


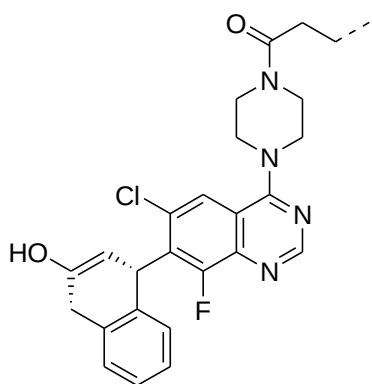
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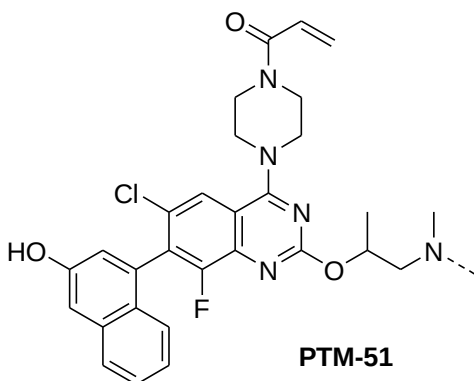






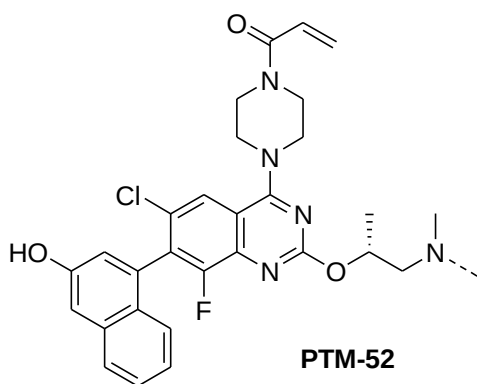
PTM-50

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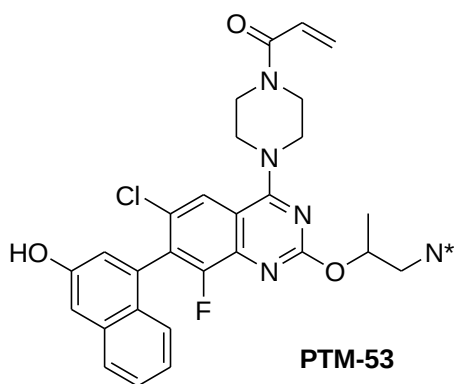
PTM-51

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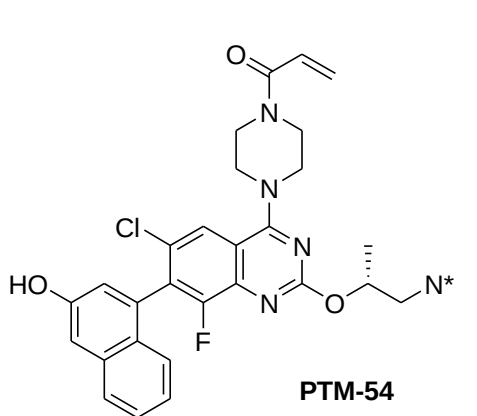
PTM-52

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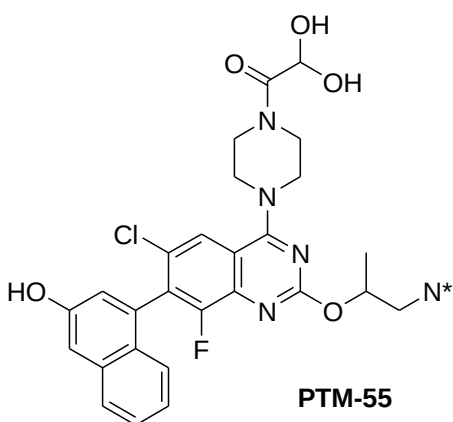
PTM-53

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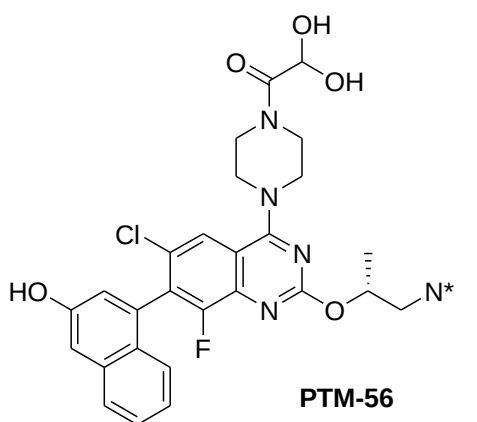
PTM-54

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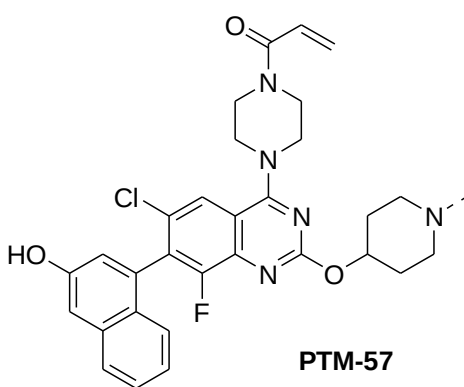
PTM-55

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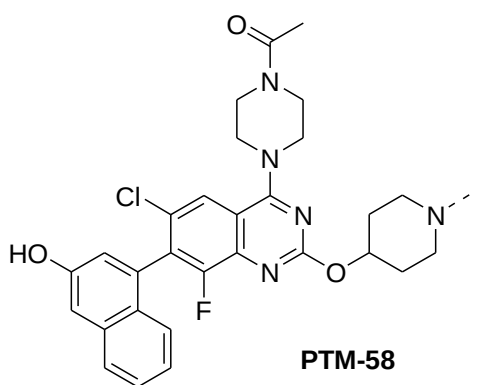
PTM-56

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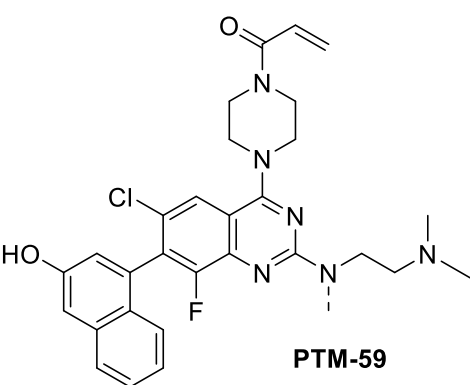
PTM-57

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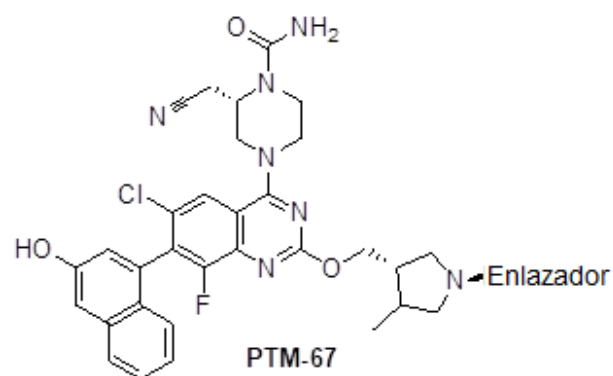
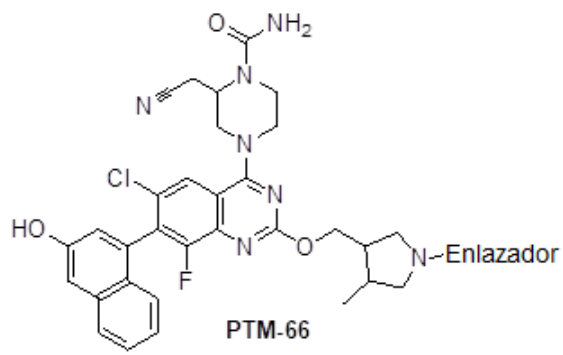
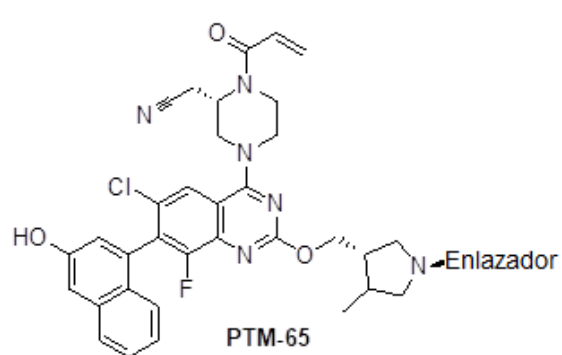
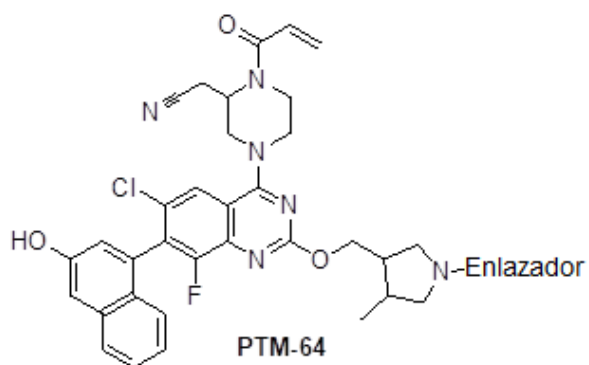
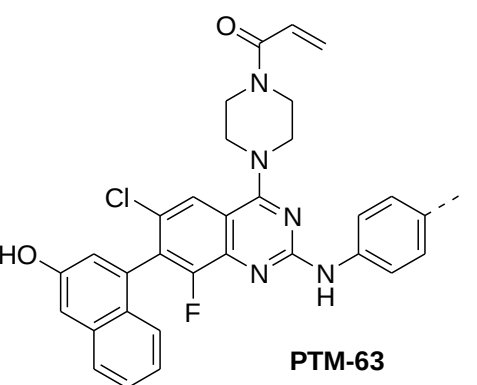
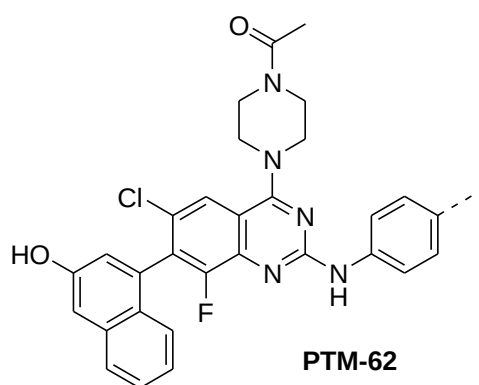
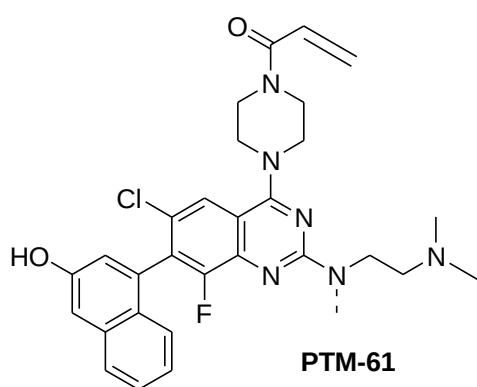
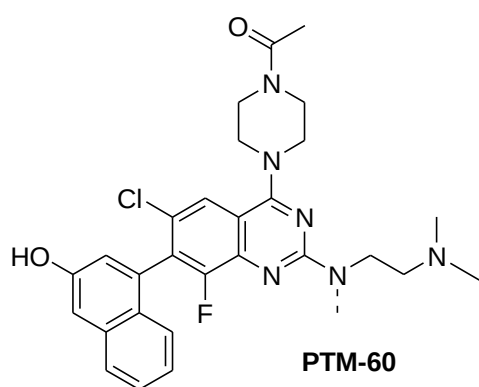
PTM-58

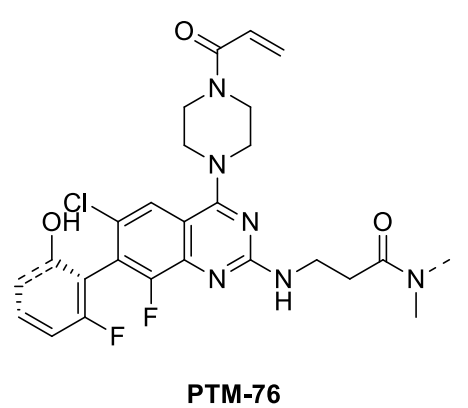
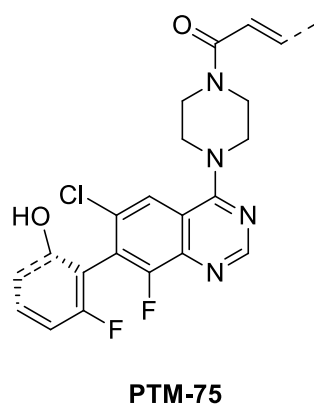
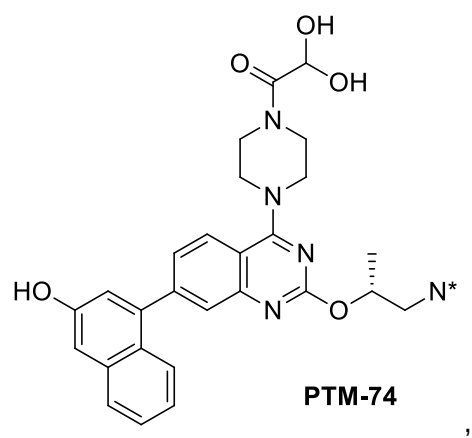
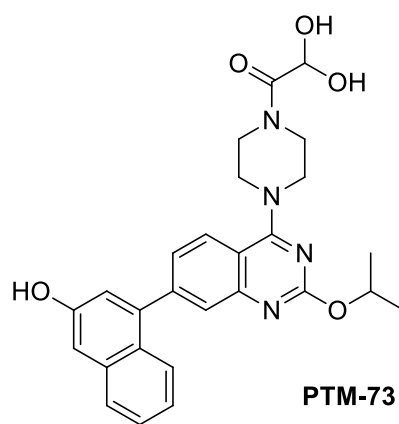
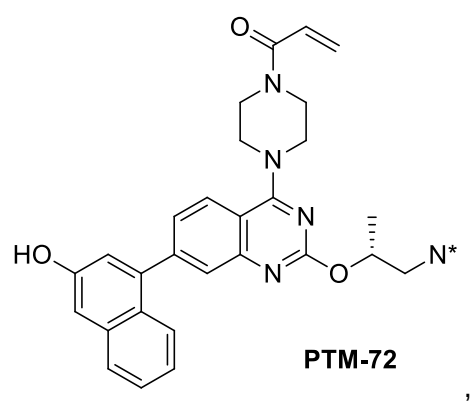
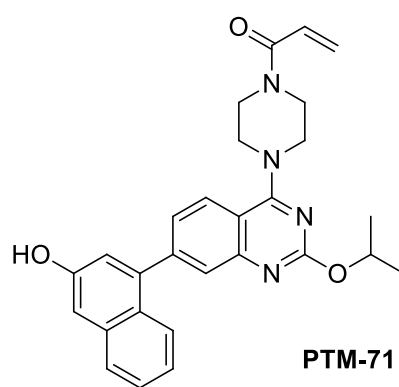
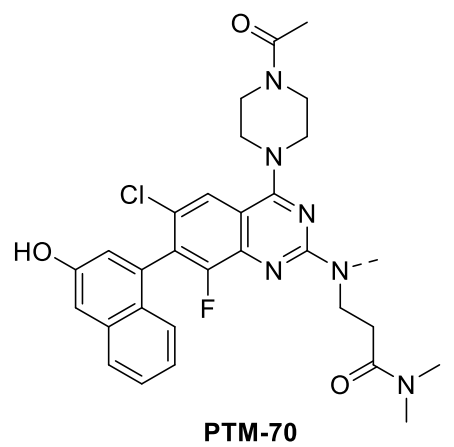
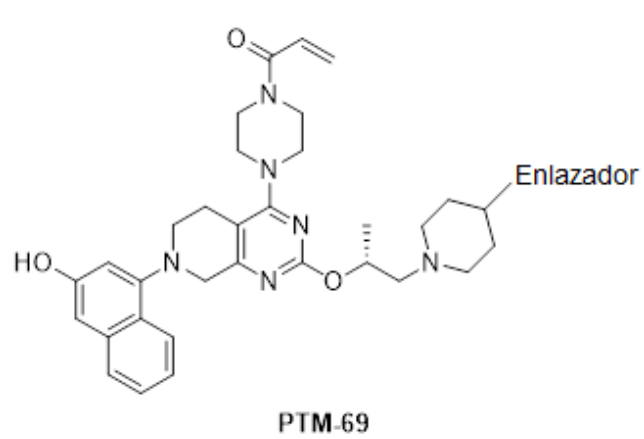
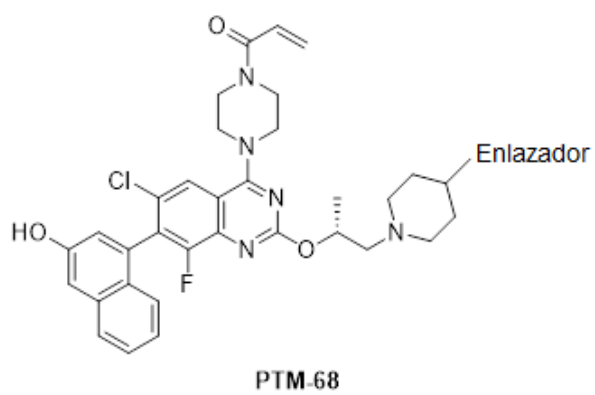
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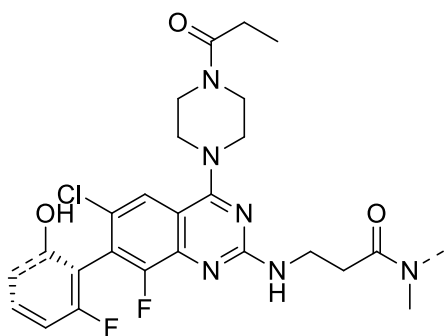


PTM-59

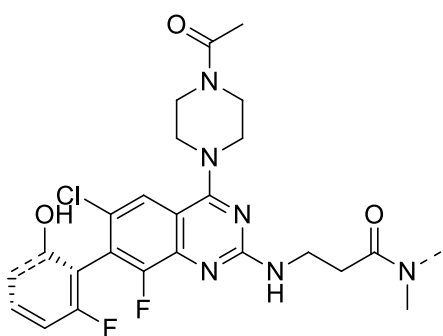
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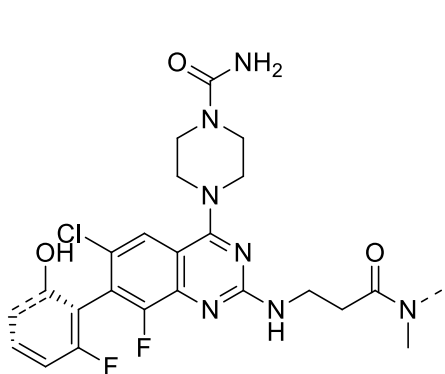




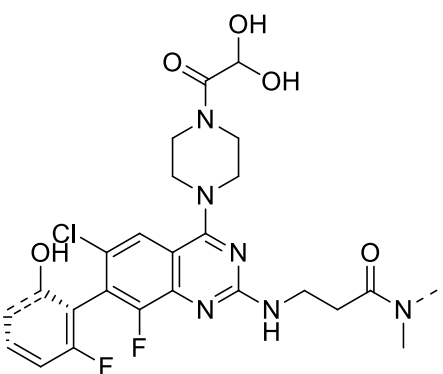
PTM-77



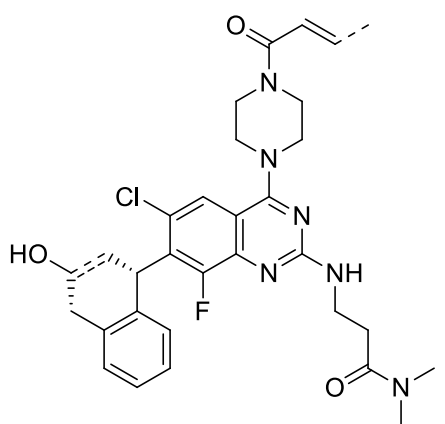
PTM-78



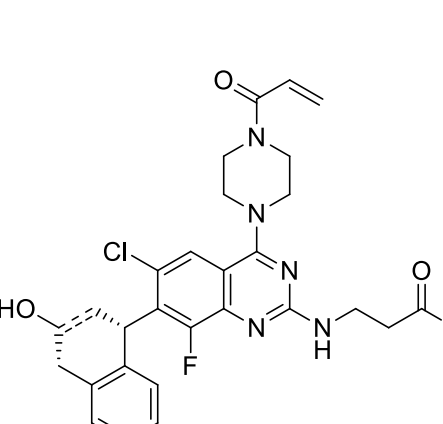
PTM-79



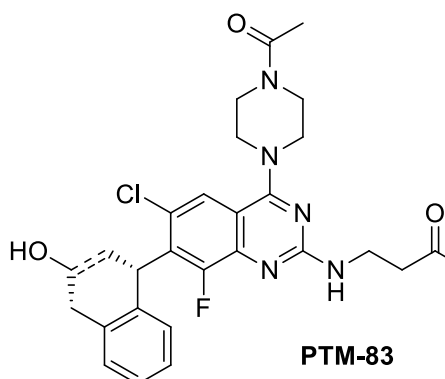
PTM-80



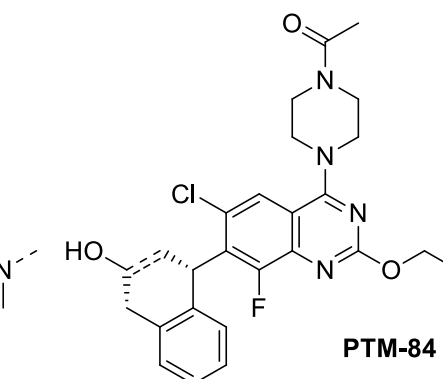
PTM-81



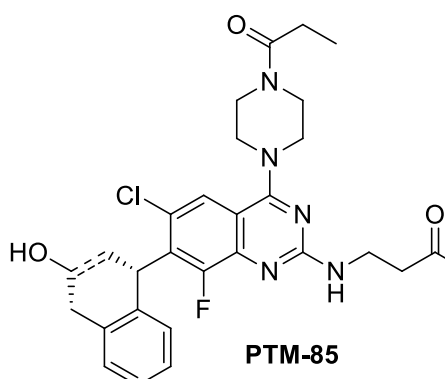
PTM-82



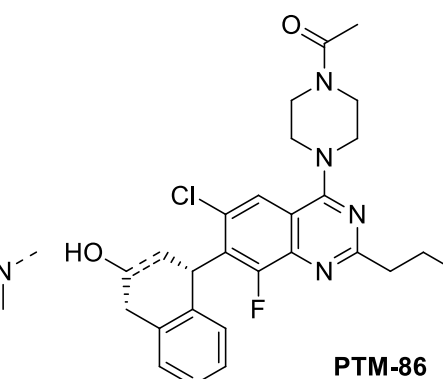
PTM-83



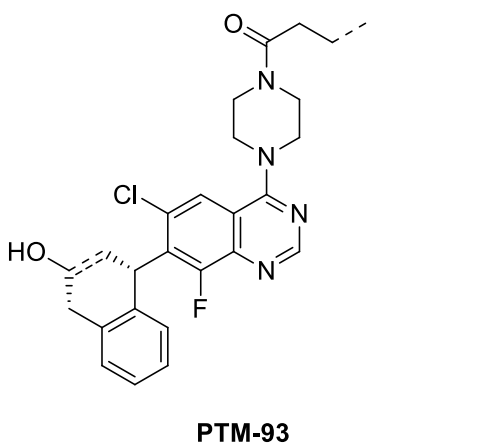
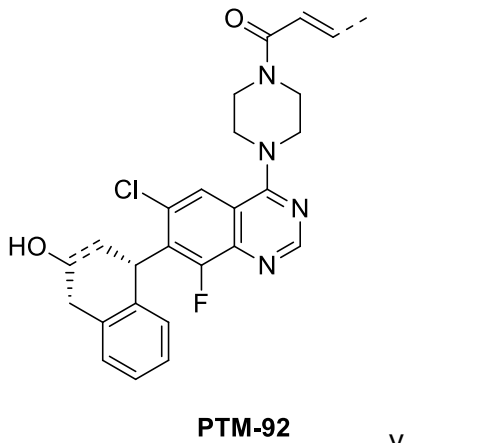
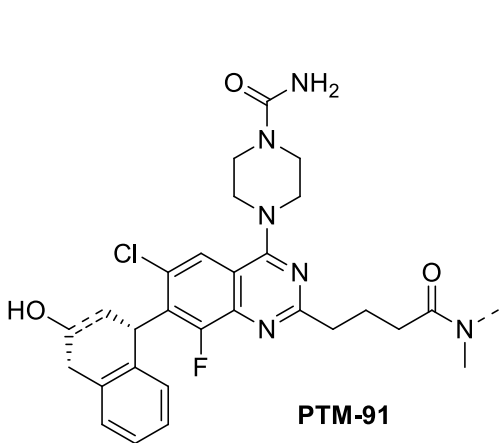
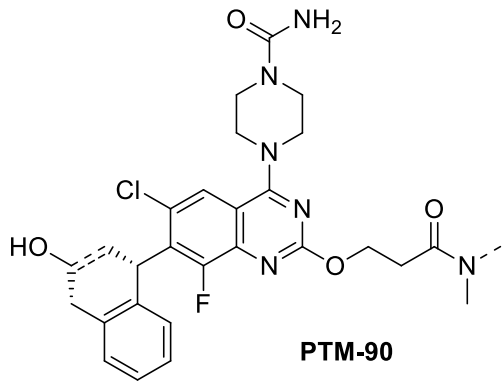
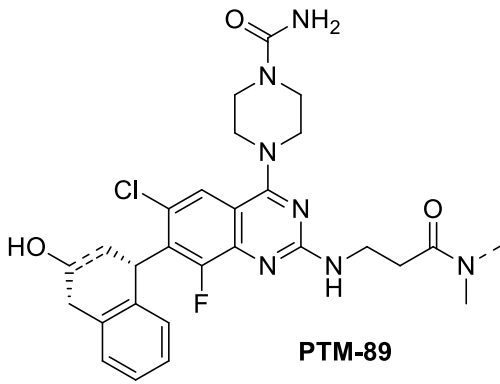
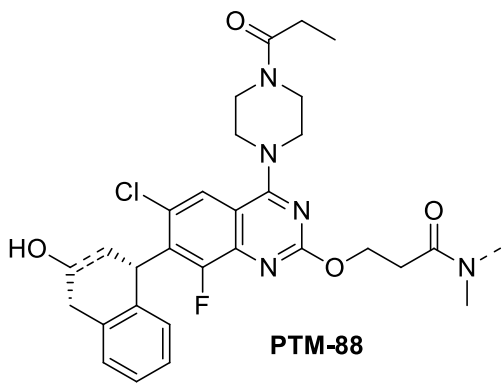
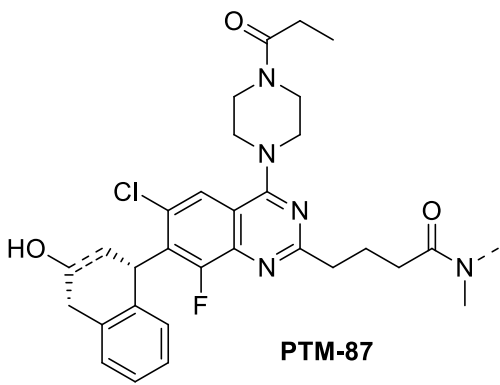
PTM-84



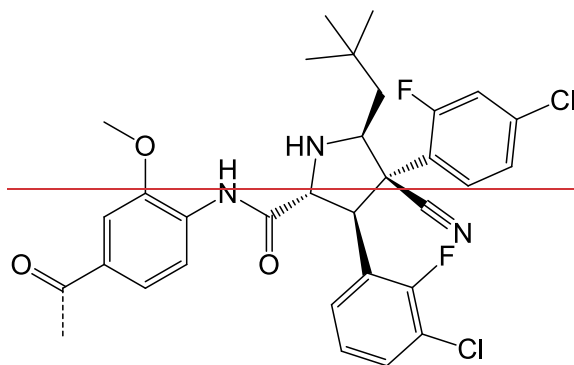
PTM-85



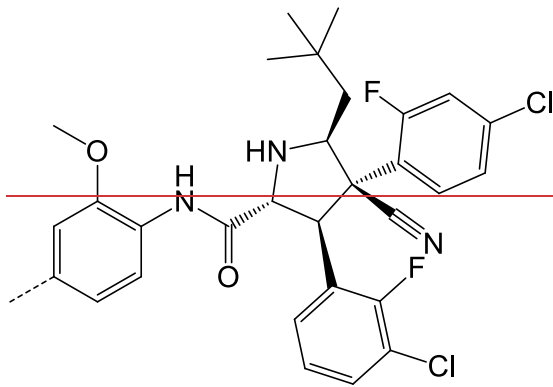
PTM-86



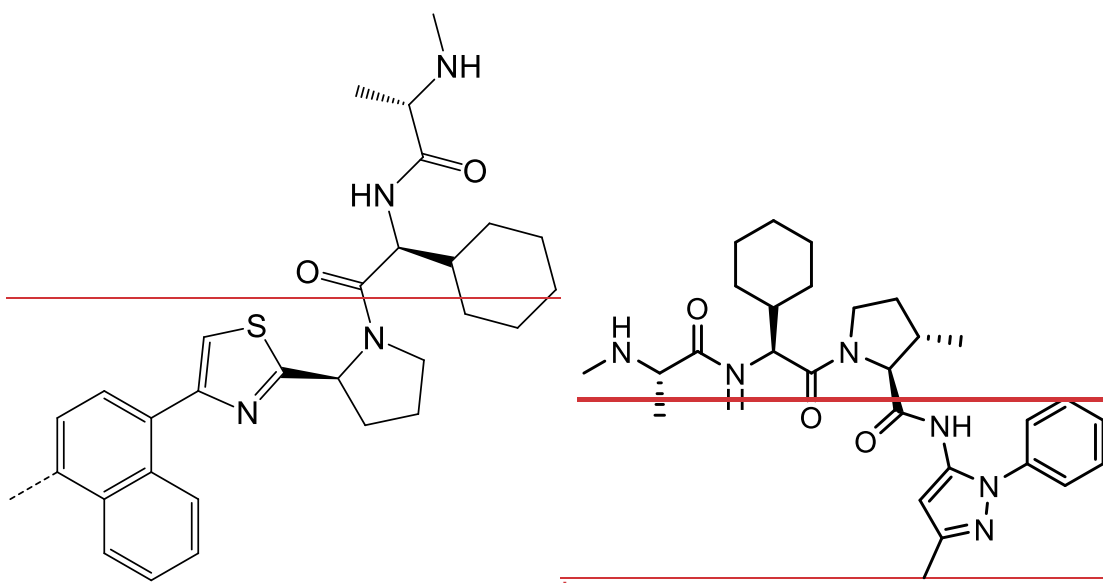
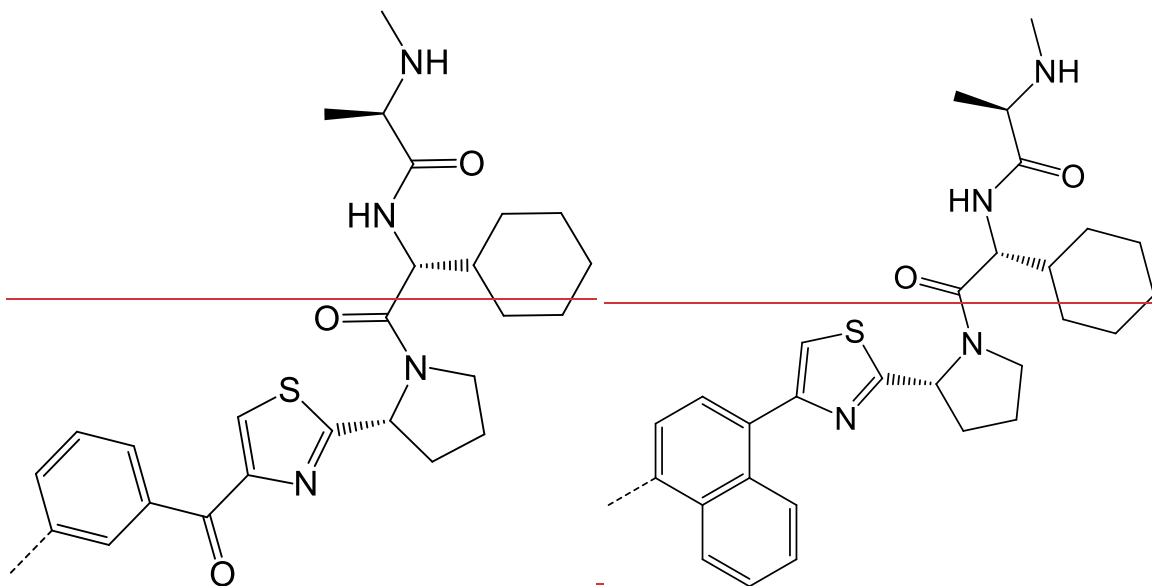
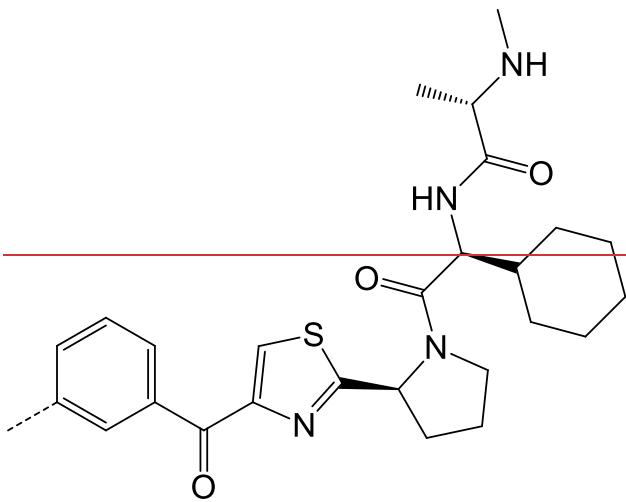
4. ~~El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el MLM se selecciona de entre:~~

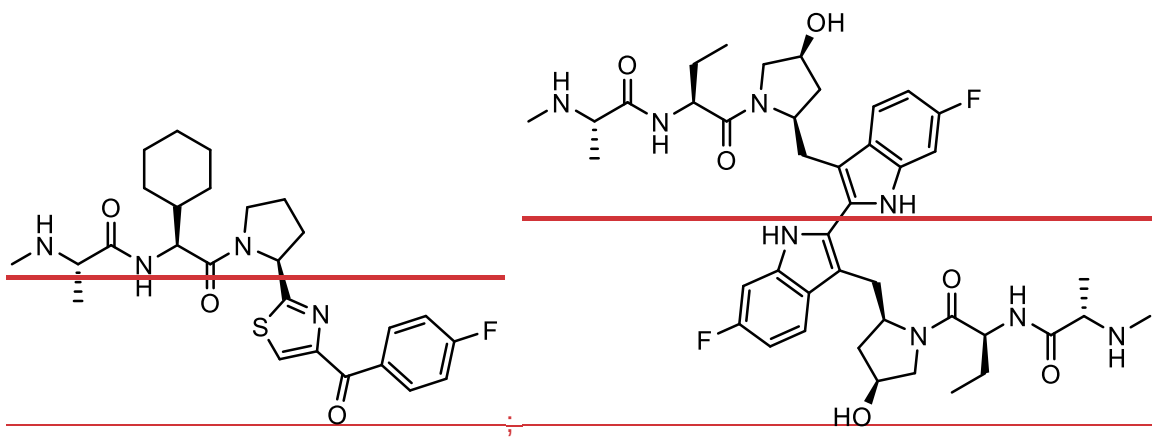
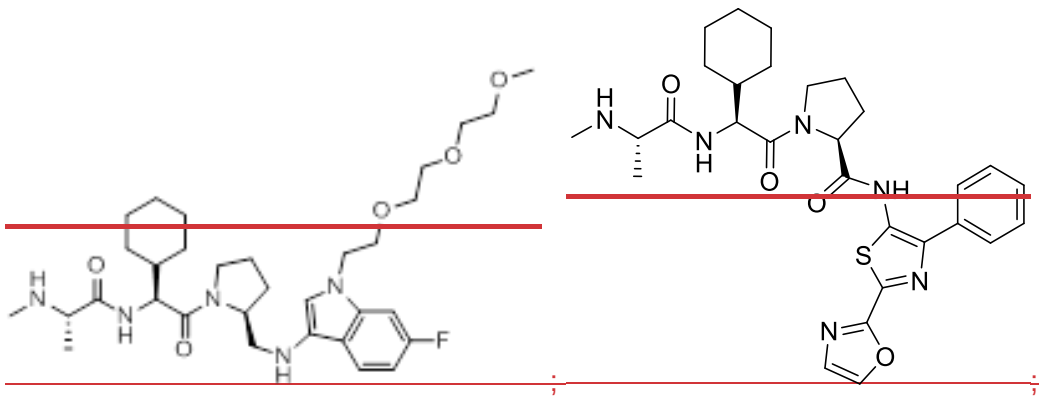
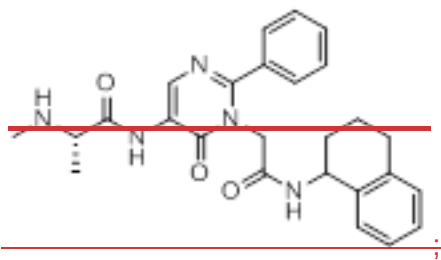
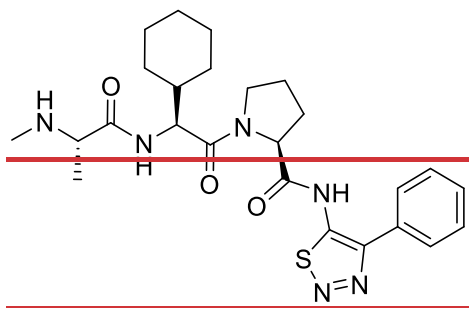
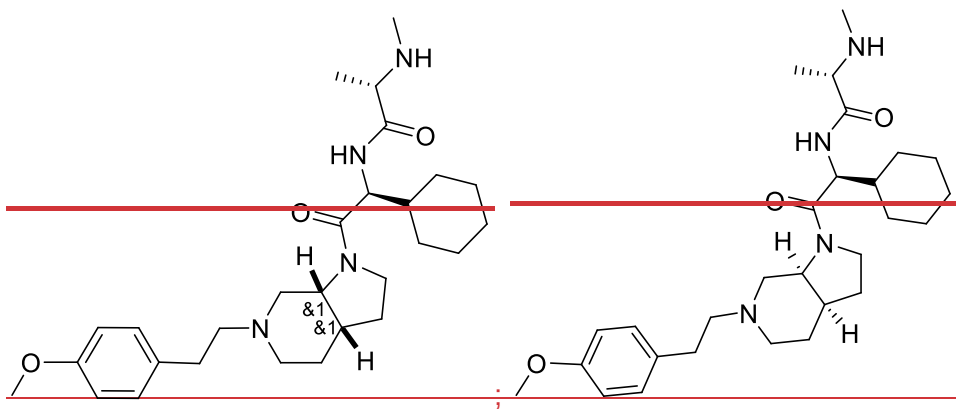
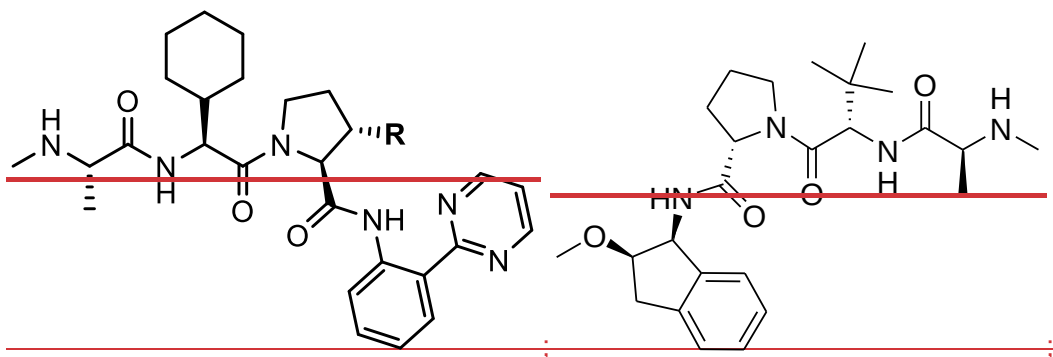


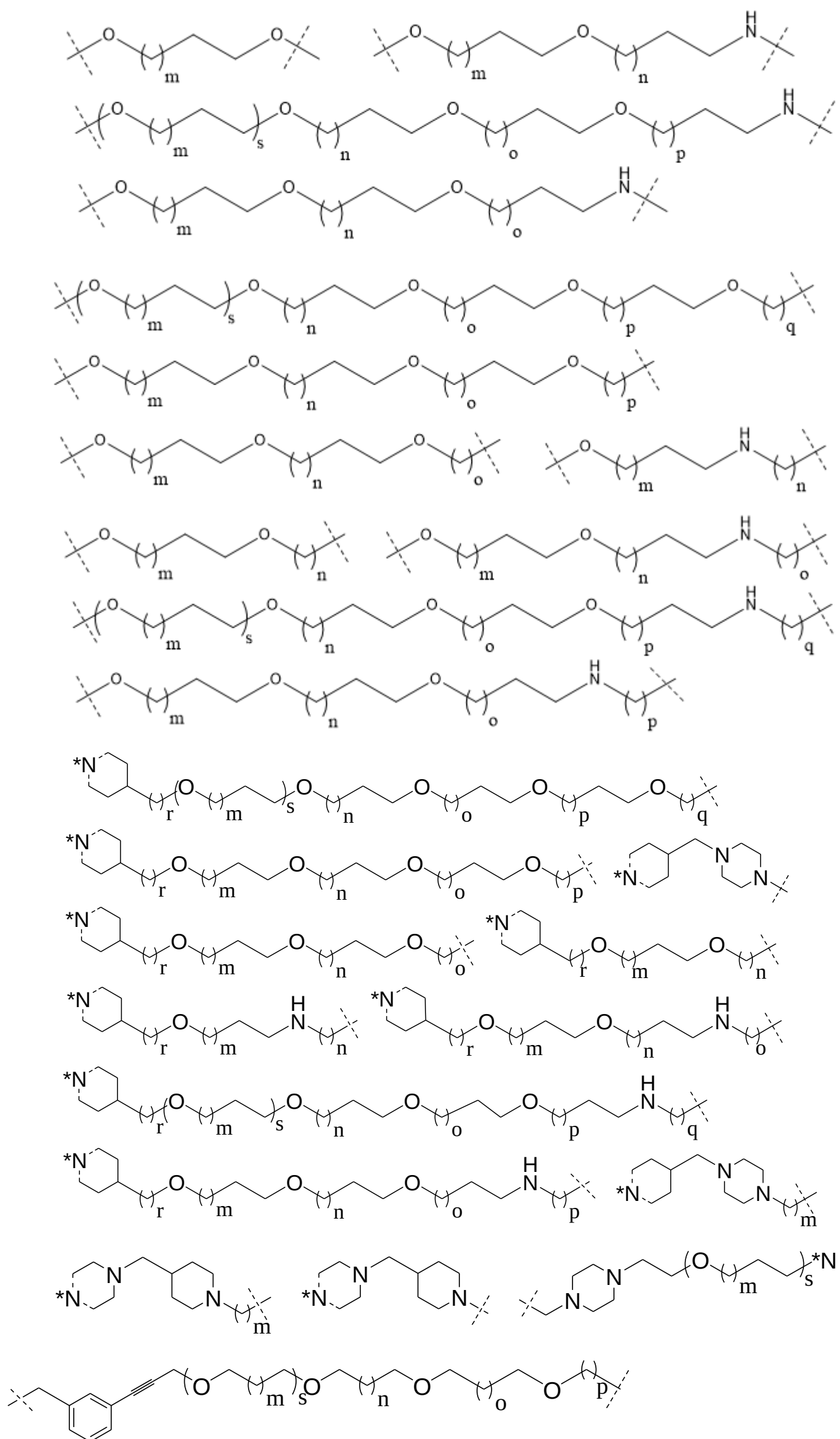
~~y~~

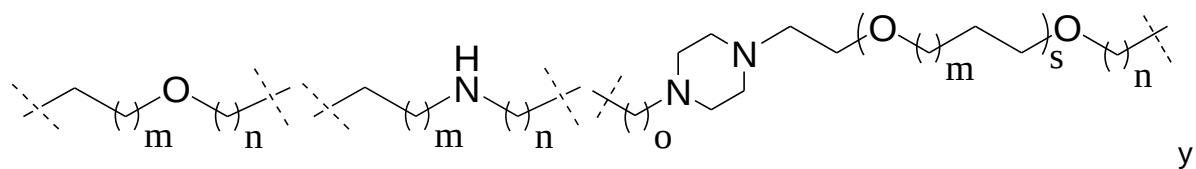


5. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el ILM se selecciona de entre:









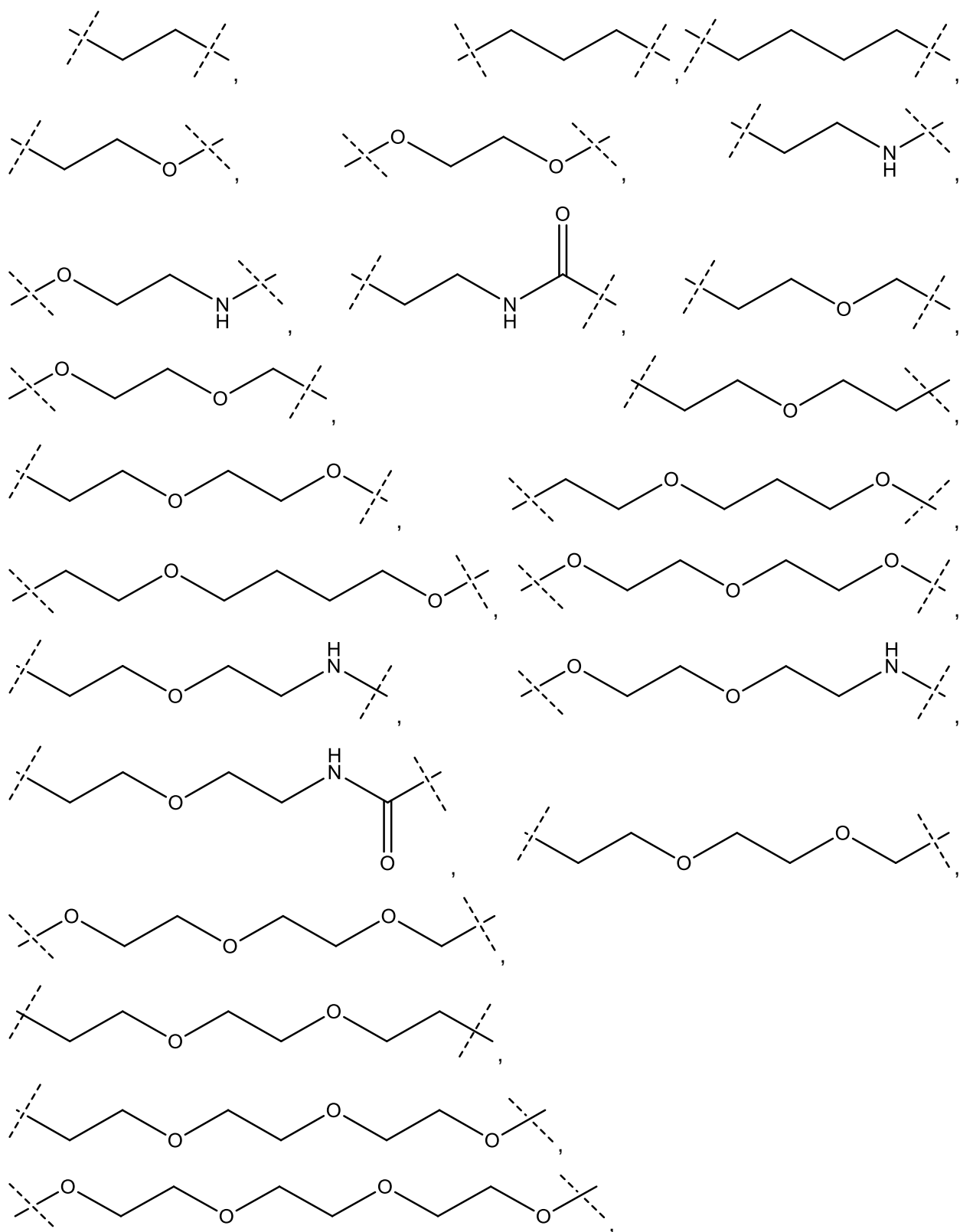
alquilo C₁₋₆; Θ_1

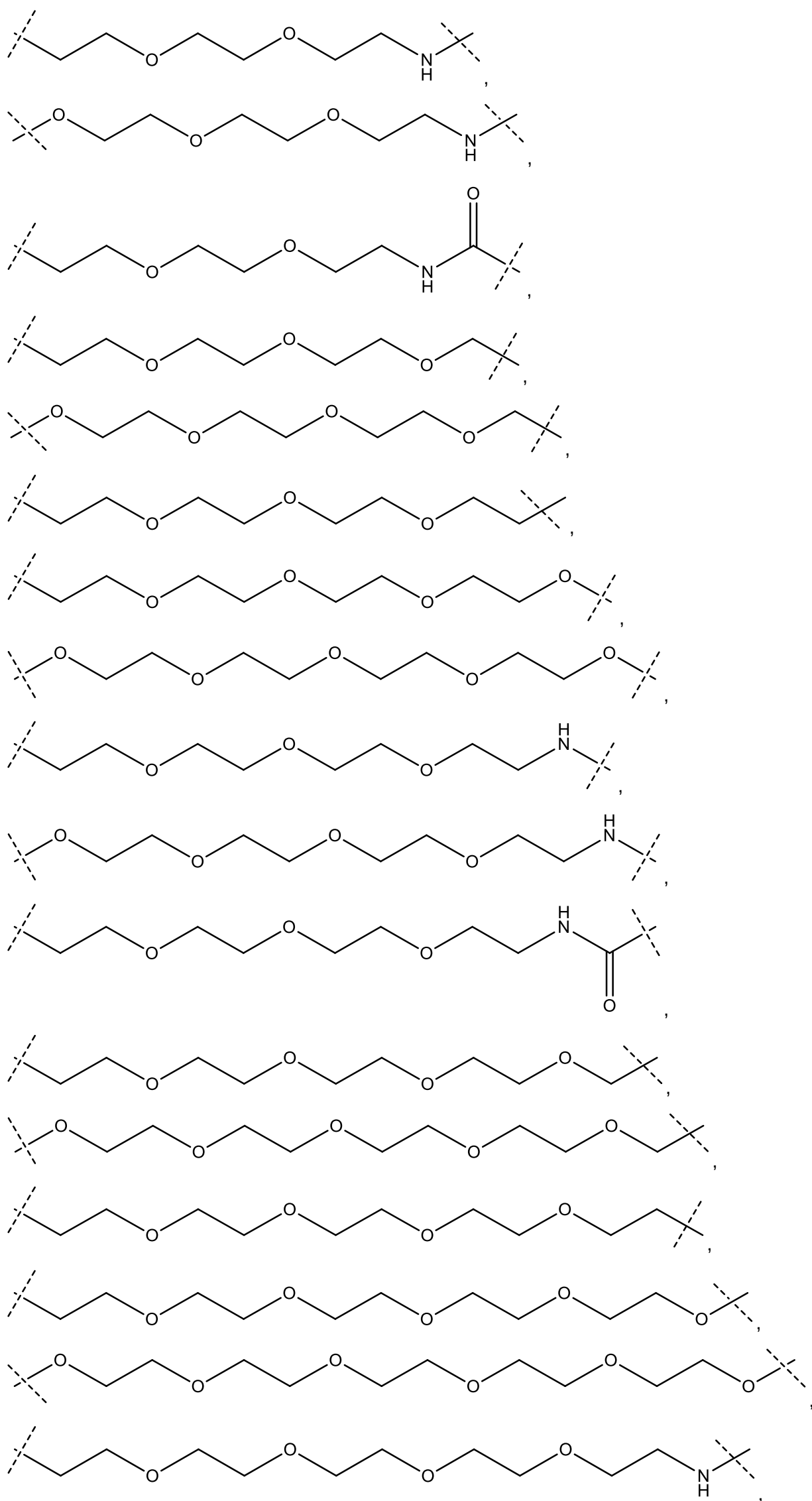
donde:

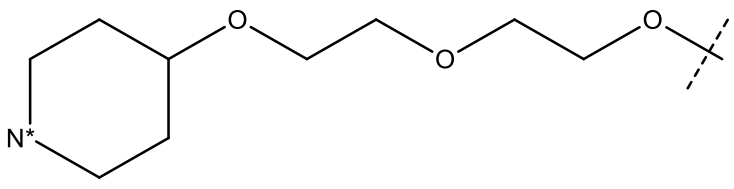
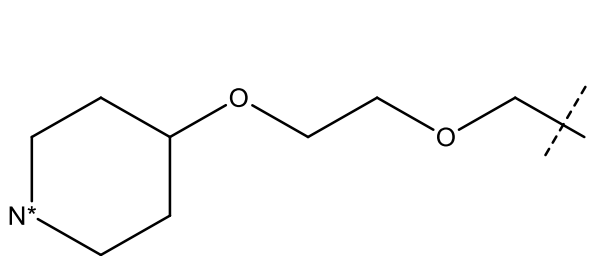
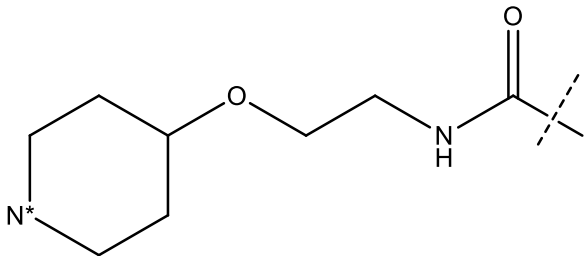
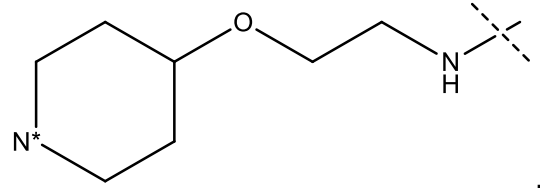
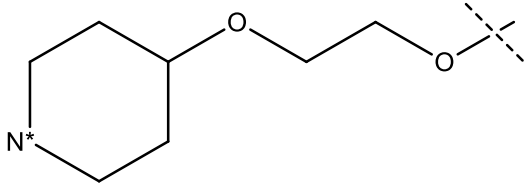
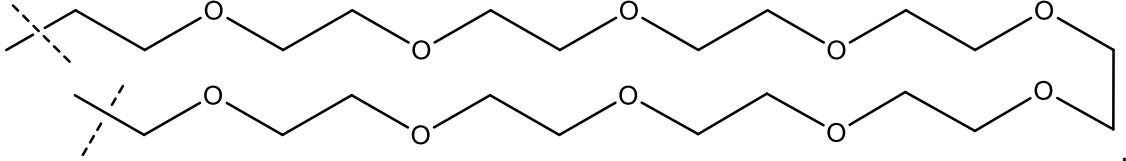
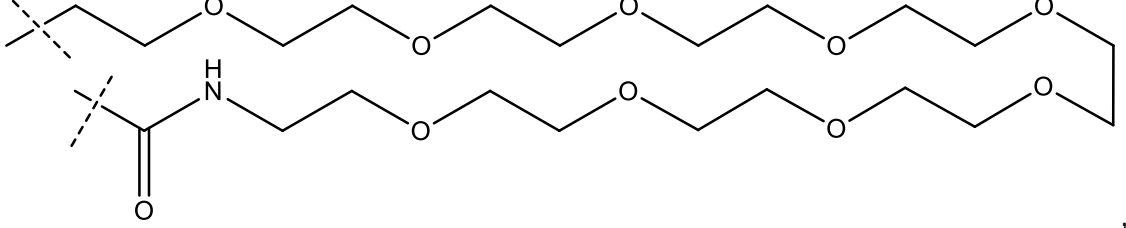
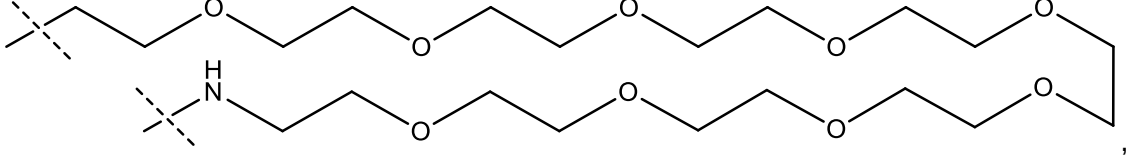
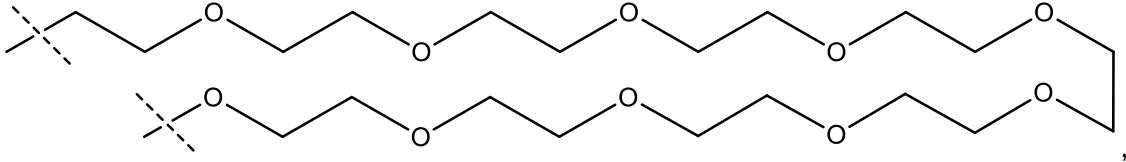
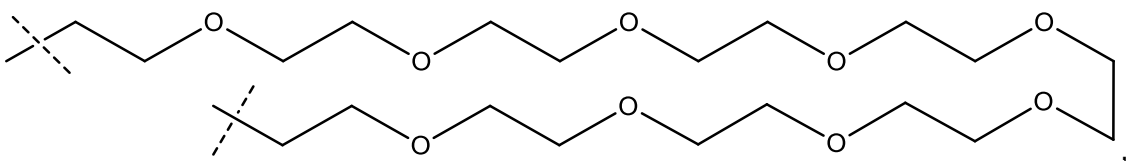
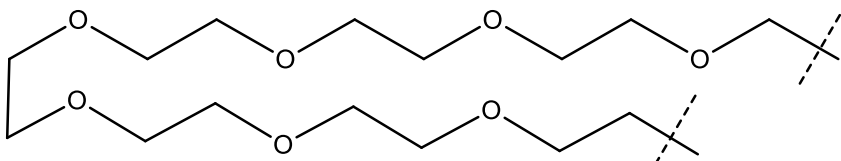
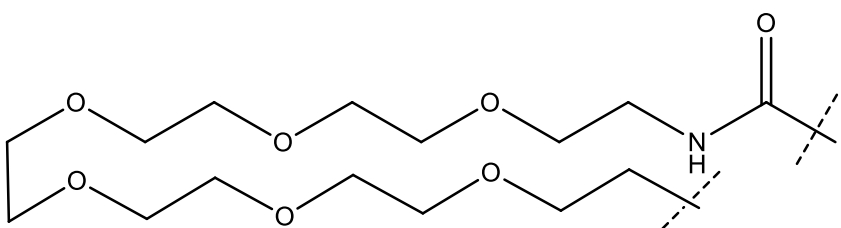
*N del heterocicloalquilo es compartido con el PTM; y

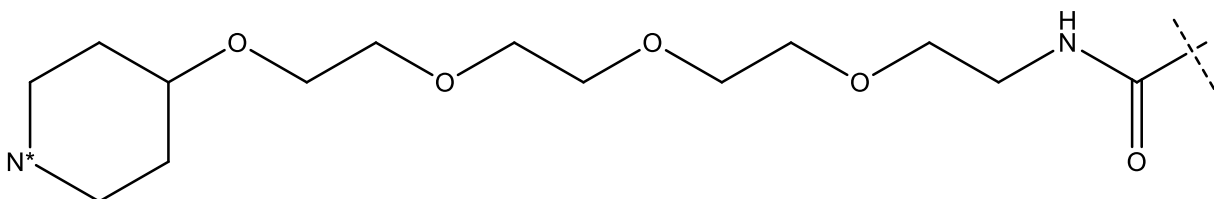
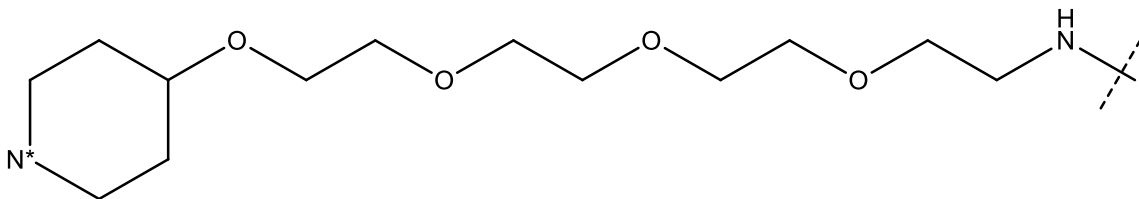
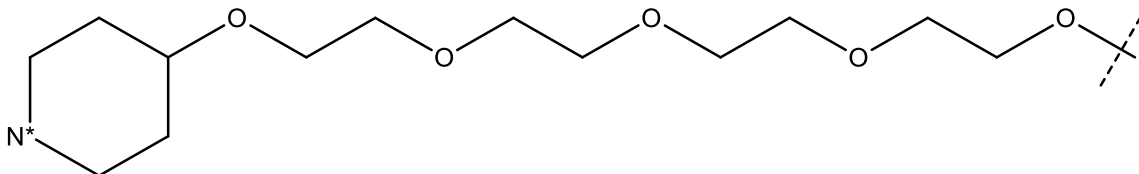
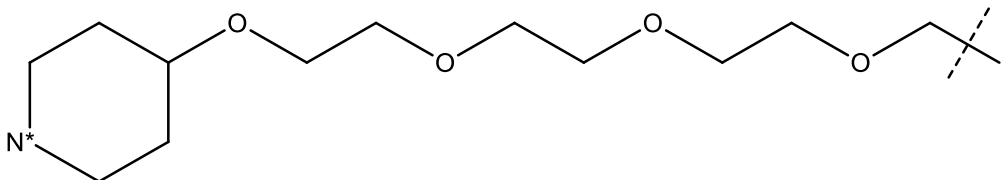
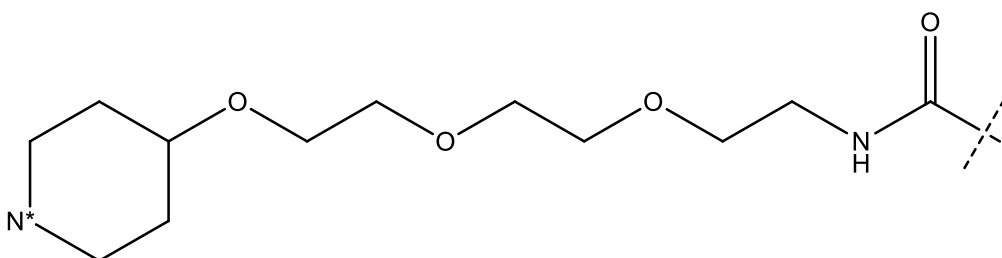
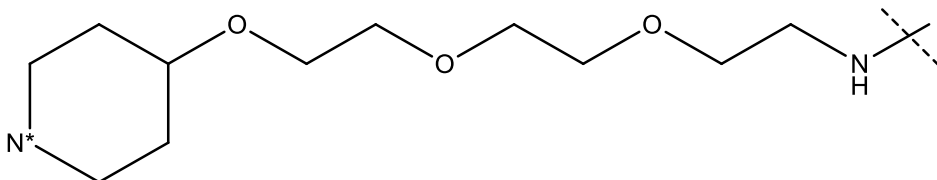
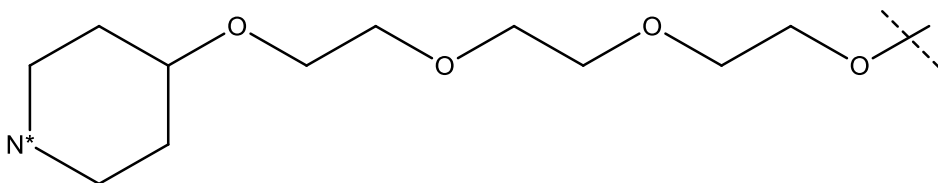
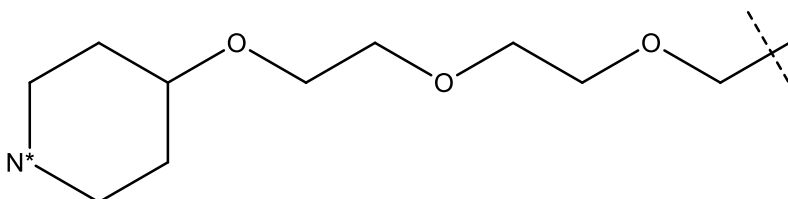
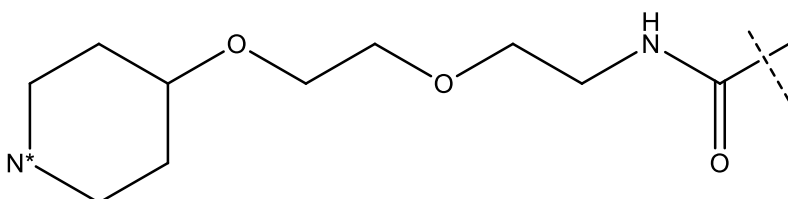
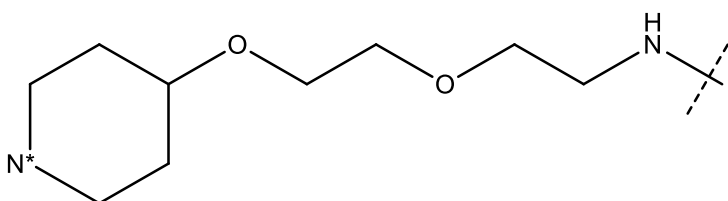
cada m, n, o, p, q, r y s se selecciona de manera independiente de entre 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 y 20.

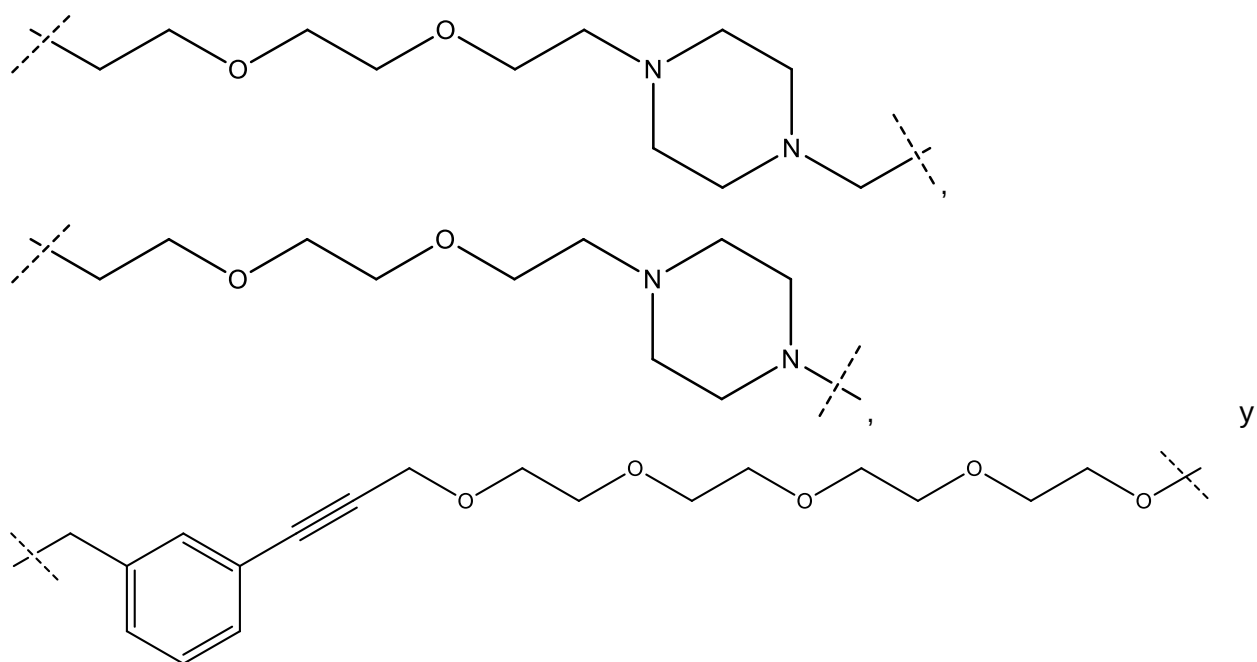
7.5. El compuesto **bifuncional** de acuerdo con cualquiera de las reivindicaciones 1 a **53**, en donde el L se selecciona de entre:









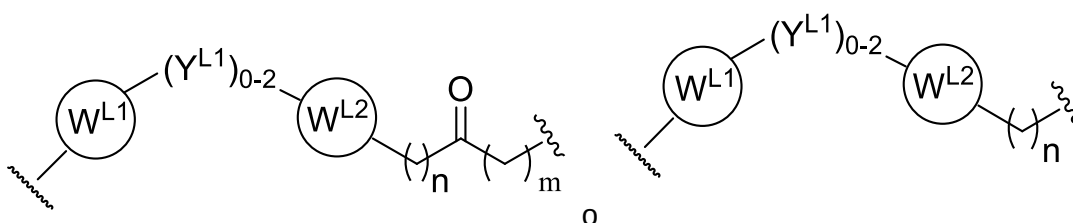


donde N* del heterocicloalquilo es compartido con el PTM.

8.6. El compuesto ~~bifuncional~~ de acuerdo con cualquiera de las reivindicaciones 1 a ~~53~~, en donde el L es ~~un grupo~~ polietileno ~~exiglico~~ con 1 a 10 unidades de etilenglicol opcionalmente sustituido con arilo.

9.7. El compuesto ~~bifuncional~~ de acuerdo con cualquiera de las reivindicaciones 1 a ~~53~~, donde el L es un alquilo C₁₋₅₀, donde cada carbono opcionalmente se sustituye con (1) un heteroátomo seleccionado de entre átomos de N, S, P o Si que tiene una cantidad adecuada de hidrógenos y/o sustituciones para completar la valencia, (2) un cicloalquilo o cicloalquilo bicíclico opcionalmente sustituido, (3) un heterocicloalquilo o heterocicloalquilo opcionalmente sustituido, (4) un arilo o arilo bicíclico opcionalmente sustituido, o (5) heteroarilo o heteroarilo bicíclico opcionalmente sustituido, con la condición de que no haya enlaces heteroátomo-heteroátomo.

10.8. El compuesto ~~bifuncional~~ de acuerdo con cualquiera de las reivindicaciones 1 a ~~53~~, en donde el L es:



donde:

cada uno de W^{L1} y W^{L2} de manera independiente está ausente, o es un anillo de 4-8 miembros con 0-4 heteroátomos, opcionalmente sustituido con RQ_i;

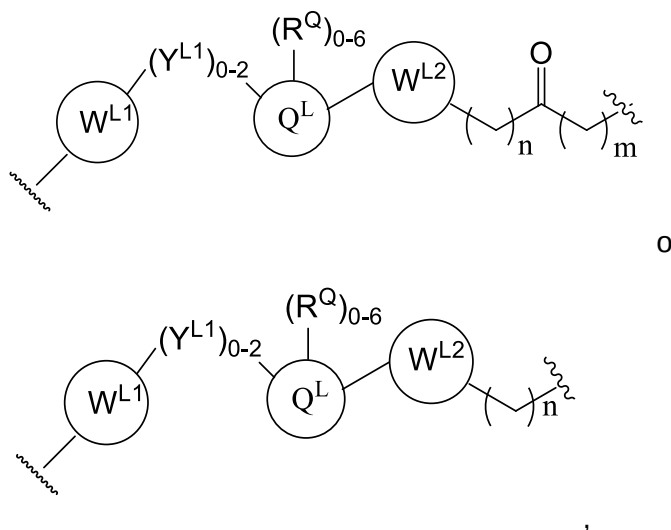
cada RQ es de manera independiente ~~un~~-H, halo, OH, CN, ~~CF₃~~, alquilo C₁₋₆ opcionalmente sustituido, alcoxi C₁₋₆ opcionalmente sustituido, o 2 ~~grupos~~-RQ tomados junto con el átomo al que se unen forman un sistema de anillo de 4-8 miembros que contiene 0-4 heteroátomos;

cada Y^{L1} es ~~cada uno~~ de manera independiente un enlace, o alquilo C₁₋₆ opcionalmente sustituido, ~~y en donde~~ ~~opcionalmente~~ uno o más átomos de C se remplazan opcionalmente con O; ~~o alcoxi C₁₋₆ opcionalmente sustituido~~;

m y n es son independientemente 0, -1, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y

 indica el punto de unión a l PTM o al ULM.

11-9. El compuesto ~~bifuncional~~ de acuerdo con cualquiera de las reivindicaciones 1 a ~~53~~, donde el L es:



en donde:

cada uno de W^{L1} y W^{L2} de manera independiente está ausente o es arilo, heteroarilo, cíclico, heterocíclico, alquilo C_{1-6} , ~~y opcionalmente en donde~~ uno o más átomos de C se rempazan opcionalmente con O o N, alquenilo C_{1-6} , ~~y opcionalmente en donde~~ uno o más átomos de C se rempazan opcionalmente con O, alquinilo C_{1-6} , ~~y opcionalmente en donde~~ uno o más átomos de C se rempazan opcionalmente con O, bicíclico, biarilo, biheteroarilo o biheterocíclico, cada uno opcionalmente sustituido con R^Q ; ~~1~~

cada R^Q es de manera independiente ~~un~~-H, halo, OH, CN, CF_3 , hidroxilo, nitro, $C\equiv CH$, alquenilo C_{2-6} , alquinilo C_{2-6} , alquilo C_{1-6} opcionalmente sustituido, alcoxi C_{1-6} opcionalmente sustituido, Oalquilo C_{1-3} opcionalmente sustituido, OH, NH_2 , $NR^{Y1}R^{Y2}$, o CN, o 2 ~~grupos~~- R^Q , tomados junto con el átomo al que se unen, forman un sistema de anillo de 4-8 miembros que contiene 0-4 heteroátomos;

cada Y^{L1} es de manera independiente un enlace, NR^{Y1} , O, S, NR^{Y2} , $CR^{Y1}R^{Y2}$, $C=O$, $C=S$, SO, SO_2 , alquilo C_{1-6} opcionalmente sustituido, ~~y en donde opcionalmente~~ uno o más átomos de C se rempazan opcionalmente con O; ~~alcoxi C_{1-6} opcionalmente sustituido~~, o anillo alicíclico o aromático de 3-6 miembros con 0-4 heteroátomos;

Q^L es ~~un~~-anillo alicíclico o aromático de 3-6 miembros con 0-4 heteroátomos, opcionalmente con puente, opcionalmente sustituido con 0-6 R^Q ; ~~1~~

cada R^Q es de manera independiente H, alquilo C_{1-6} opcionalmente sustituido, o 2 ~~grupos~~- R^Q , tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

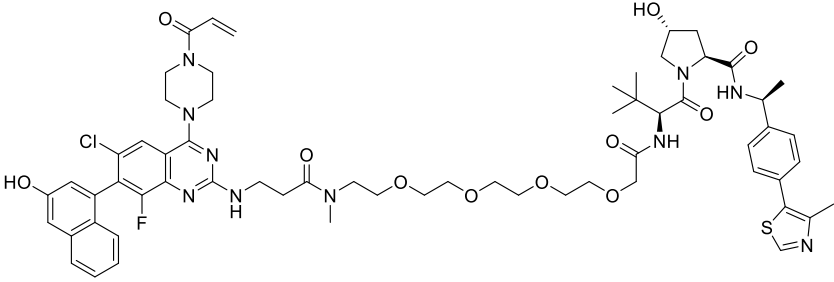
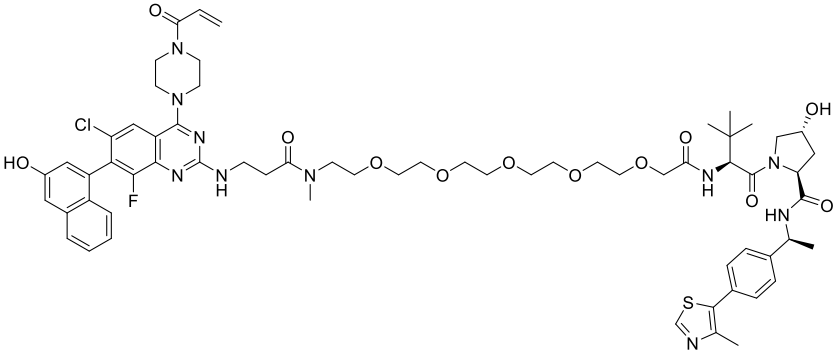
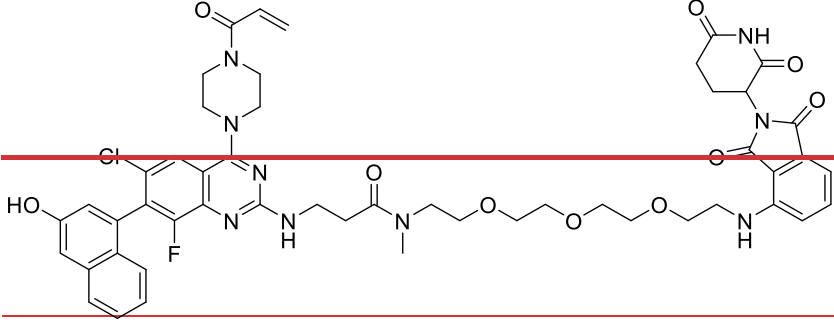
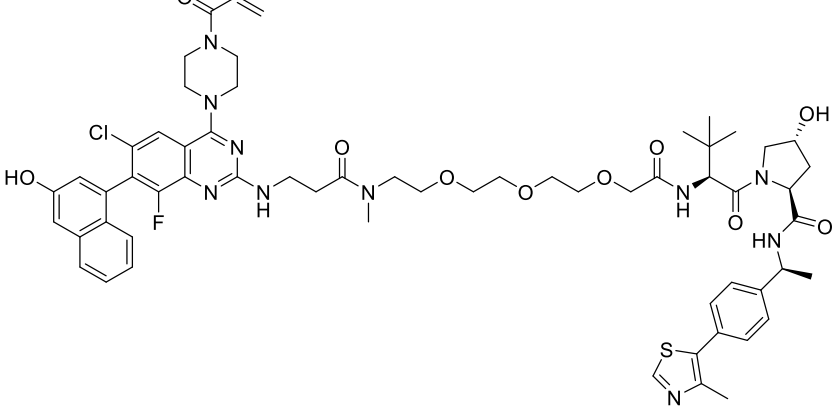
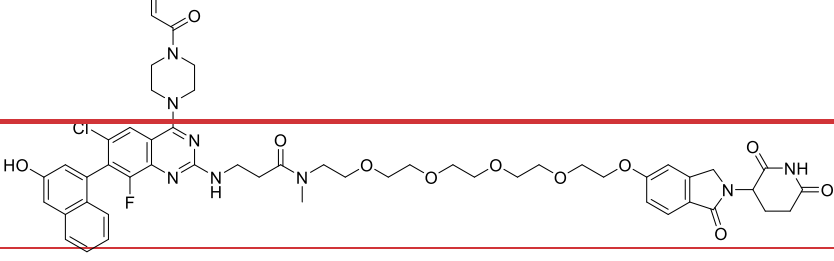
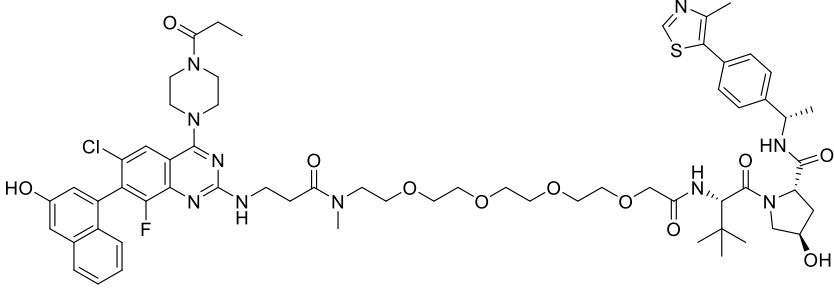
R^{Y1} y R^{Y2} son cada uno de manera independiente seleccionado de entre H, OH, y alquilo C_{1-6} opcionalmente sustituido por 1 o más halo o alcoxilo C_{1-6} , o R^1 , y R^2 tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

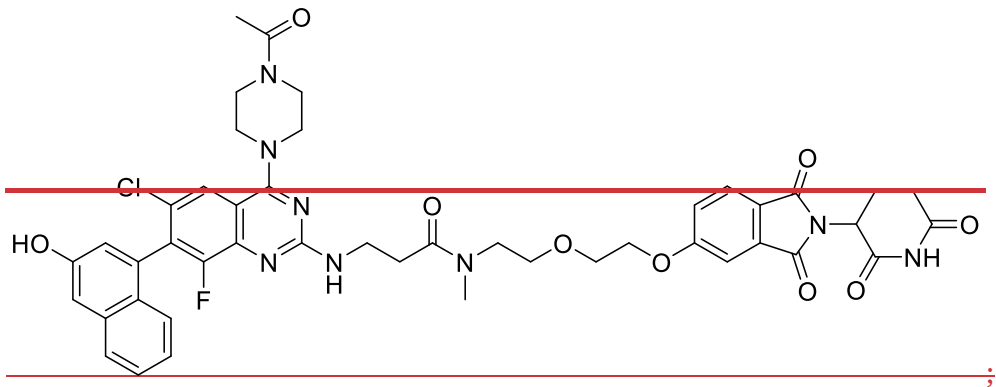
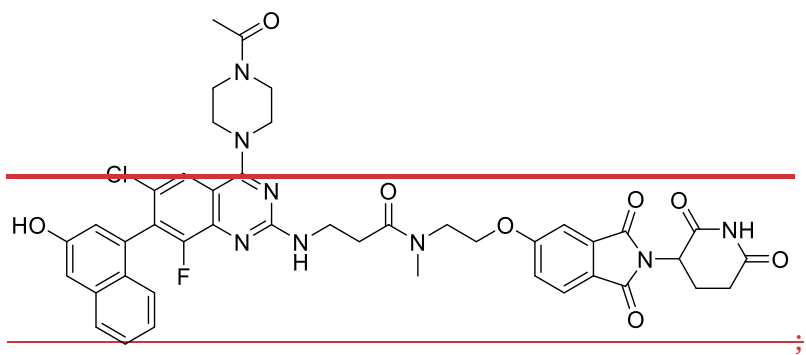
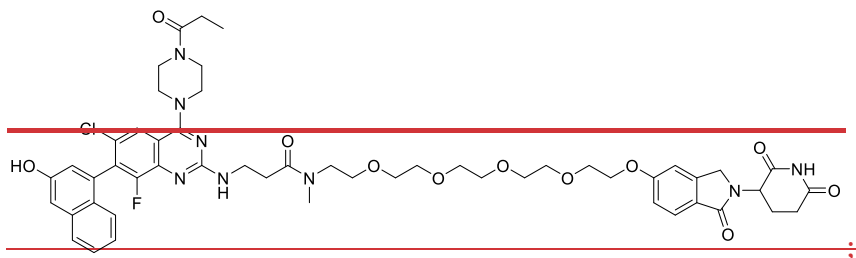
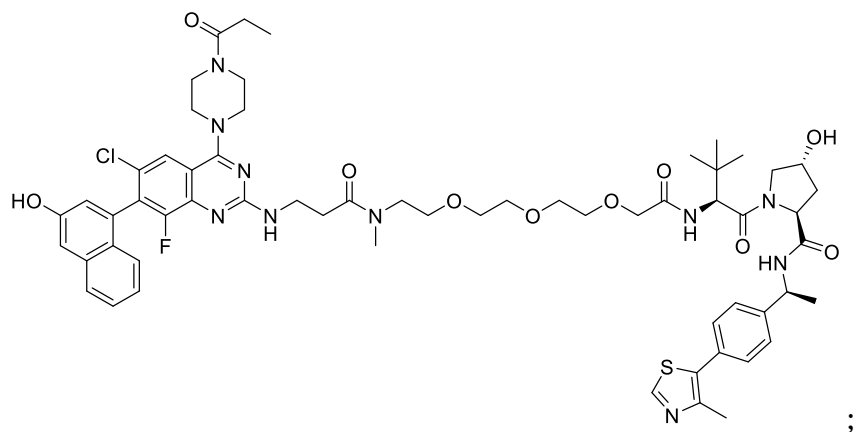
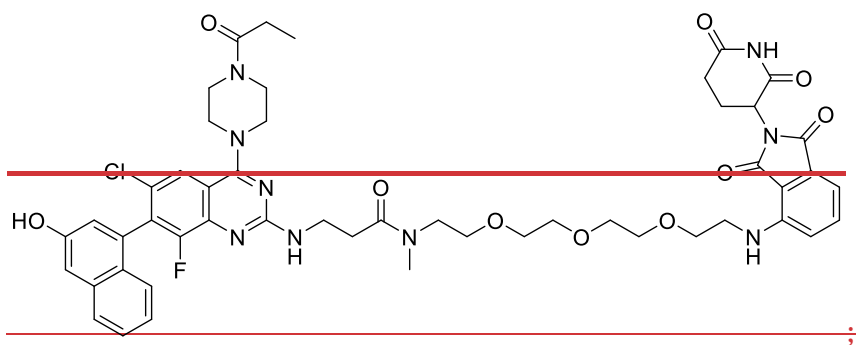
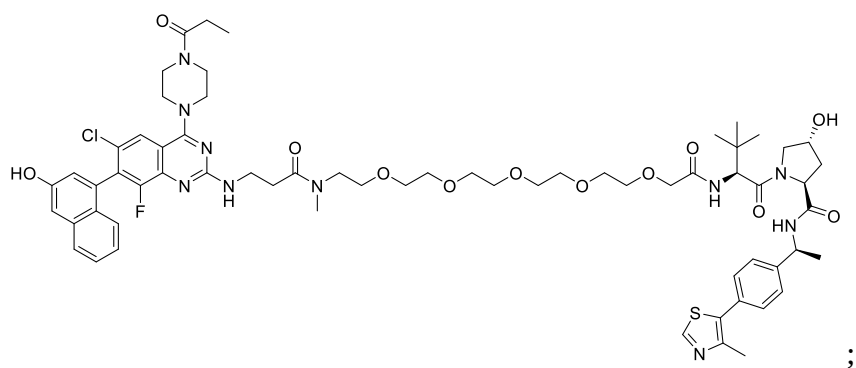
m y n son cada uno independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y

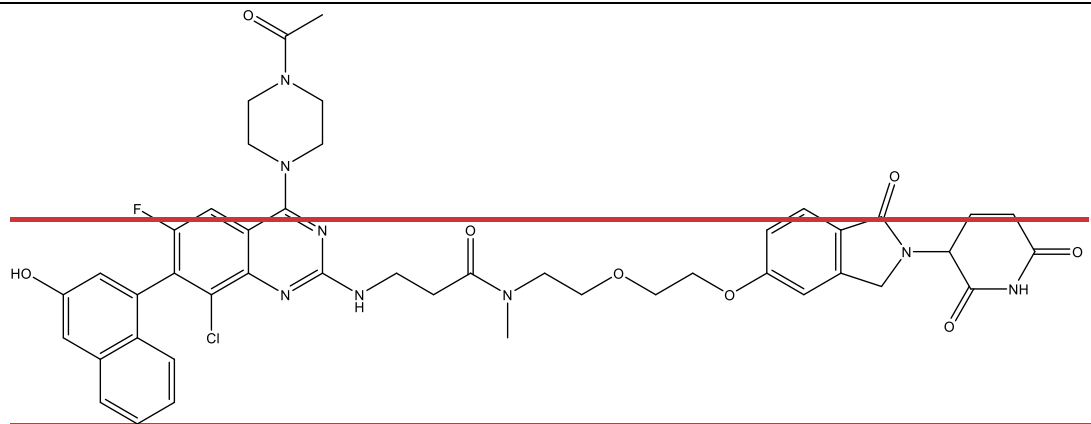
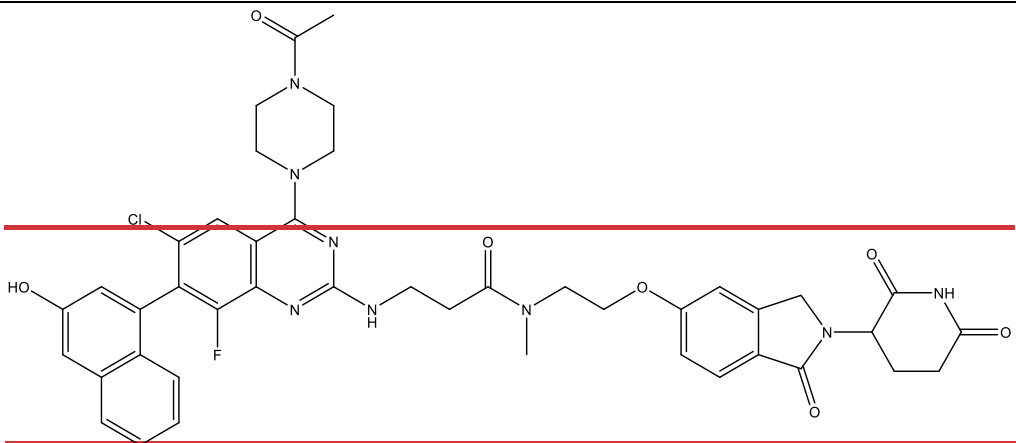
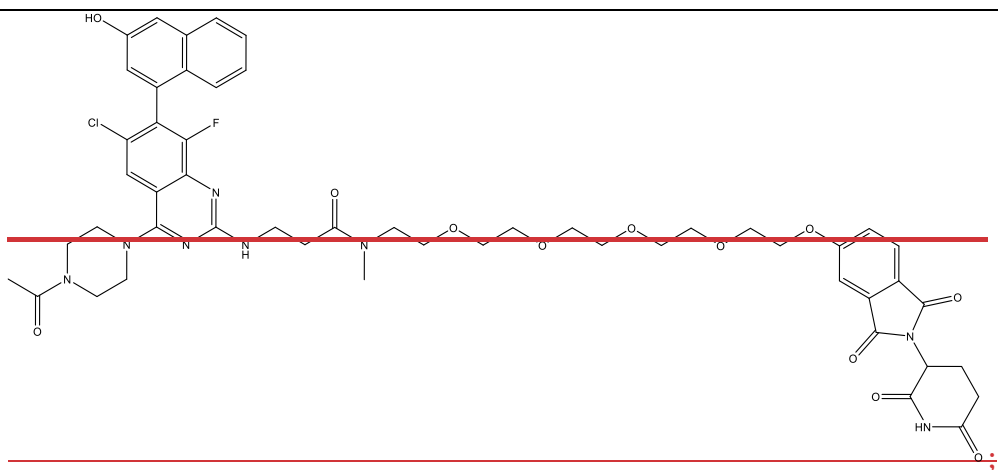
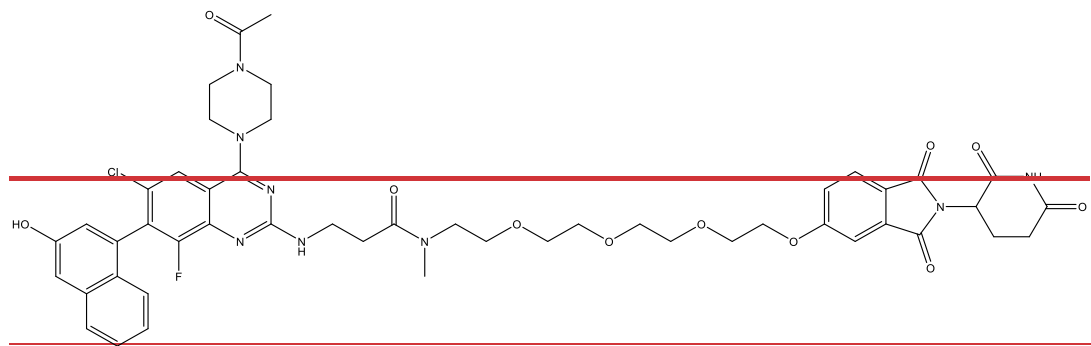
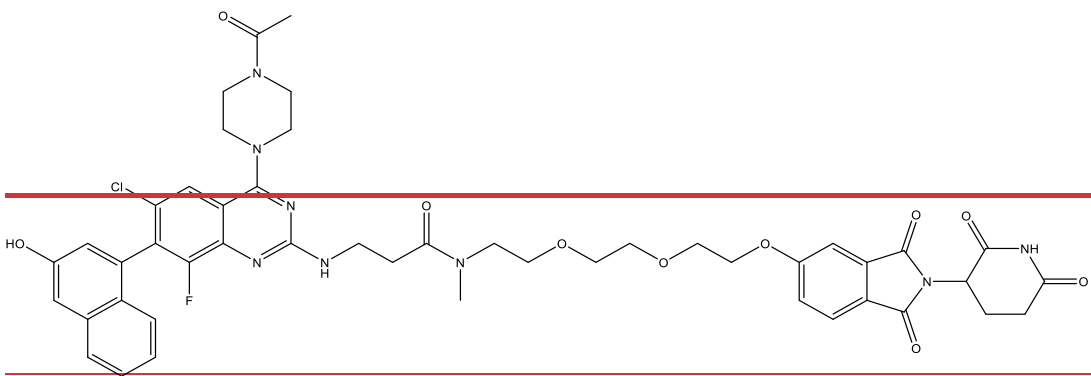
 indica el punto de unión a ~~los restos~~ PTM o al ULM.

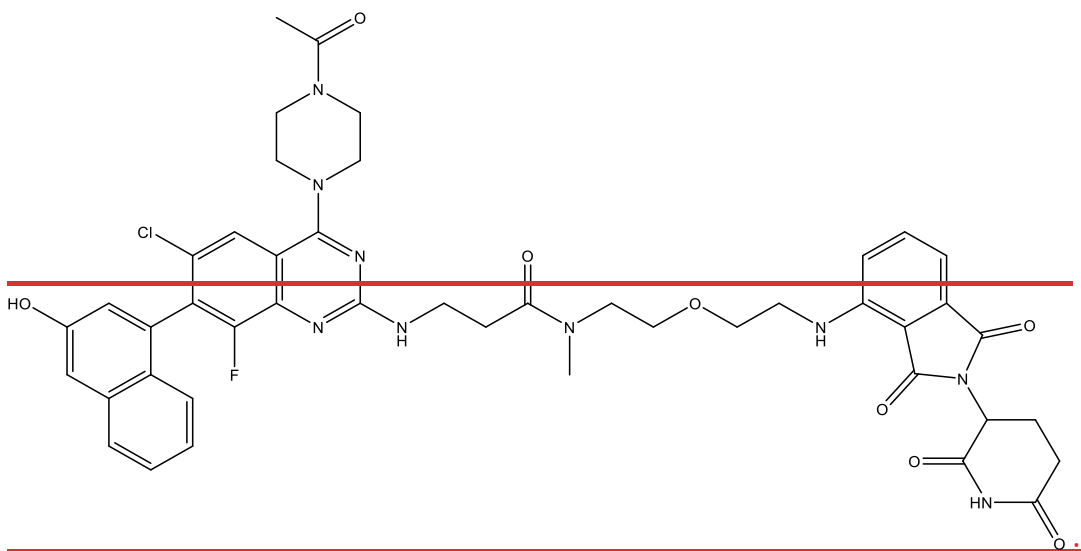
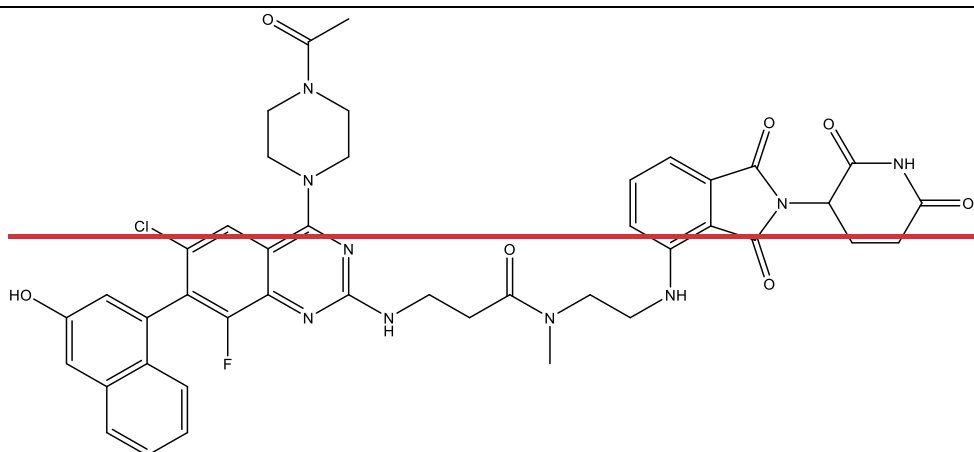
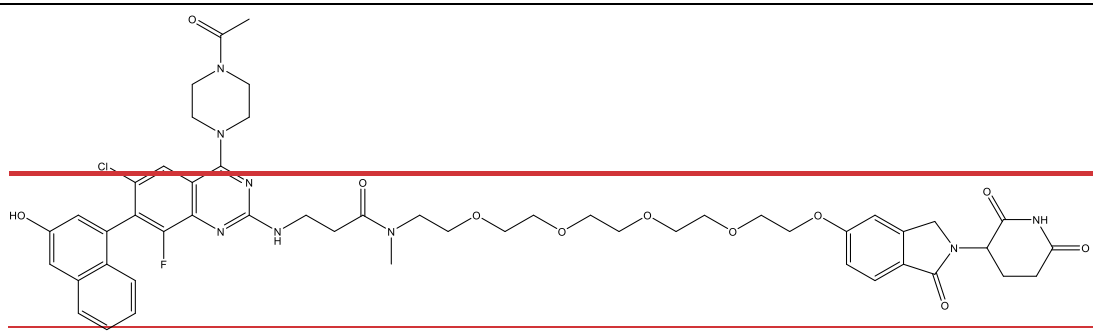
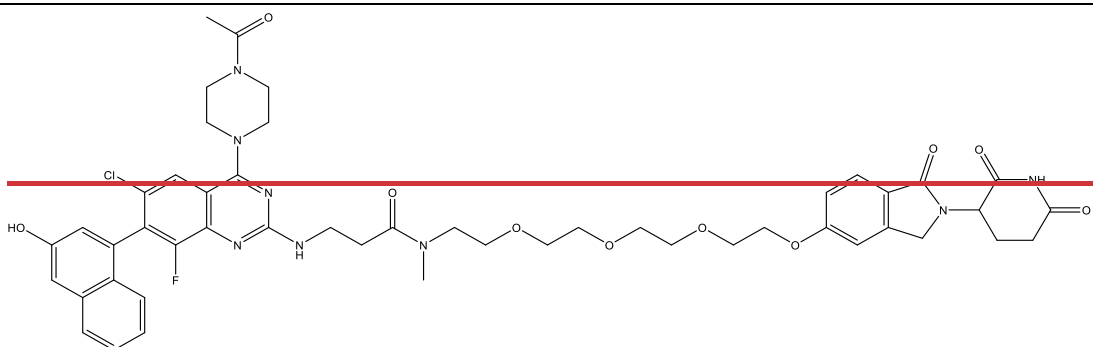
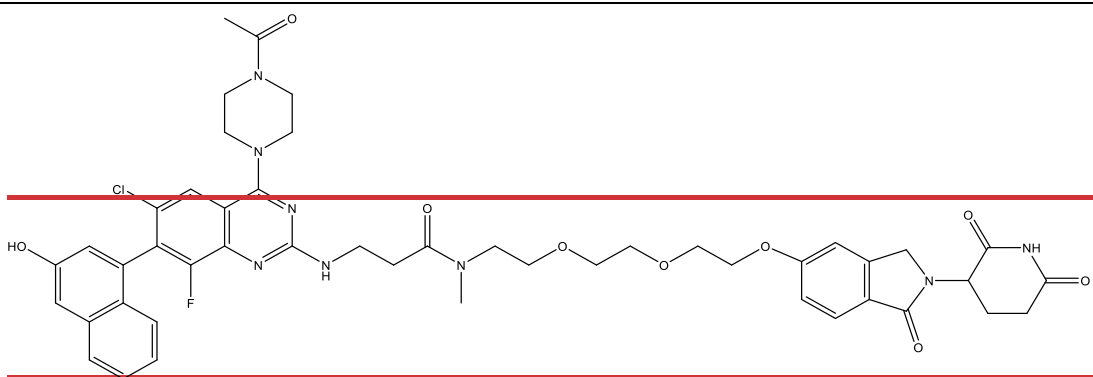
12-10. ~~Un~~-El compuesto ~~bifuncional~~ de acuerdo con cualquiera de las reivindicaciones 1

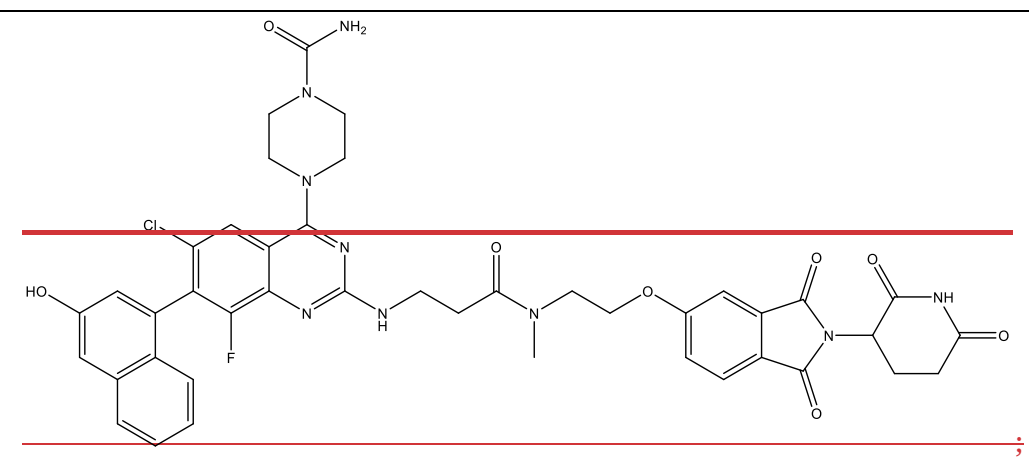
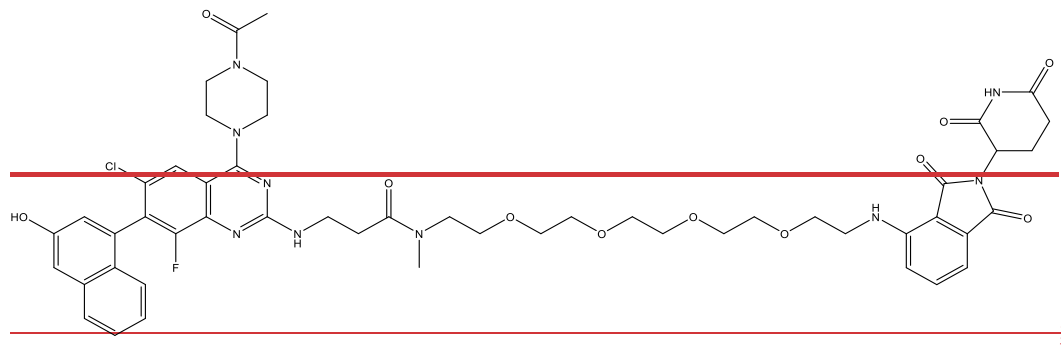
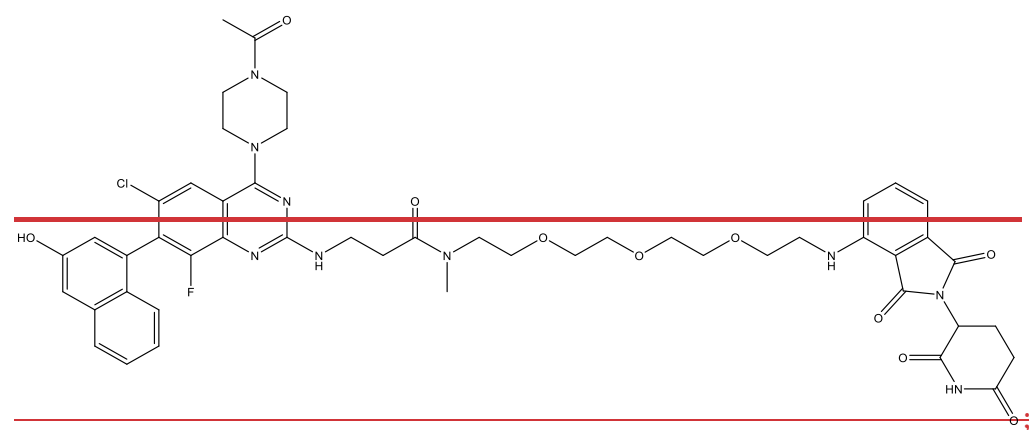
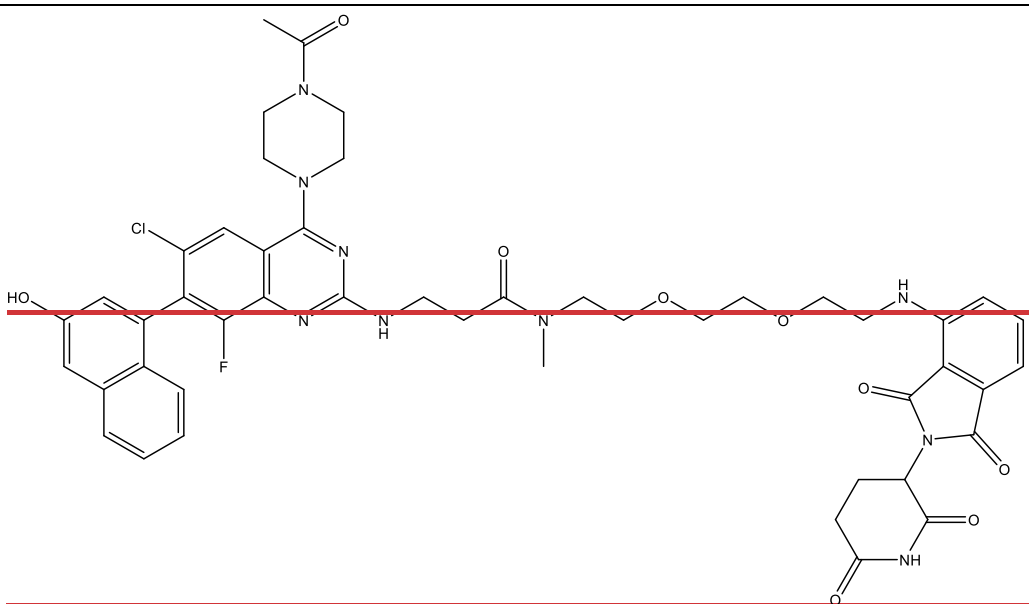
a 9, en donde el compuesto es seleccionado de entre:

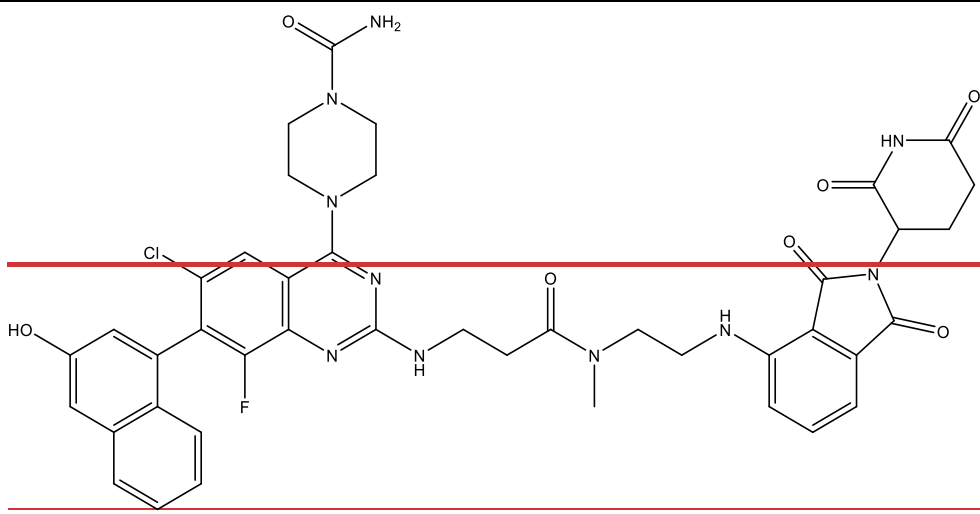
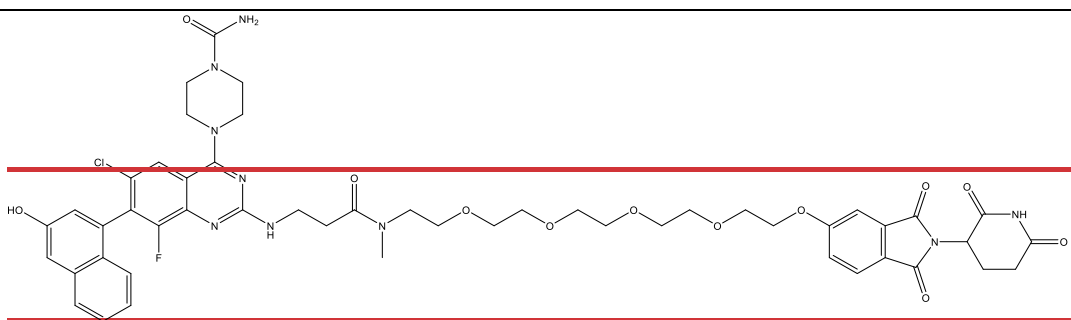
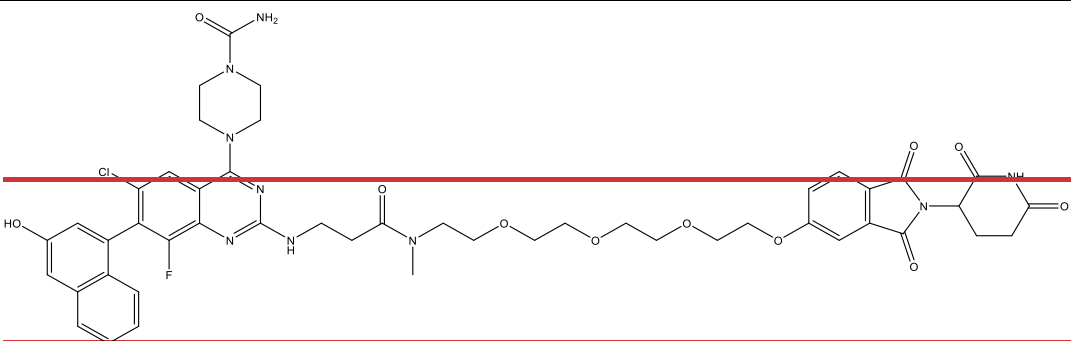
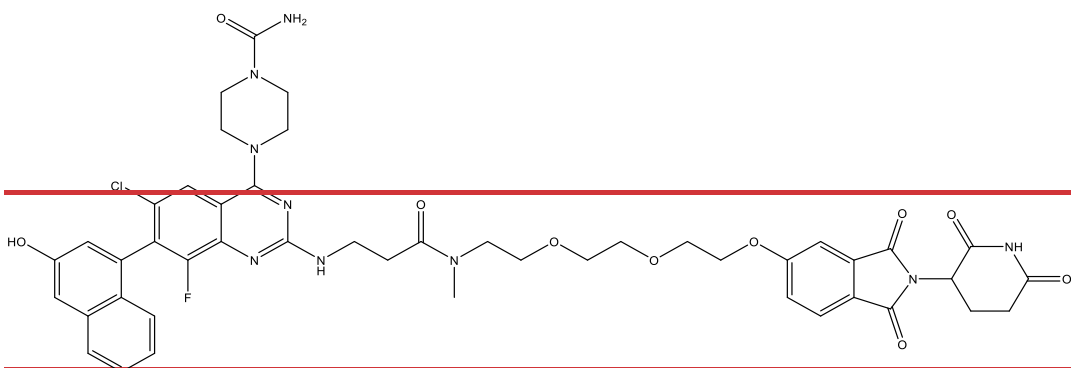
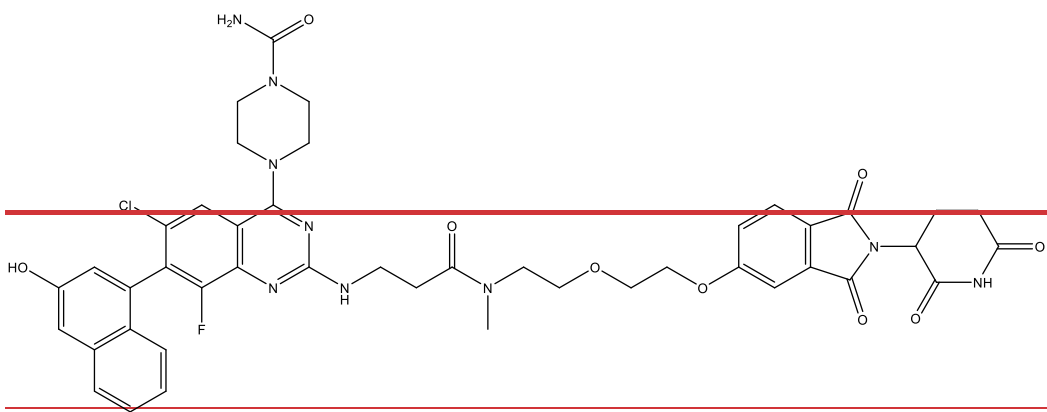
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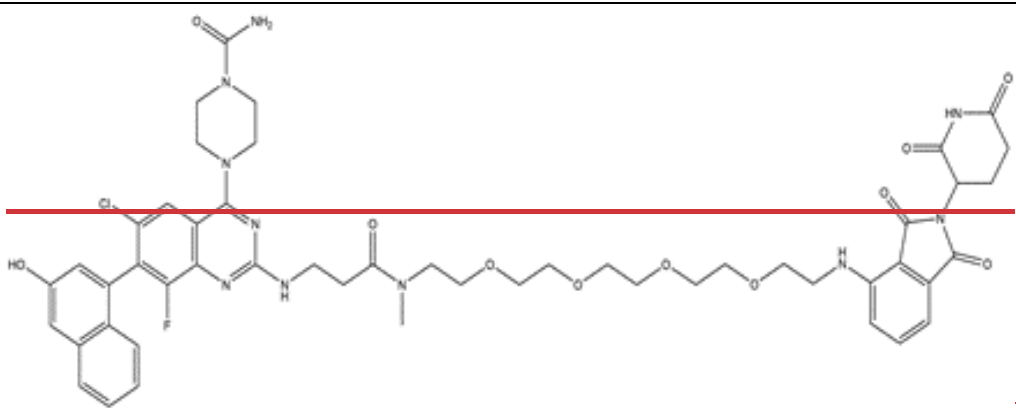
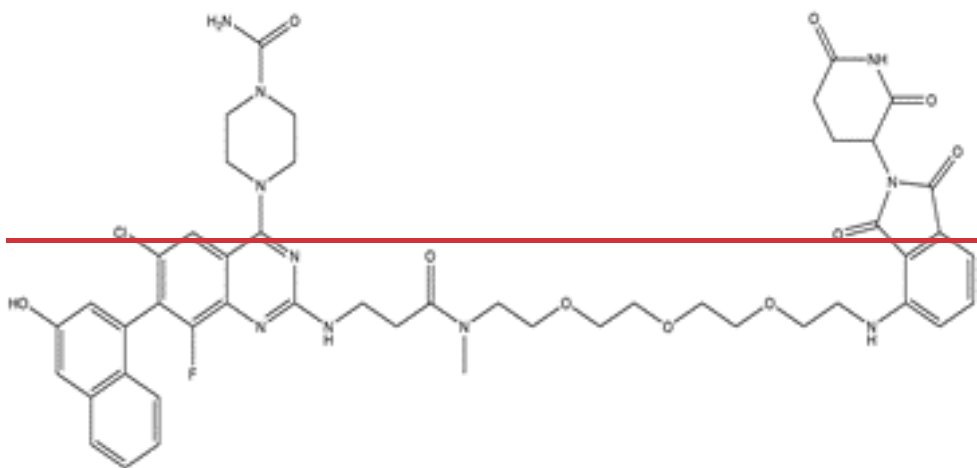
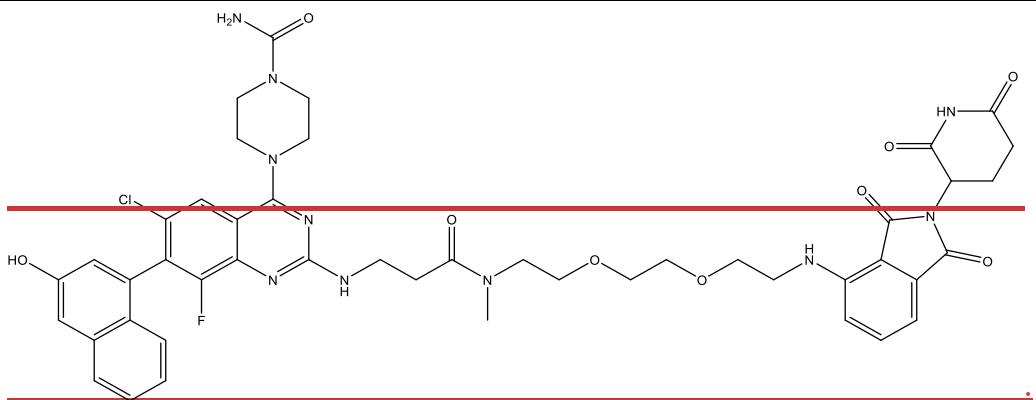
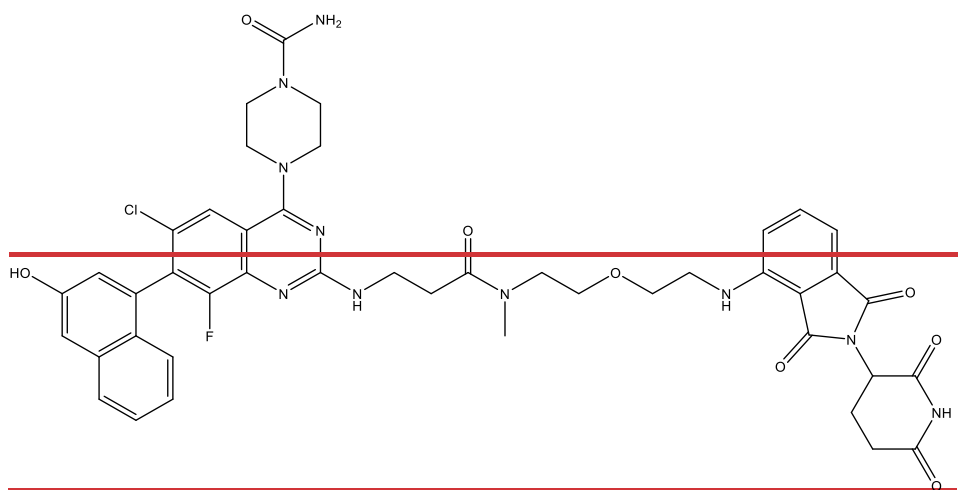


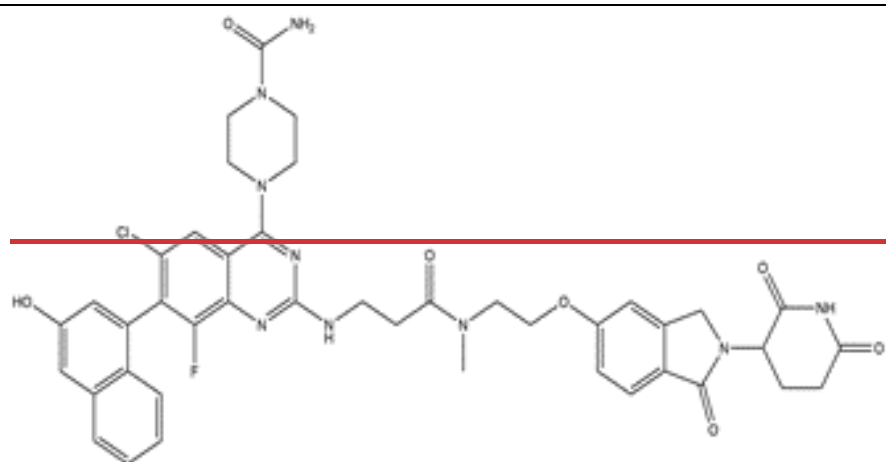




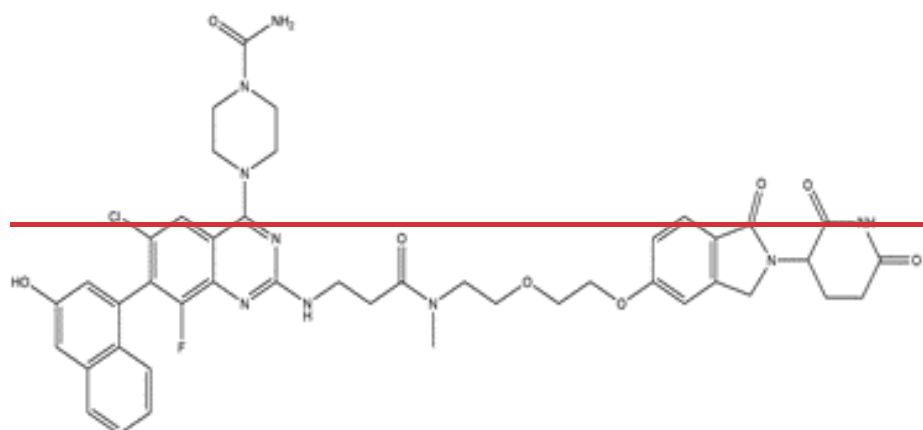




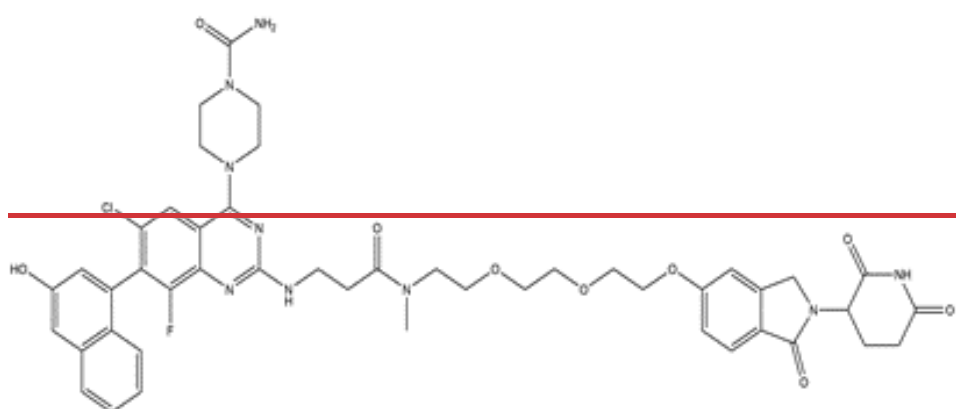




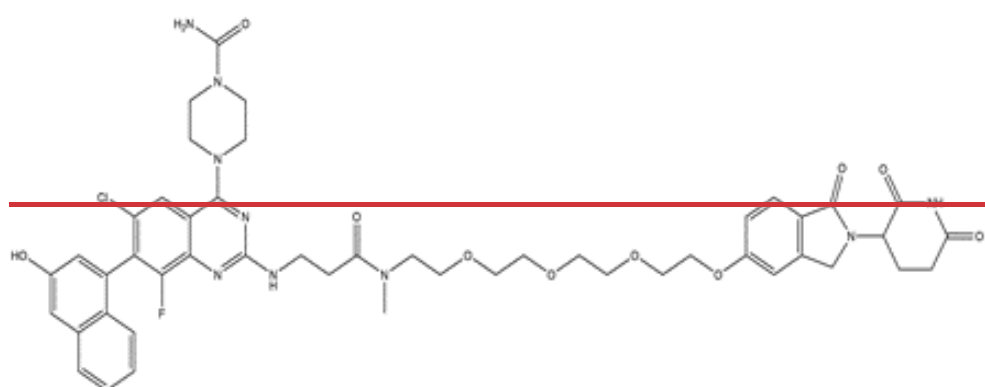
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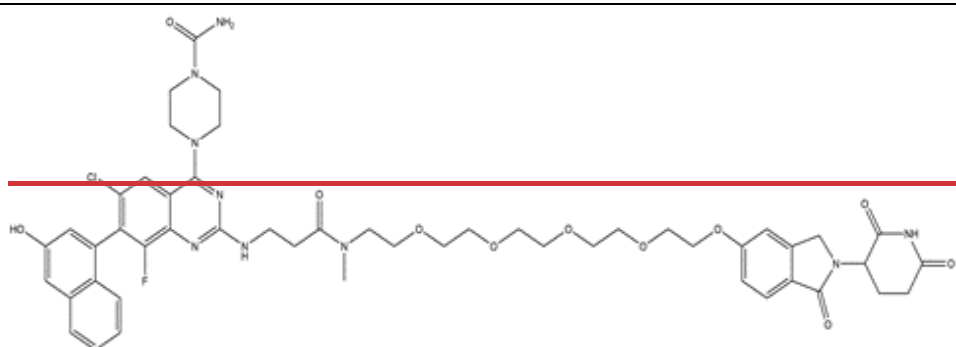
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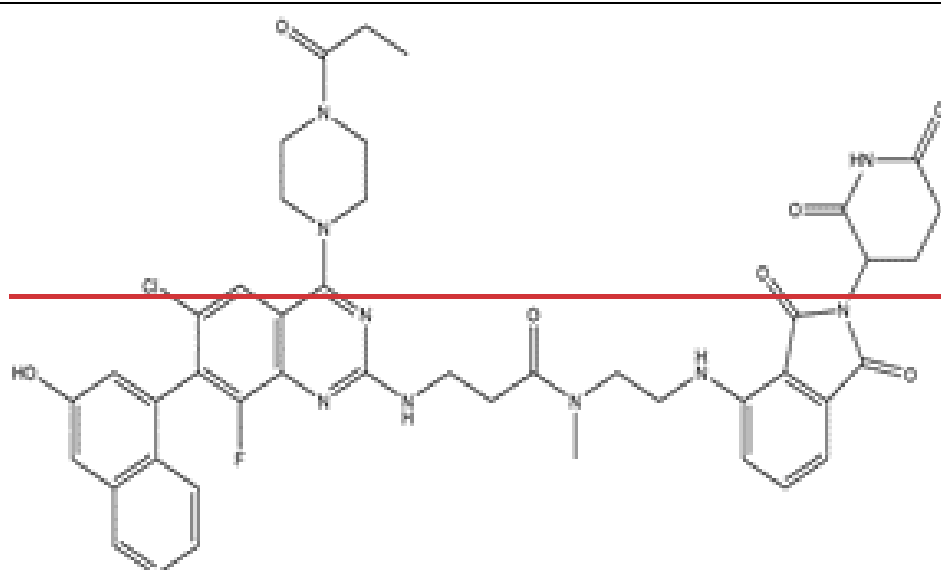
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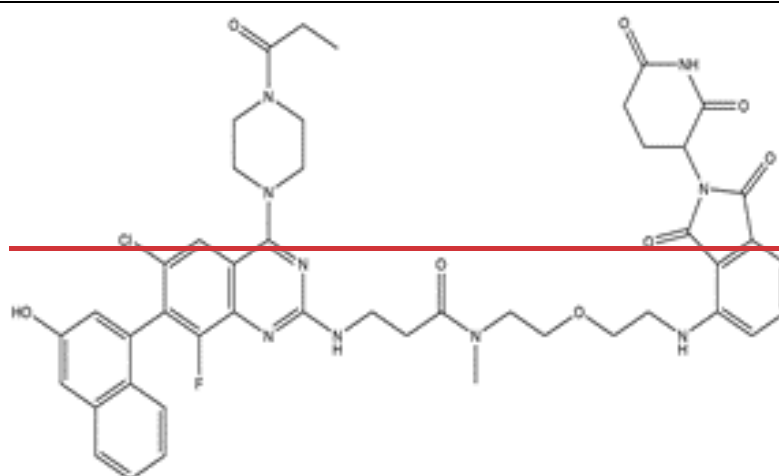
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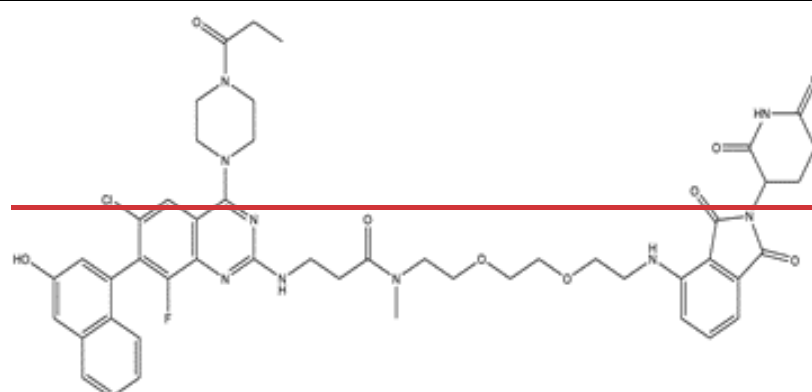
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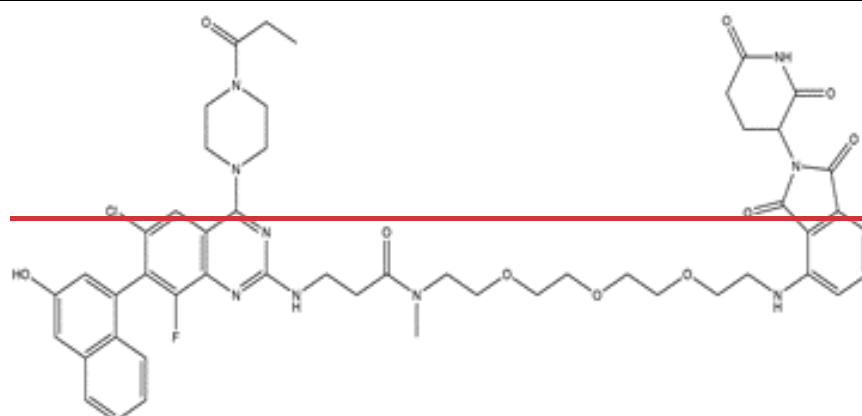
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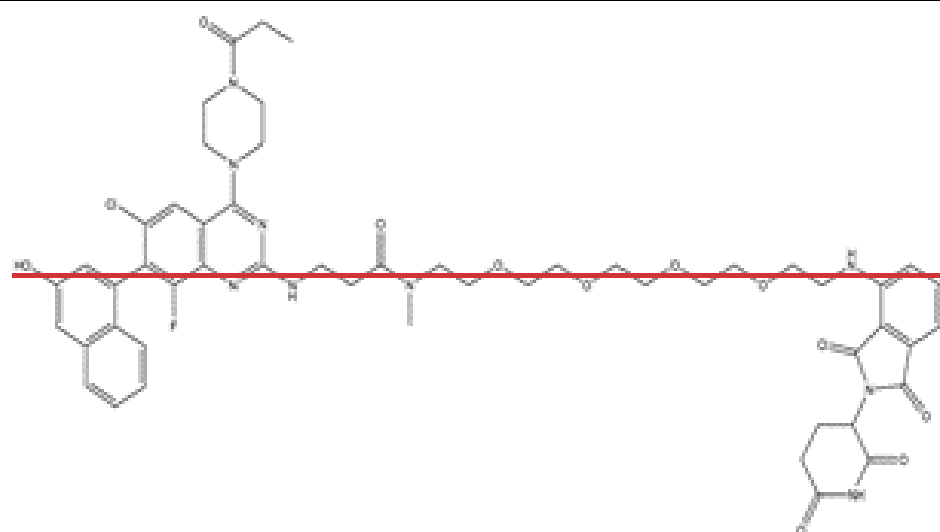
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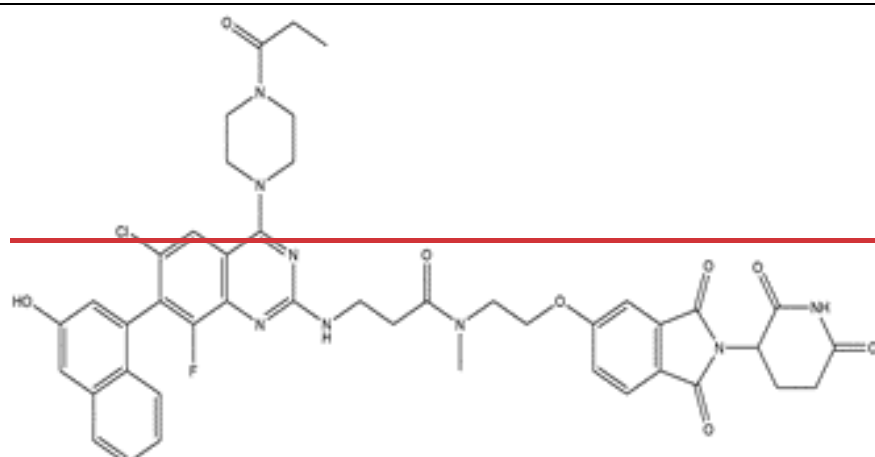
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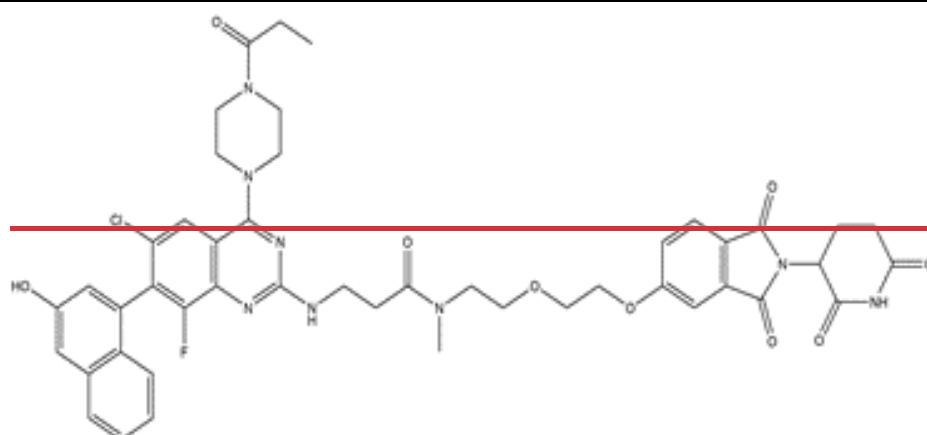
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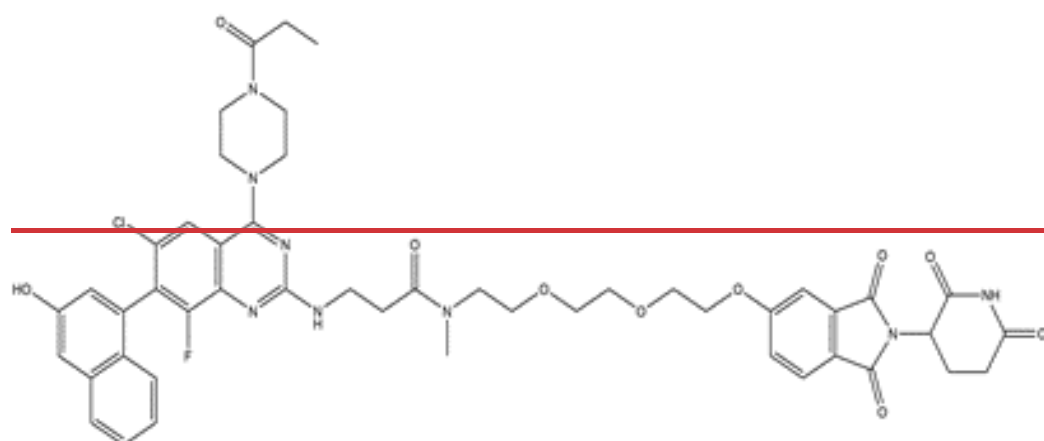
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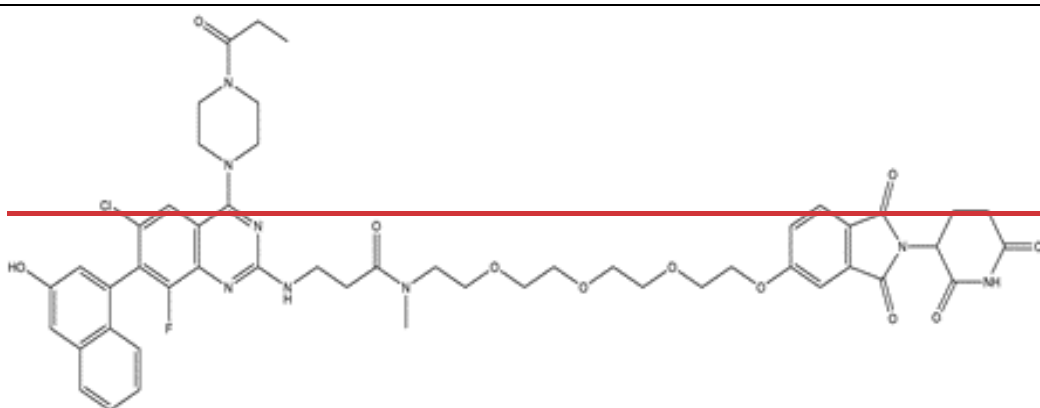
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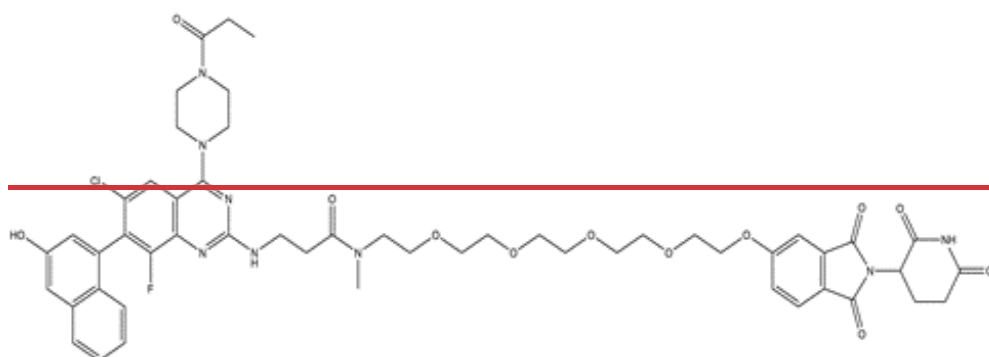
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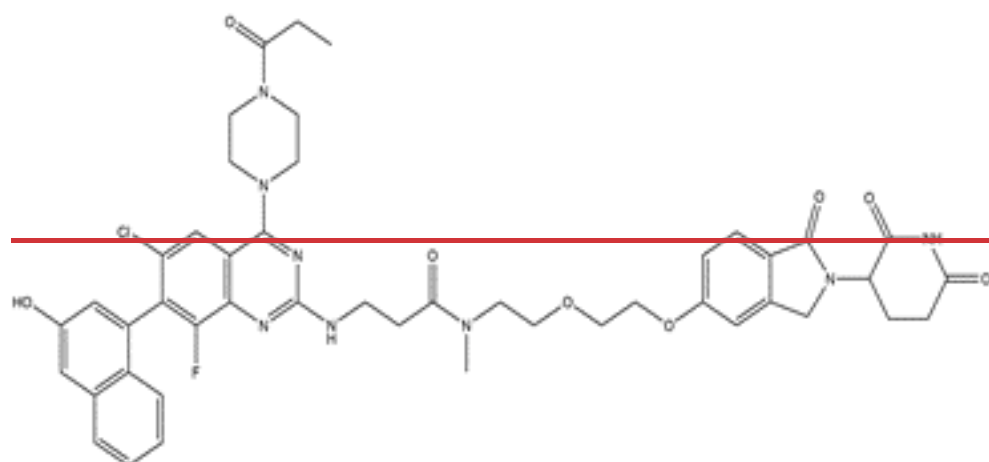
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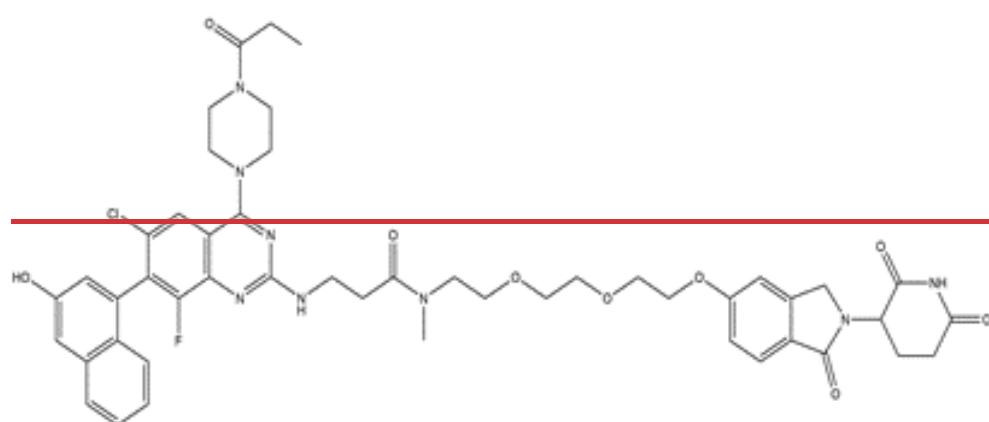
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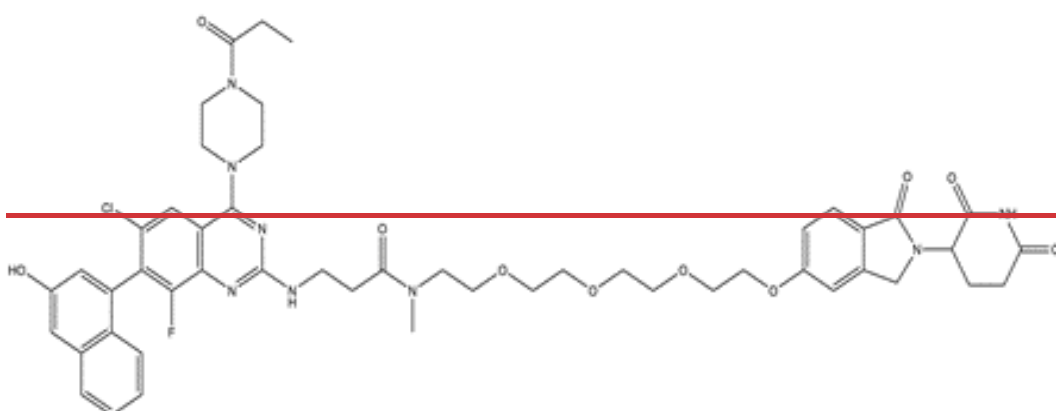
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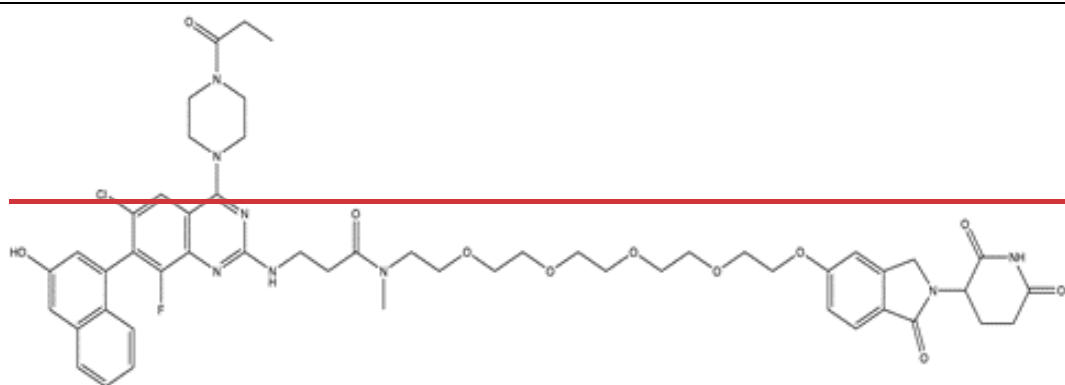
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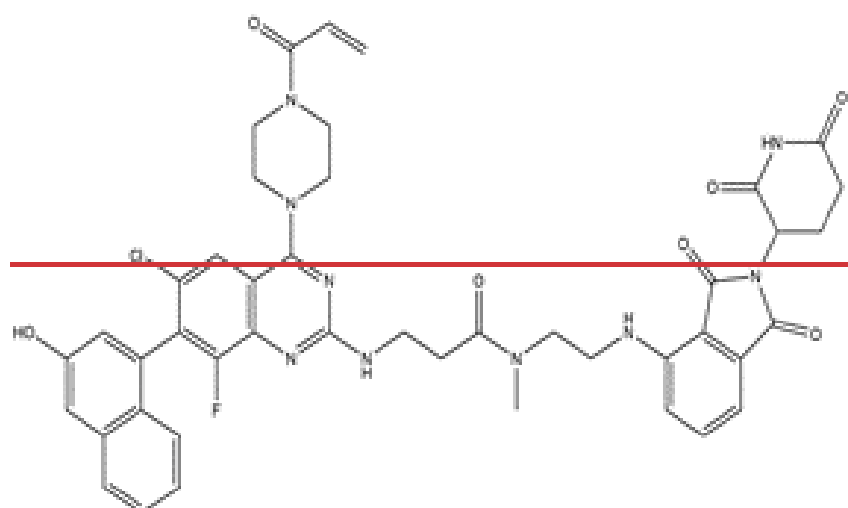
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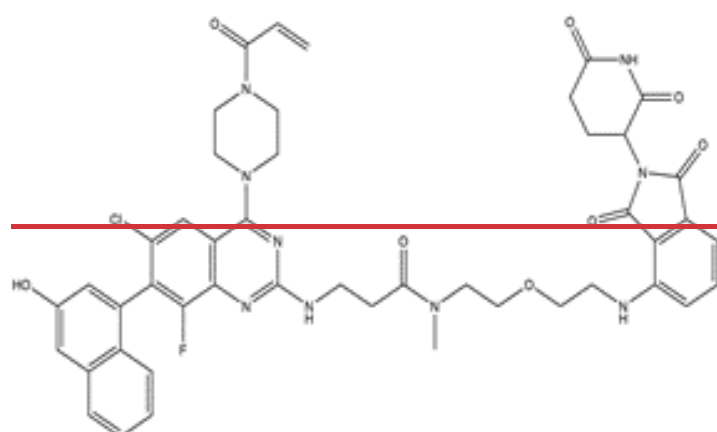
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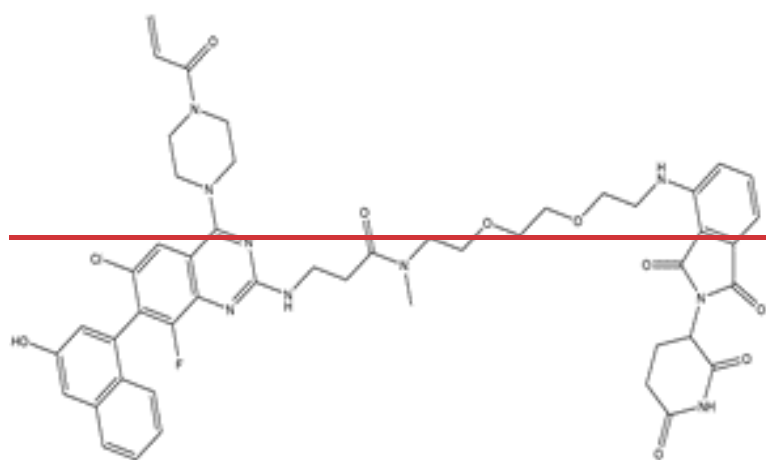
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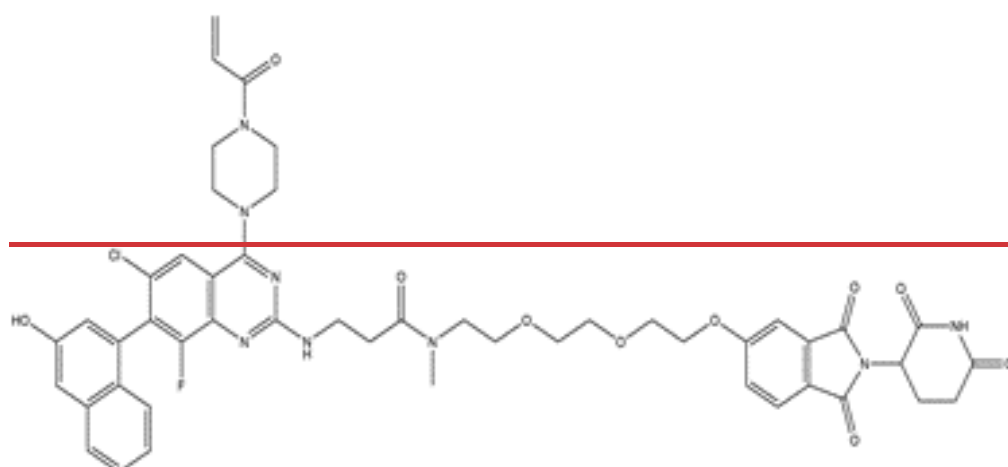
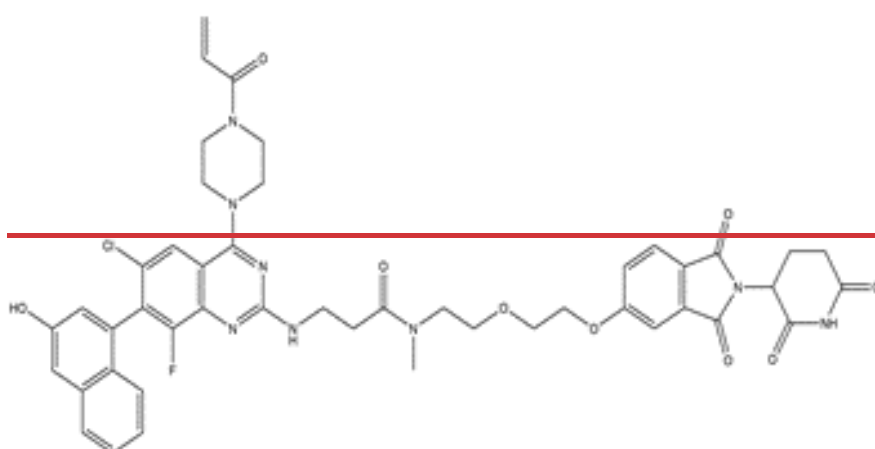
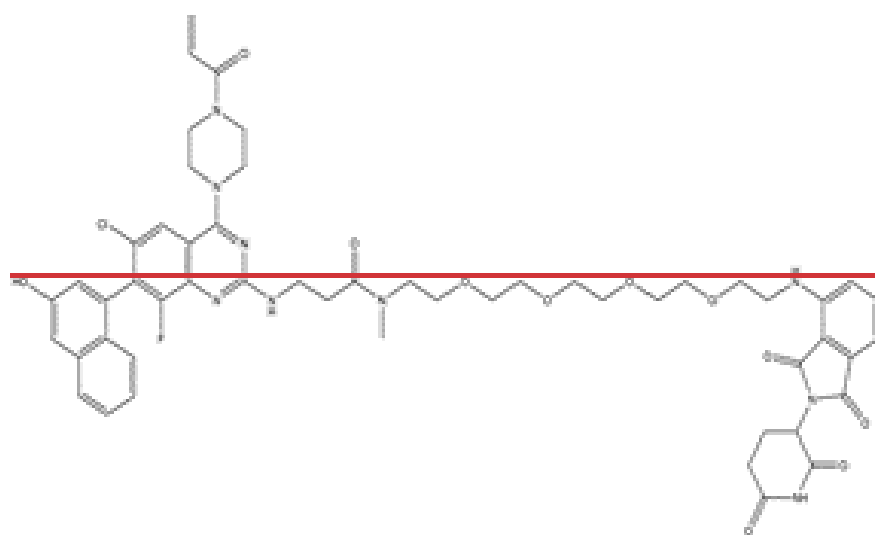
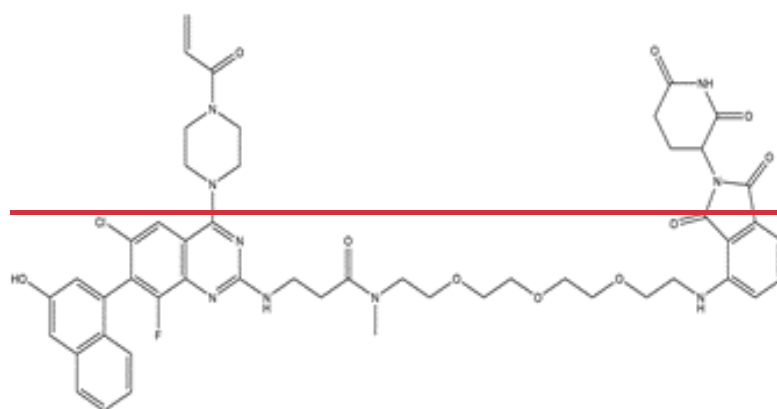
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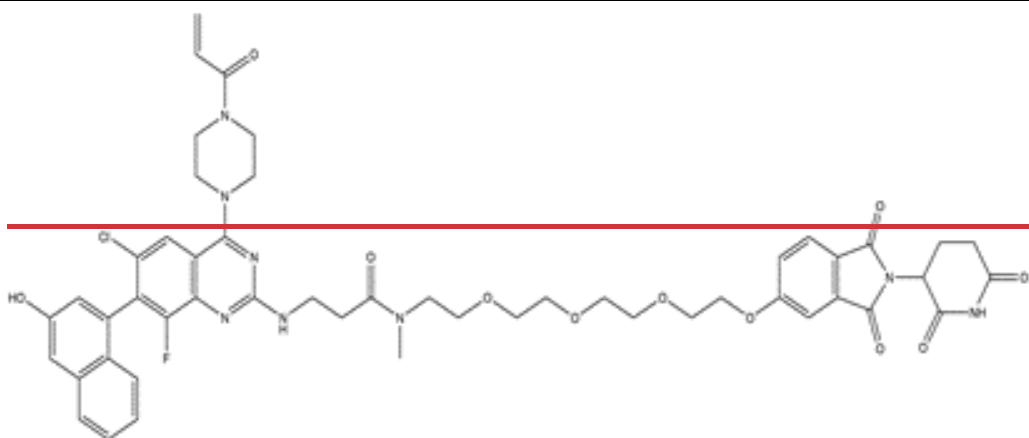


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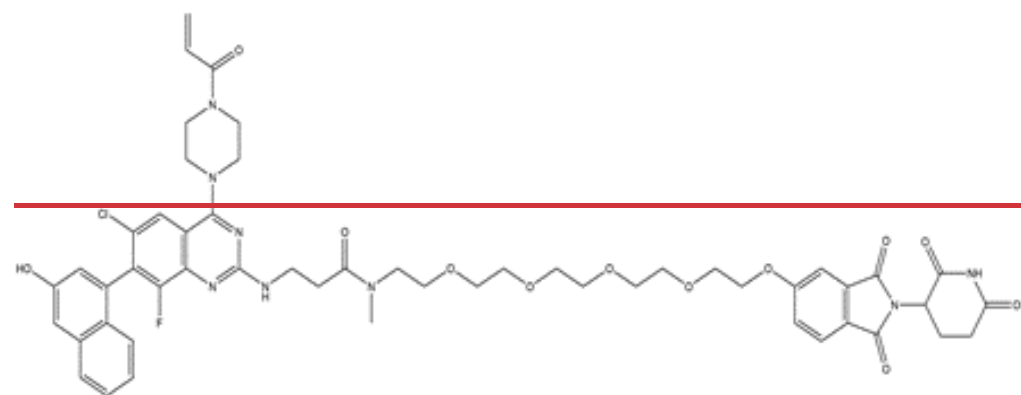


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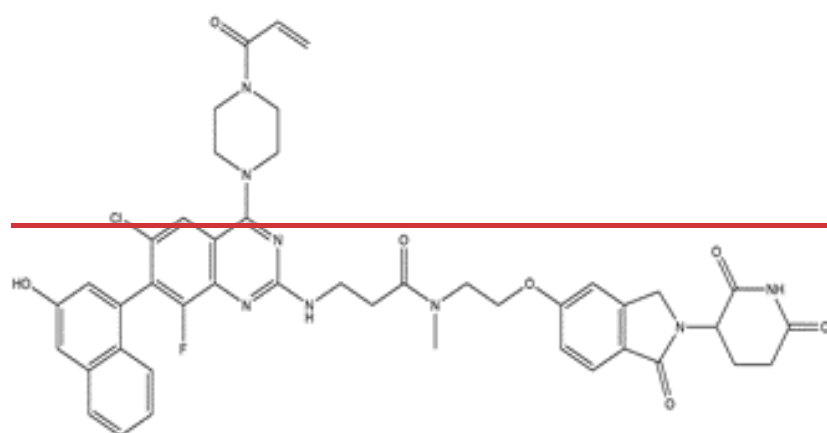




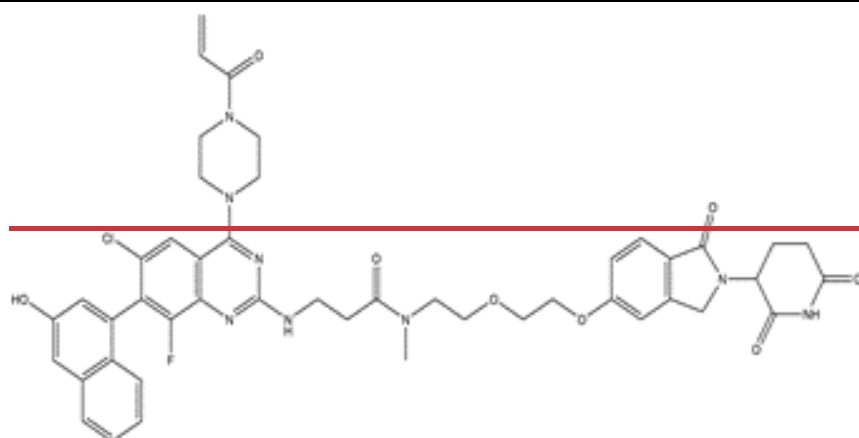
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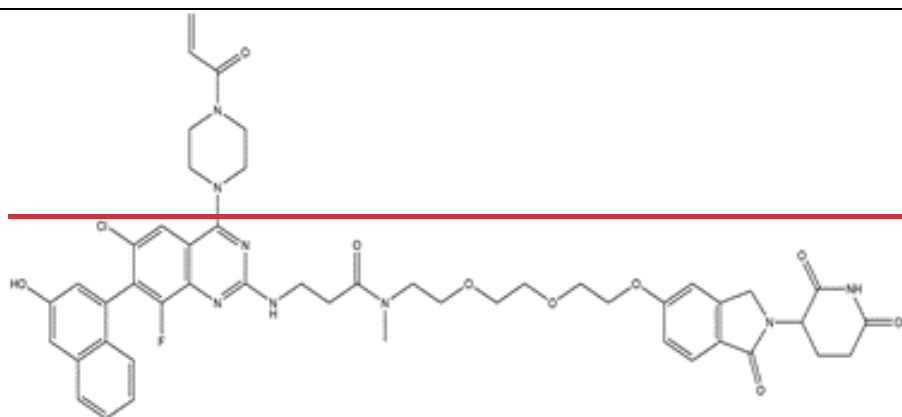
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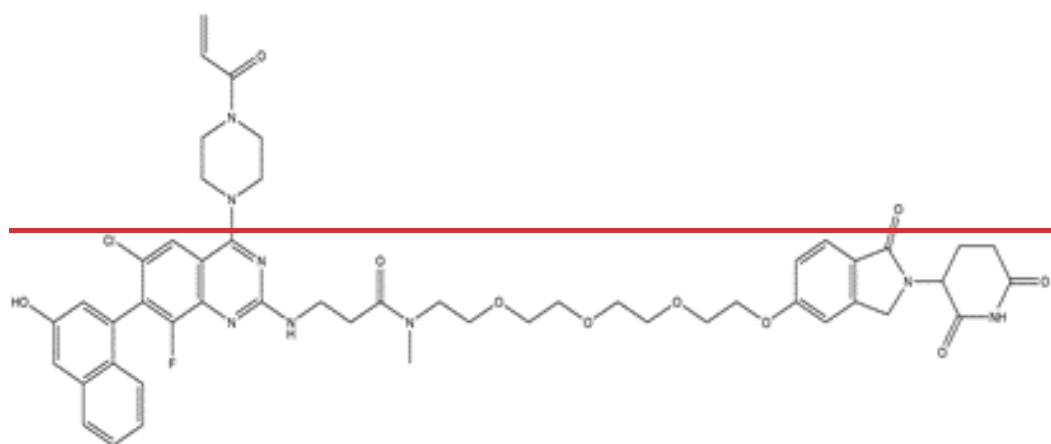
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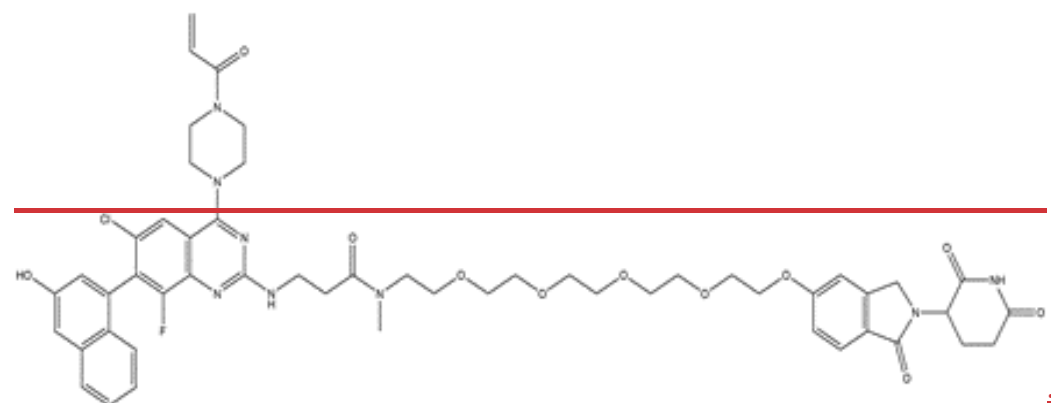
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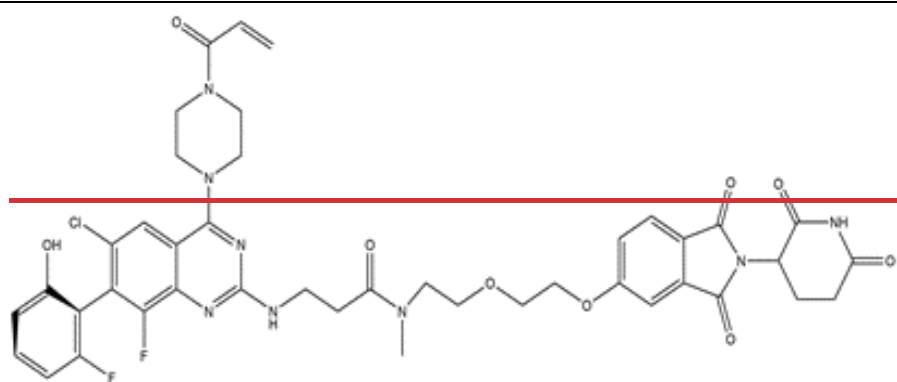
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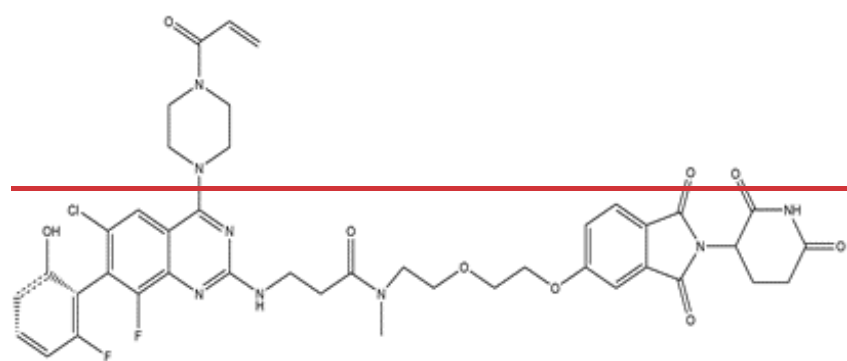
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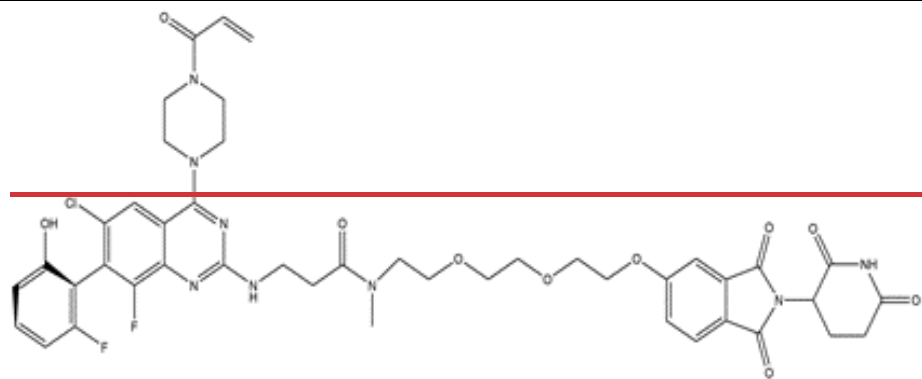
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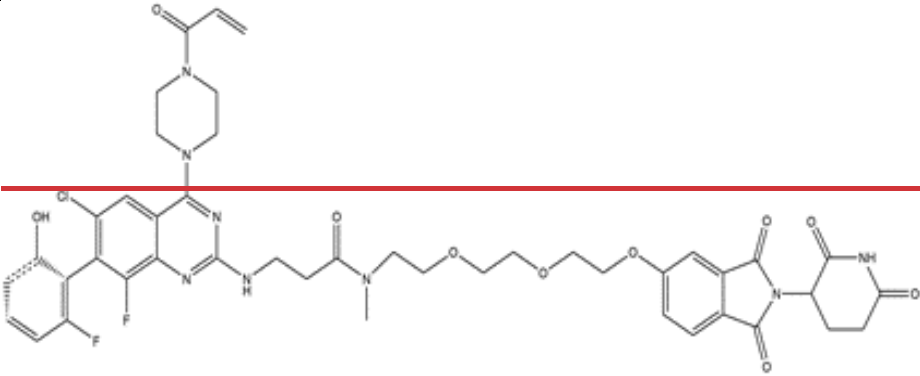
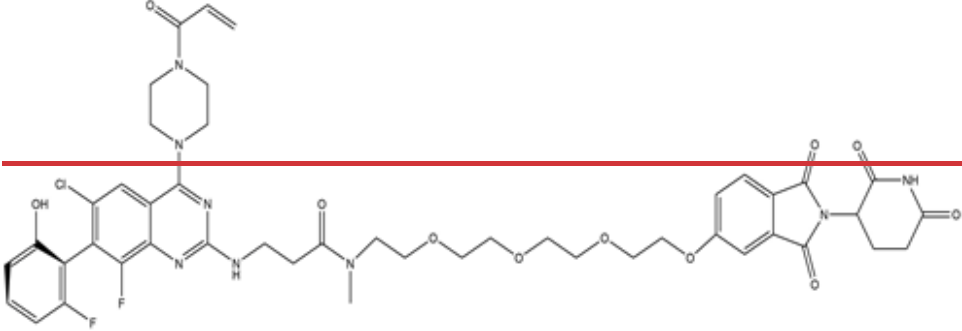
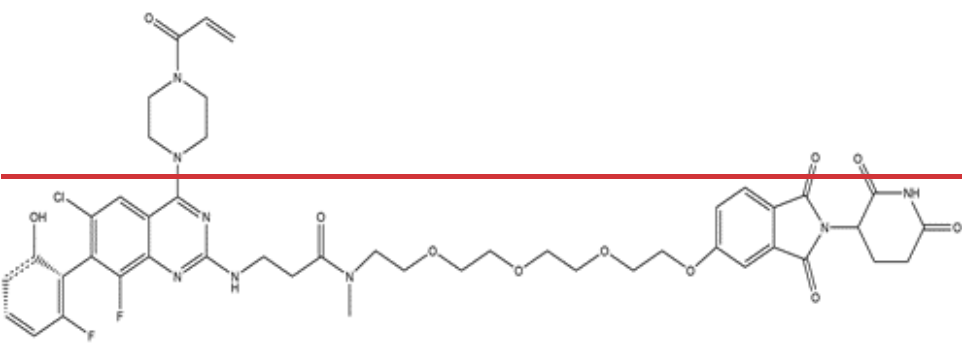
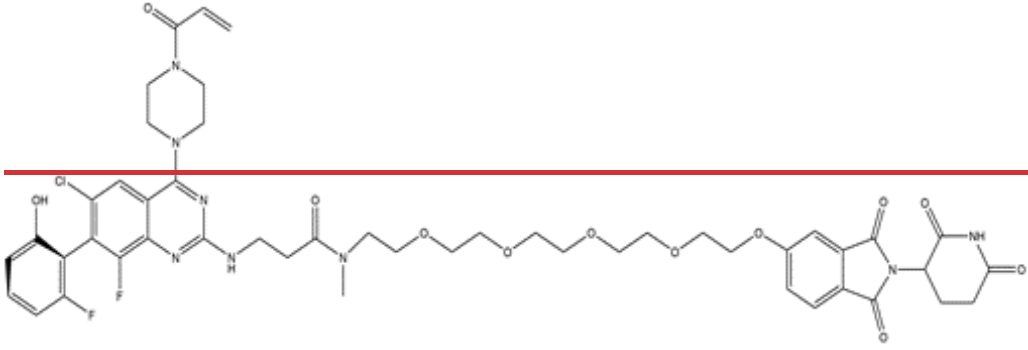
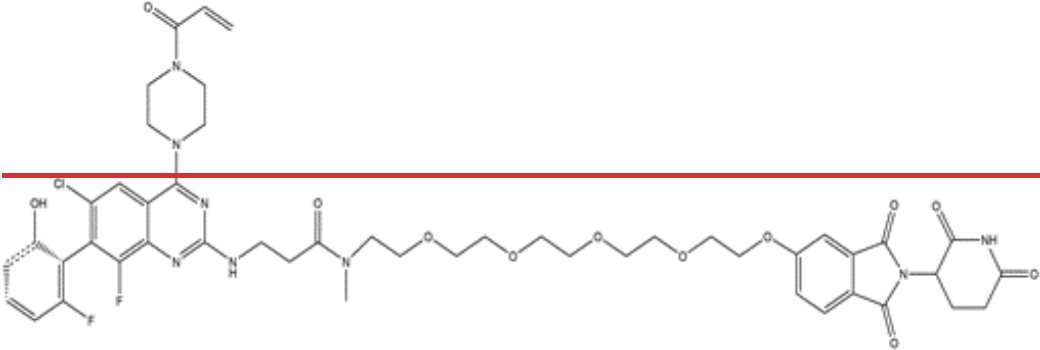
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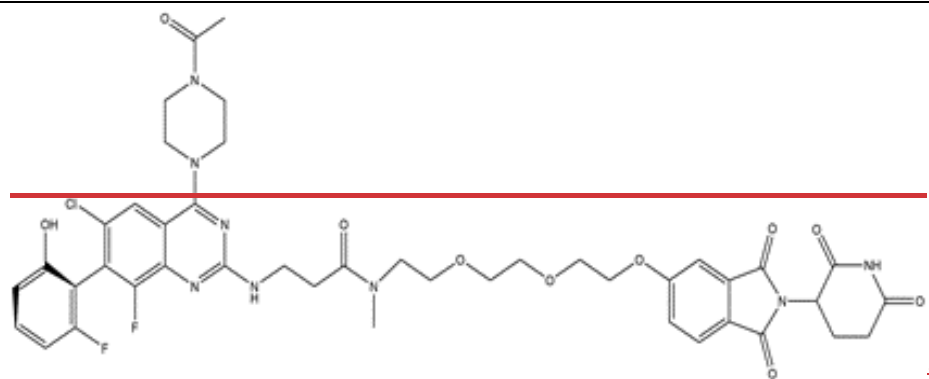
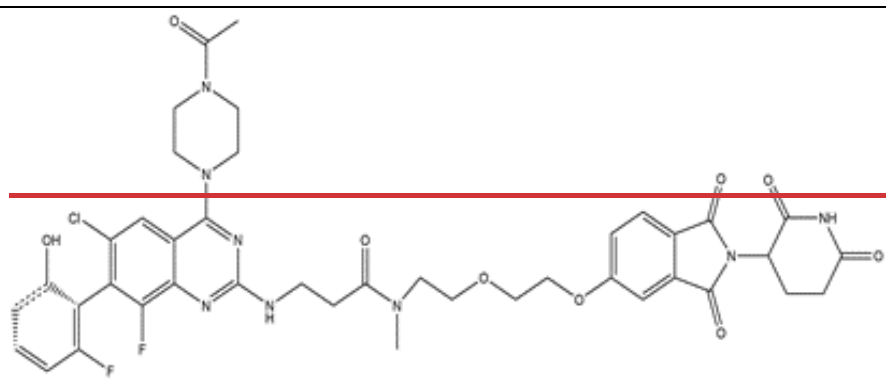
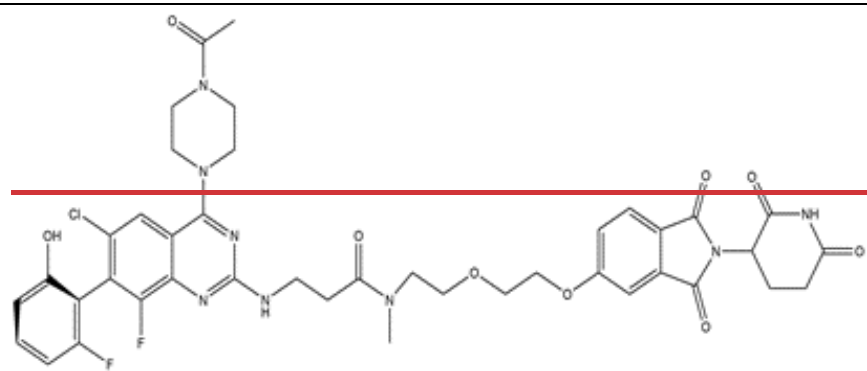
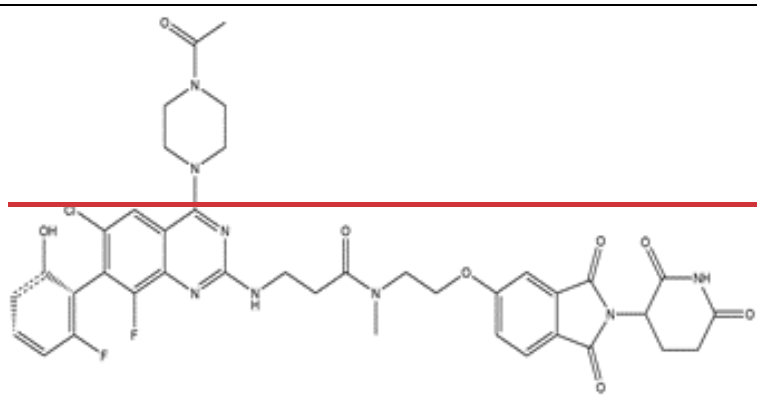
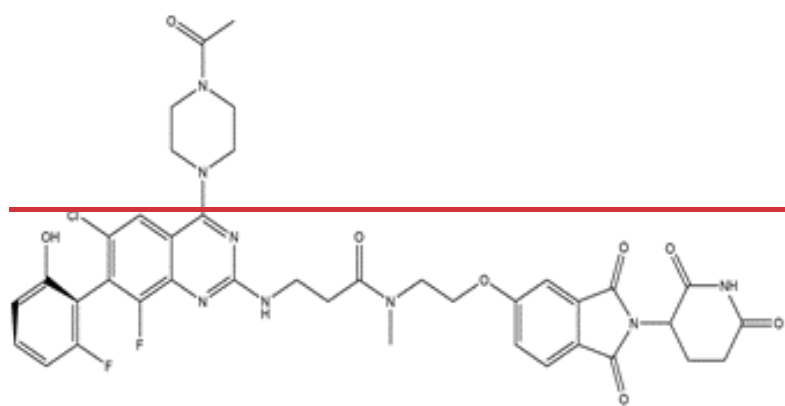


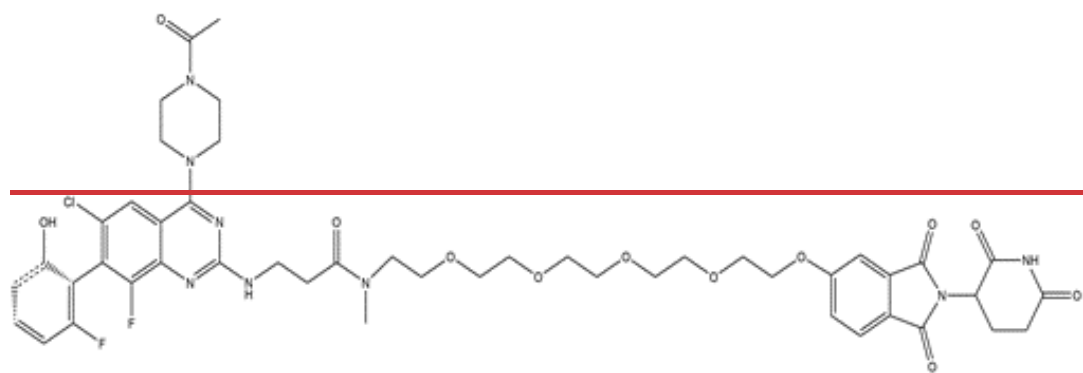
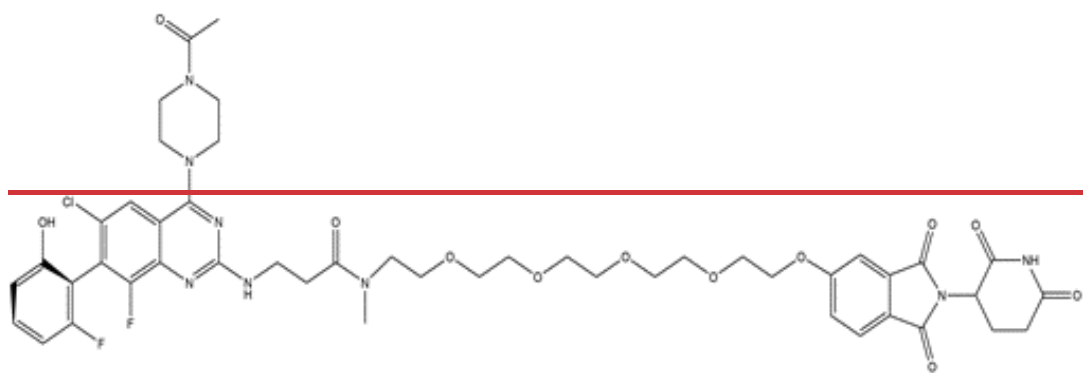
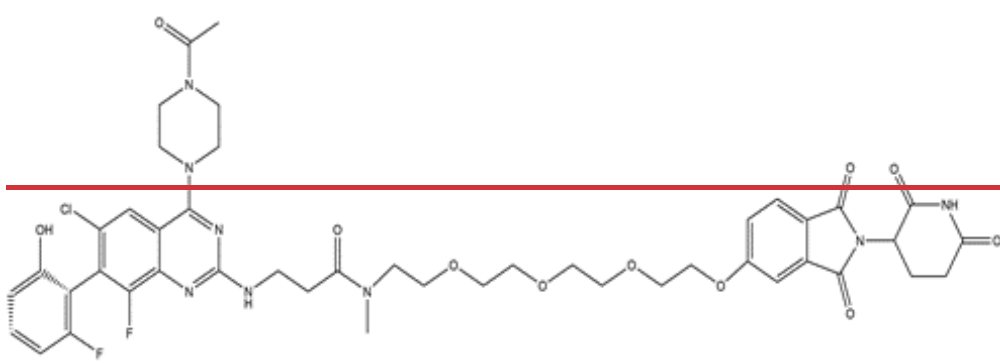
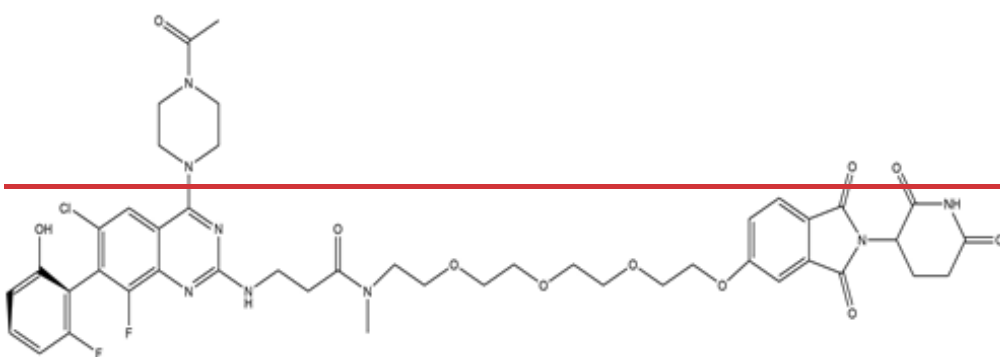
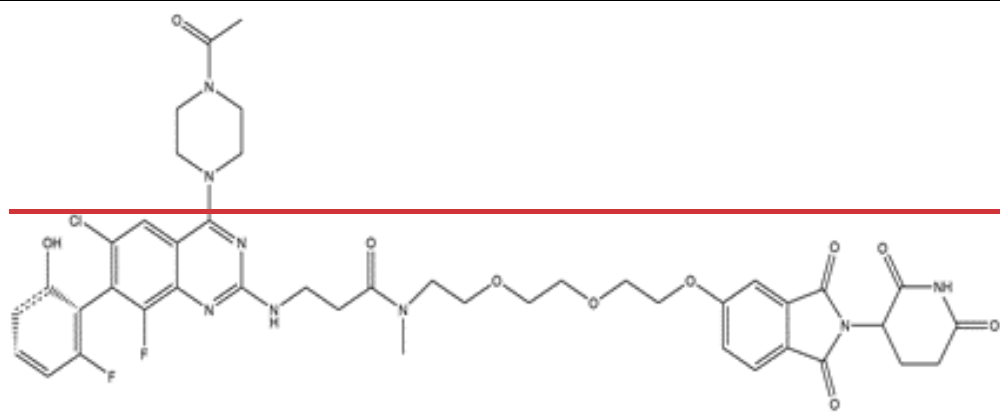
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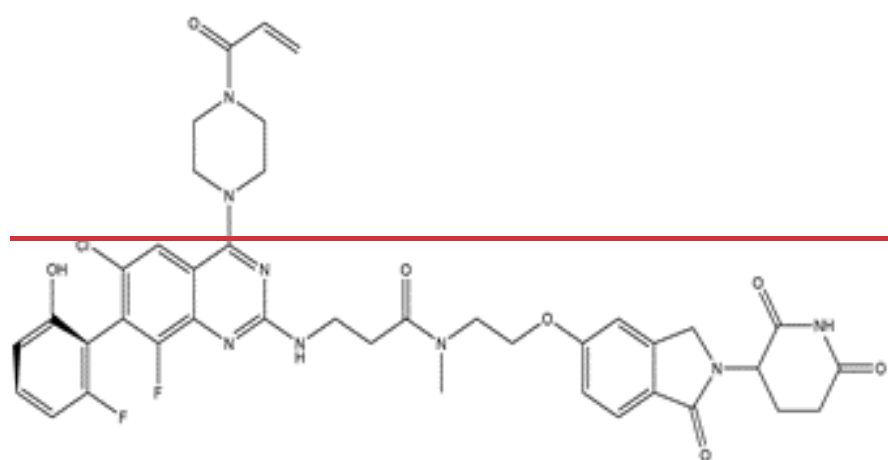


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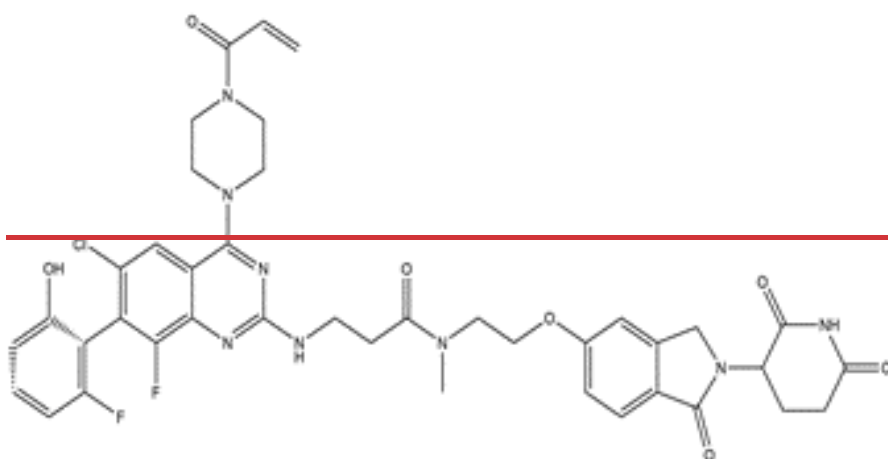
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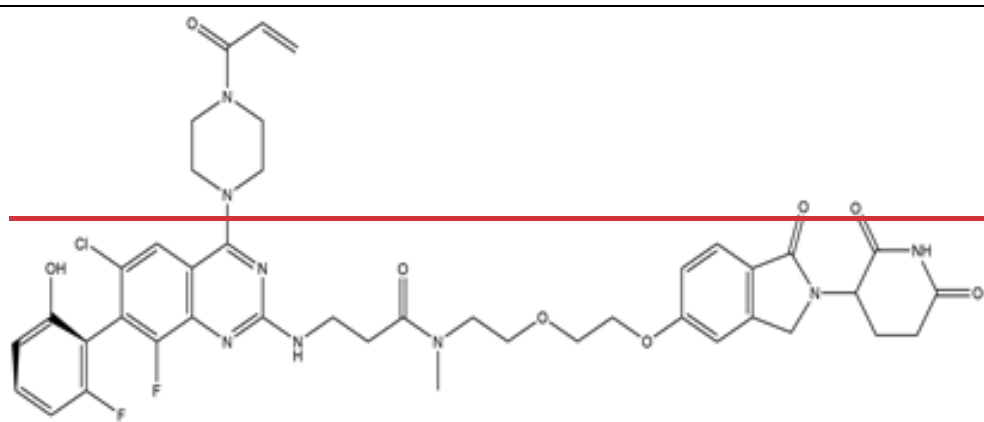




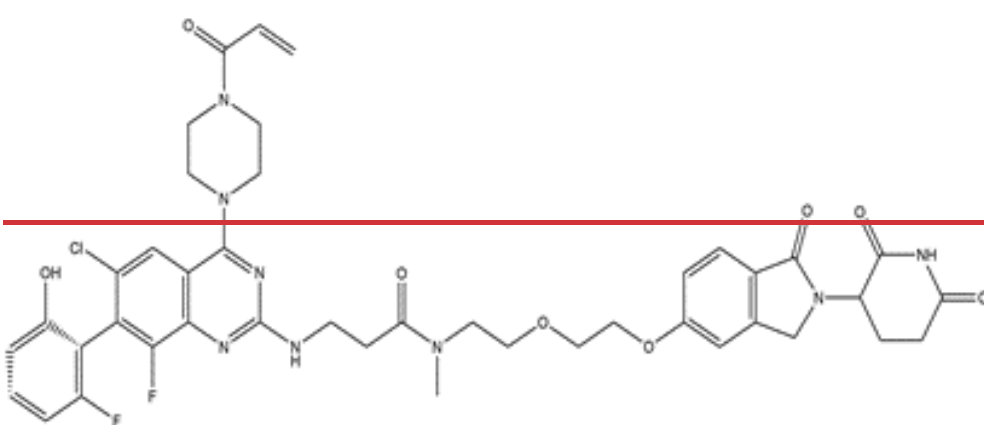
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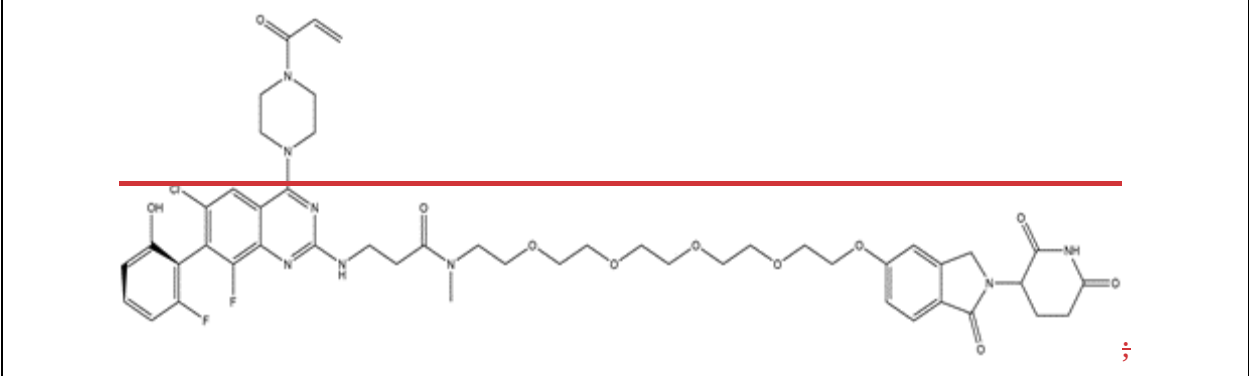
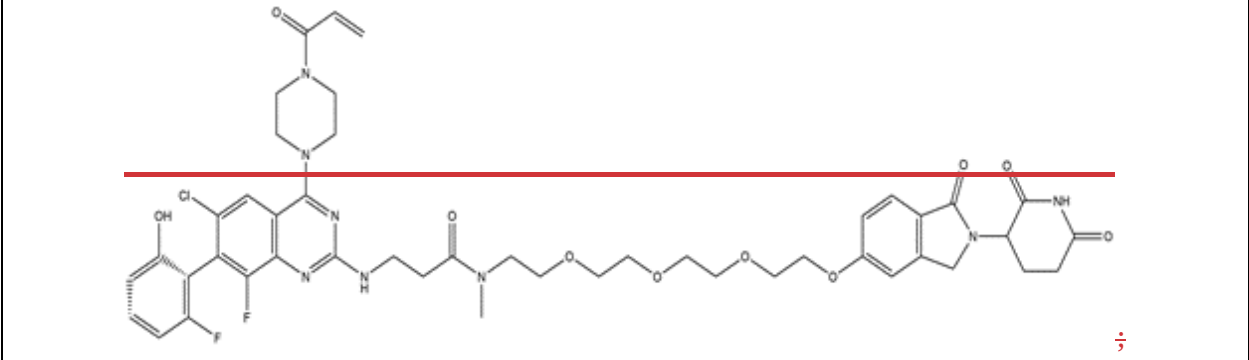
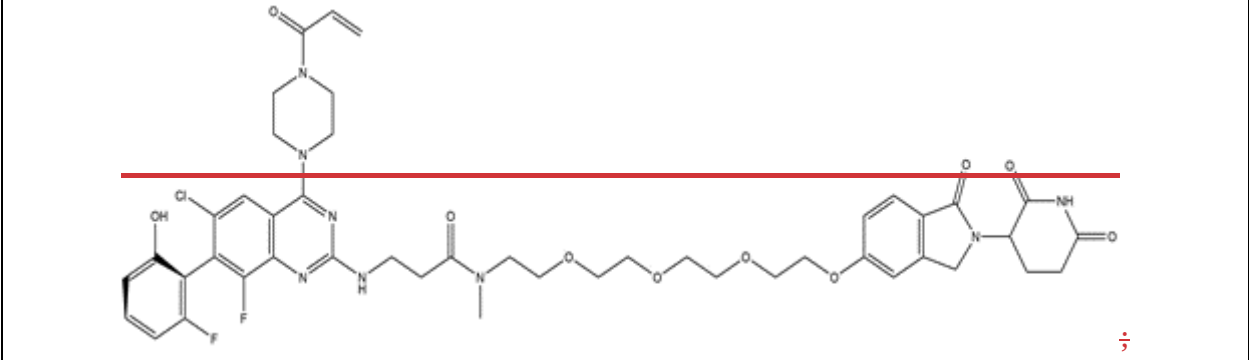
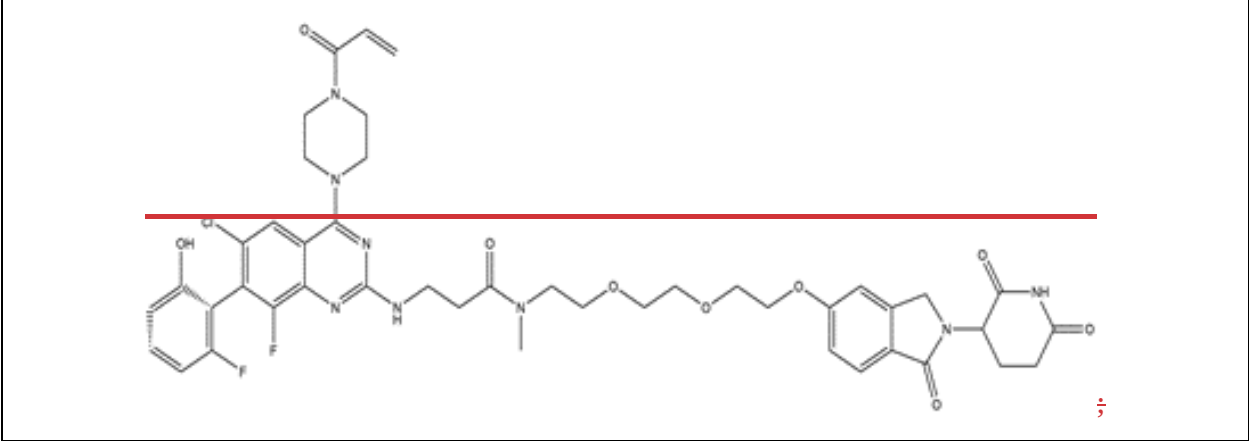
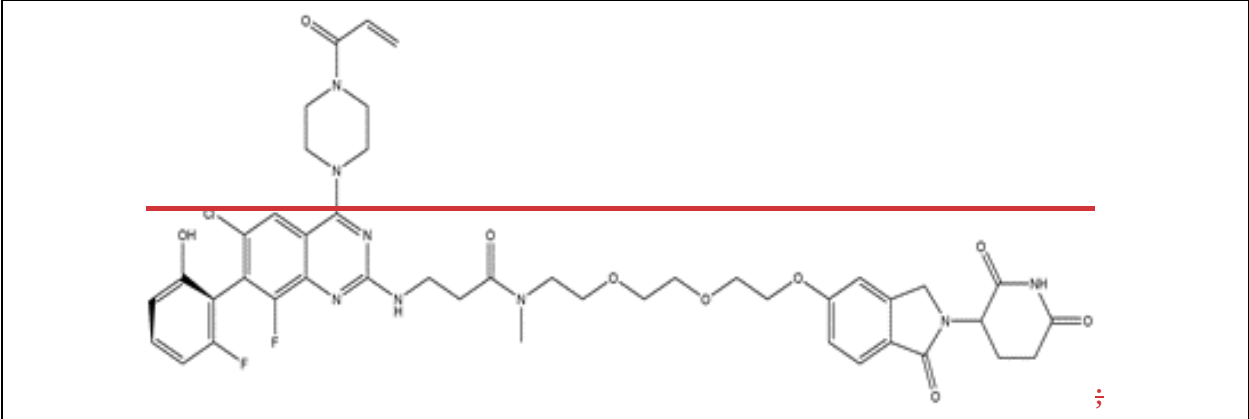
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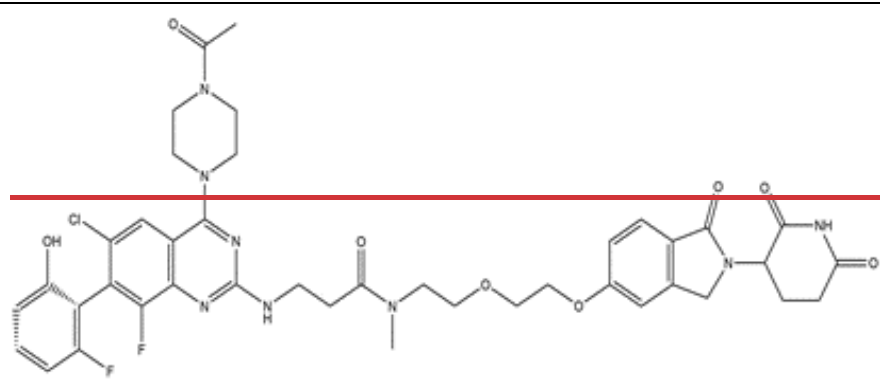
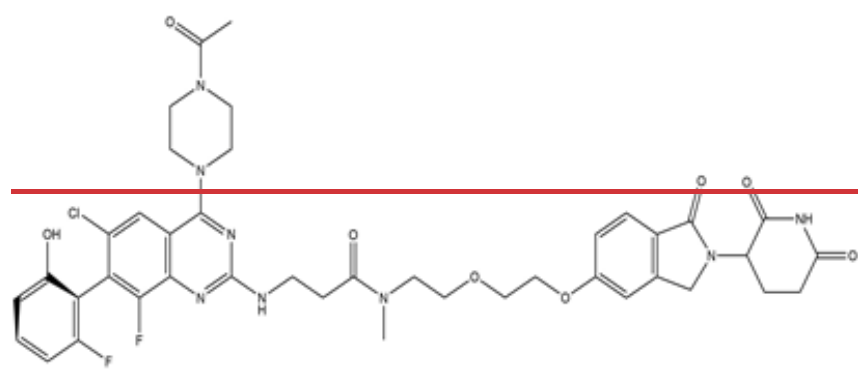
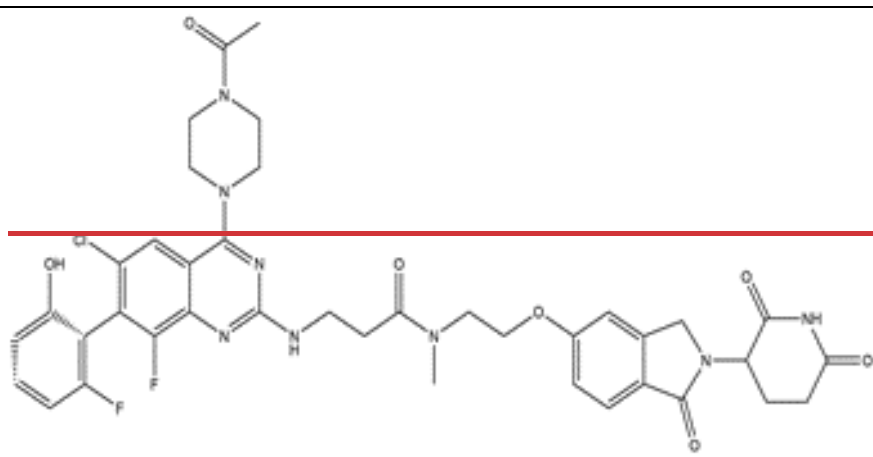
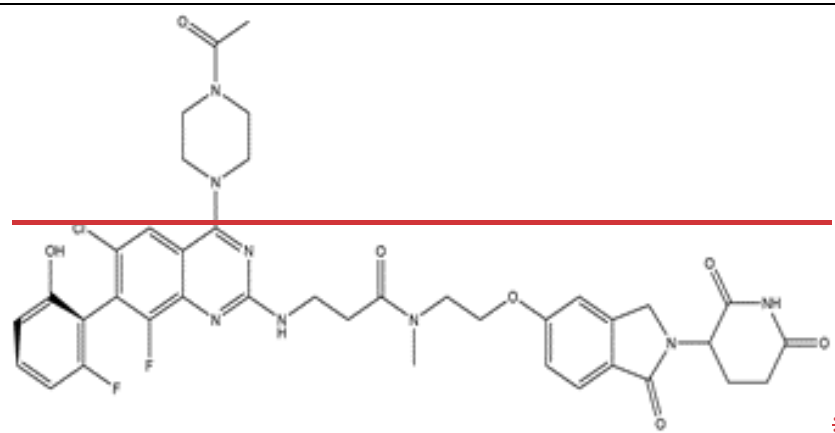
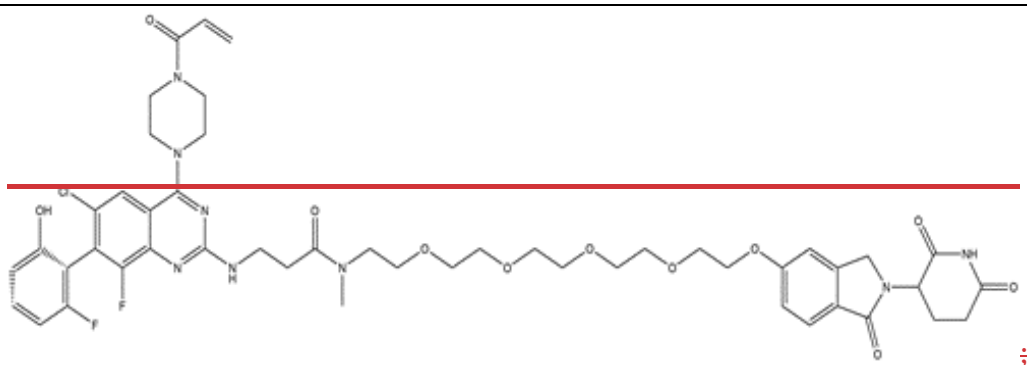


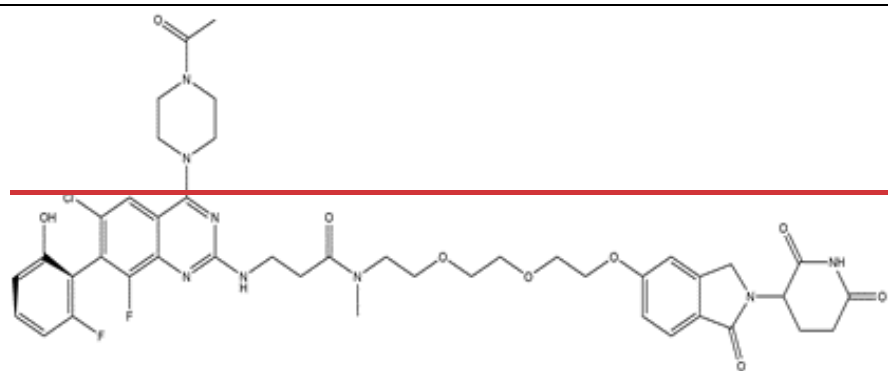
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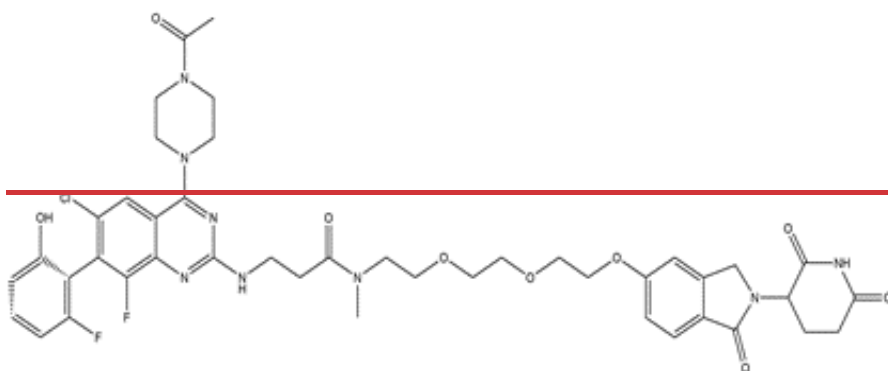
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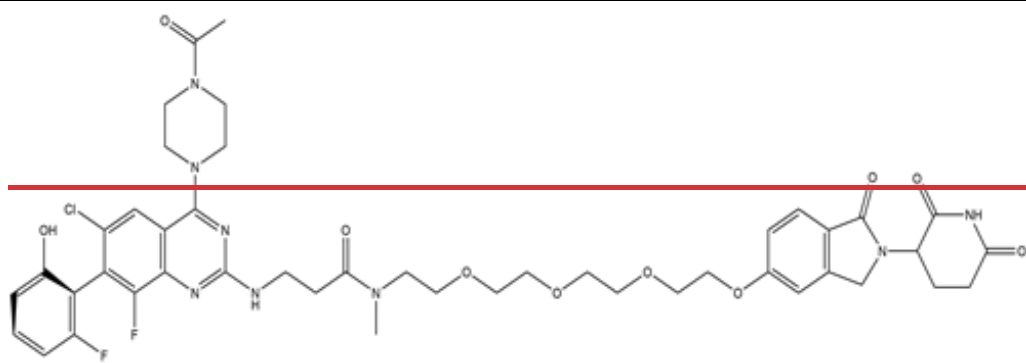




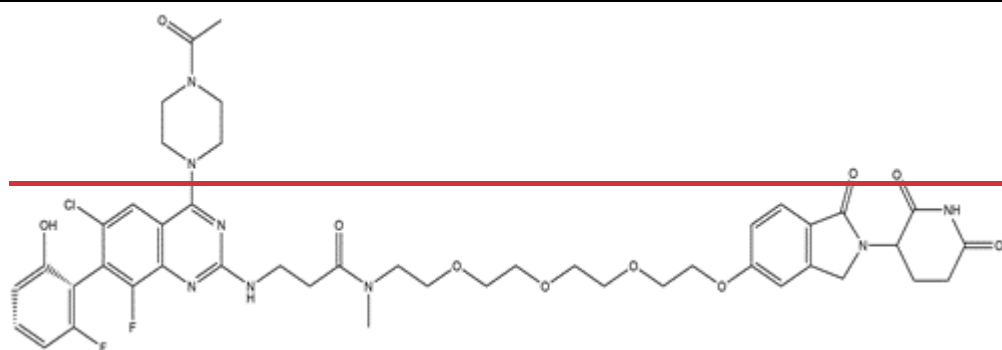
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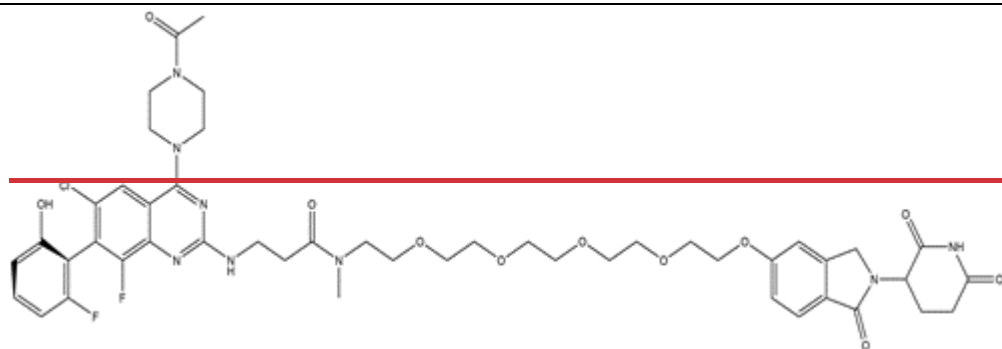
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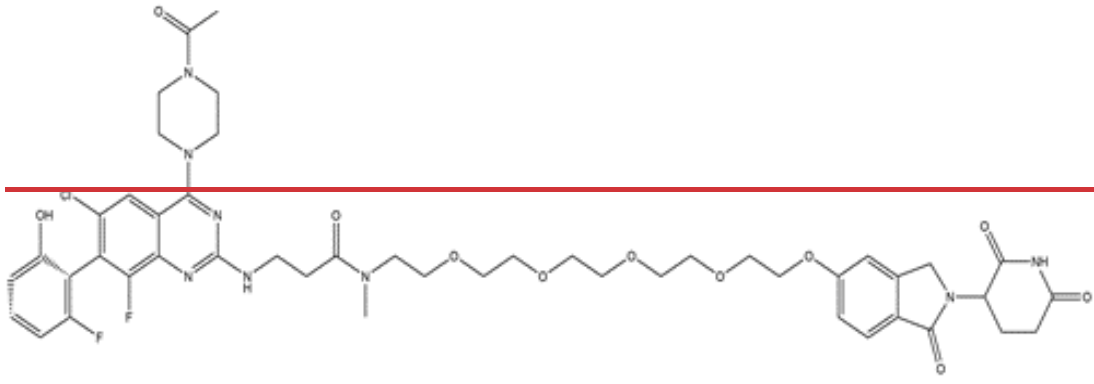
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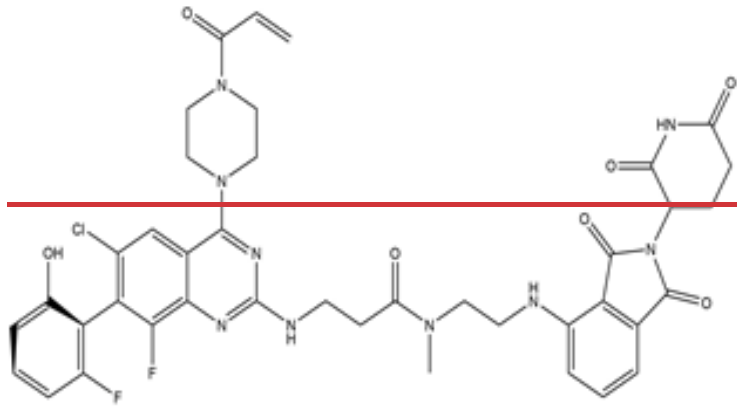
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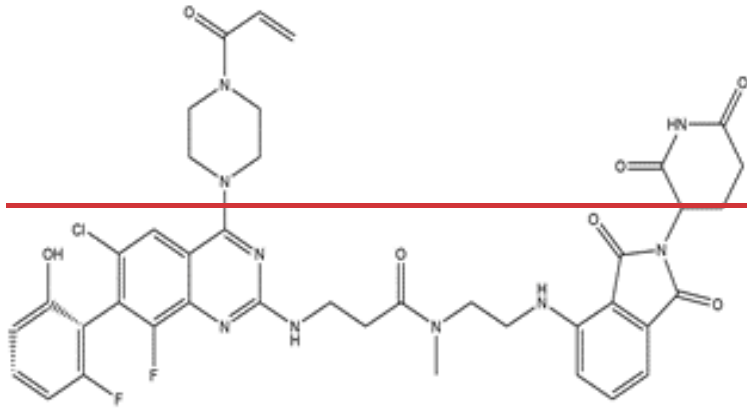
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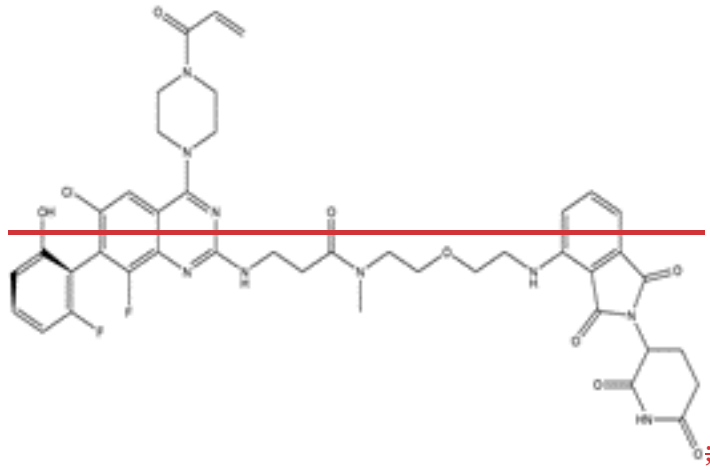
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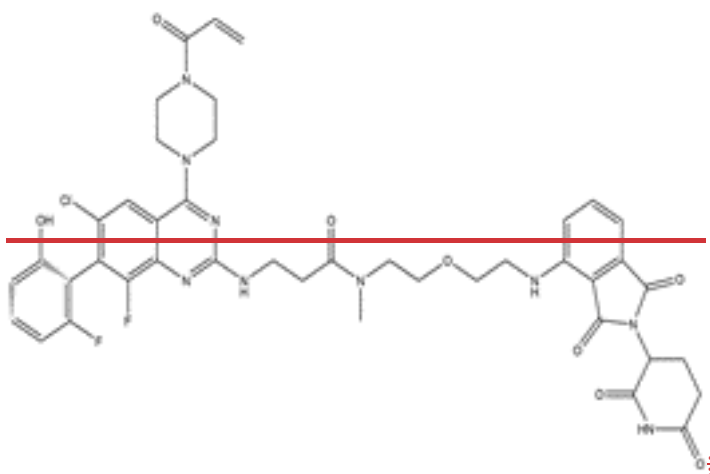
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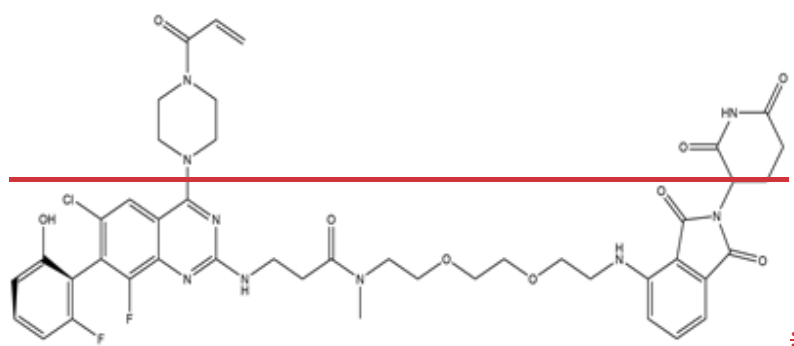
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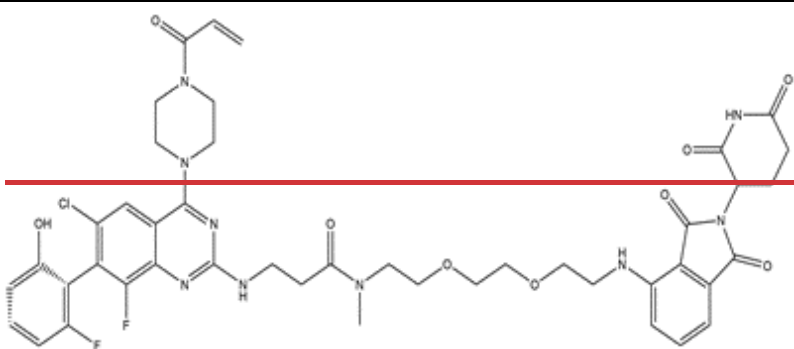
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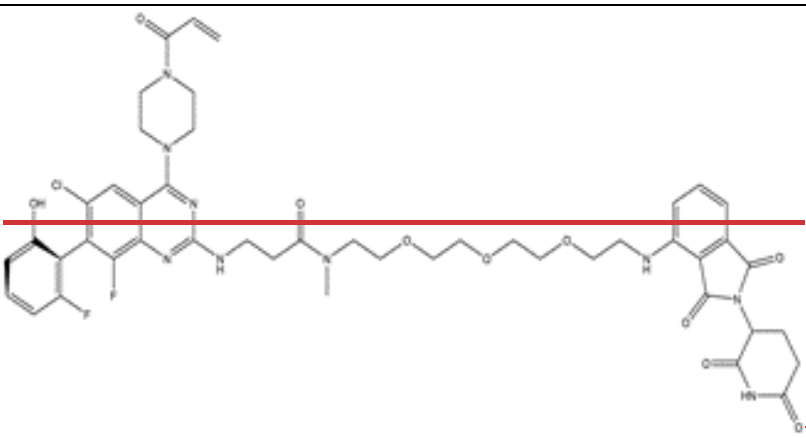
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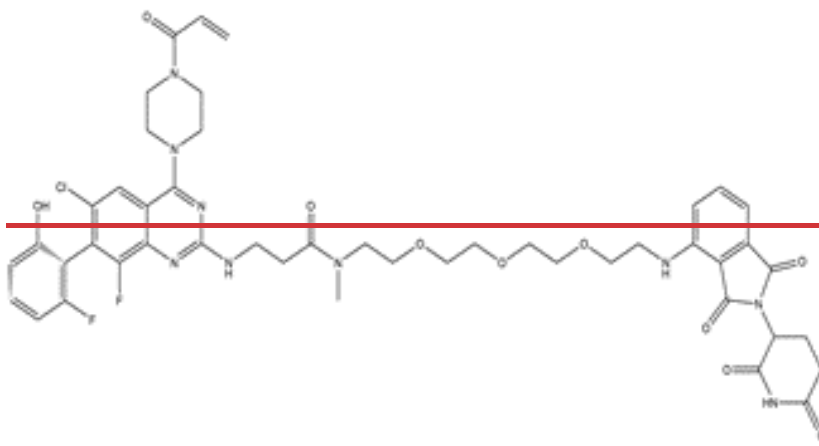
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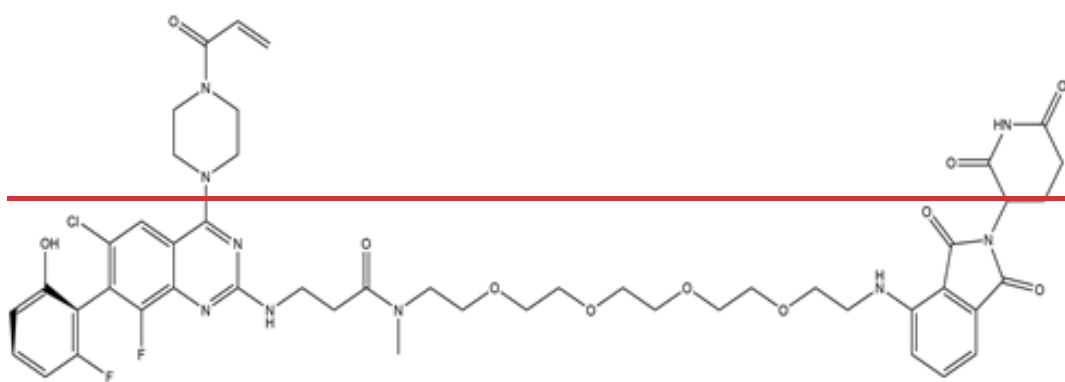
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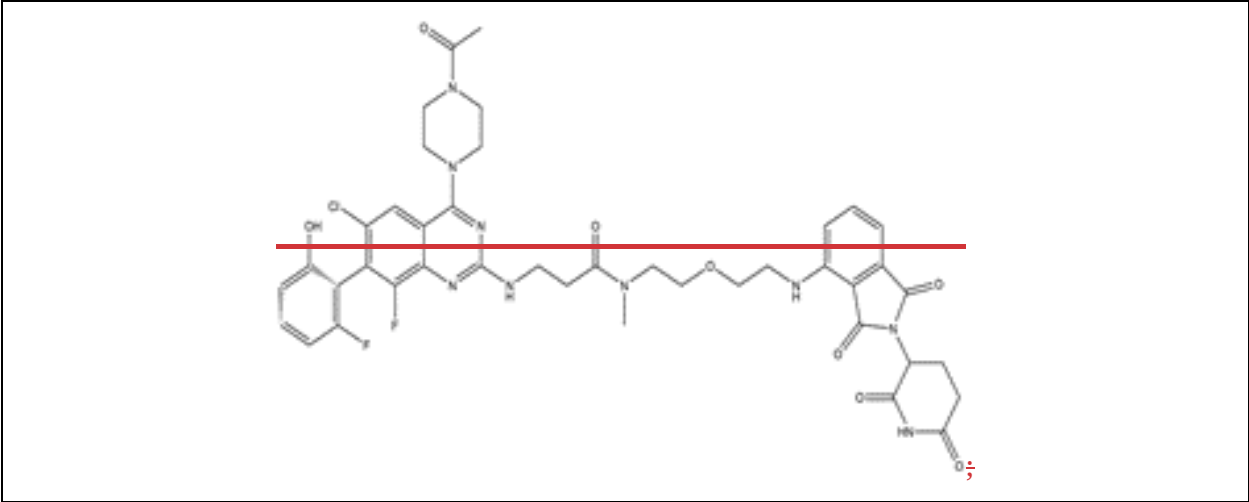
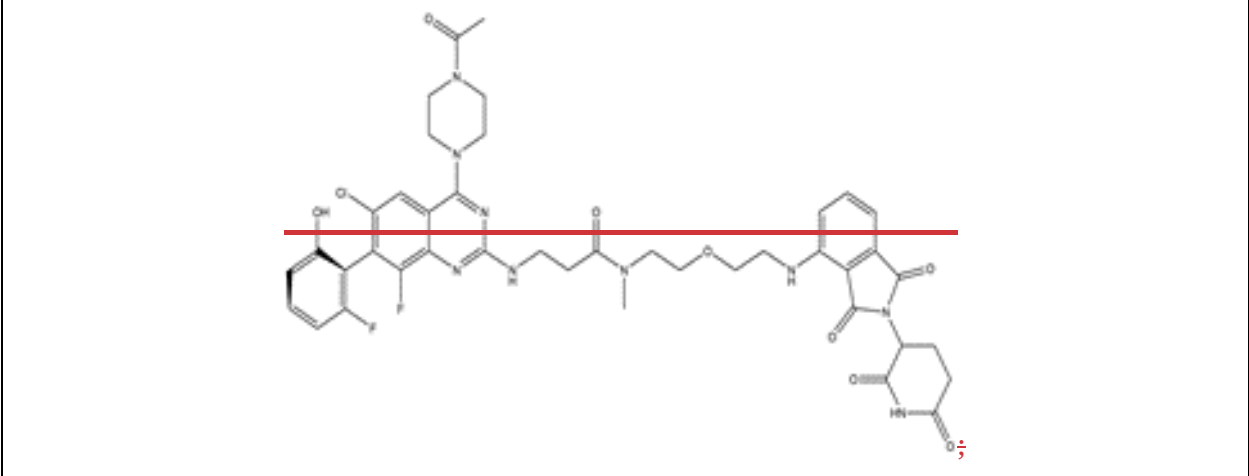
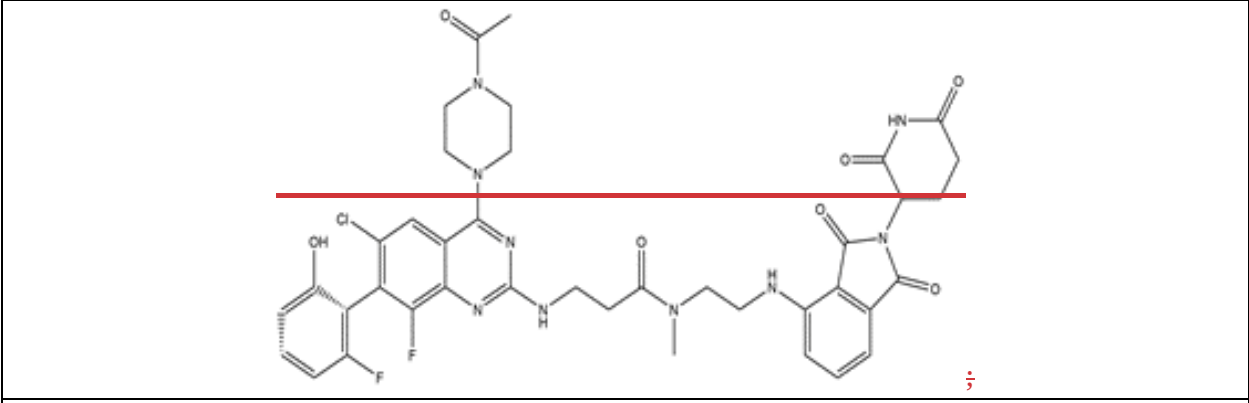
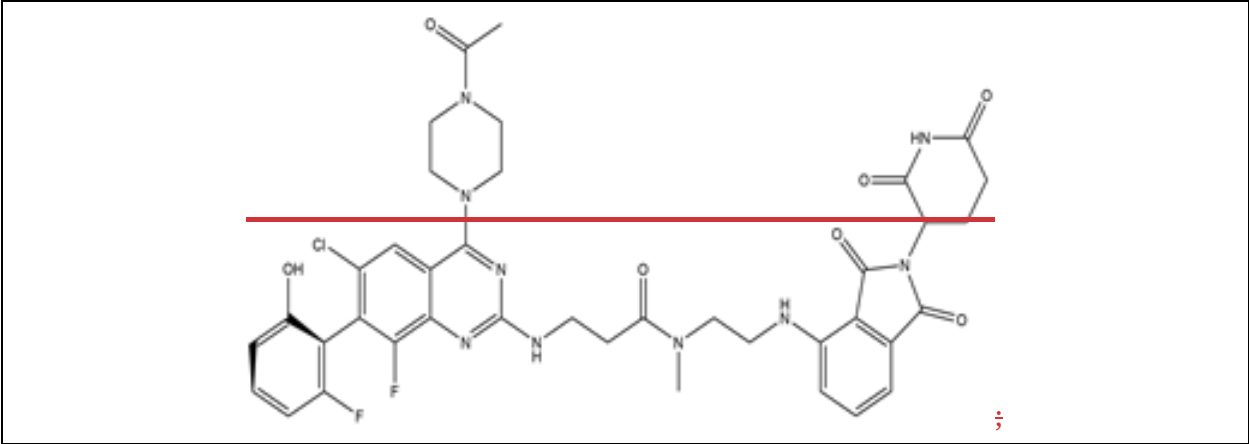
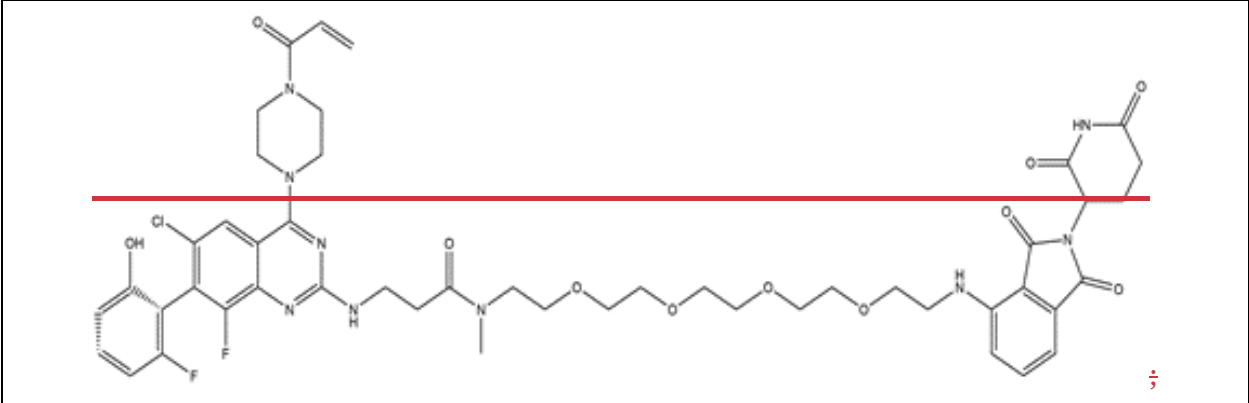
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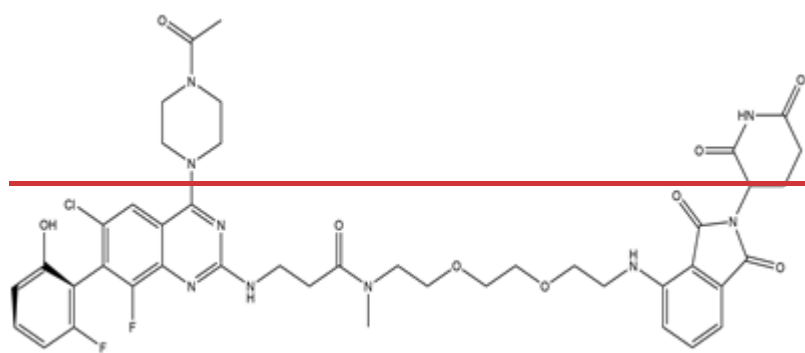


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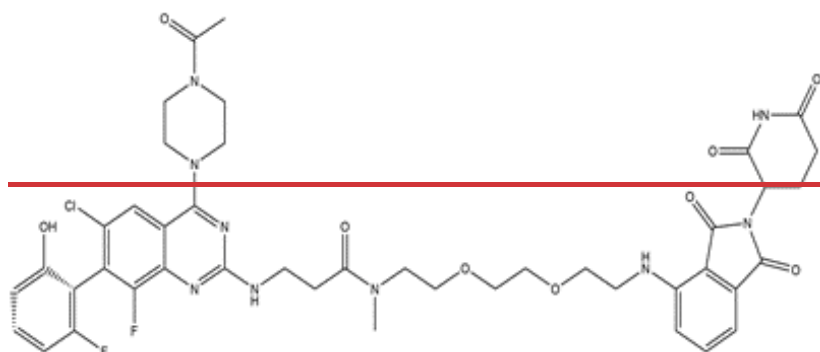


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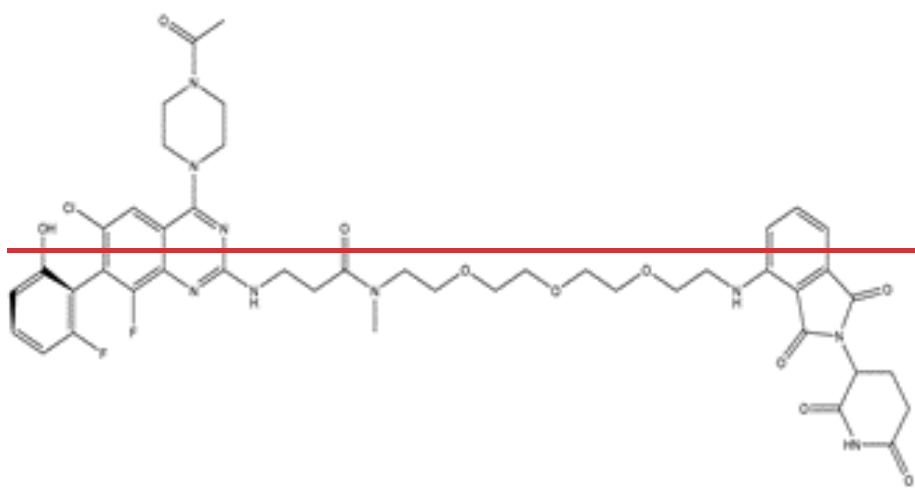




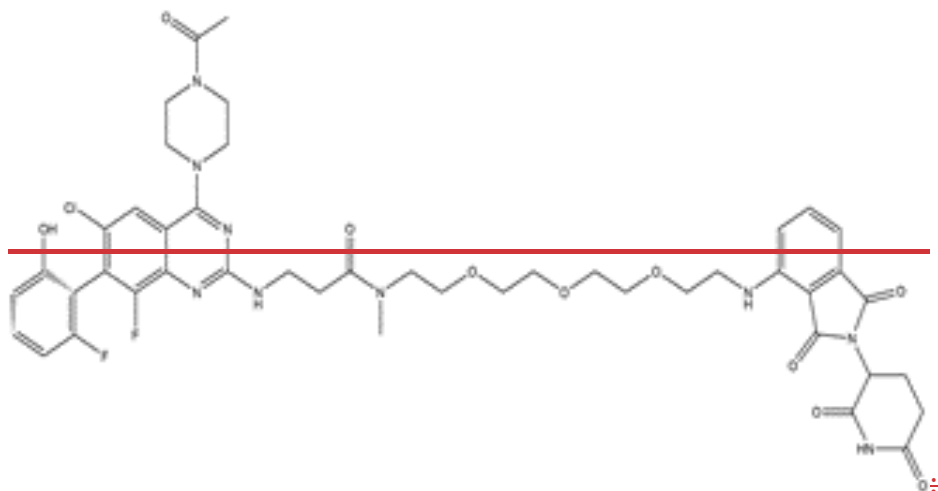
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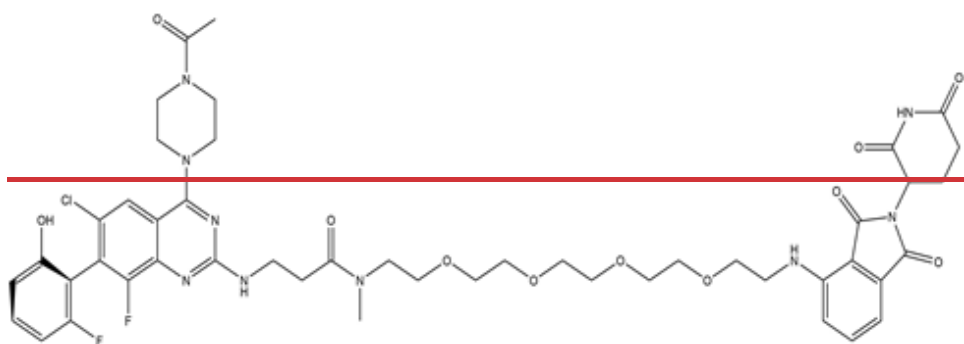
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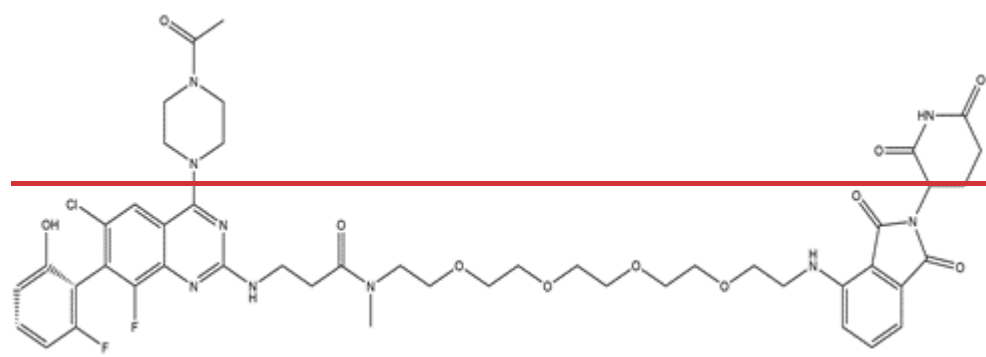
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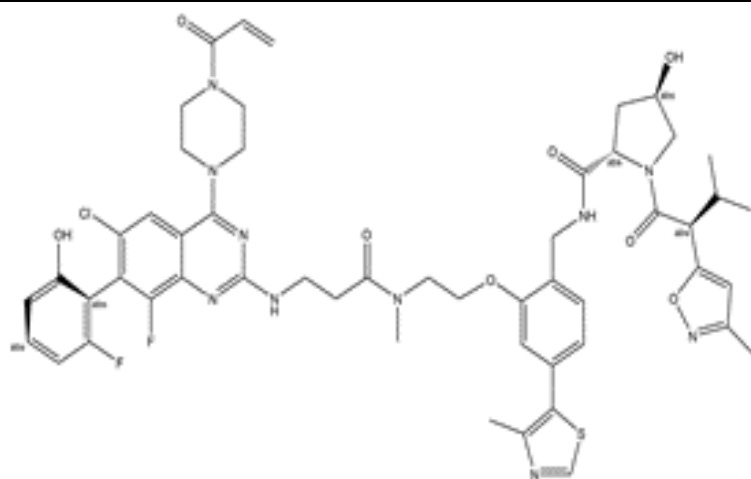
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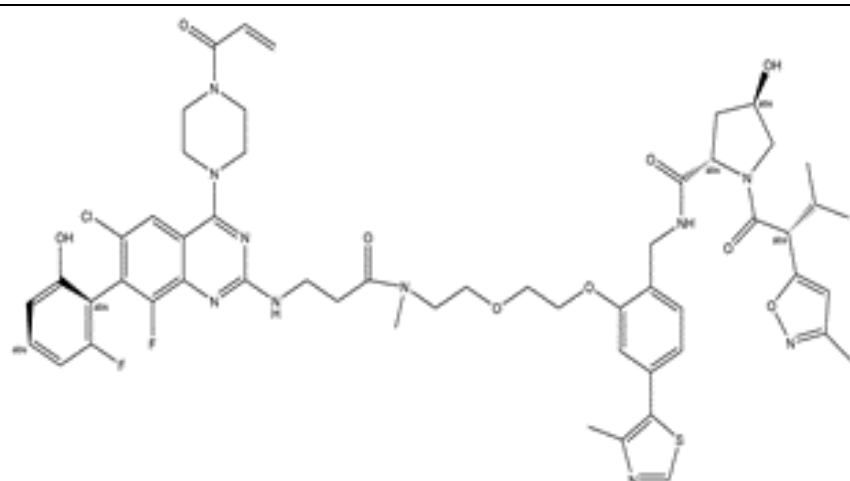
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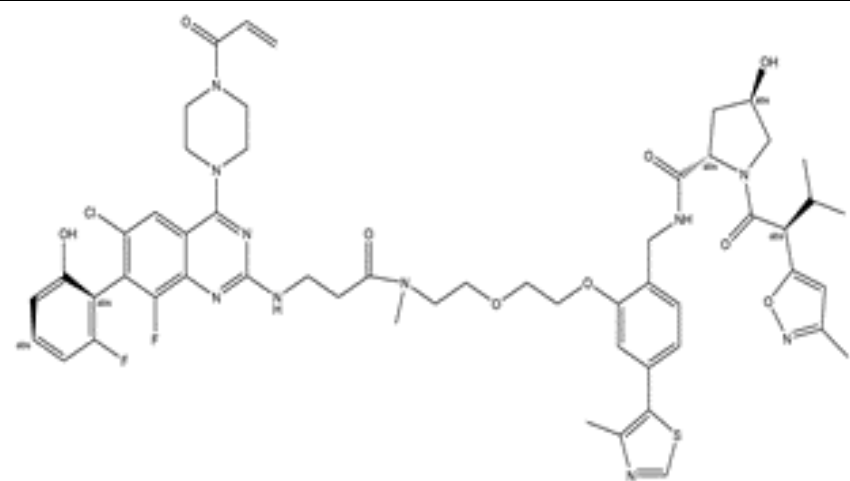
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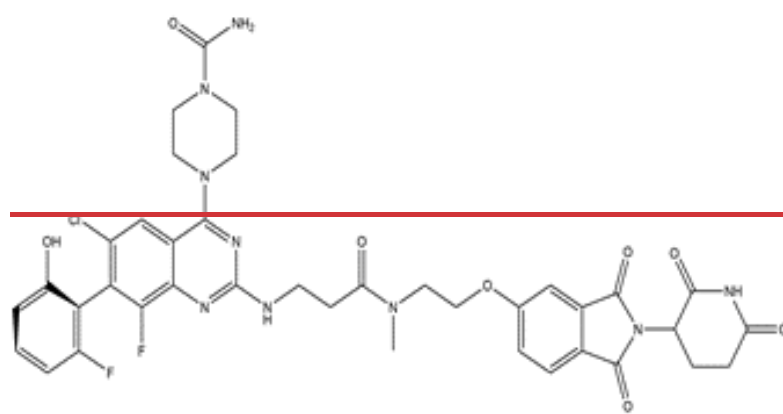
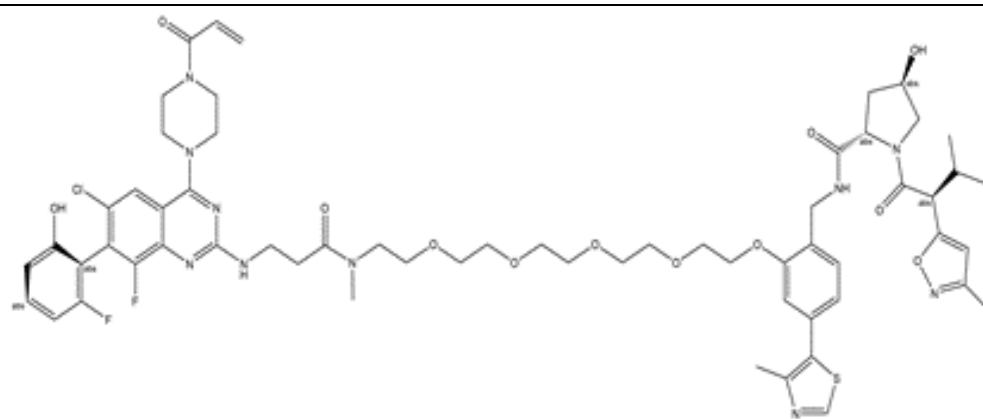
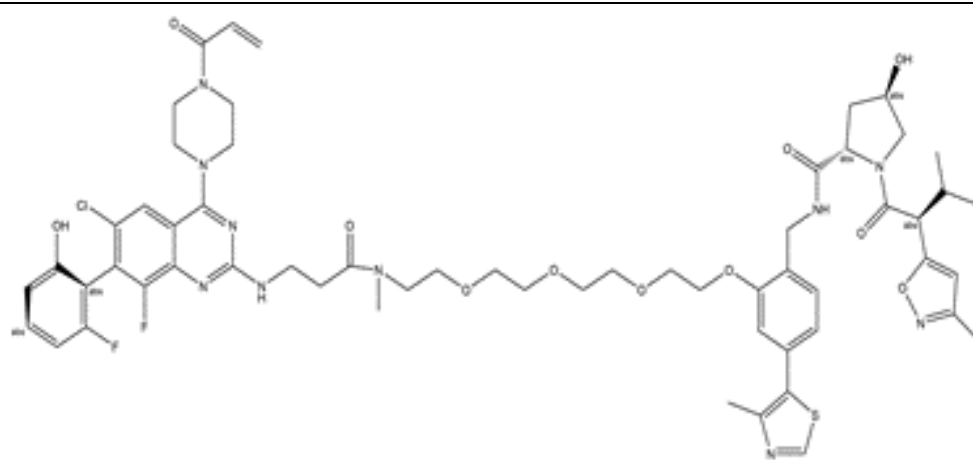
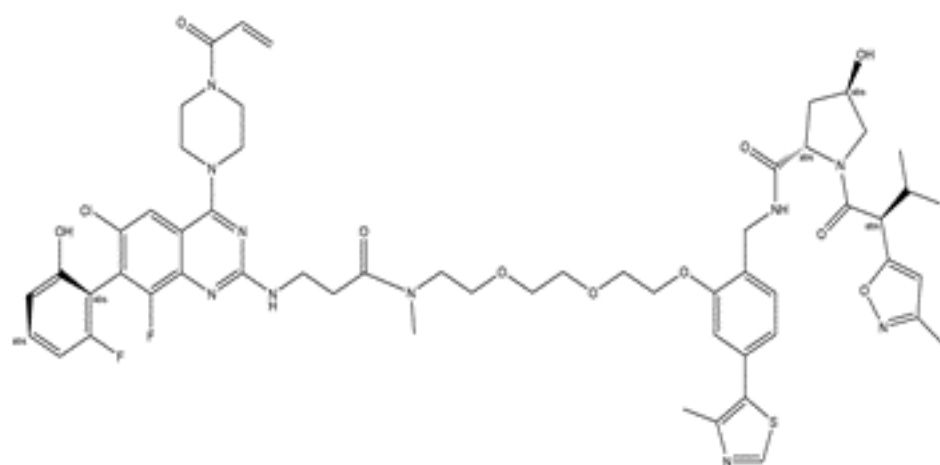
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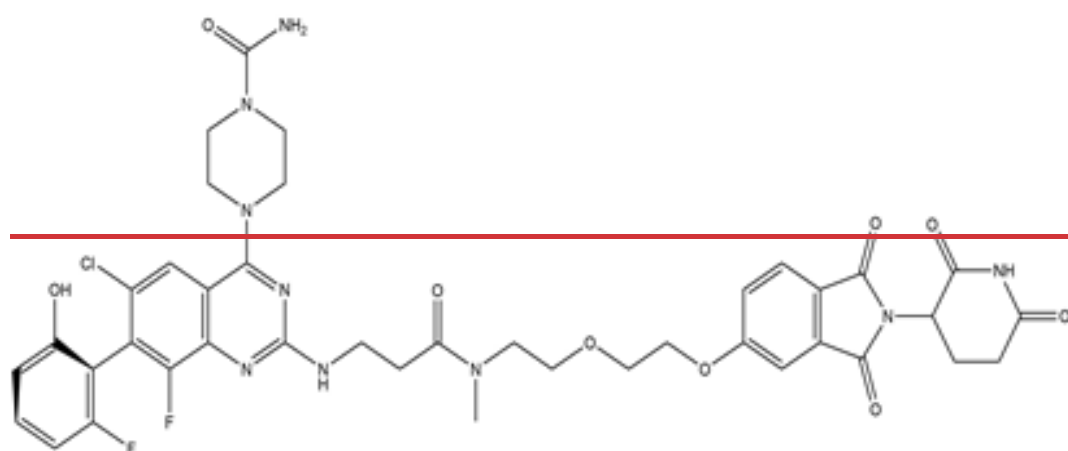


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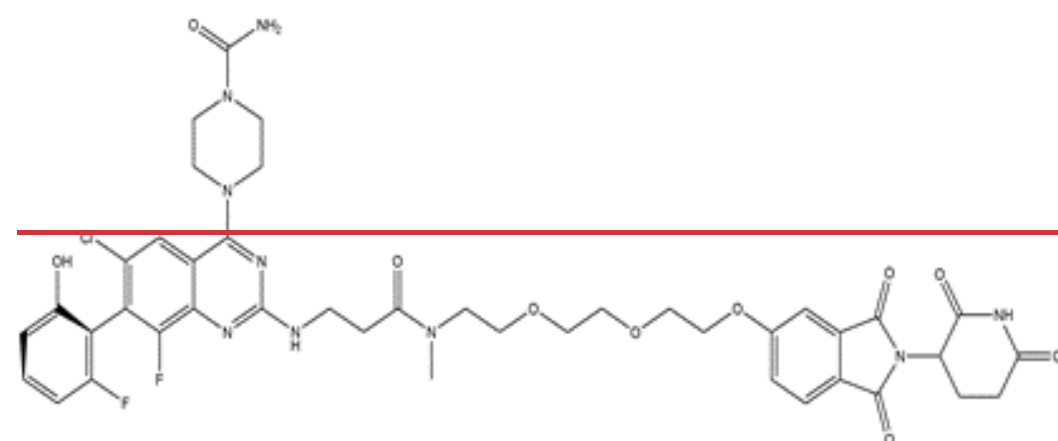


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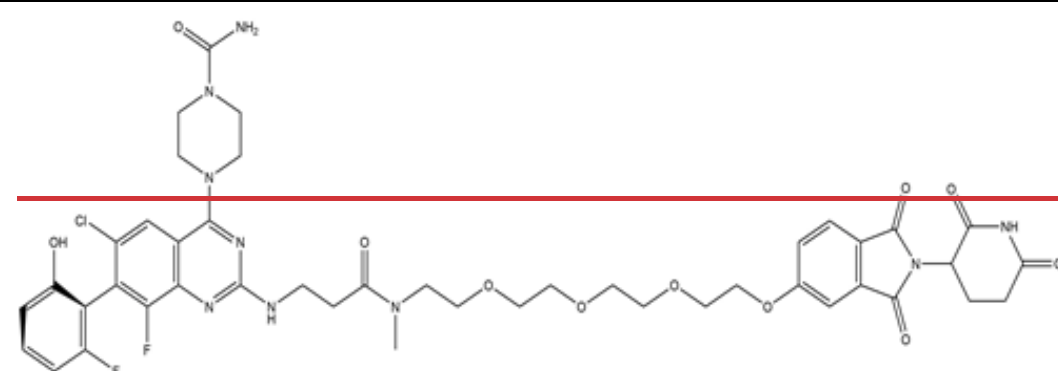




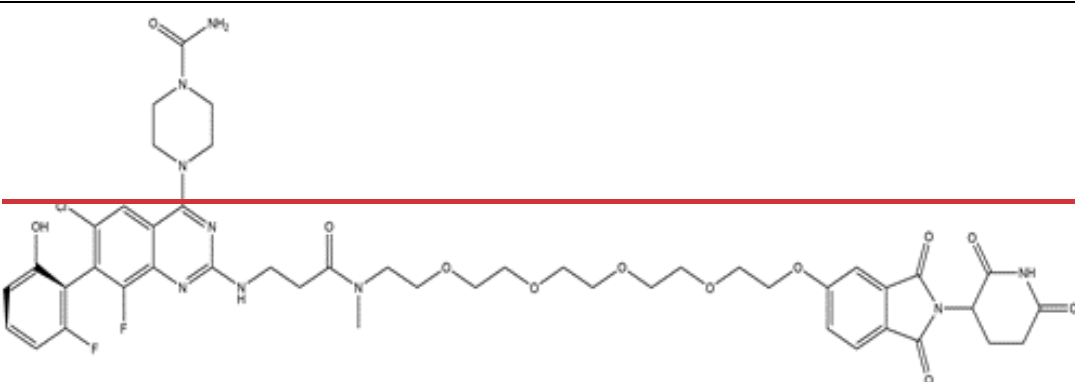
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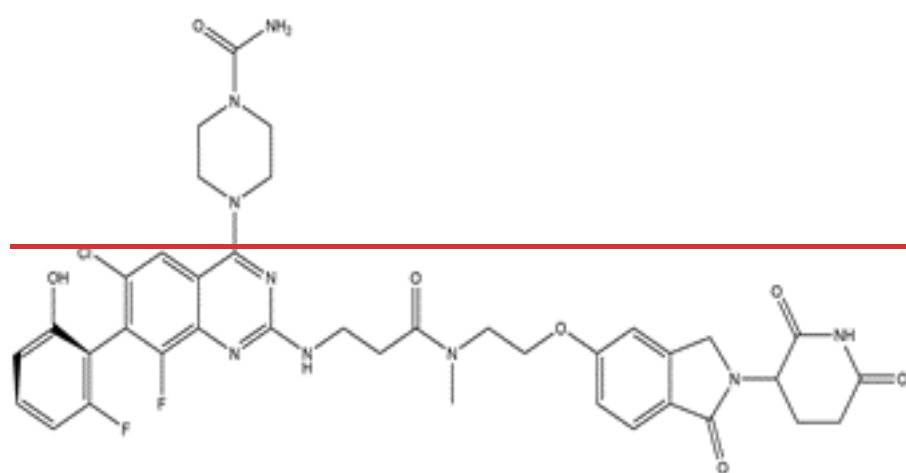
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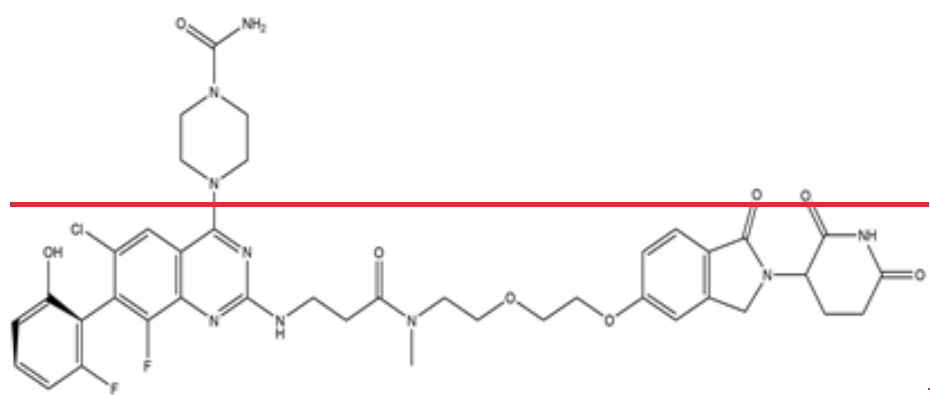
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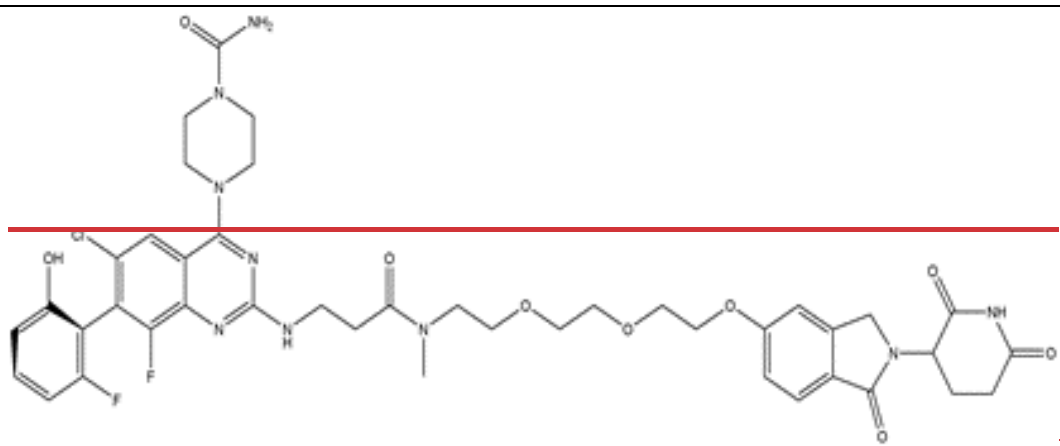
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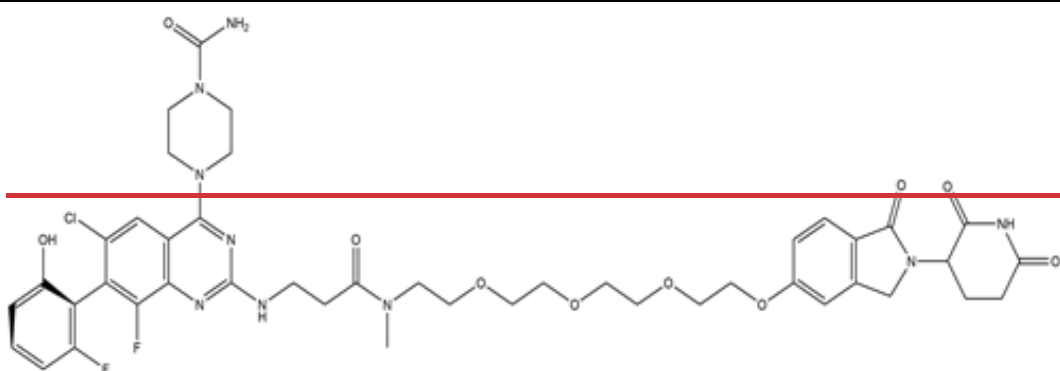
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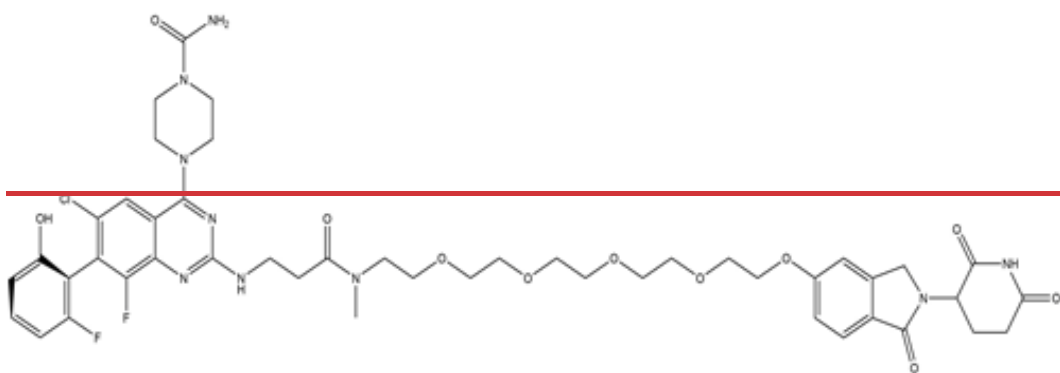
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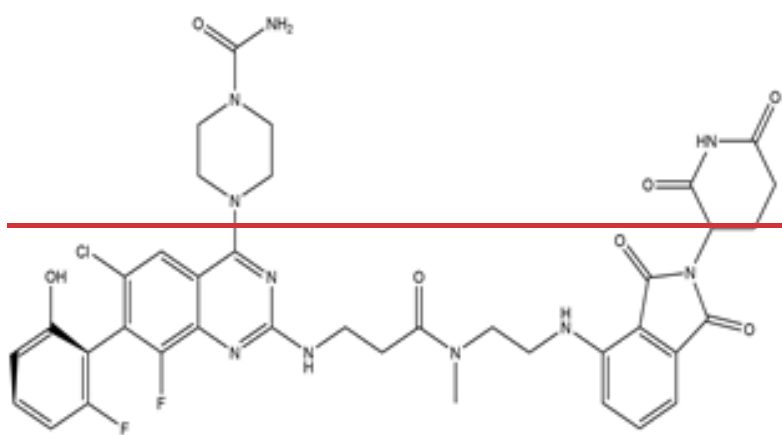
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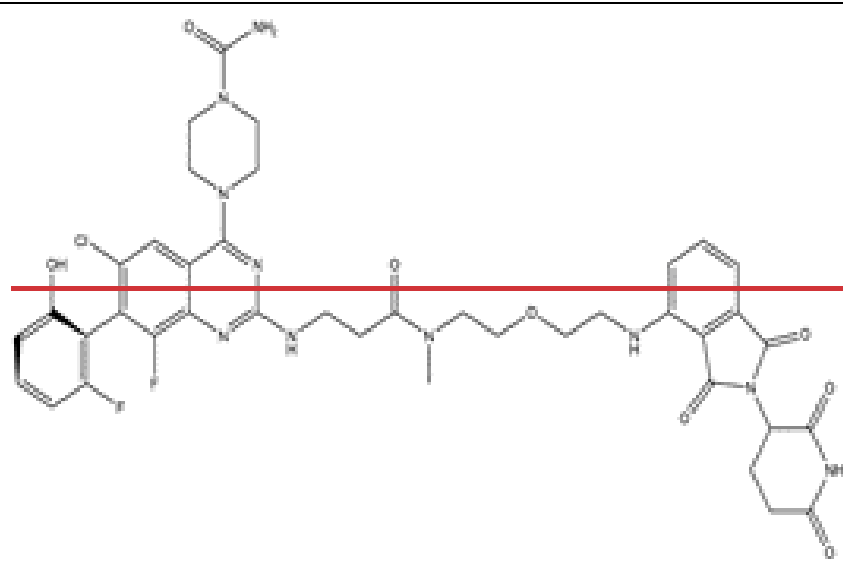
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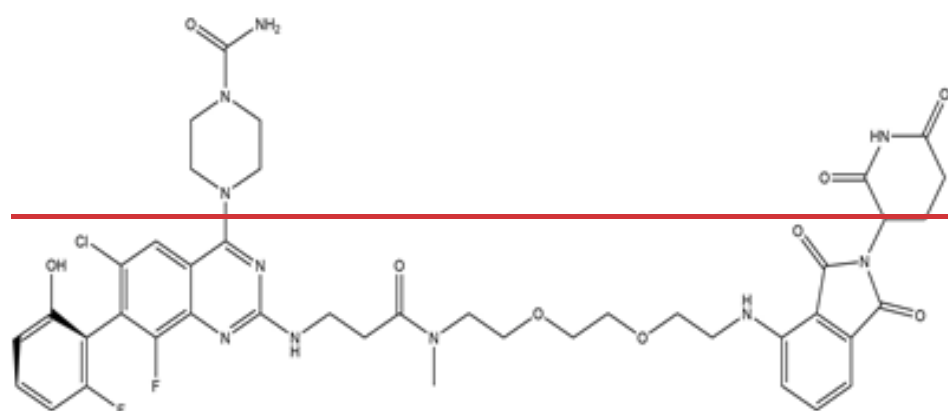
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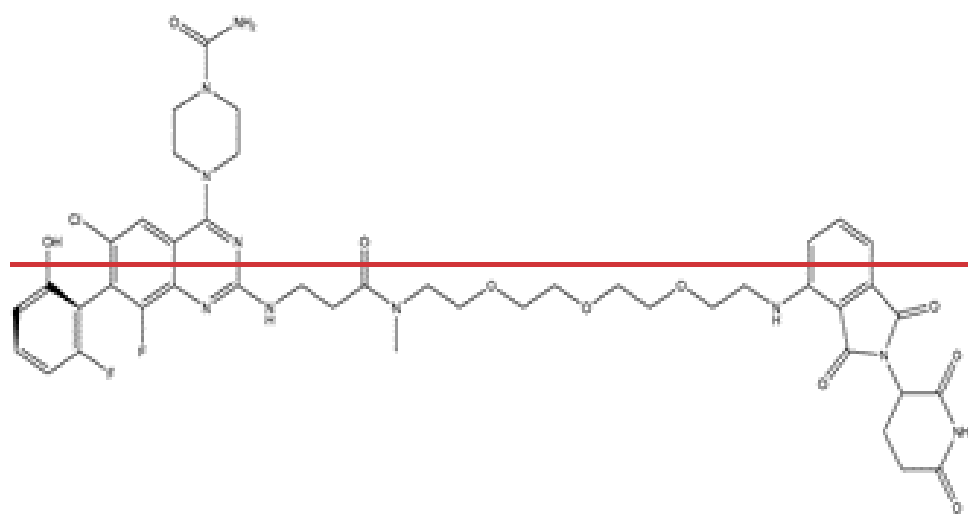
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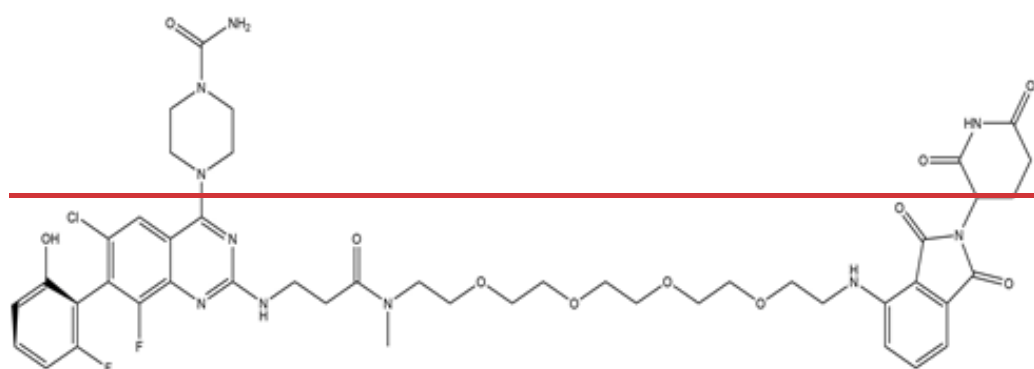
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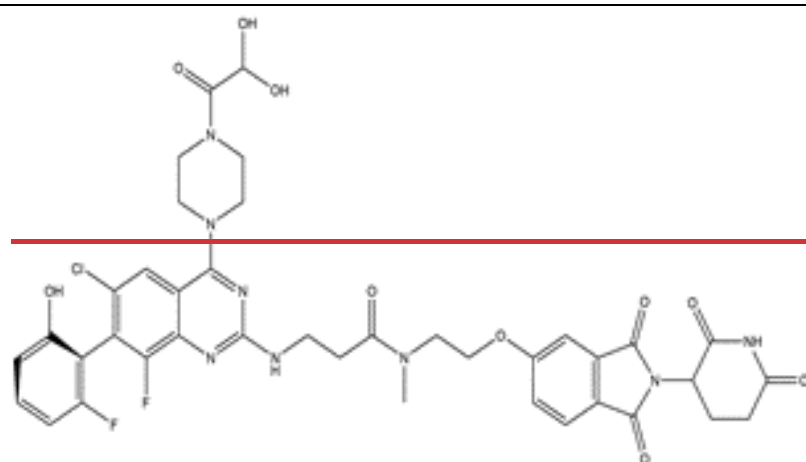
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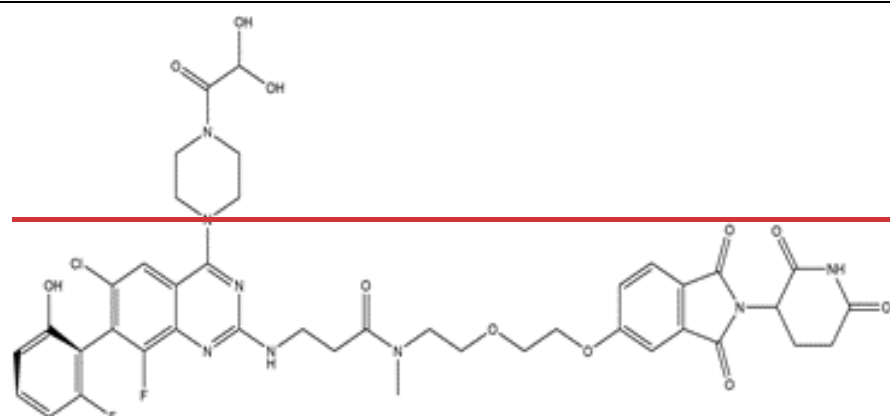
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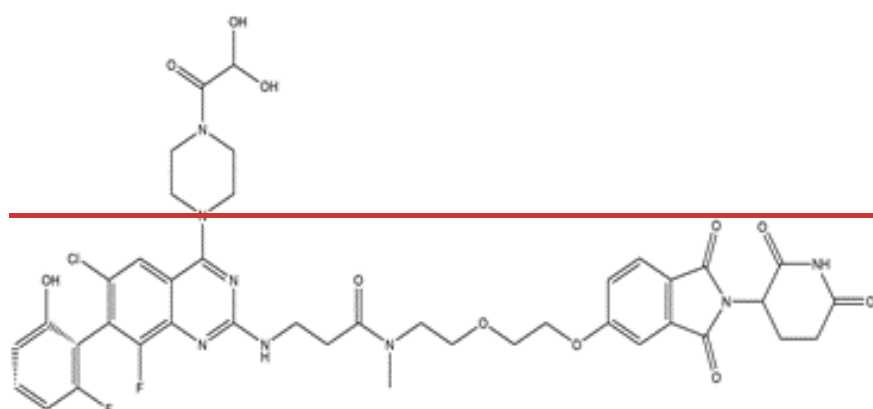
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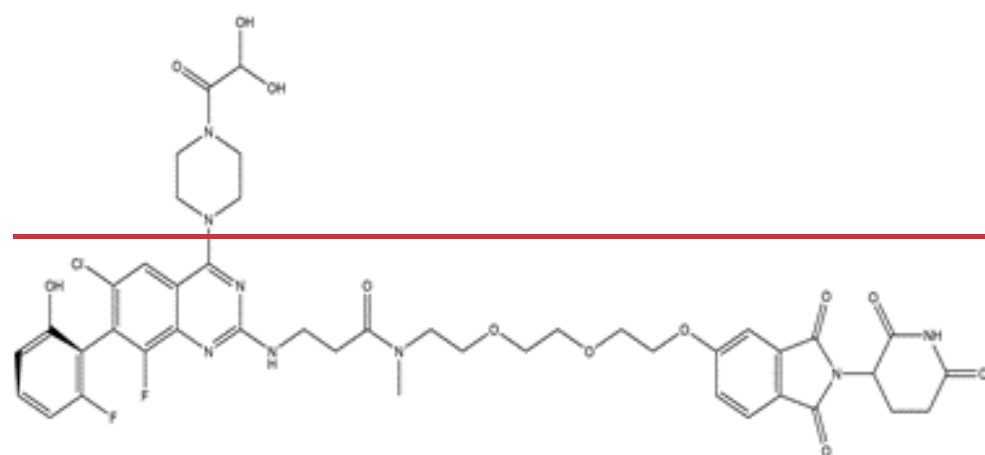
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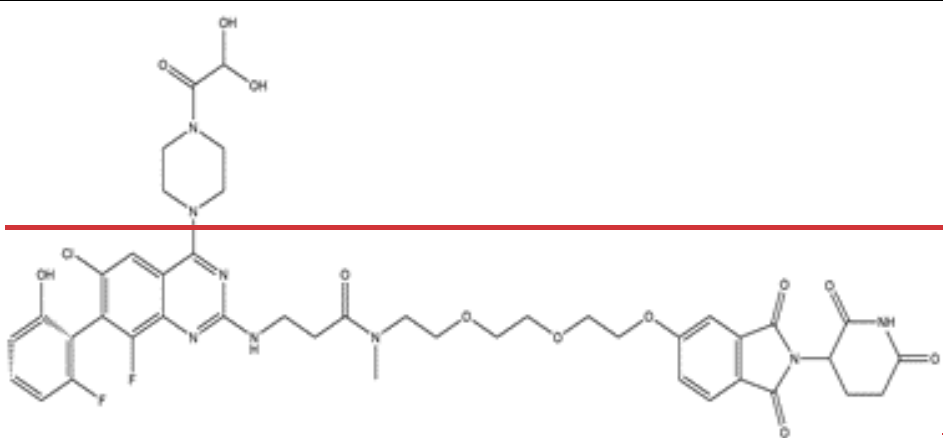
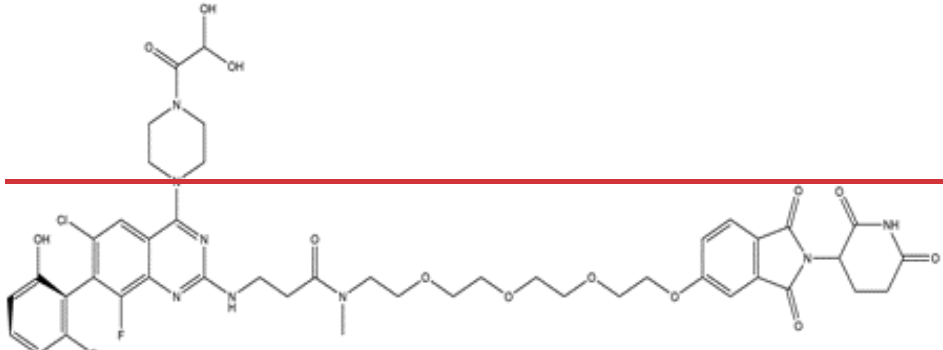
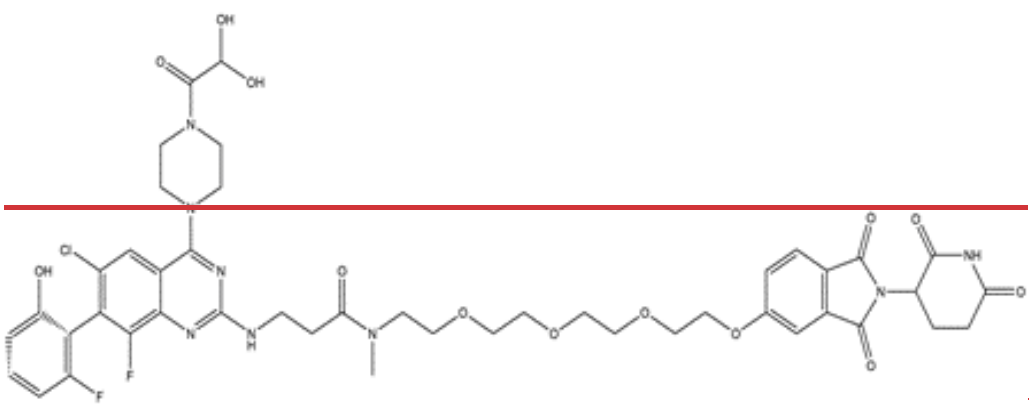
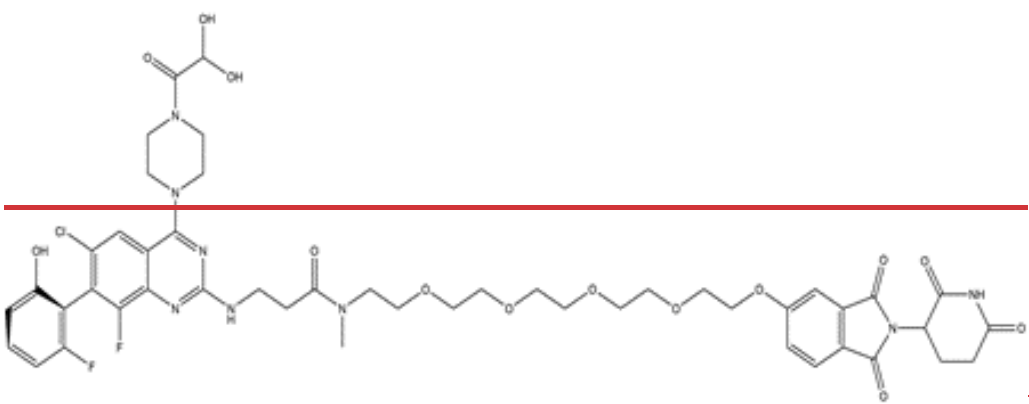
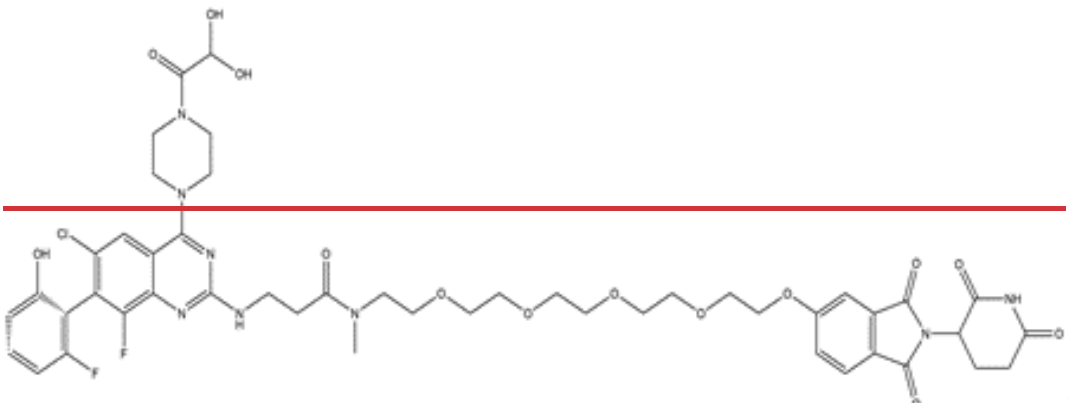
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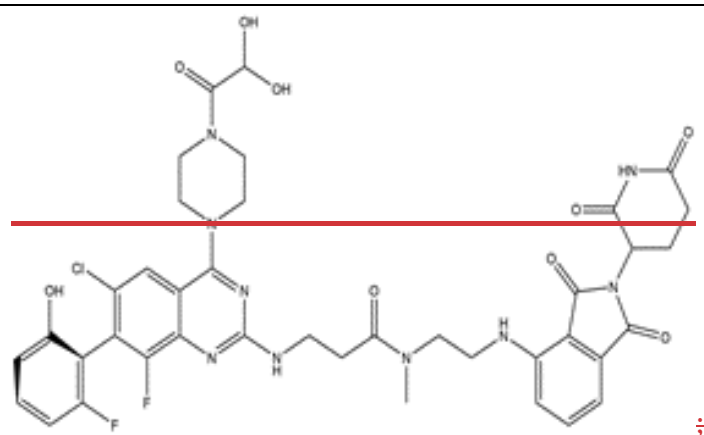


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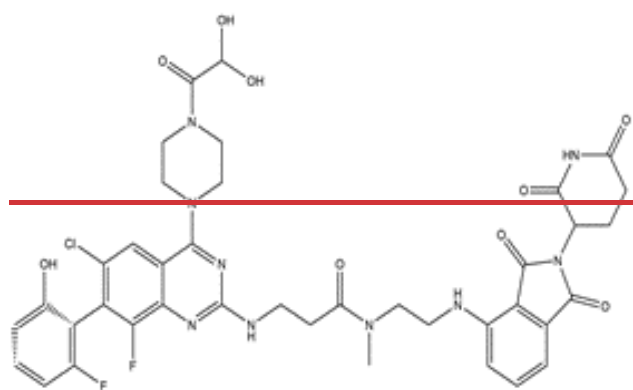


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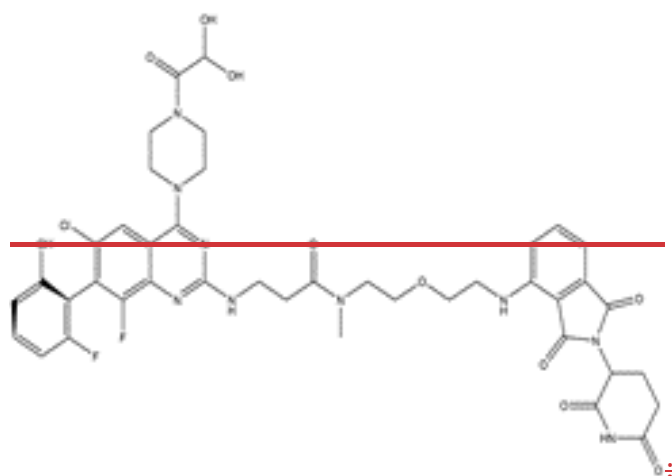
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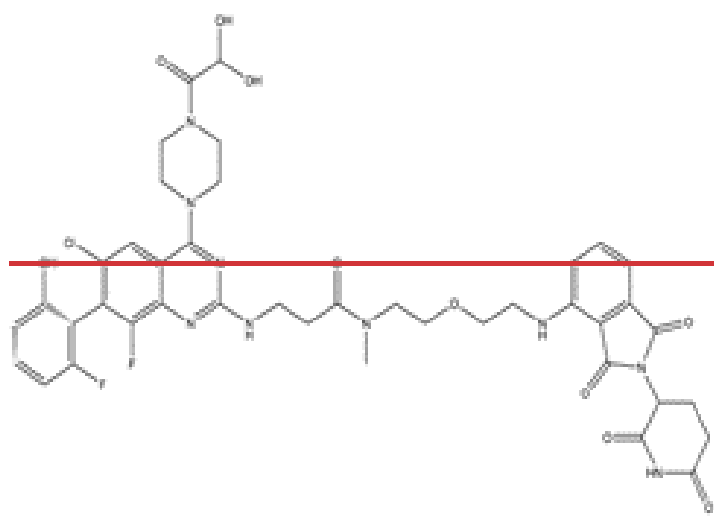
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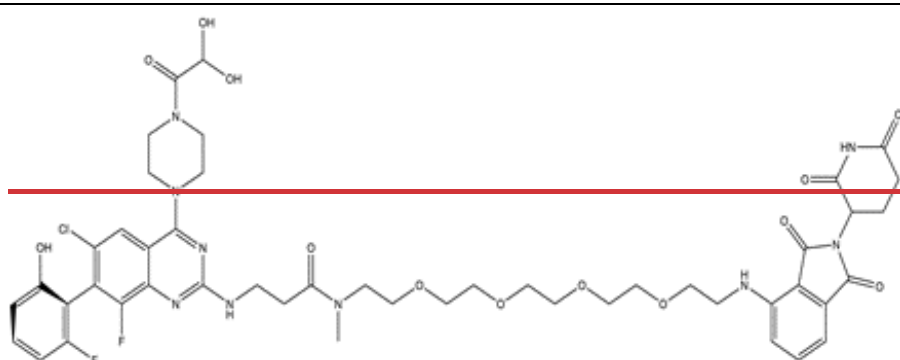
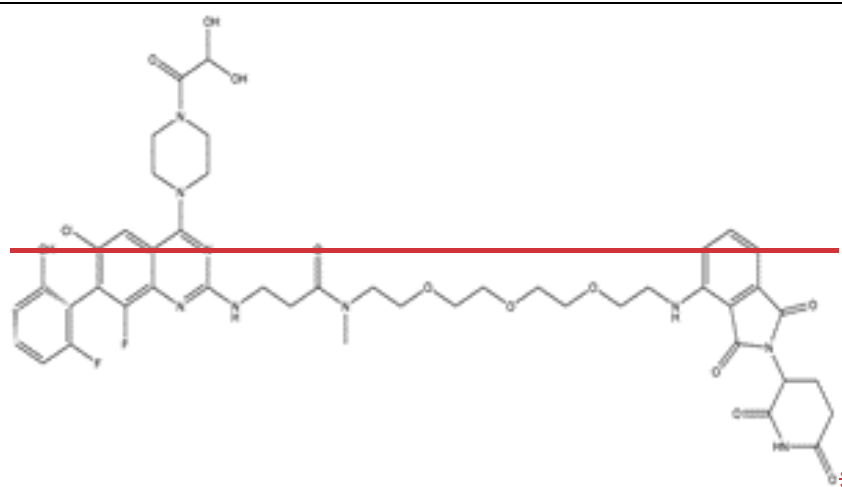
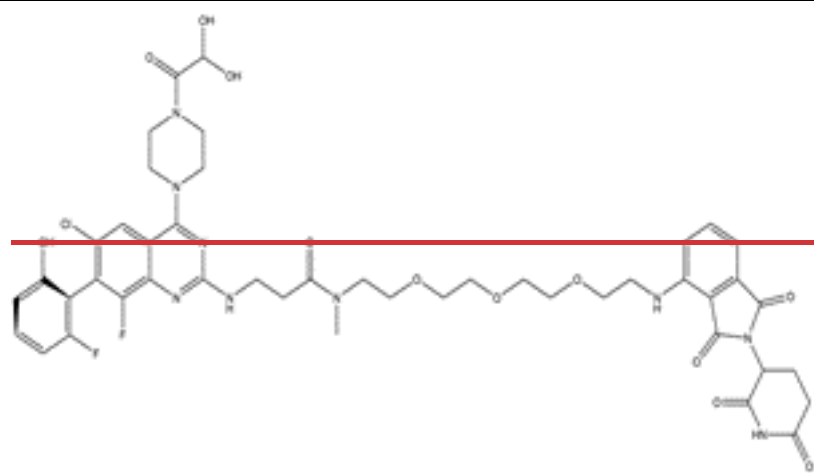
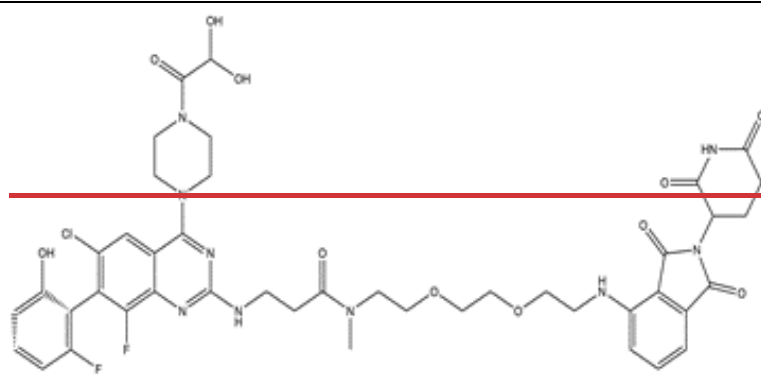
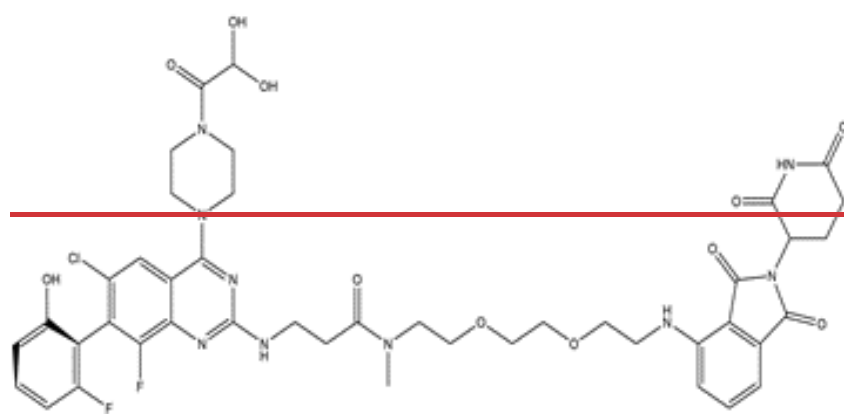
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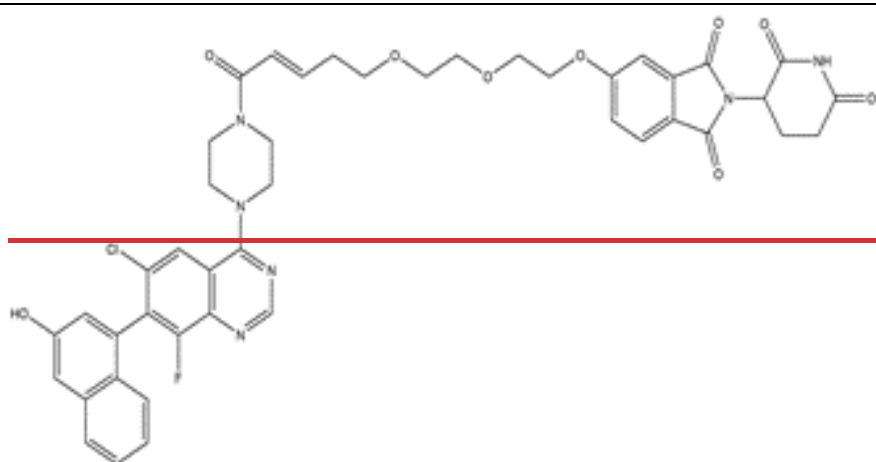
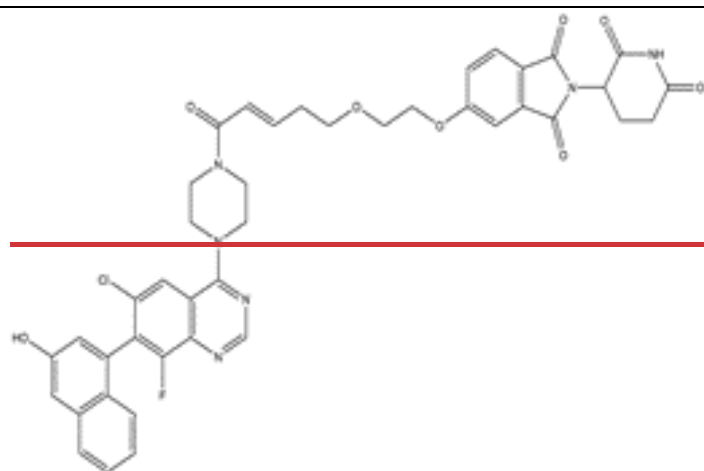
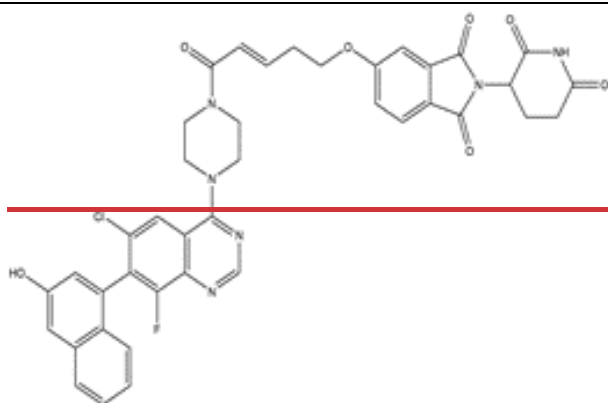
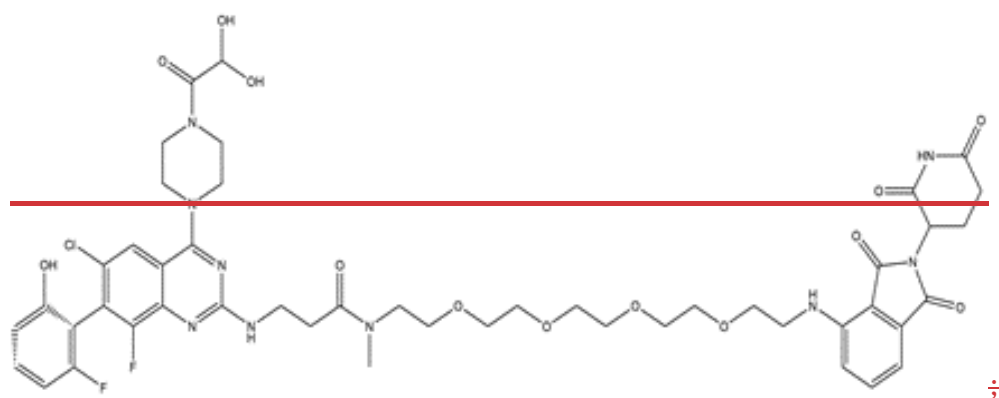


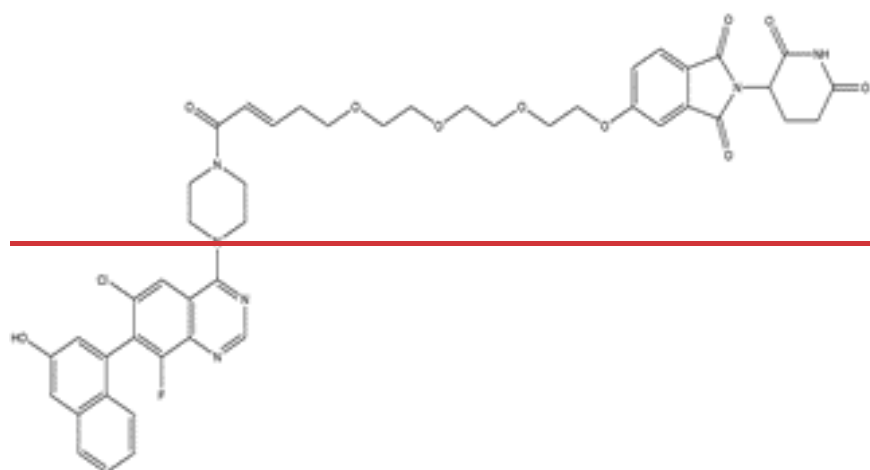
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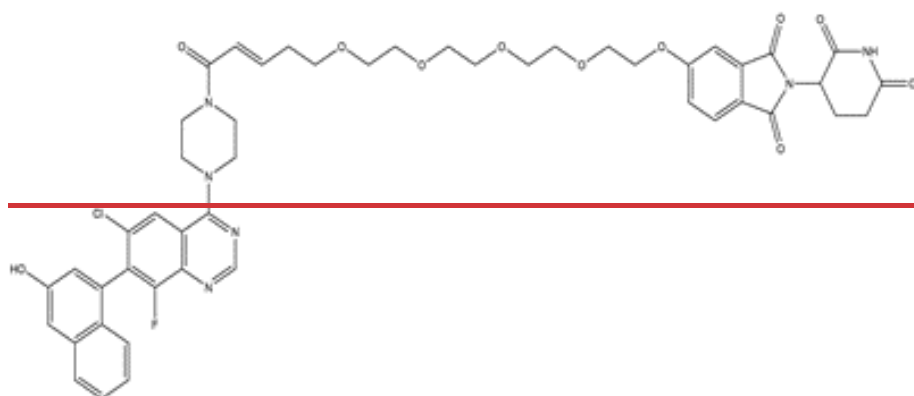
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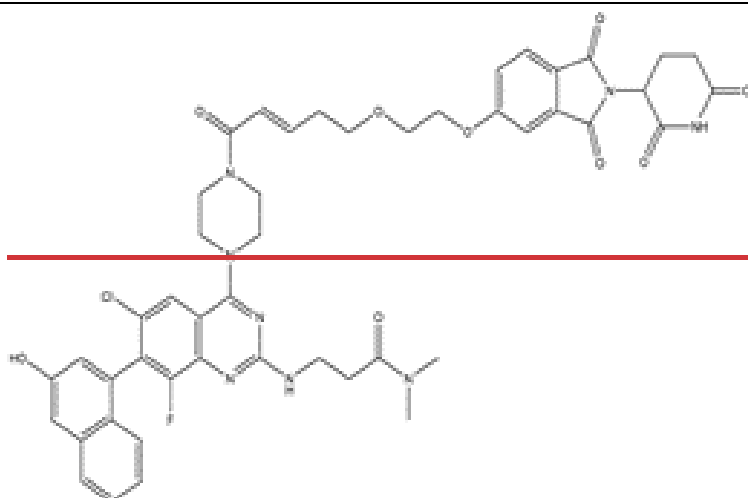




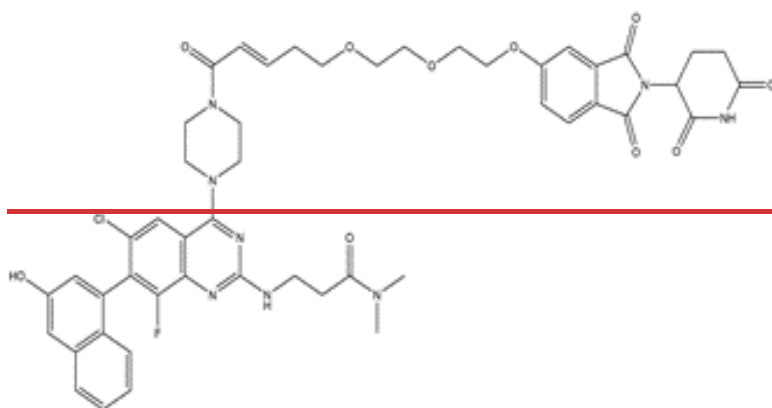
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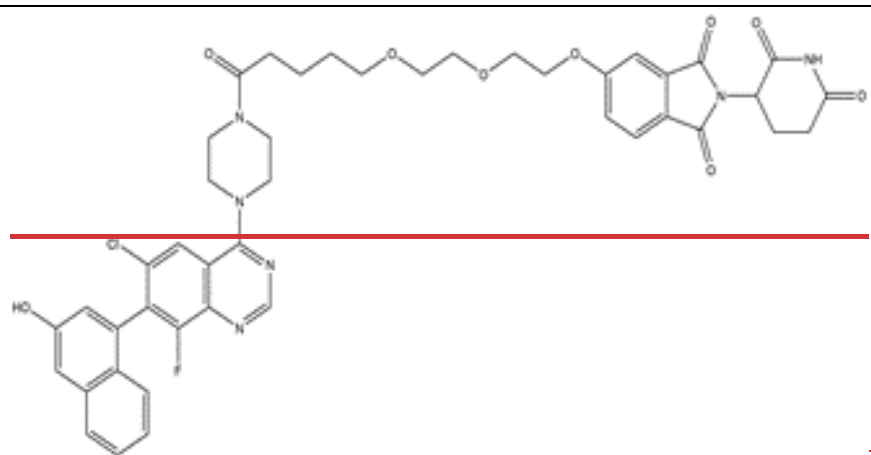
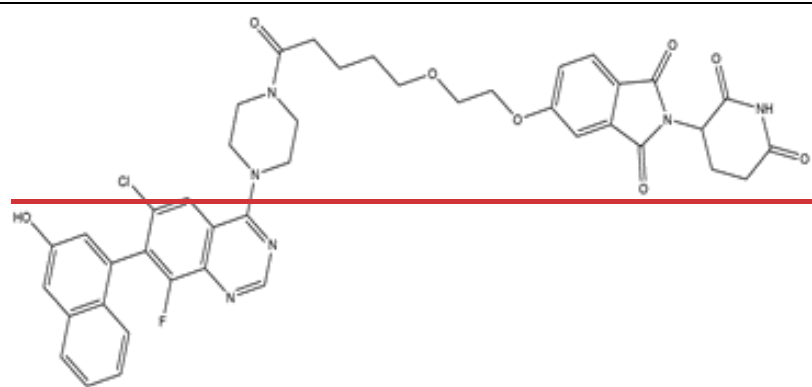
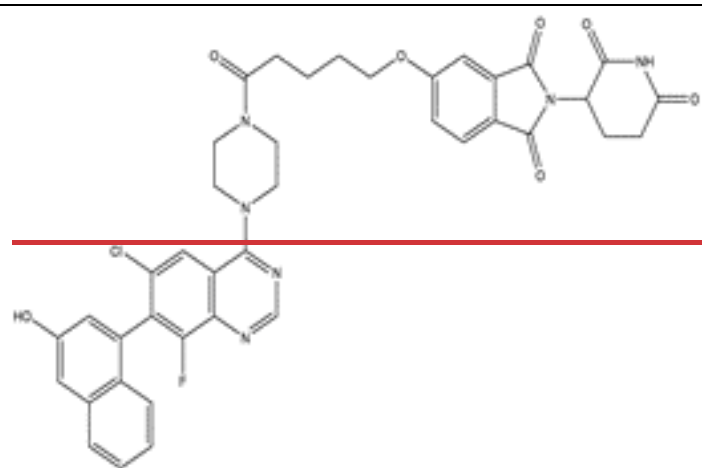
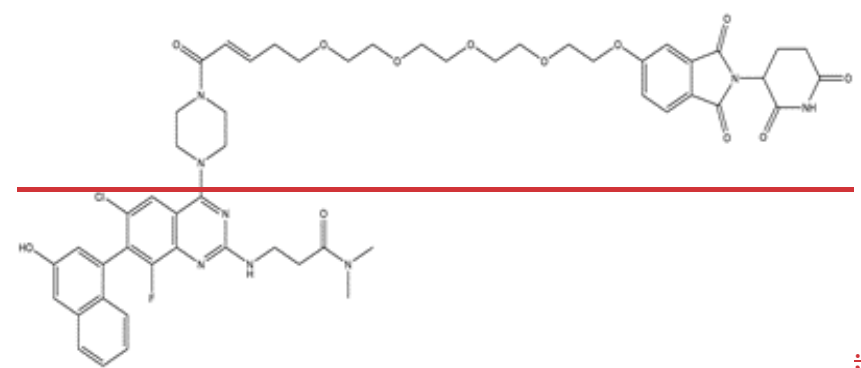
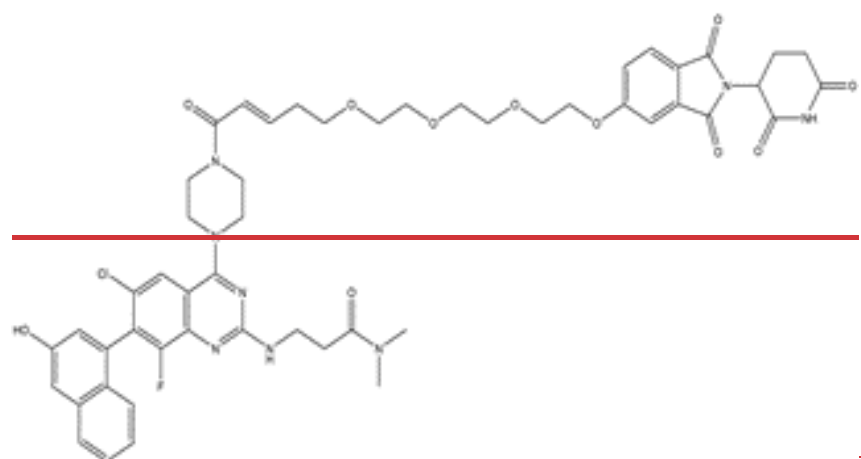
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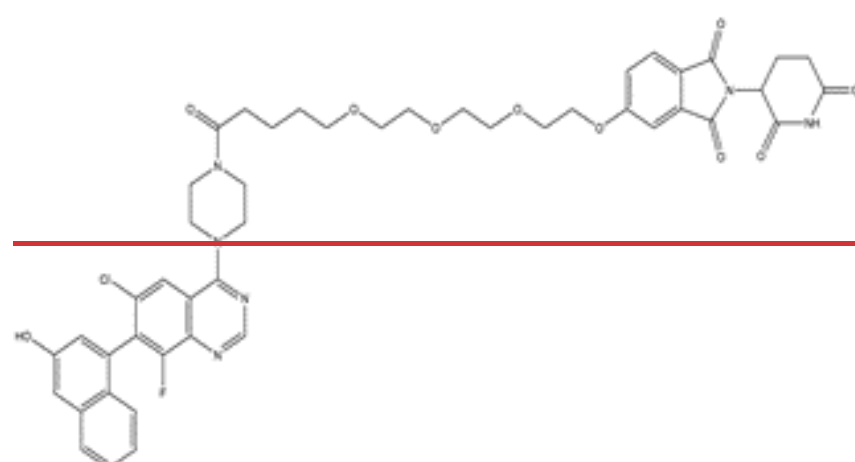


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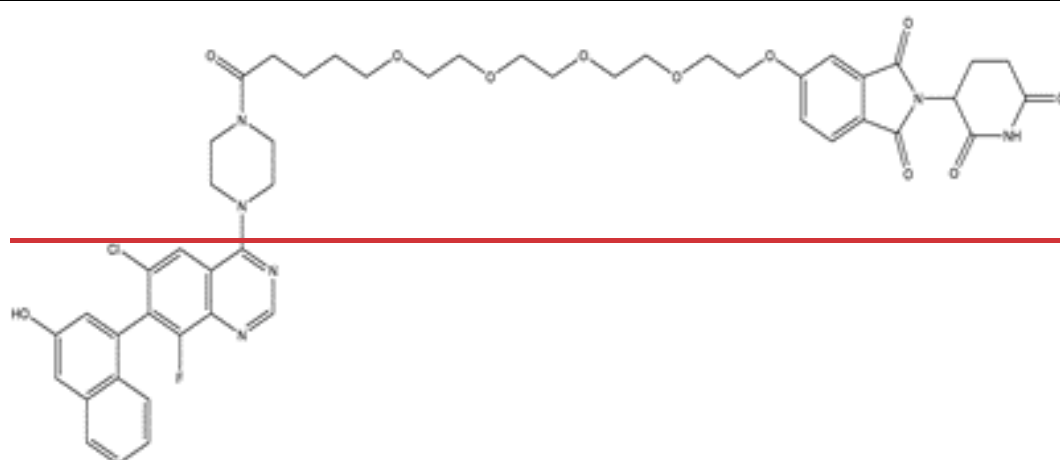


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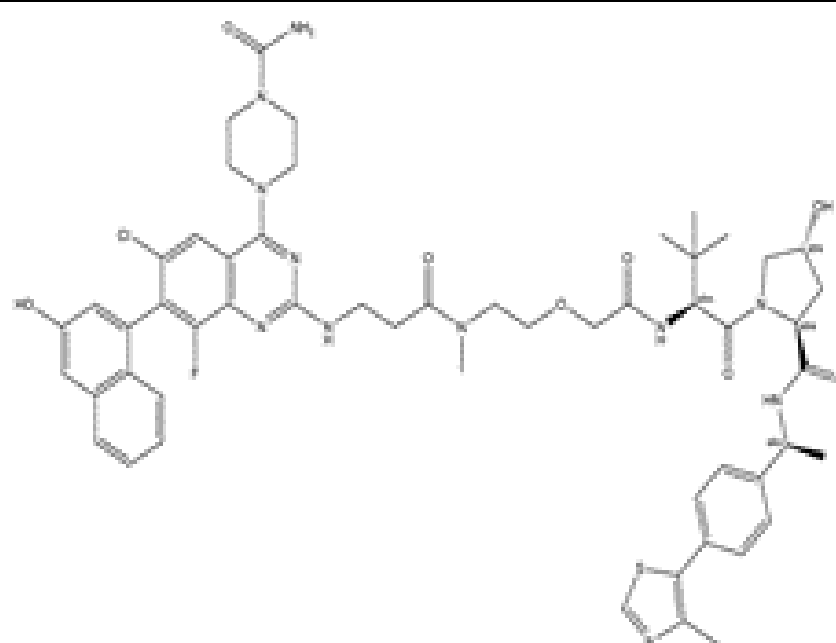




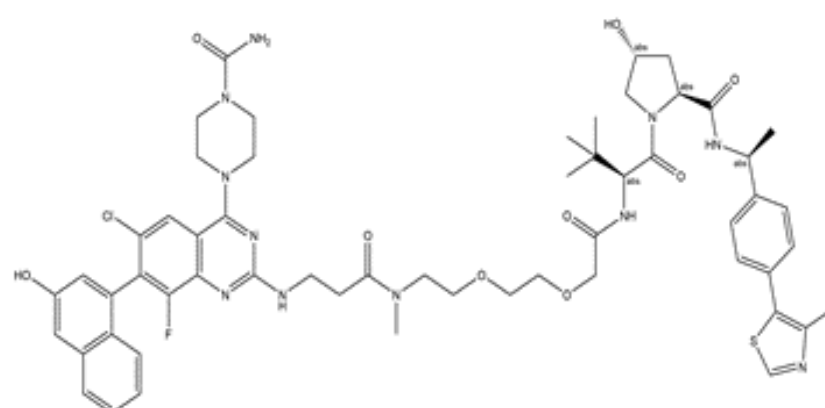
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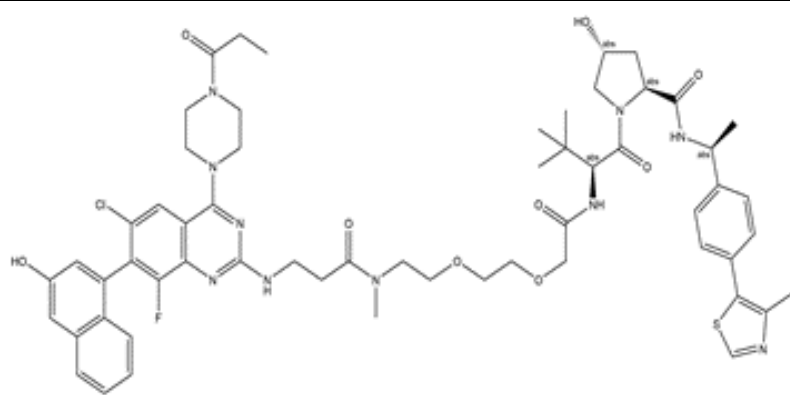
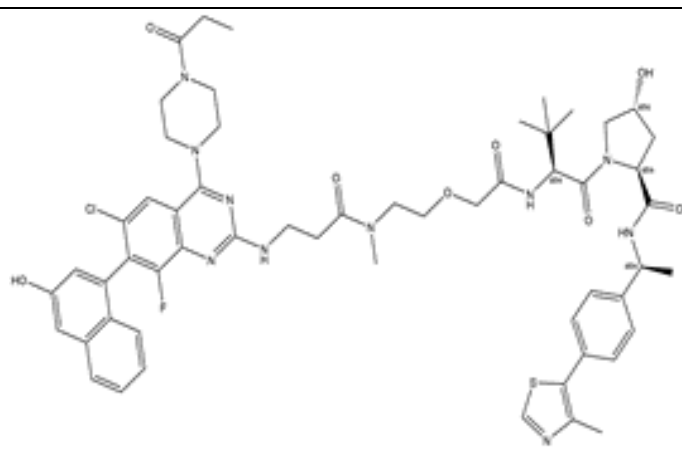
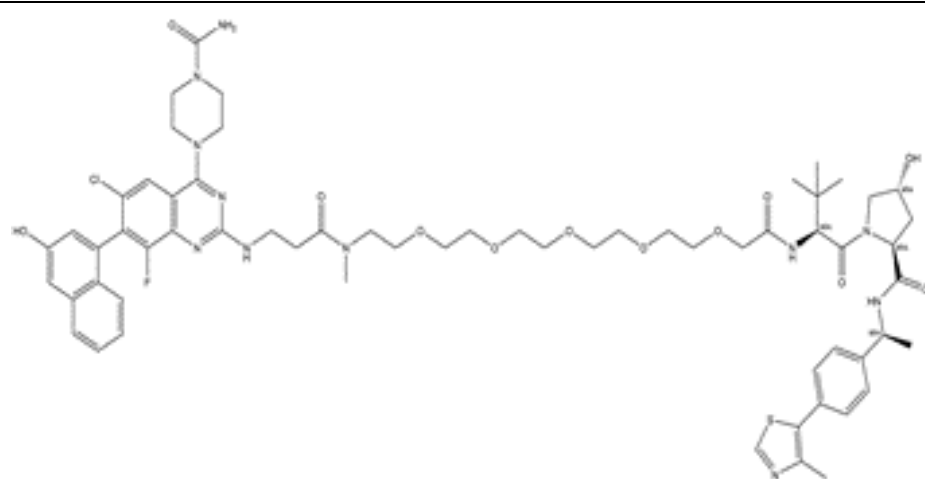
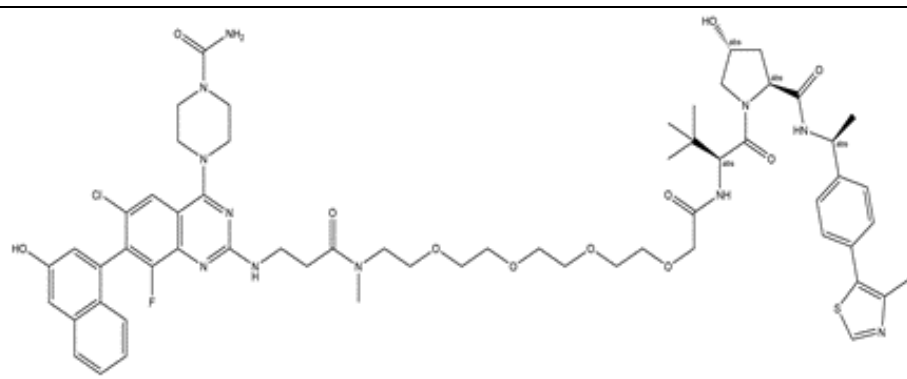
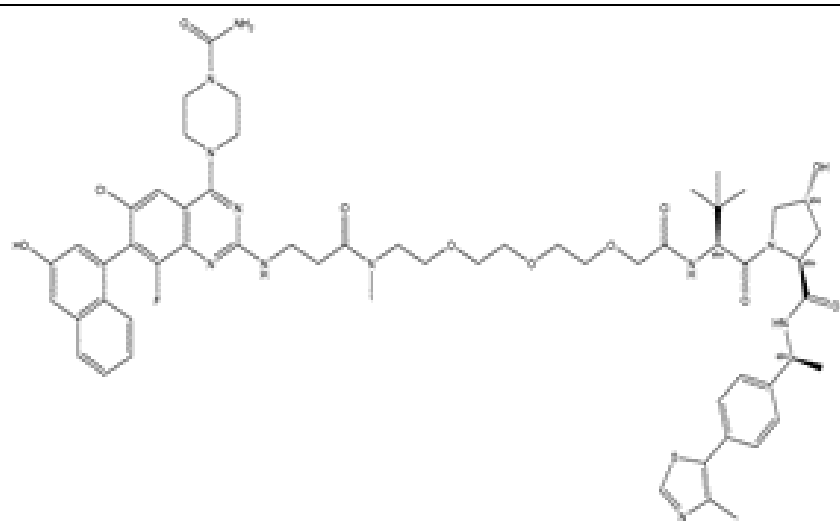
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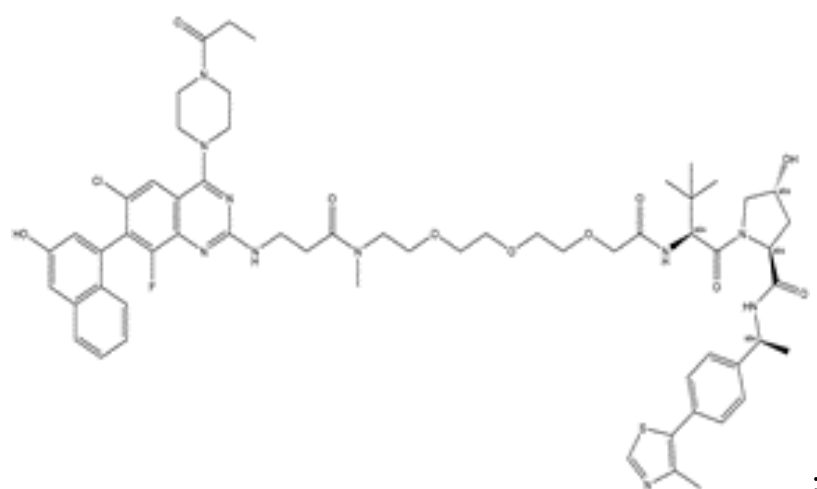


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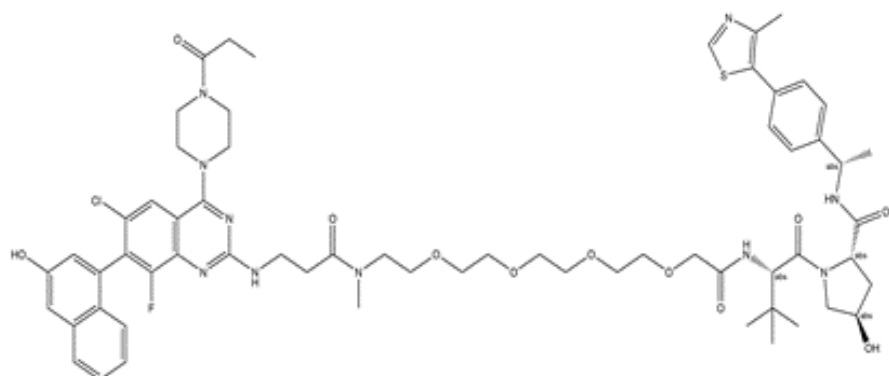


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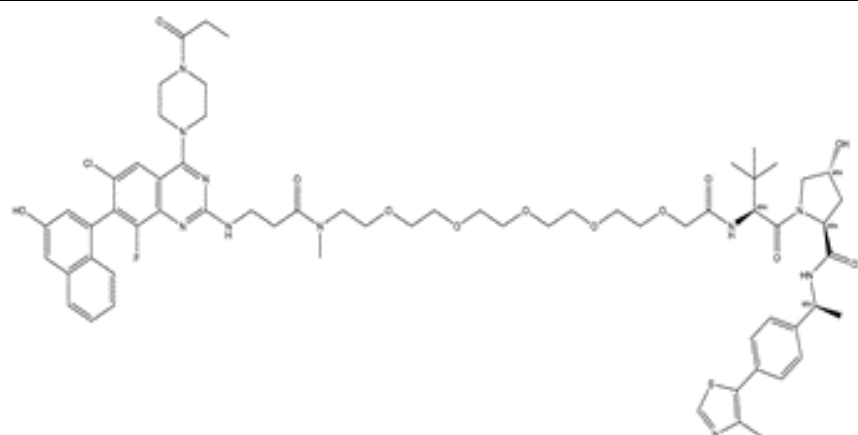




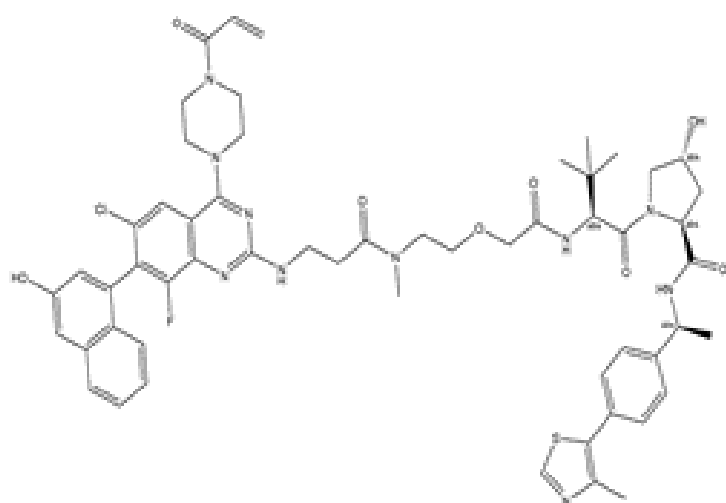
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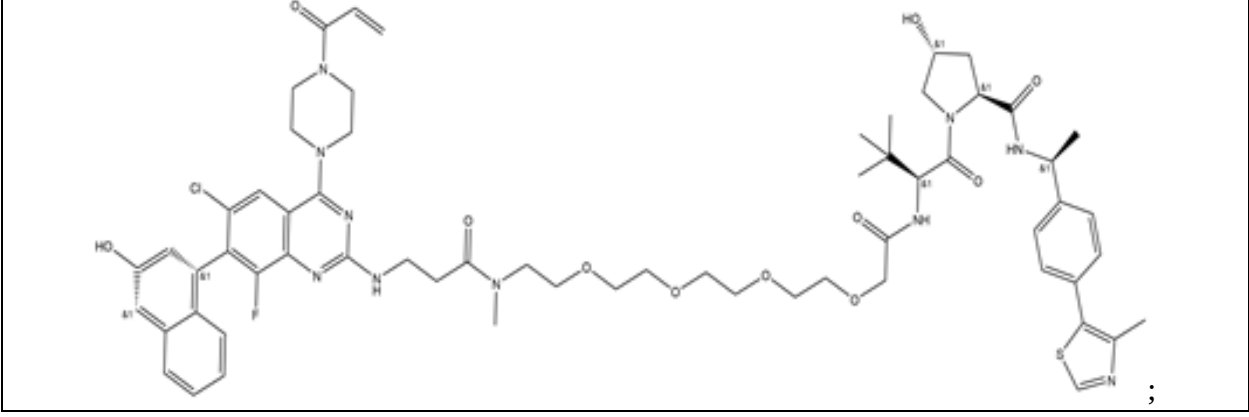
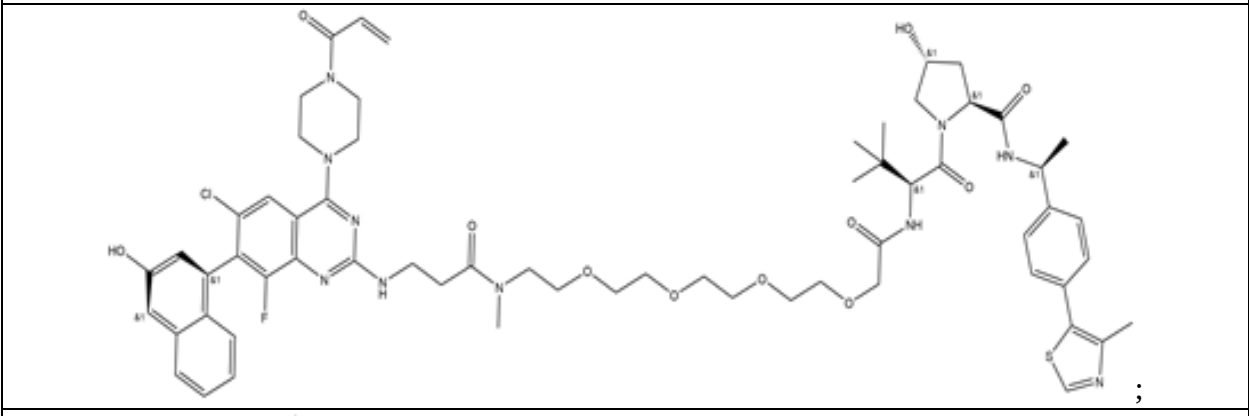
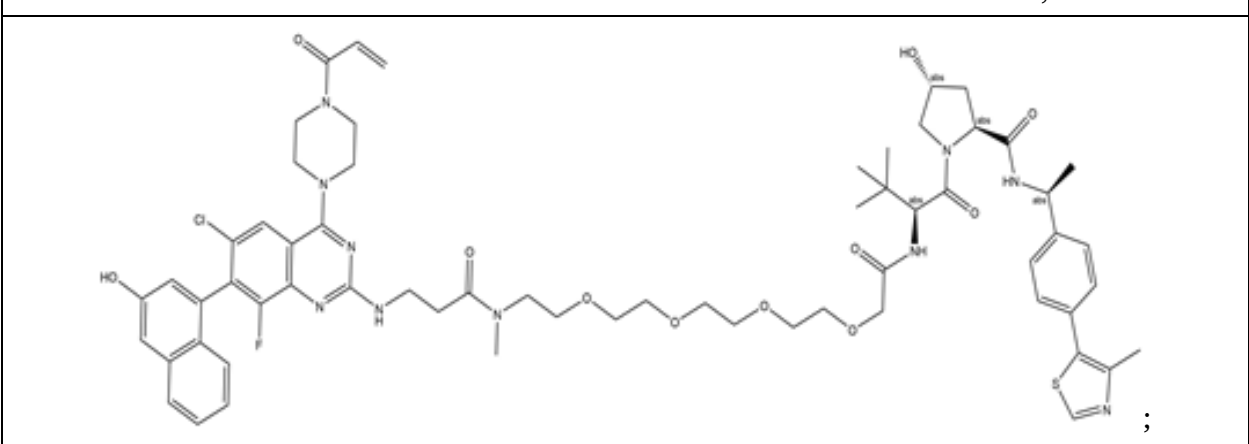
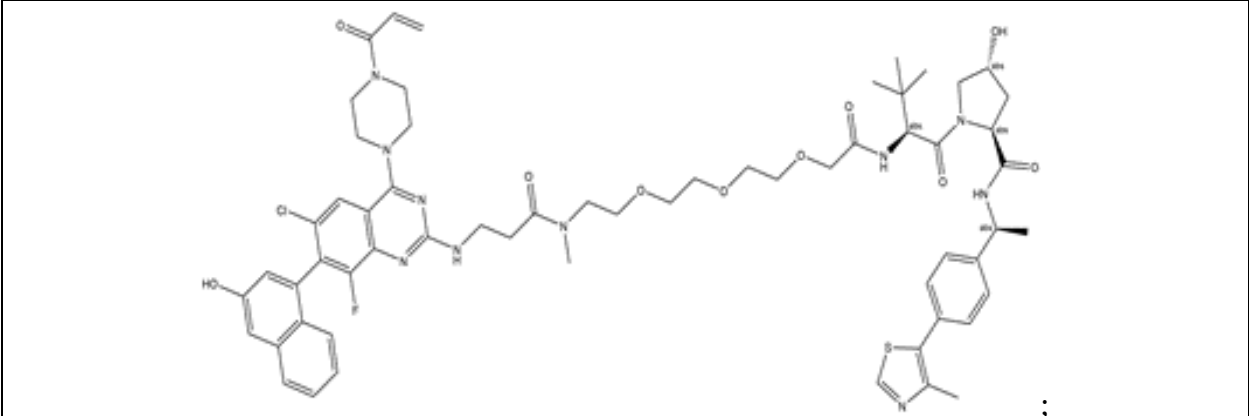
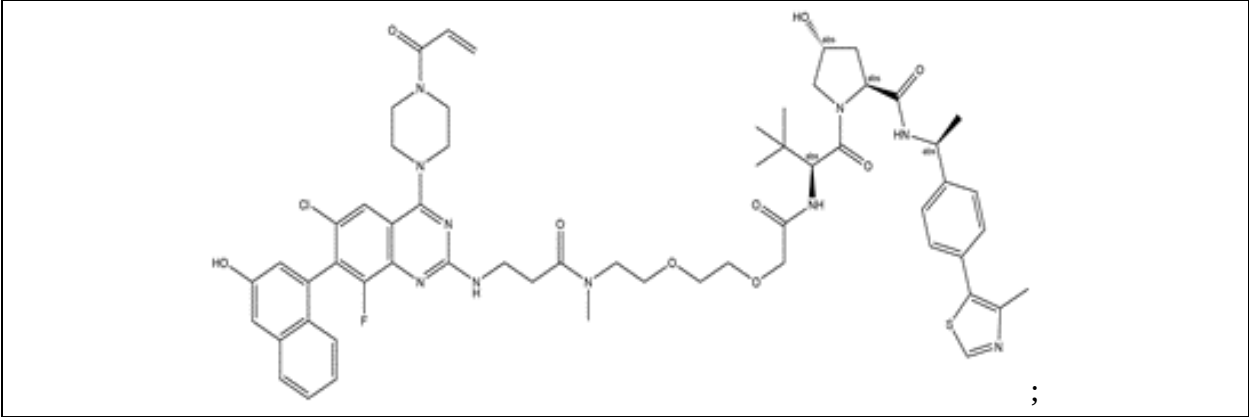
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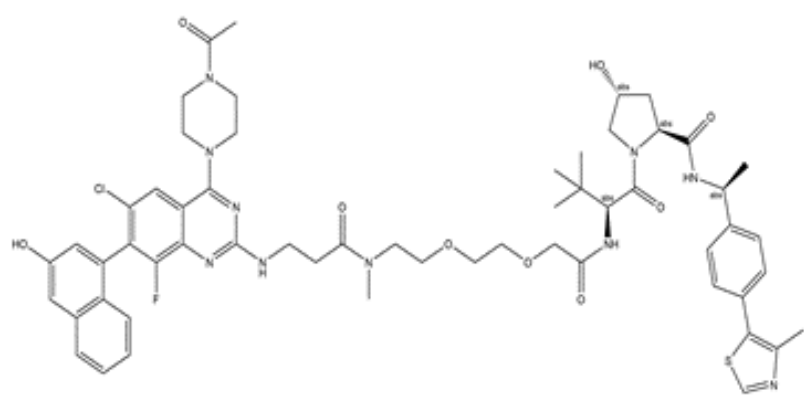
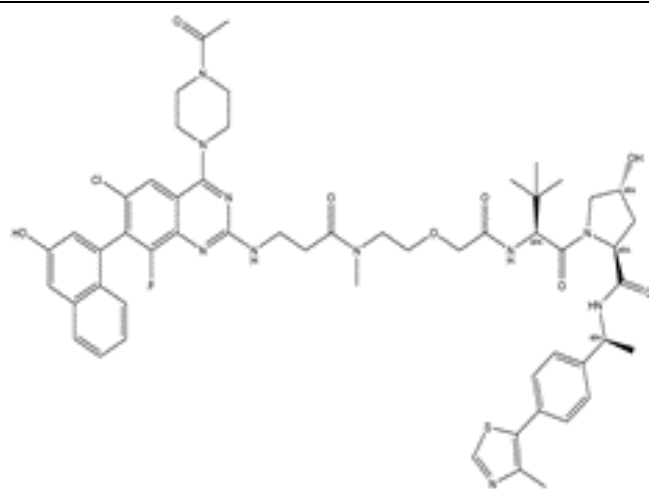
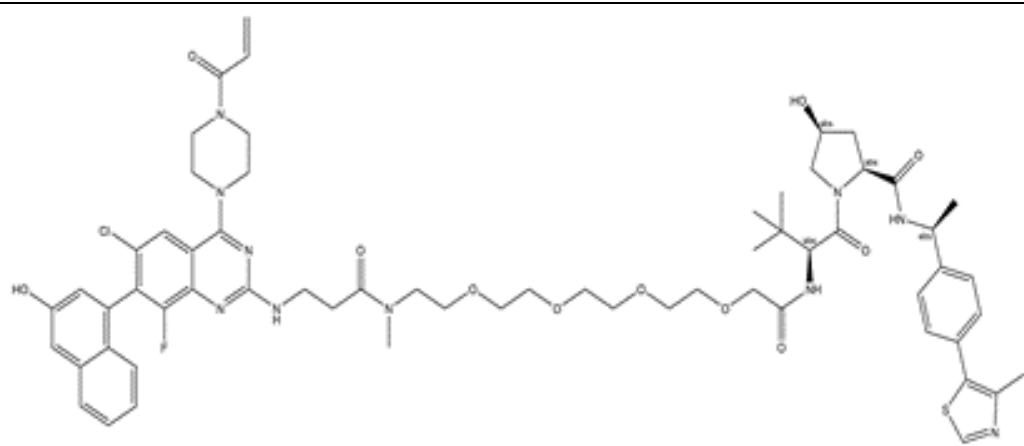
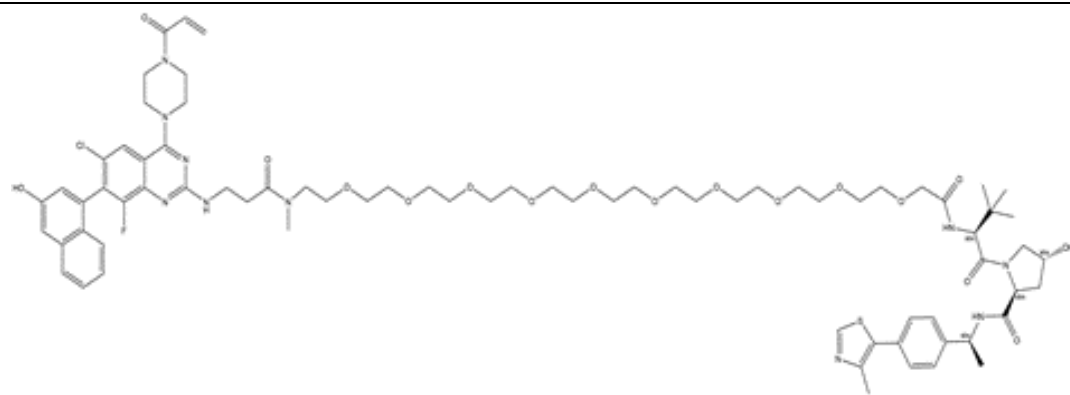
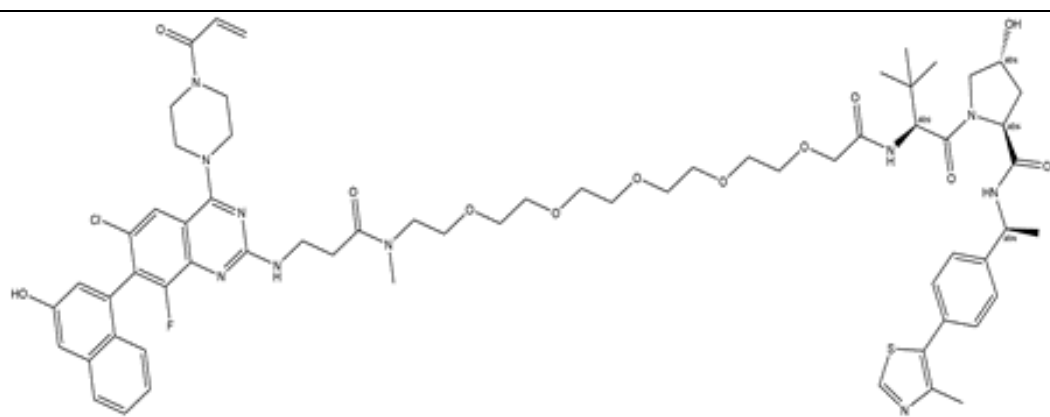


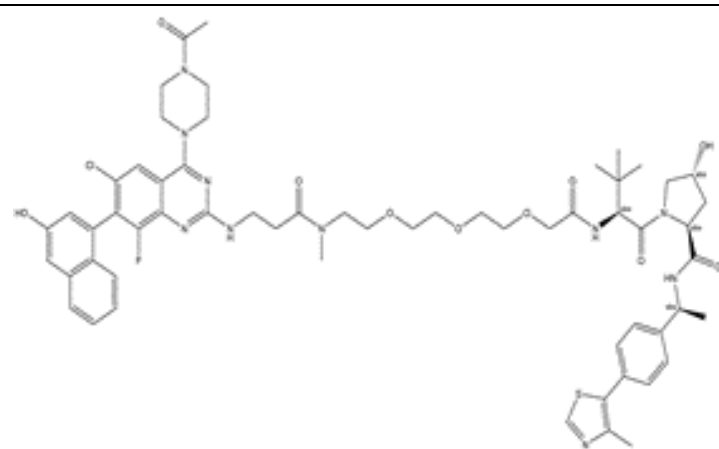
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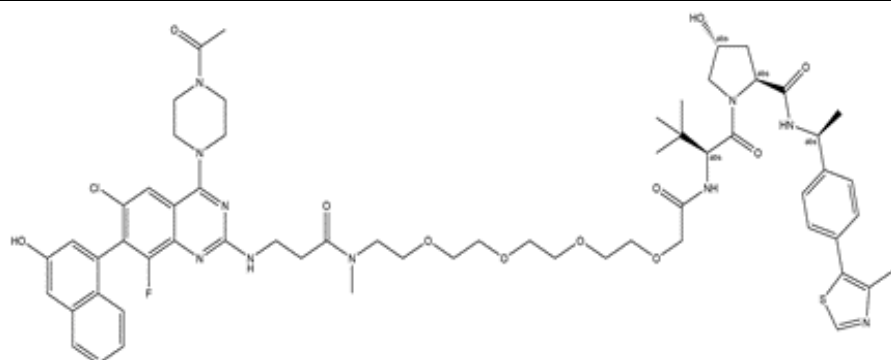
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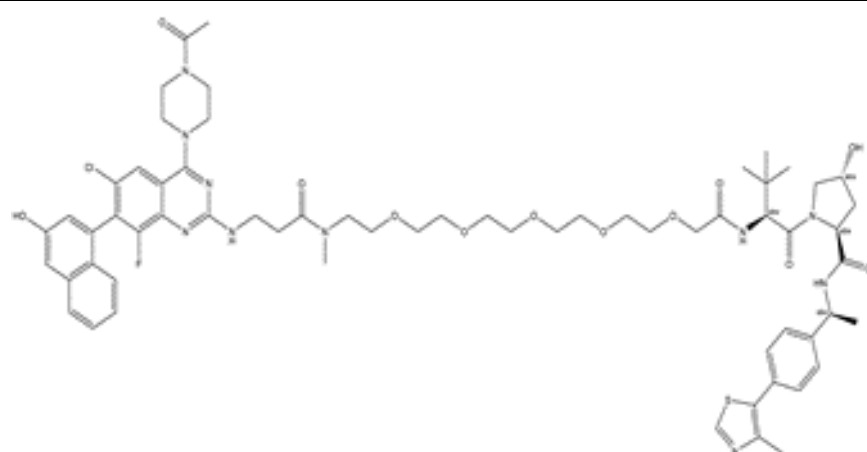




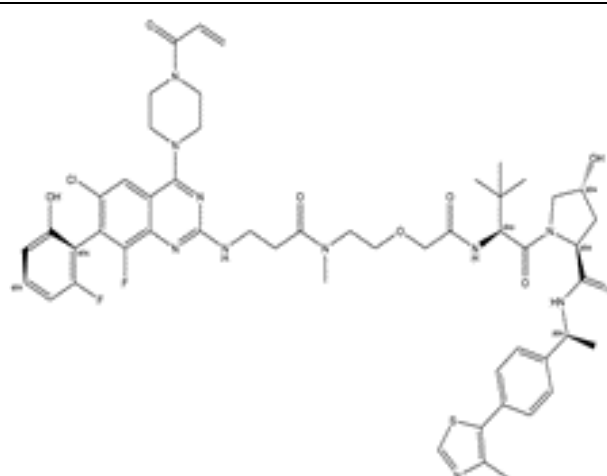
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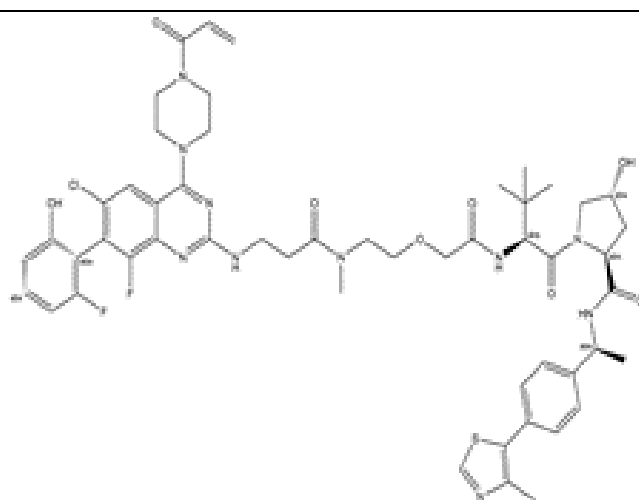
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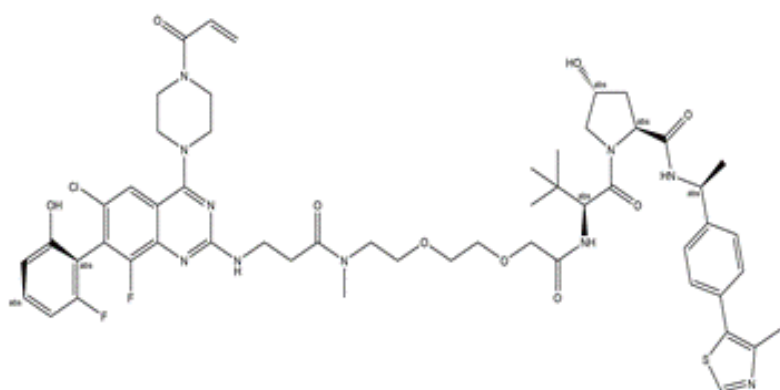
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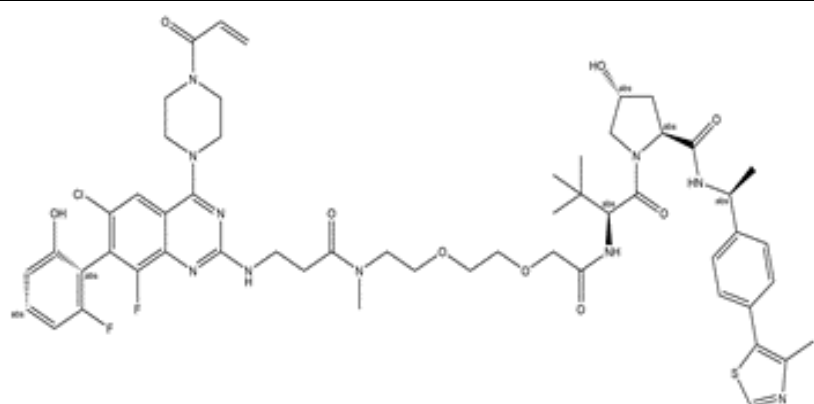
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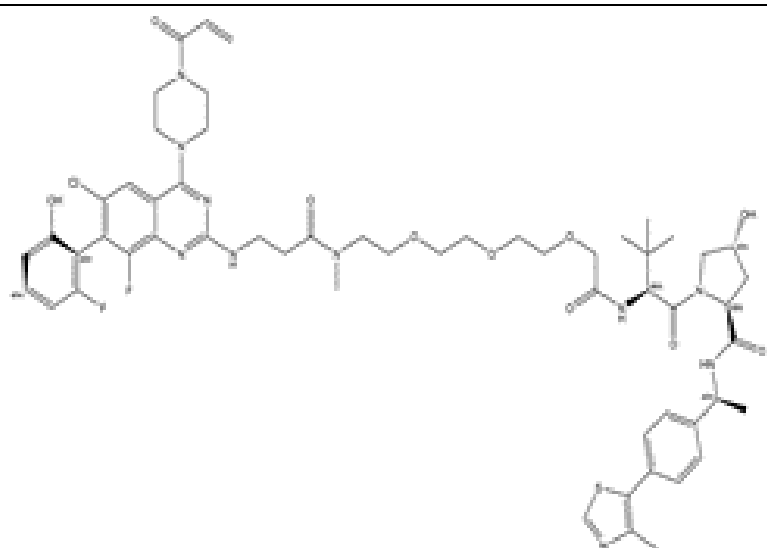
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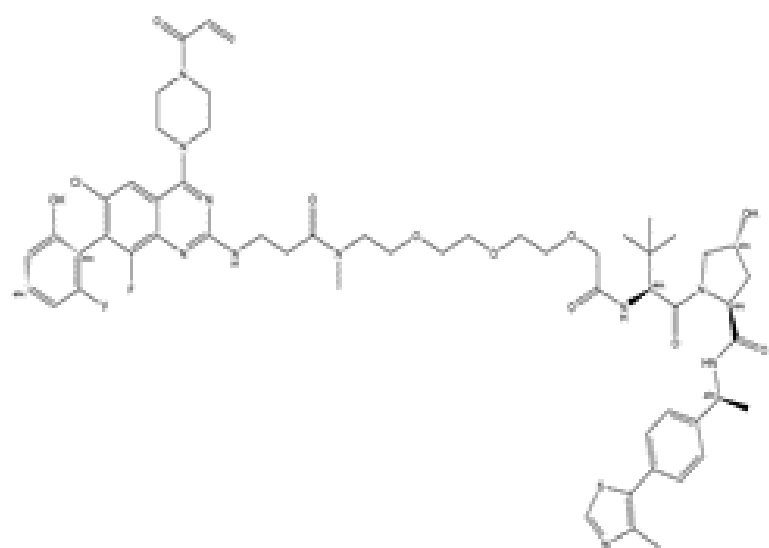
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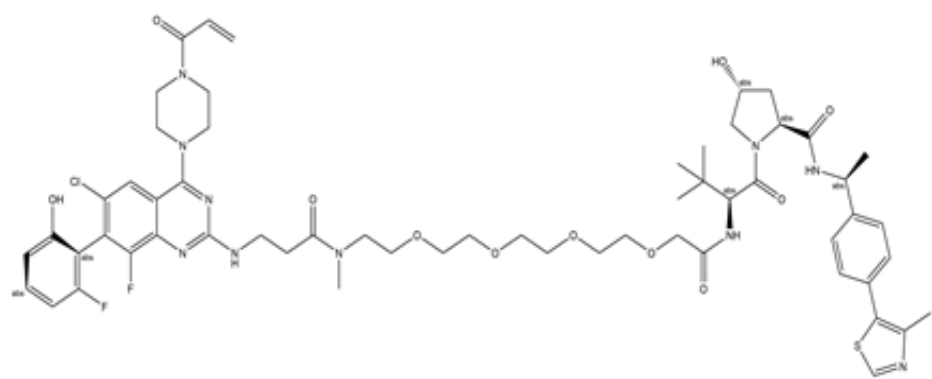
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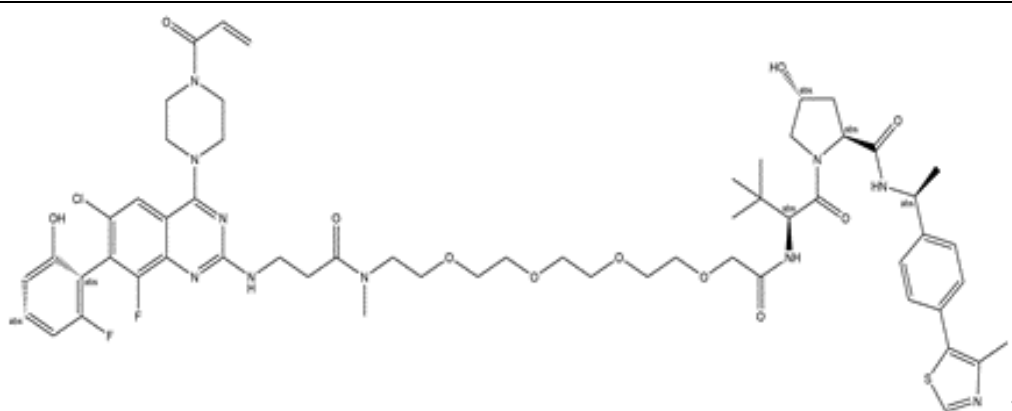
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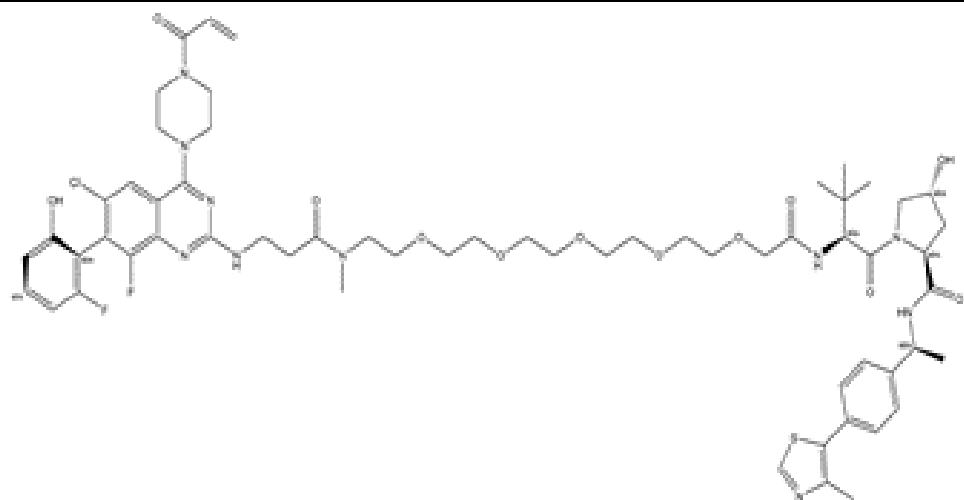
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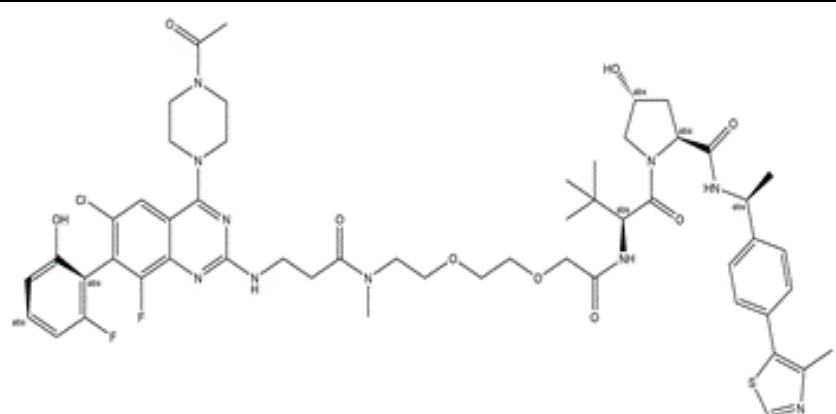
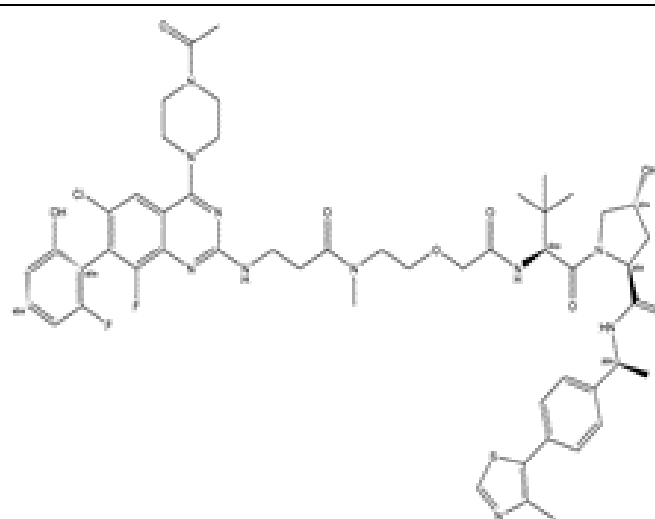
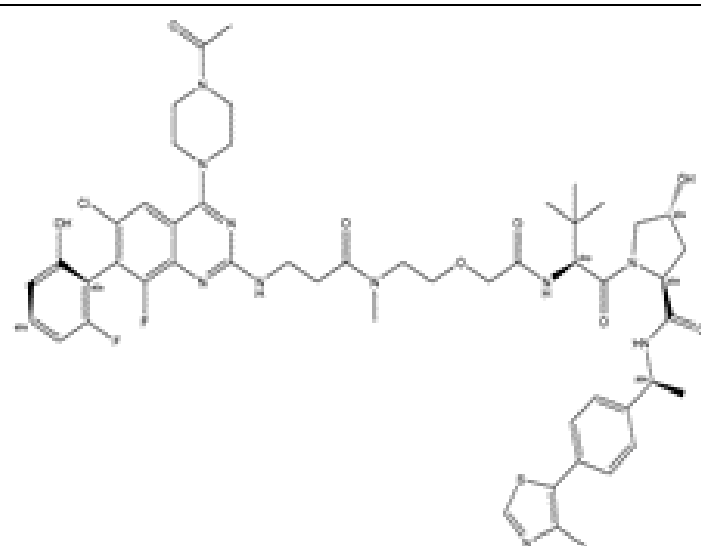
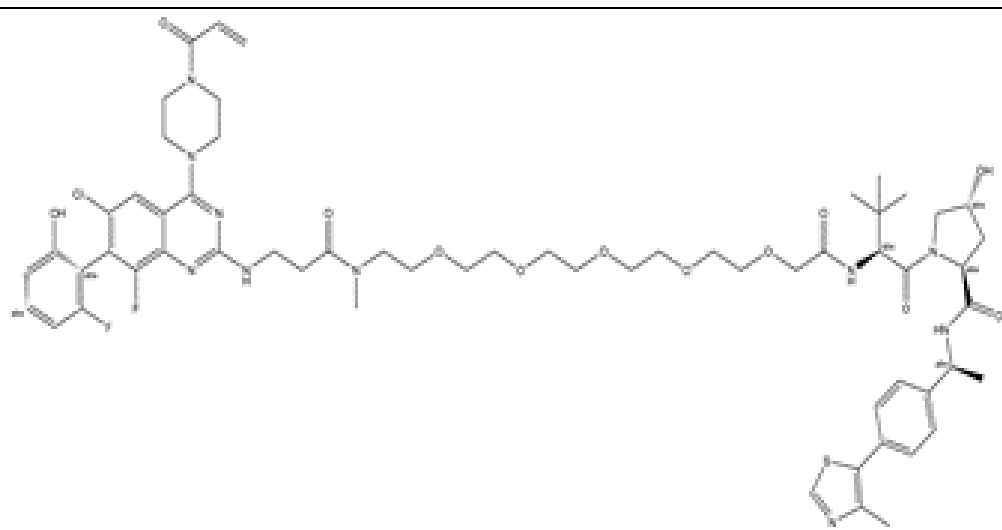
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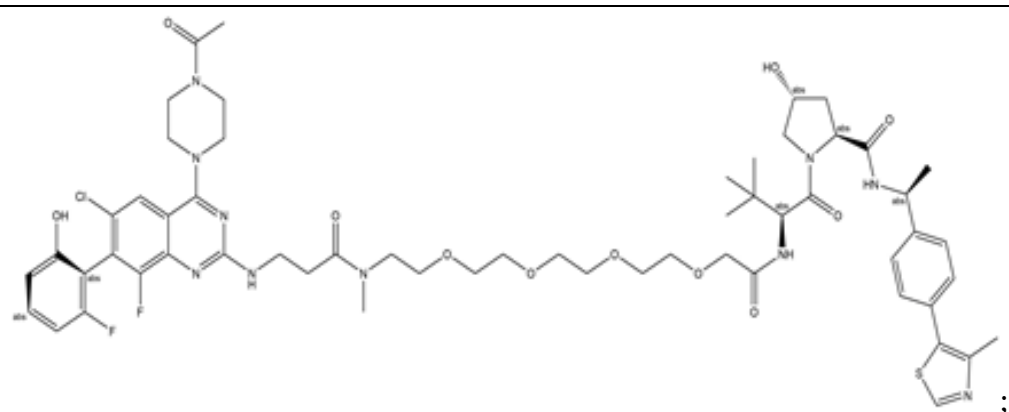
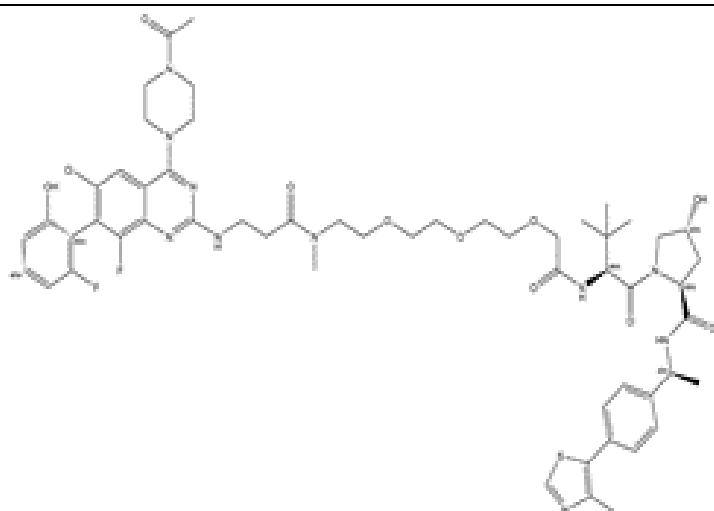
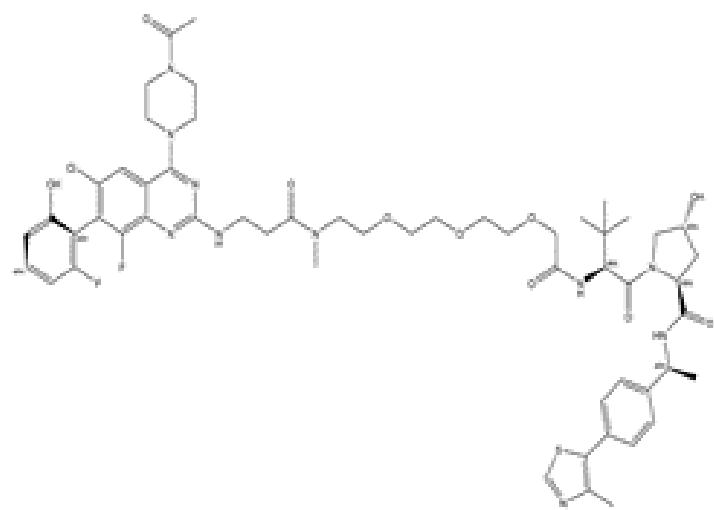
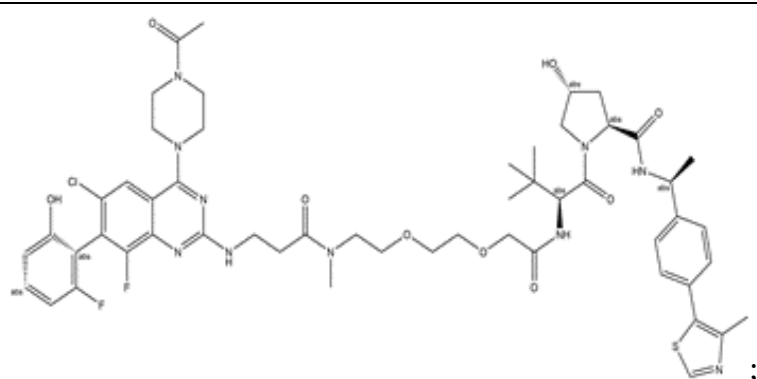


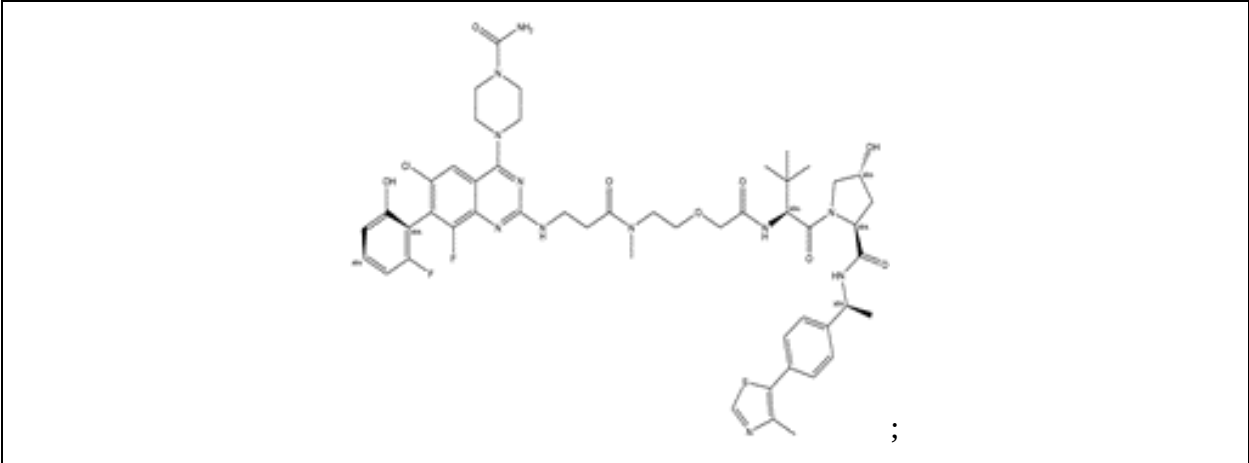
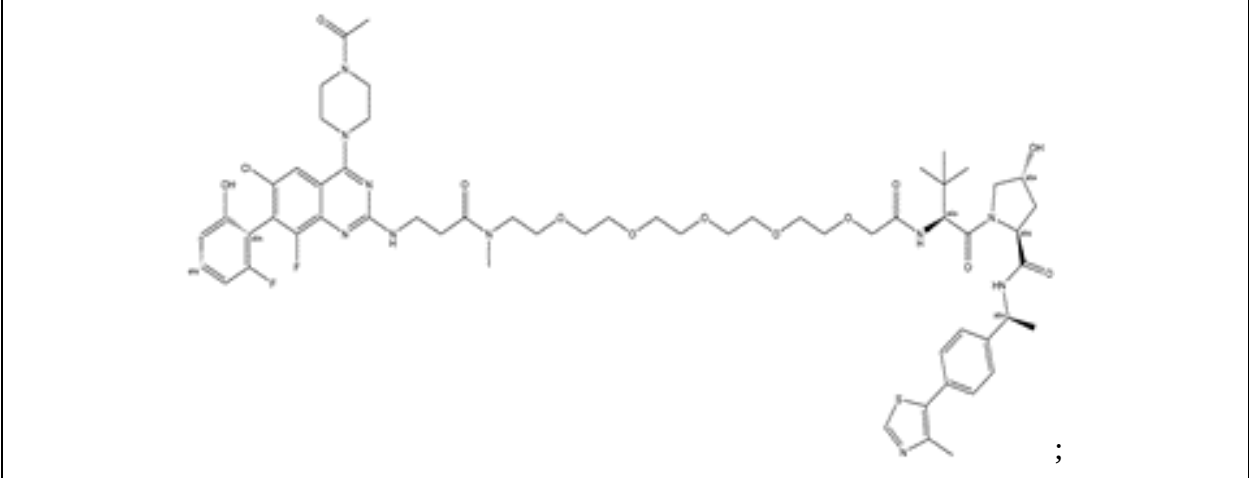
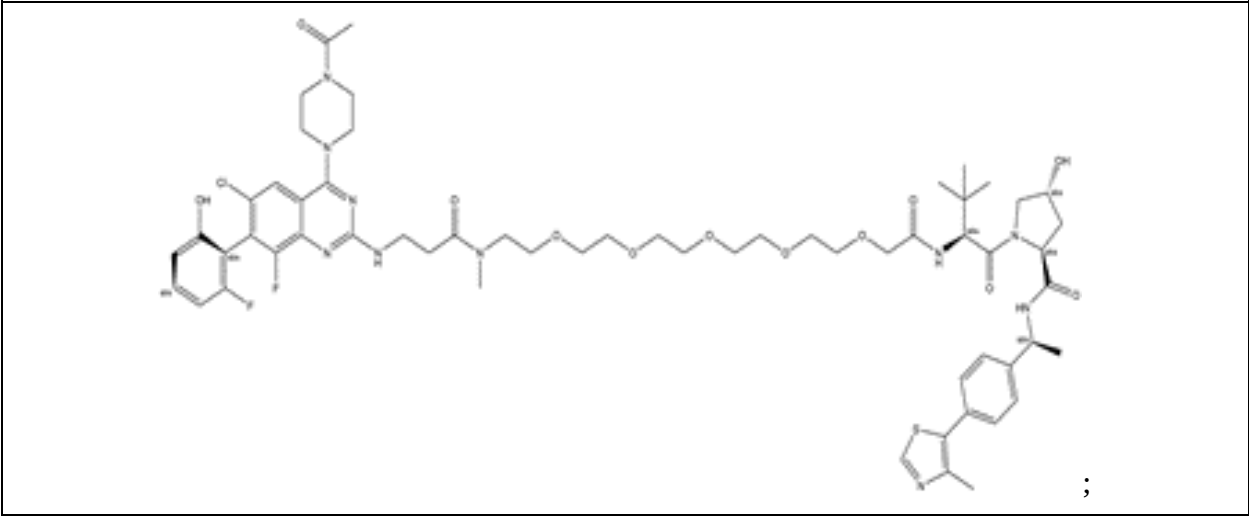
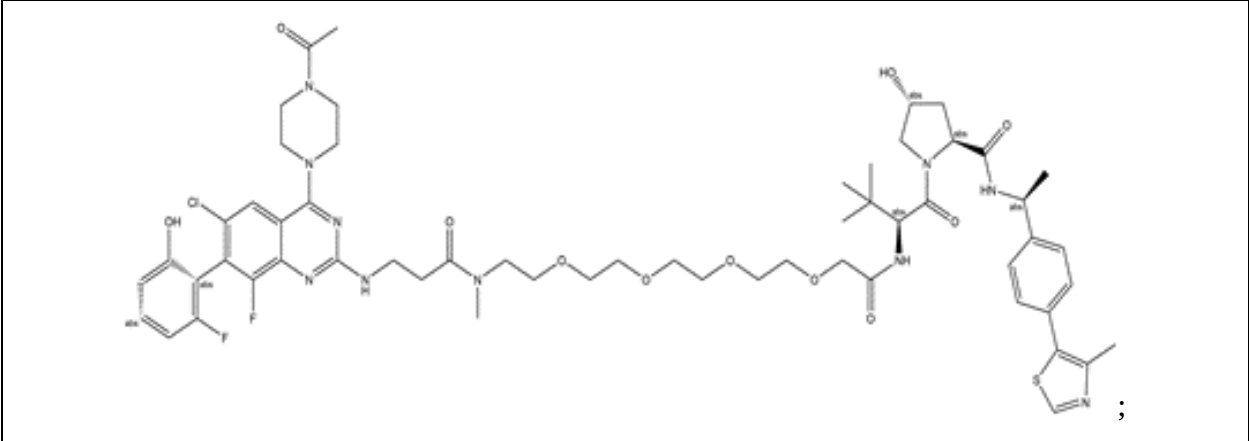
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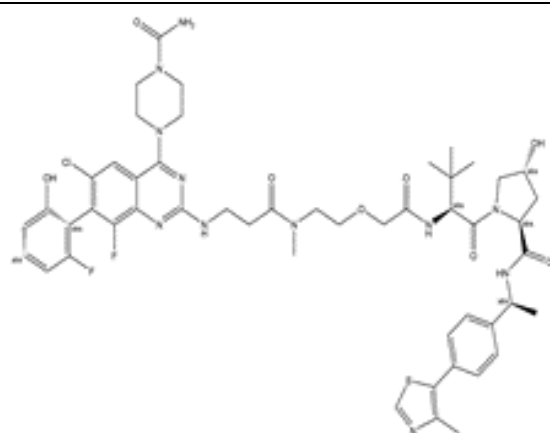


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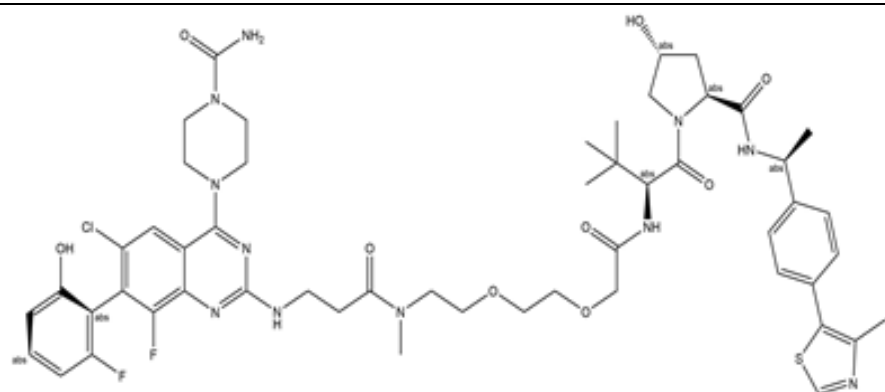




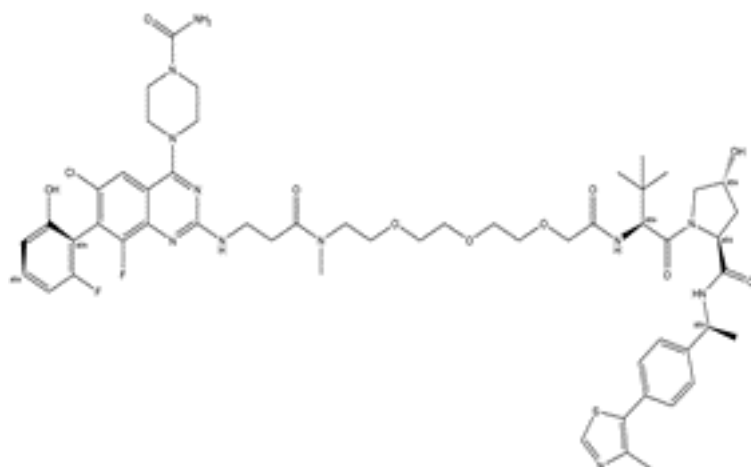




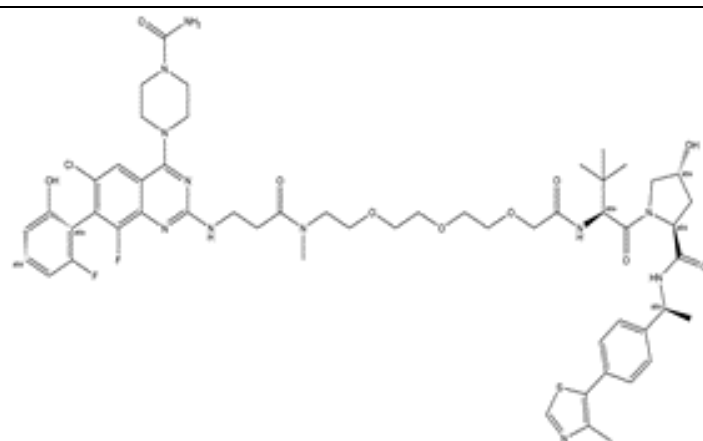
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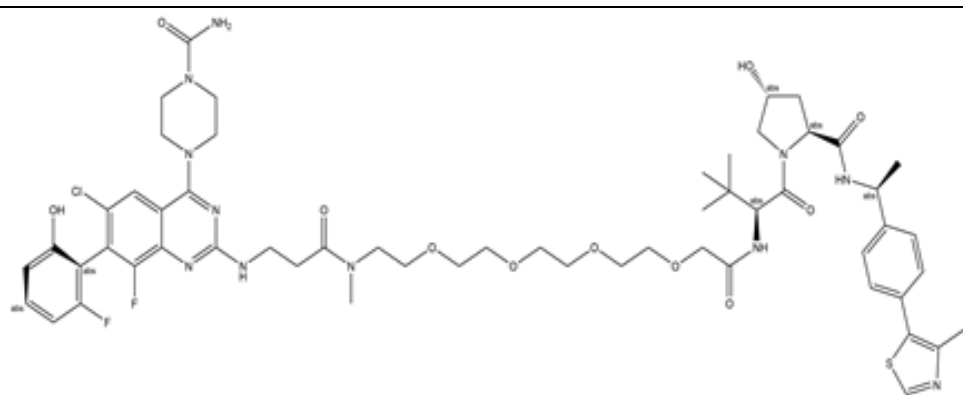
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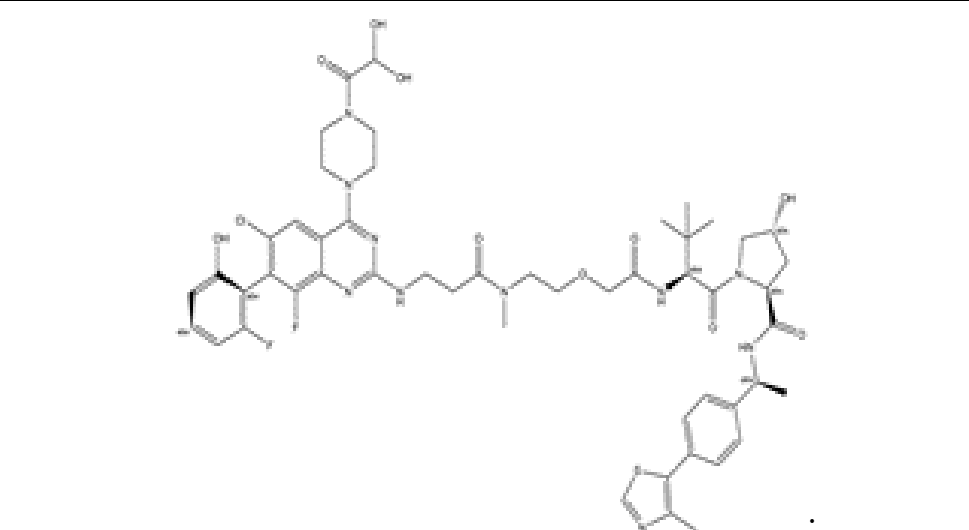
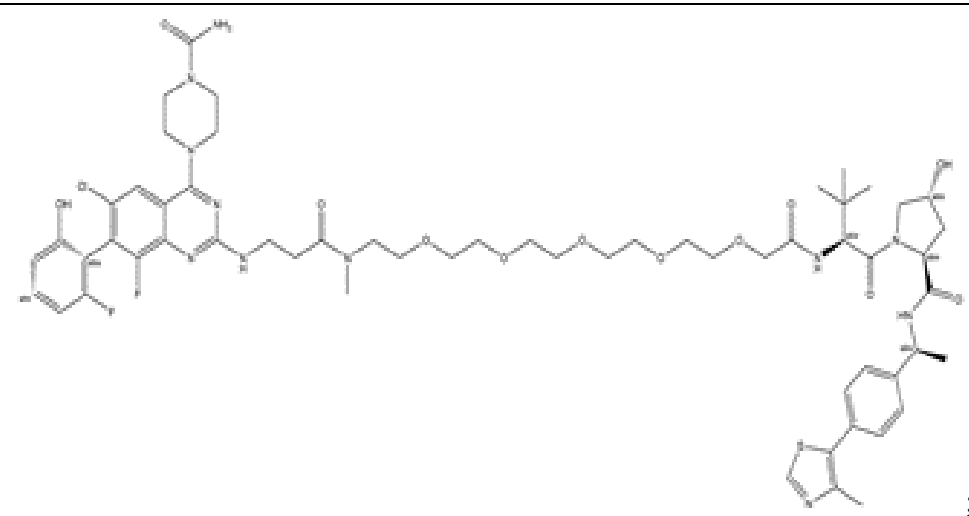
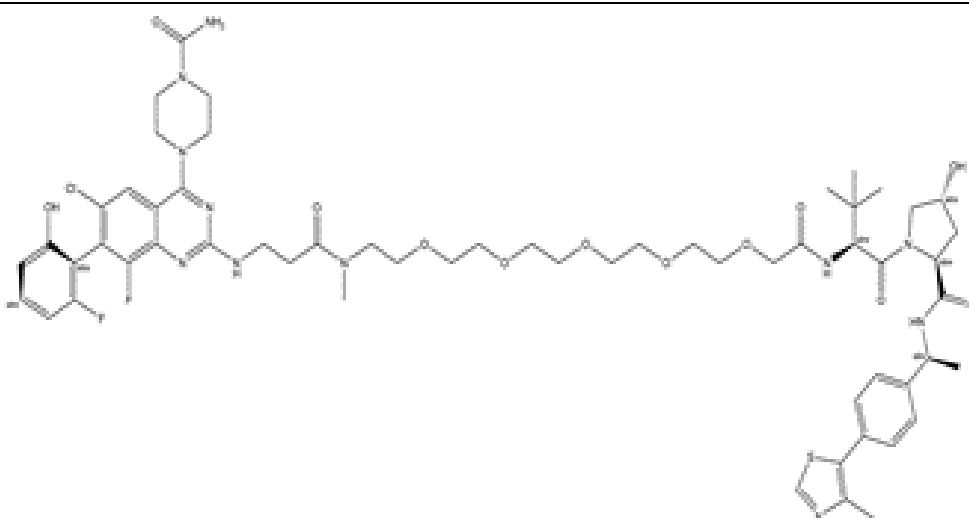
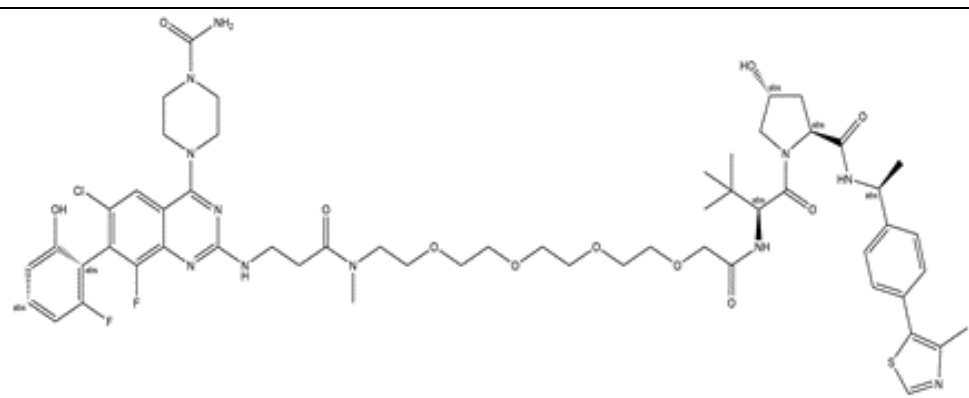
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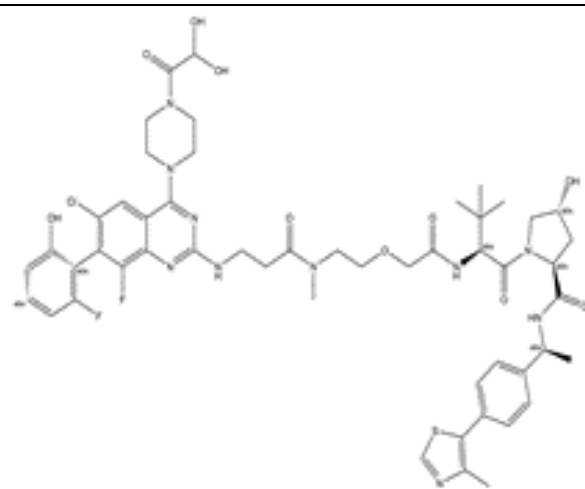


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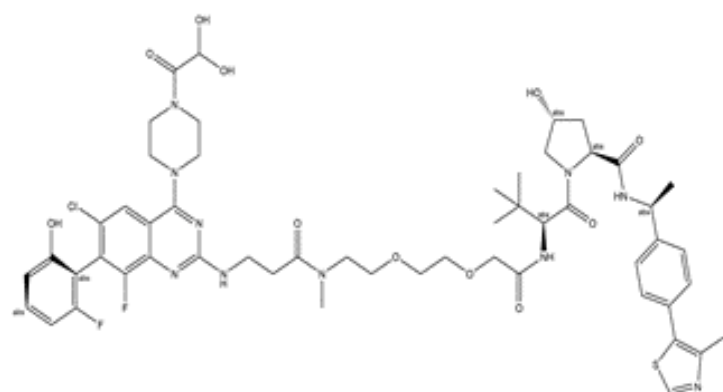


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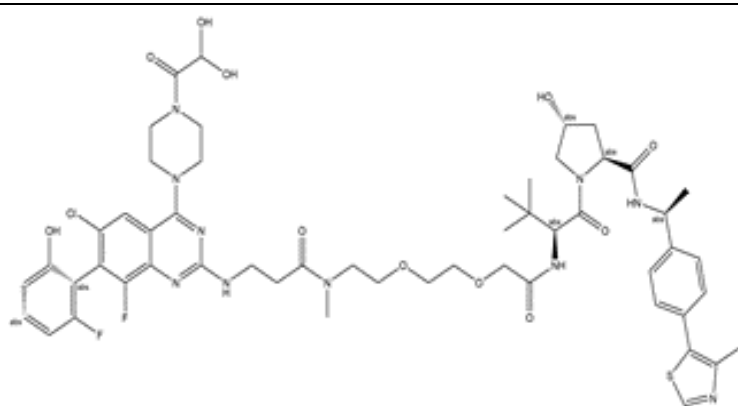




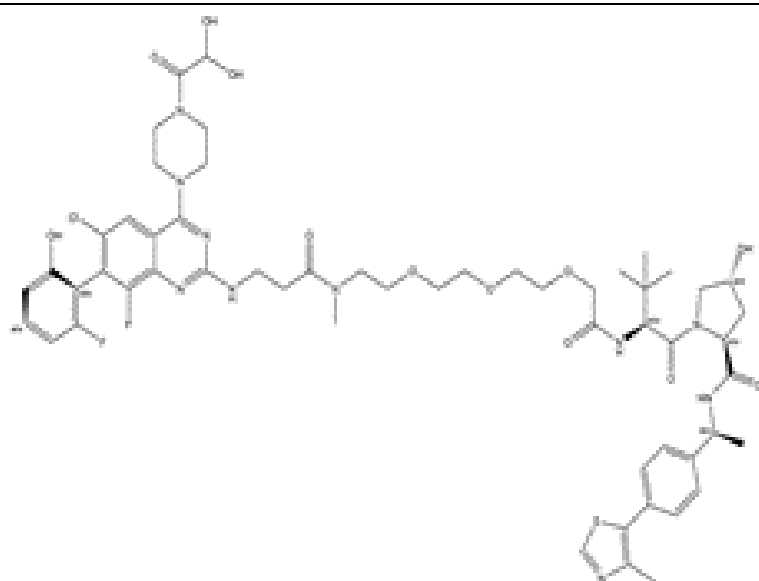
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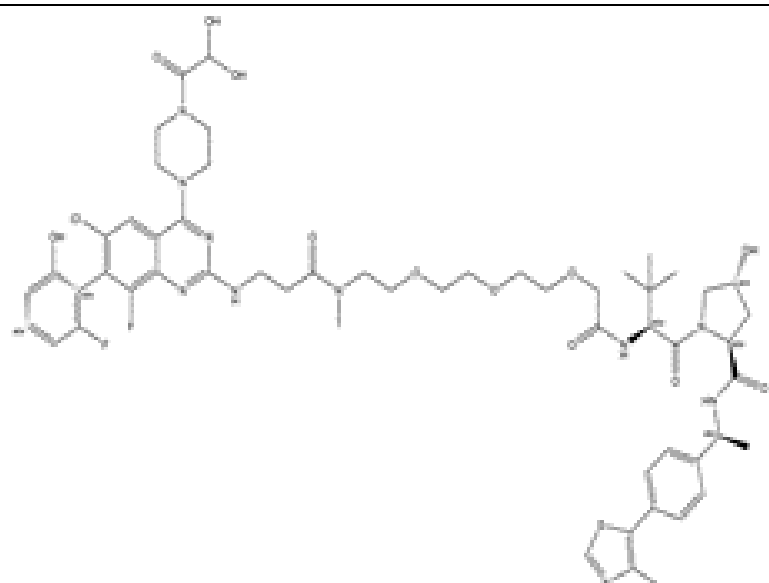
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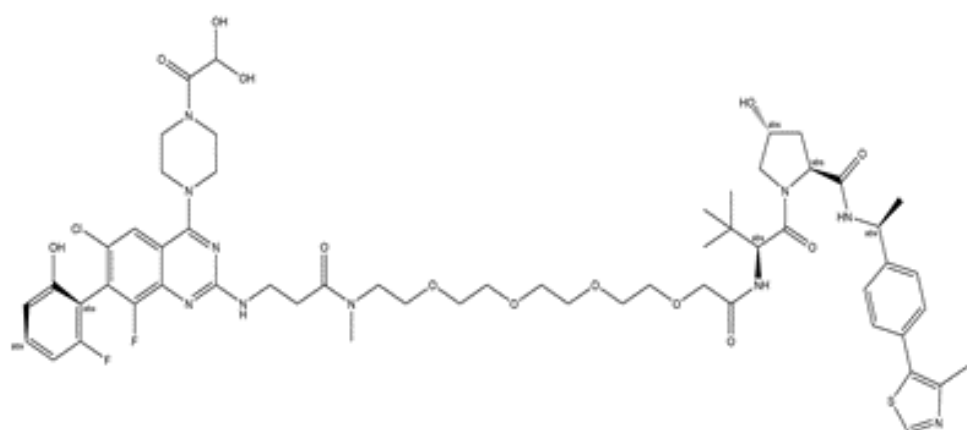
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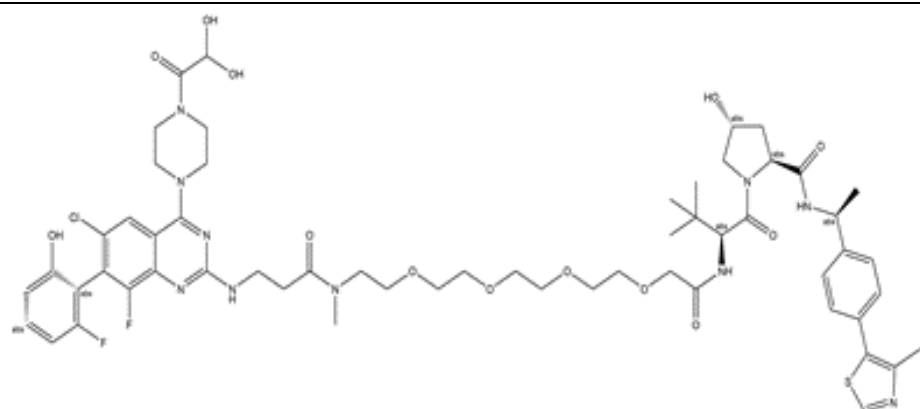
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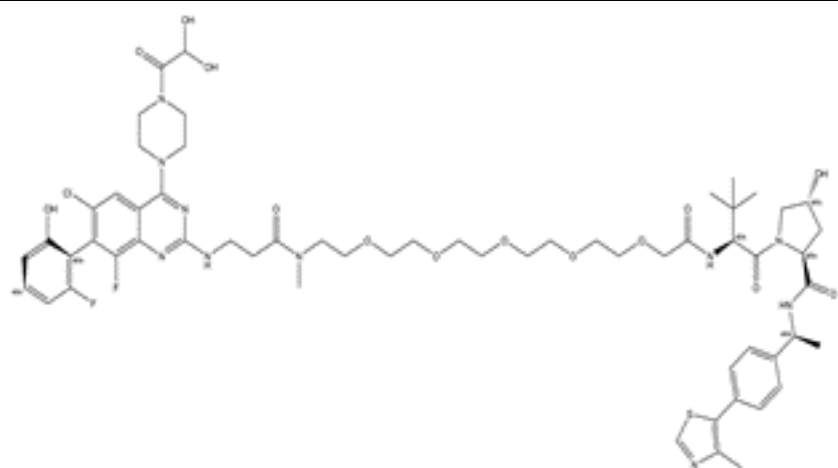
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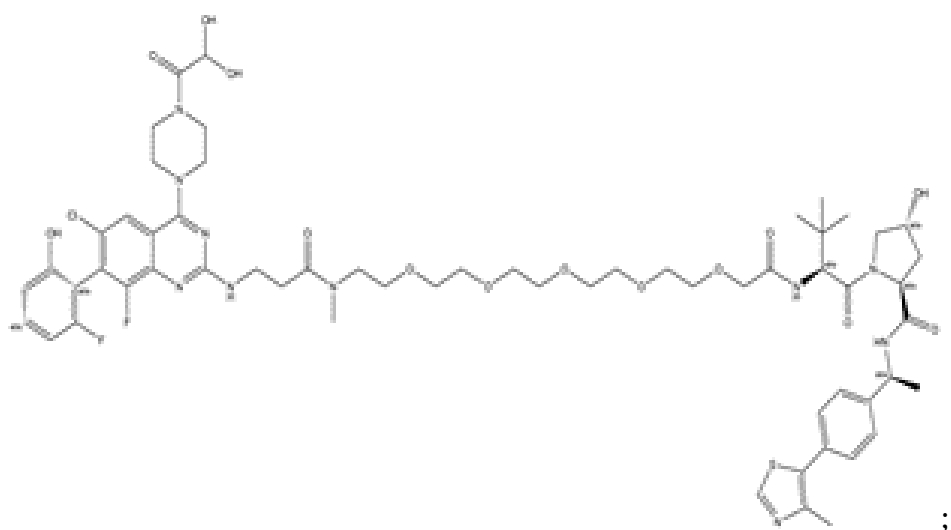
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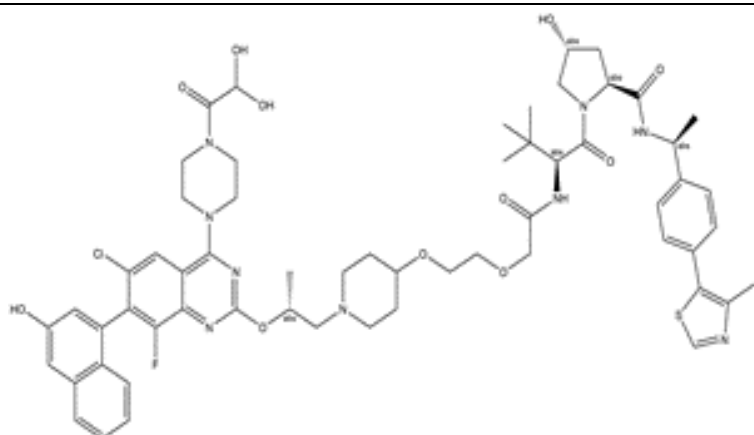
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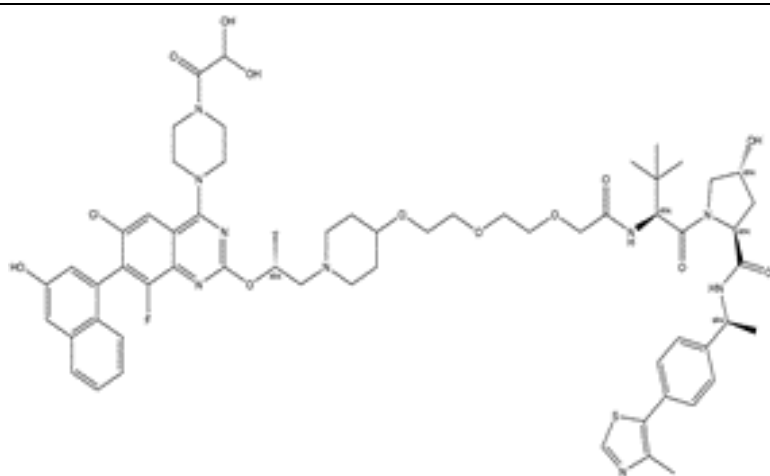
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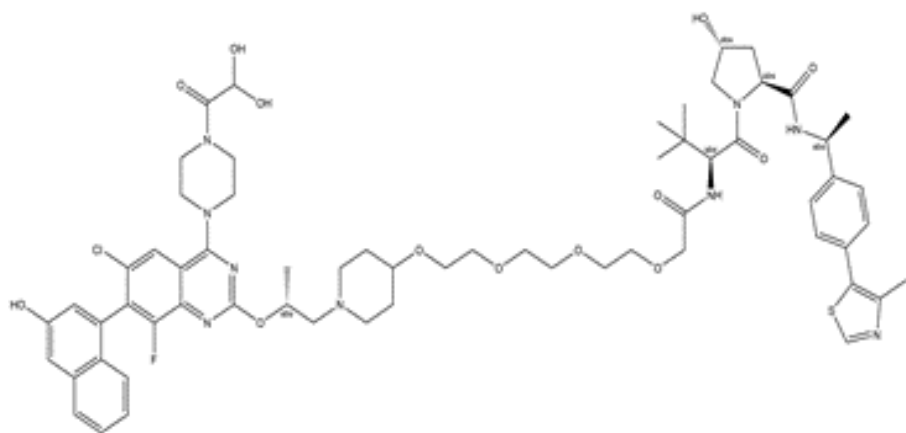
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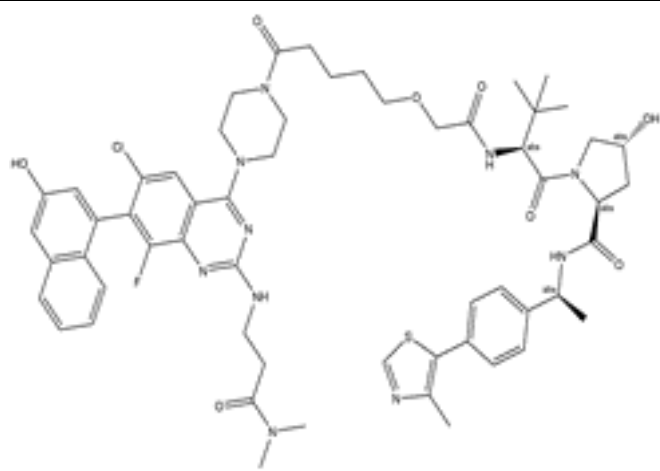
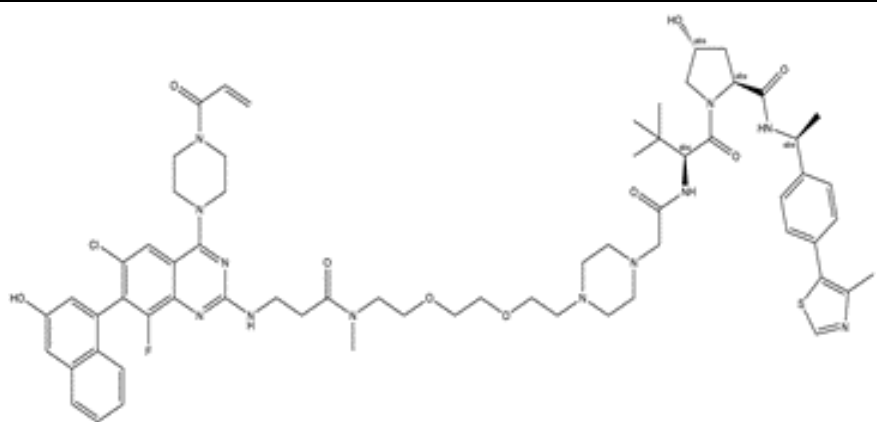
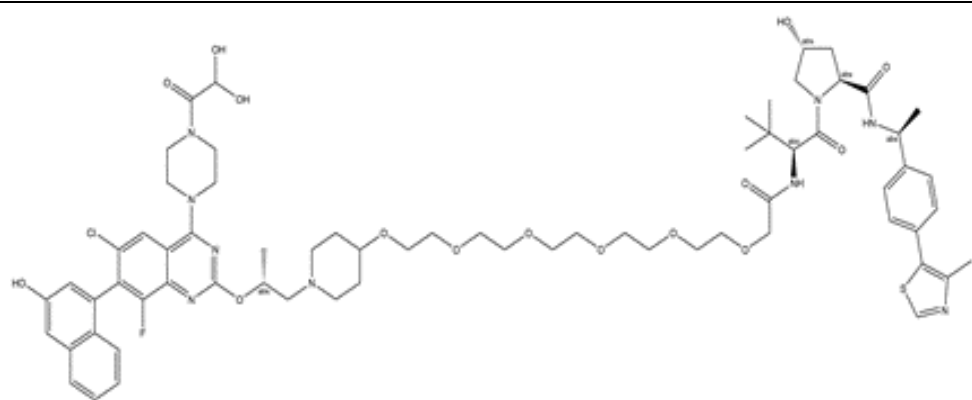
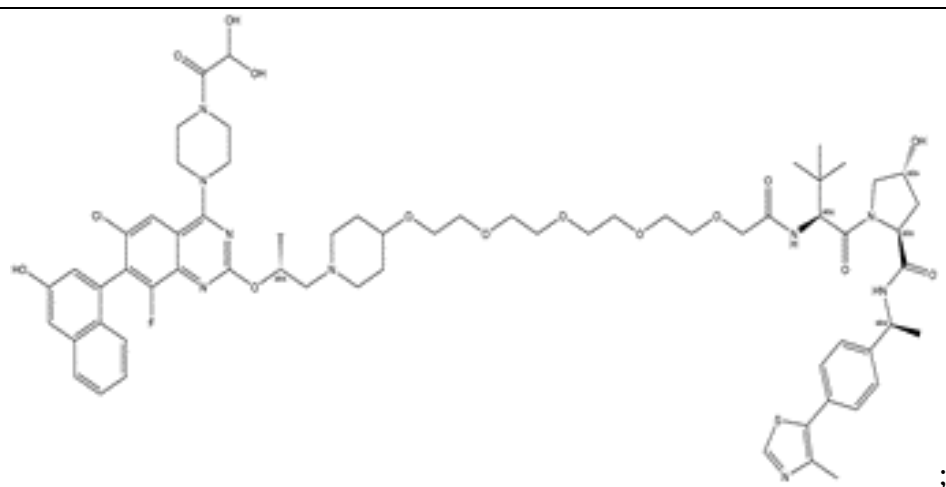
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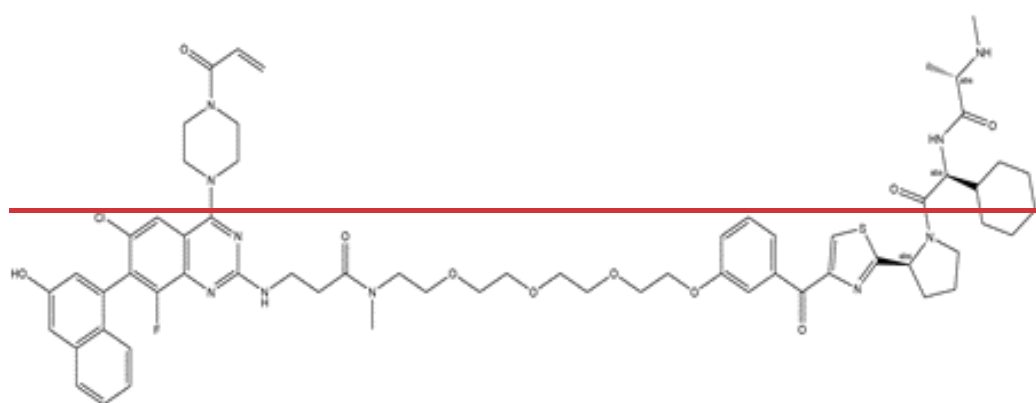
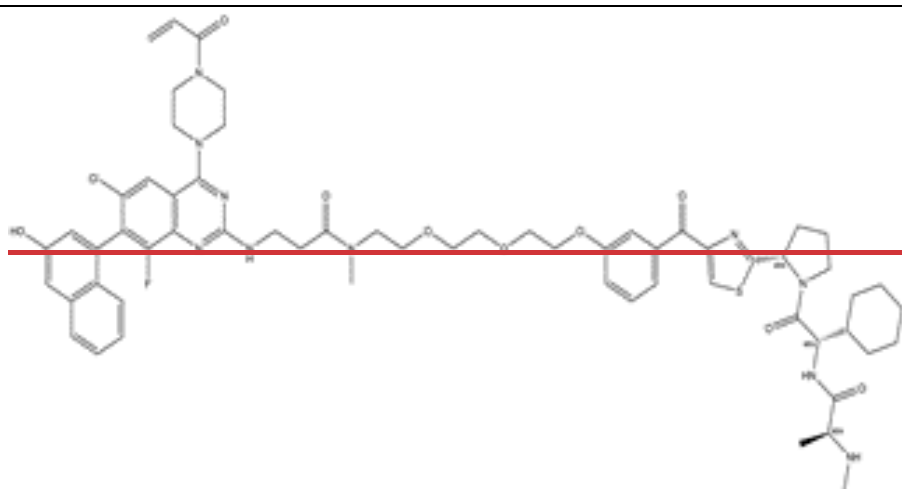
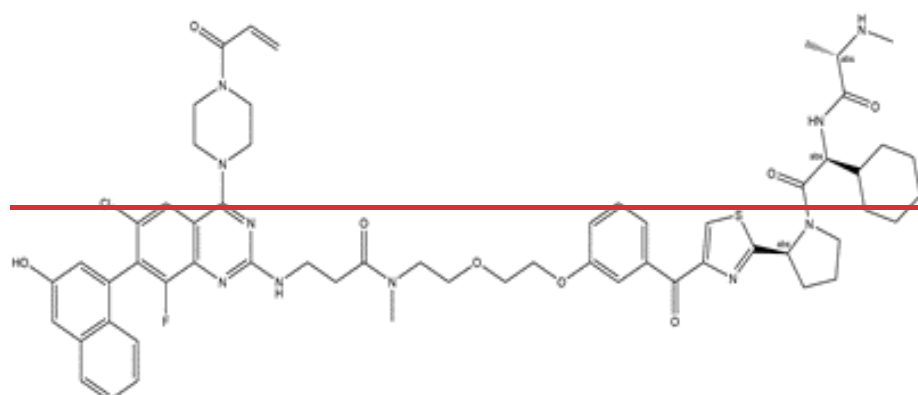
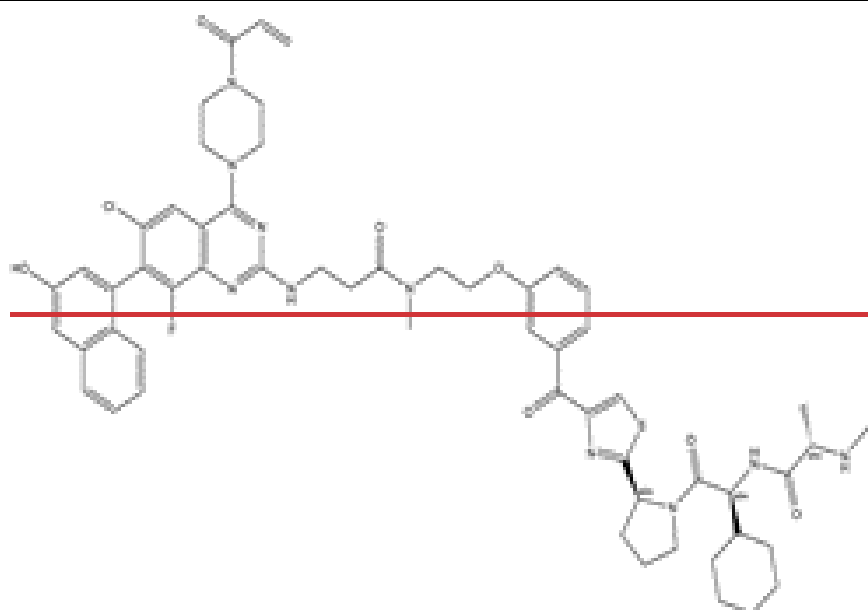


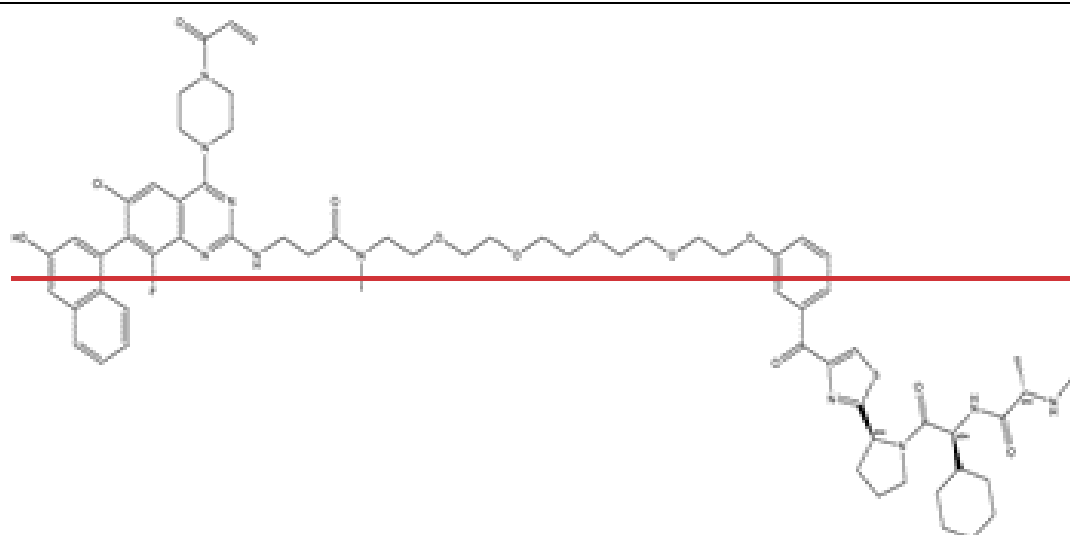
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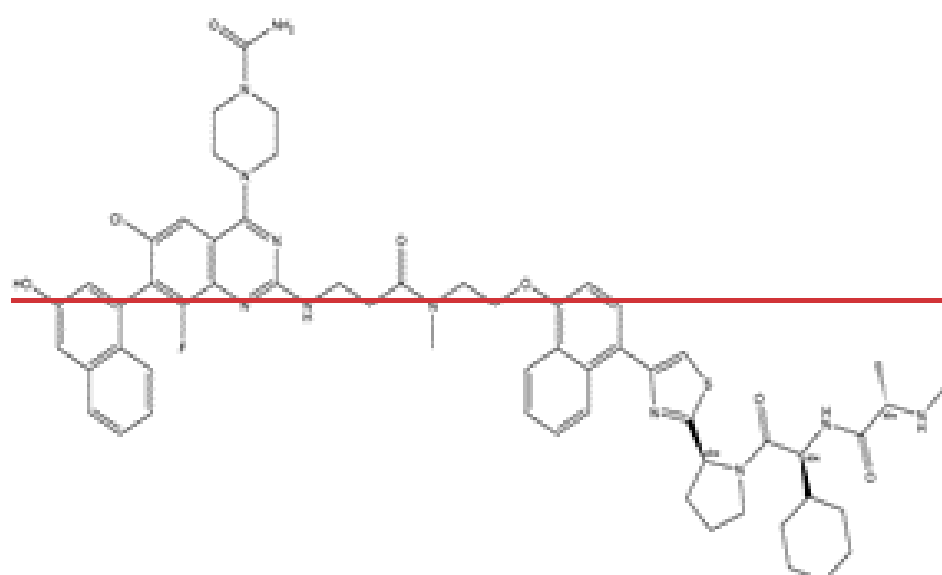
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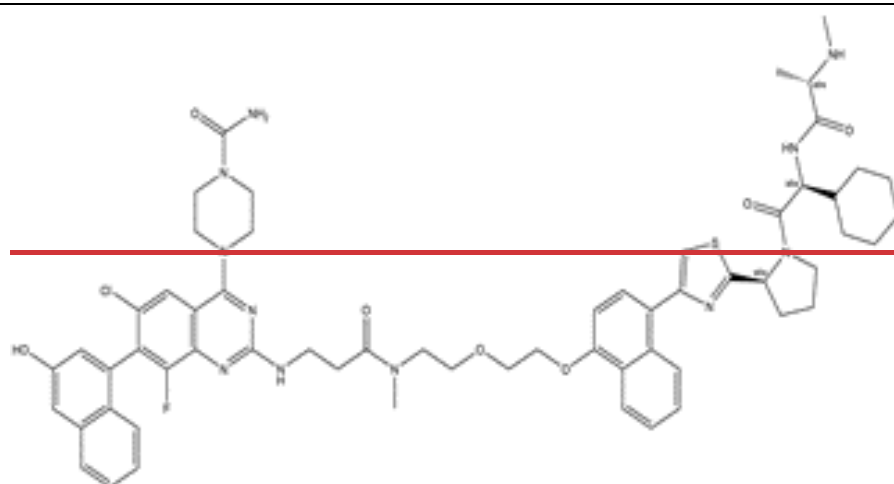




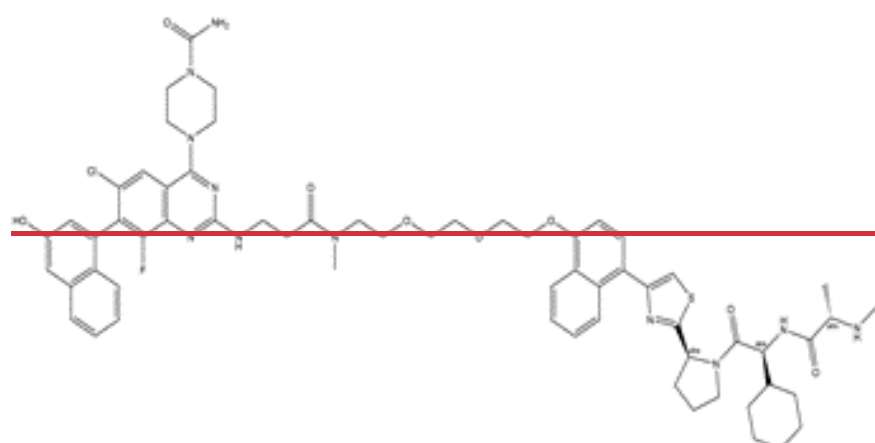
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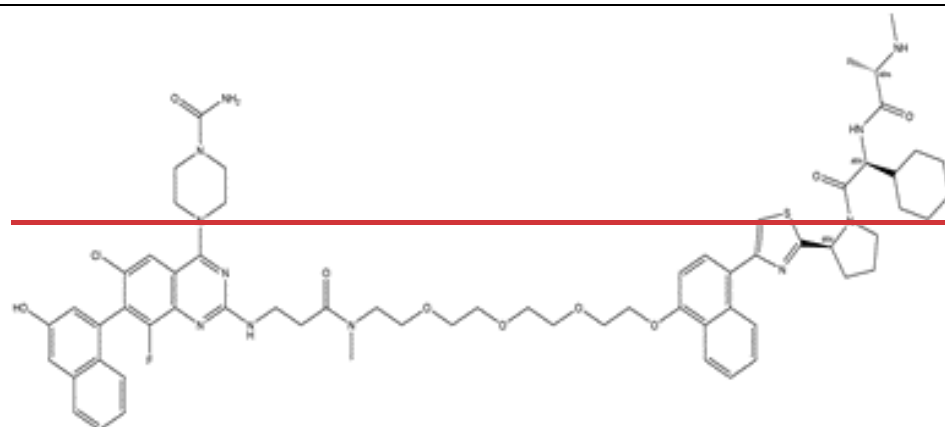
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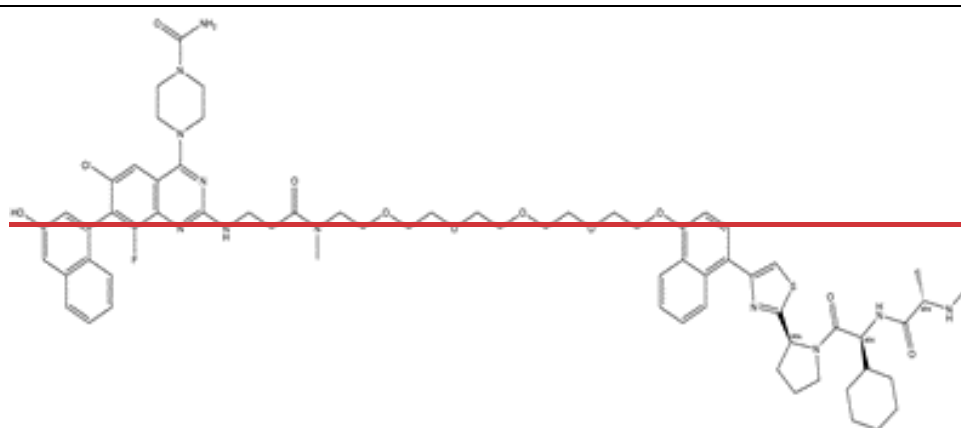
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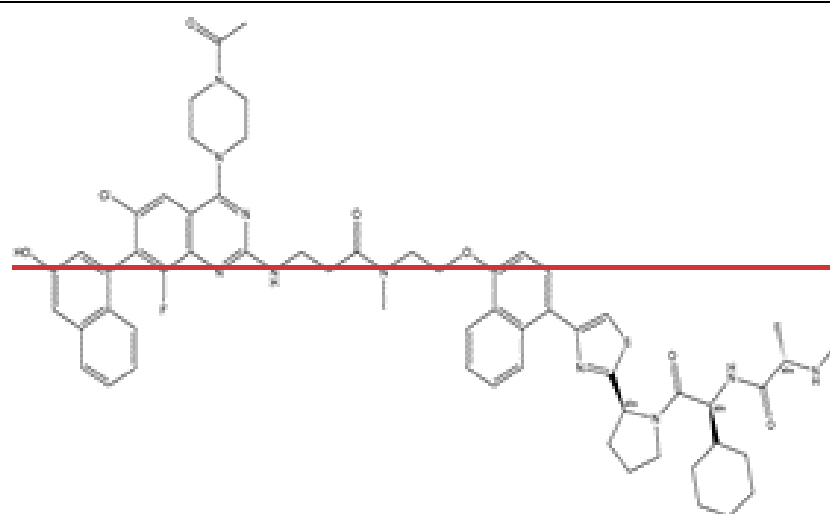
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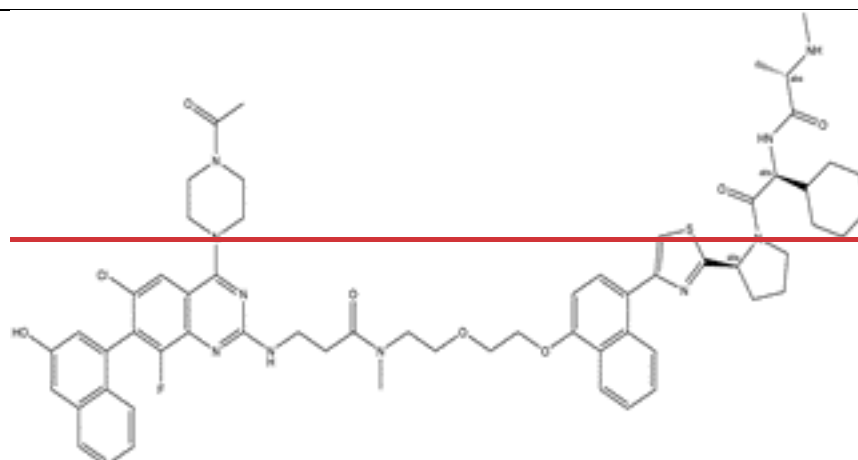
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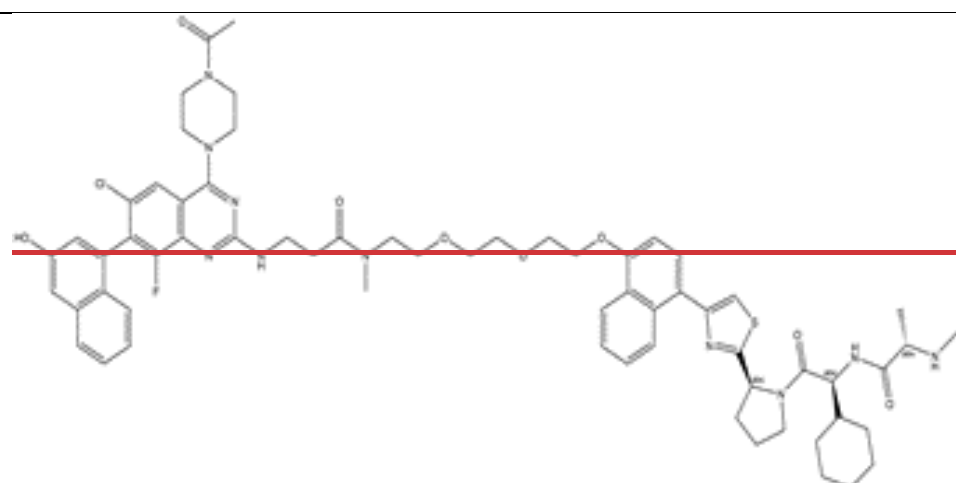
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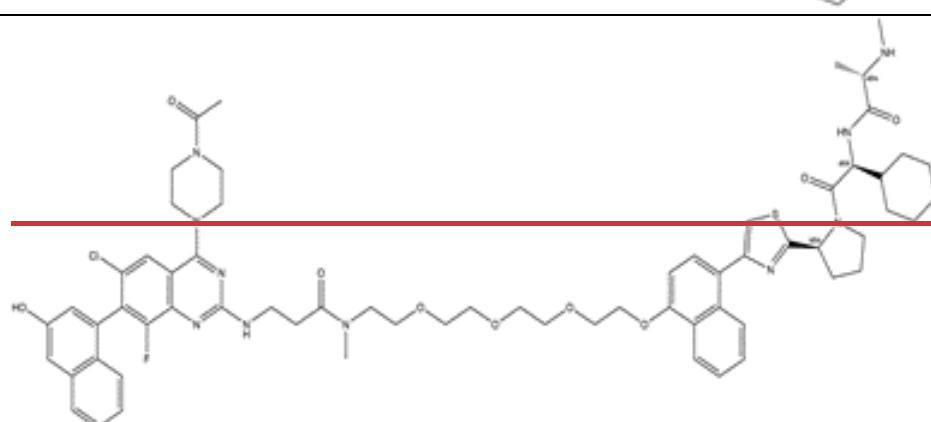
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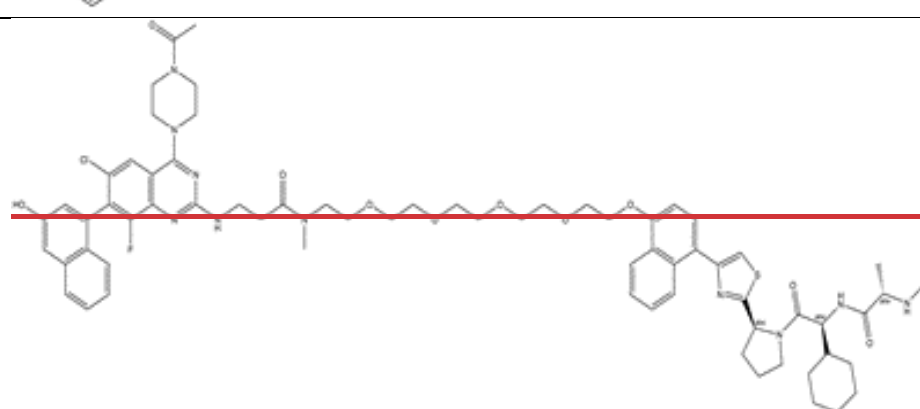
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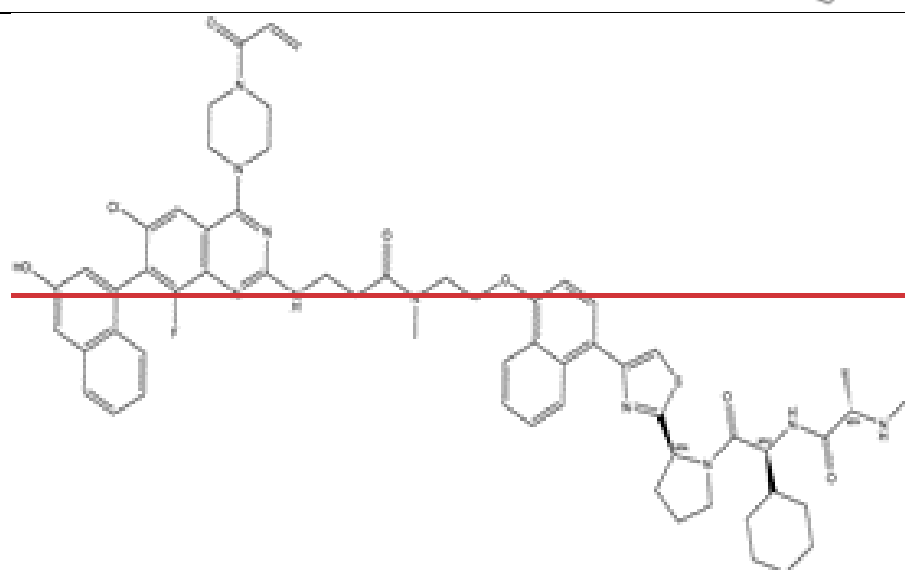
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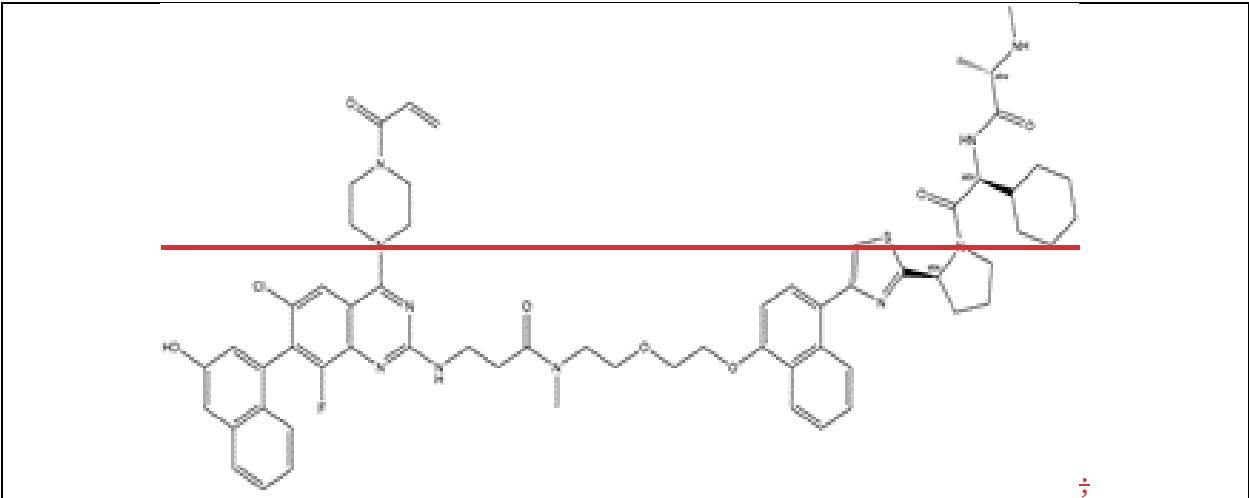
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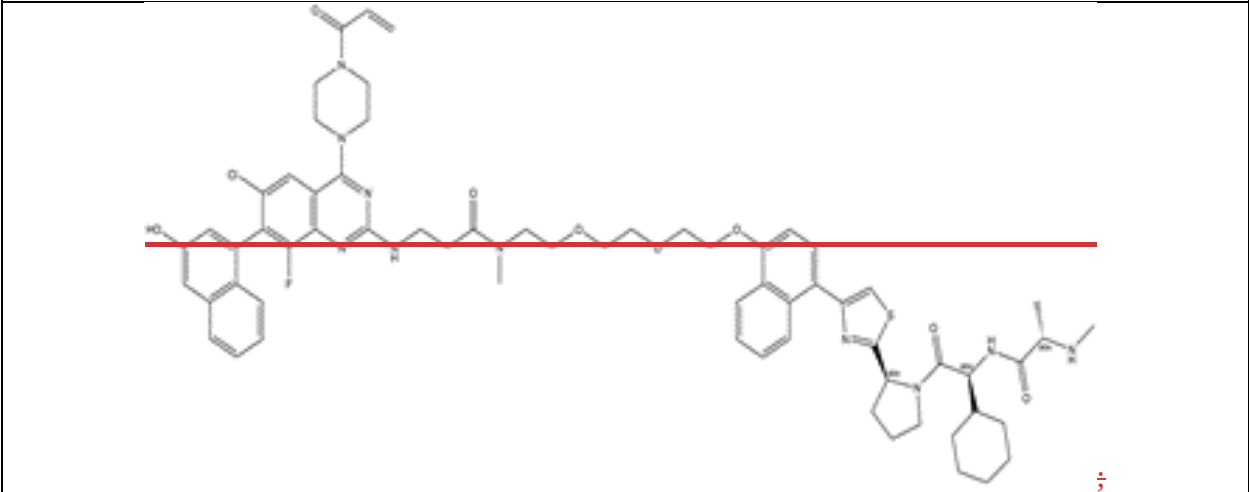
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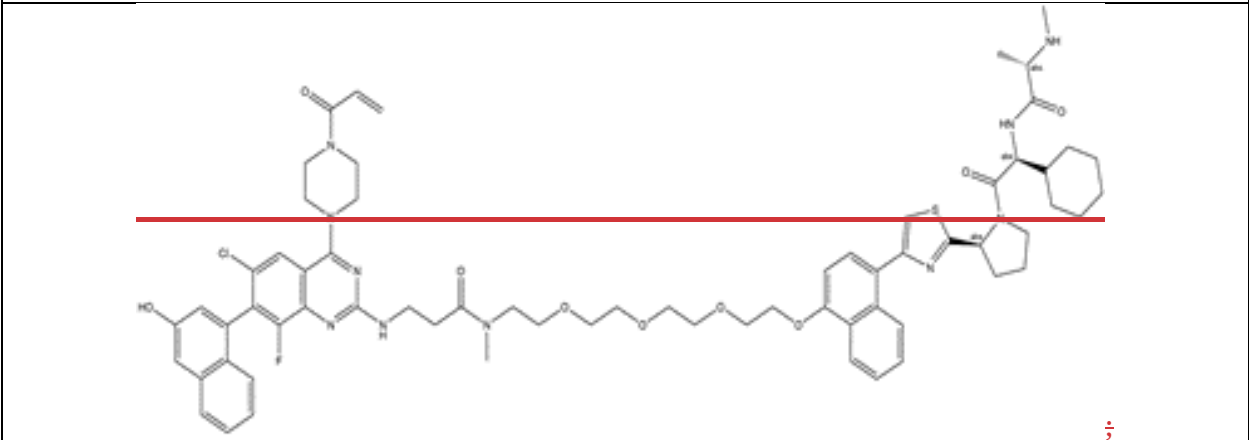
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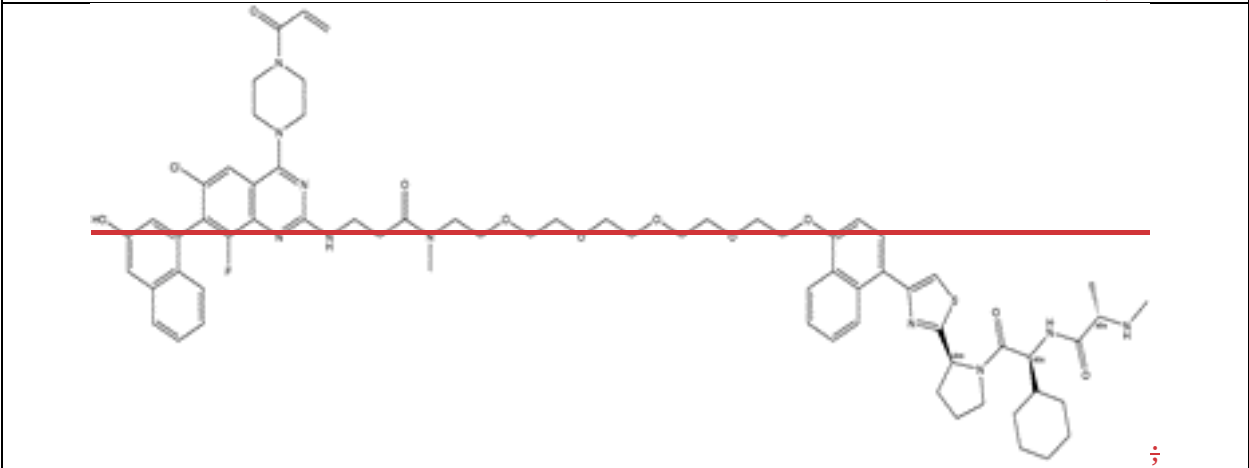
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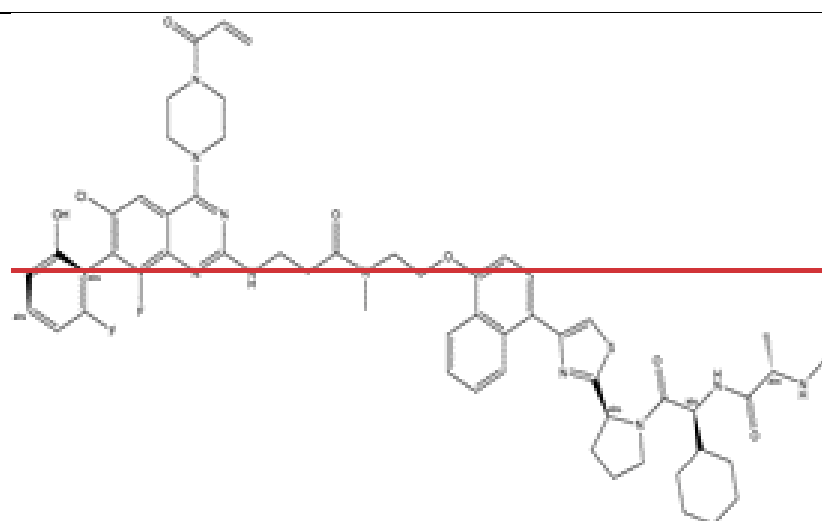
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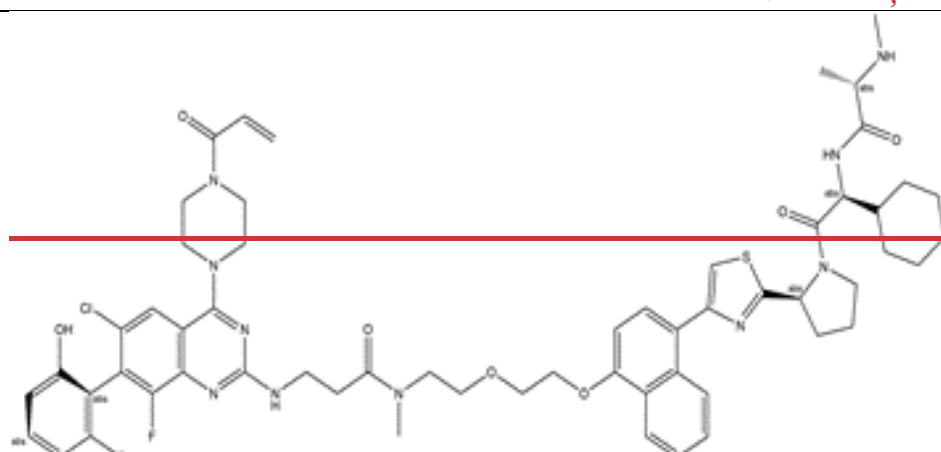
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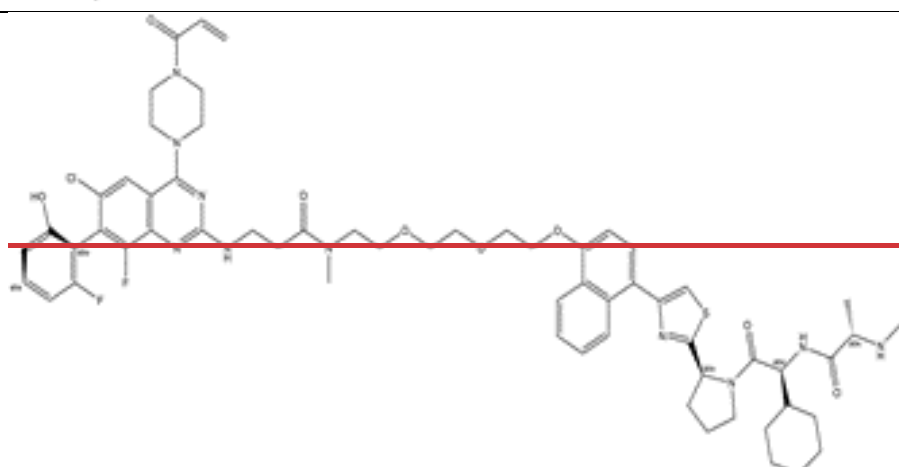
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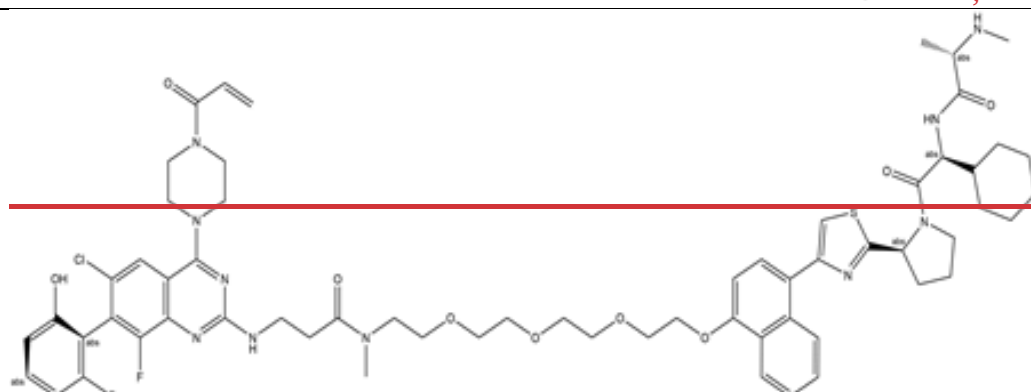
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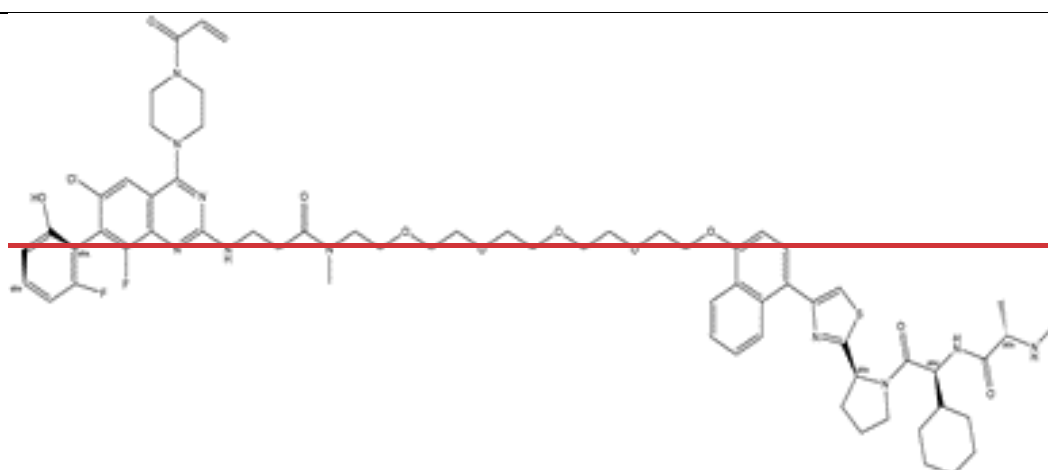
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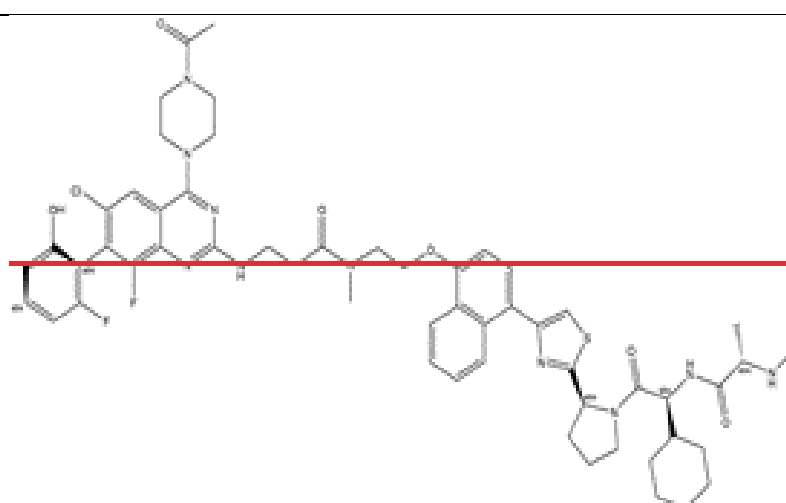
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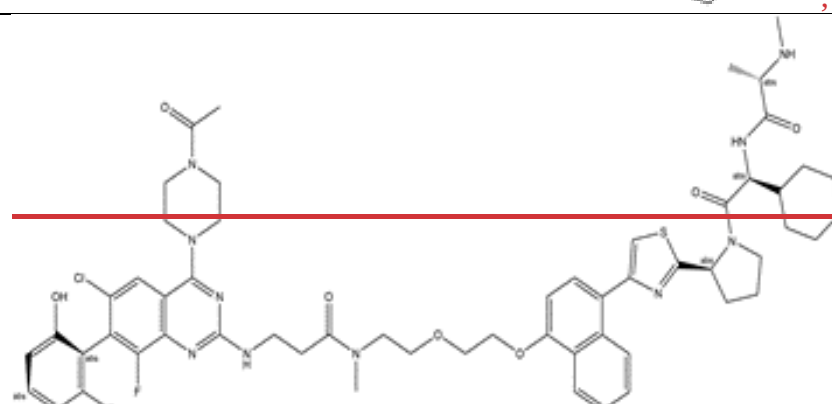
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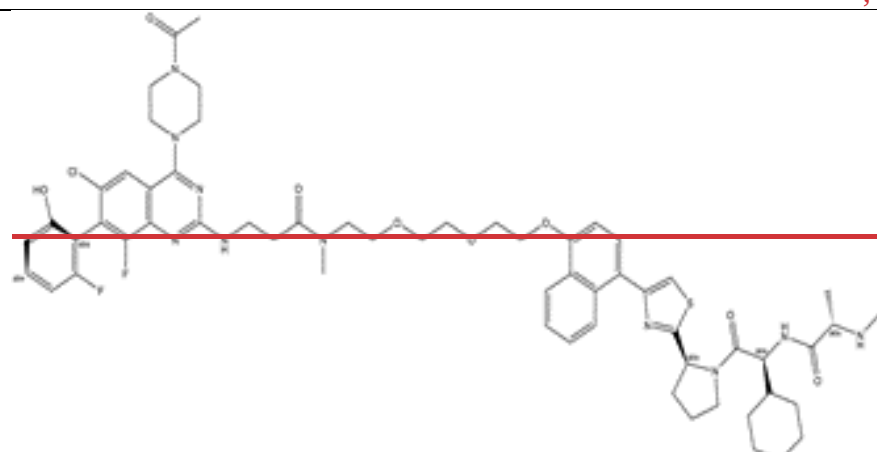
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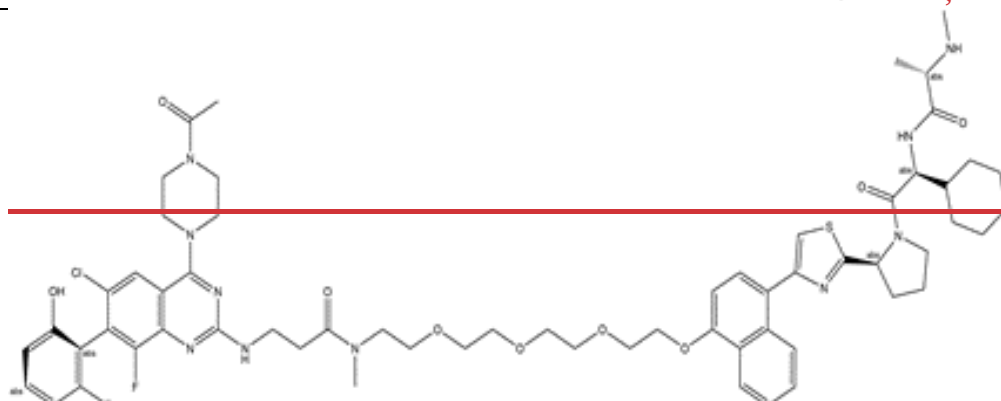
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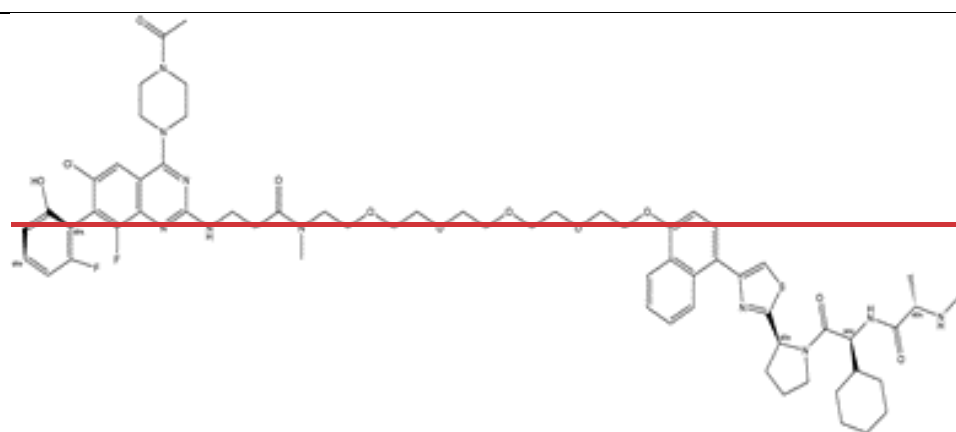
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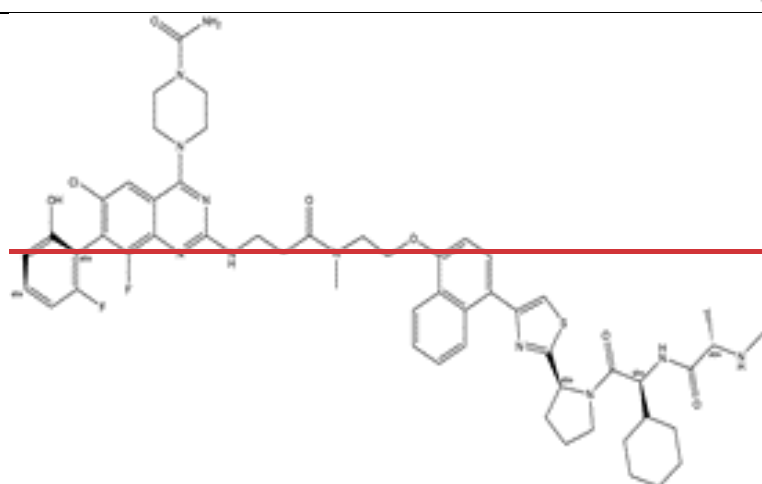
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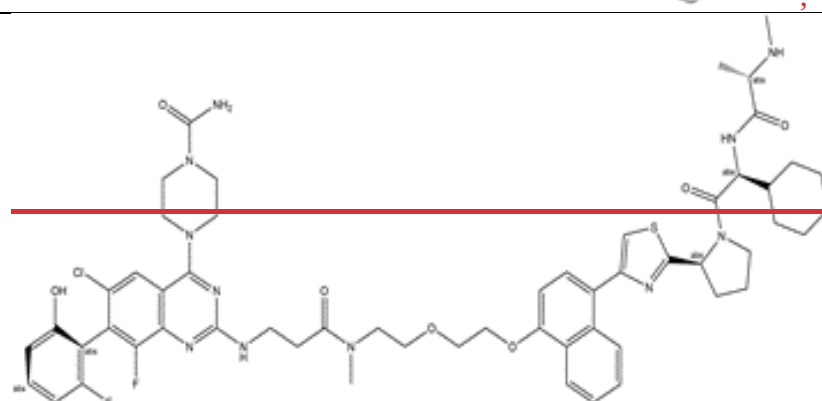
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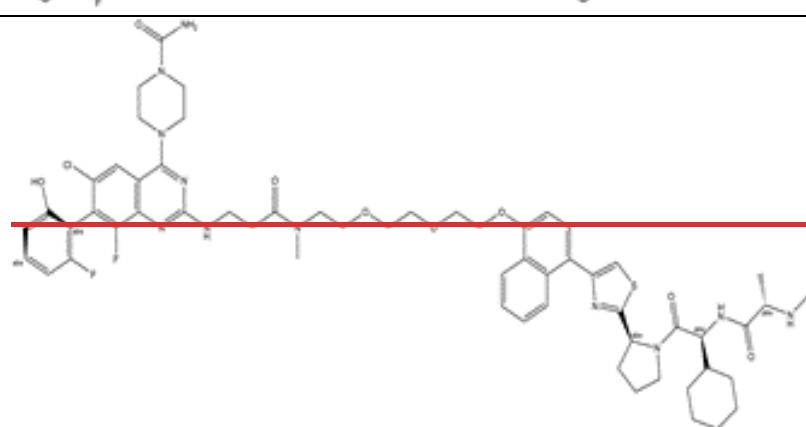
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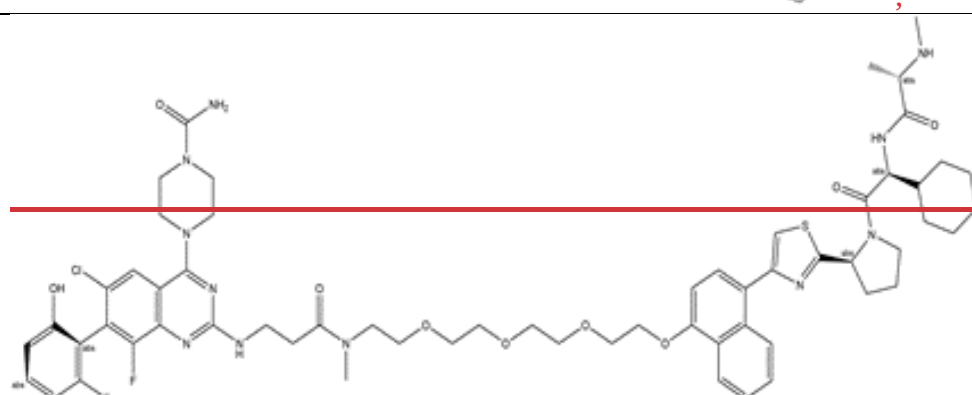
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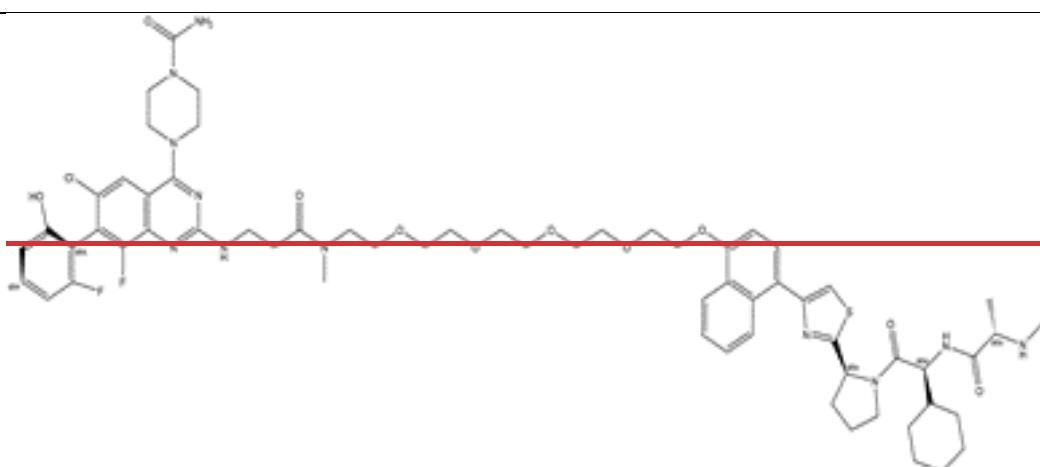
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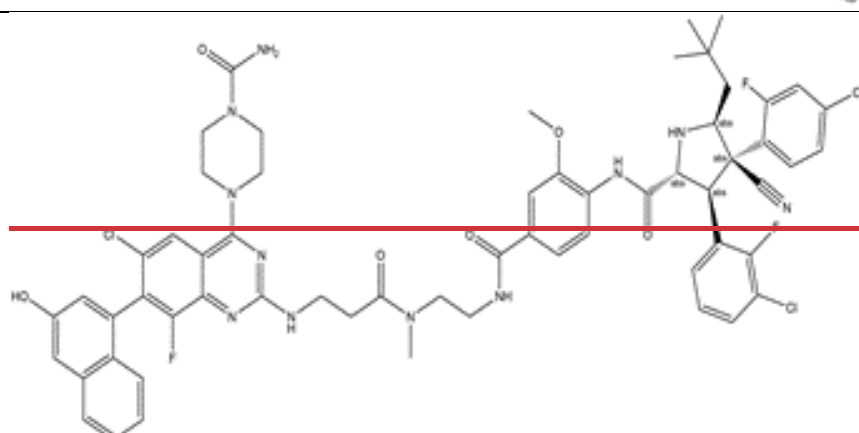
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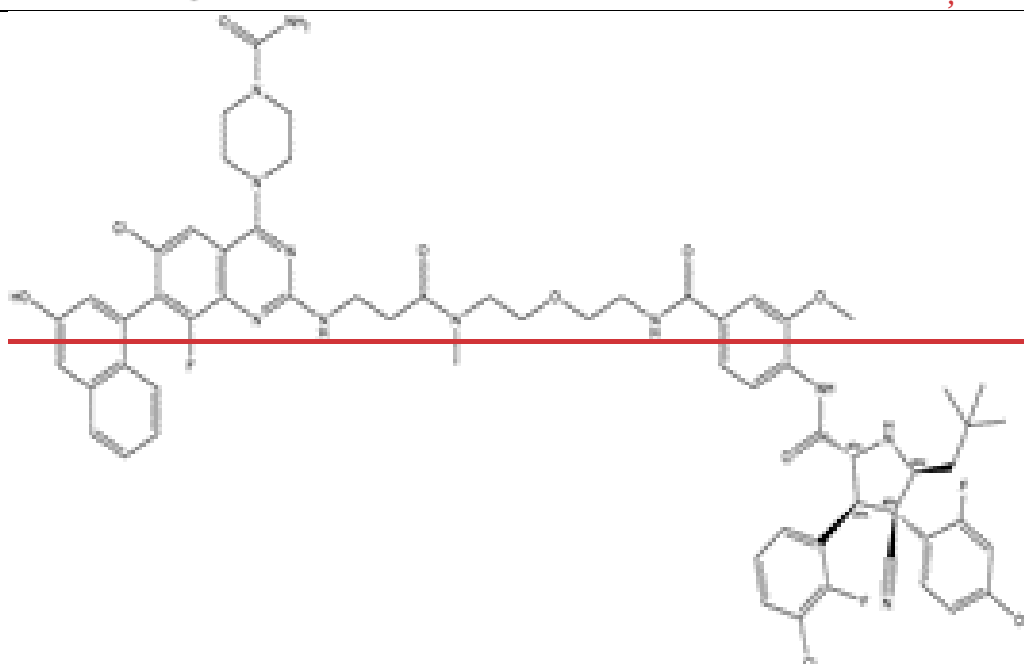
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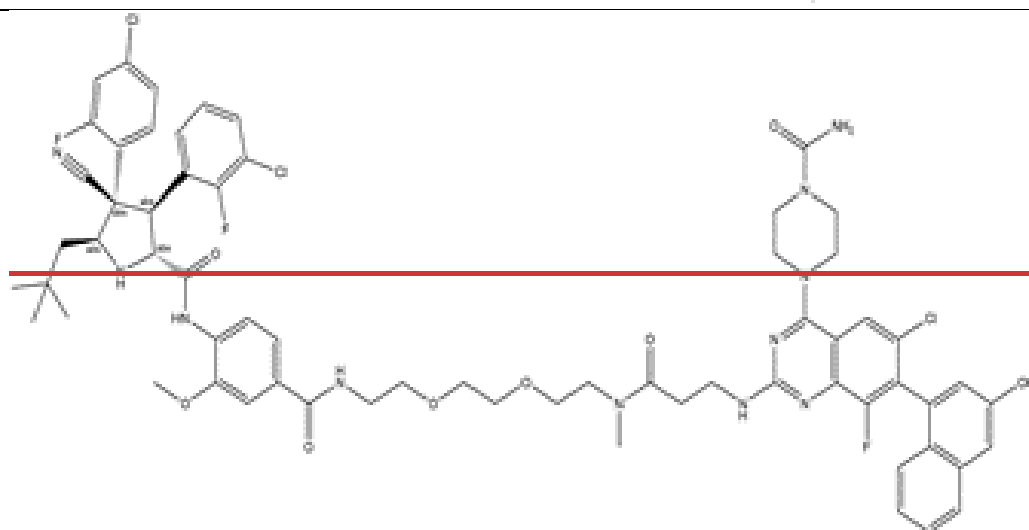
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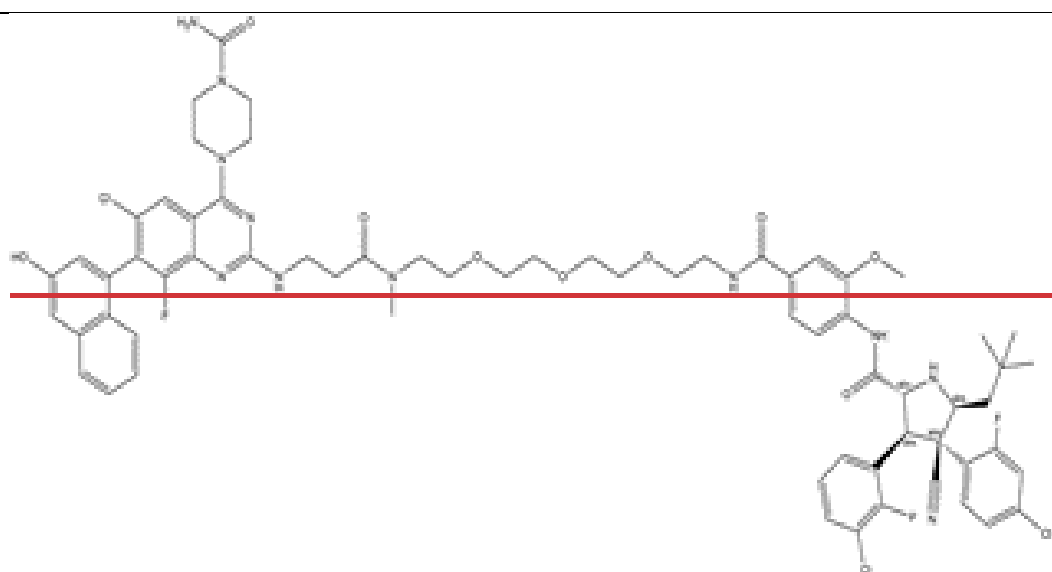
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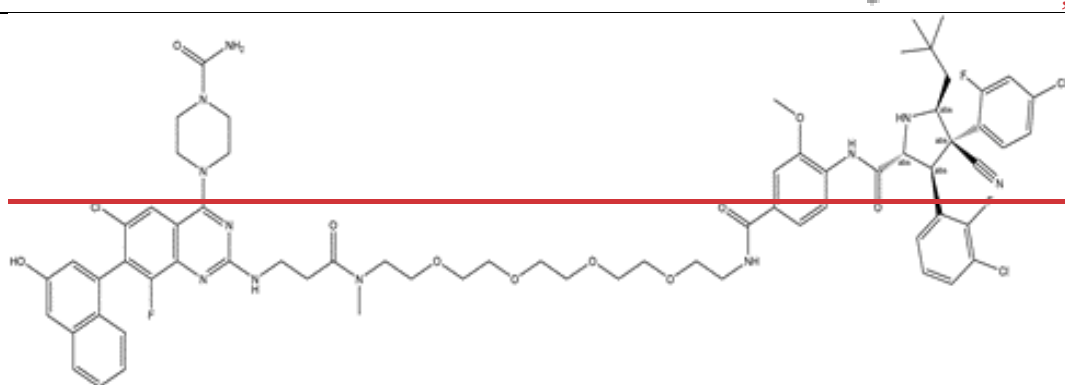
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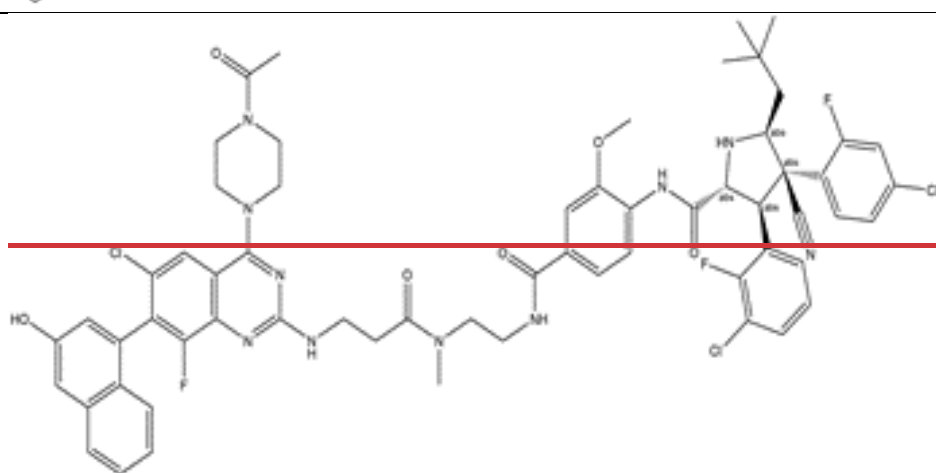
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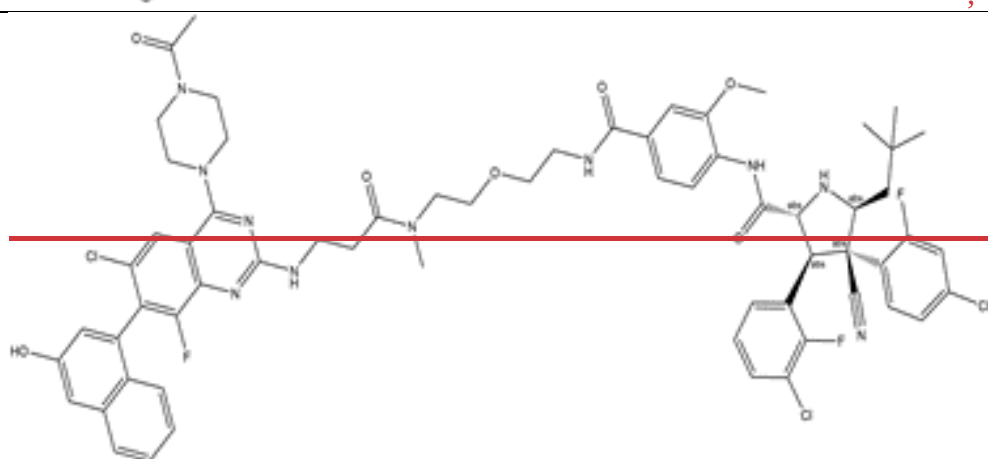
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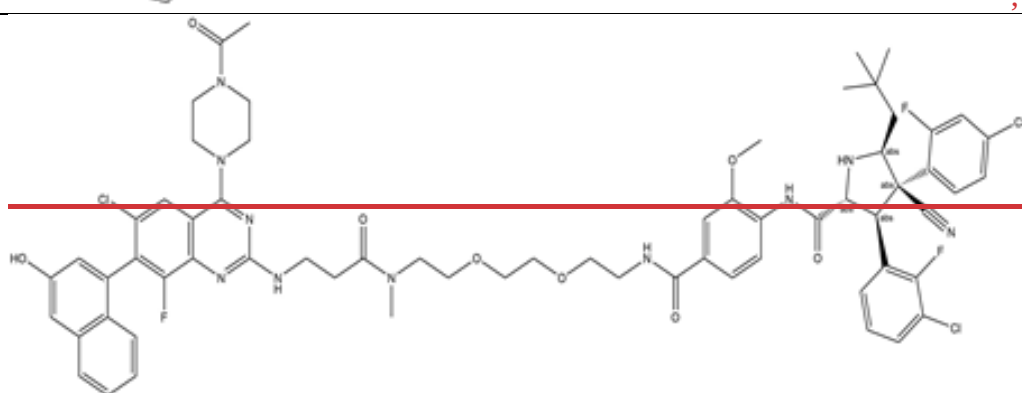
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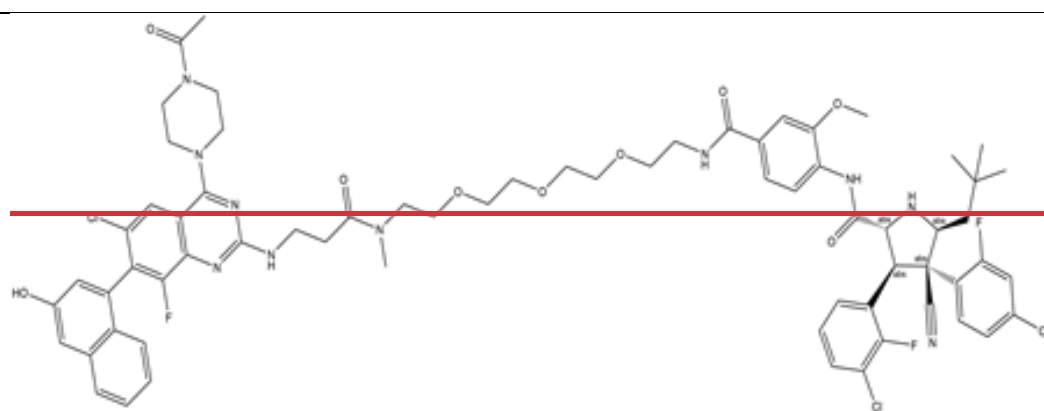
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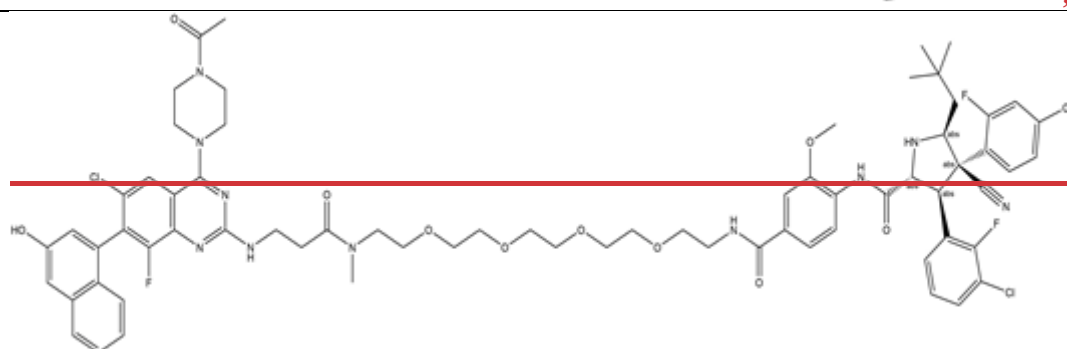
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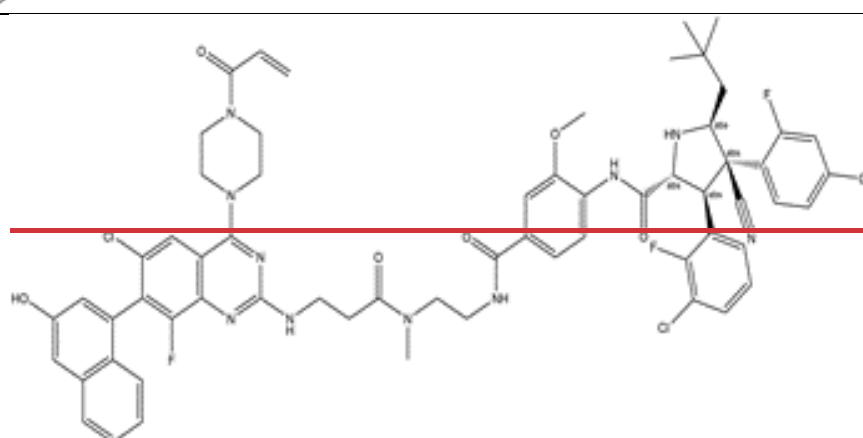
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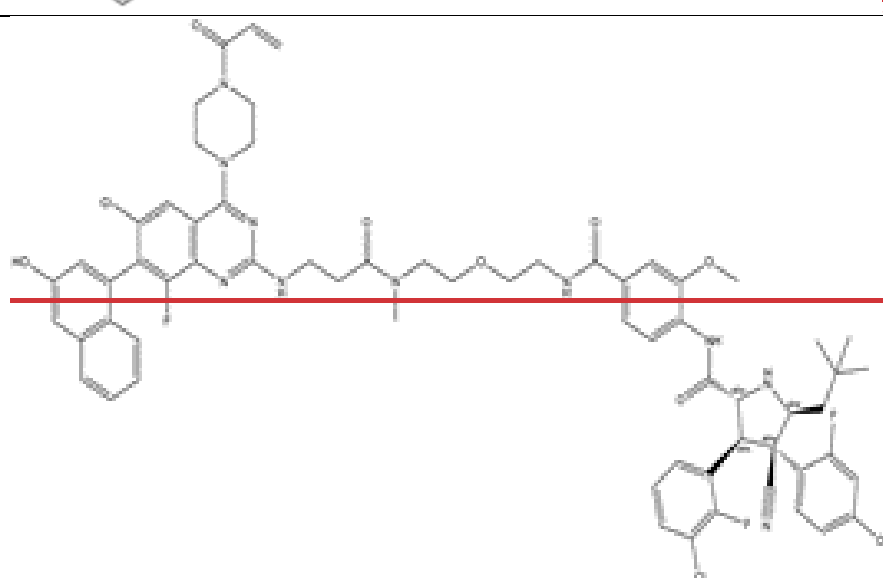
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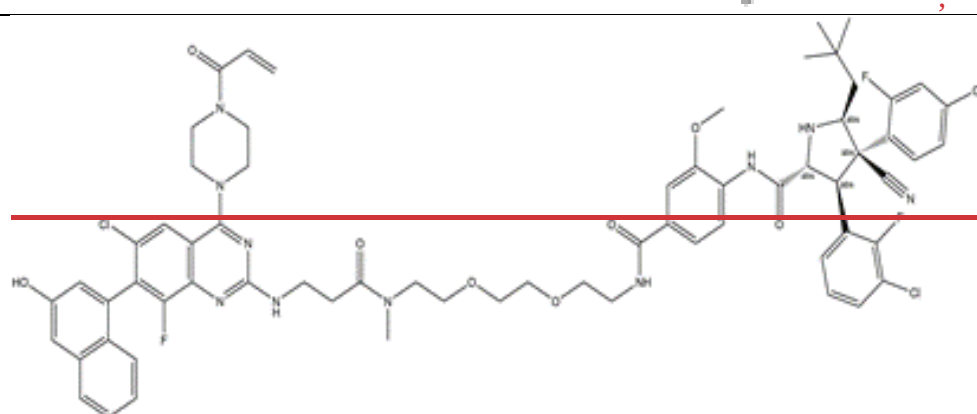
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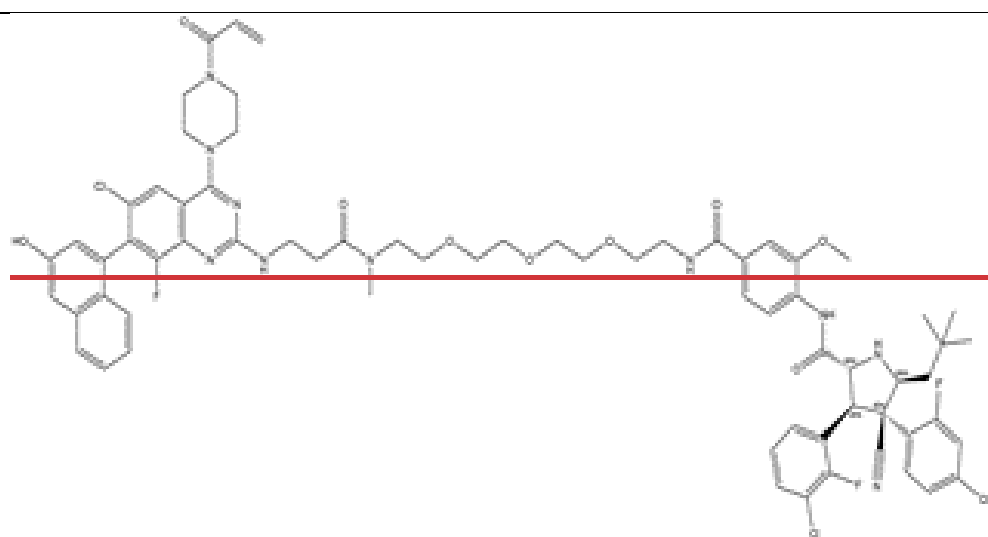
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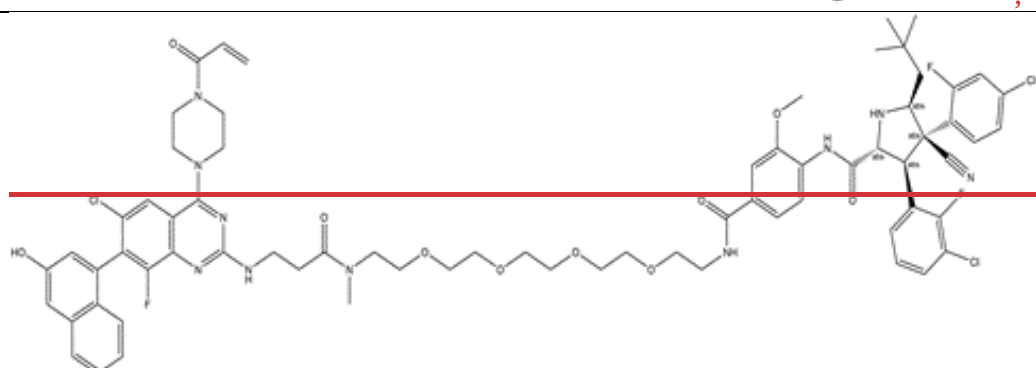
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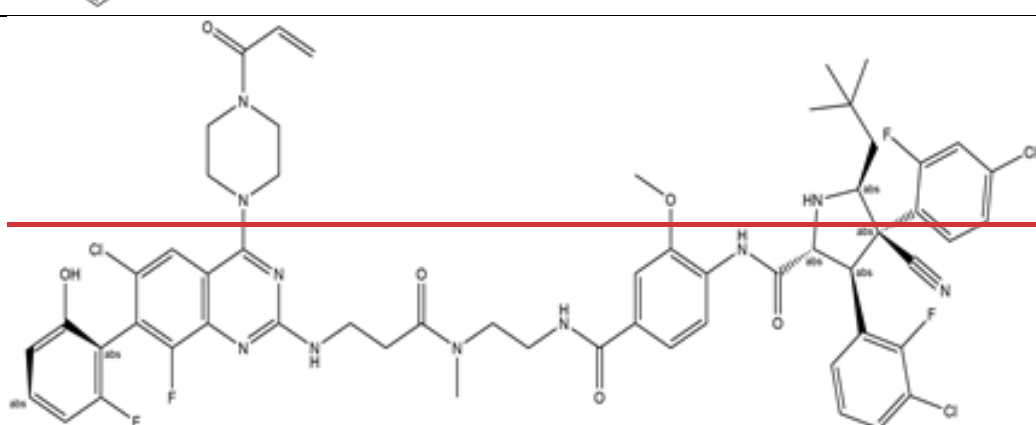
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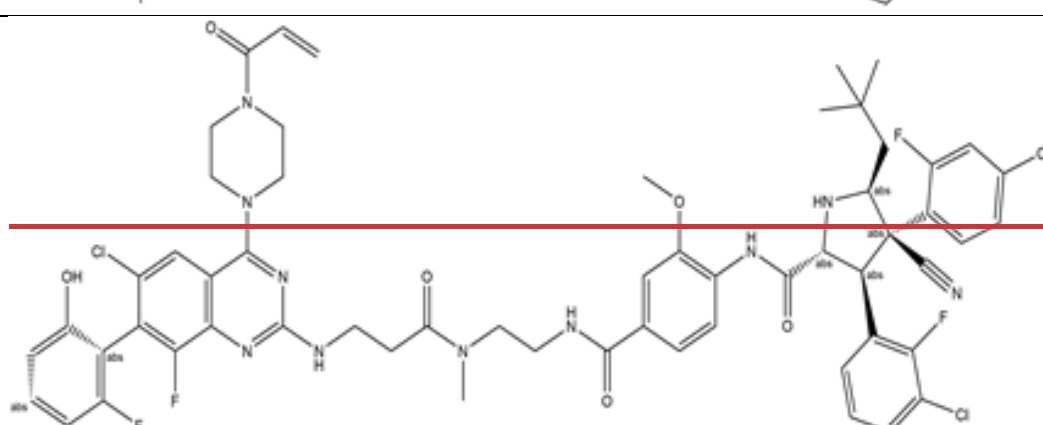
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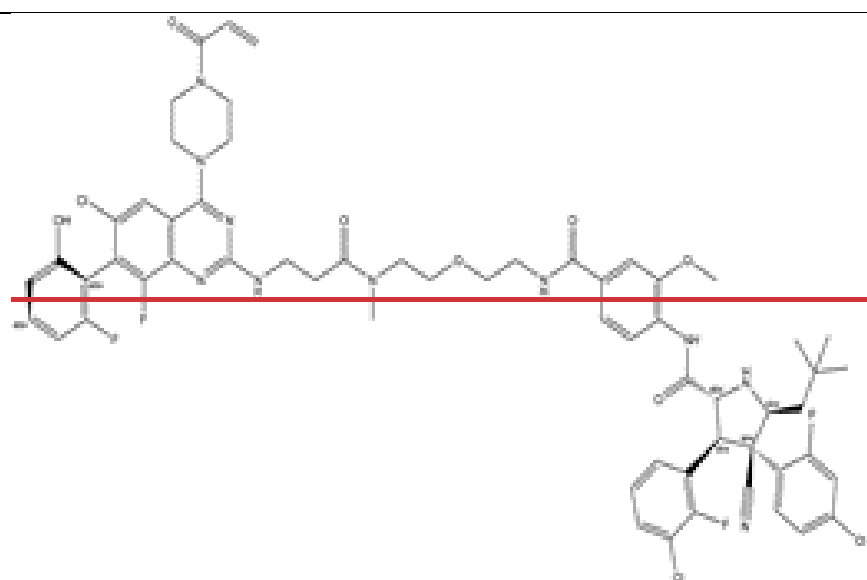
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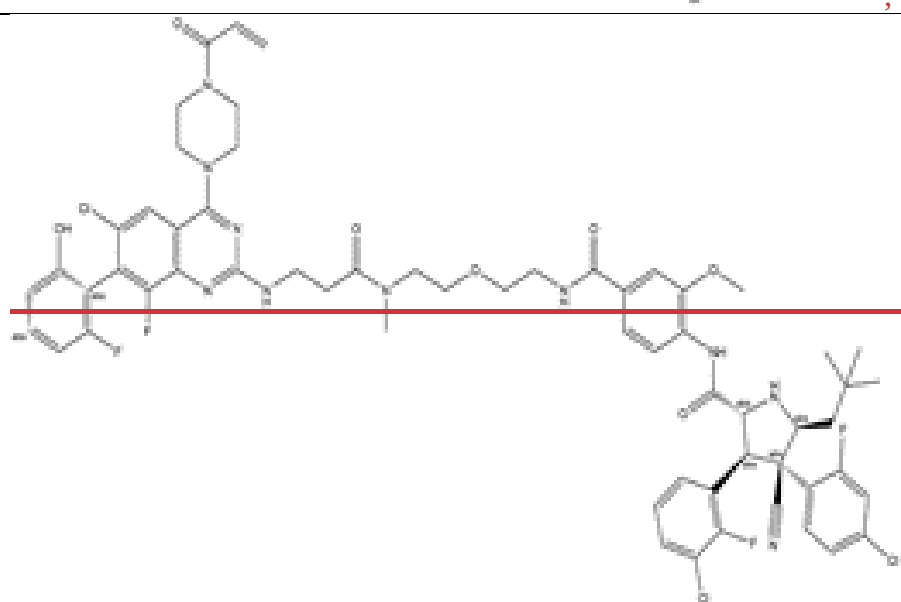
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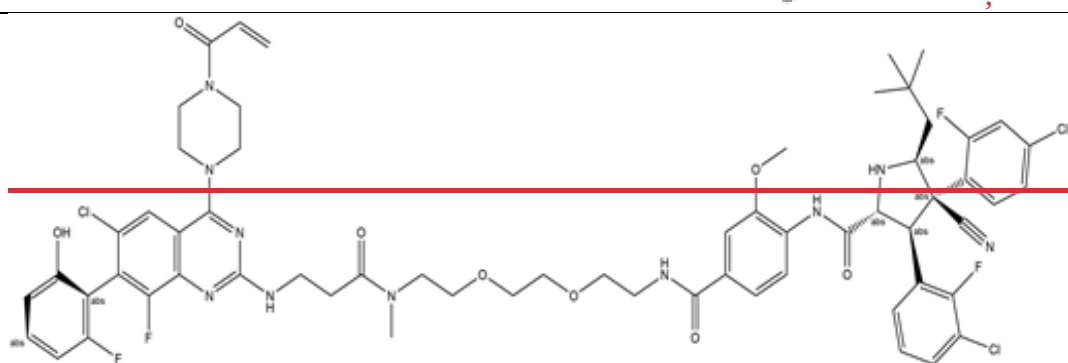
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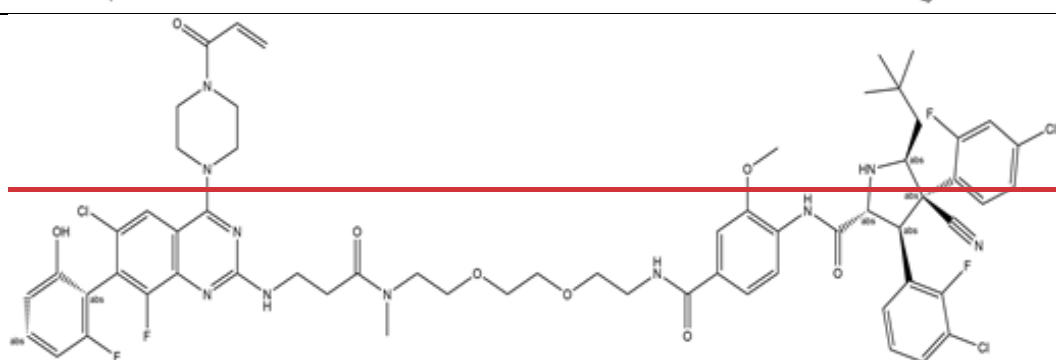
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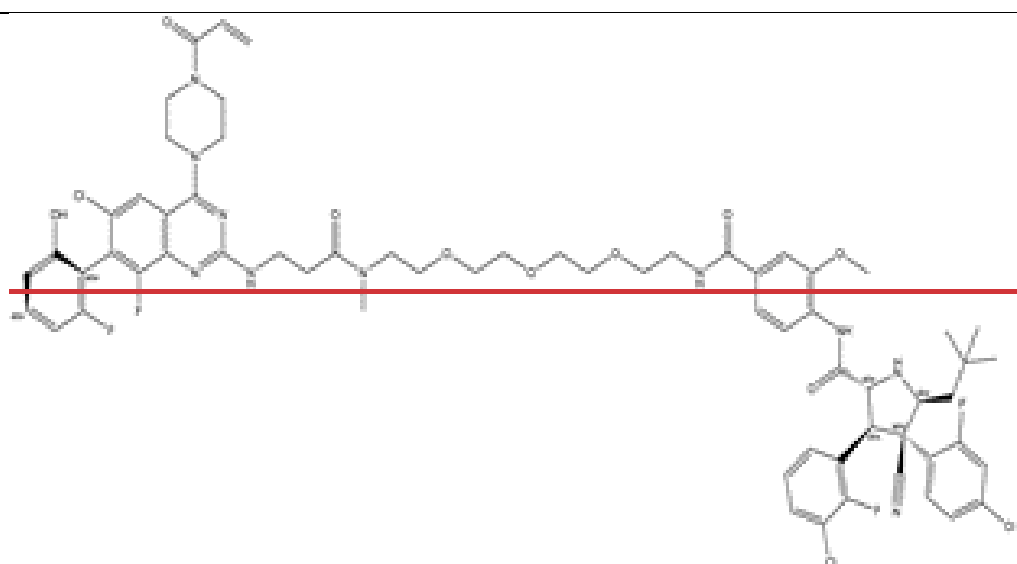
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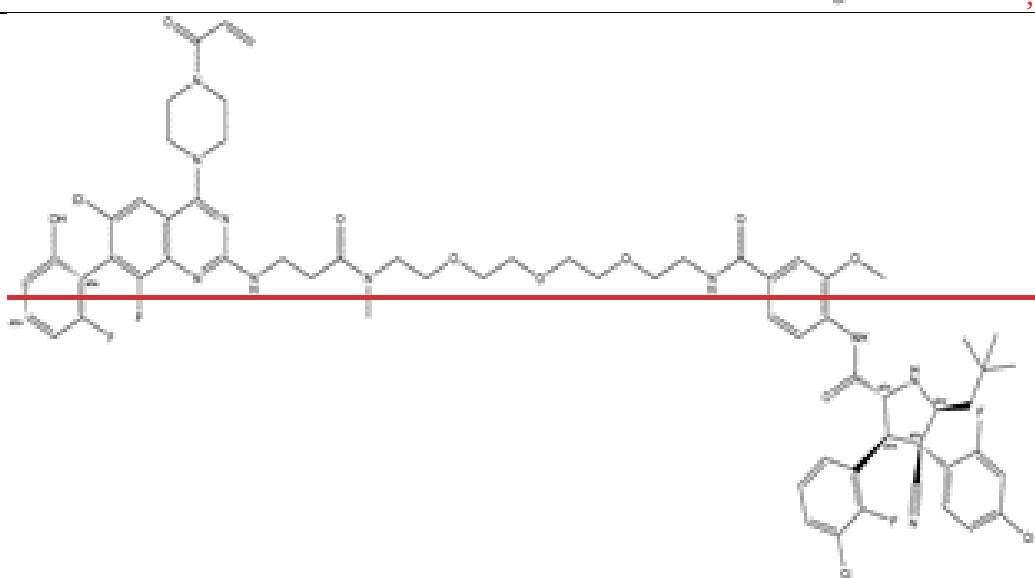
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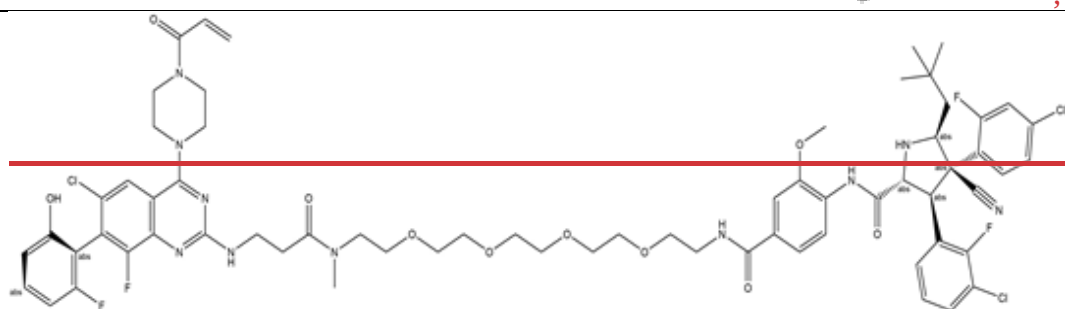
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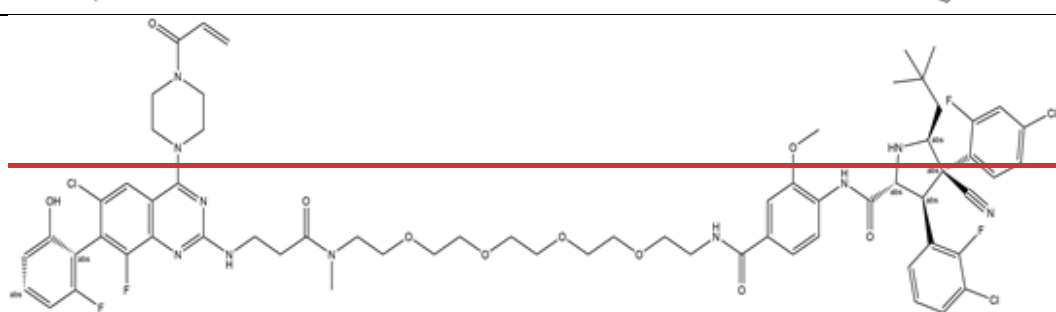
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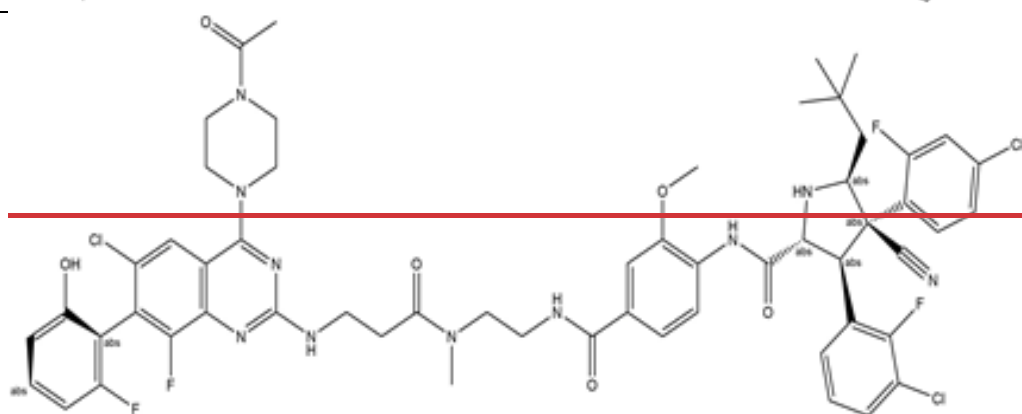
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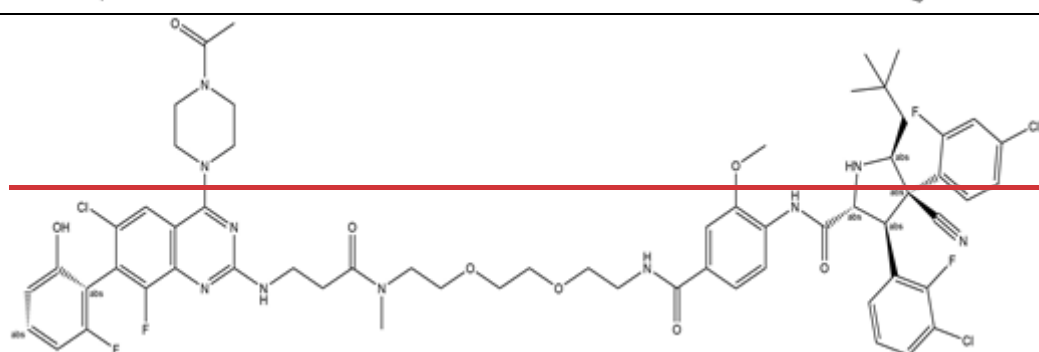
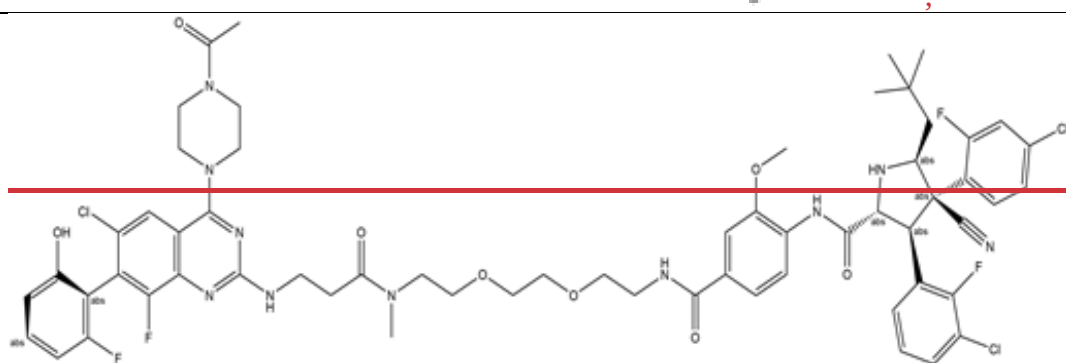
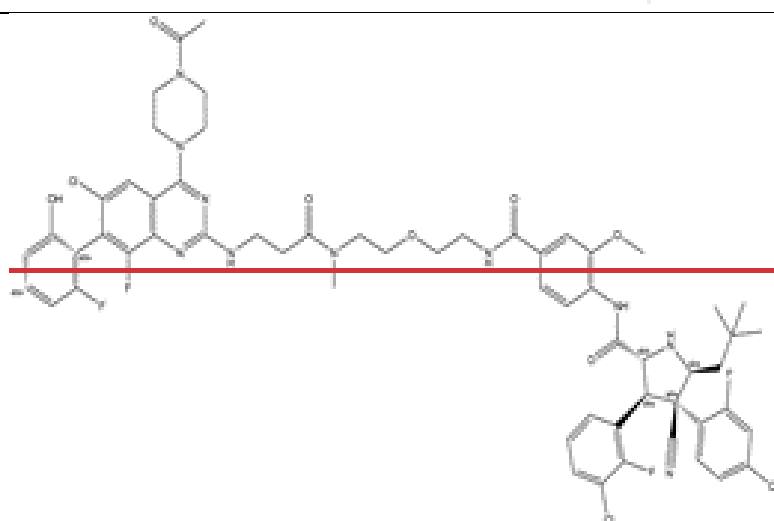
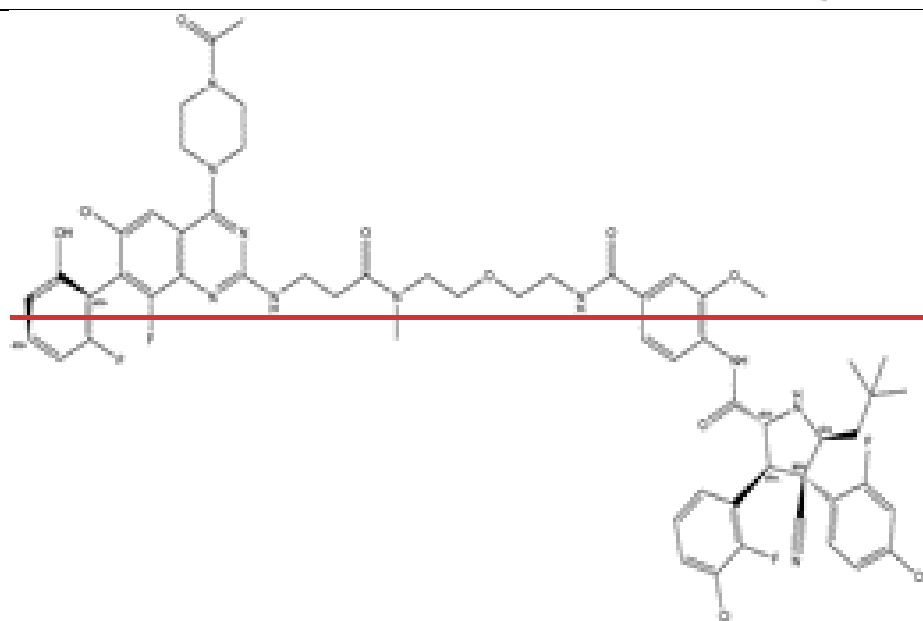
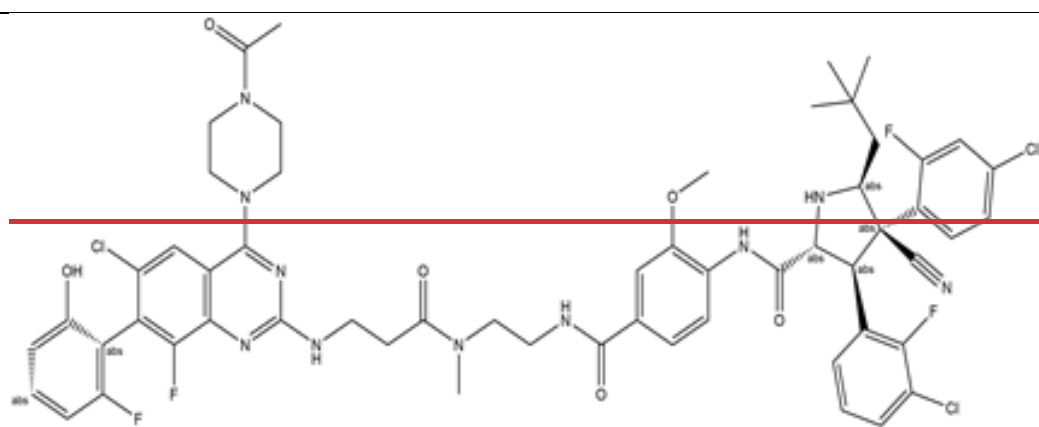
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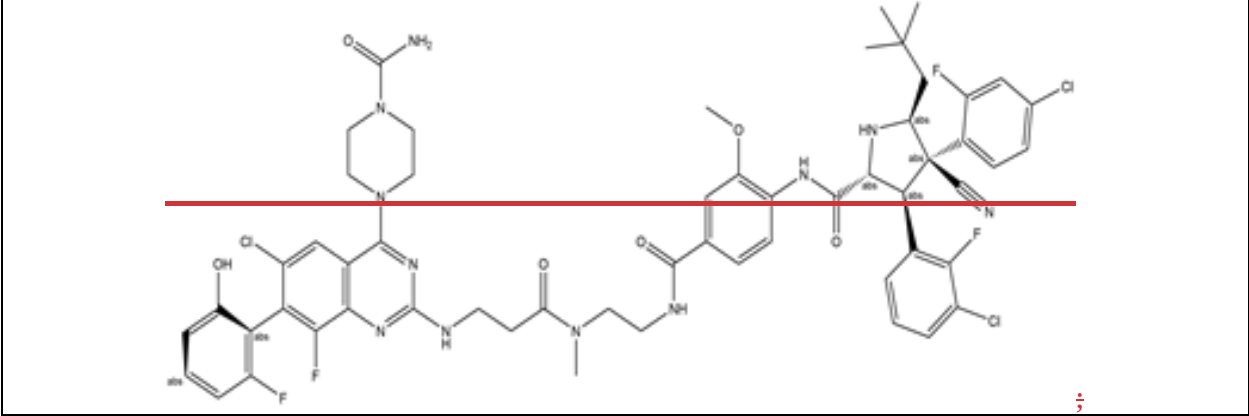
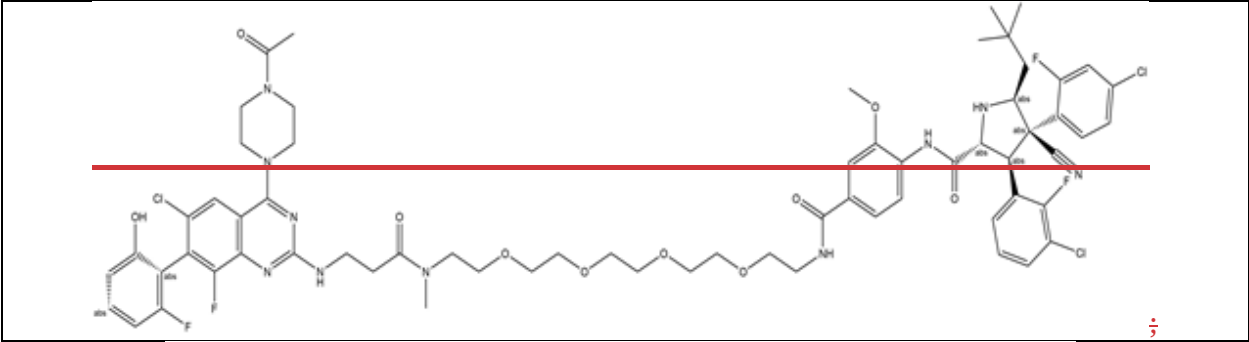
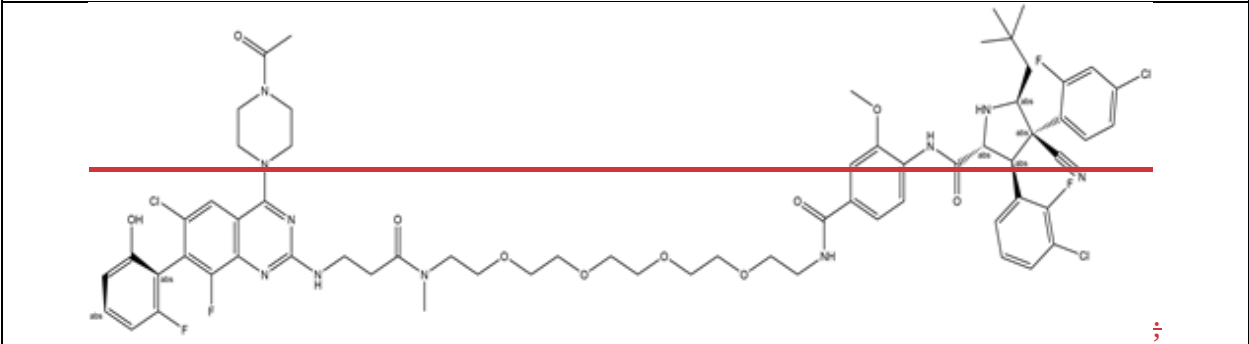
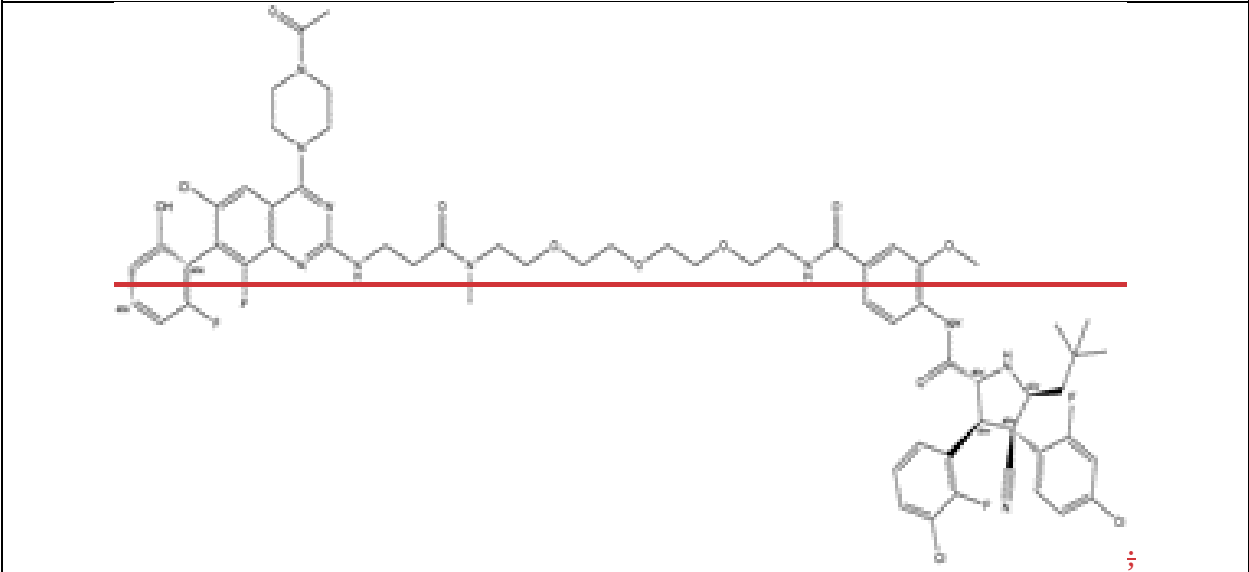
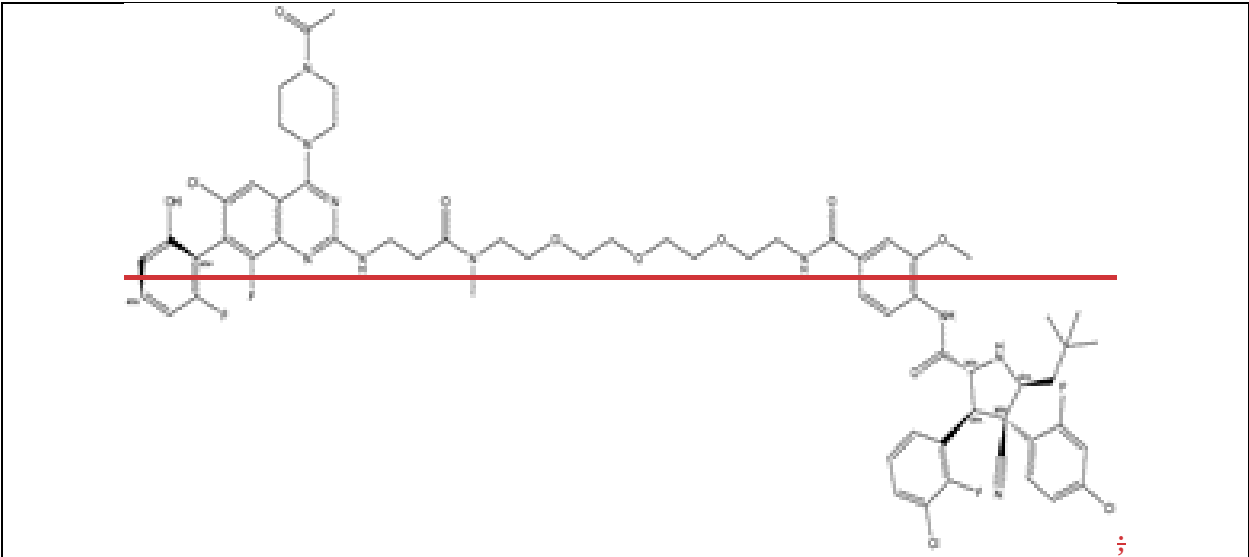


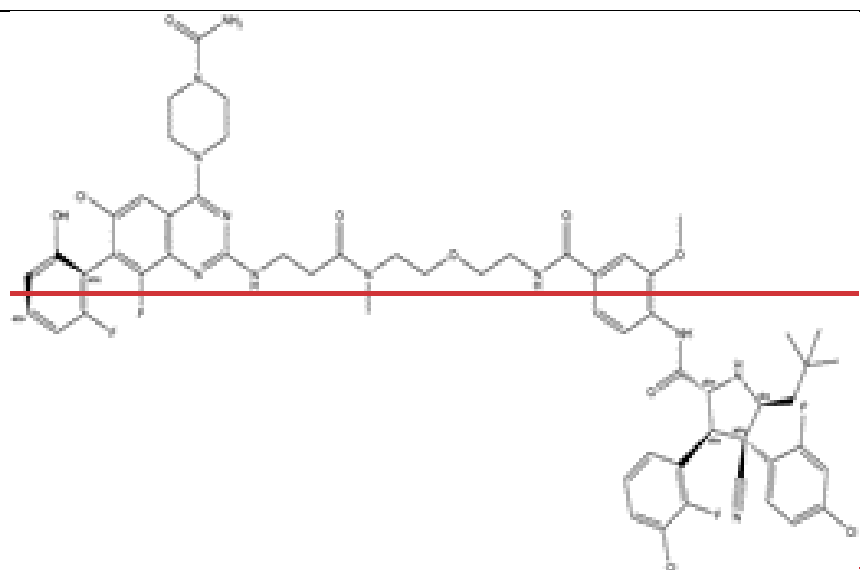
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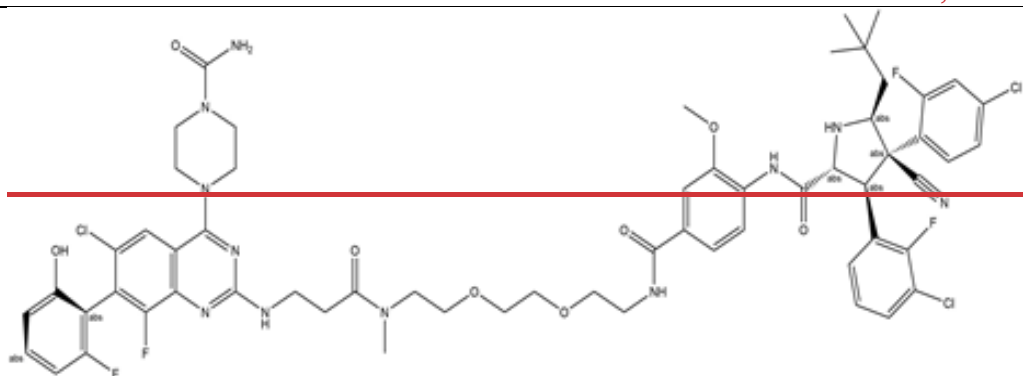
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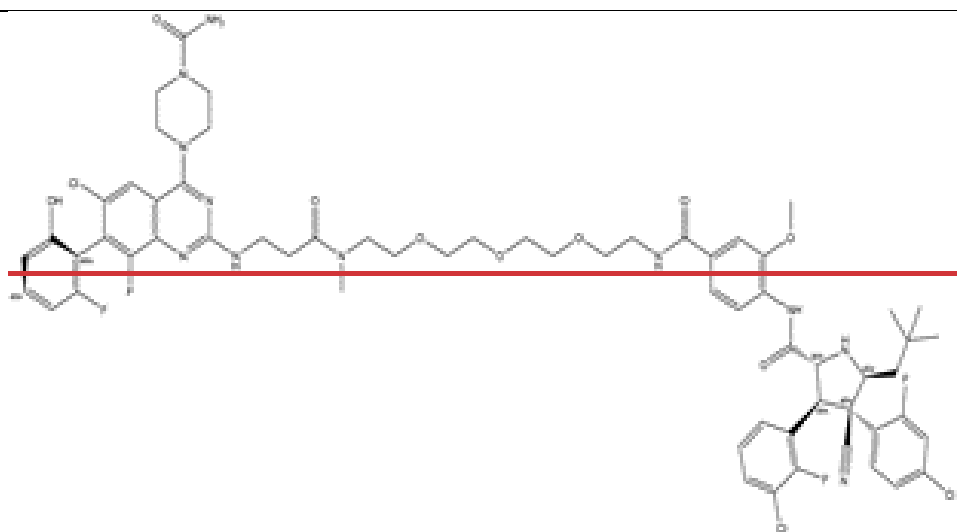




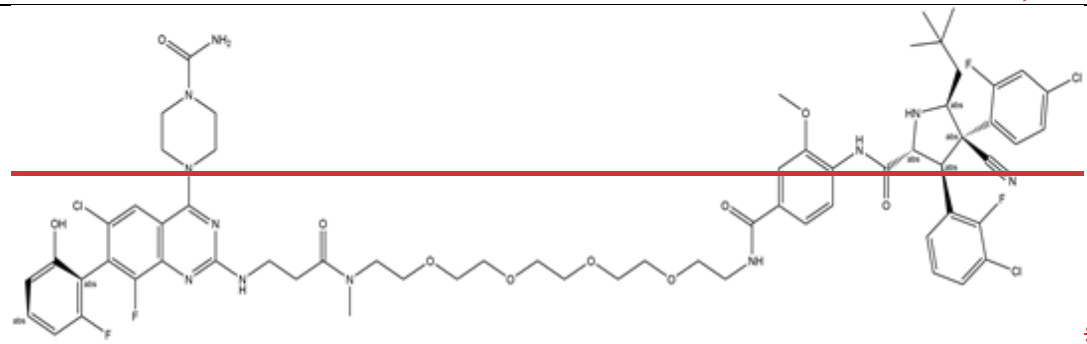
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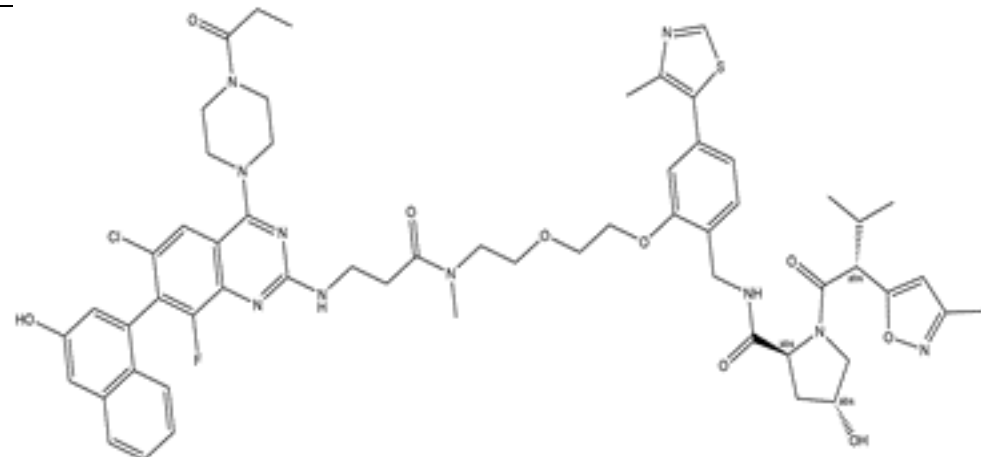
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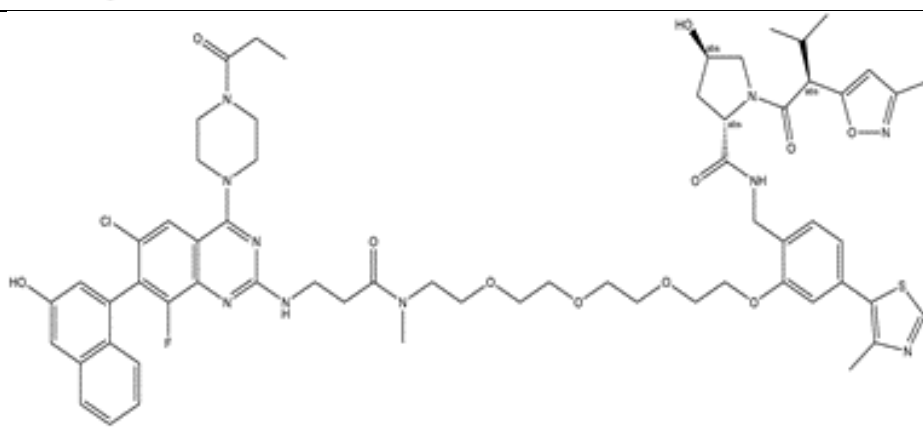
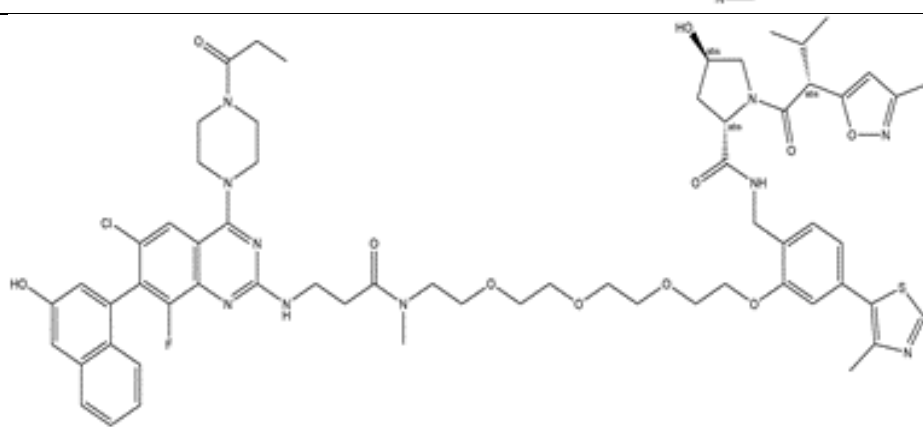
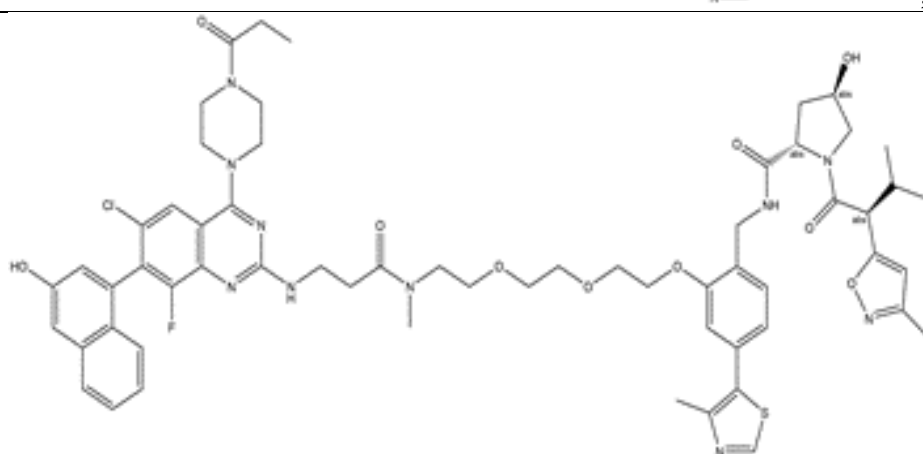
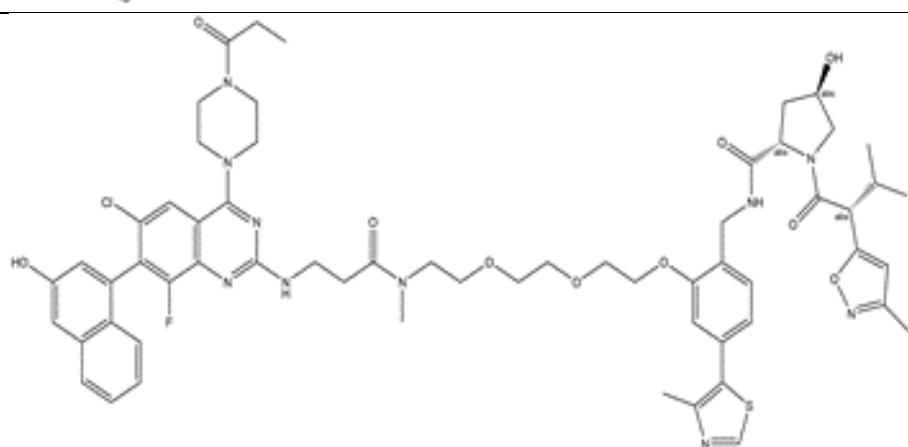
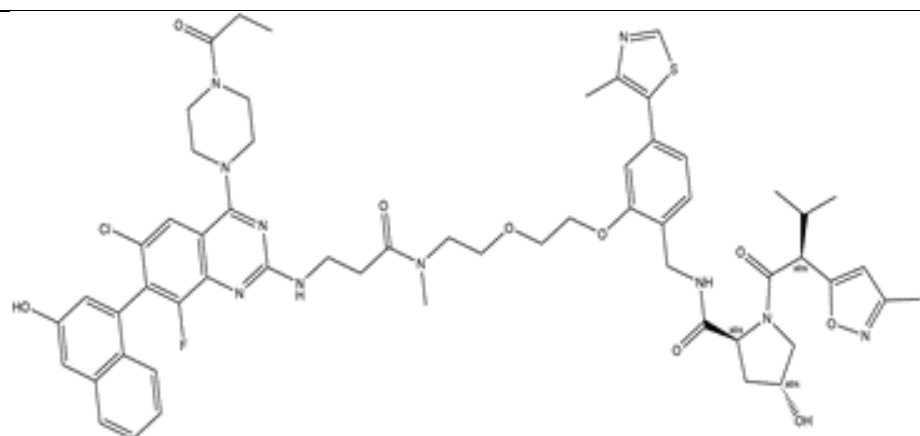
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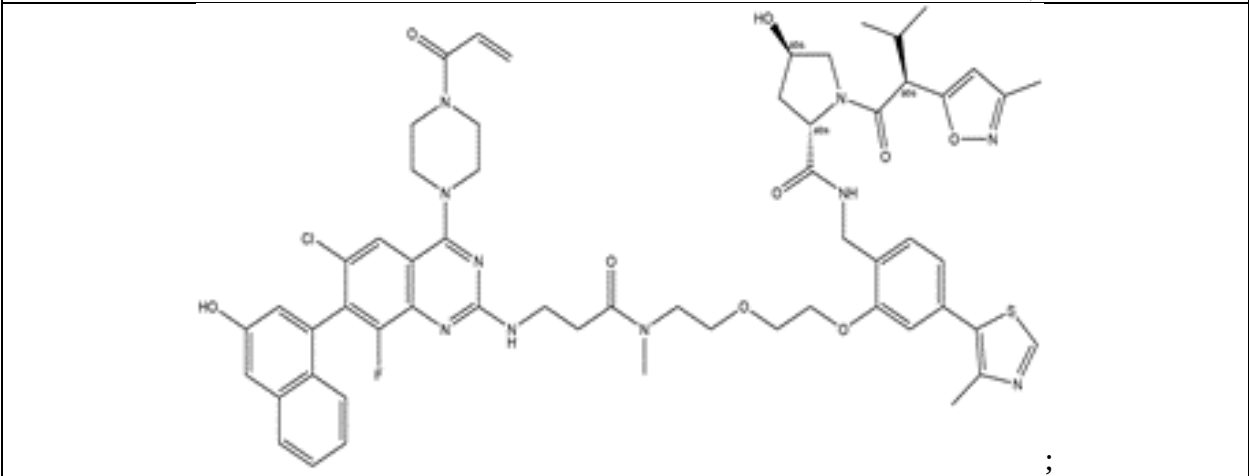
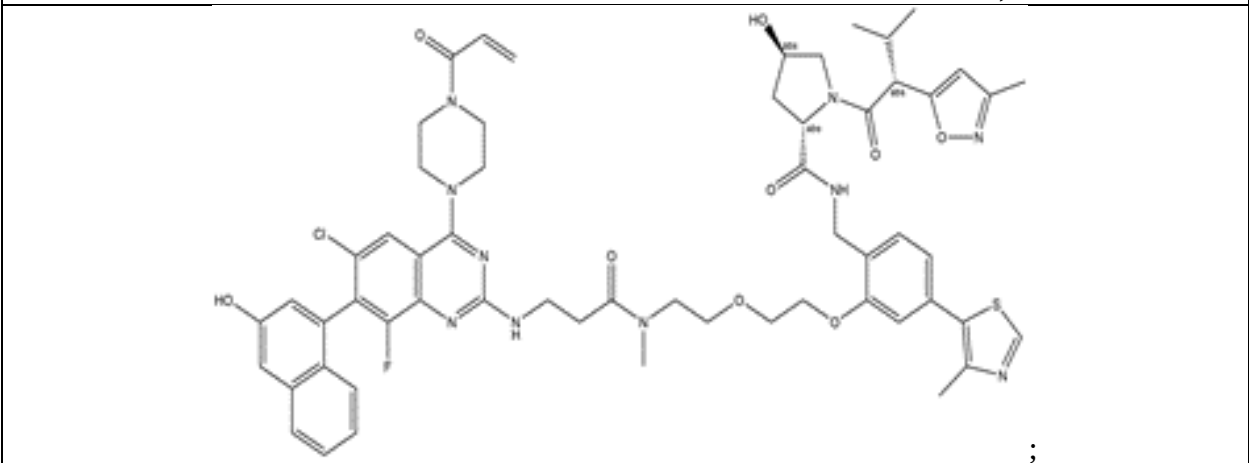
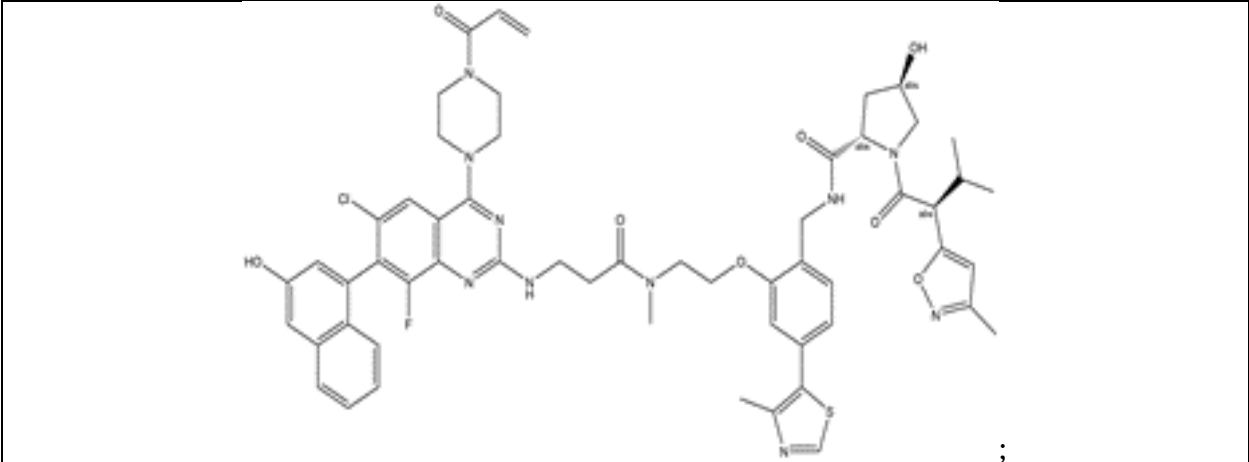
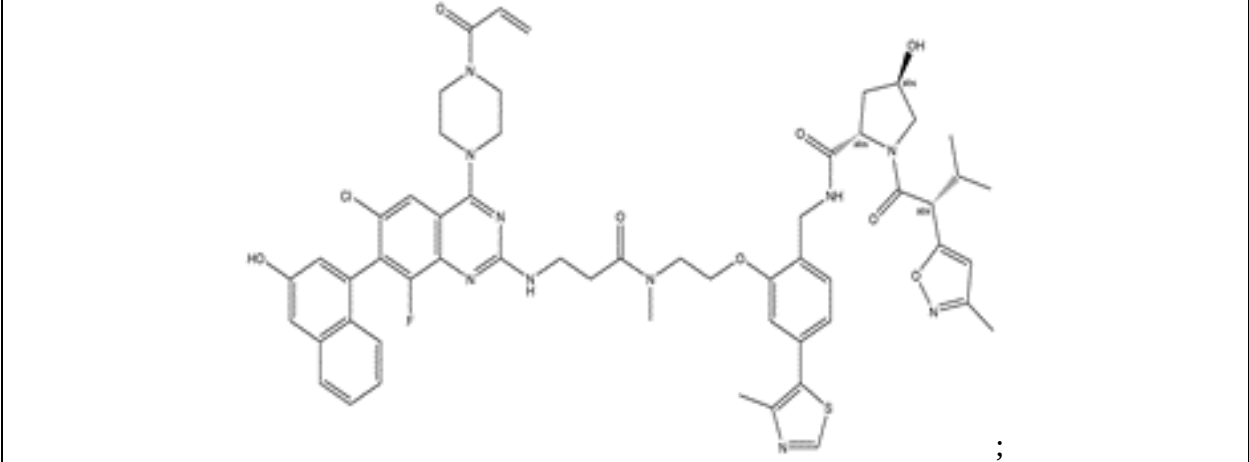
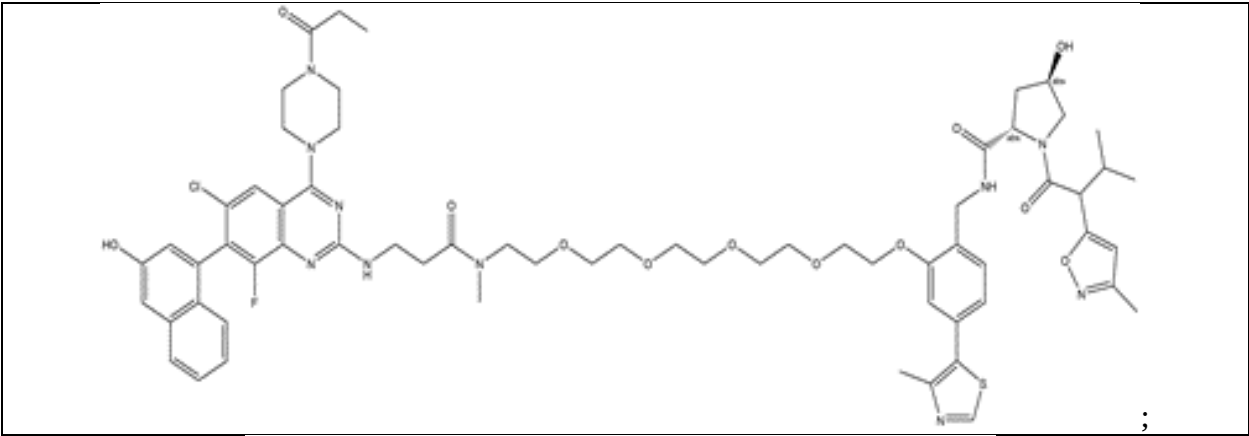


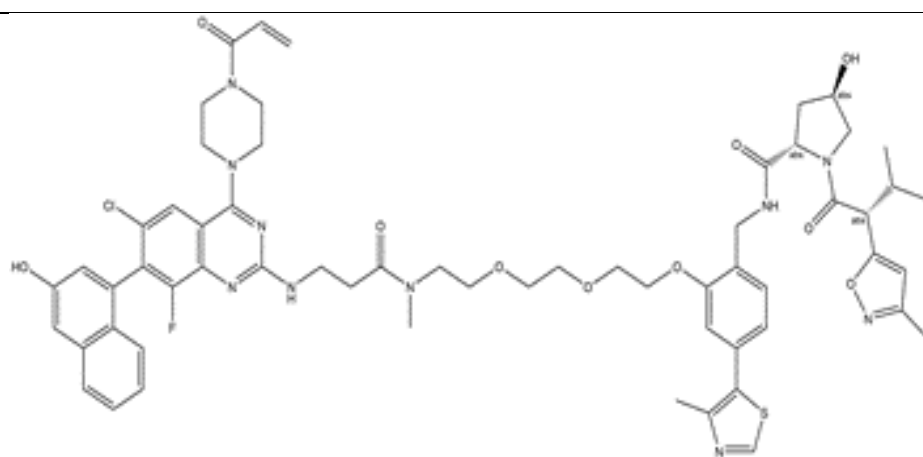
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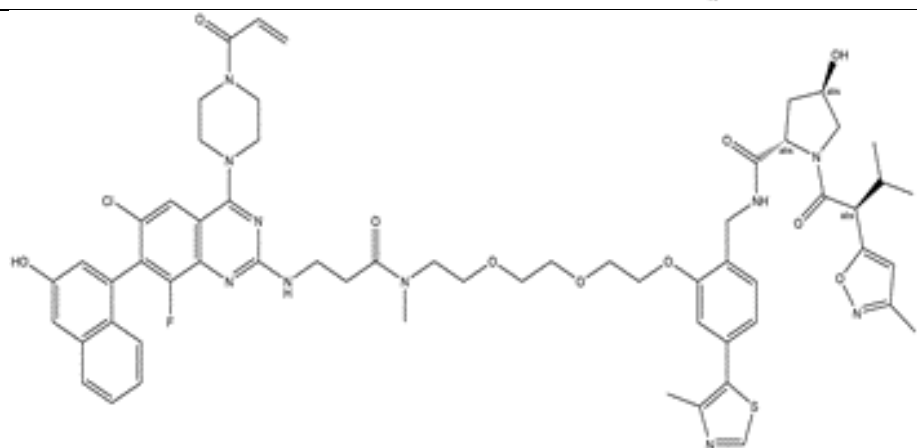
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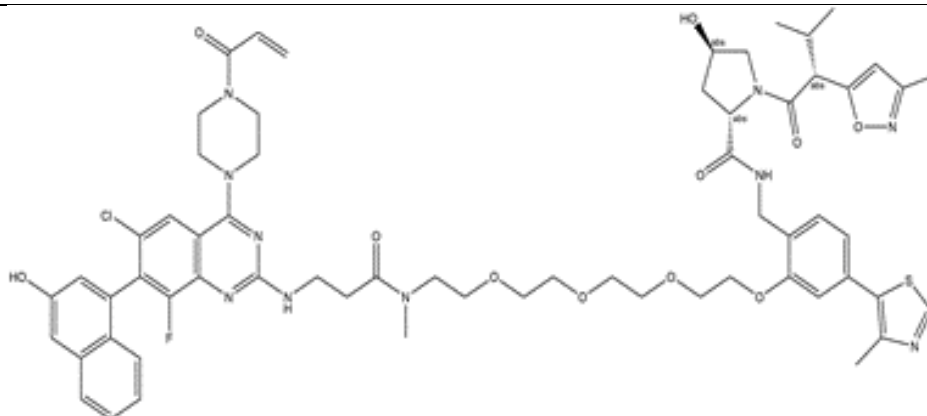




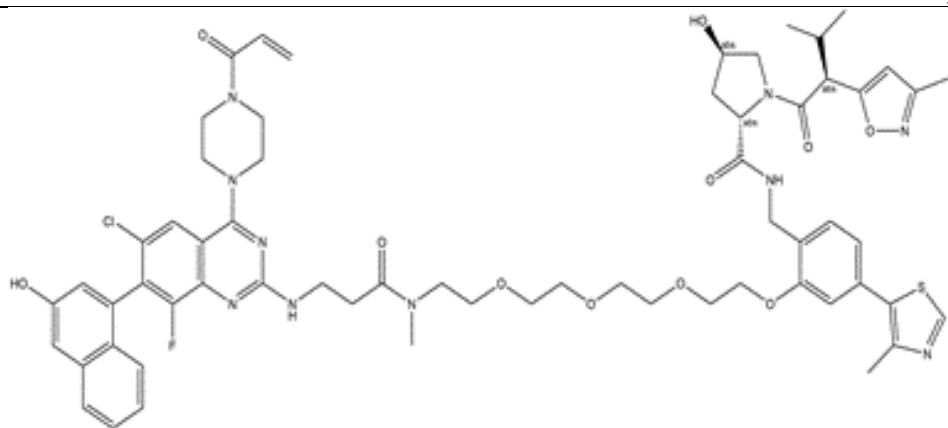
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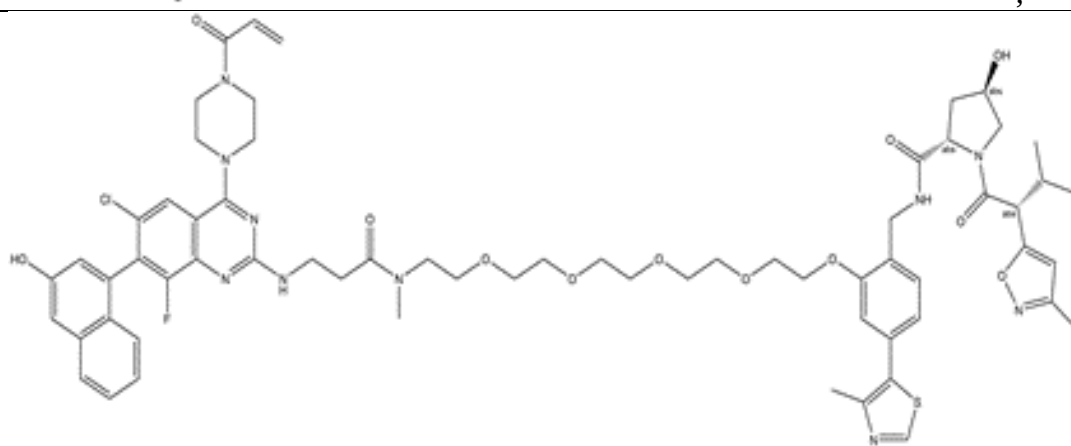
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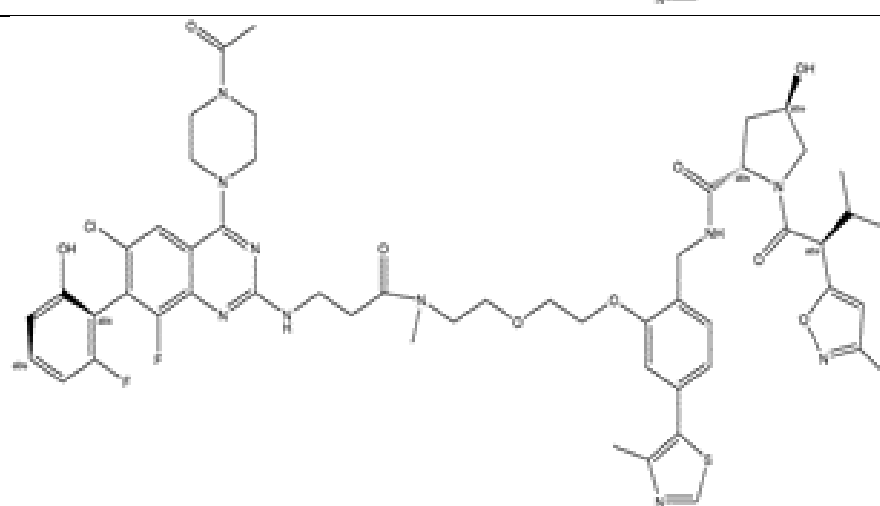
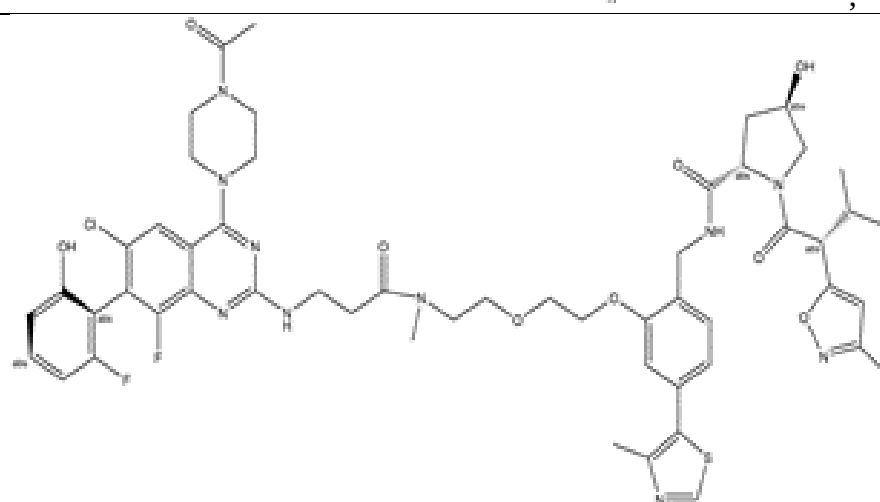
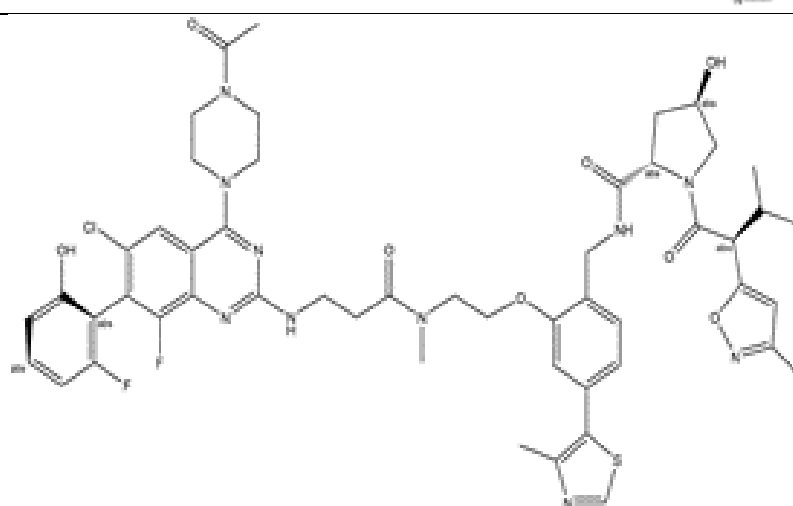
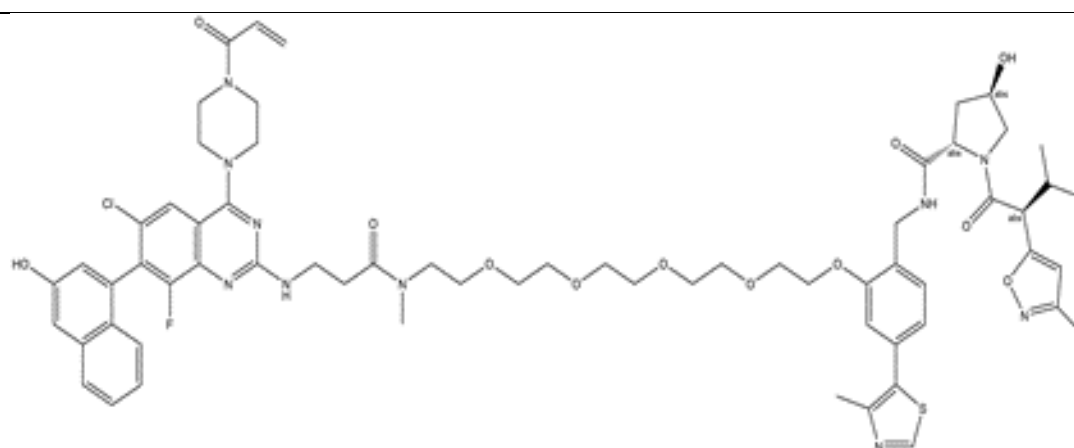
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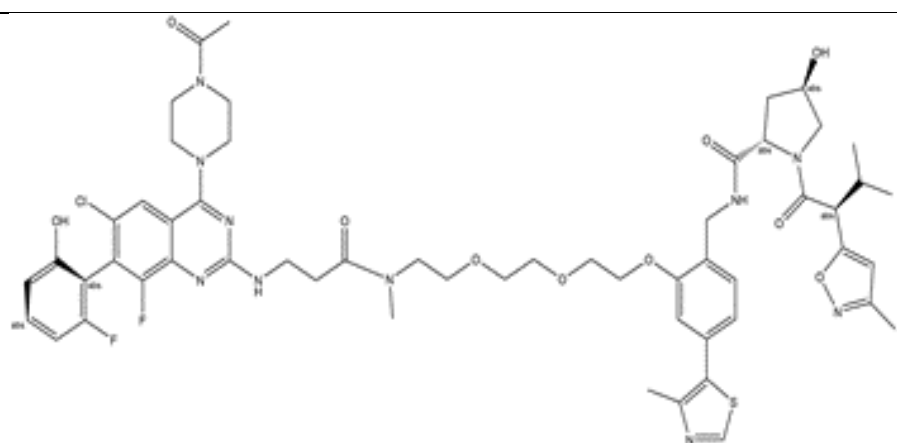


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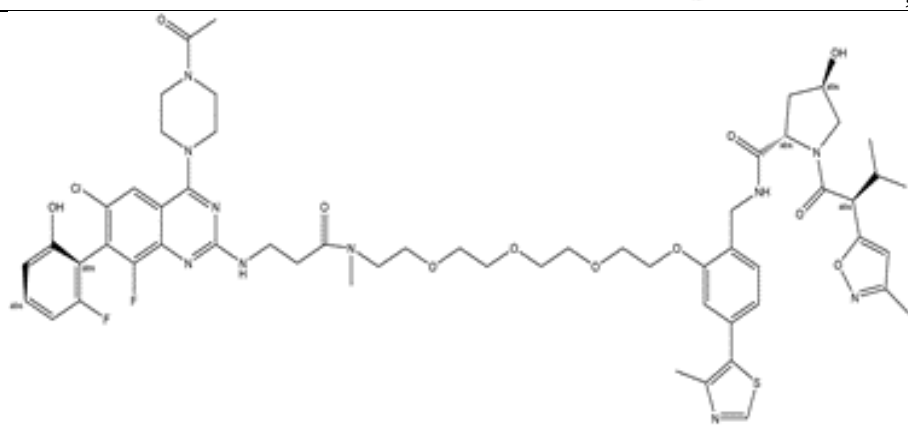


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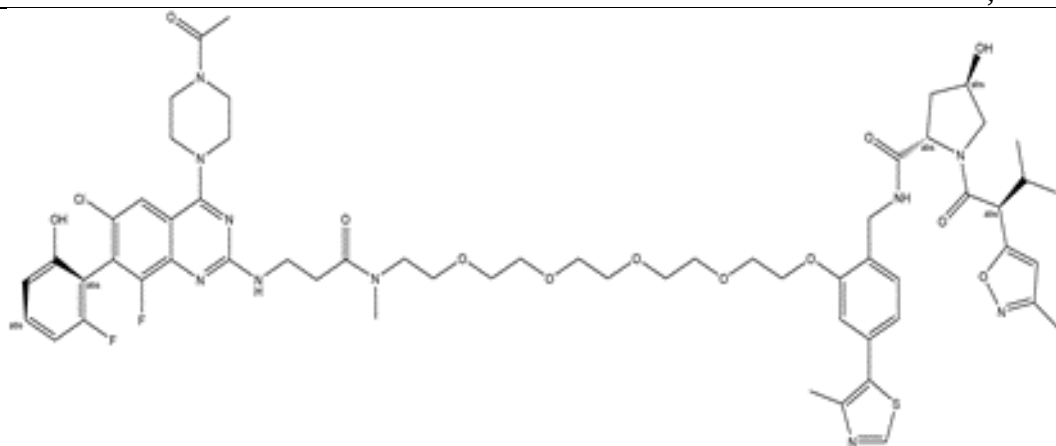




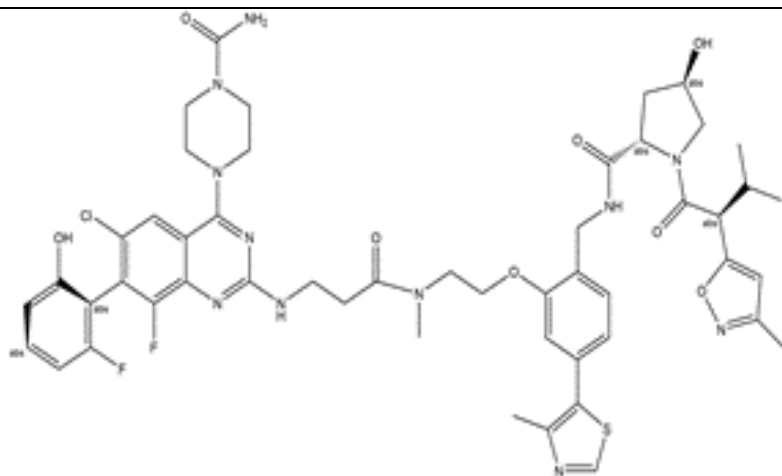
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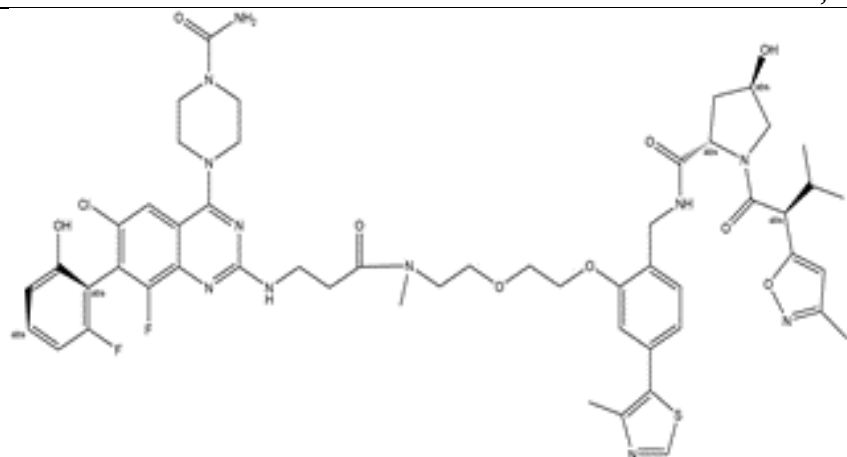
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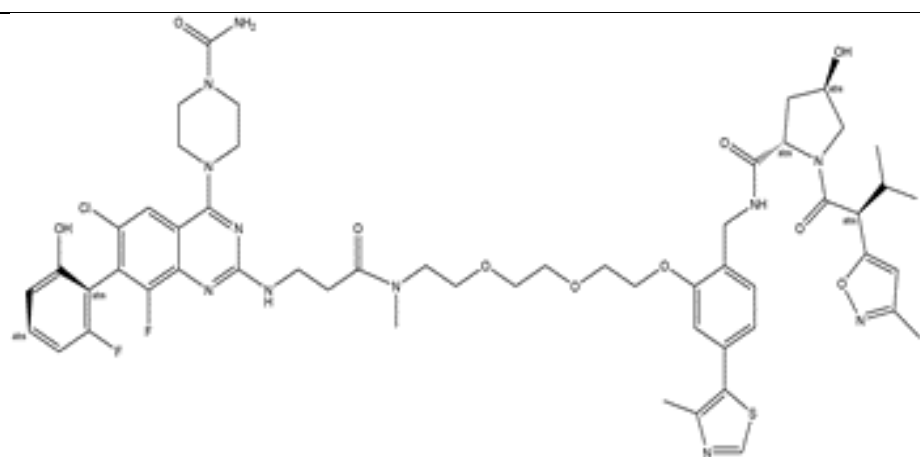
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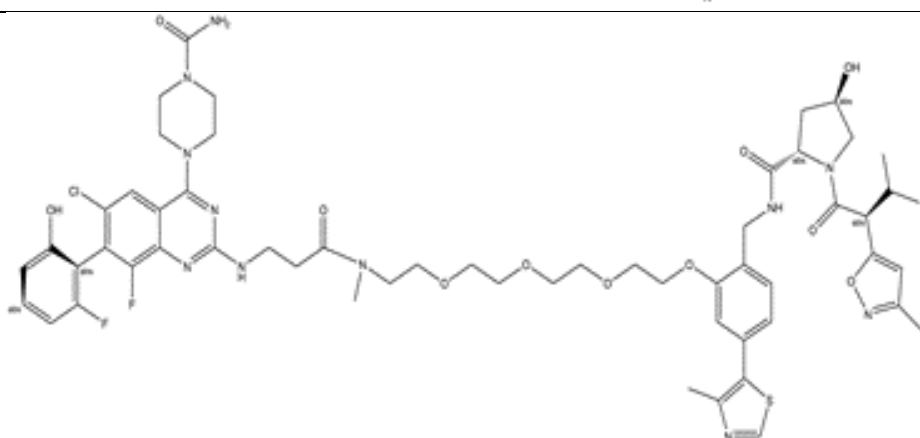
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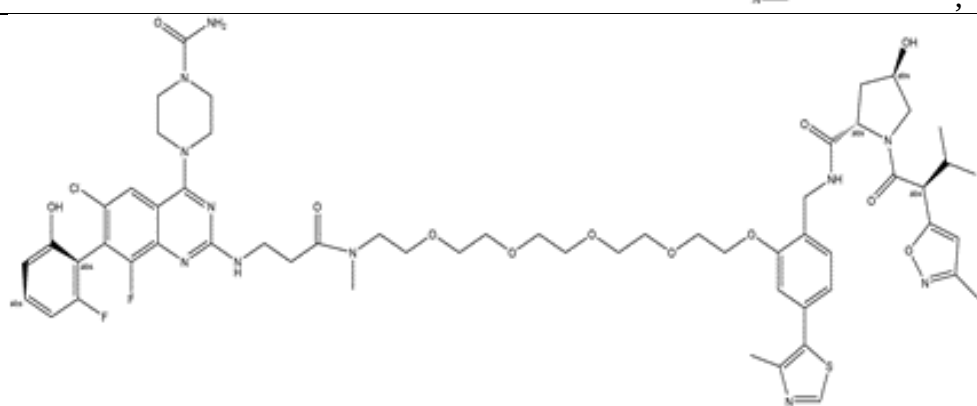
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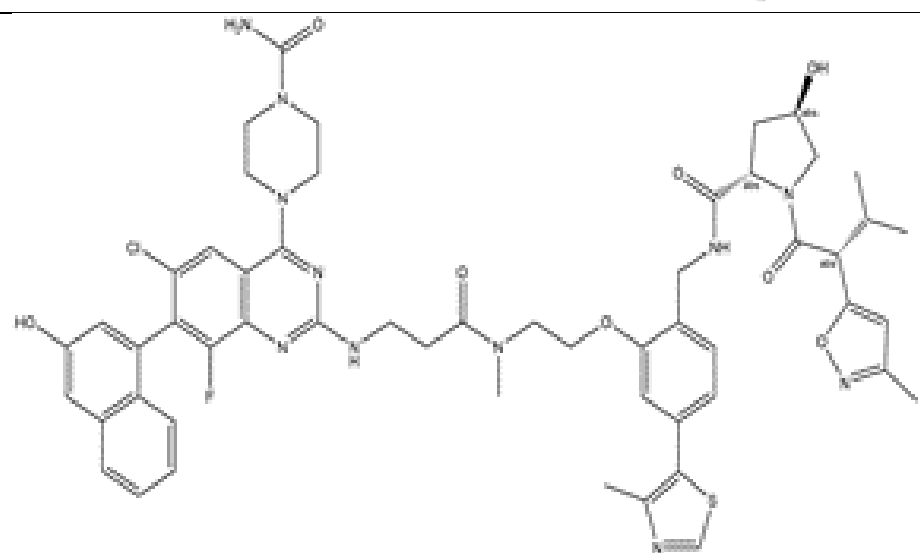
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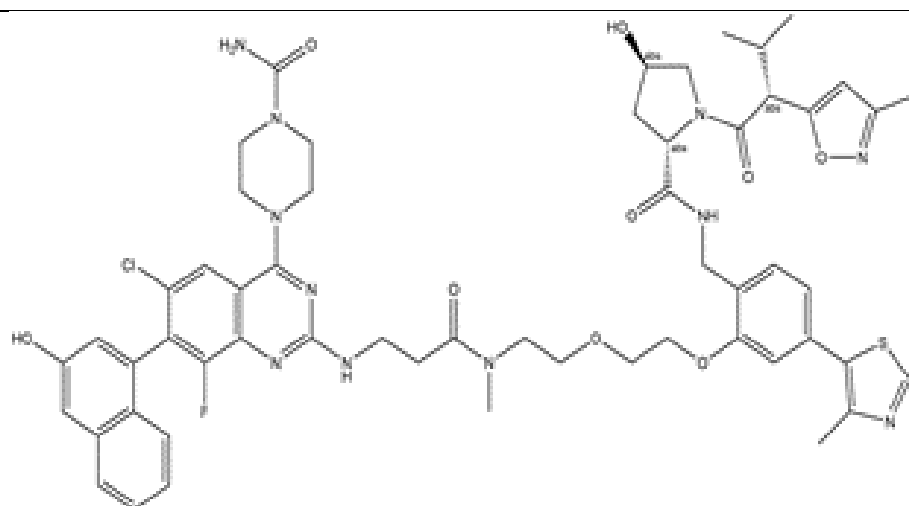
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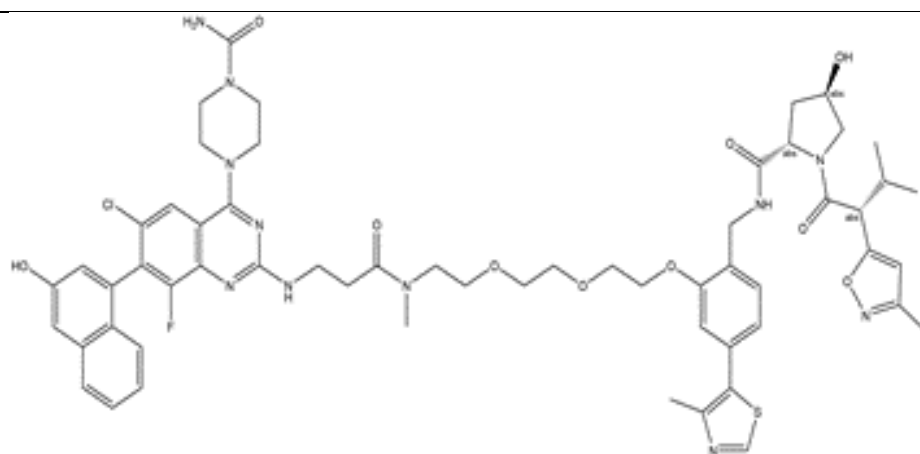
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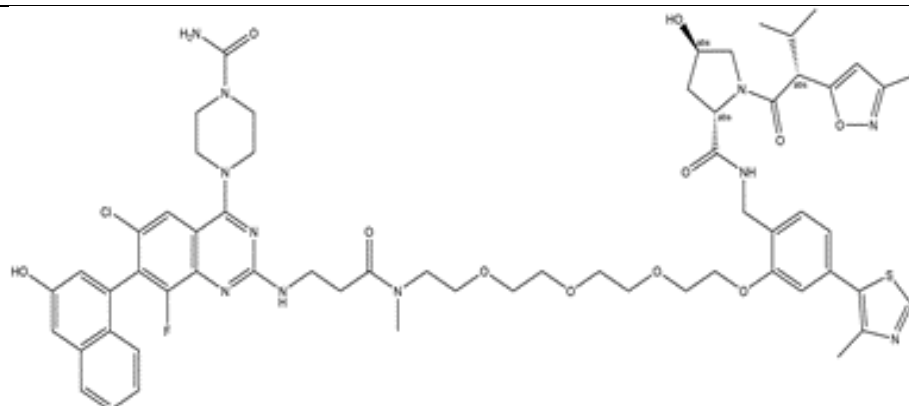
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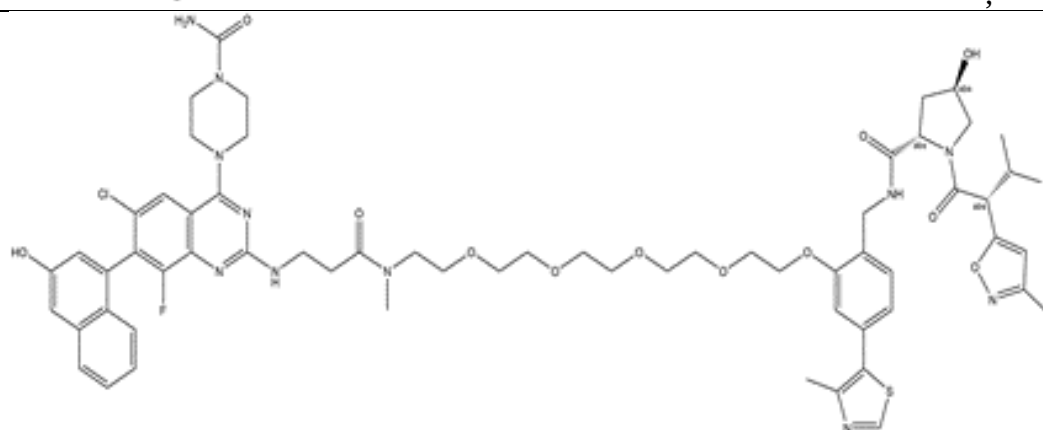
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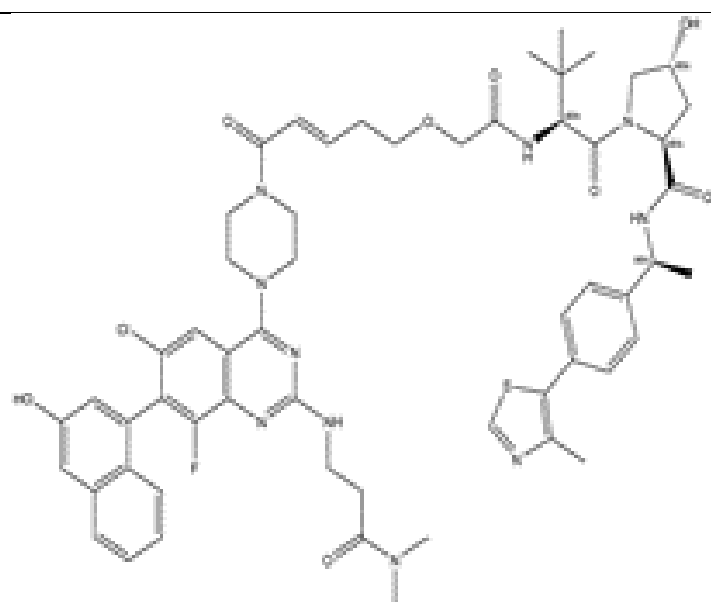
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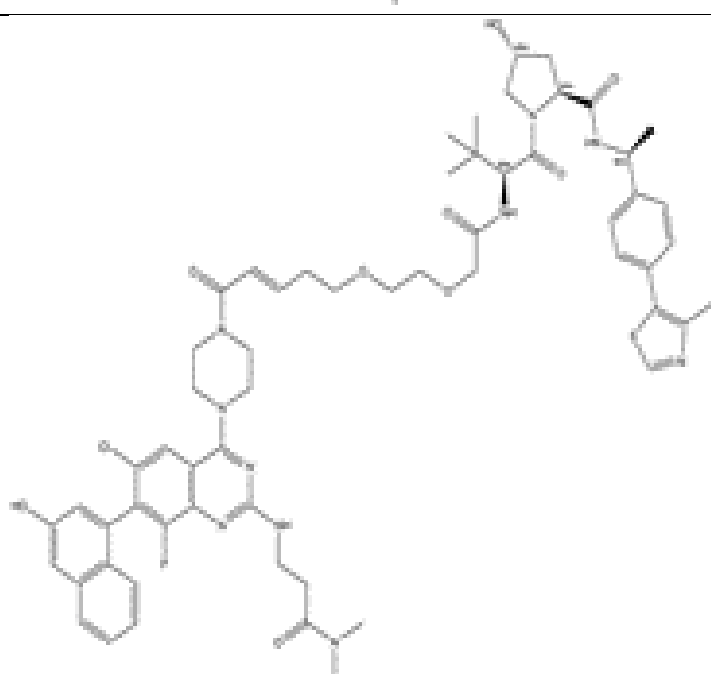
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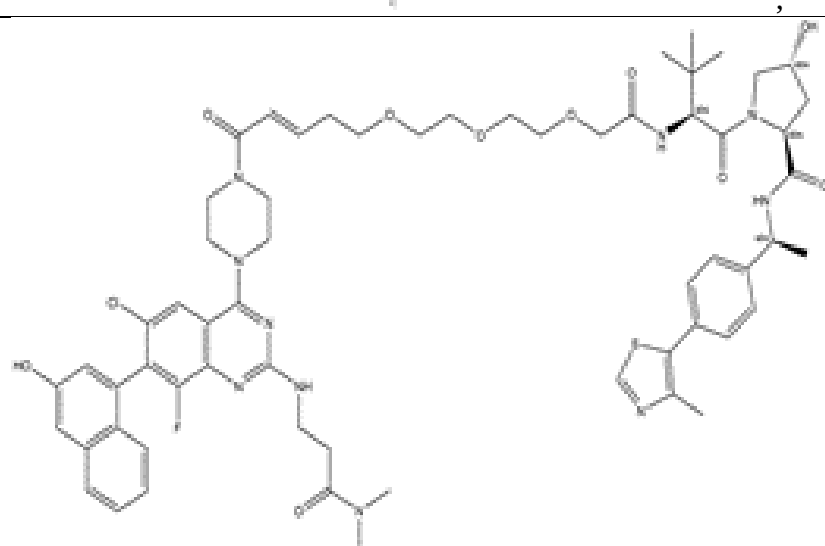
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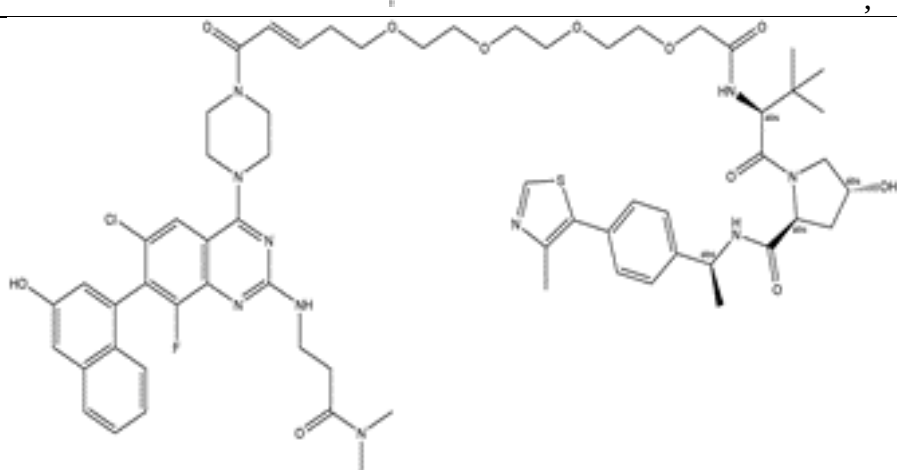
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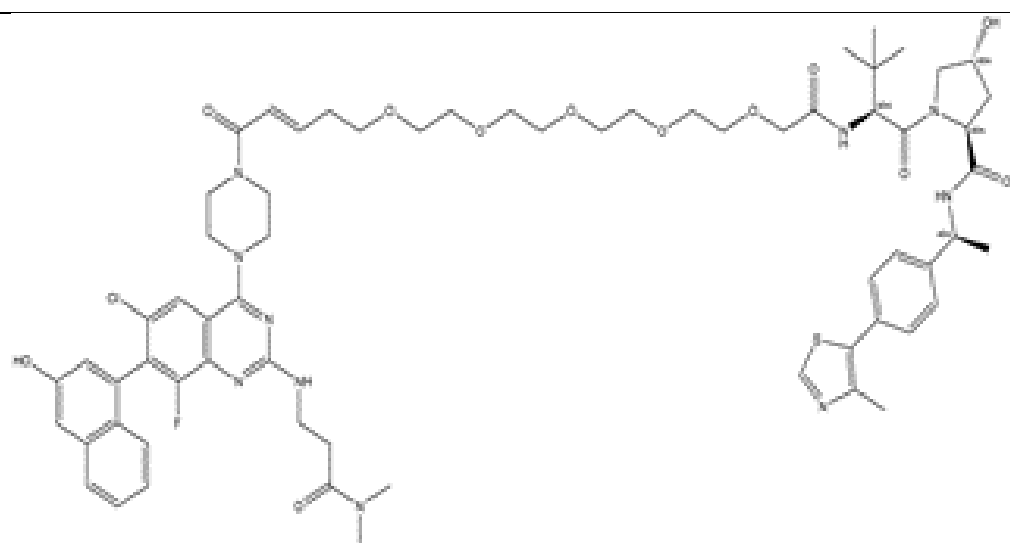
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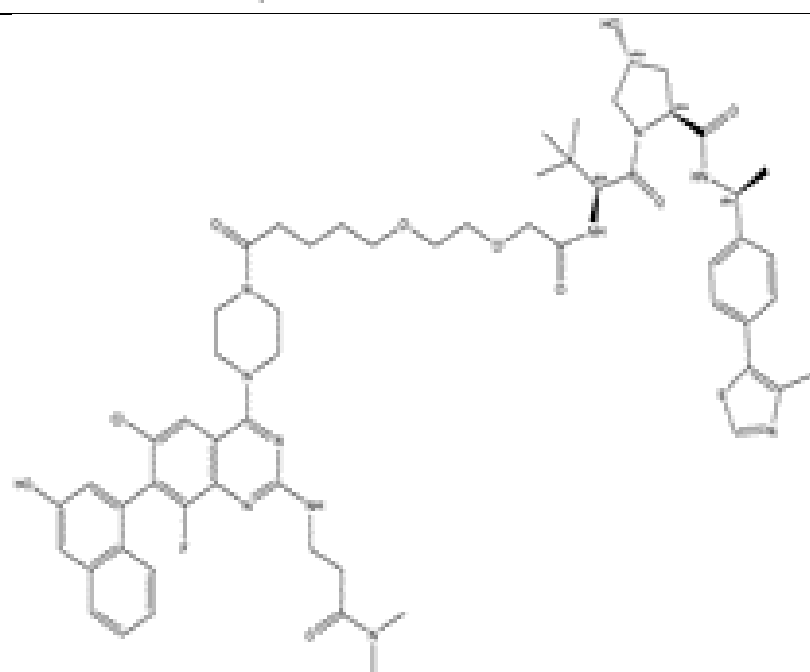
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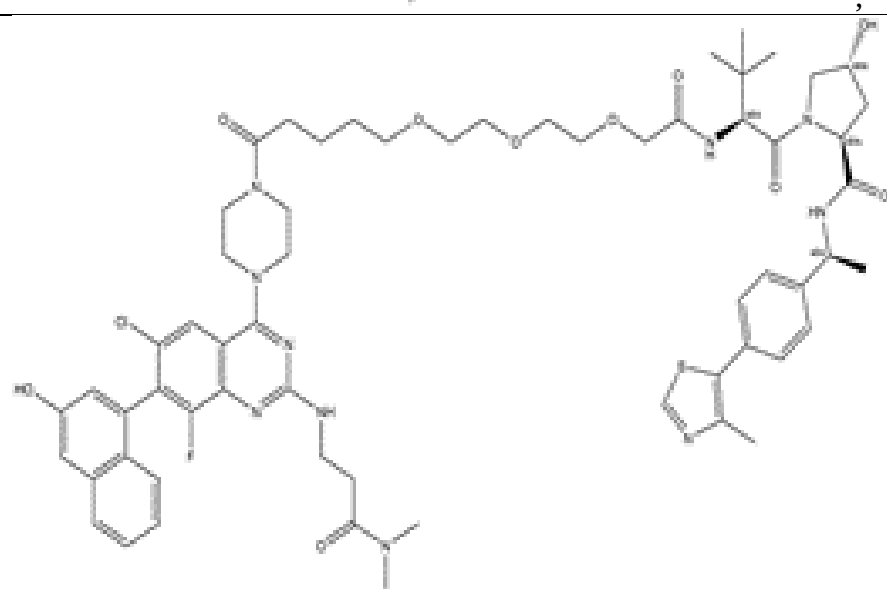
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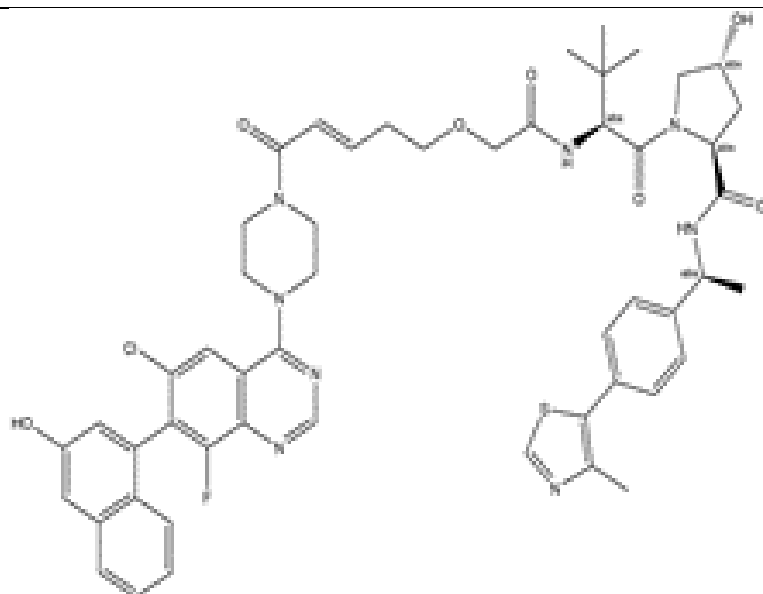
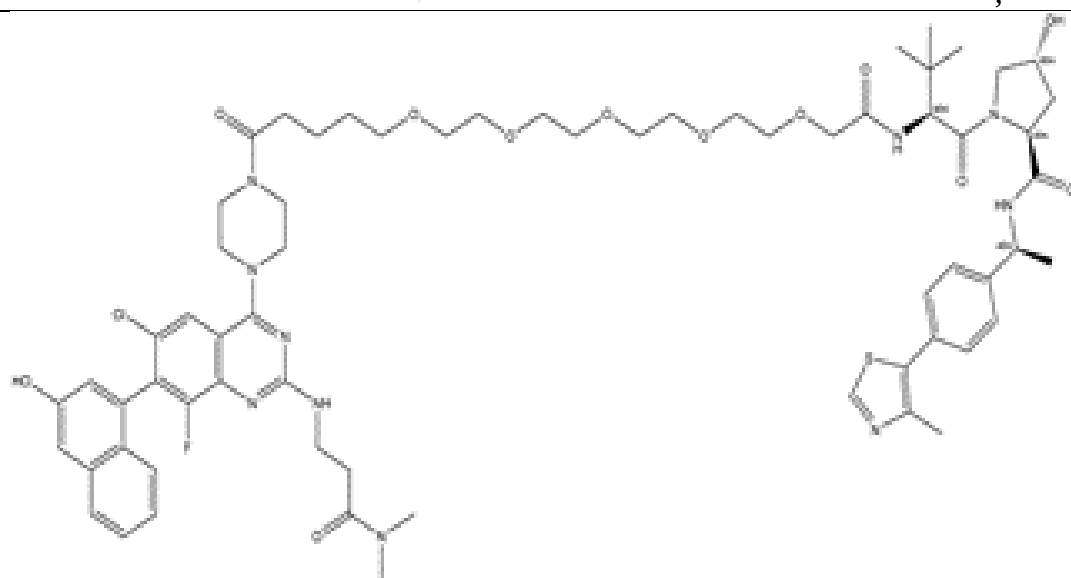
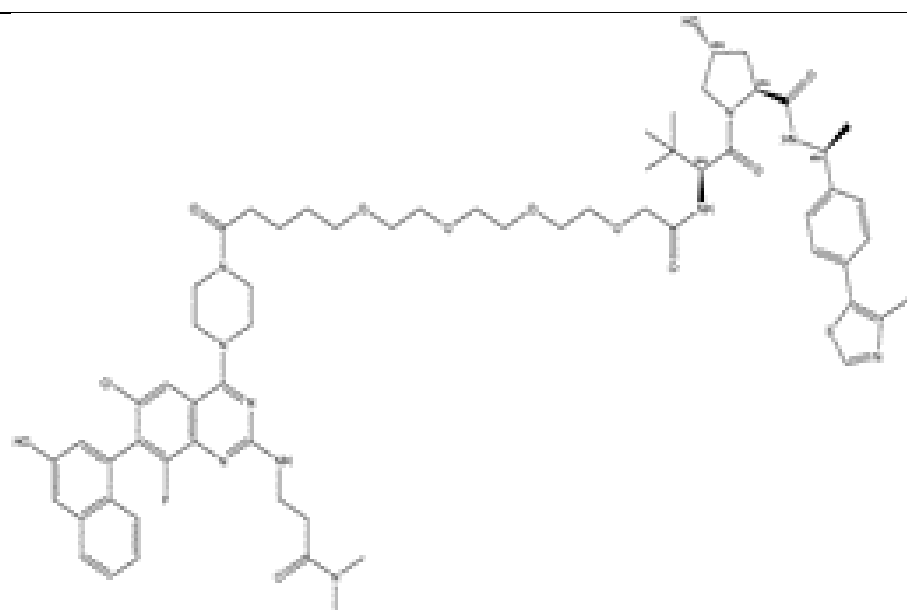
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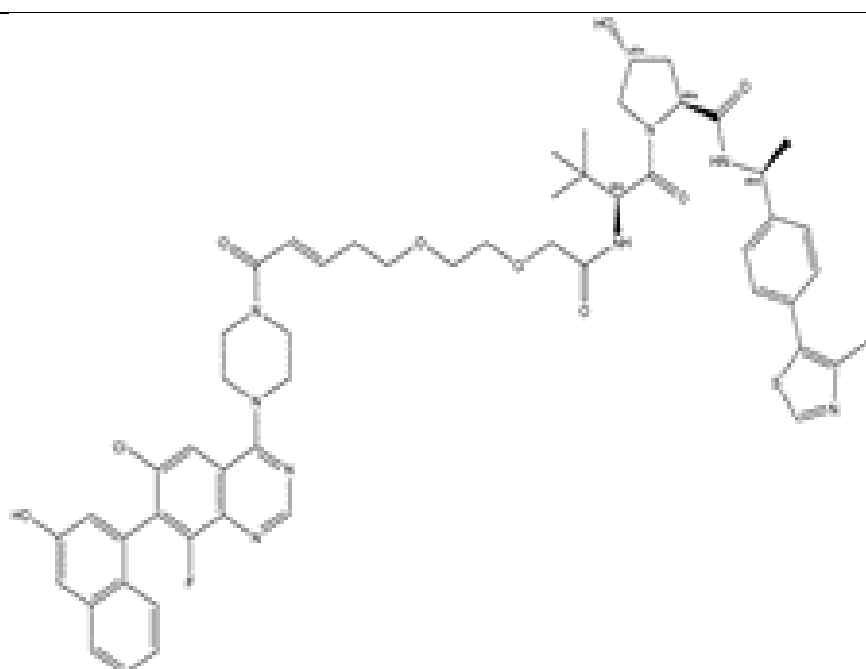


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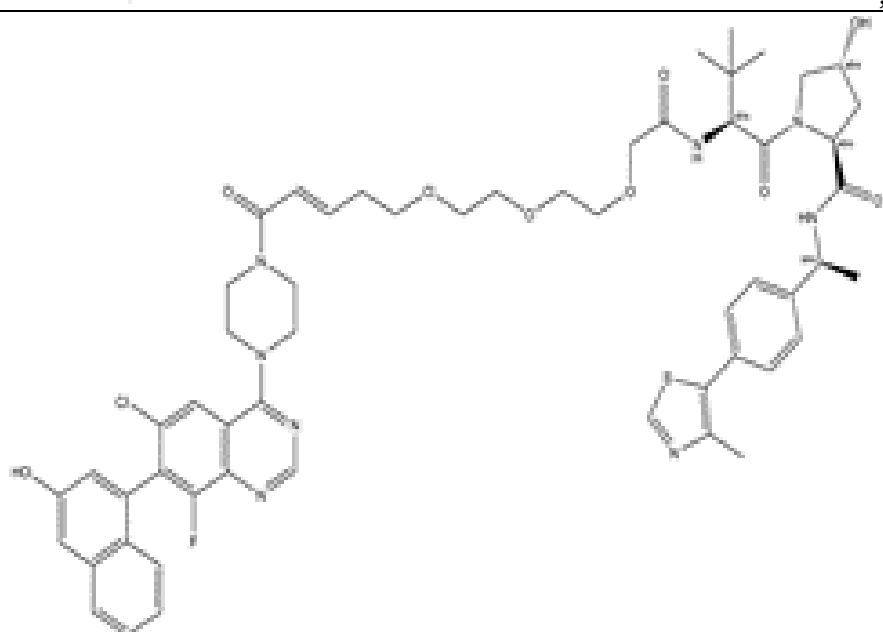


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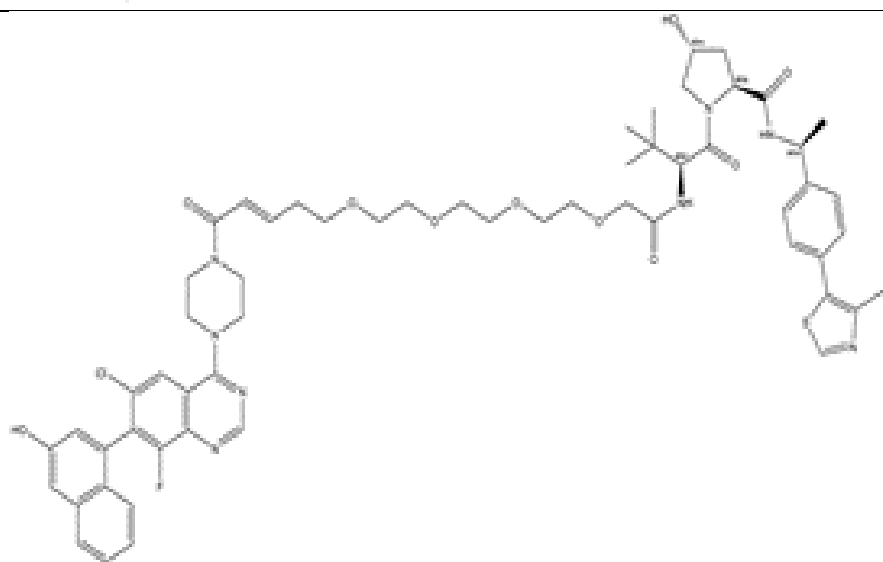




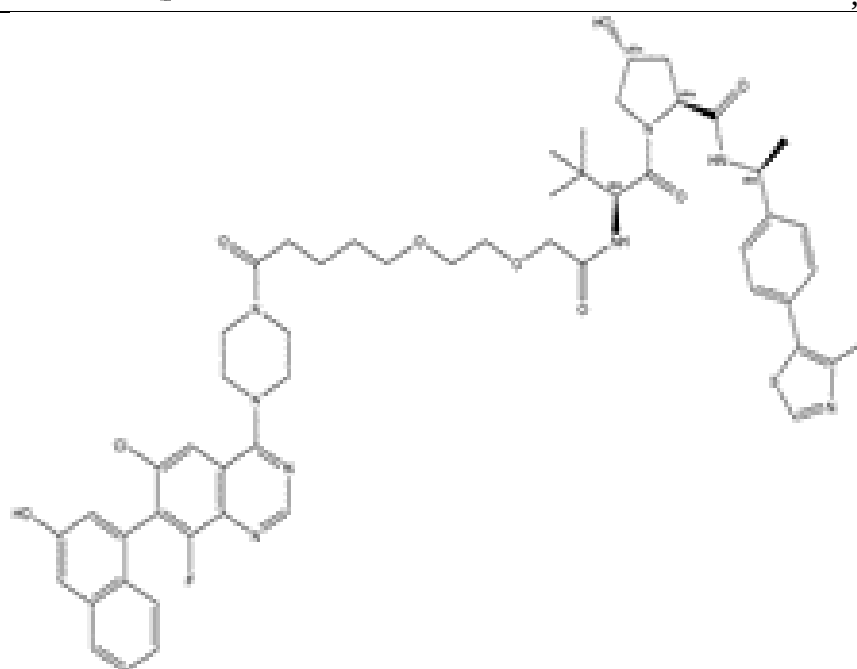
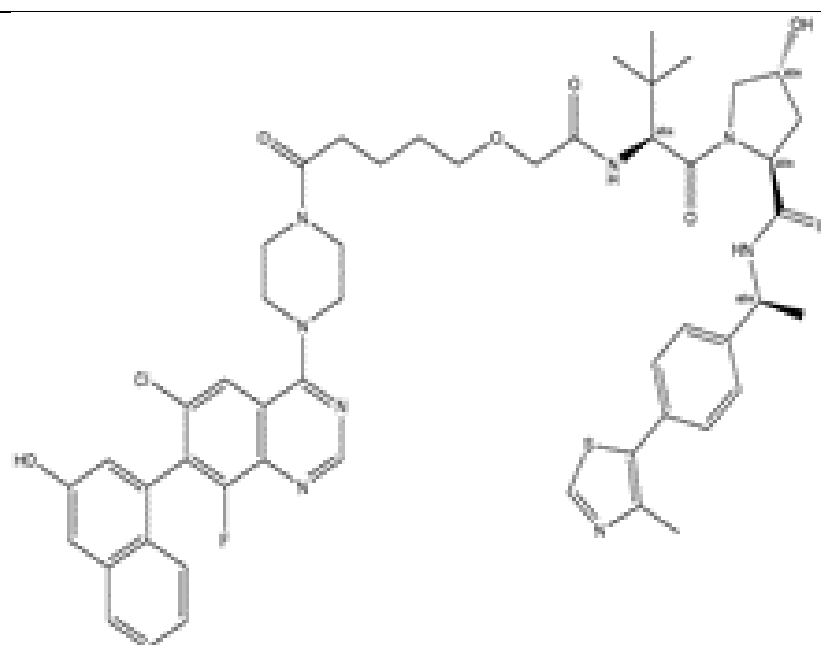
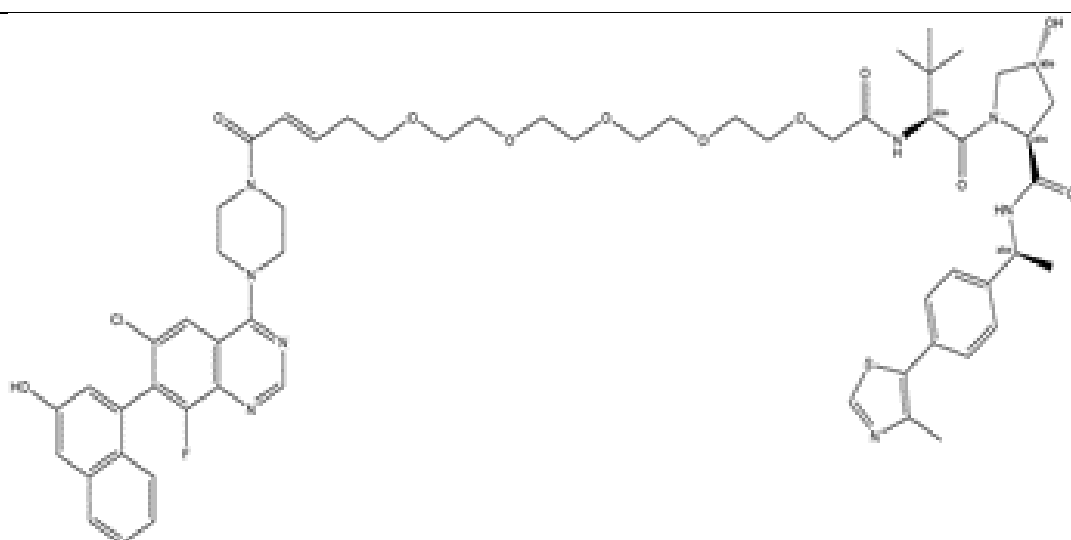
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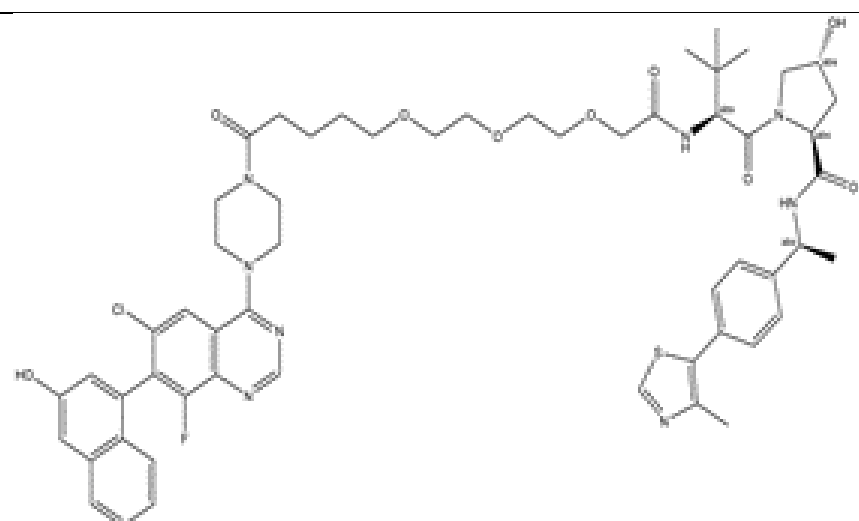


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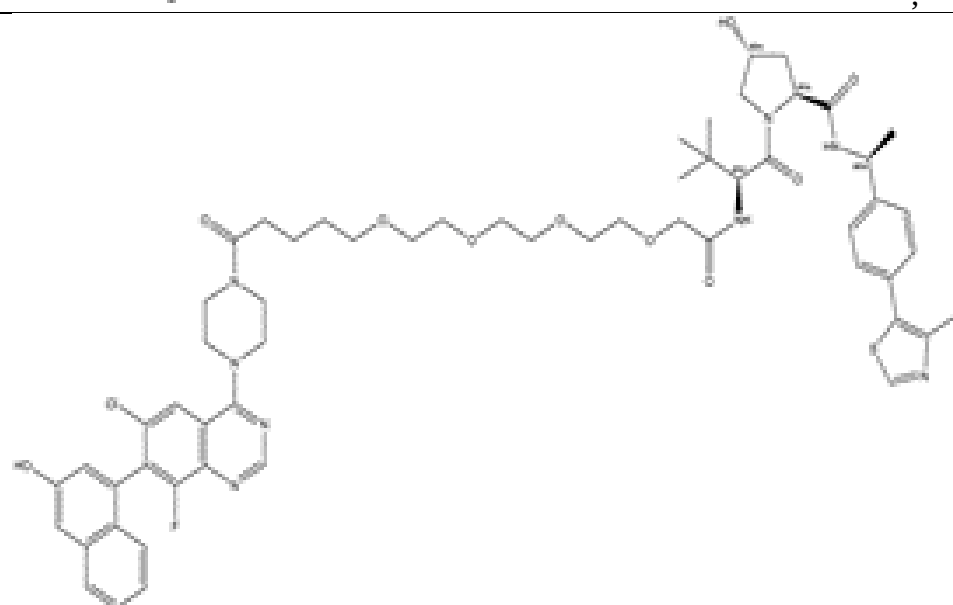


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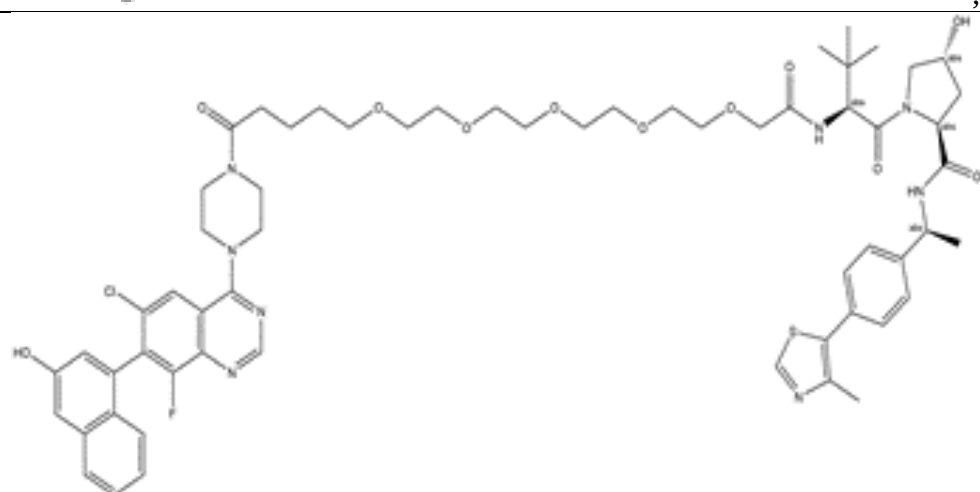




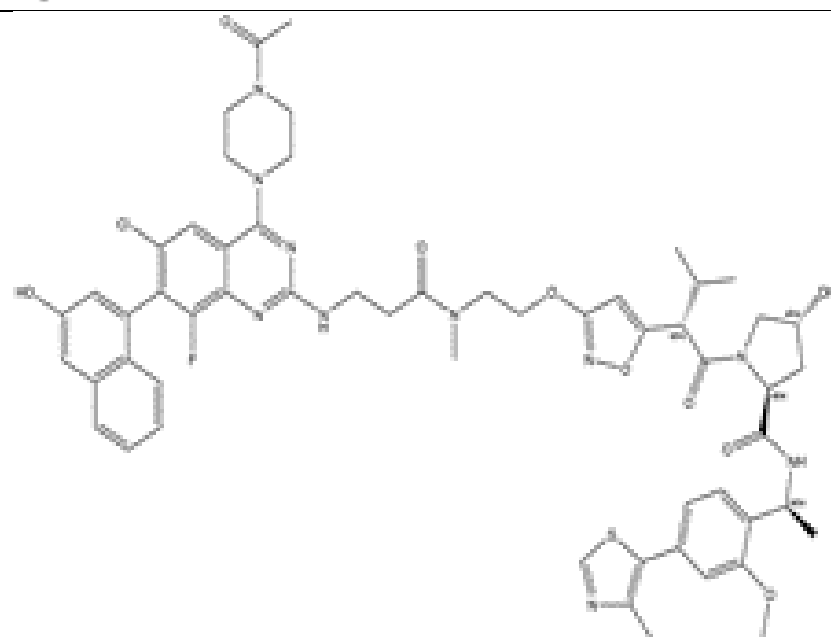
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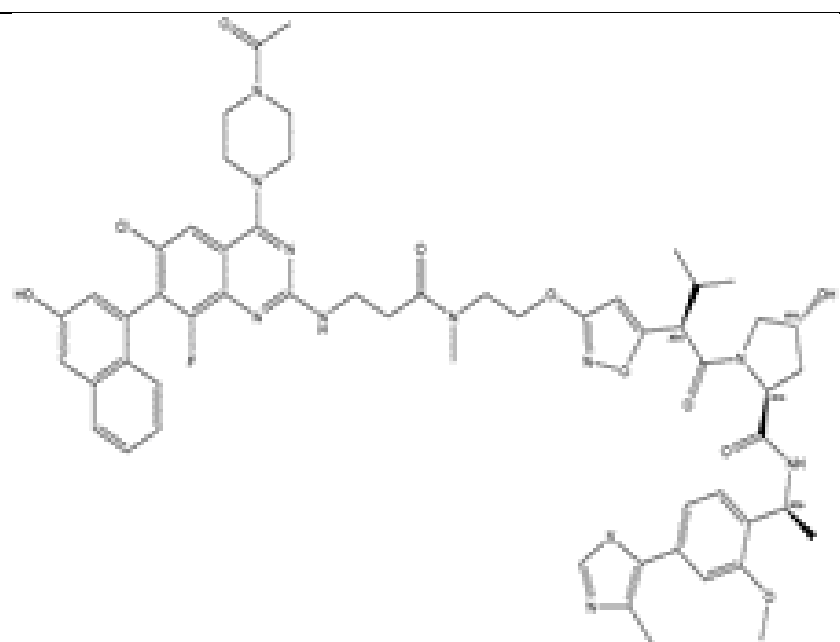
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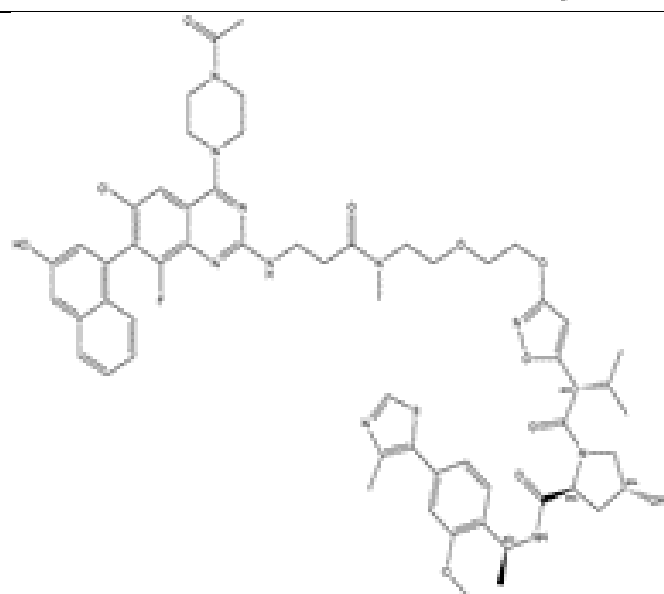
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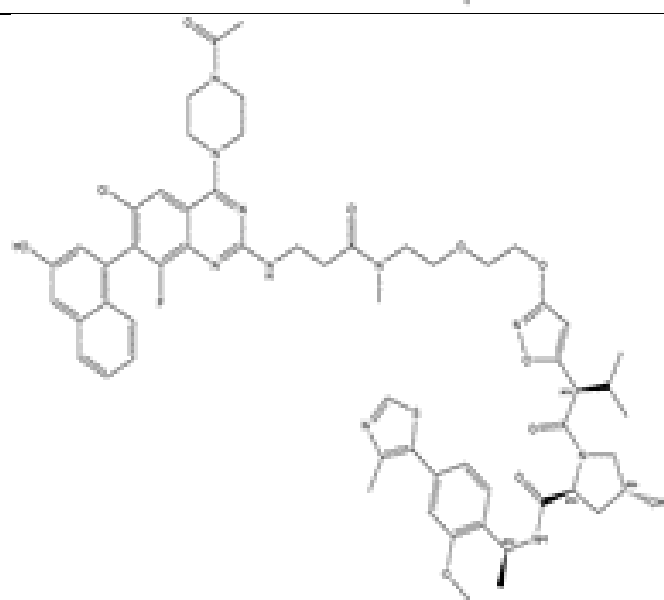
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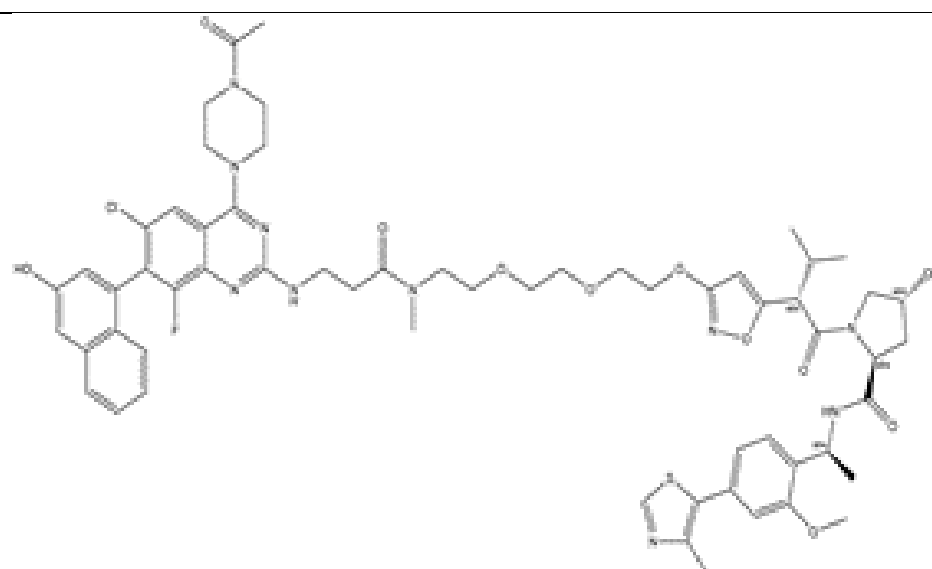
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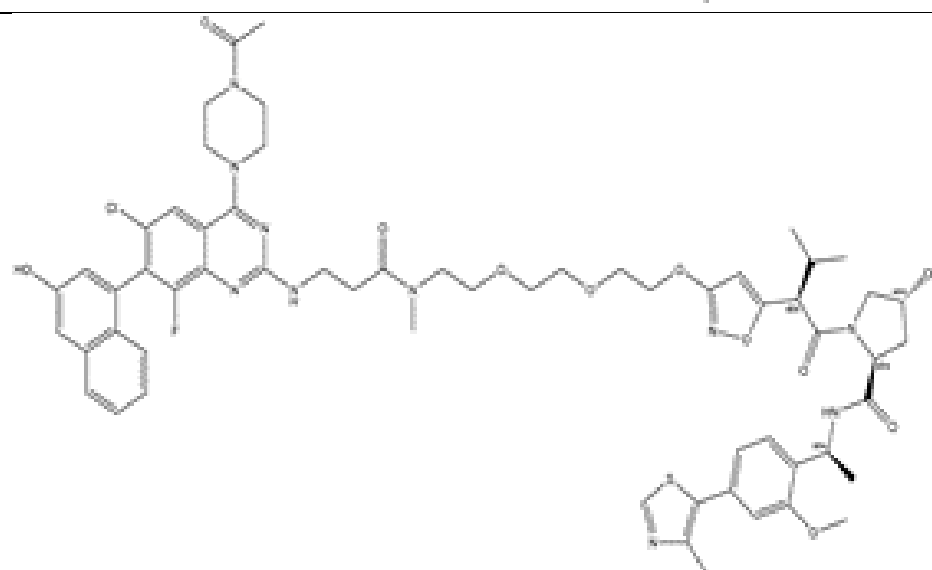
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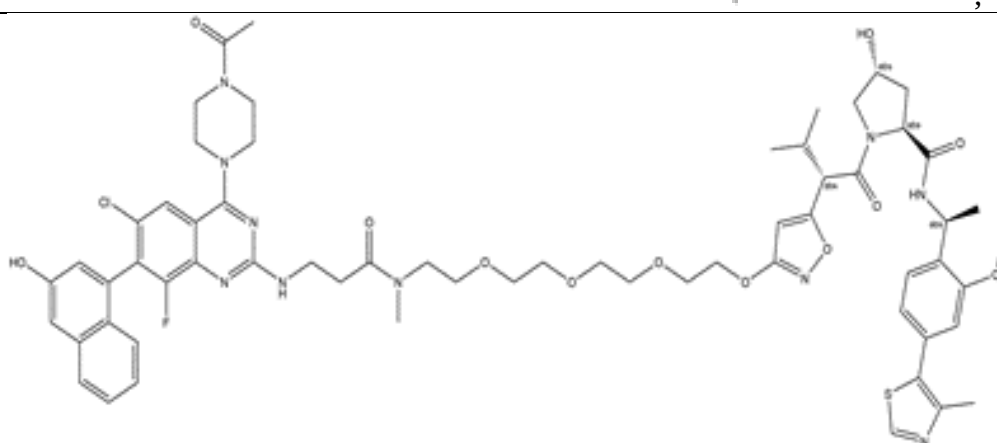
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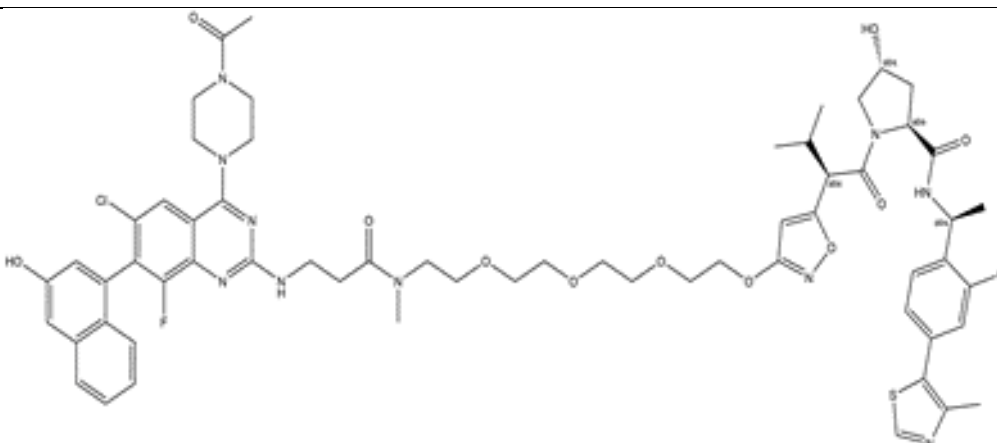
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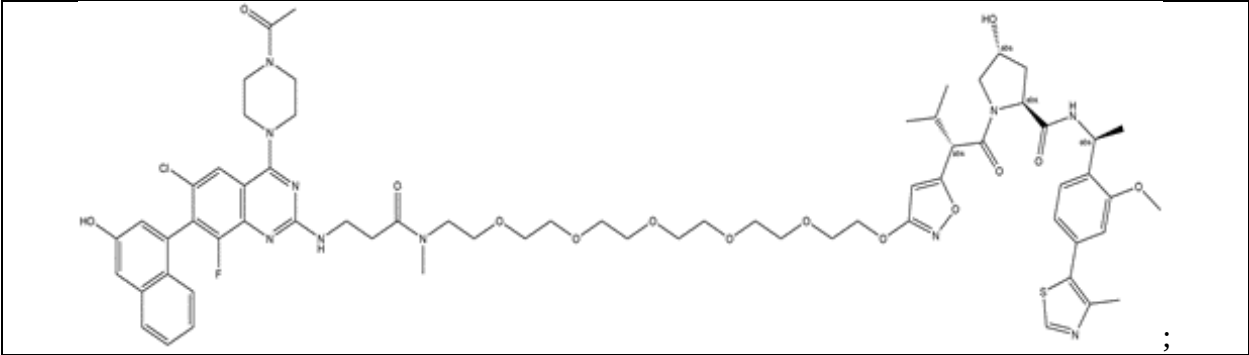
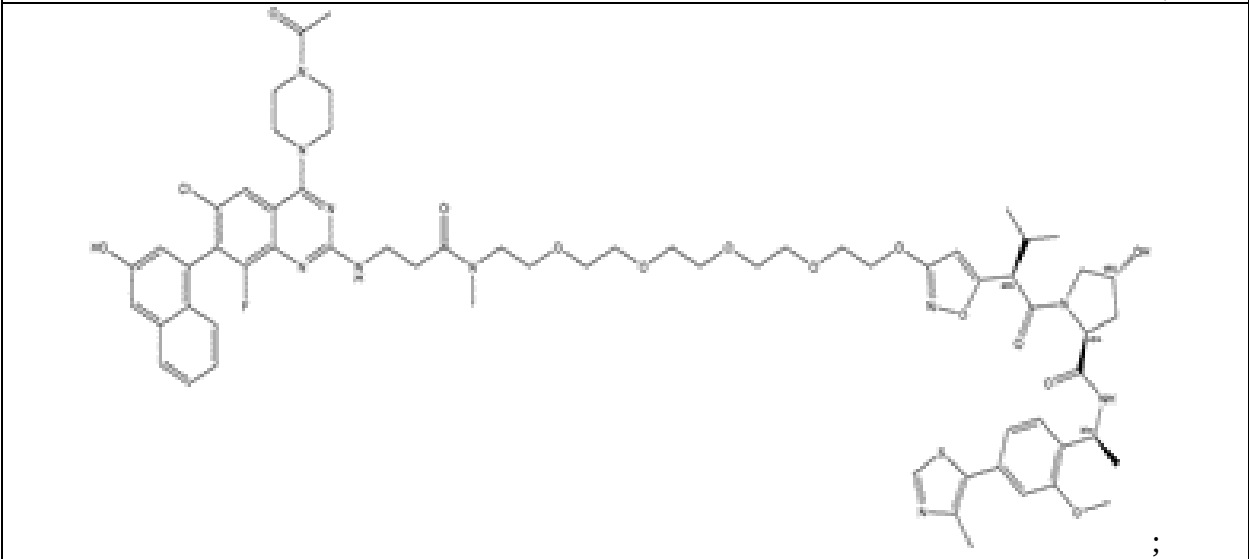
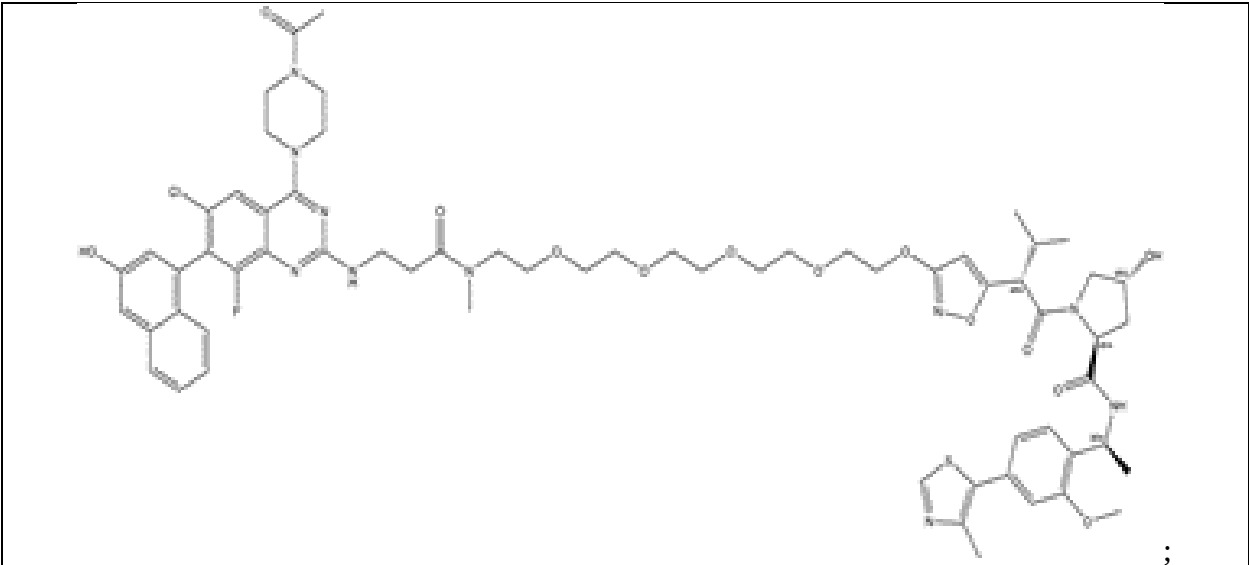
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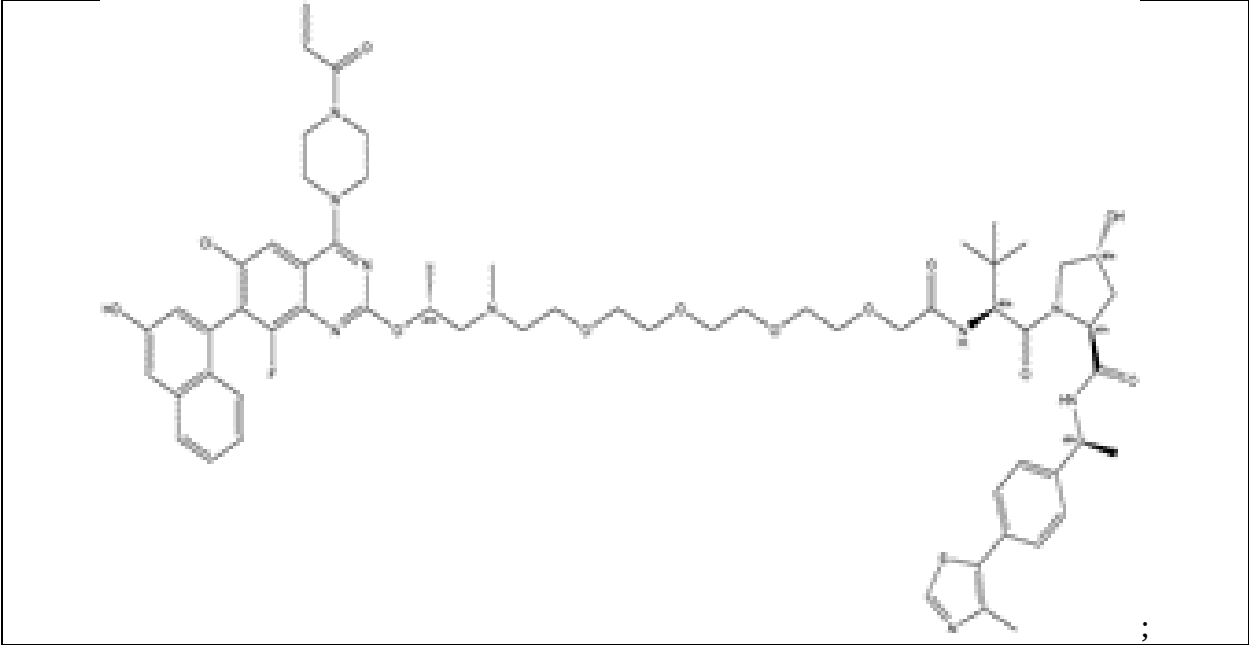
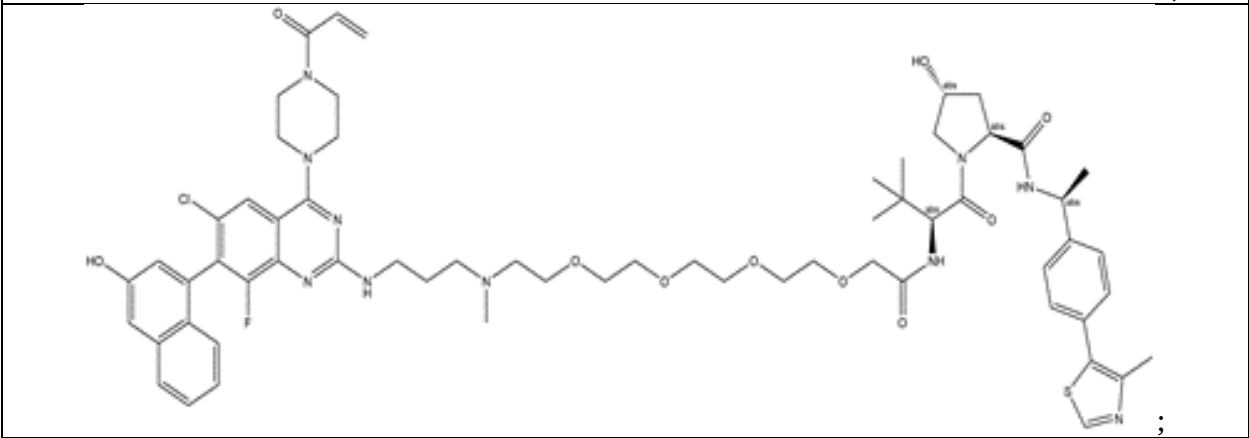
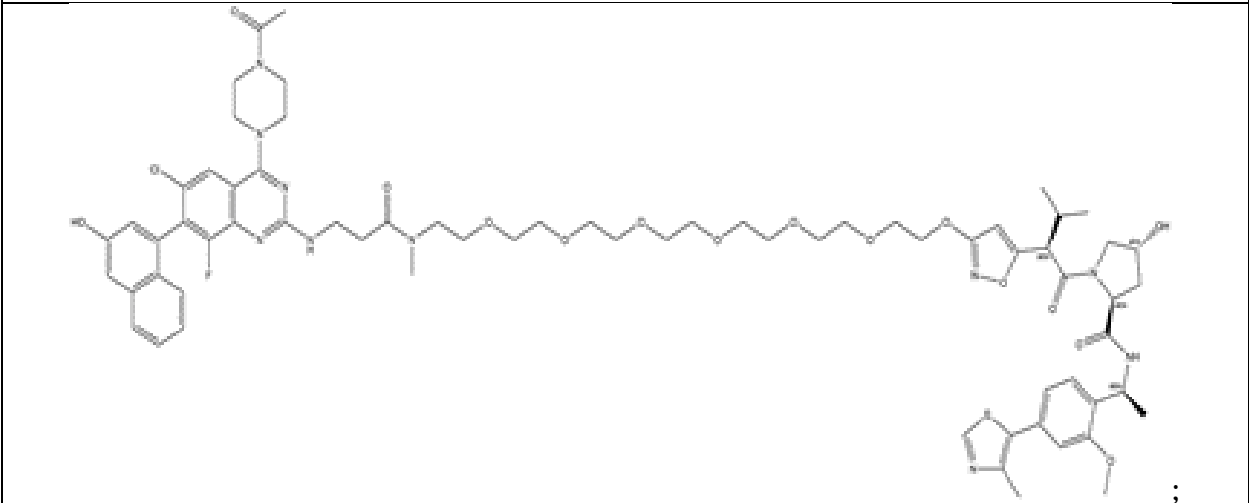
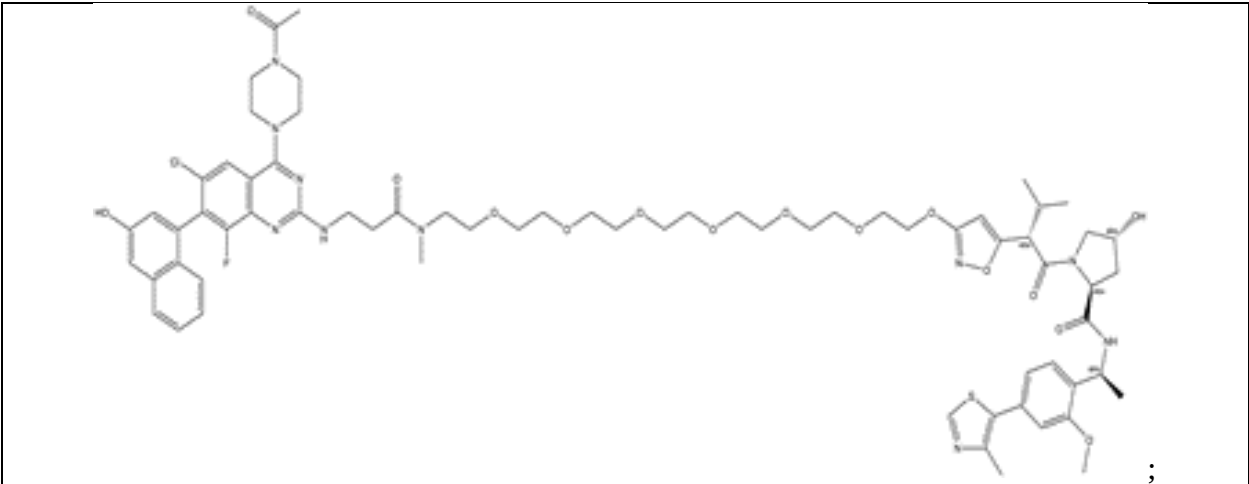


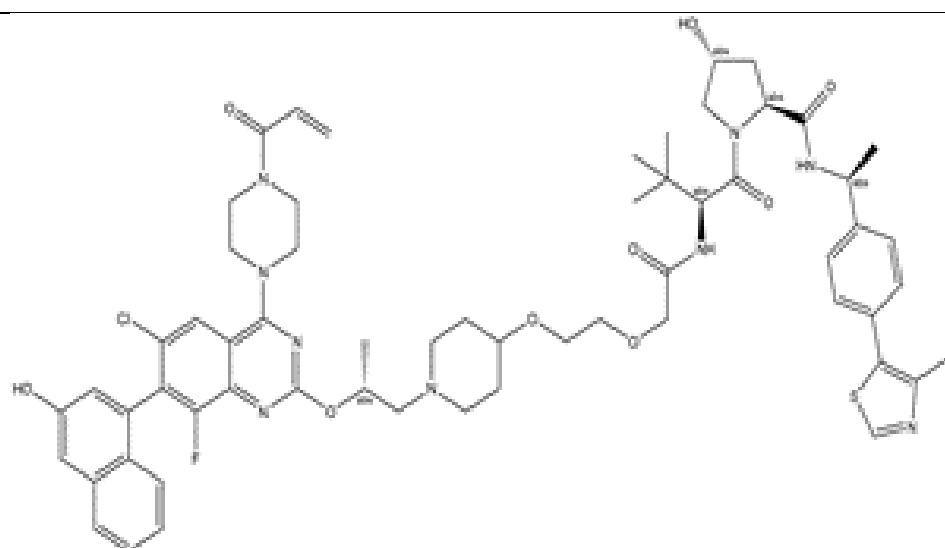
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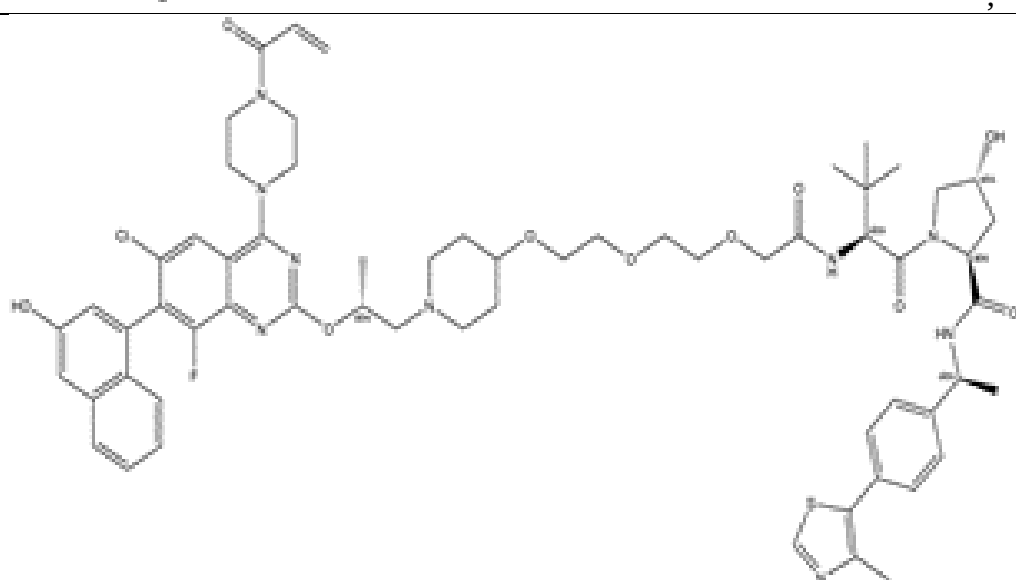
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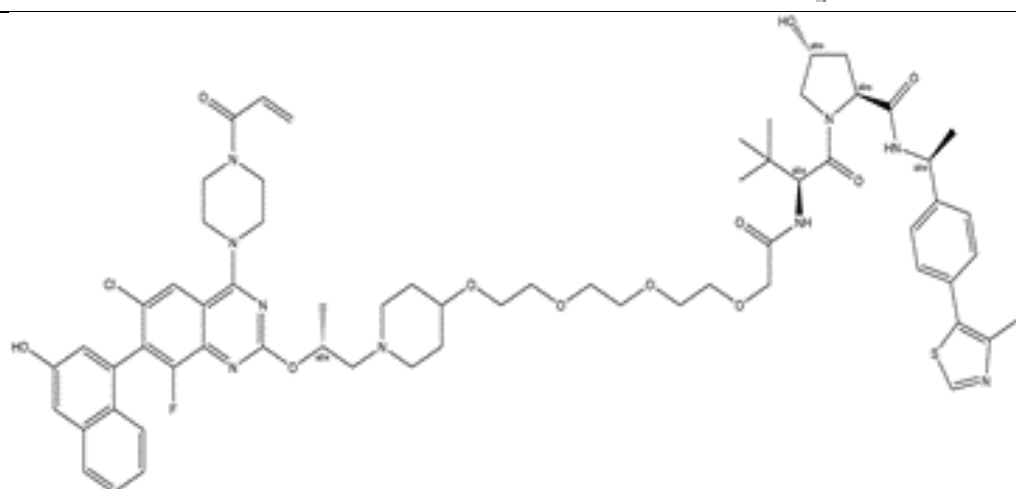




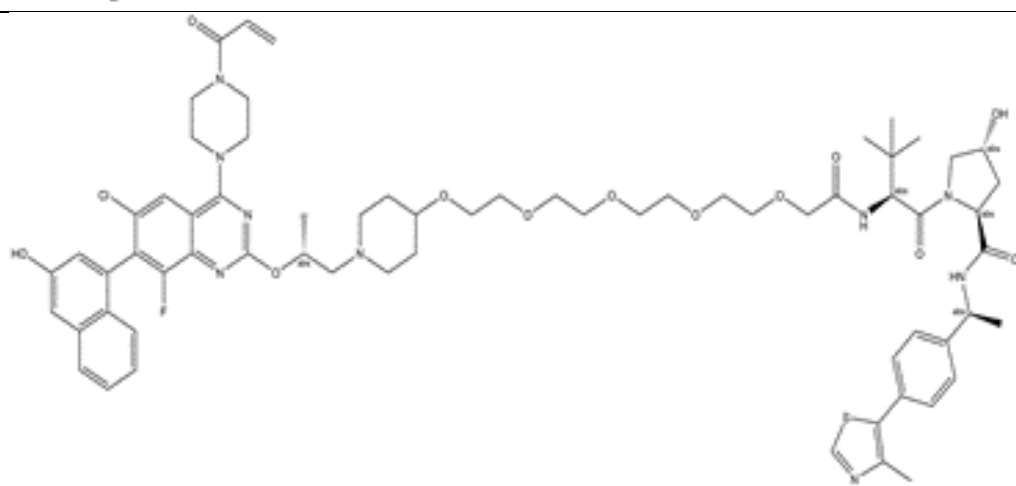
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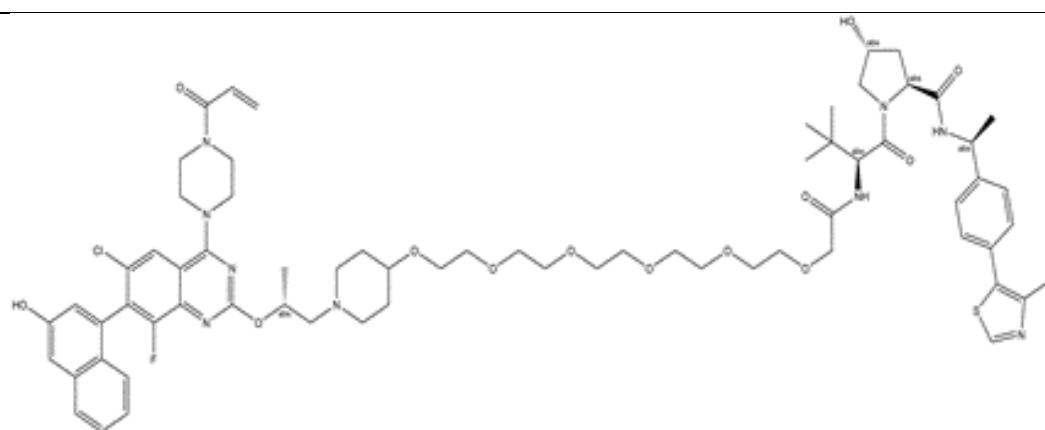
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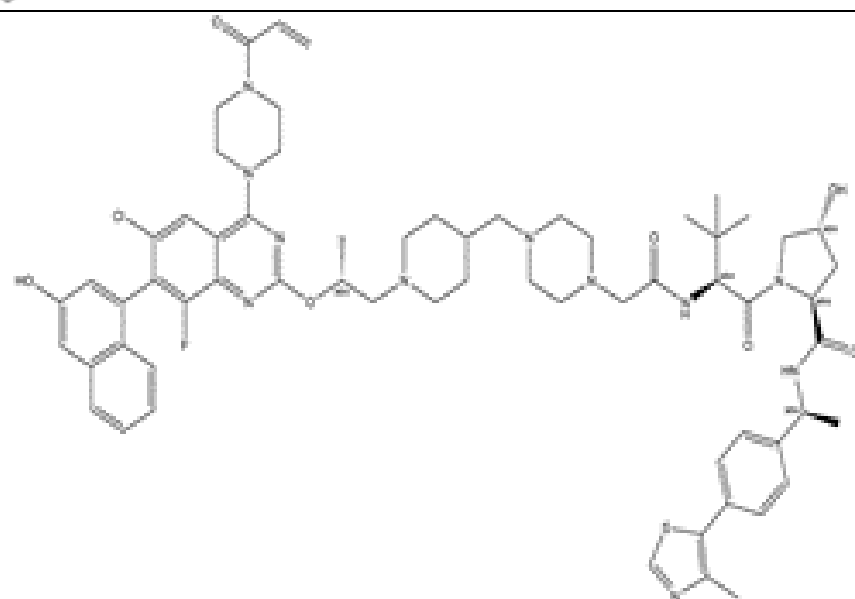
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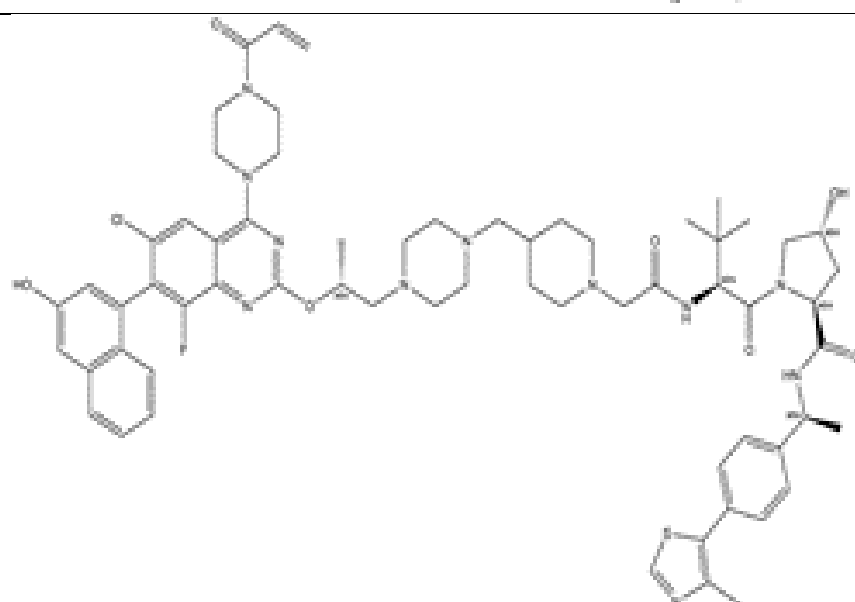
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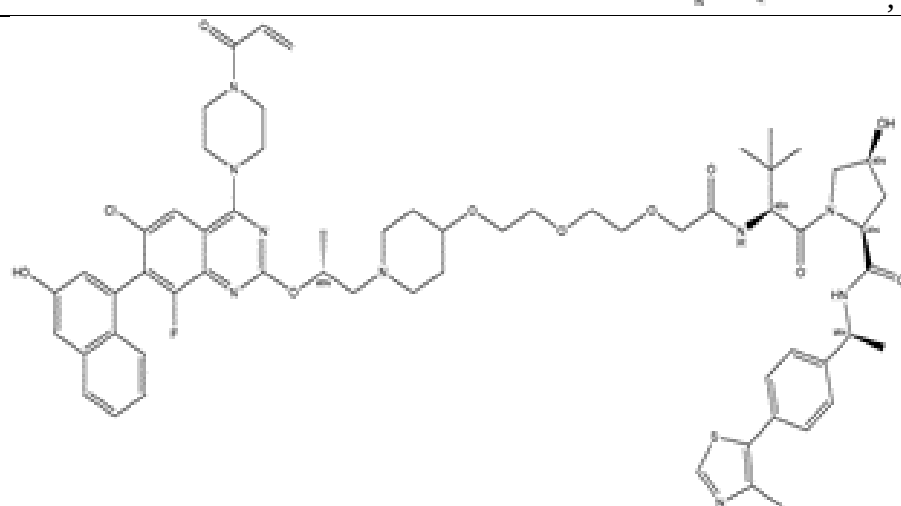
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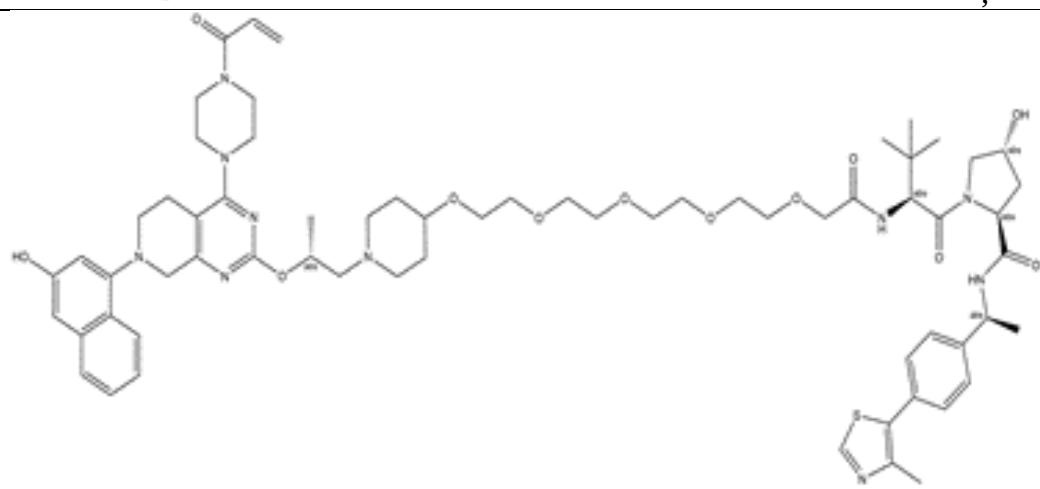
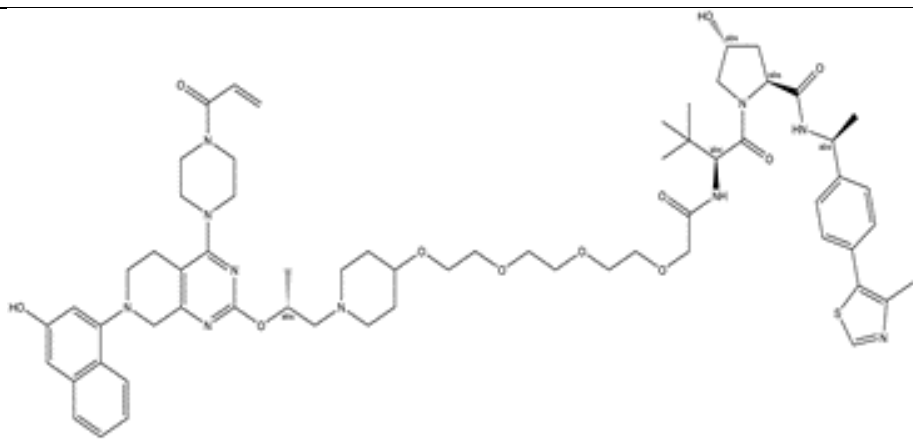
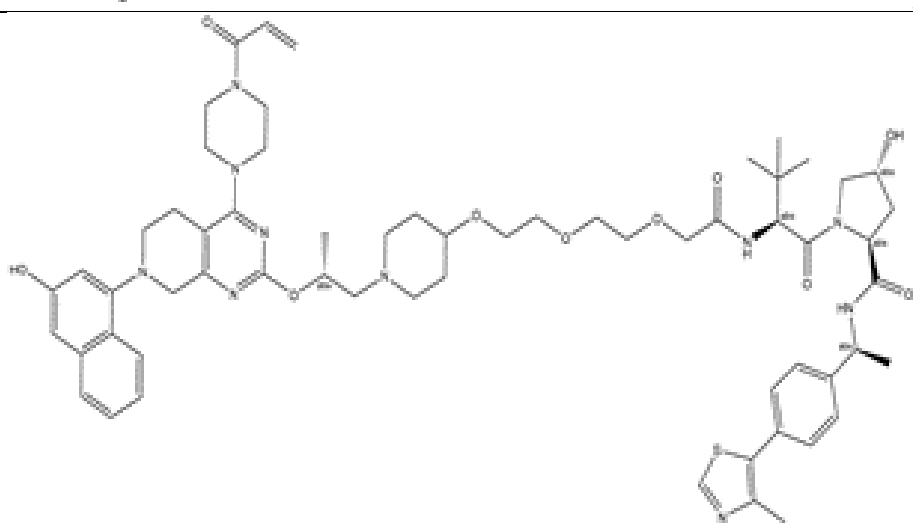
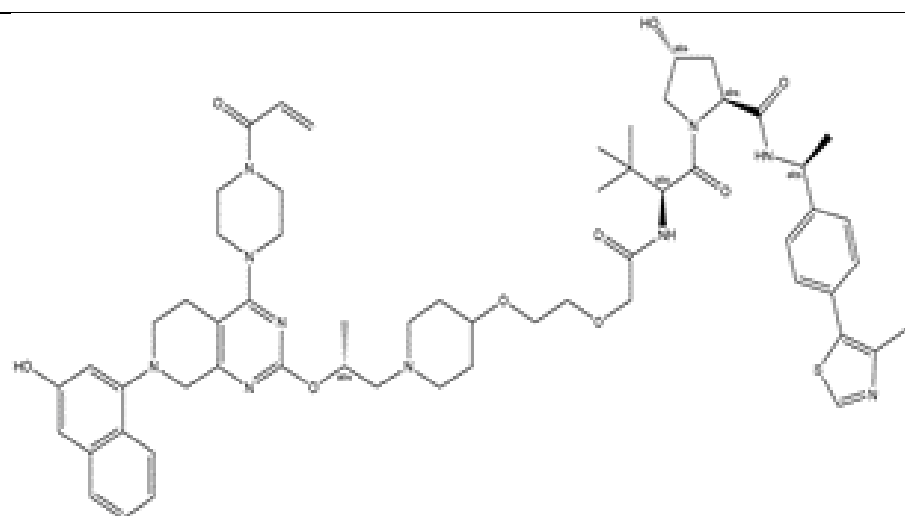
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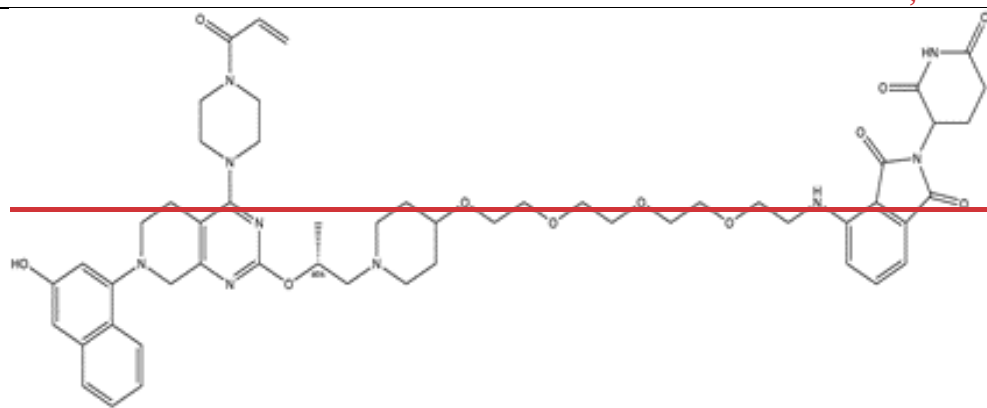
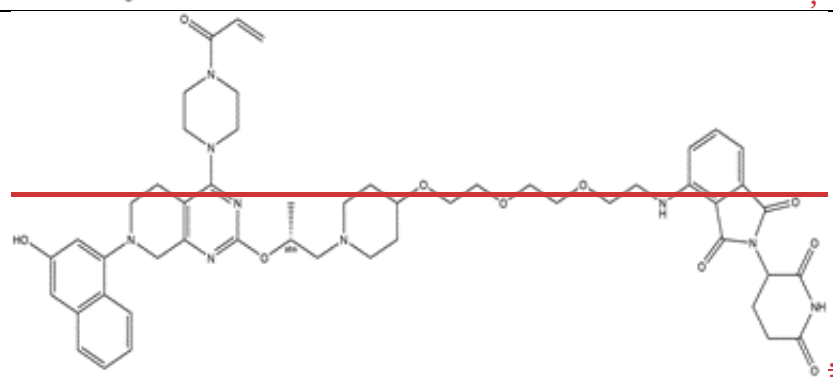
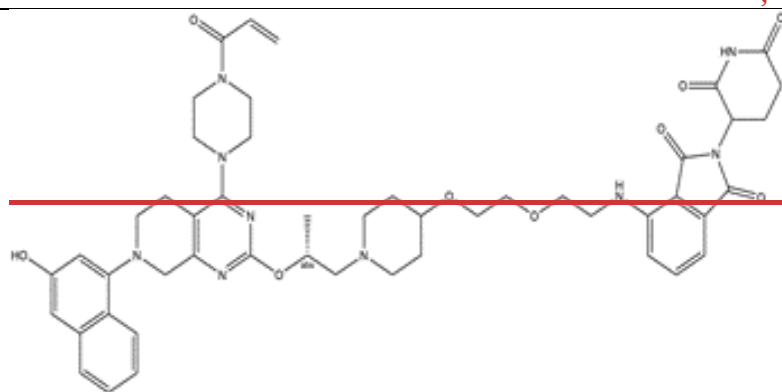
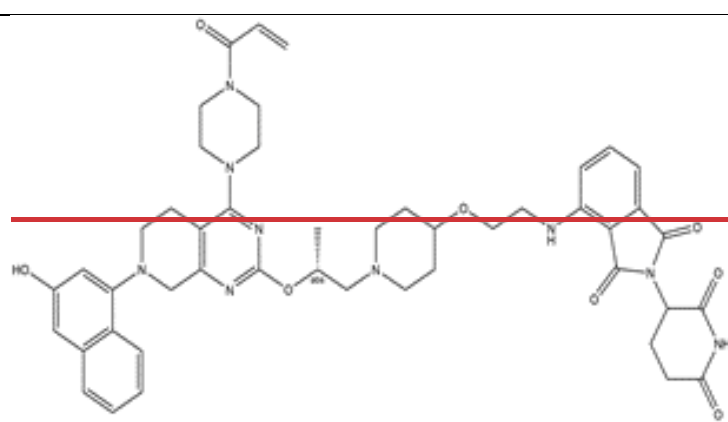
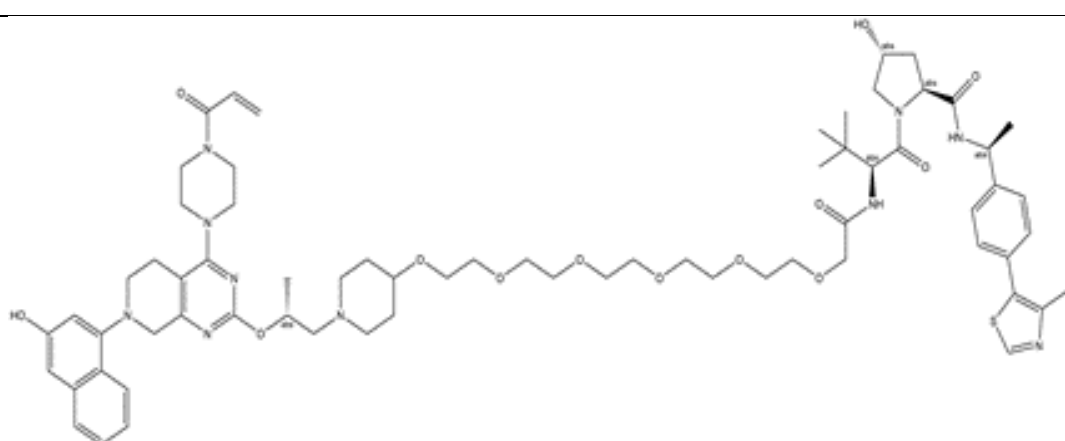


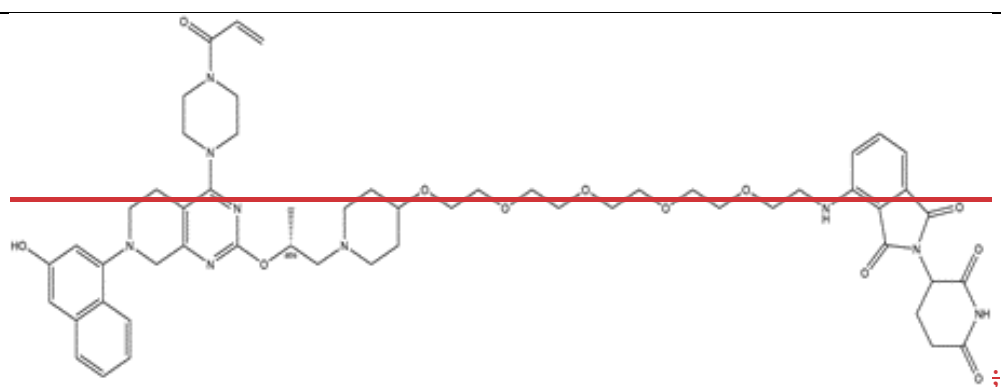
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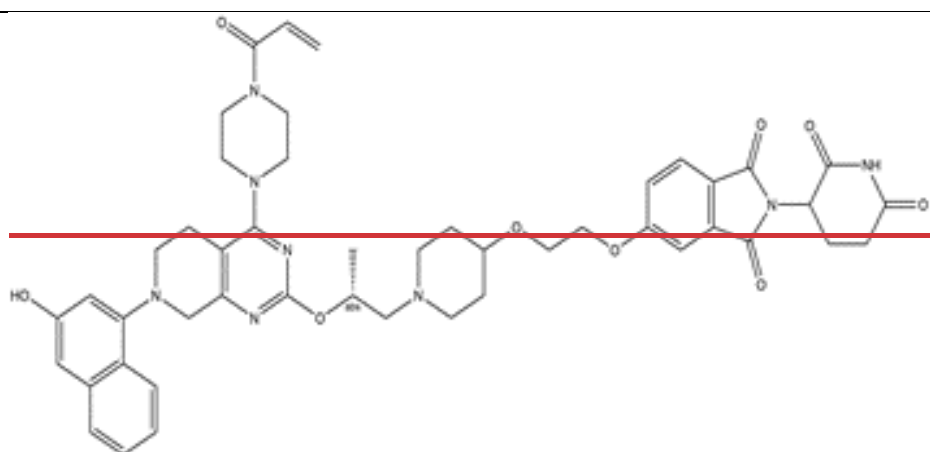
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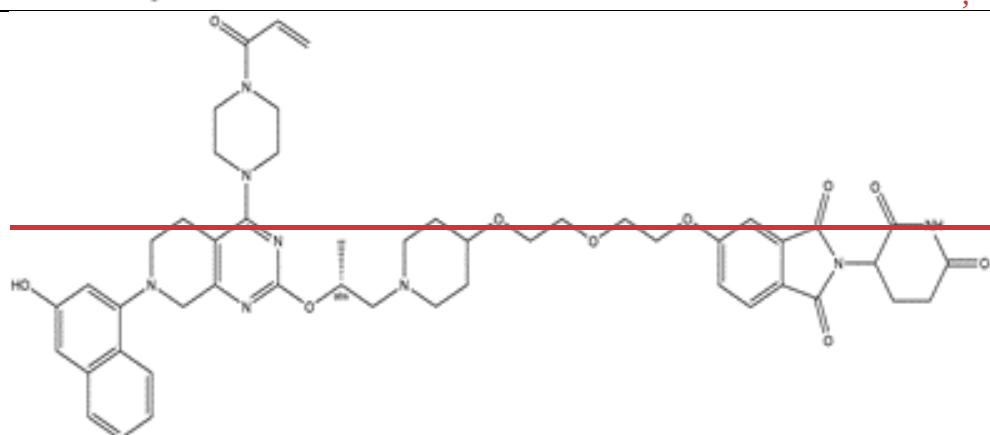




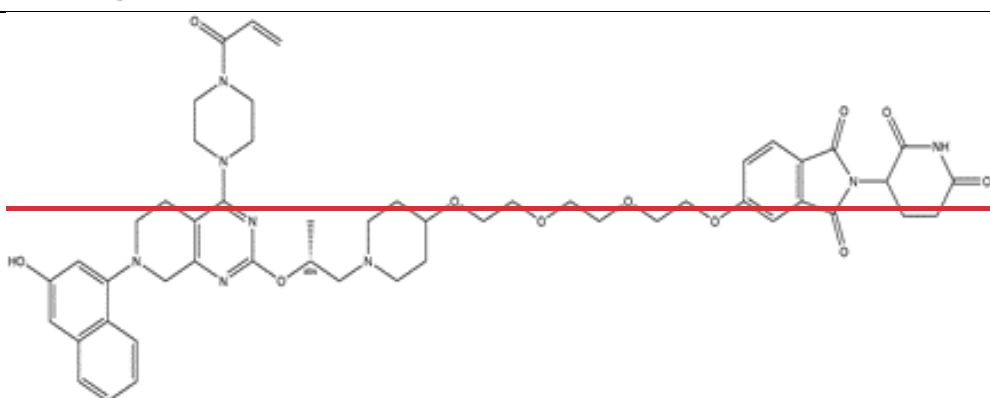
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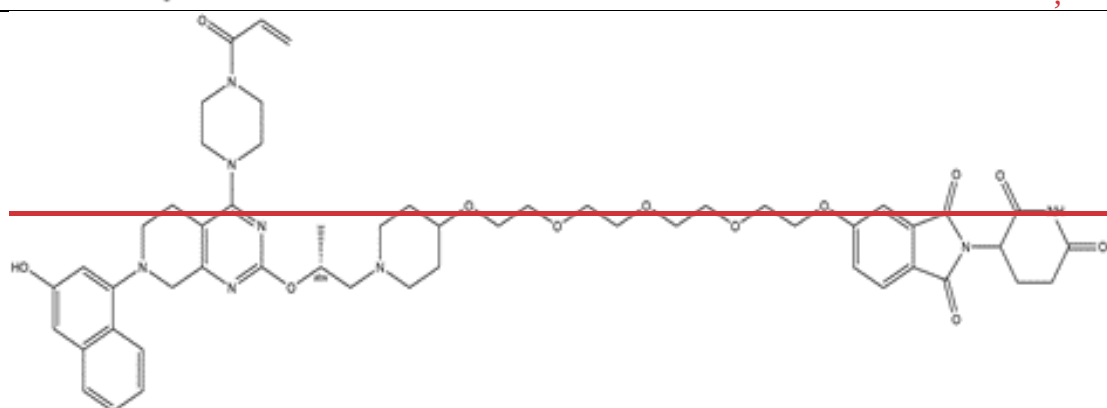
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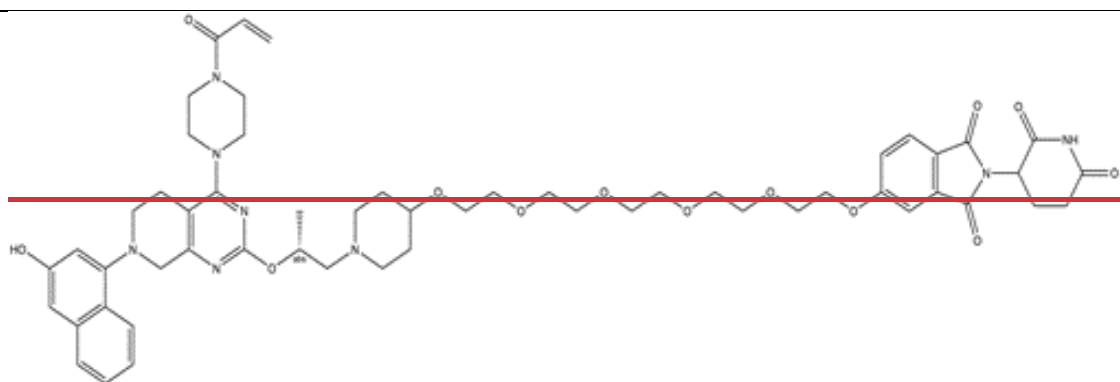
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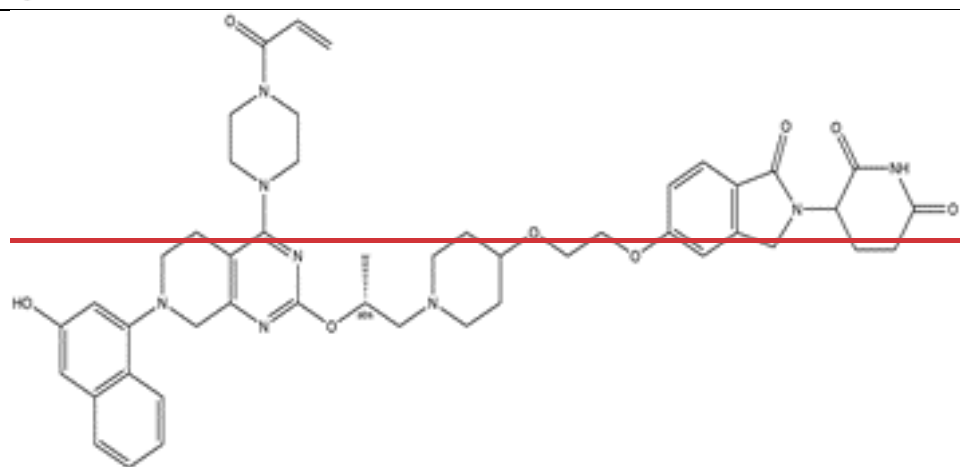
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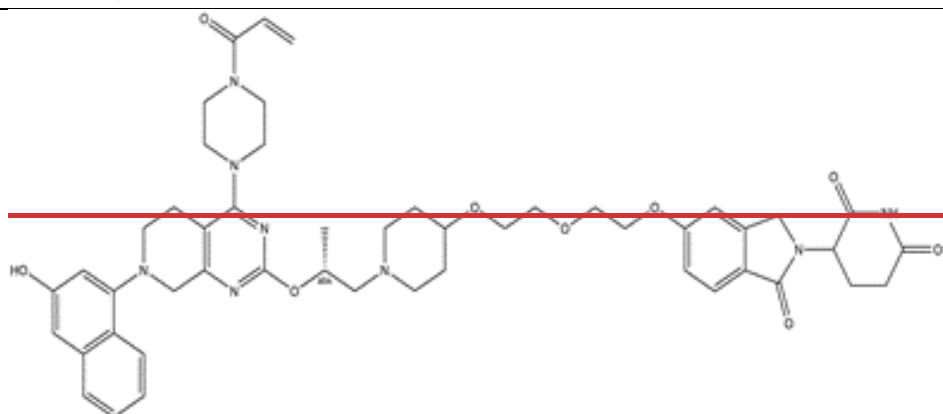
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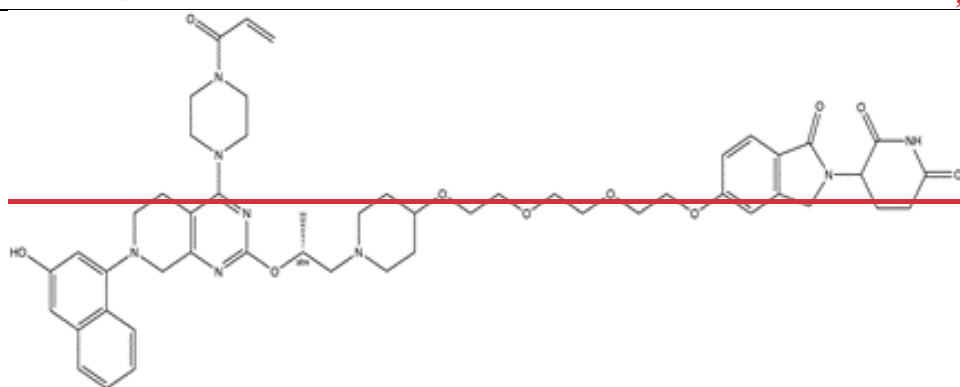
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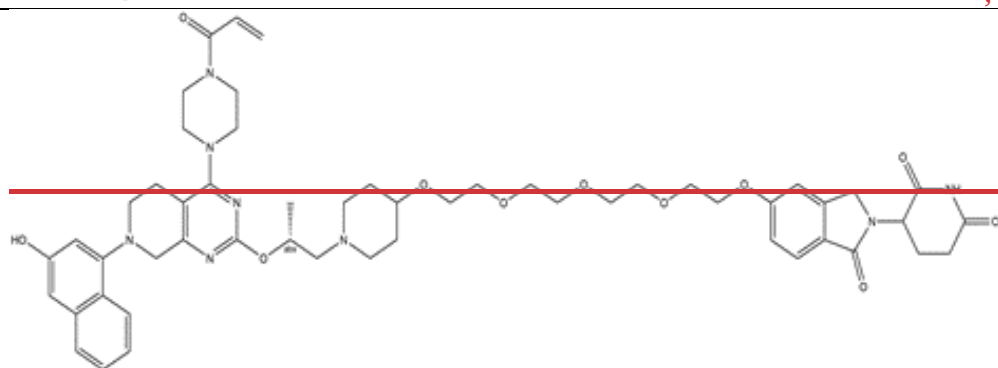
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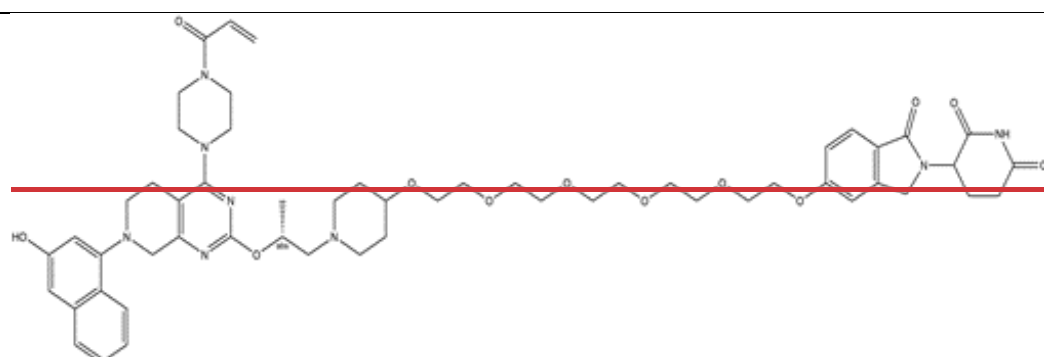
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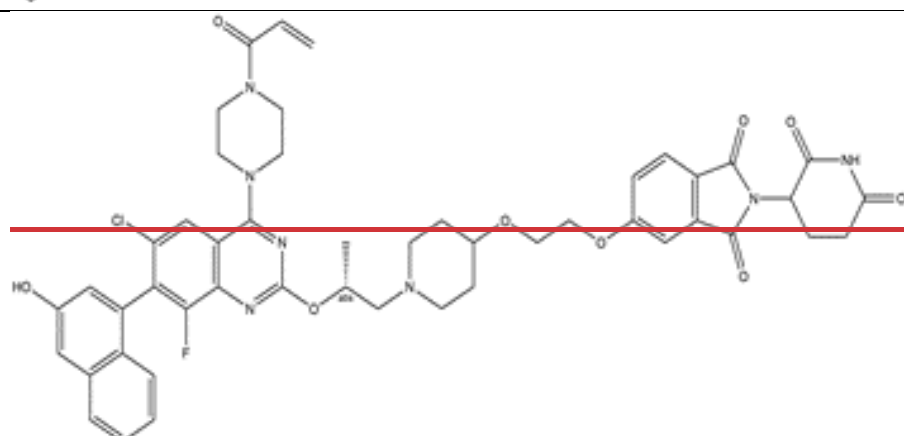
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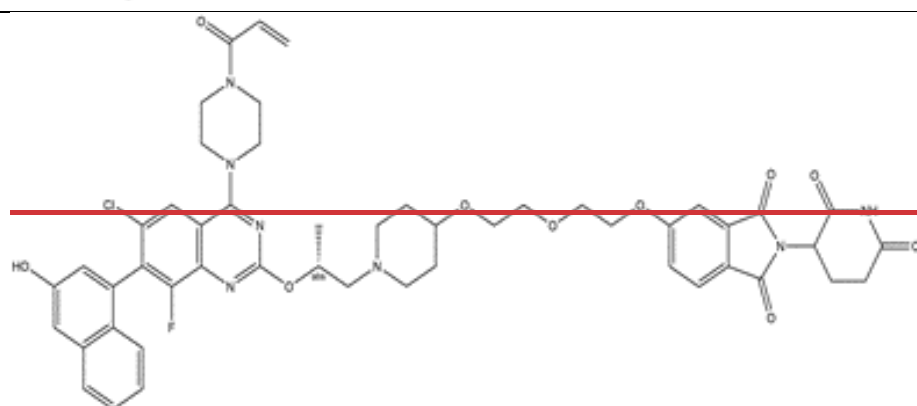
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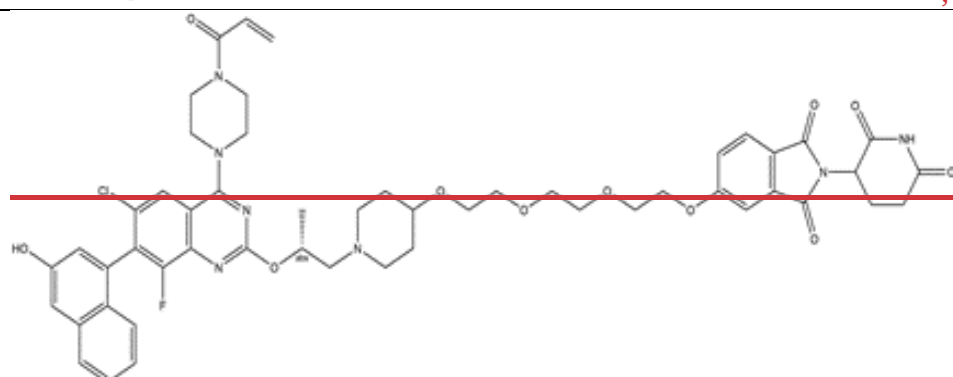
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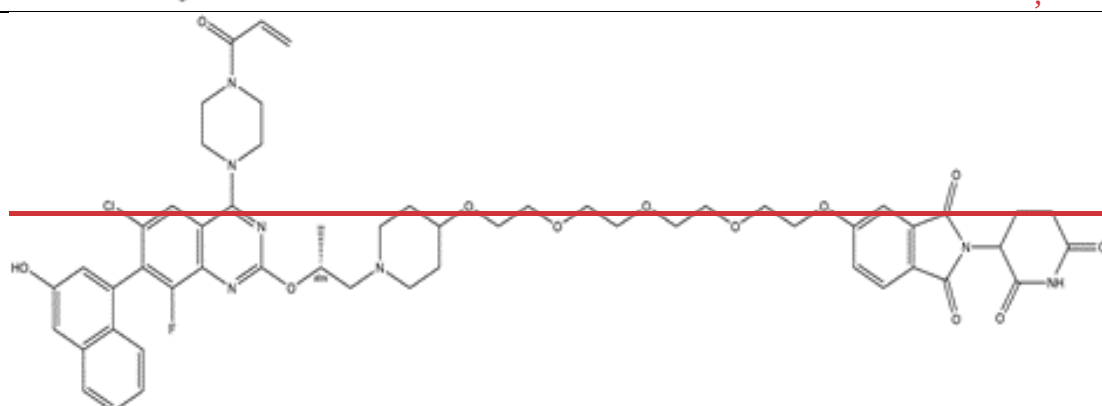
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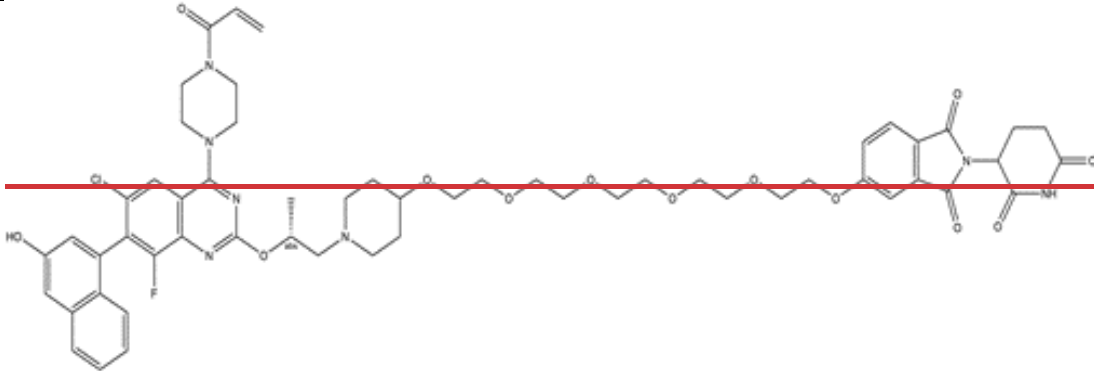
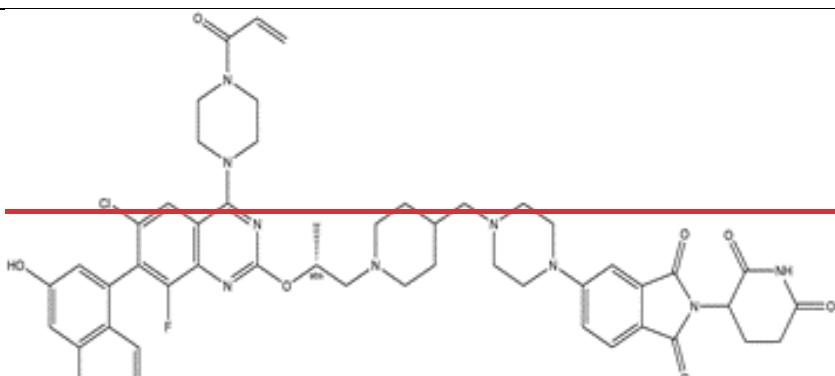
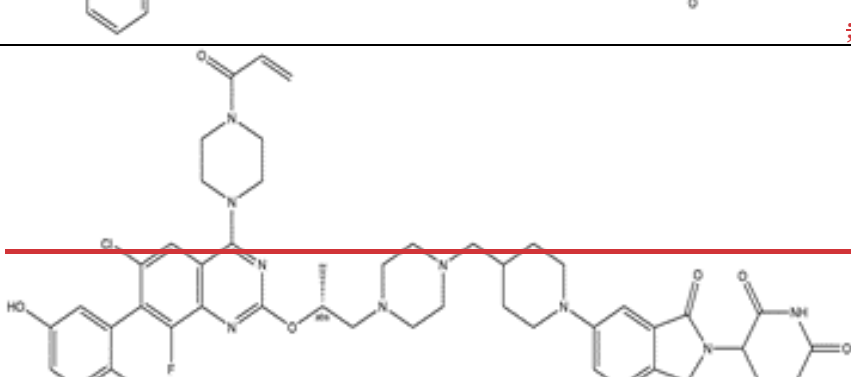
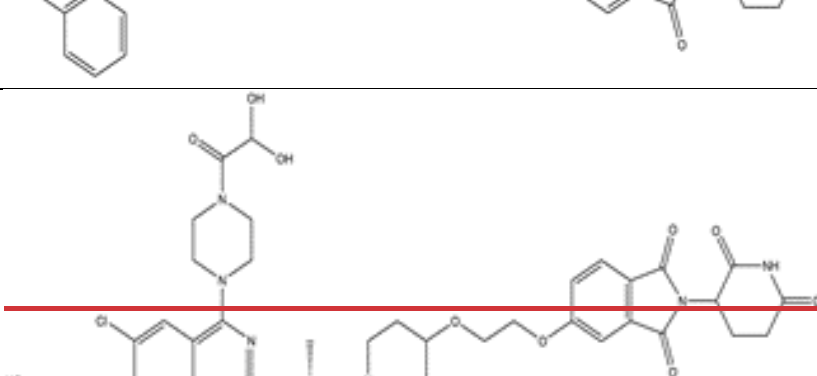
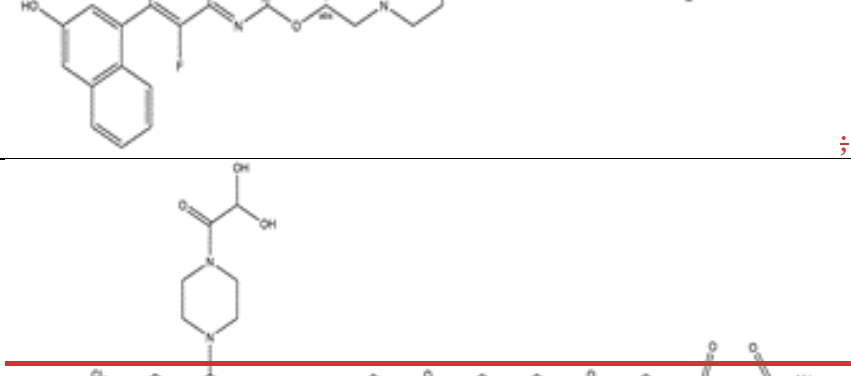
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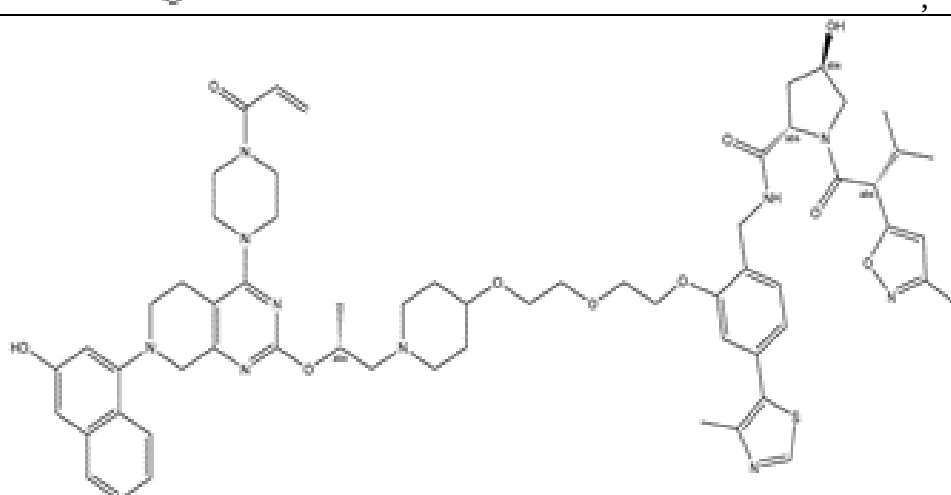
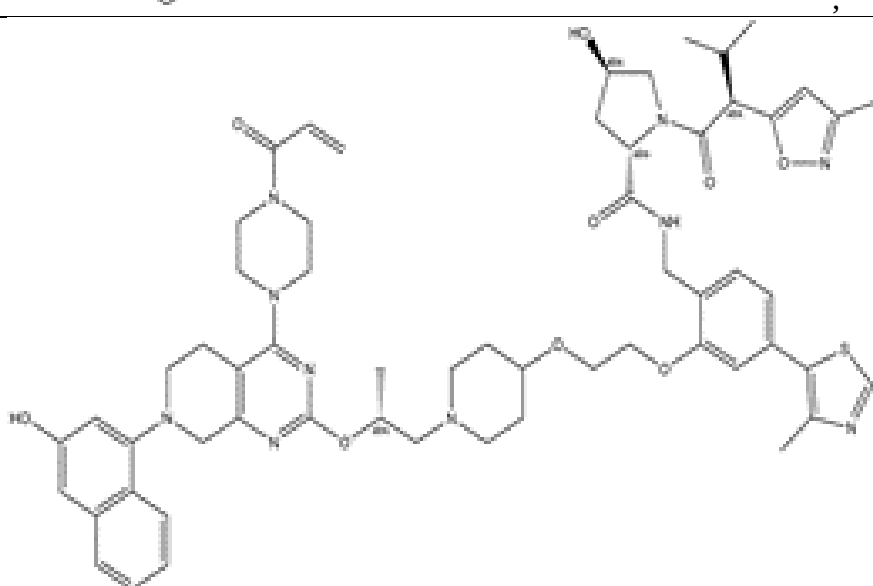
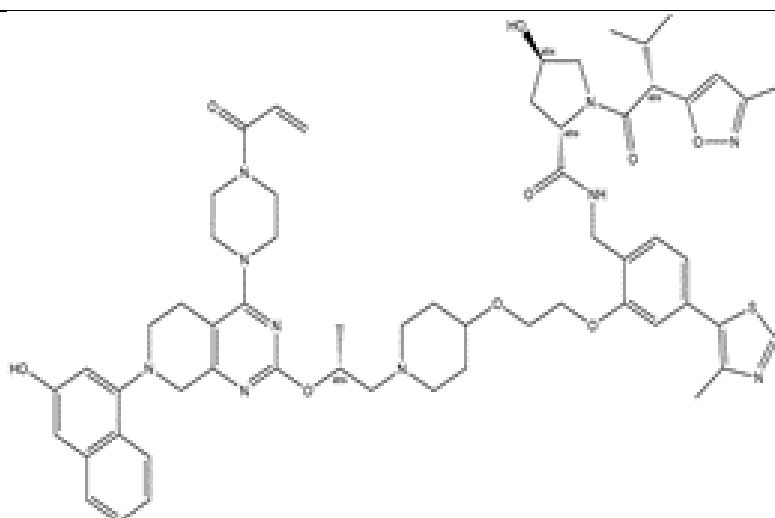
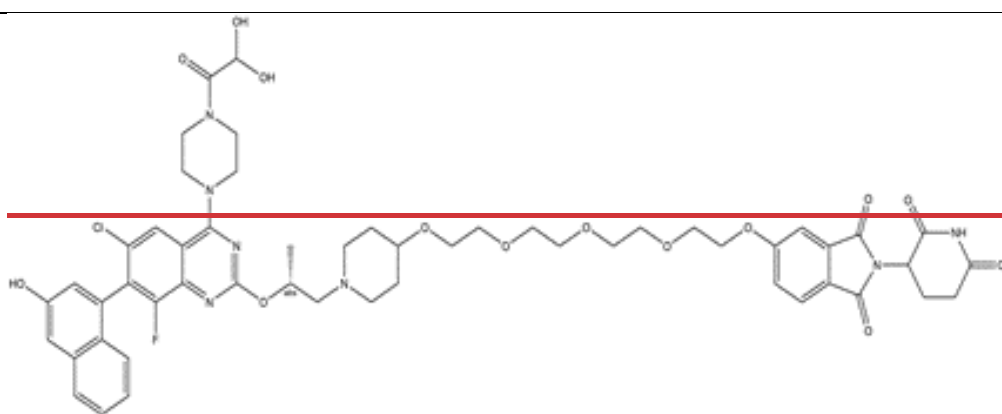


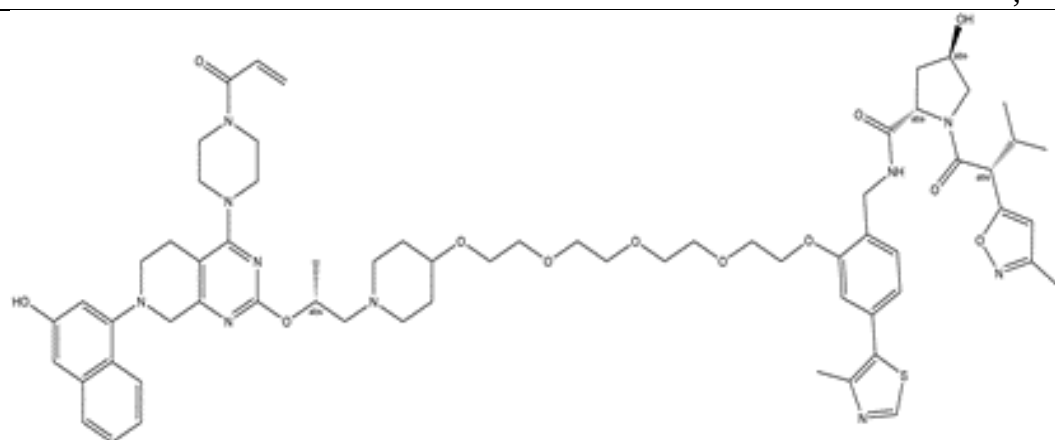
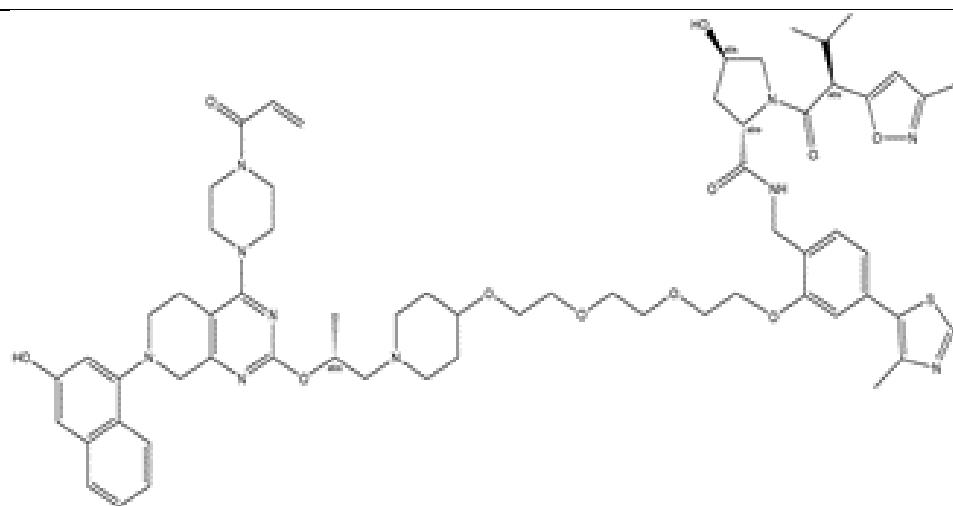
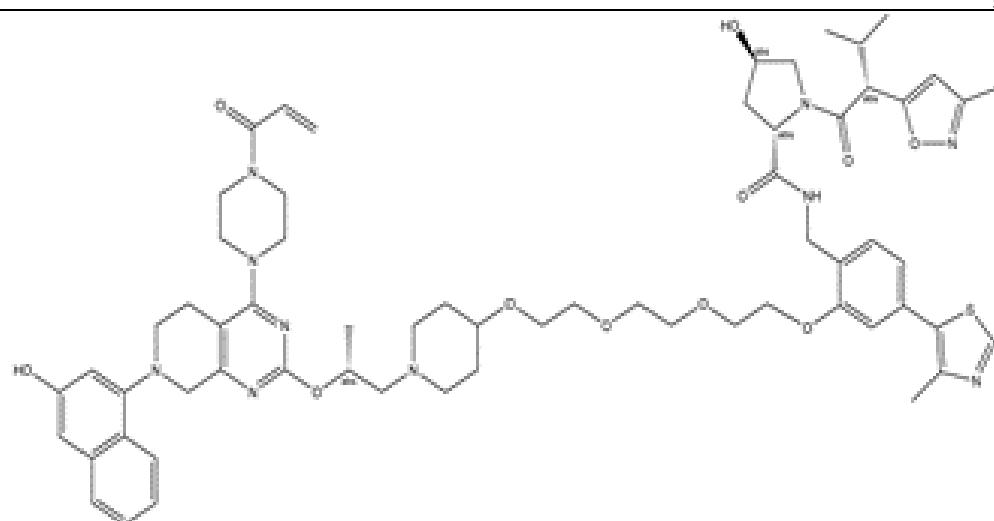
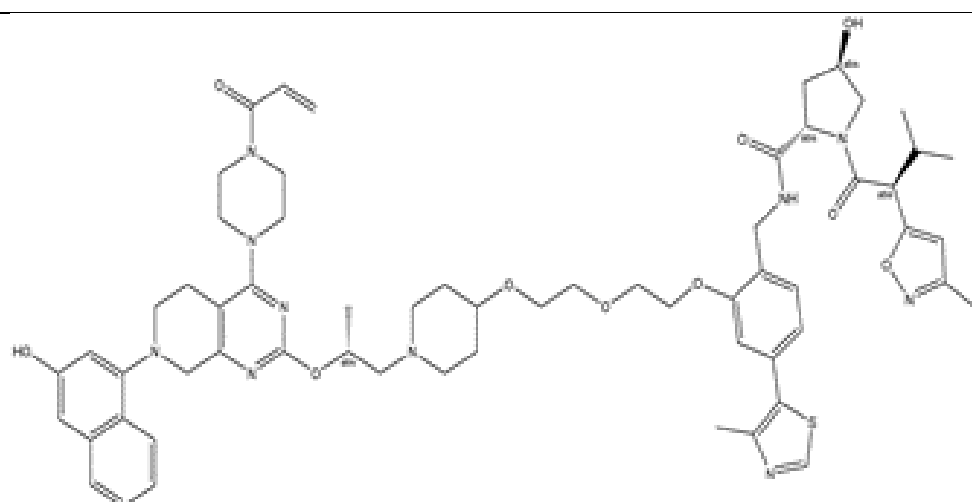
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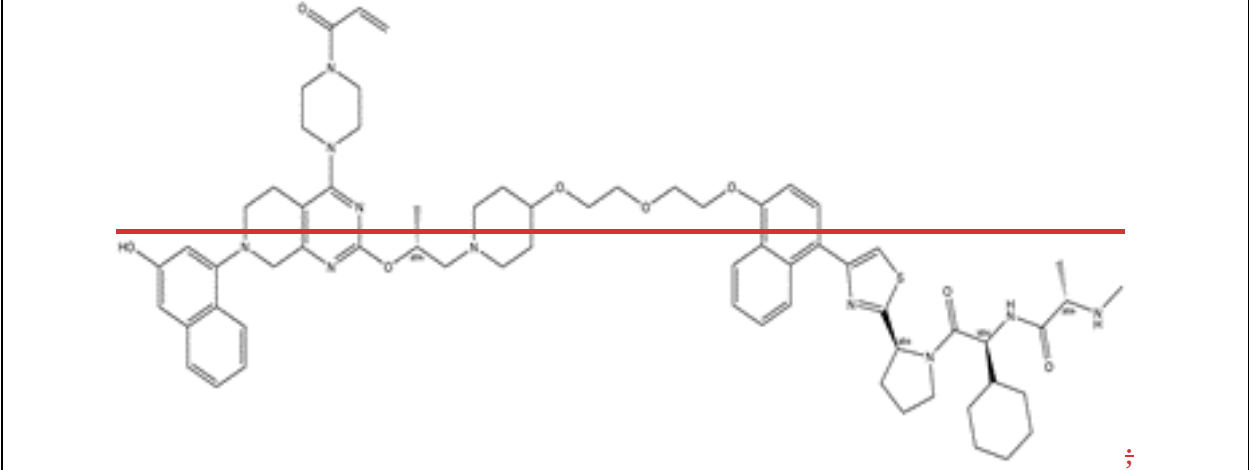
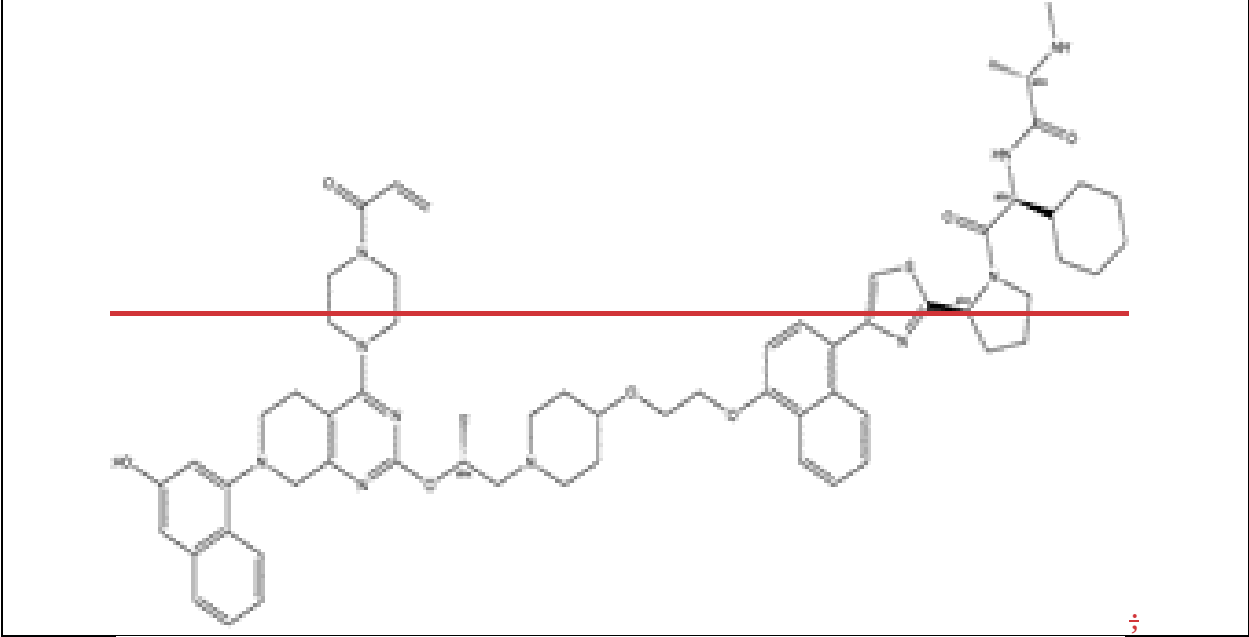
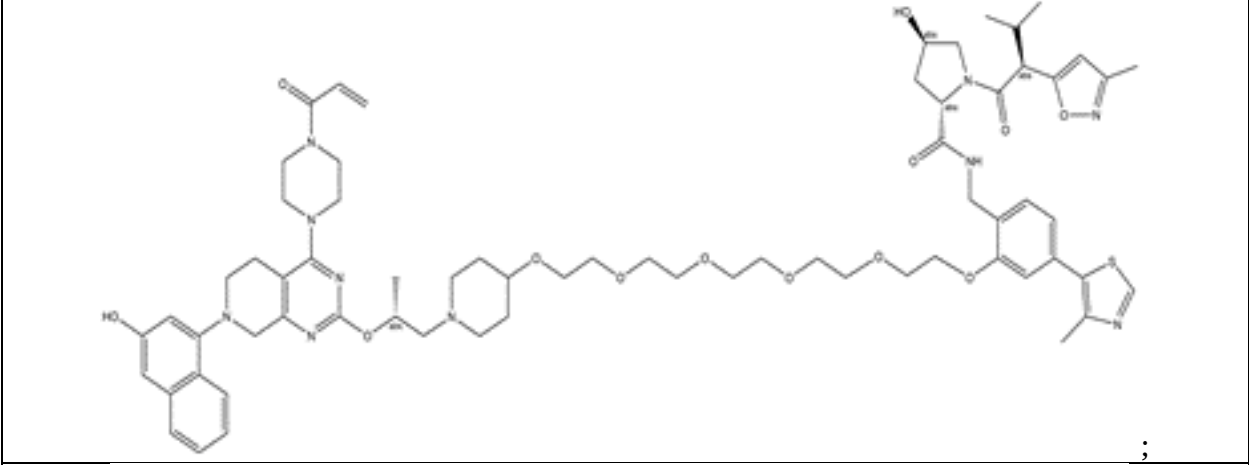
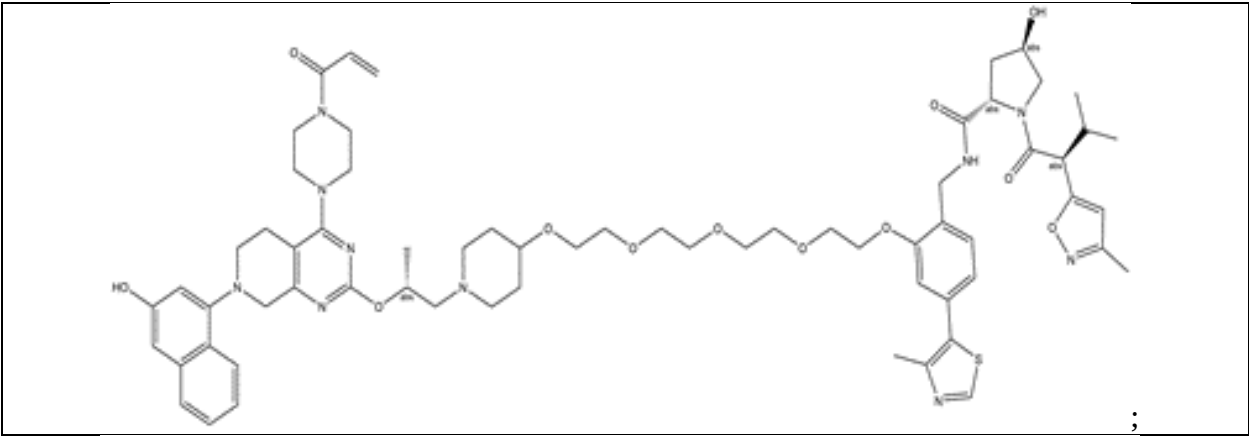


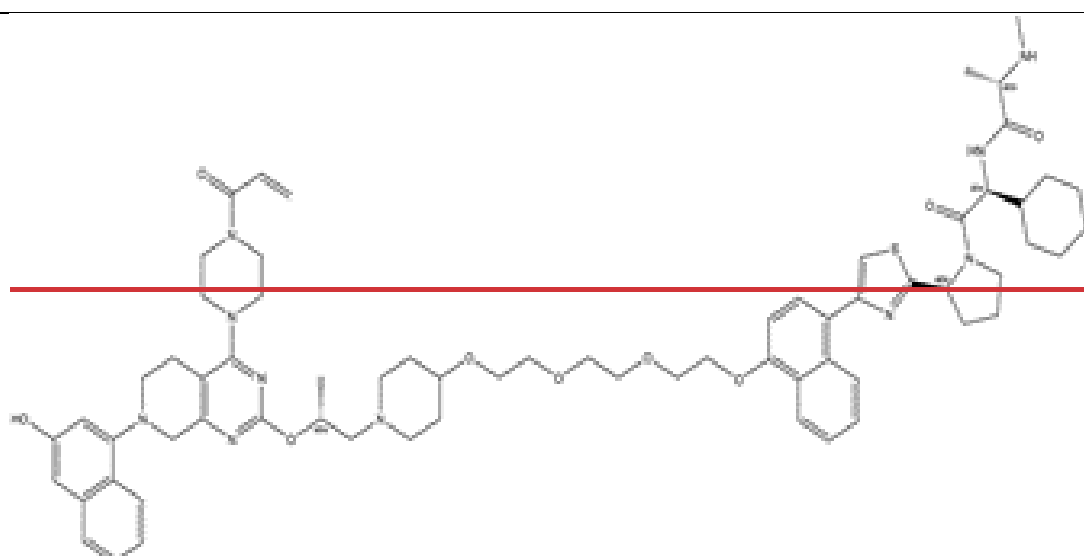
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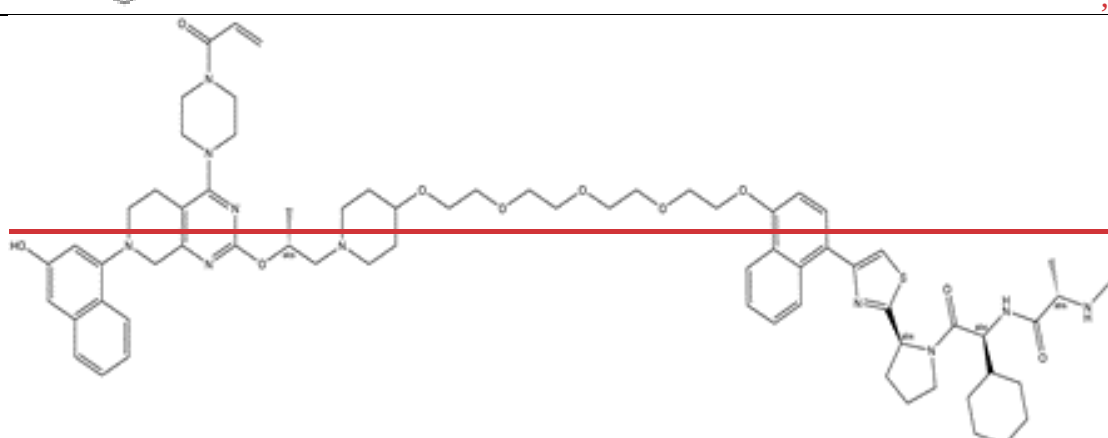




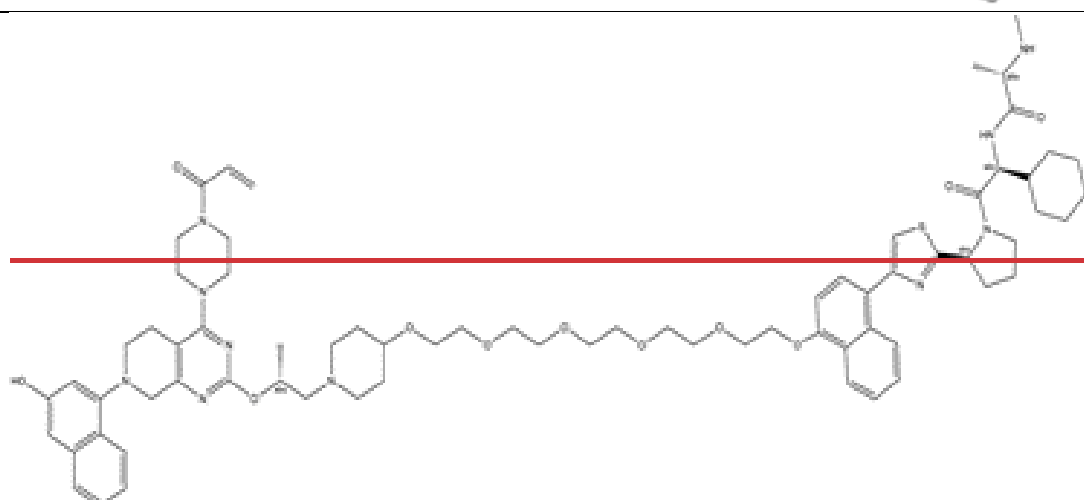




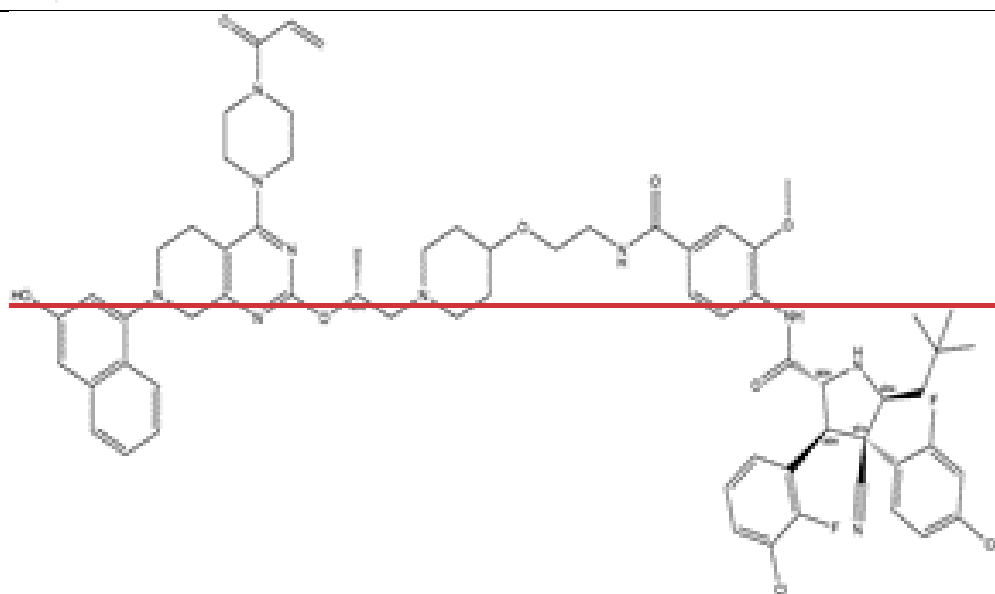
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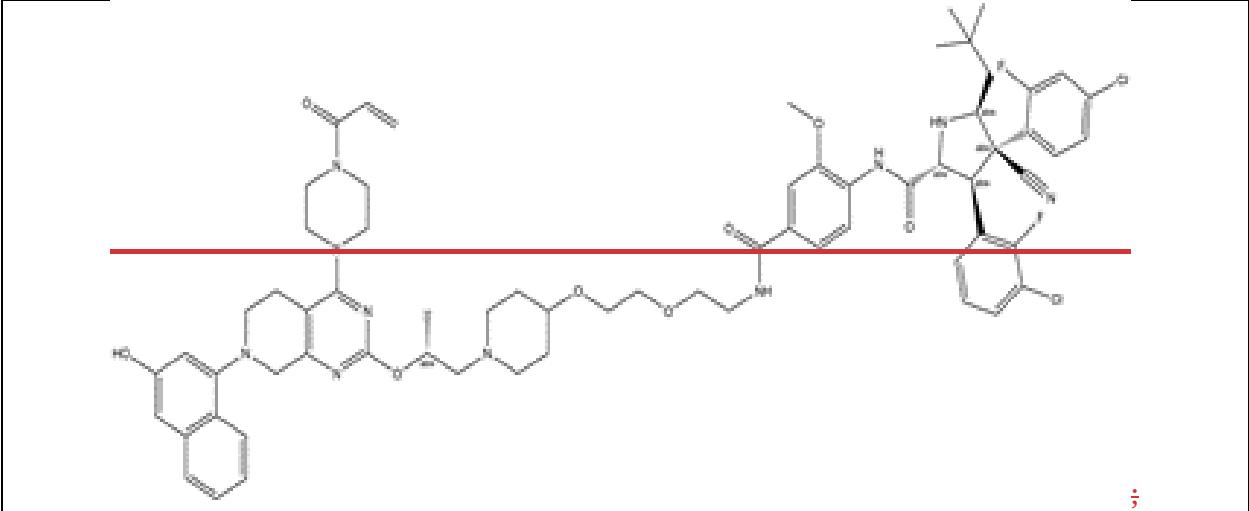
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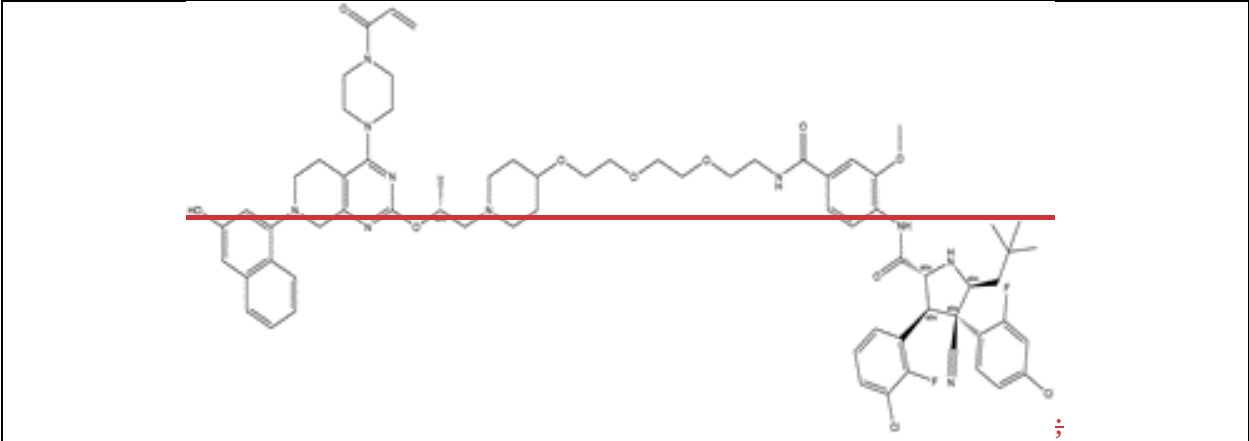
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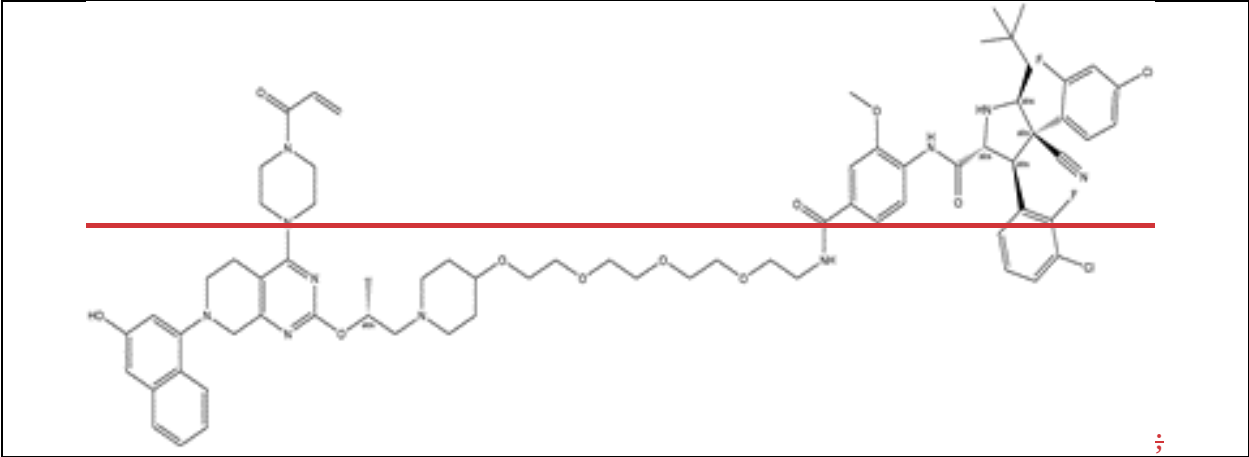
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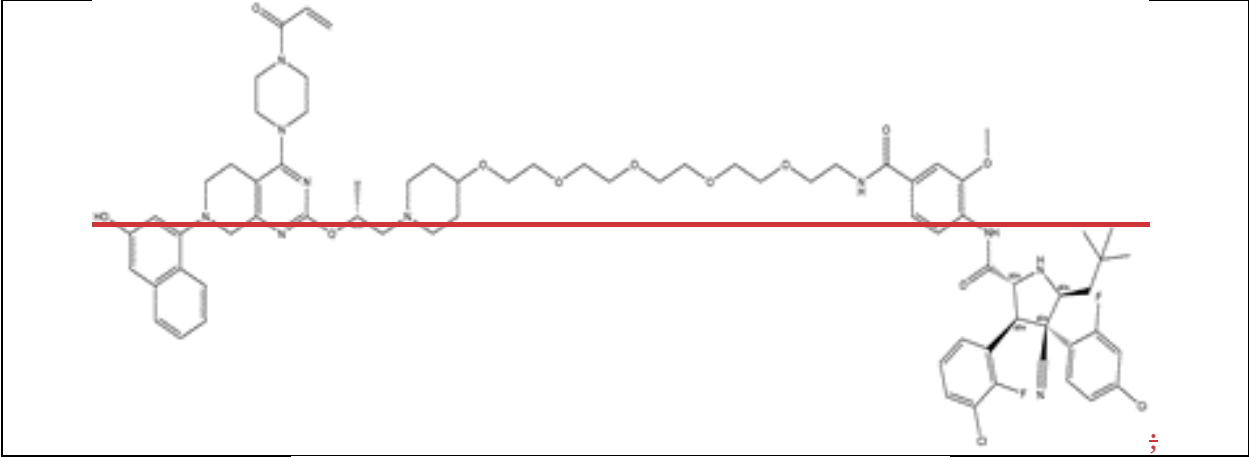
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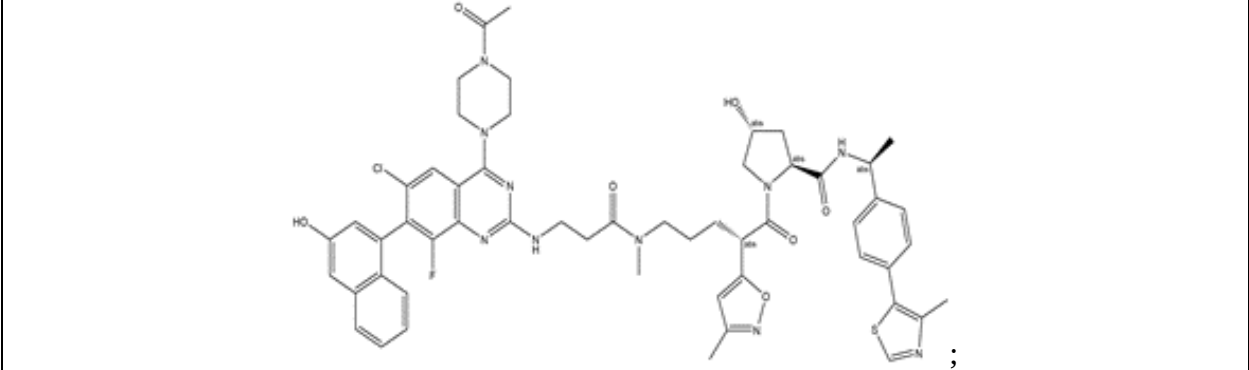
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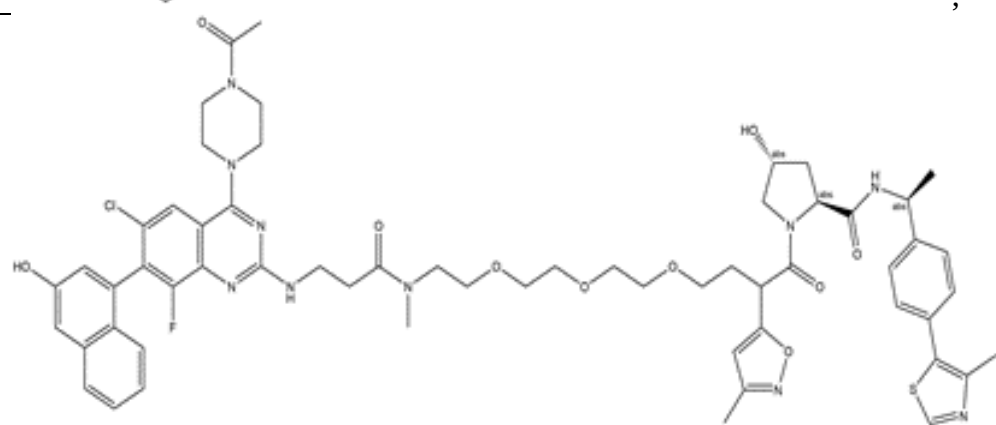
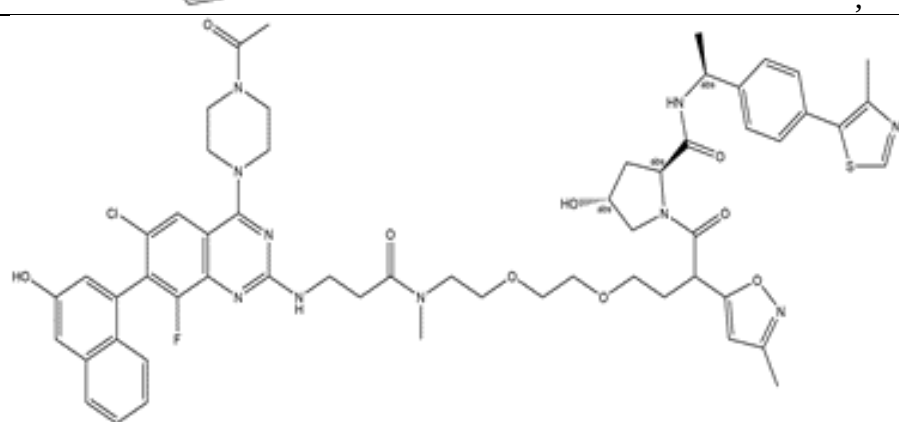
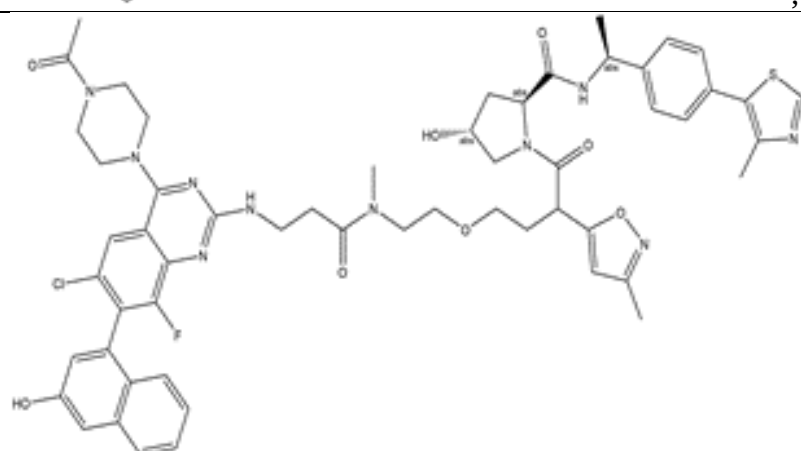
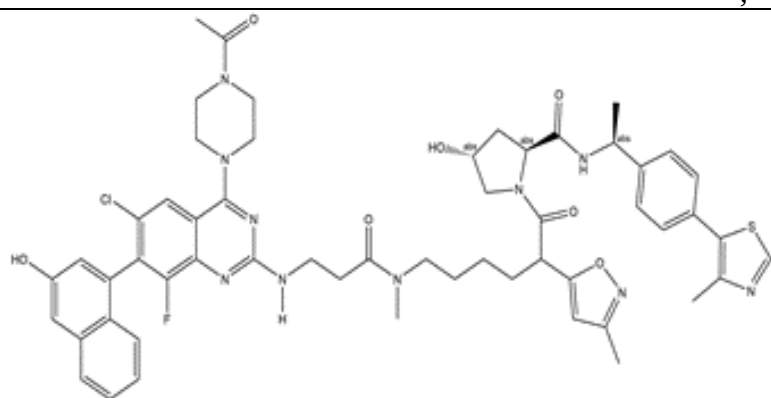
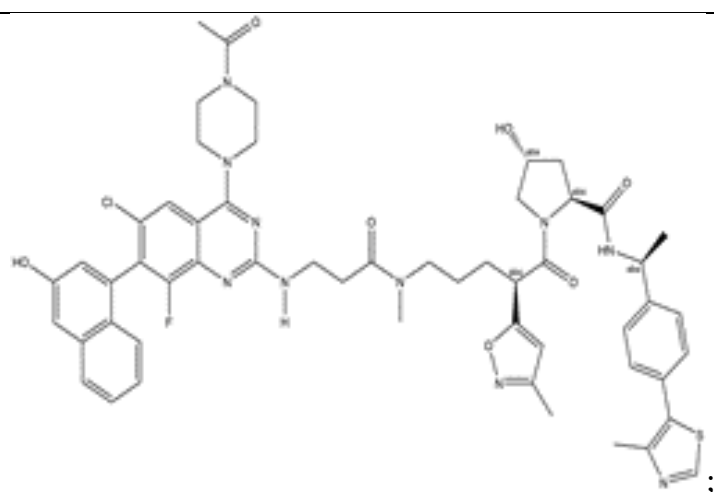
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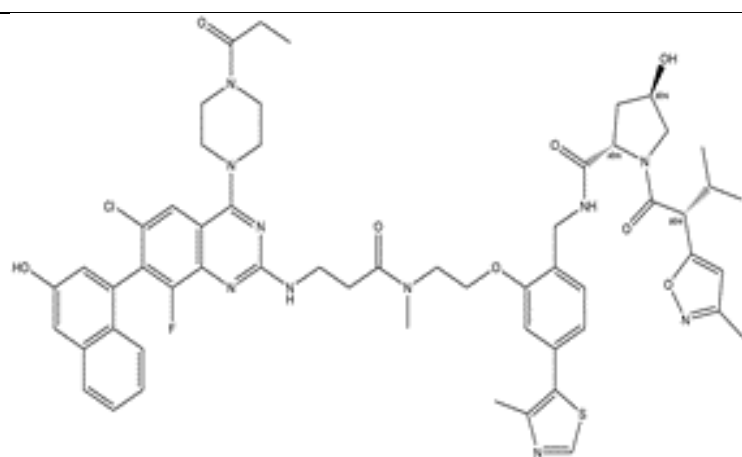


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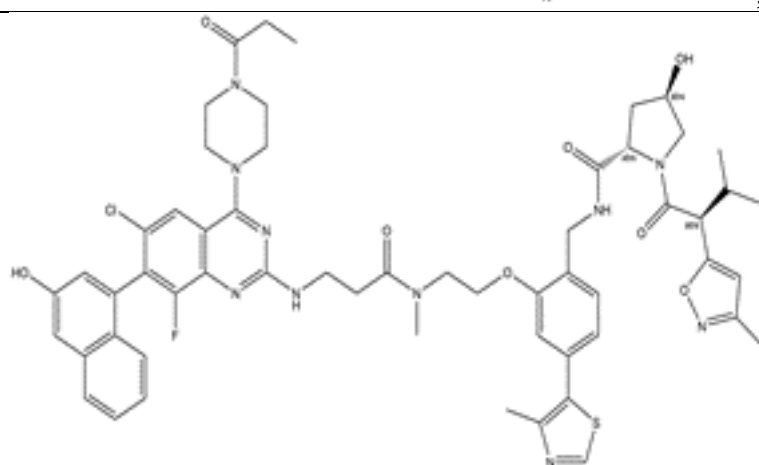


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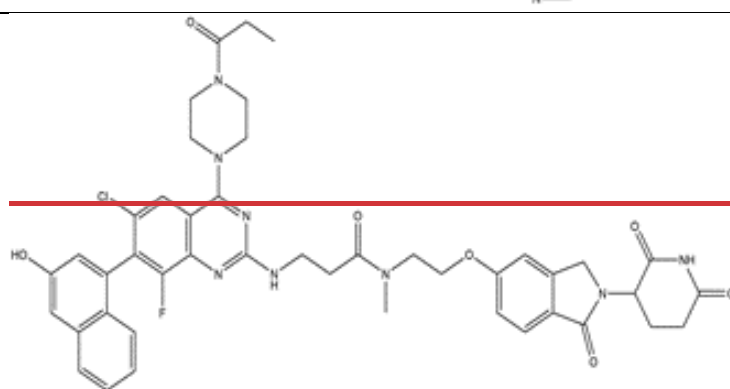




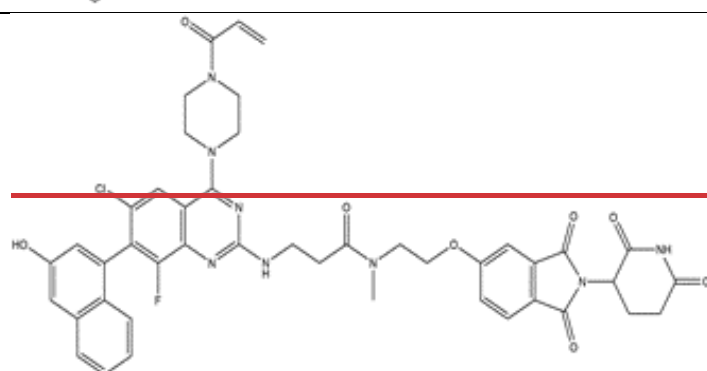
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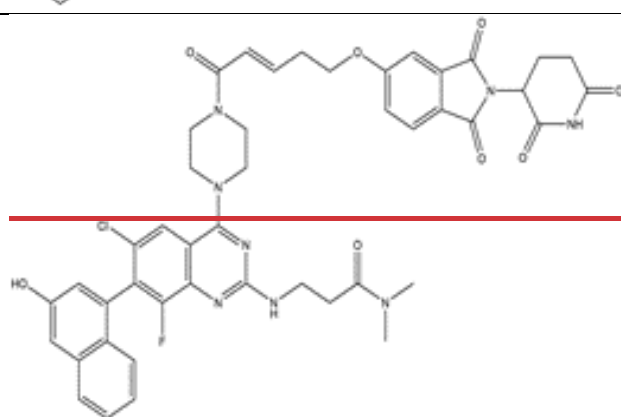
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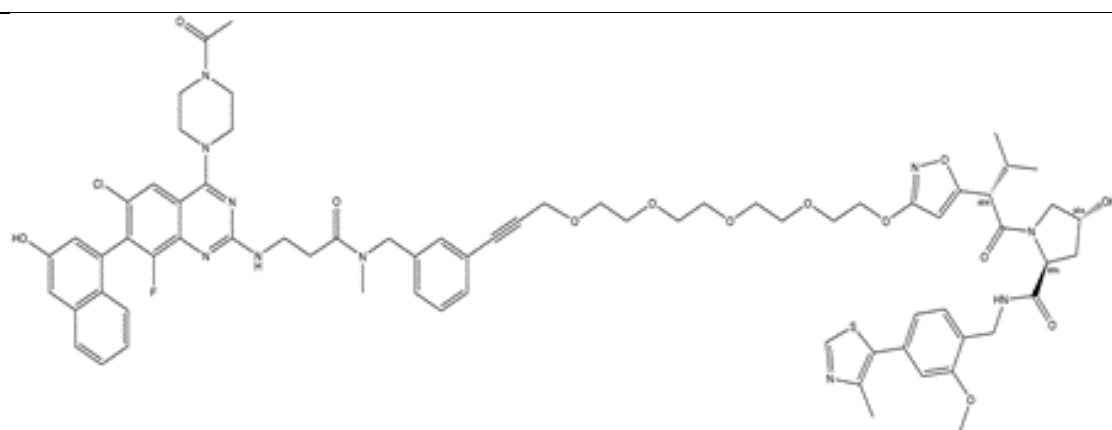
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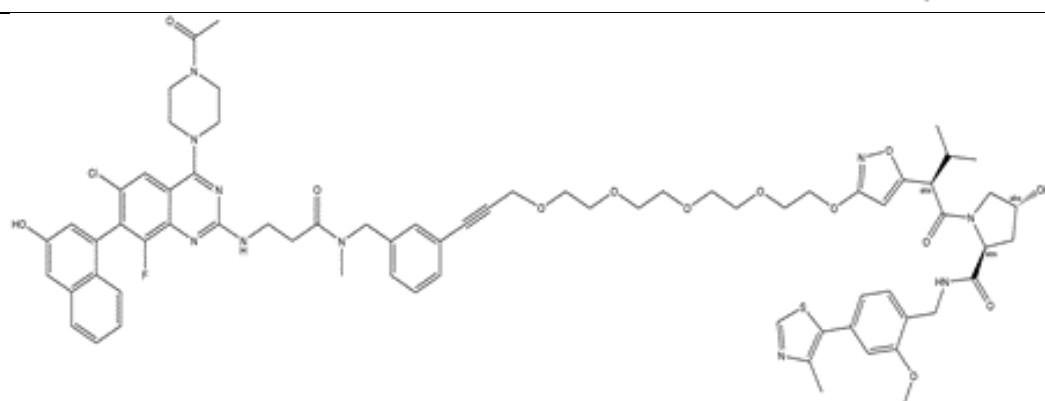
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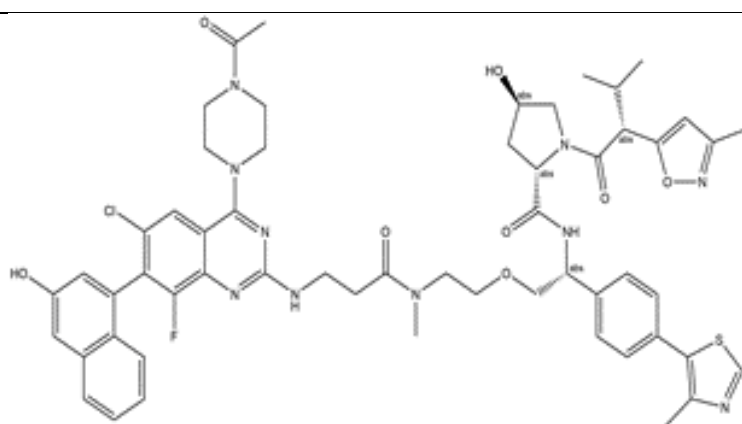
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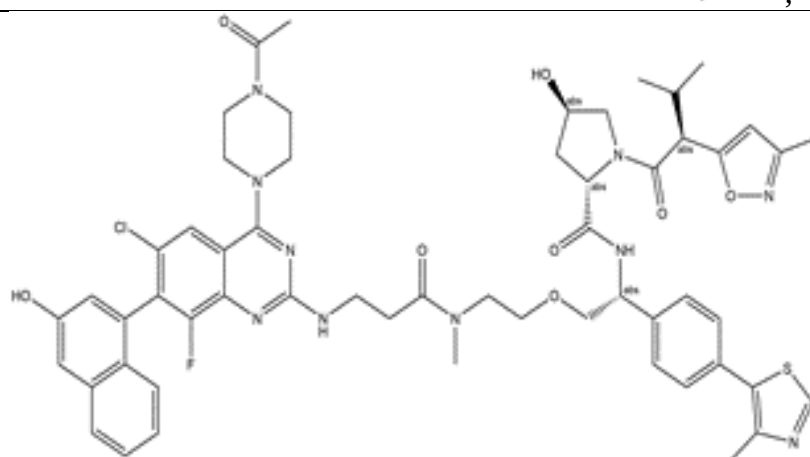
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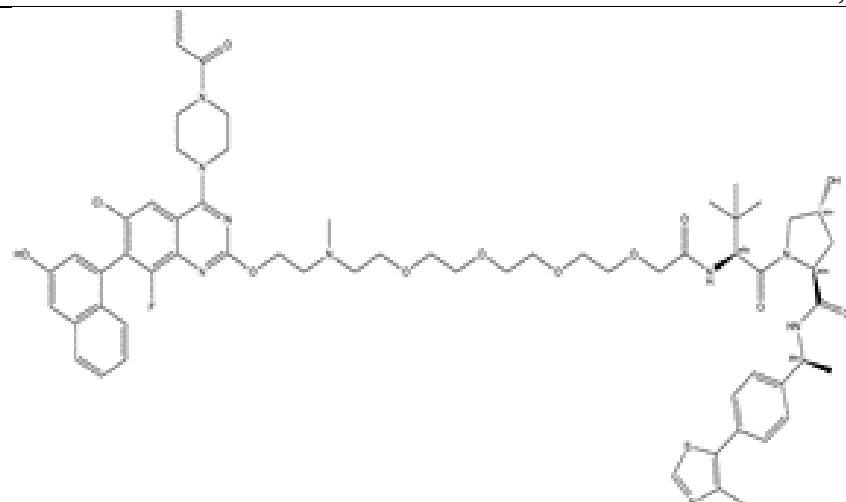
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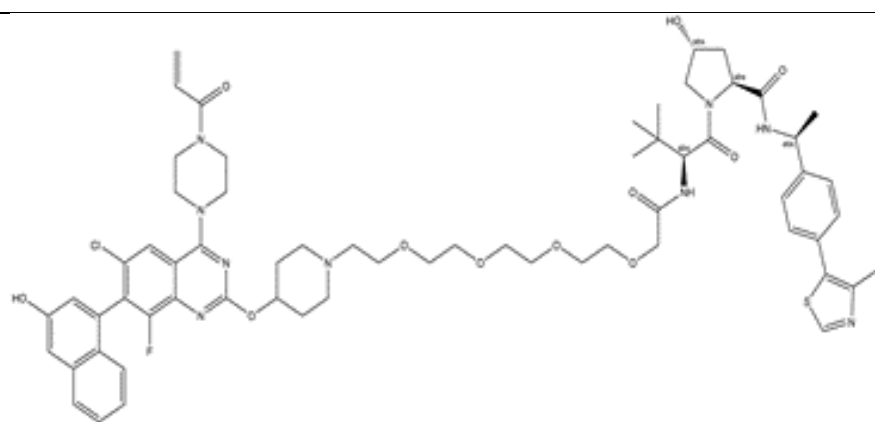
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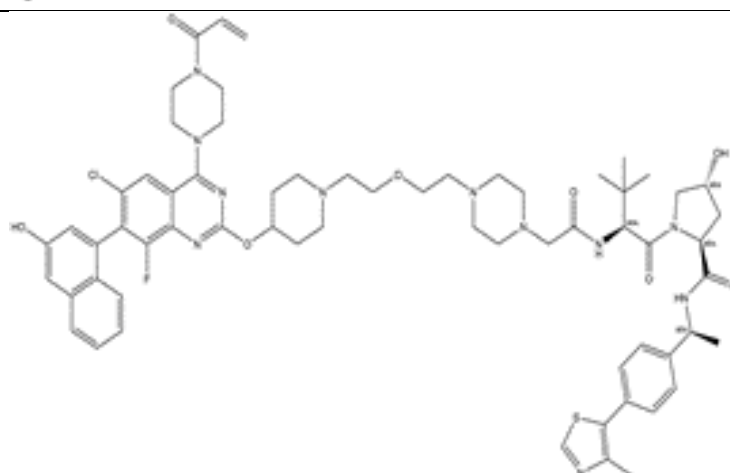
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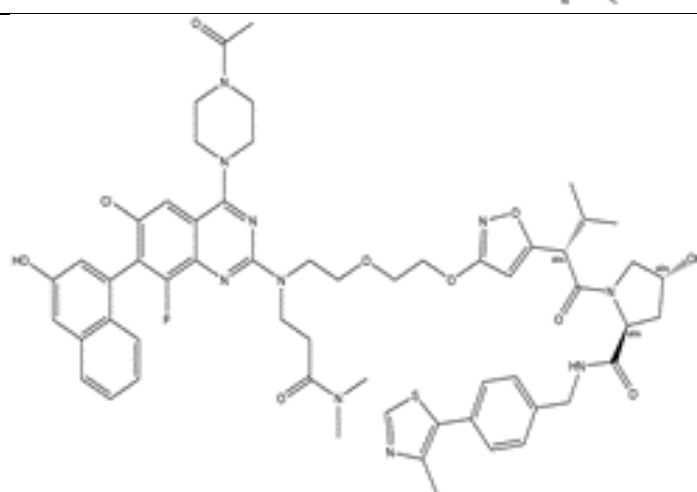
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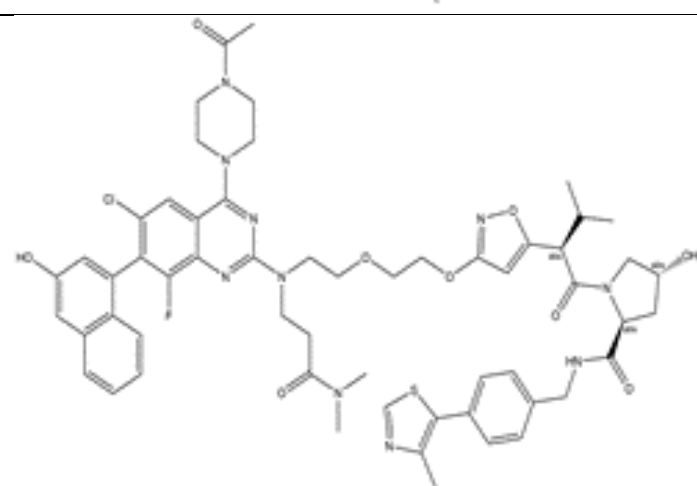
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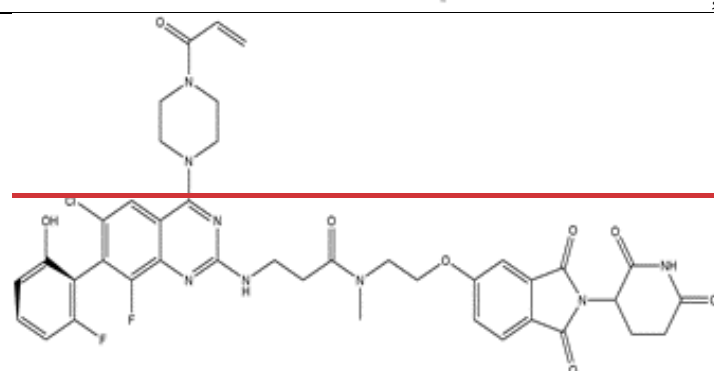
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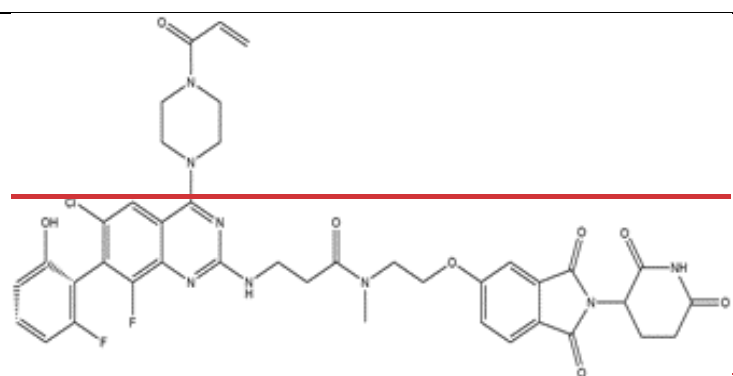
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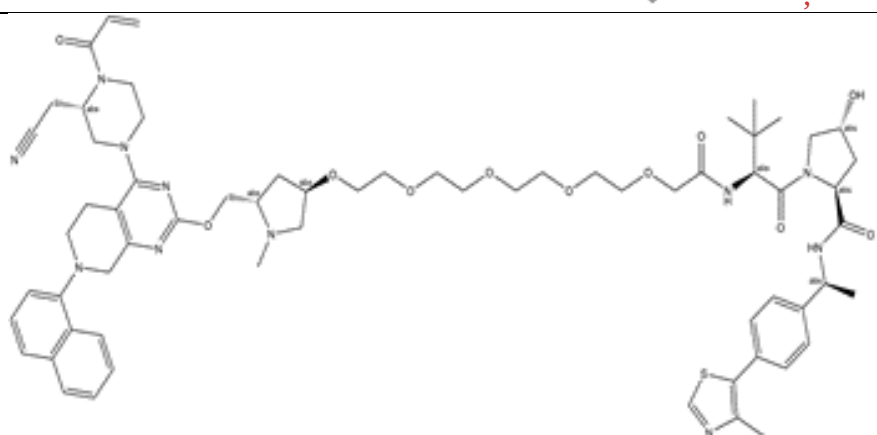
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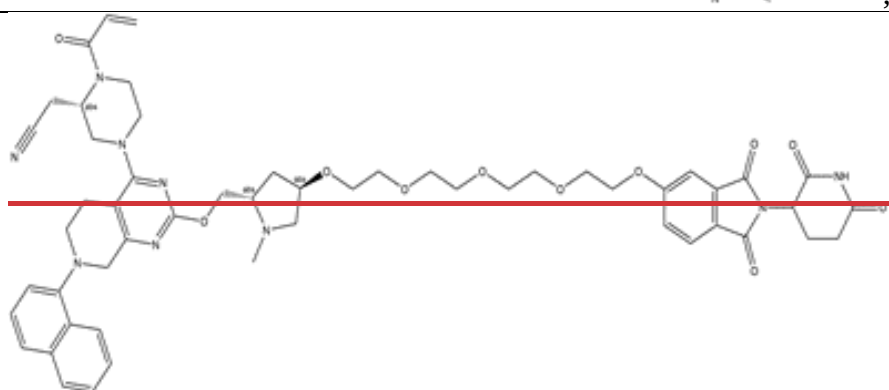
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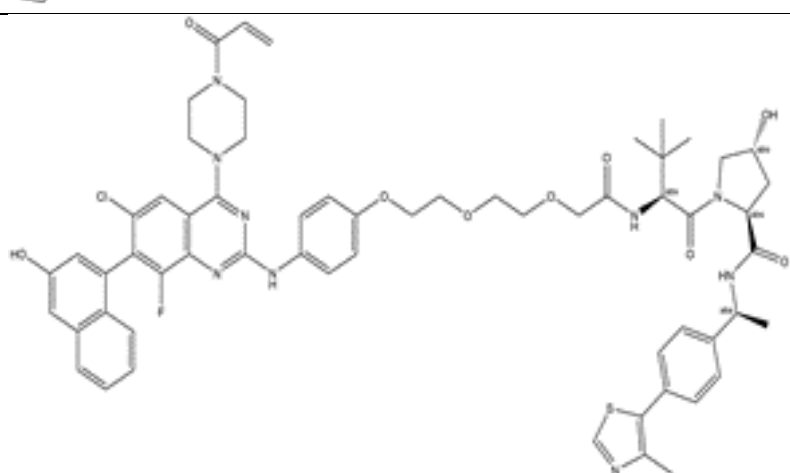
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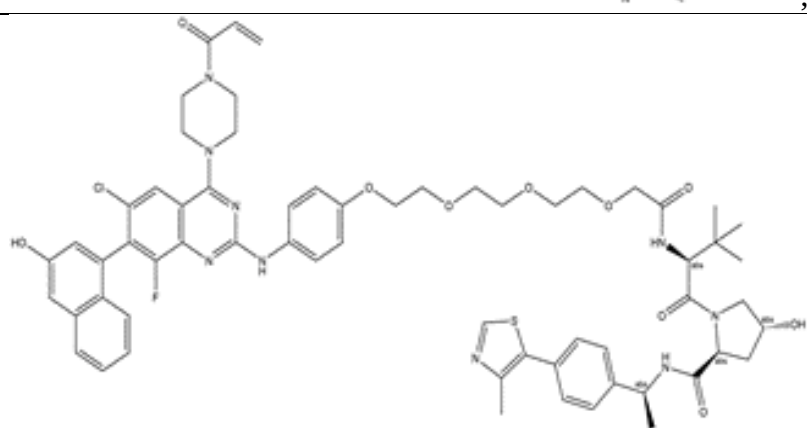
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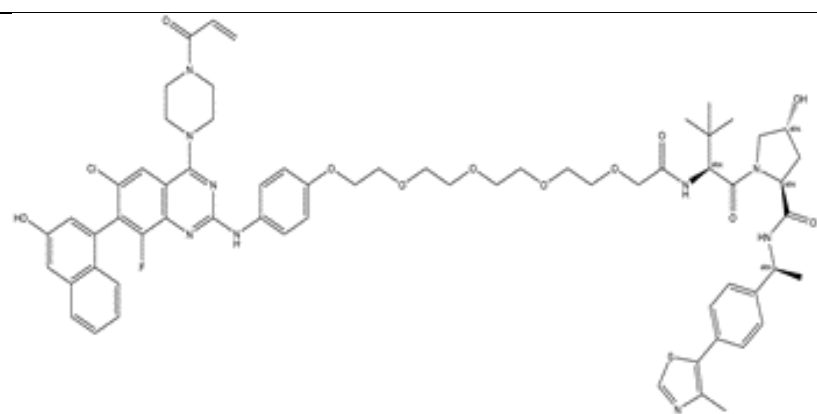
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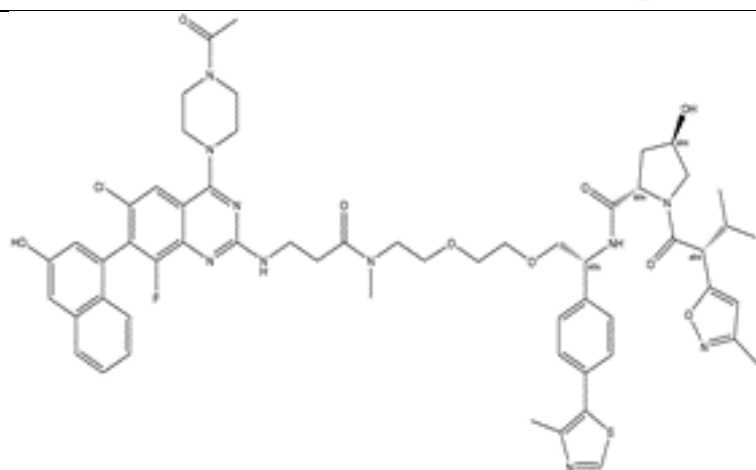
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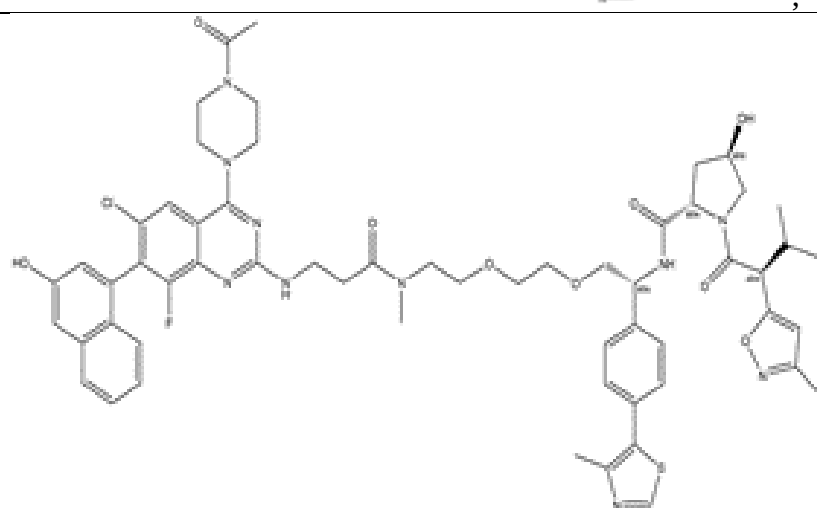
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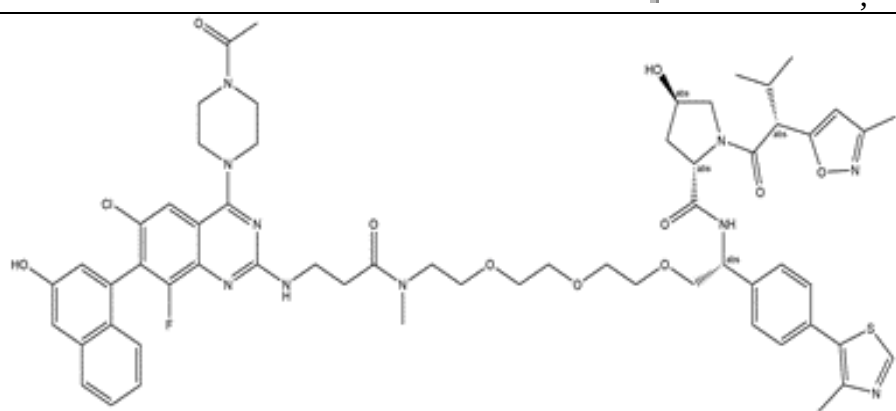
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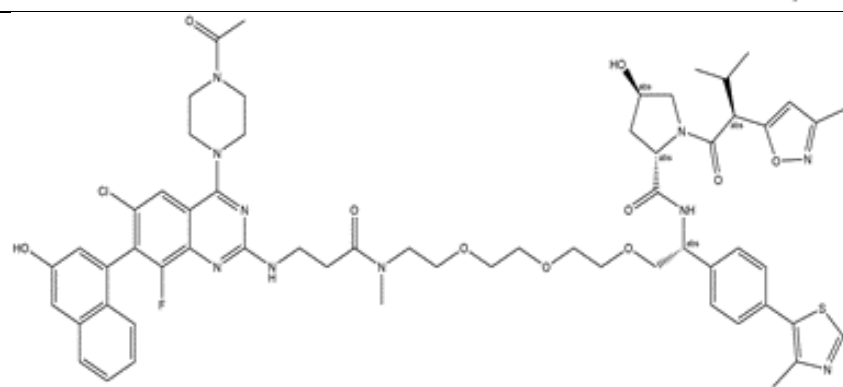
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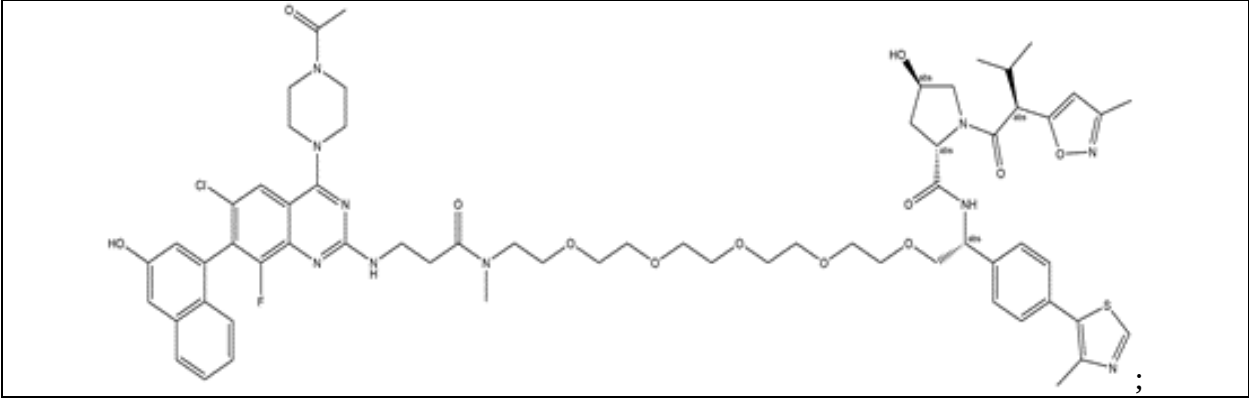
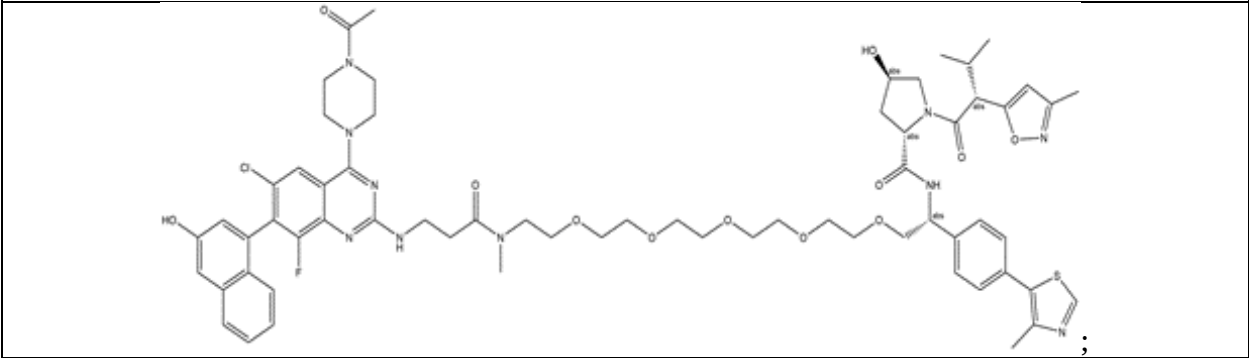
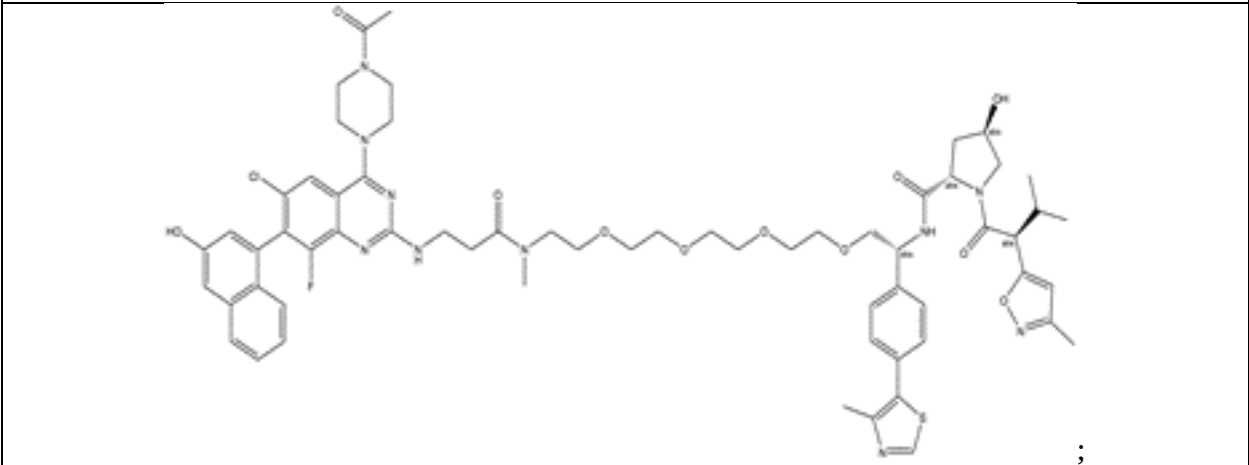
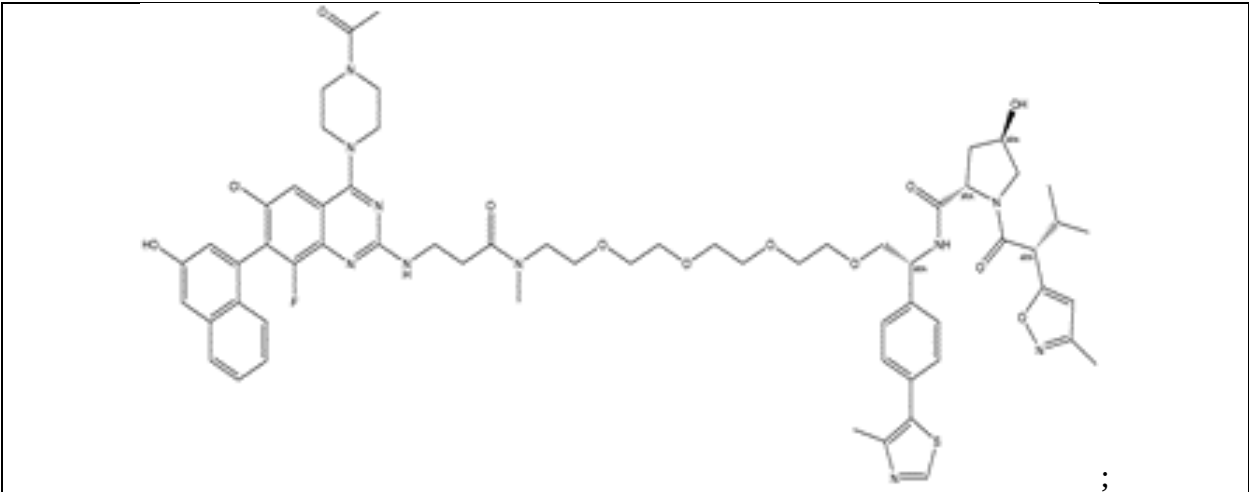
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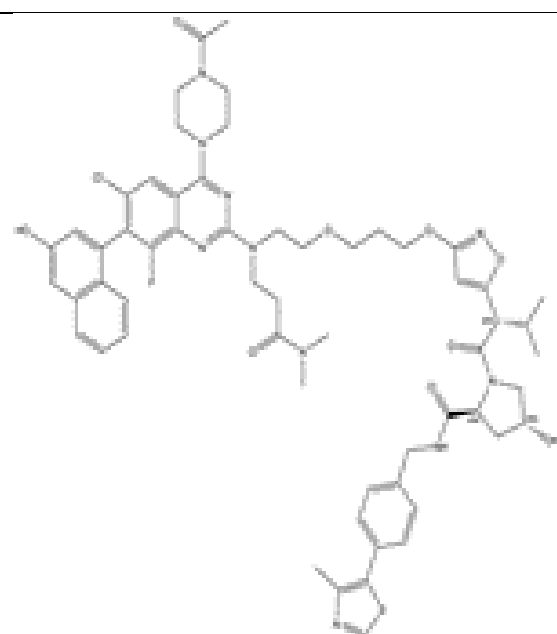


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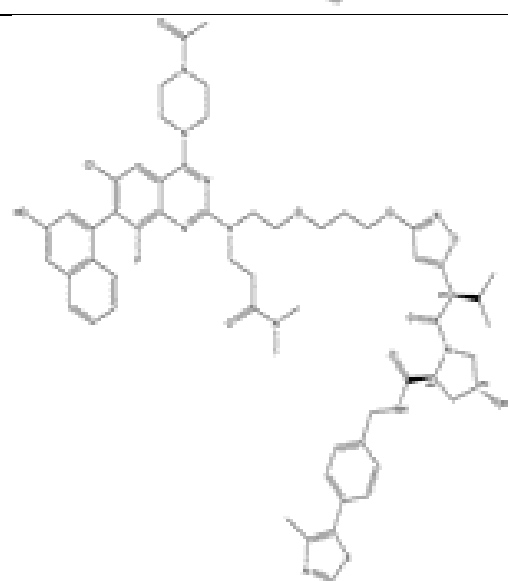


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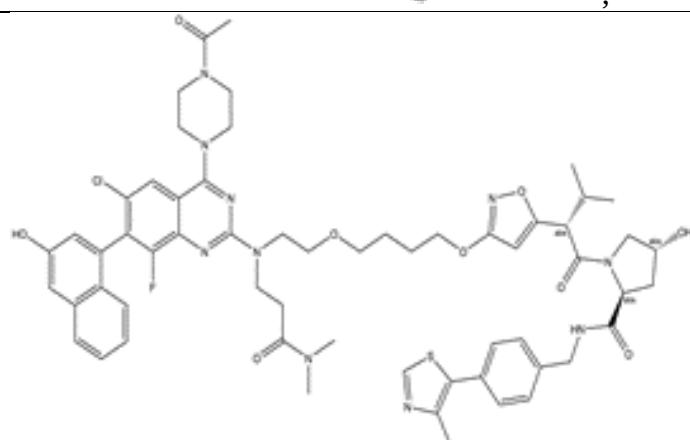




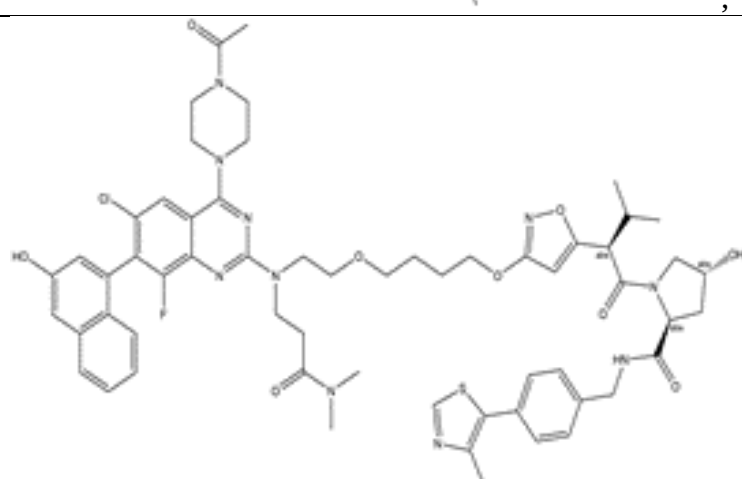
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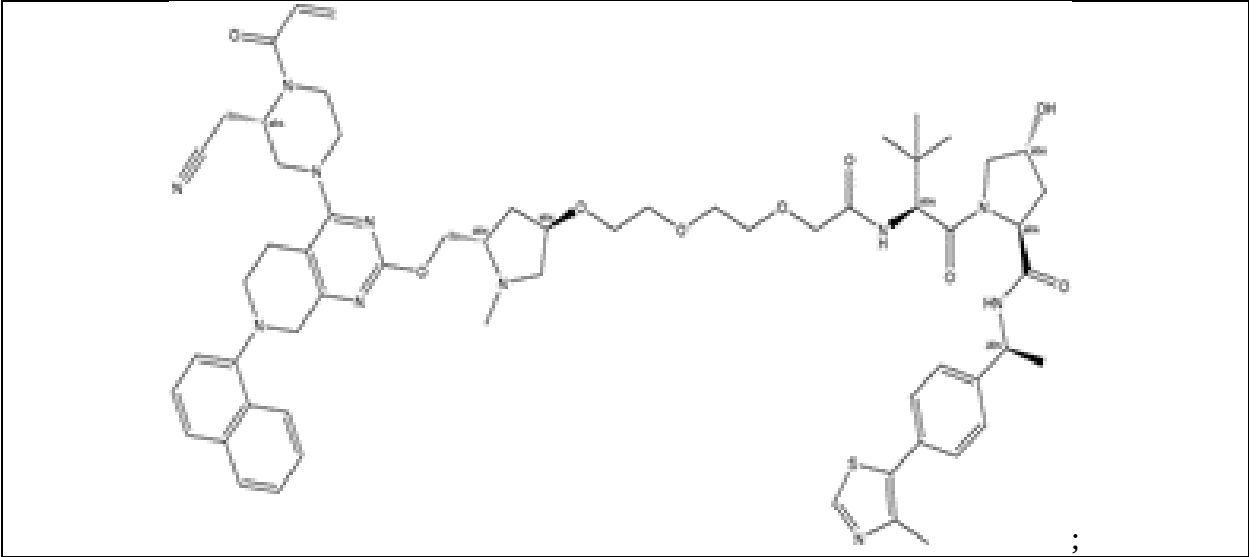
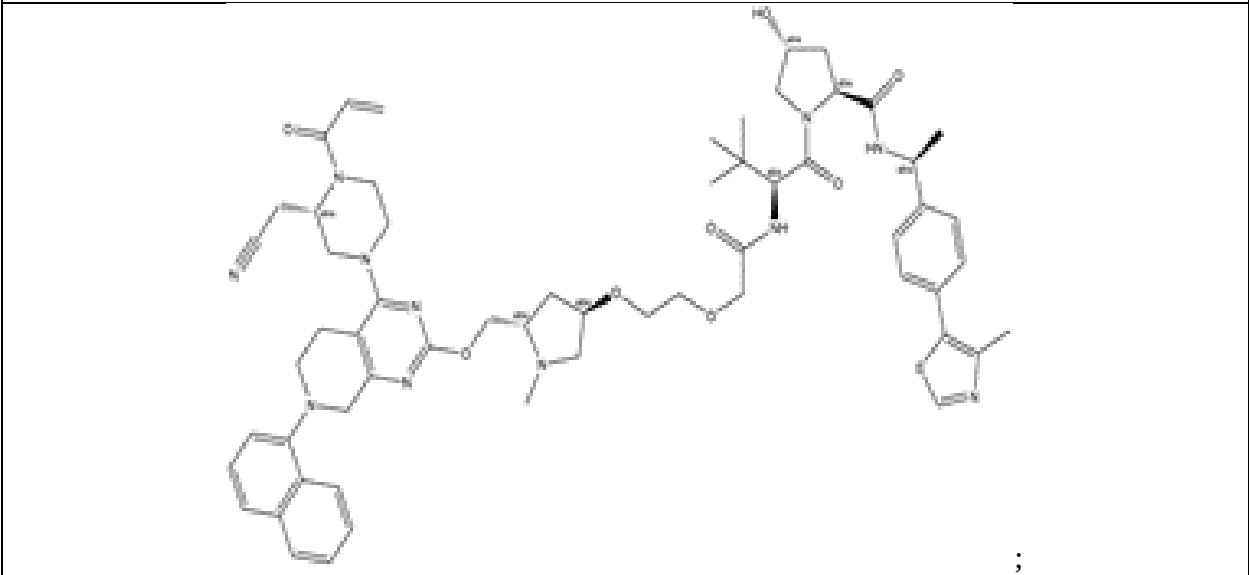
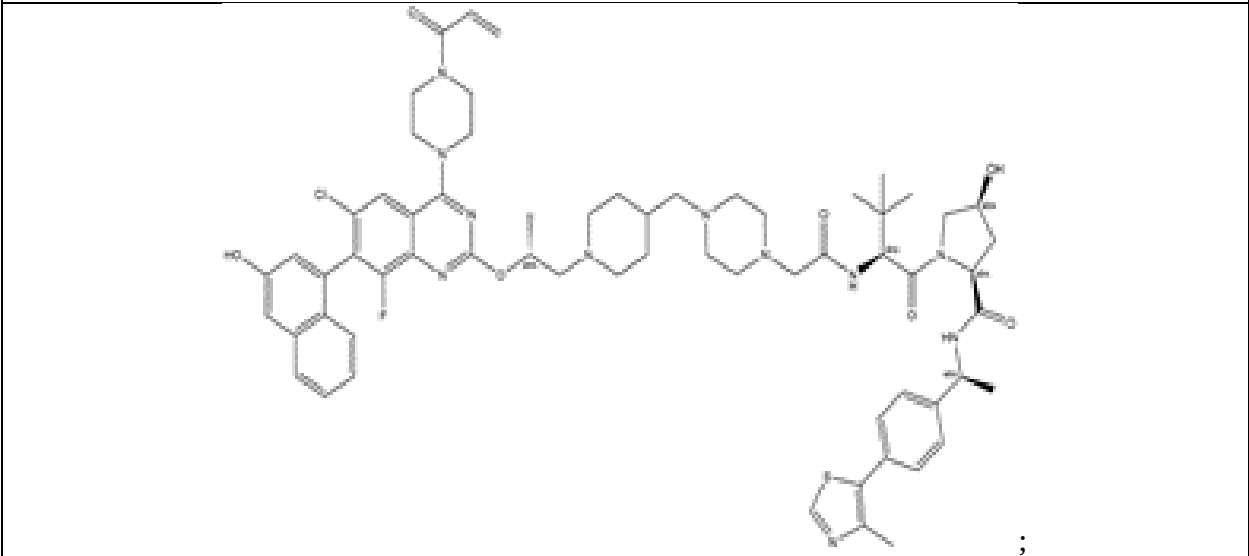
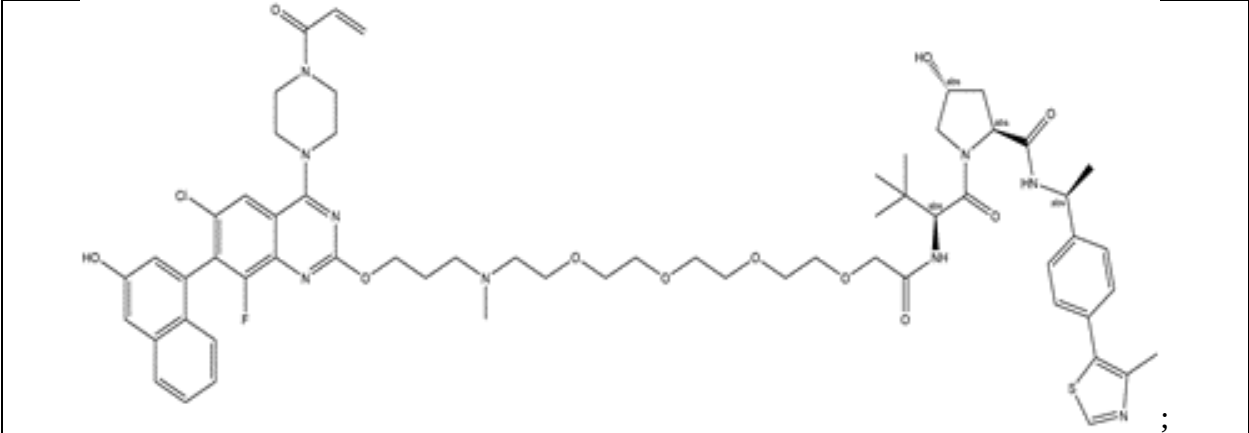
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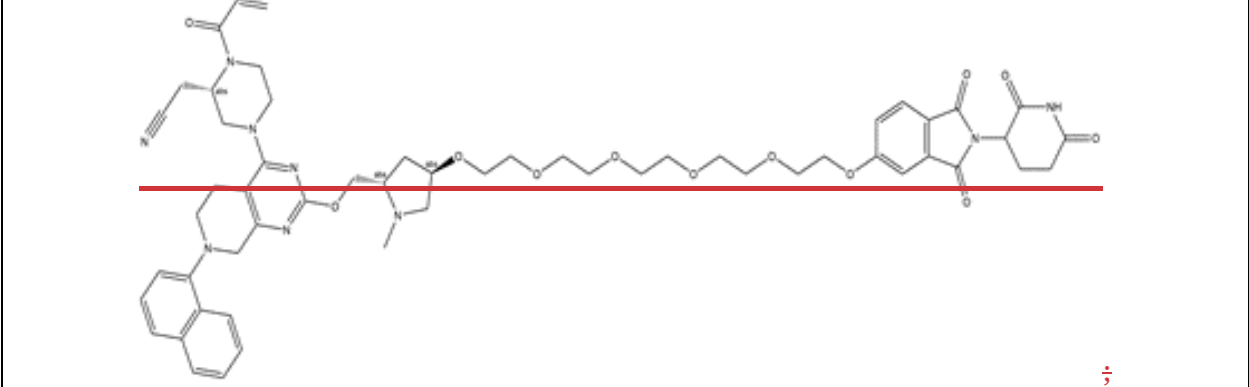
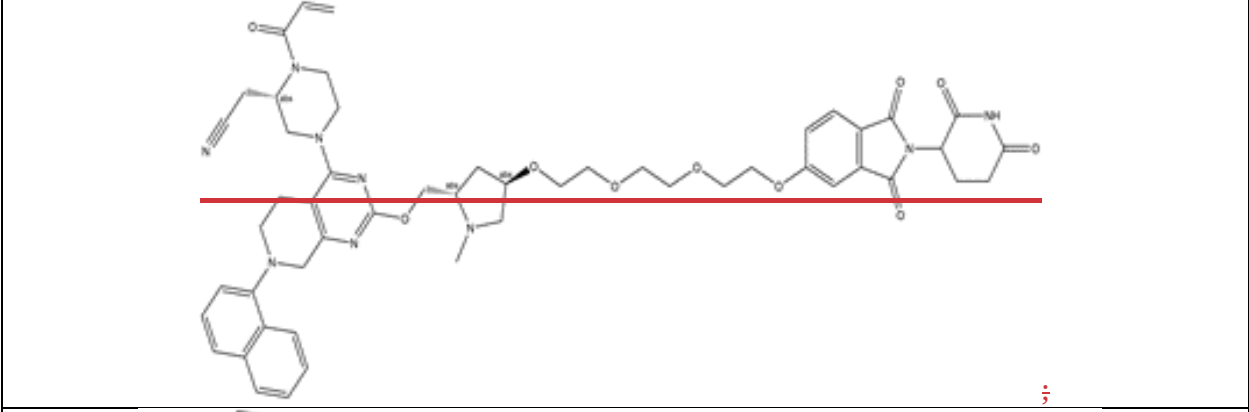
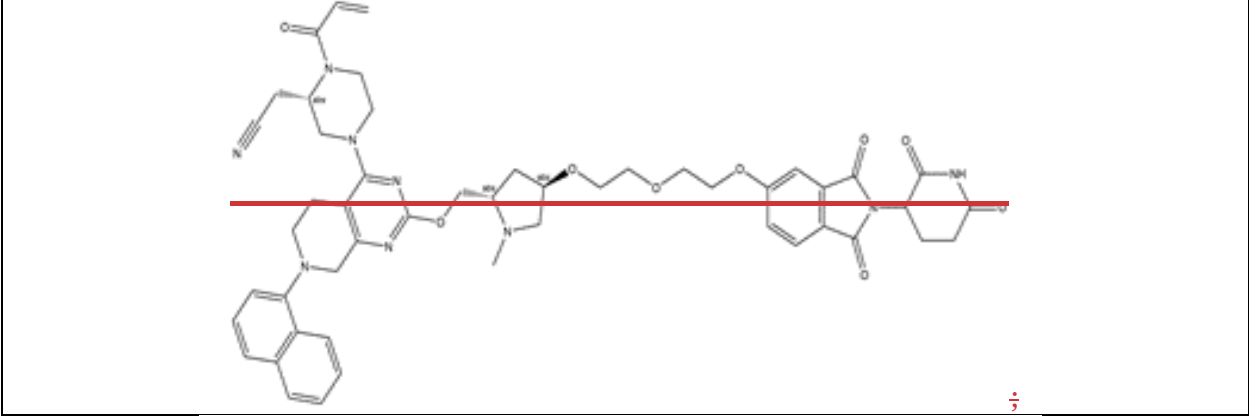
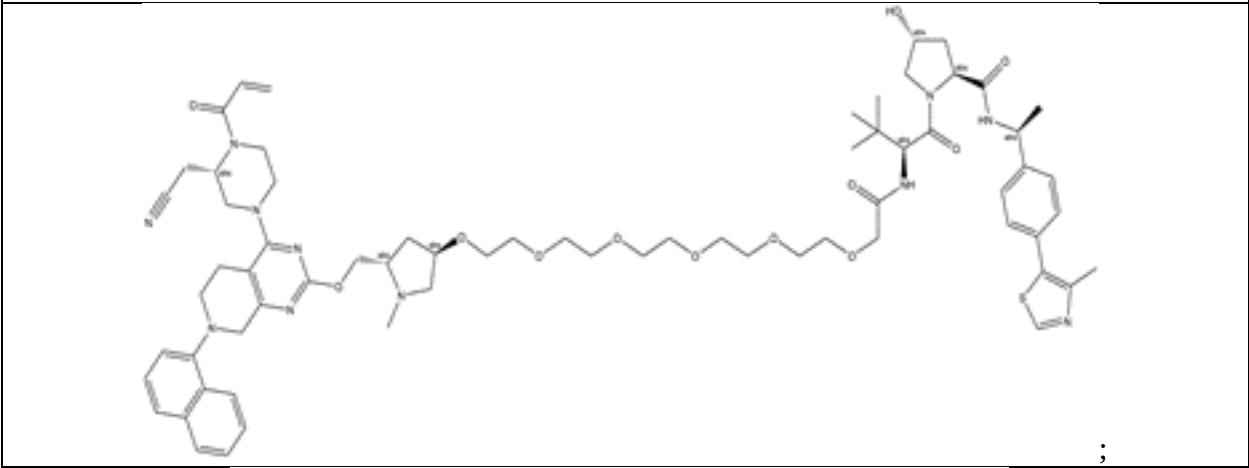
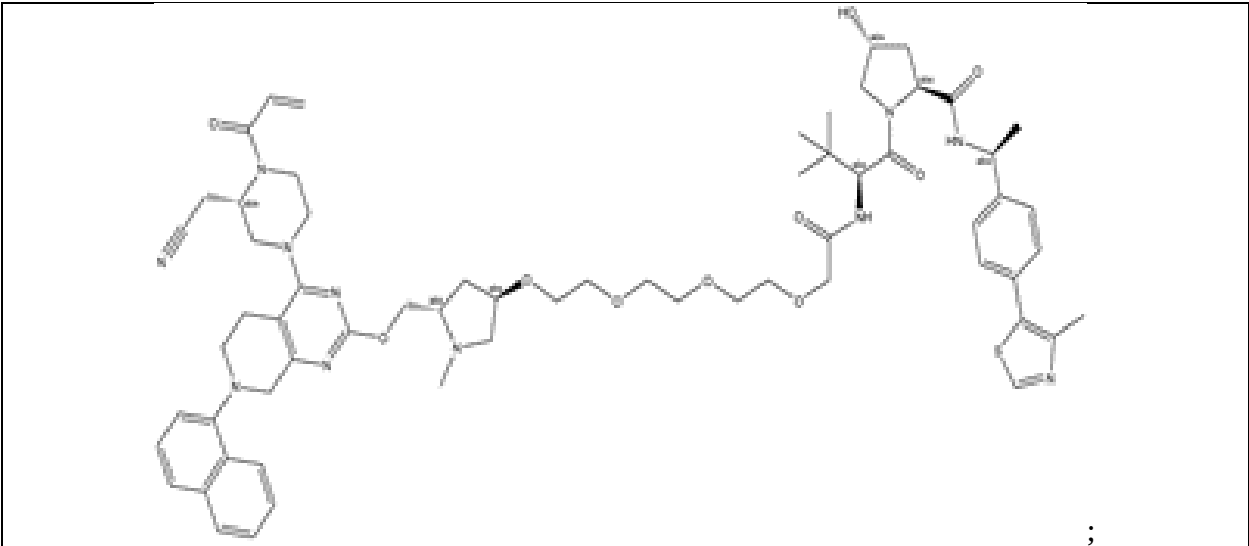


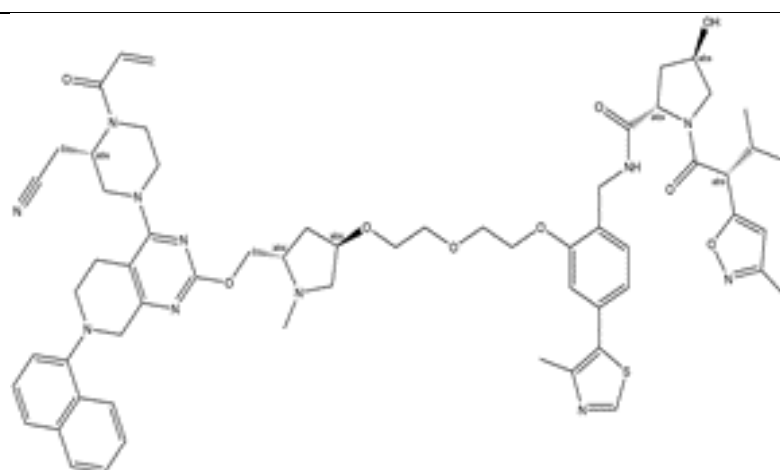
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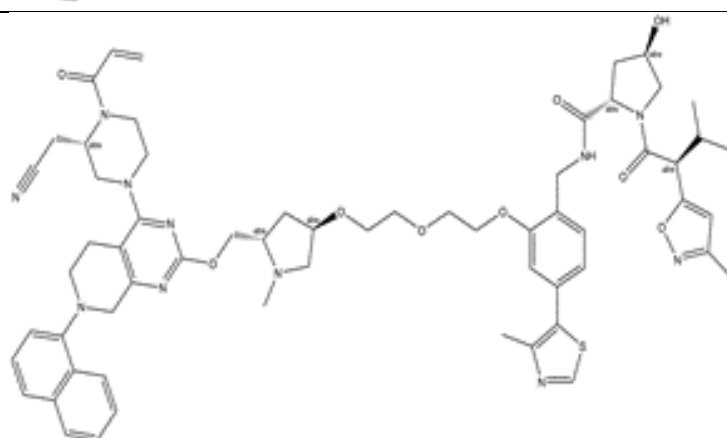
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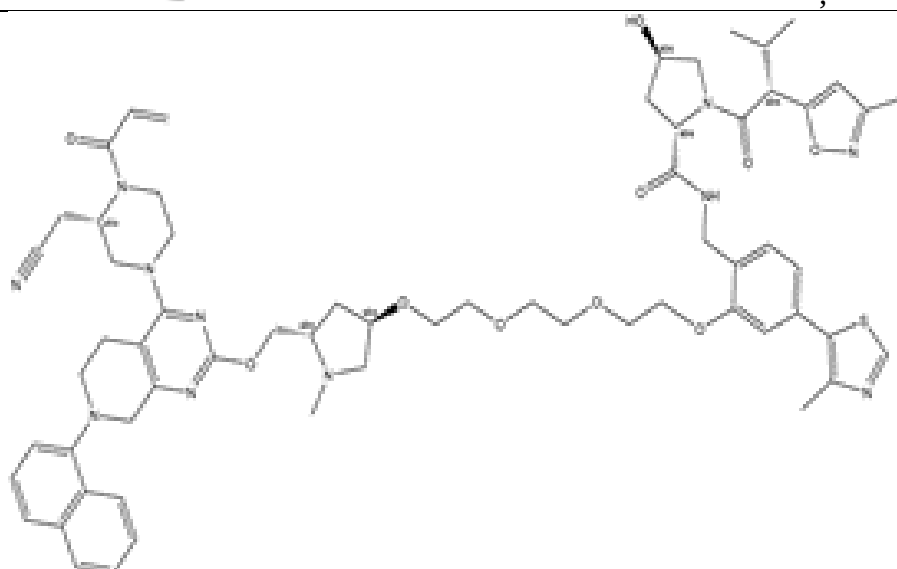




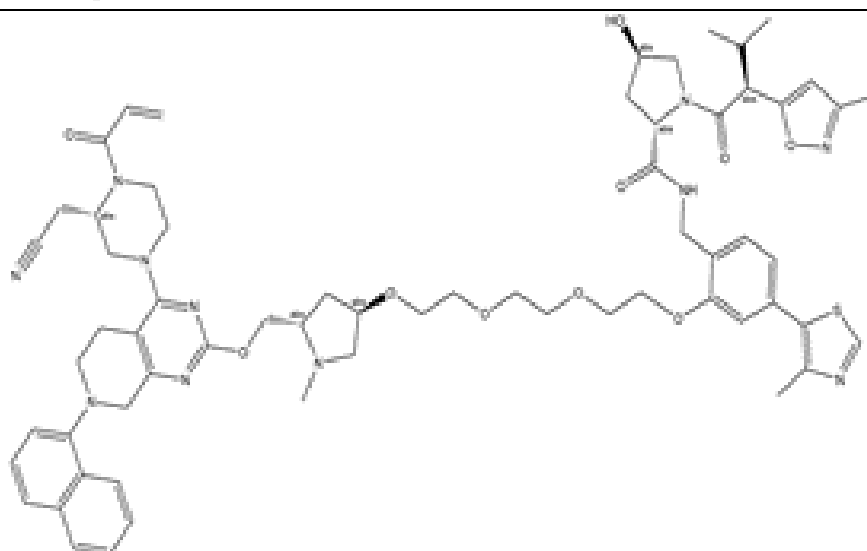
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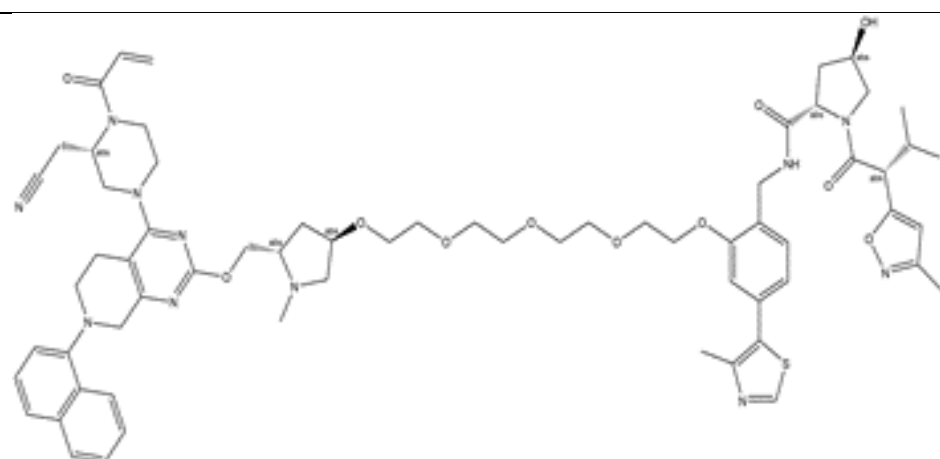
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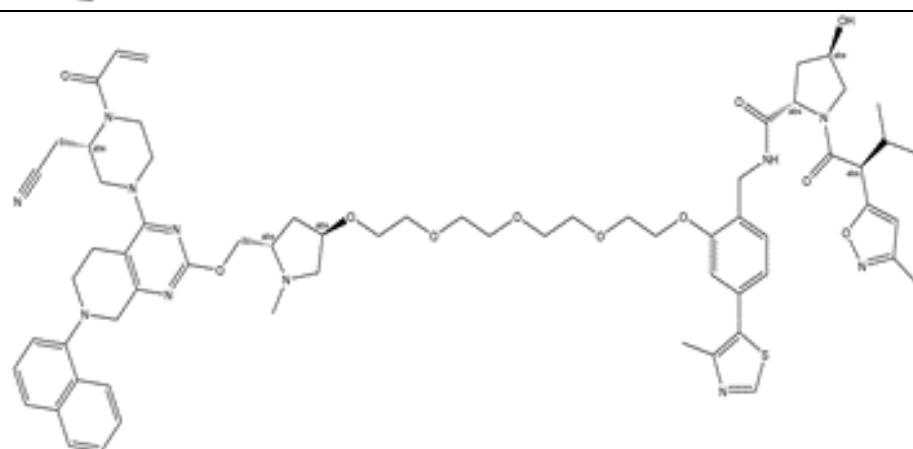
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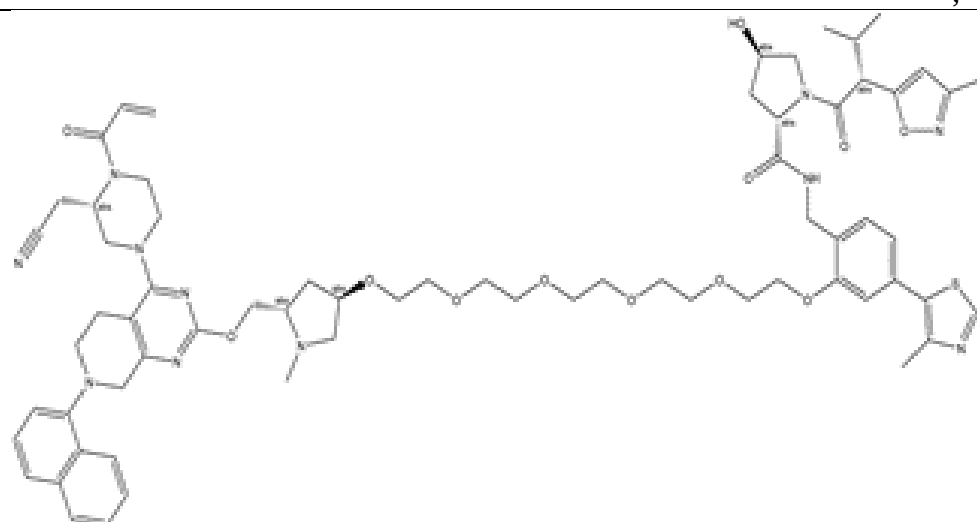
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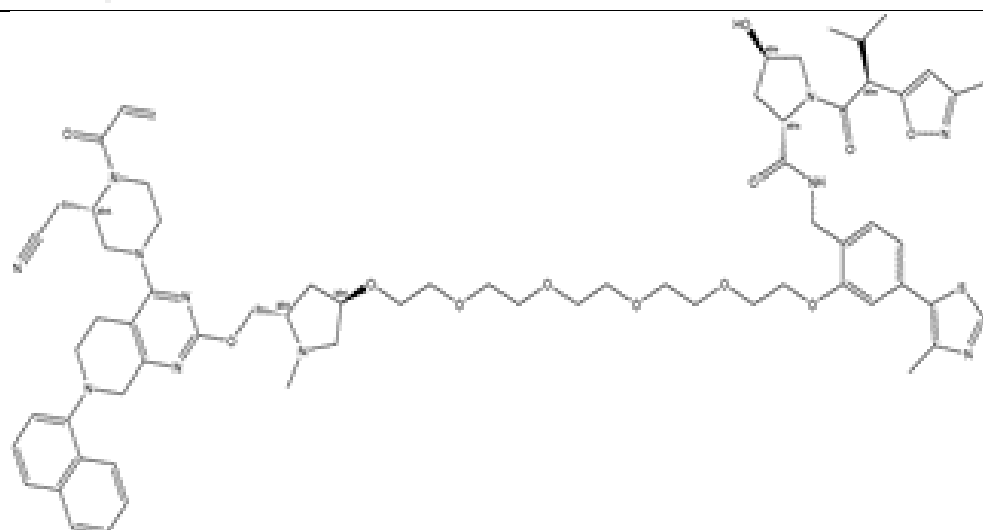
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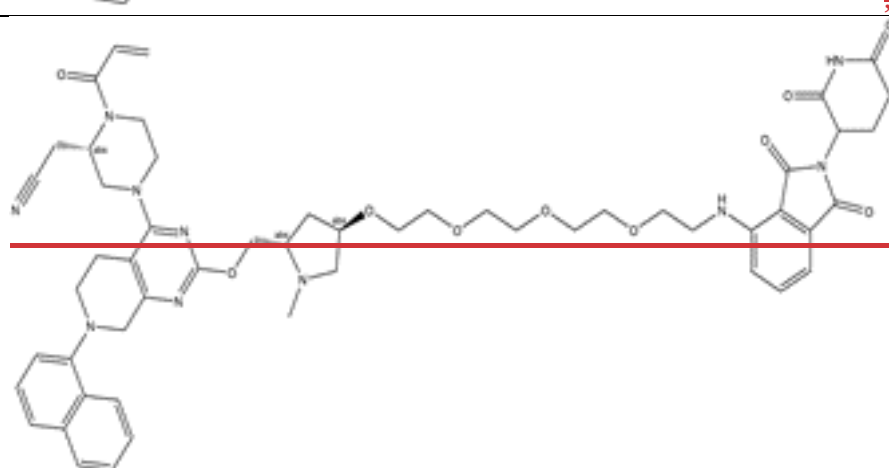
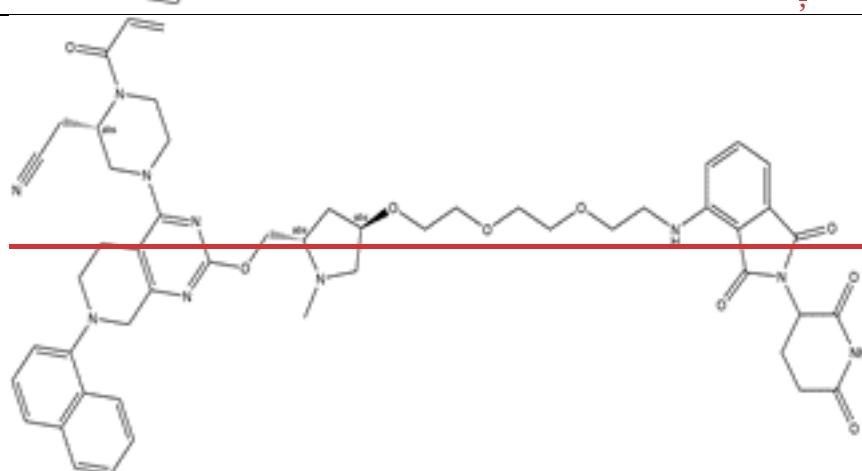
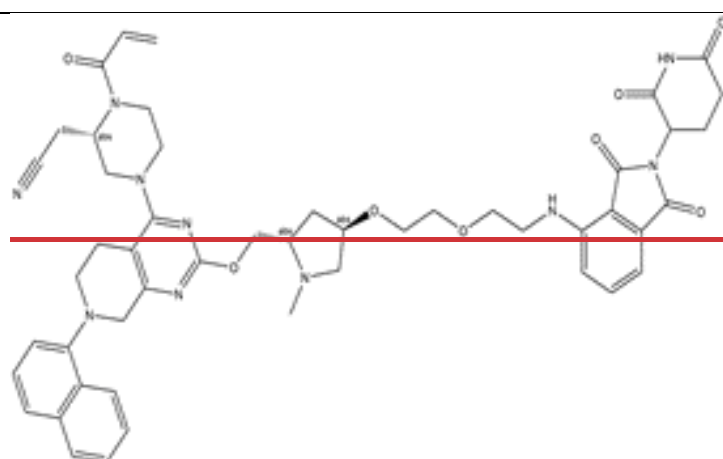
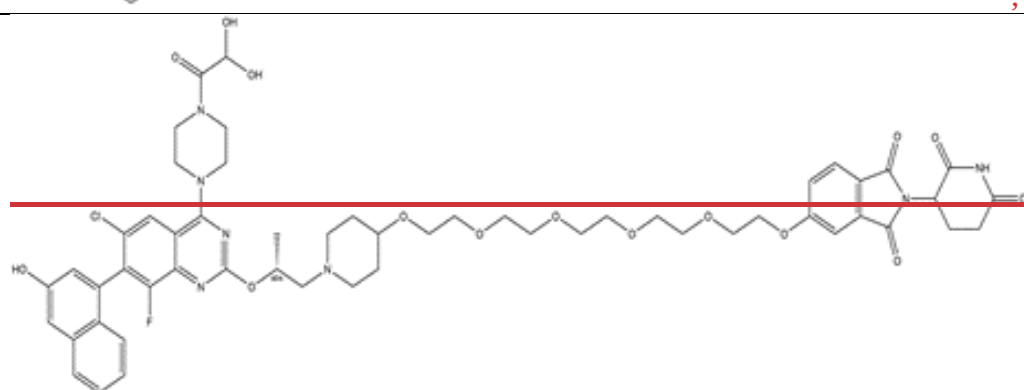
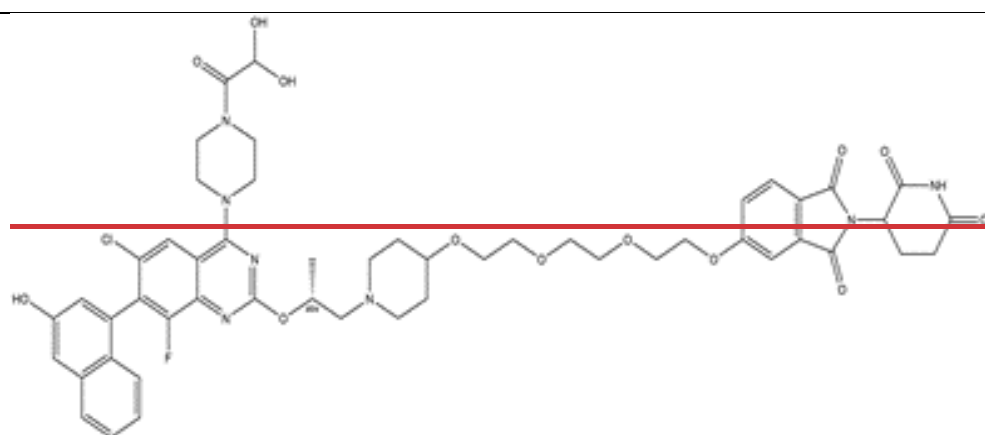
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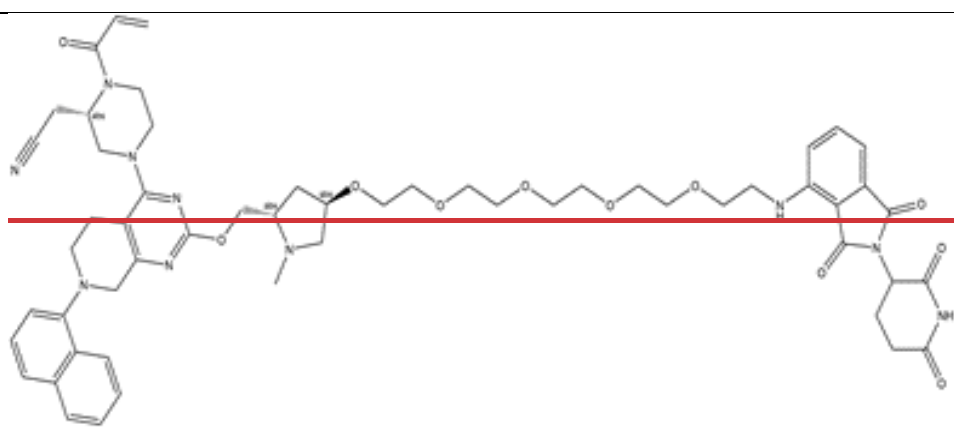


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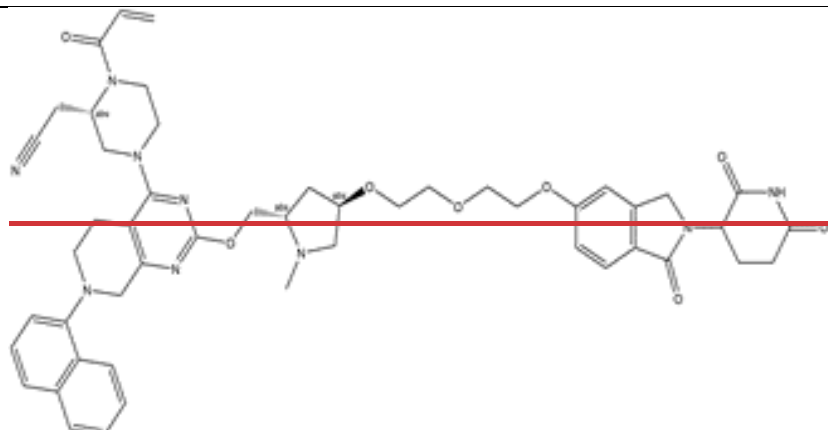


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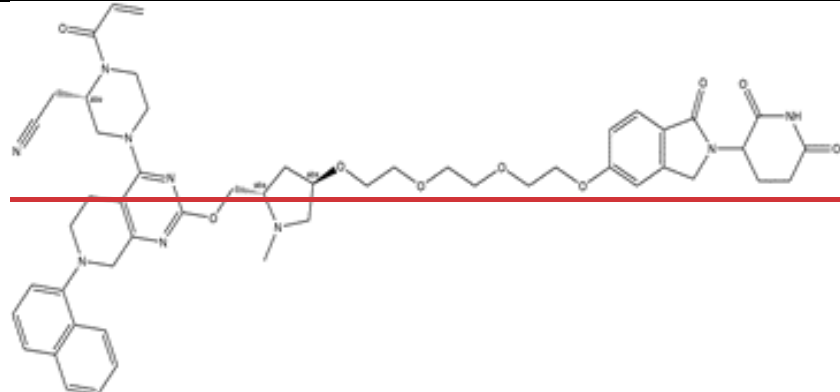




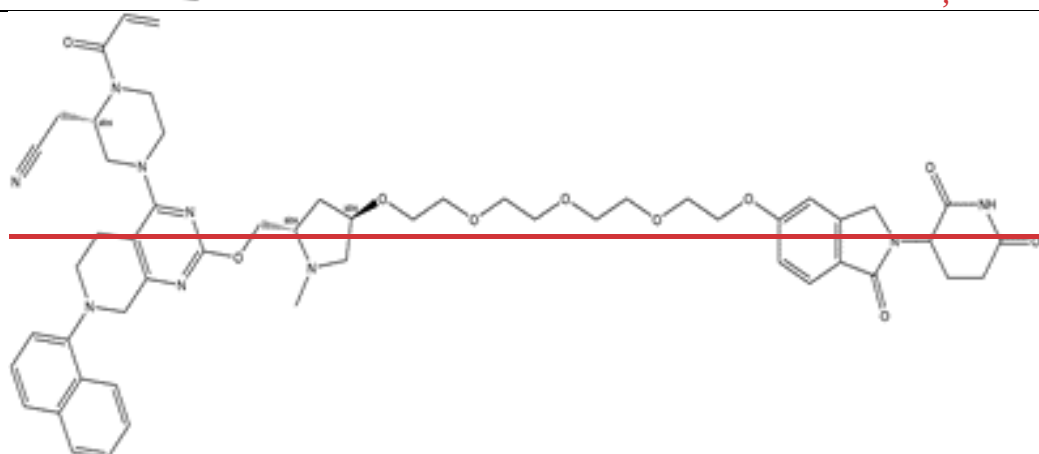
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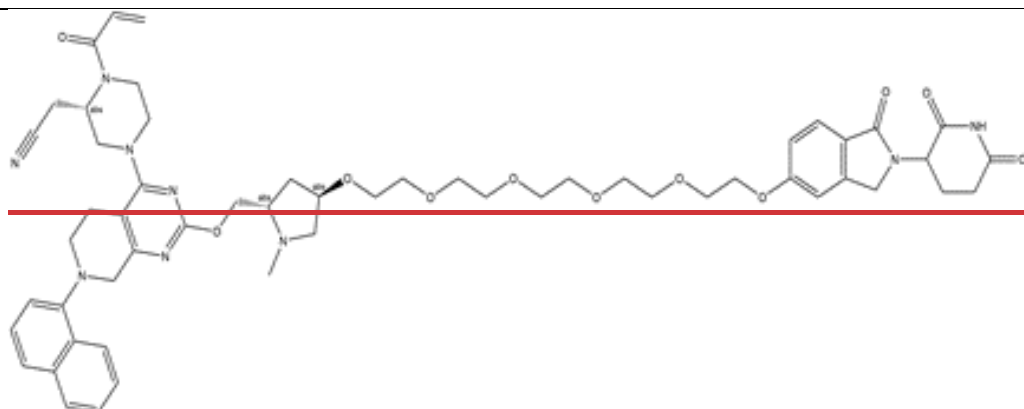
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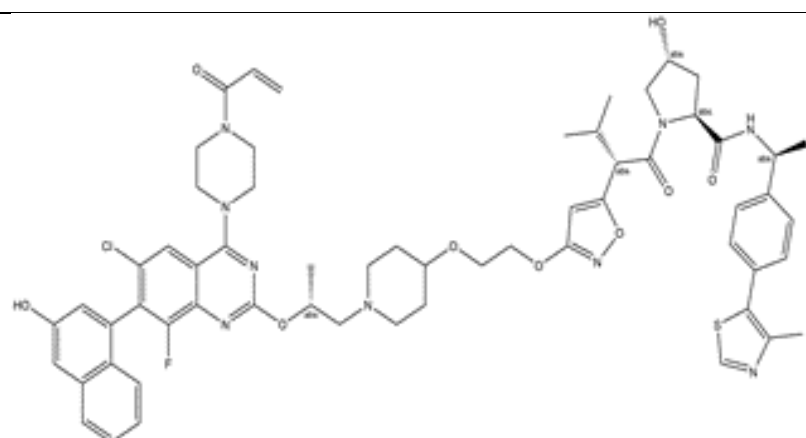
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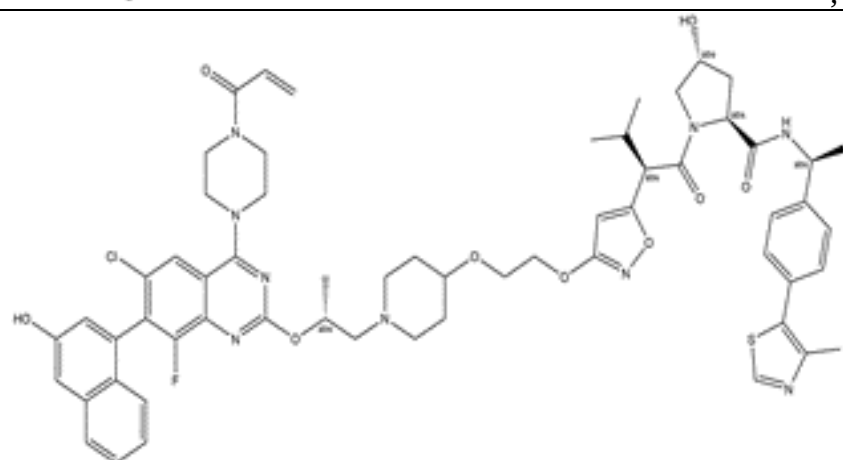
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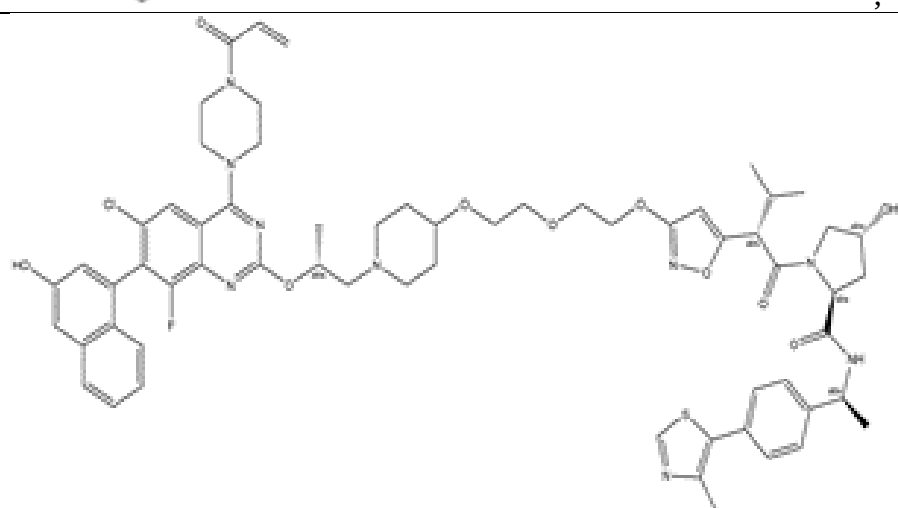
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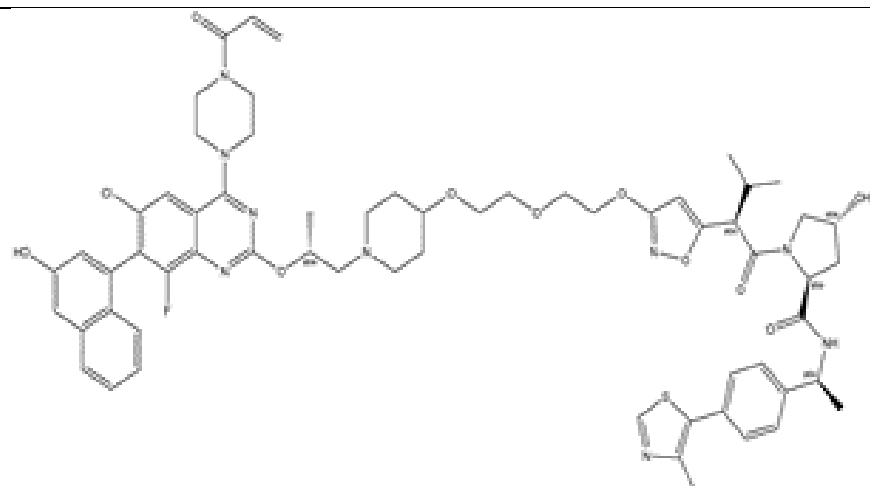
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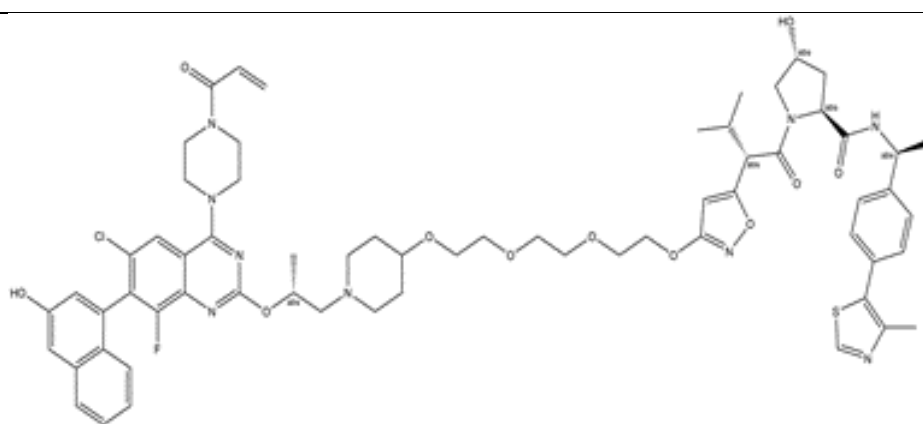
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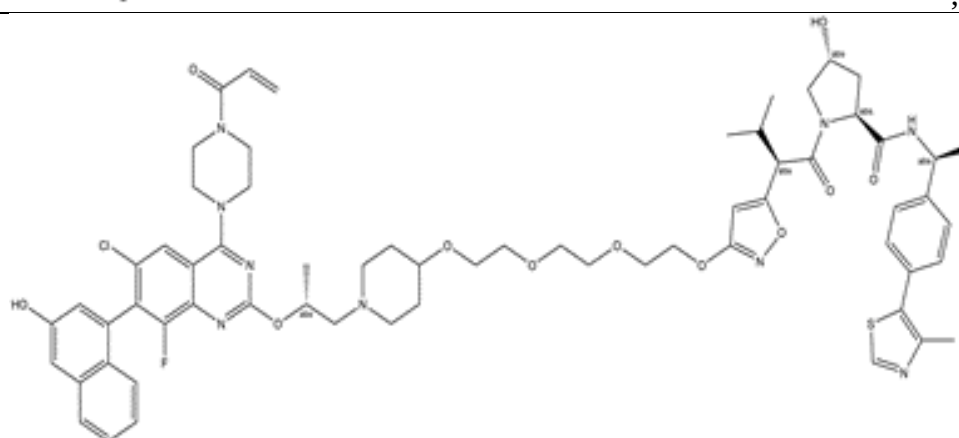
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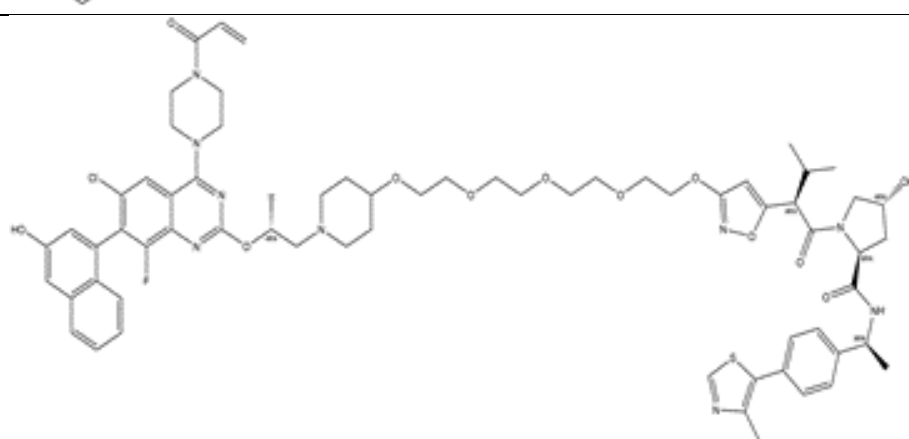
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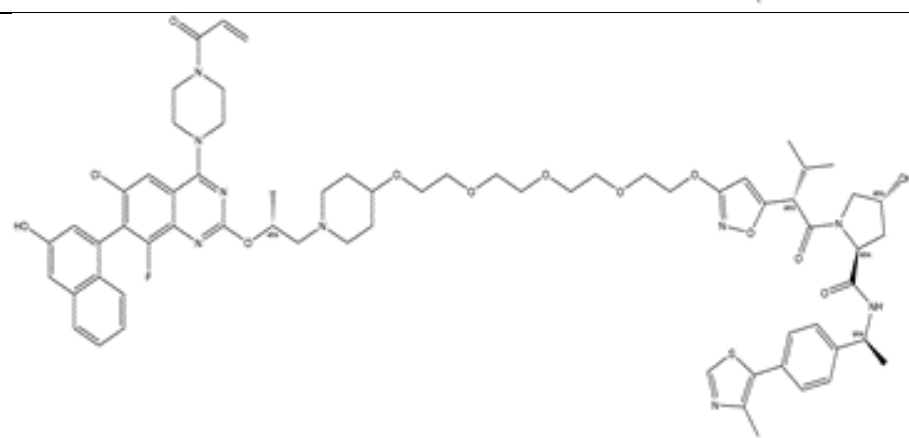
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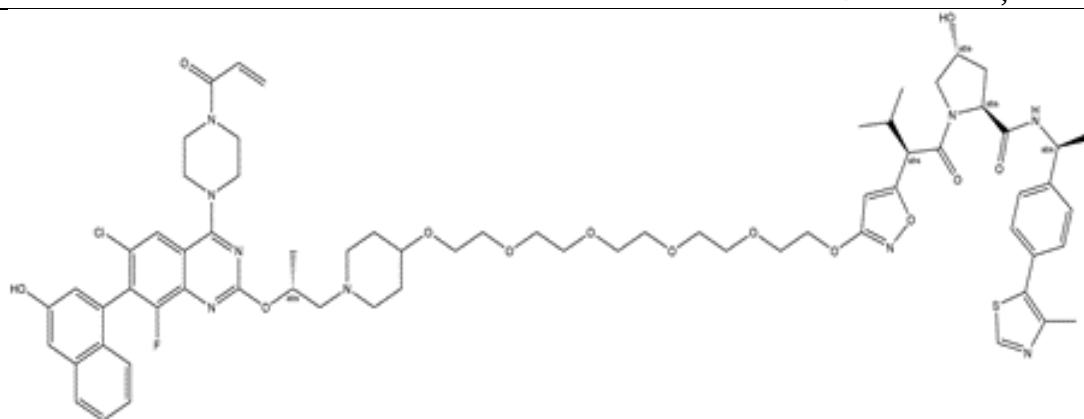
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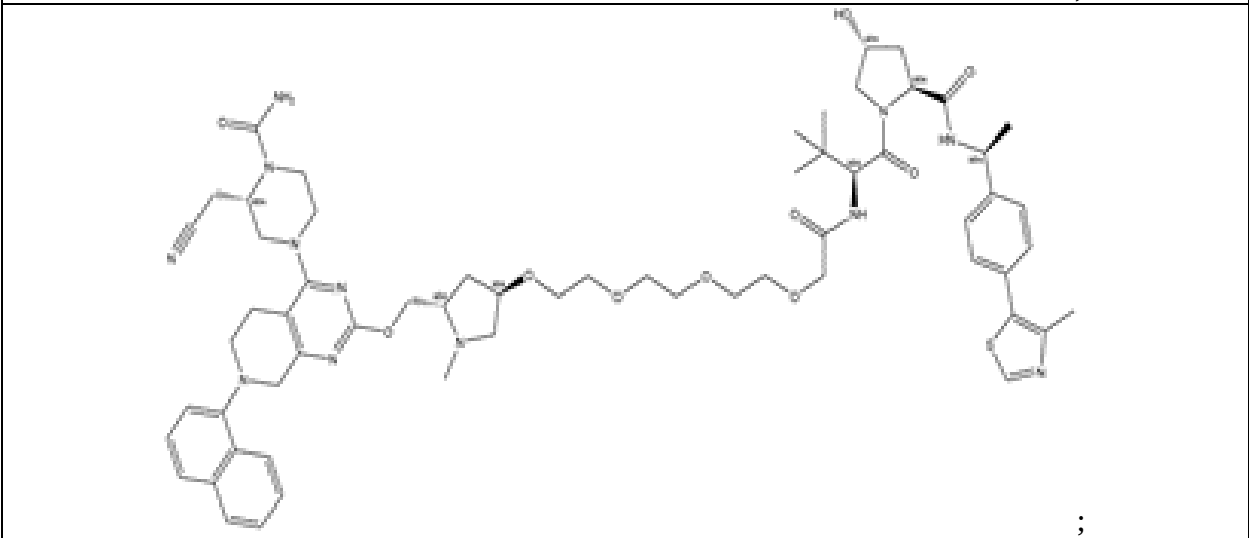
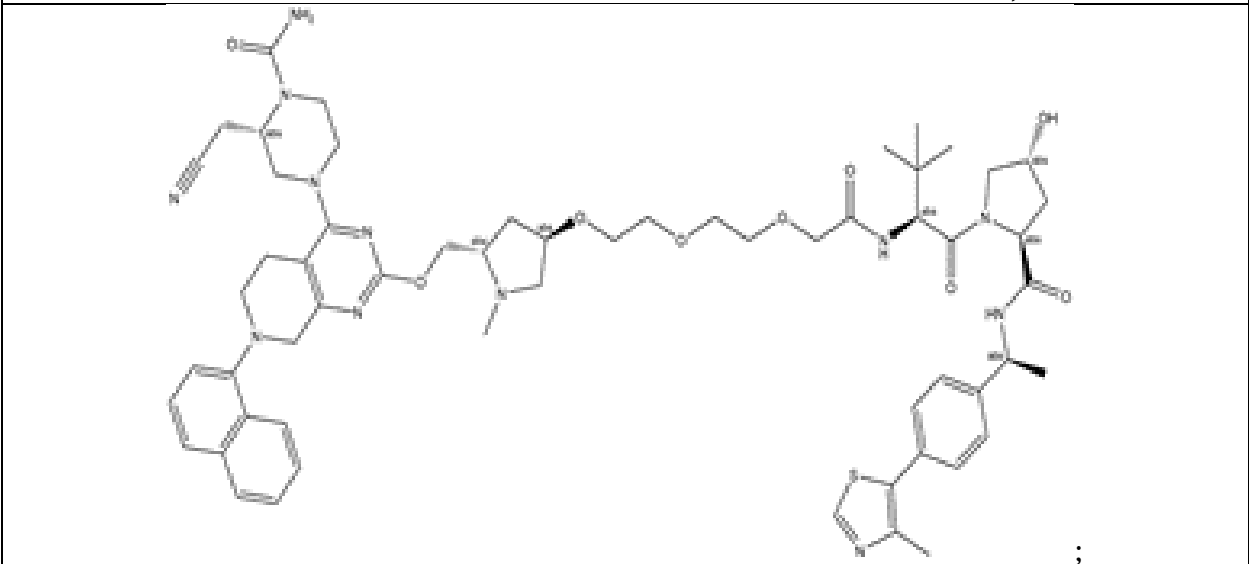
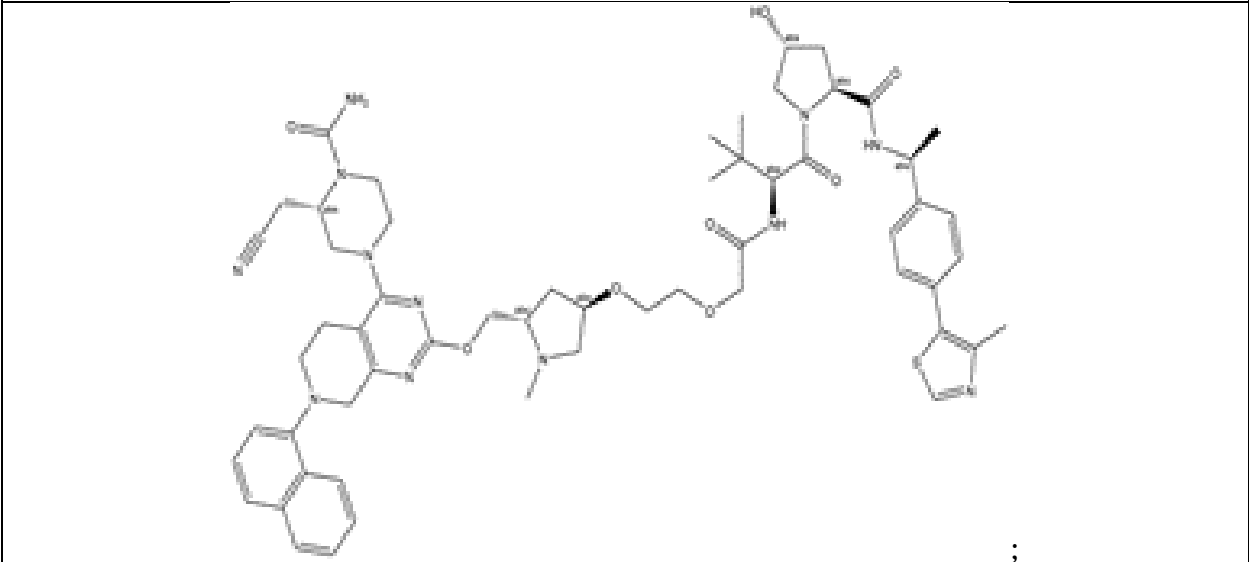
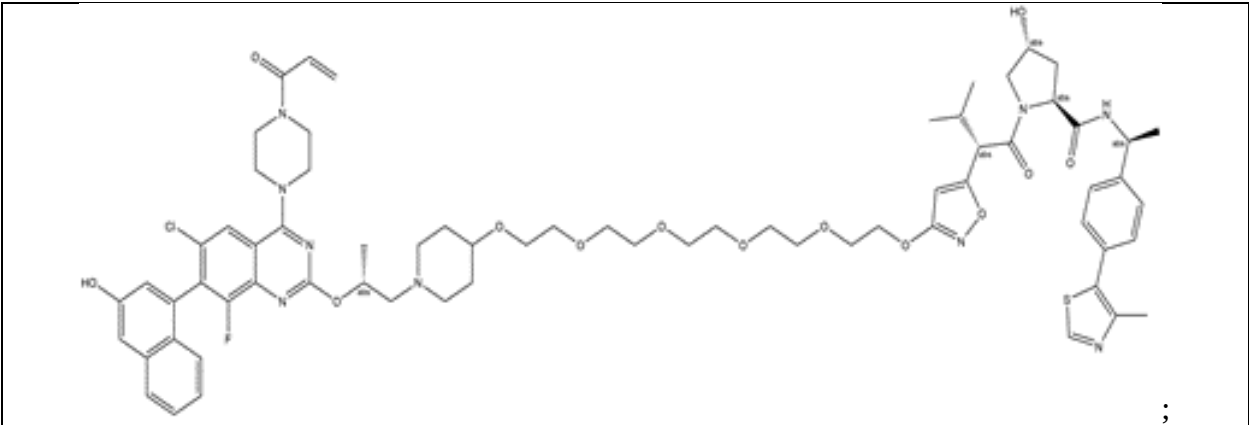
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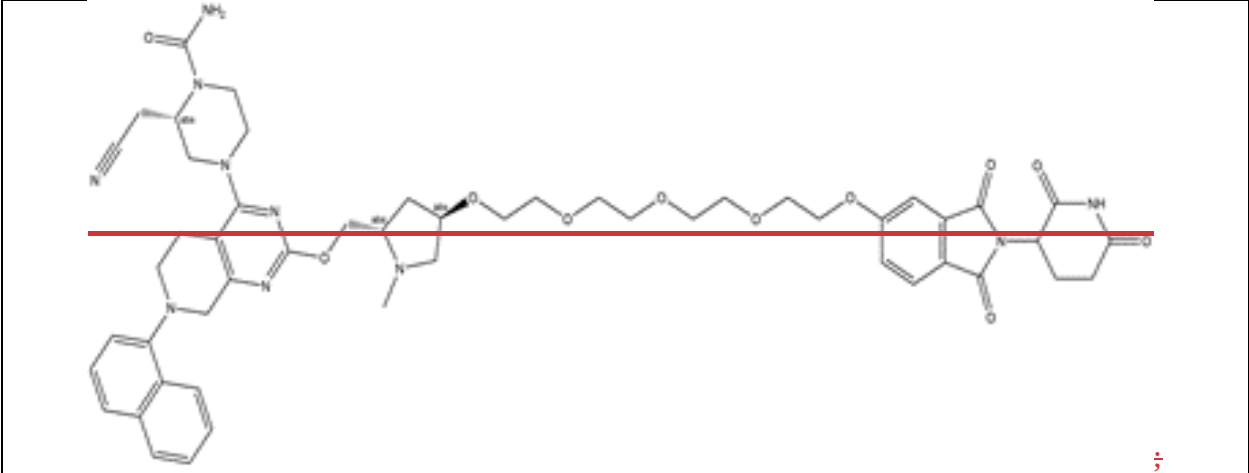
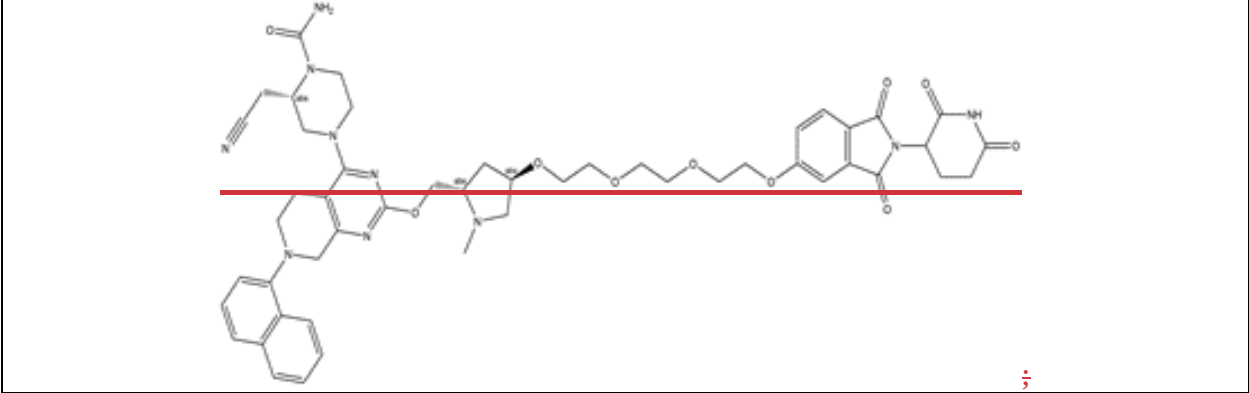
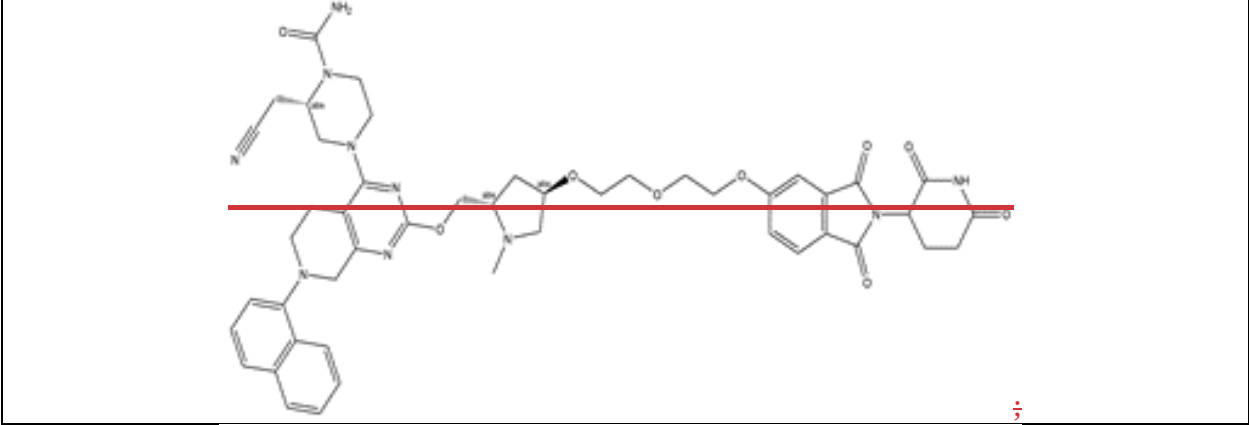
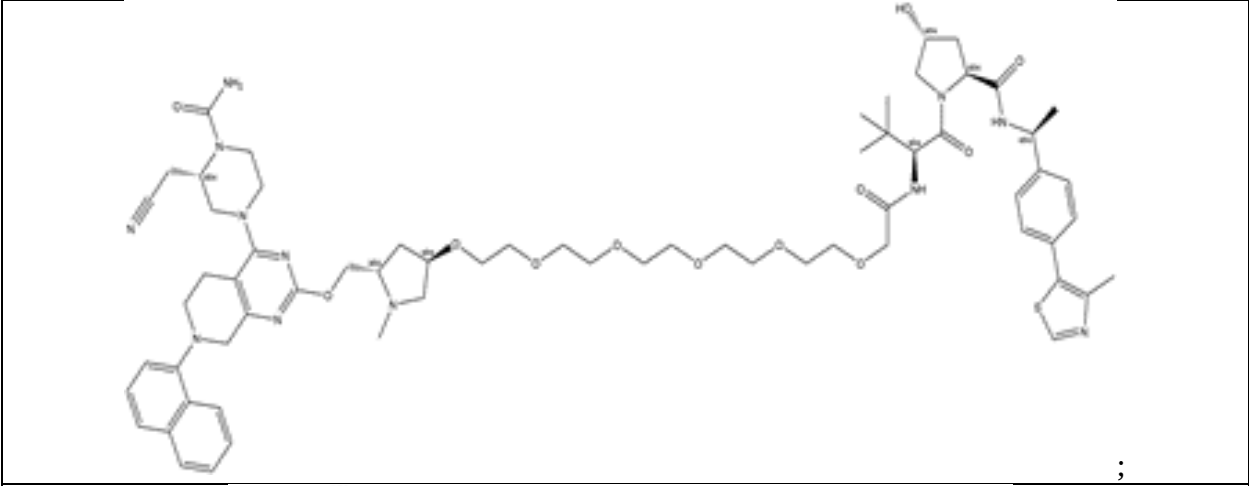
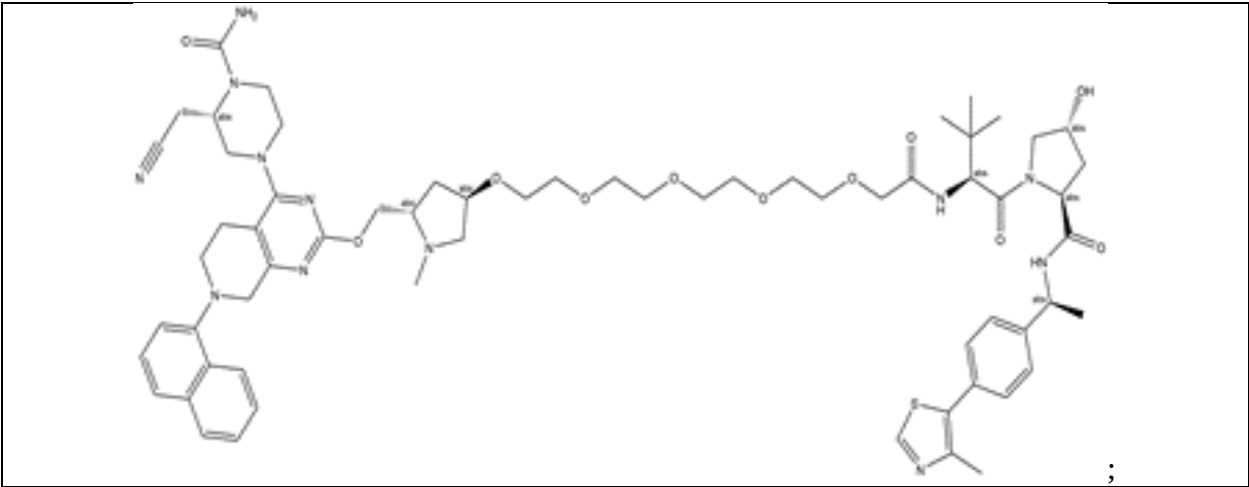


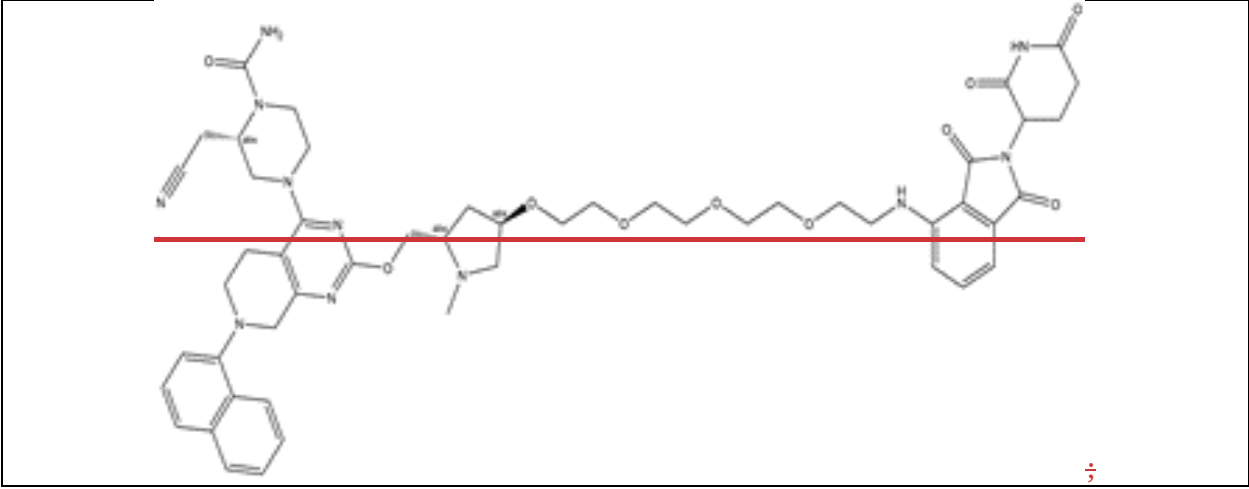
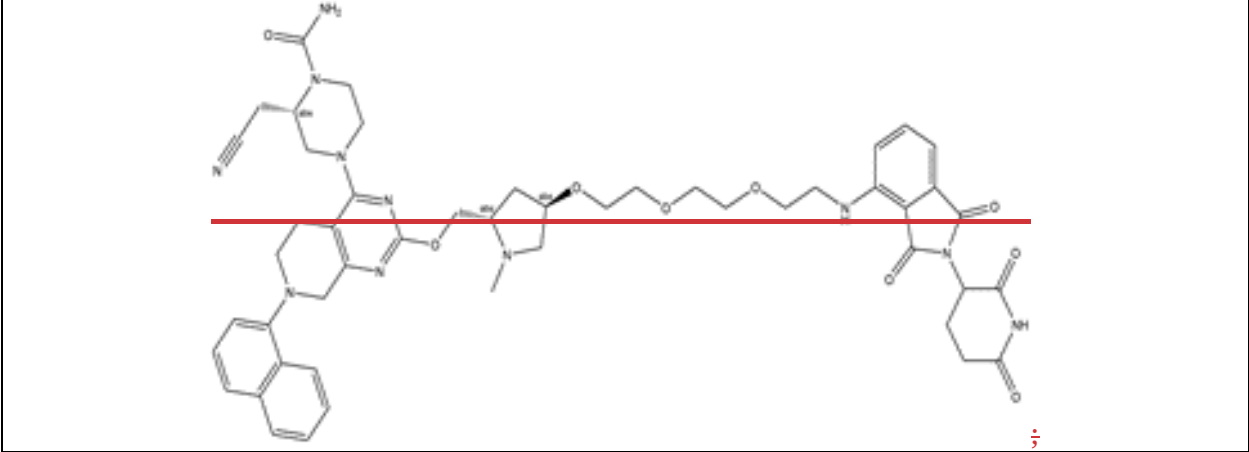
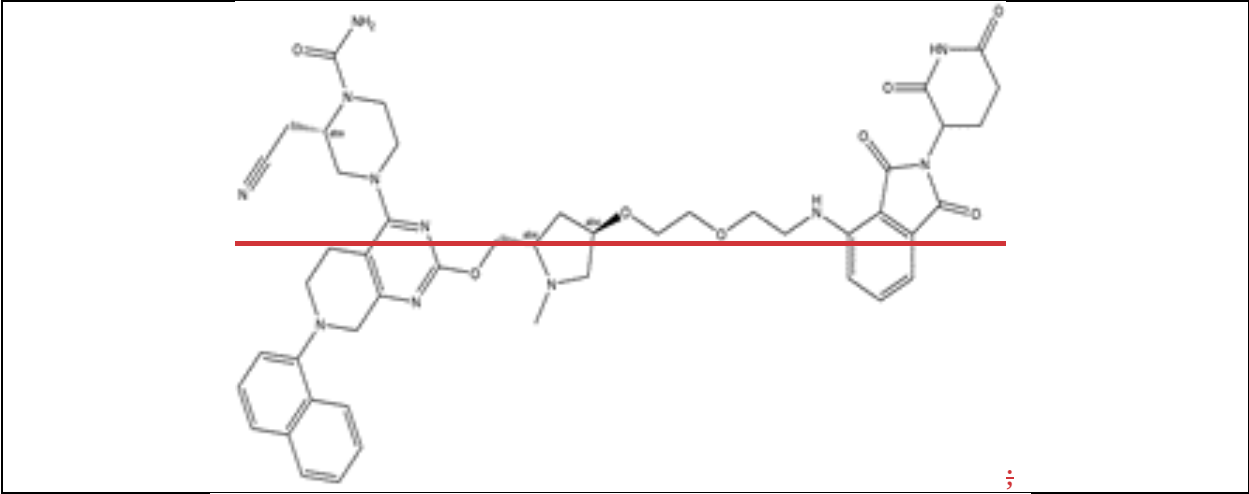
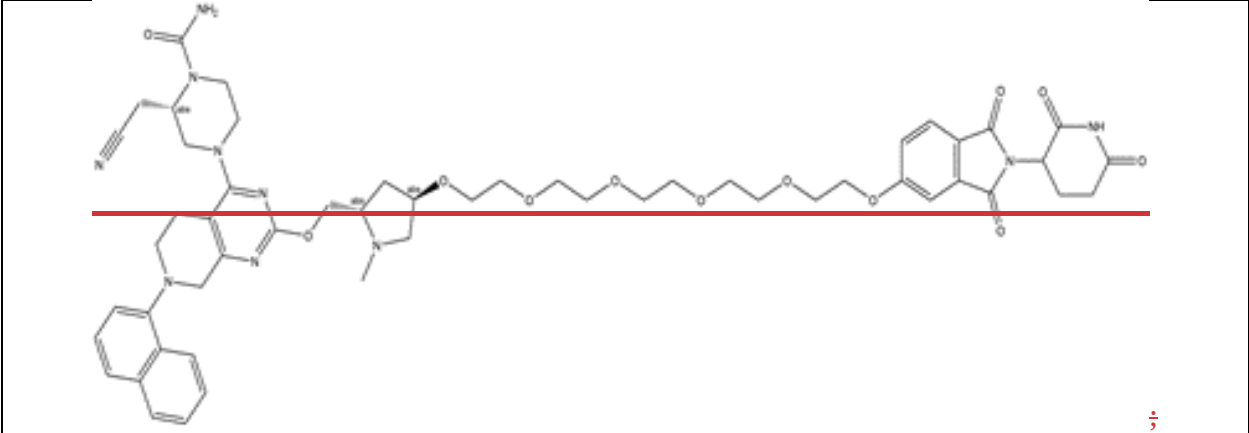
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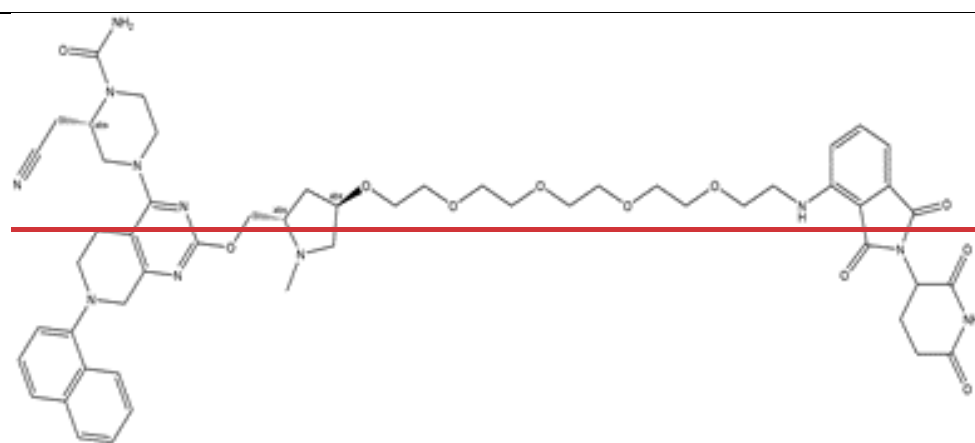


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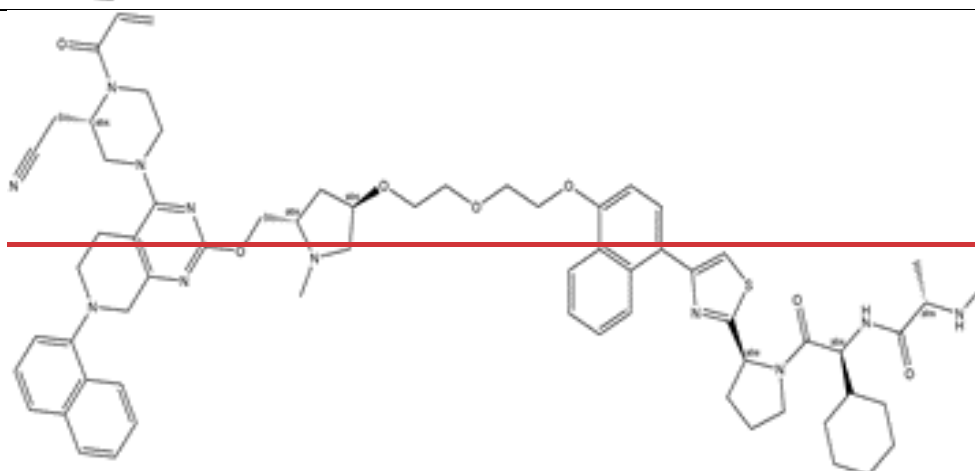




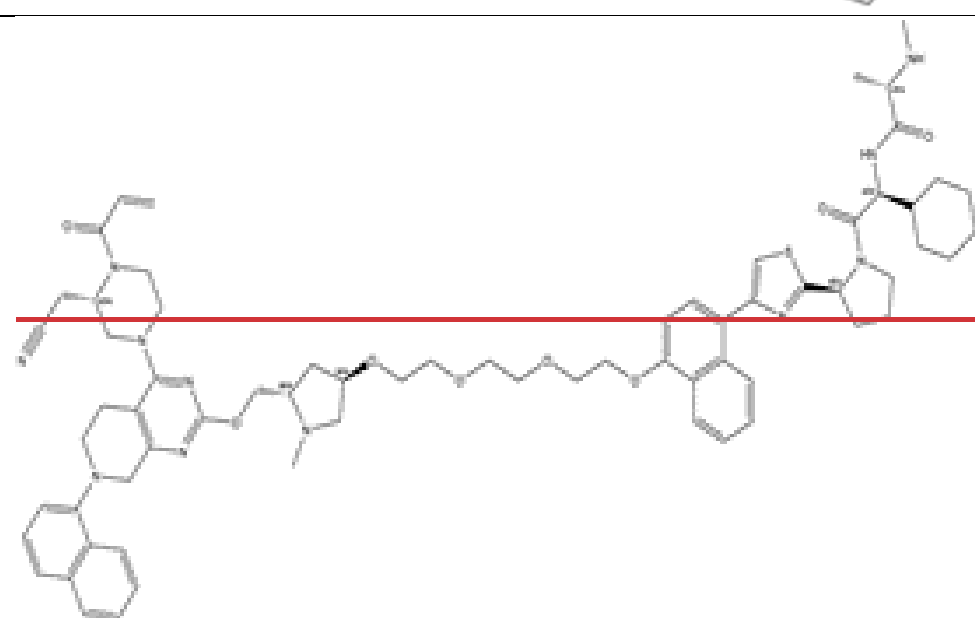




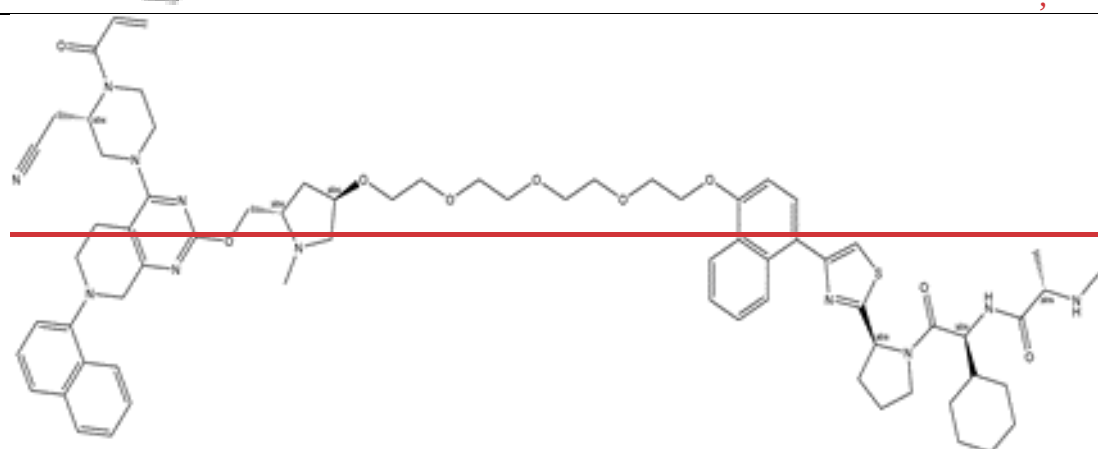
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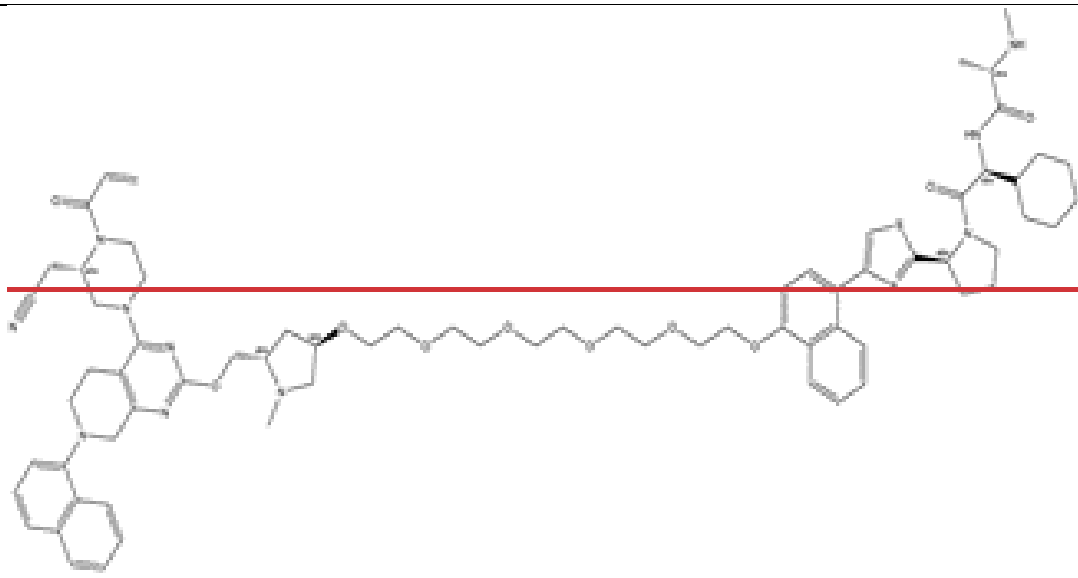
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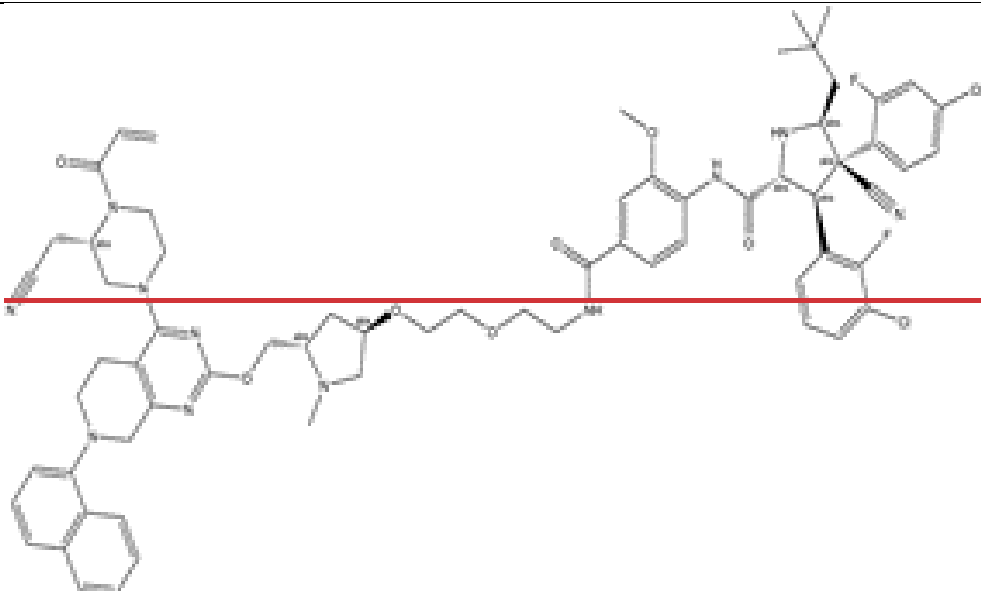
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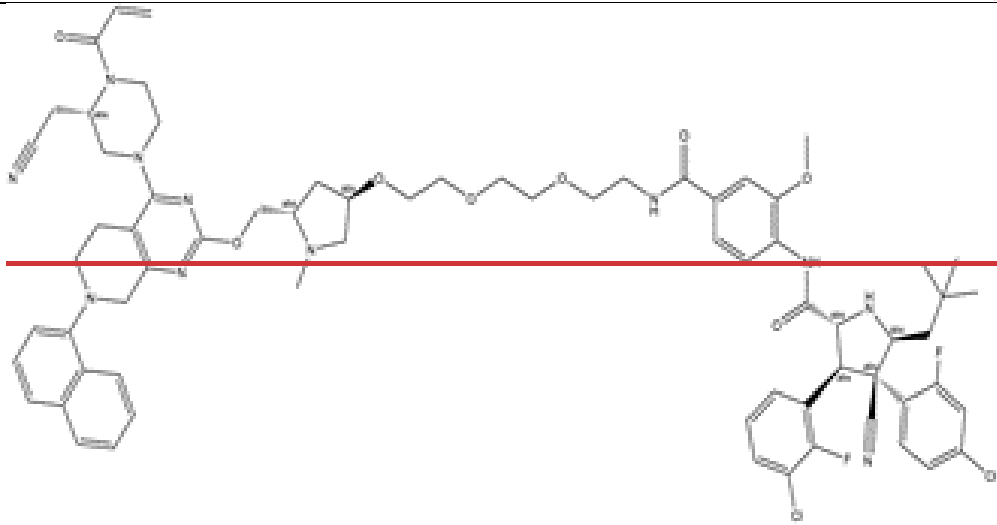
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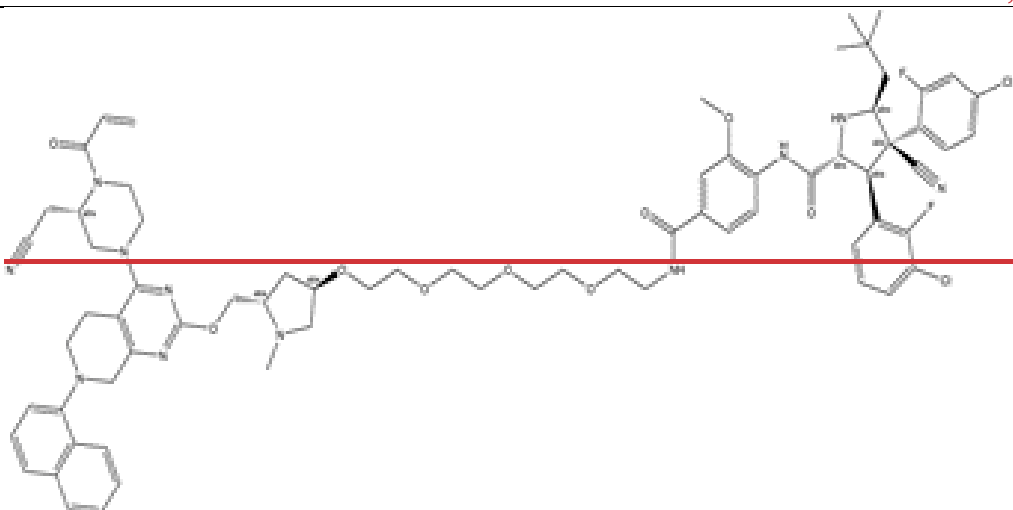
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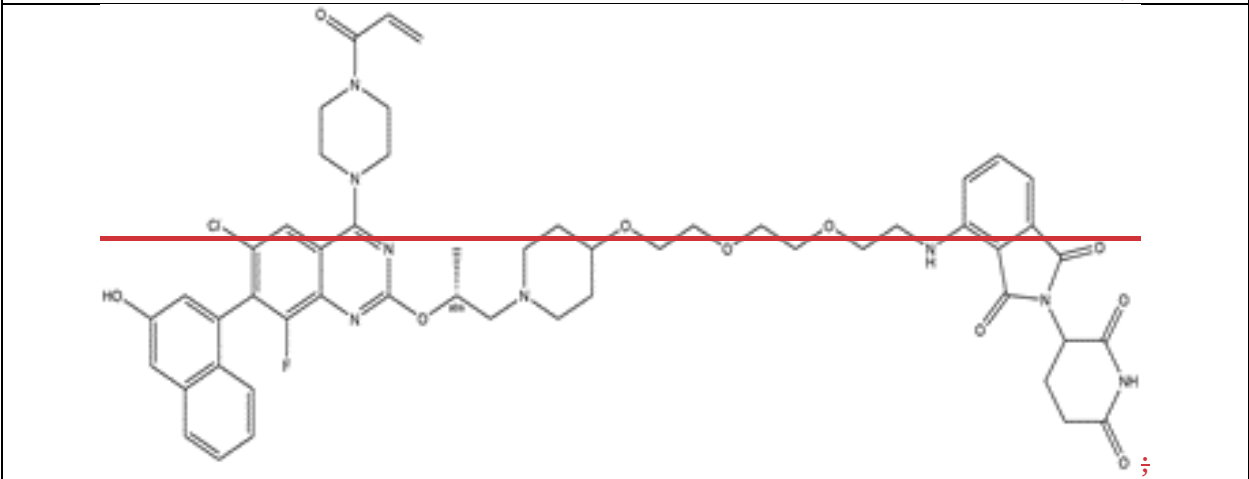
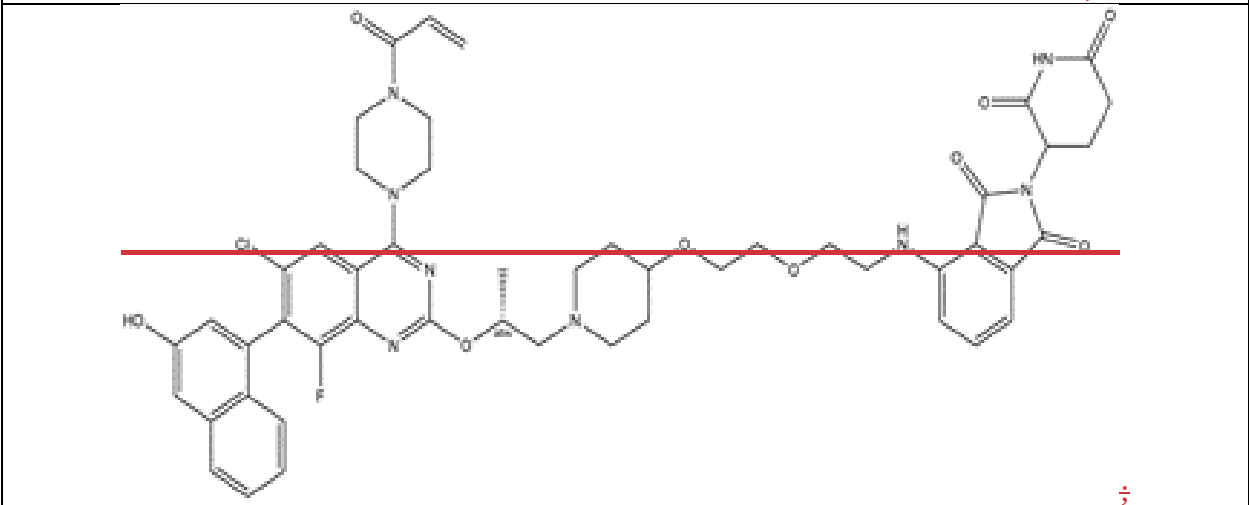
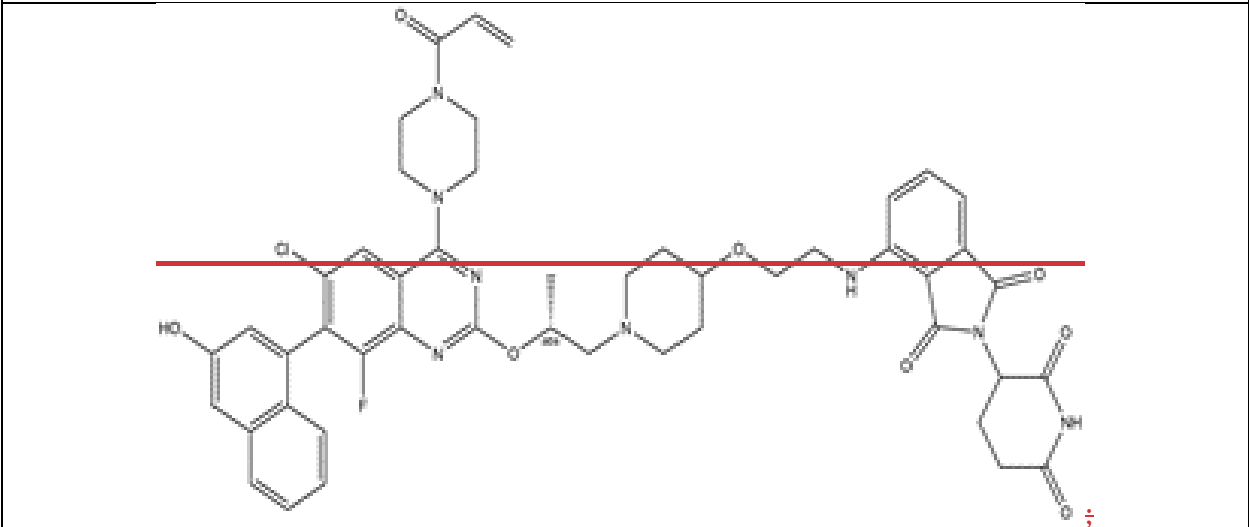
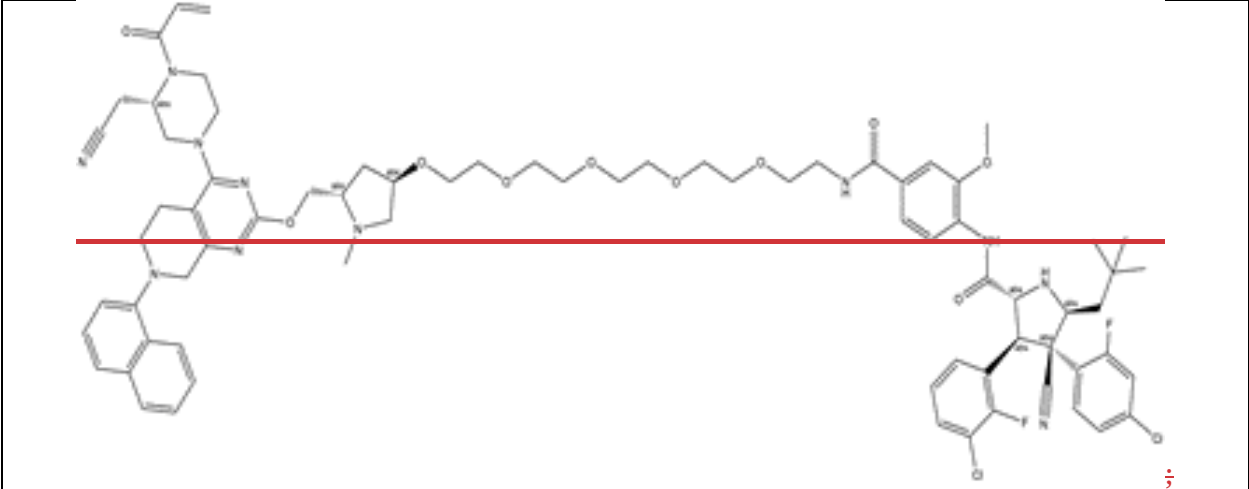
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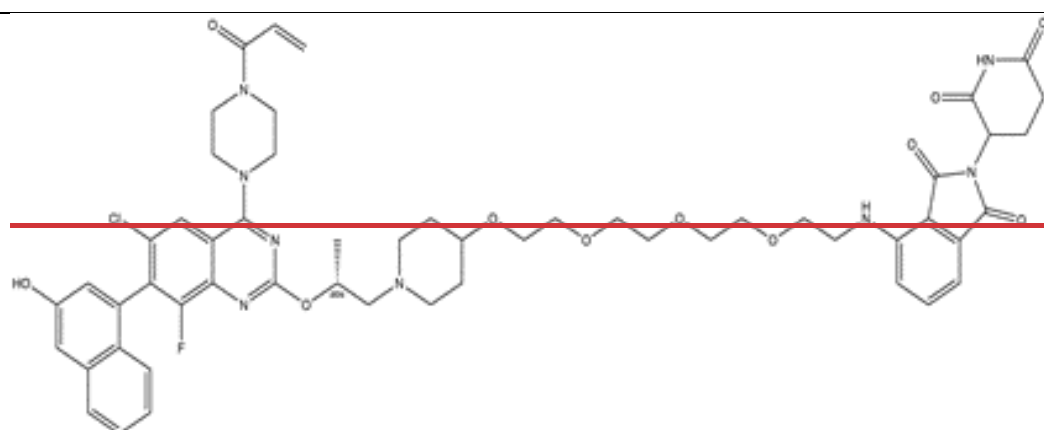


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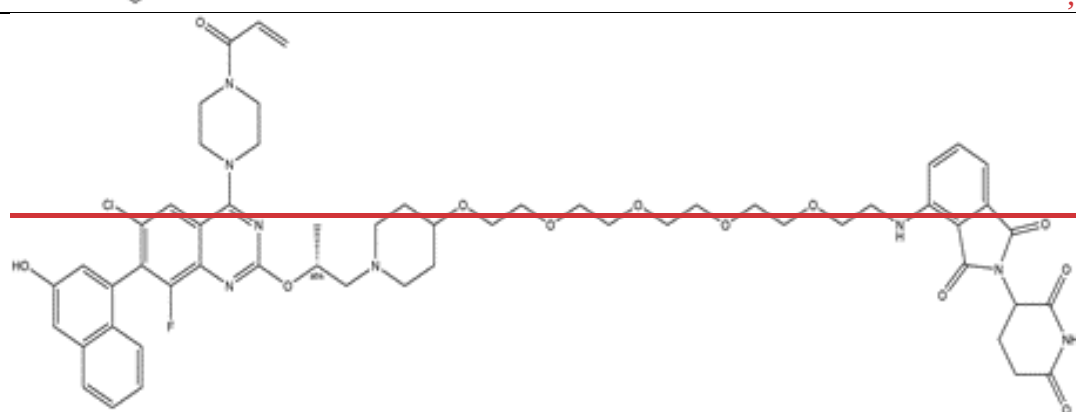


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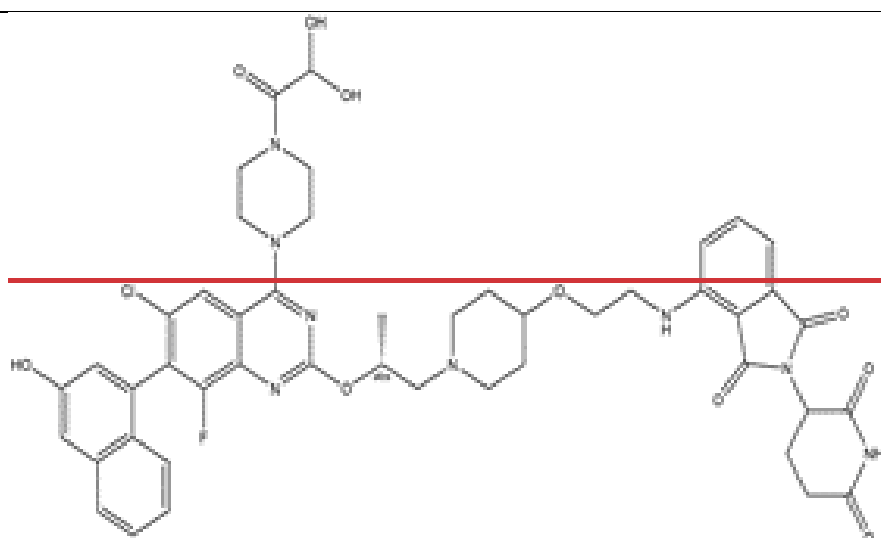




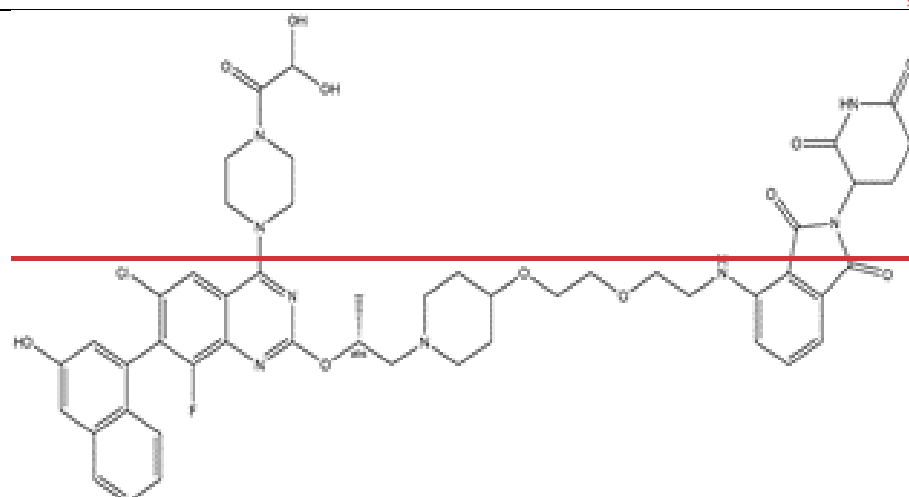
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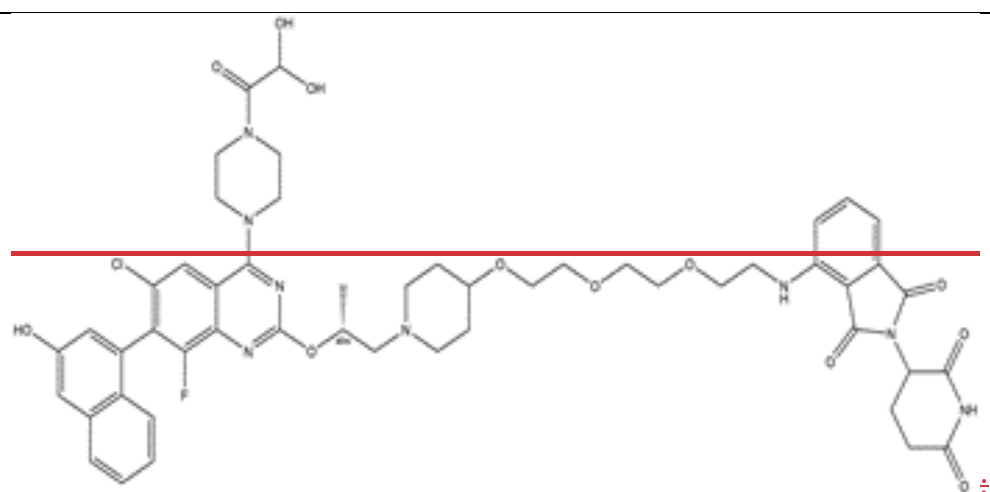
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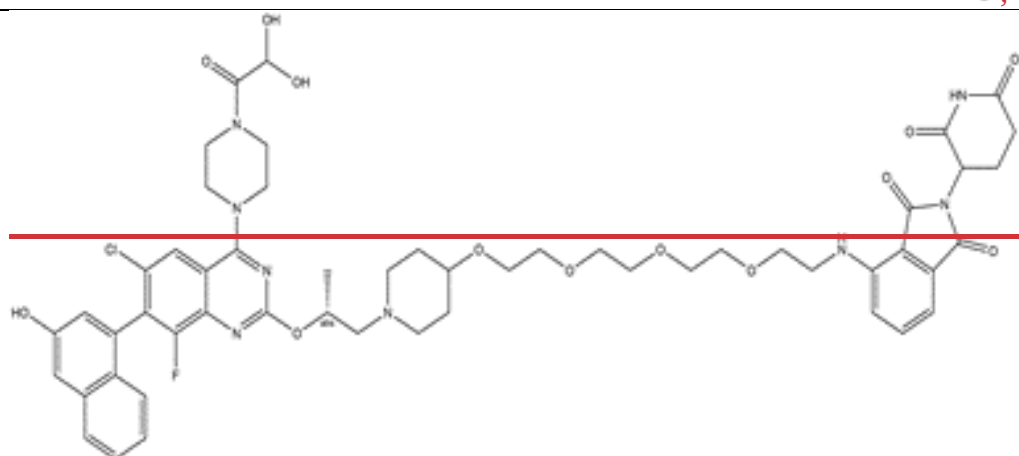
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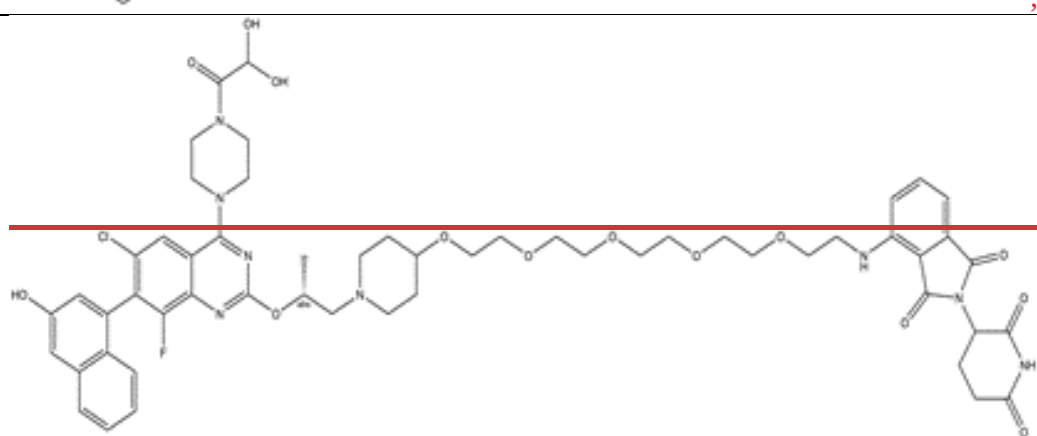
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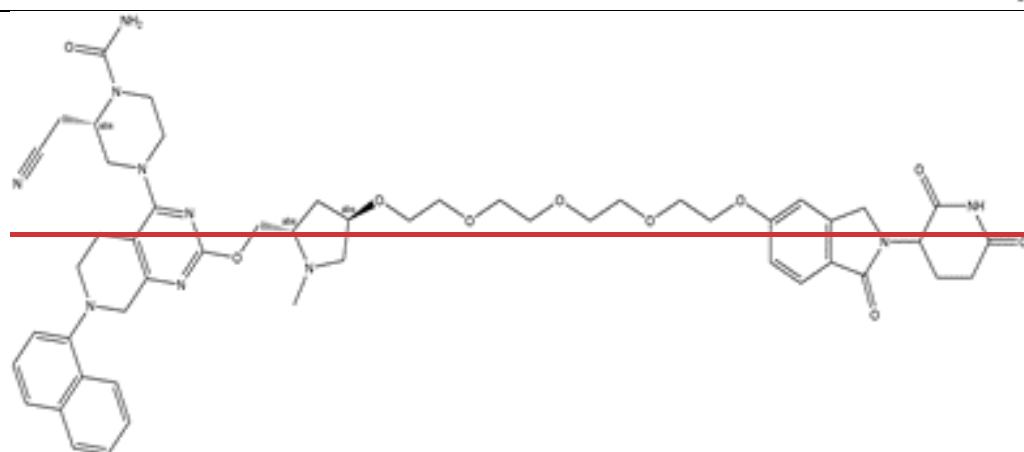
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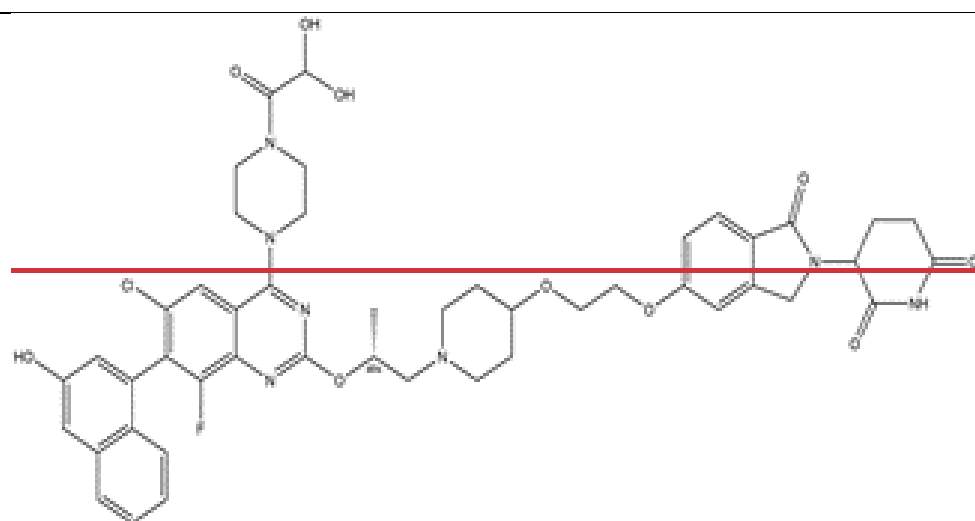
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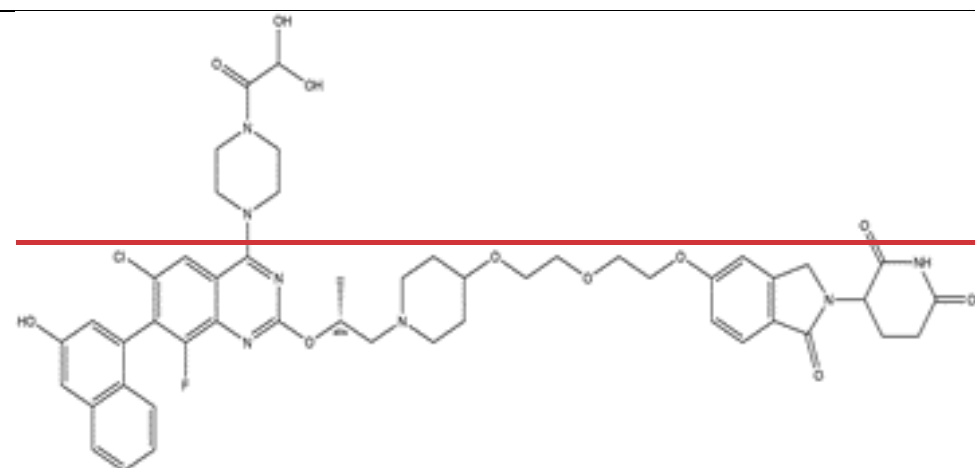
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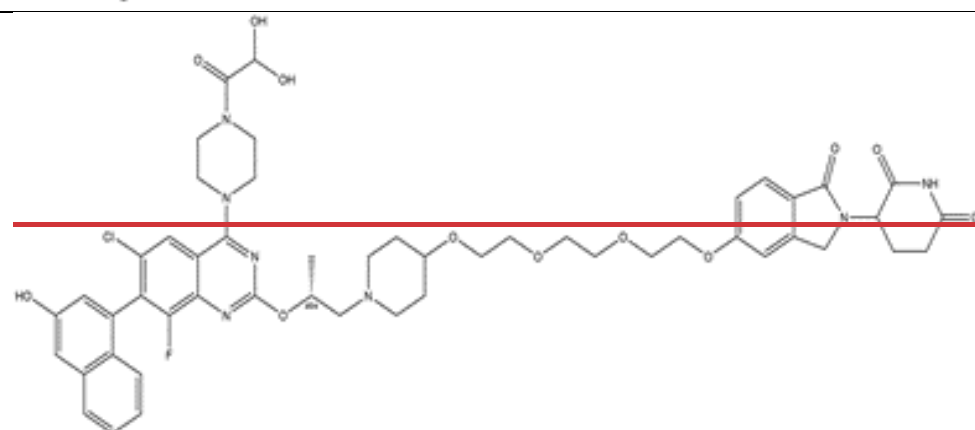
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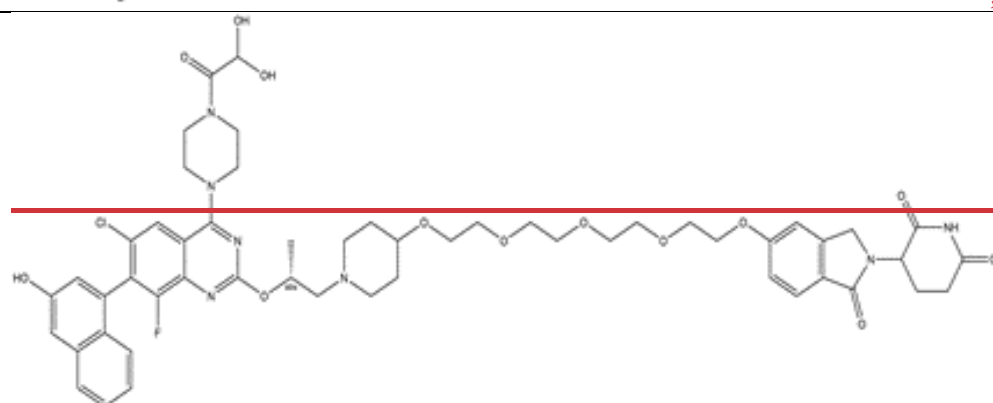
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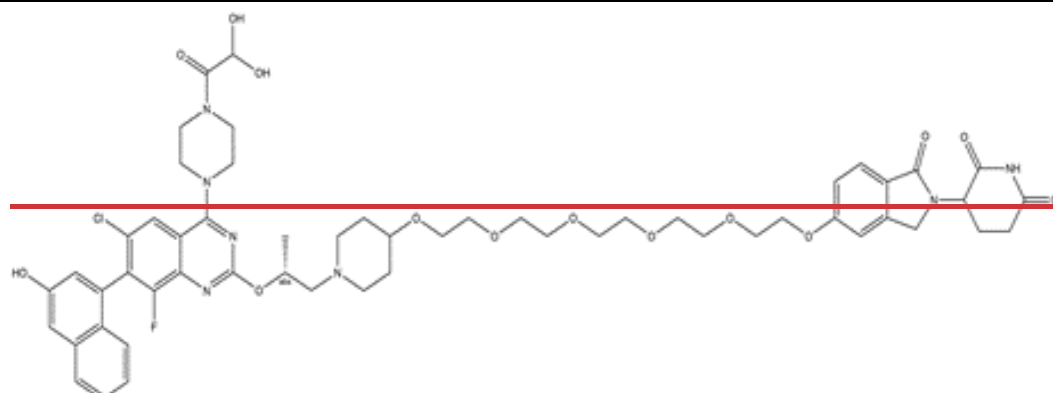
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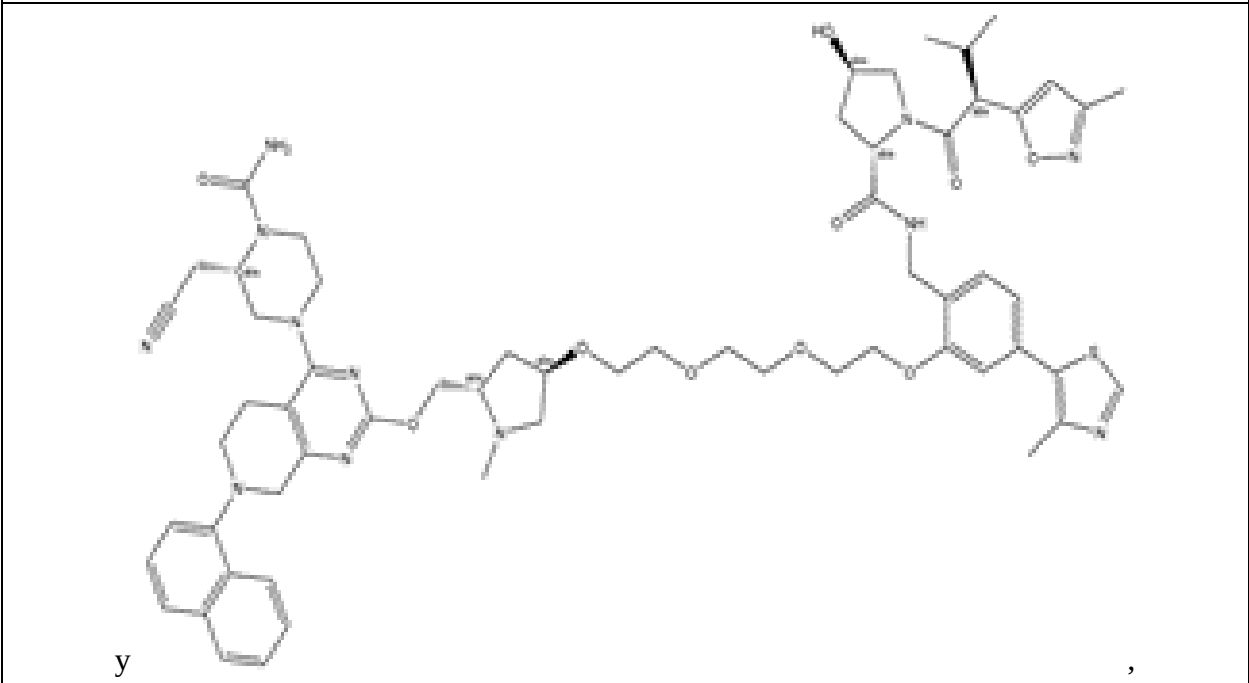
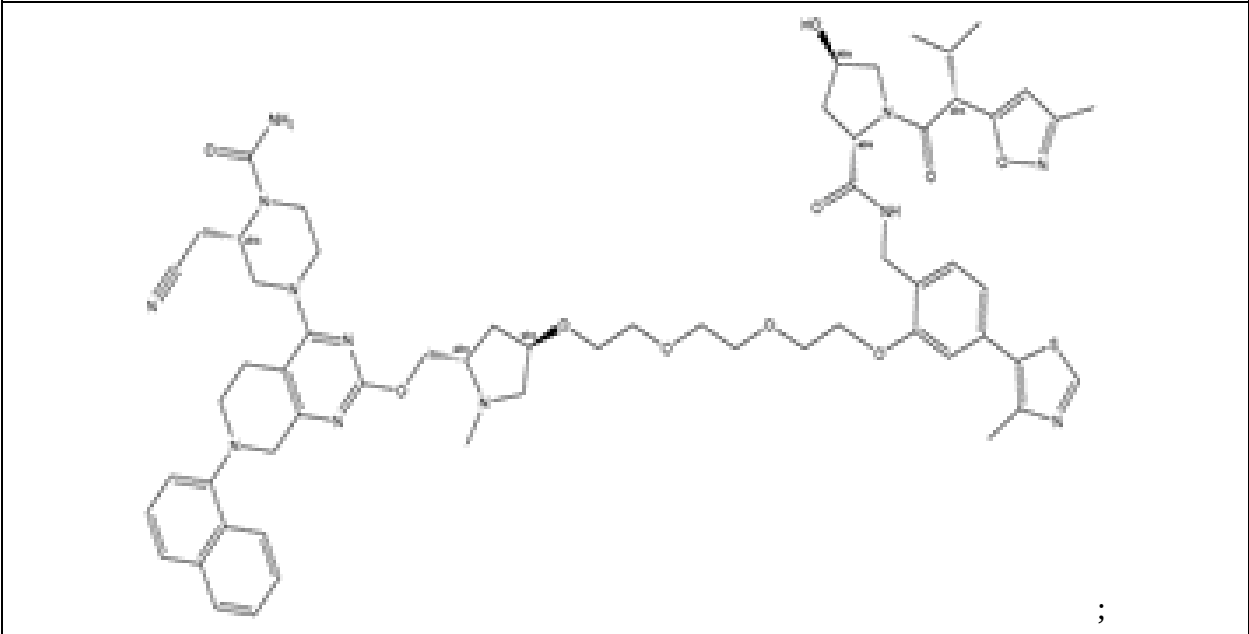
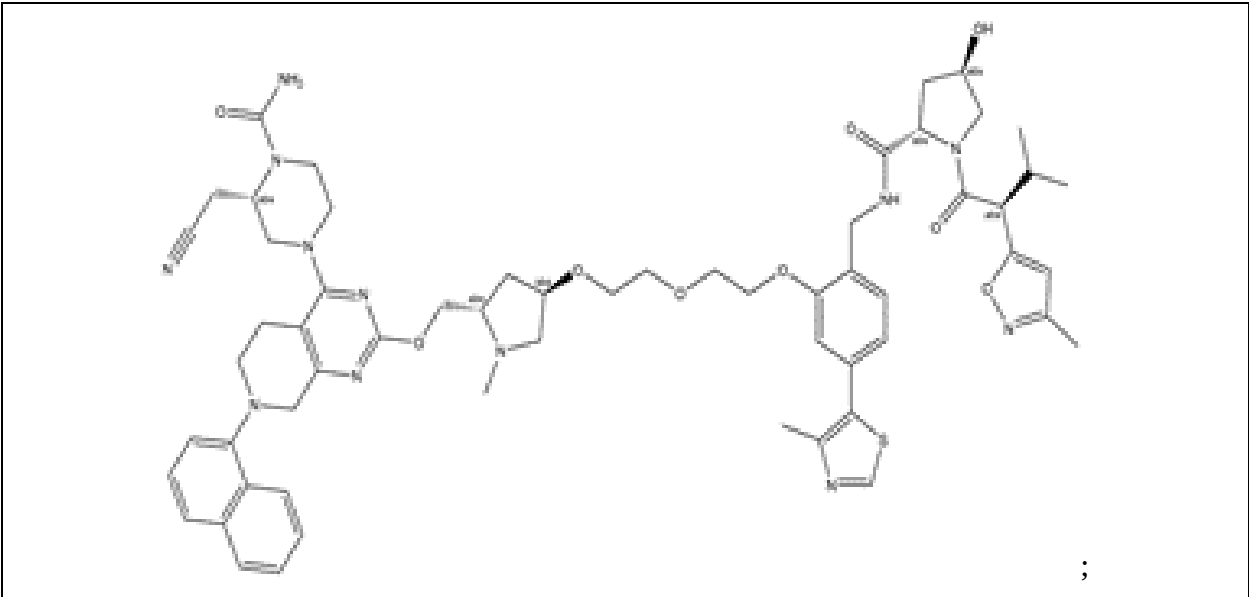
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o una sal farmacéuticamente aceptable de este.

13.11. Una composición farmacéutica que comprende un compuesto ~~bifuncional~~ de cualquiera de las reivindicaciones 1 a ~~310, y 5 a 12~~ y un portalineador farmacéuticamente aceptable.

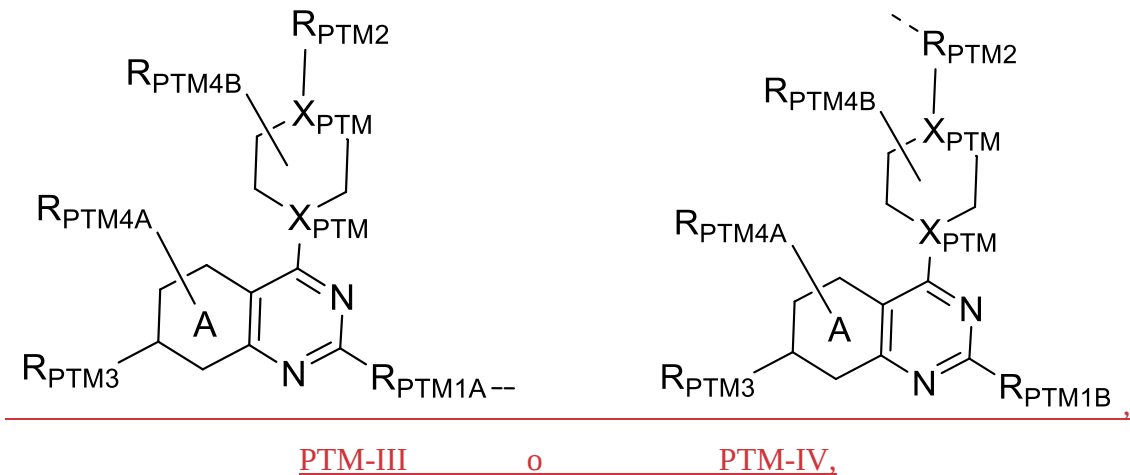
14.12. La composición farmacéutica de acuerdo con la reivindicación ~~1311~~, ~~donde la~~

~~composición~~que comprende además un agente bioactivo adicional.

~~15.13.~~ La composición farmacéutica de acuerdo con la reivindicación ~~14~~12, en donde el agente bioactivo adicional es un agente contra el cáncer.

14. La composición farmacéutica de acuerdo con la reivindicación ~~15~~13, en donde el agente contra el cáncer es un inhibidor de receptores del factor de crecimiento epidérmico.

~~16.15.~~ El compuesto de acuerdo con la reivindicación 1, donde el PTM es:



donde:



es fenilo, heteroarilo de 6 miembros, cicloalquilo de 6 miembros, o heterocicloalquilo de 6 miembros;

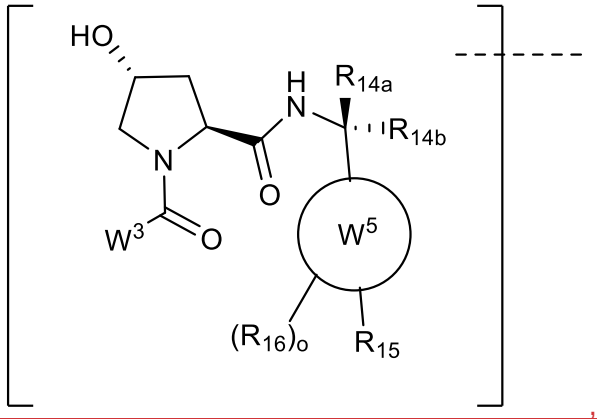
X_{PTM} es CH o N;

R_{PTM3} es alquilo, alcoxi, fenilo, o naftalenilo, cada uno opcionalmente sustituido de manera independiente con 1, 2 o 3 sustituyentes seleccionados de entre OH, H, y halógeno;

R_{PTM4A} es OH, H, halógeno, o alquilo C_{1-6} opcionalmente sustituido; y

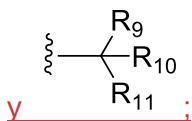
R_{PTM4B} es OH, H, $-CH_2CN$, halógeno, o alquilo C_{1-6} opcionalmente sustituido.

16. El compuesto de acuerdo con la reivindicación 1 o 15, en donde el ULM es:



donde:

W^3 se selecciona de entre arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido

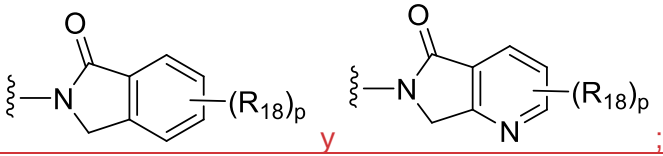


R_9 y R_{10} son cada uno de manera independiente seleccionados de entre hidrógeno, alquilo

opcionalmente sustituido, cicloalquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, y heteroarilo opcionalmente sustituido, o R₉, R₁₀, y el átomo de carbono al que se unen forma cicloalquilo opcionalmente sustituido;

R₁₁ se selecciona de entre heterociclilo opcionalmente sustituido, alcoxi opcionalmente

sustituido, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido,



R₁₂ es H o alquilo opcionalmente sustituido;

R₁₃ se selecciona de entre H, alquilo opcionalmente sustituido, alquilcarbonilo opcionalmente sustituido, (cicloalquil)alquilcarbonilo opcionalmente sustituido, aralquilcarbonilo opcionalmente sustituido, arilcarbonilo opcionalmente sustituido, (heterocicli)carbonilo opcionalmente sustituido, y aralquilo opcionalmente sustituido;

R_{14a} y R_{14b} son cada uno de manera independiente H o alquilo opcionalmente sustituido;

W⁵ es fenilo opcionalmente sustituido o un heteroarilo de 5-10 miembros opcionalmente sustituido;

R₁₅ se selecciona de entre H, halógeno, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a}SO₂R_{14b}, alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, haloalcoxi opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, y cicloheteroalquilo opcionalmente sustituido;

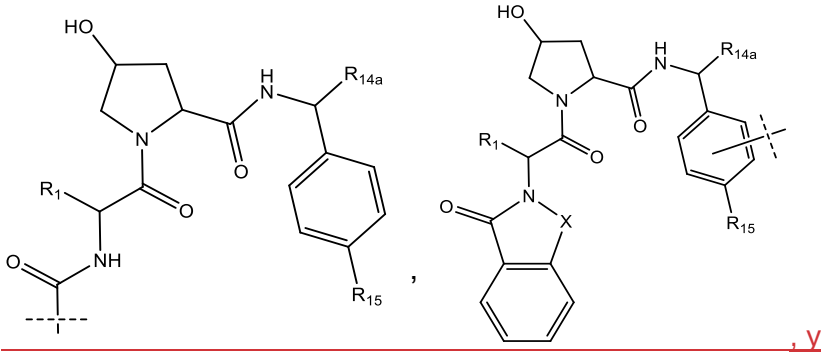
cada R₁₆ se selecciona de manera independiente de entre halo, CN, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, e hidroxil;

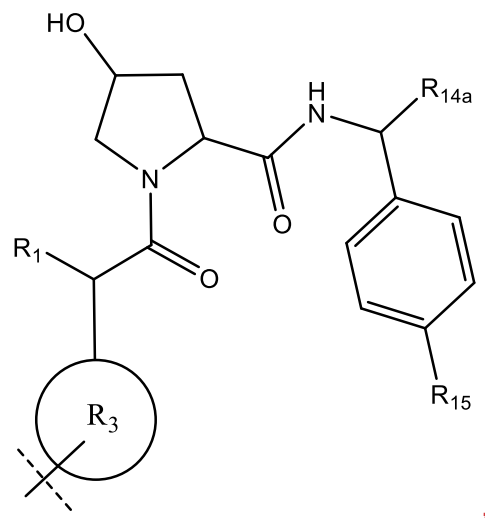
o es 0, 1, 2, 3 o 4;

cada R₁₈ se selecciona de manera independiente de entre halo, alcoxi opcionalmente sustituido, ciano, y alquilo opcionalmente sustituido, o R₁₈ es el sitio de unión del L; y

p es 0, 1, 2, 3 o 4, y  indica el sitio de unión del L.

17. El compuesto de acuerdo con cualquiera de las reivindicaciones 1, 15 y 16, en donde el ULM es seleccionada de entre:





donde:

R₁ se selecciona de entre H, alquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y heteroarilo opcionalmente sustituido;

R_{14a} es H, alquilo opcionalmente sustituido, o ciclopropilo;

R₁₅ se selecciona de entre H, halógeno, CN, OH, NO₂, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido; alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, haloalcoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, y heterocicloalquilo opcionalmente sustituido;

X es CH₂ o C=O;

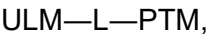
R₃ está ausente o es heteroarilo de 5 o 6 miembros opcionalmente sustituido; y



indica el sitio de unión del L.

REIVINDICACIONES

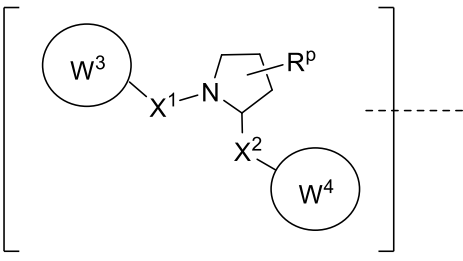
1. Un compuesto que tiene la estructura química:



o una sal farmacéuticamente aceptable de este,

donde:

el ULM es:



en donde

X¹ y X² se seleccionan cada uno de manera independiente de un enlace, O, NR^{Y3}, CR^{Y3}R^{Y4}, C=O, C=S, SO y SO₂;

R^{Y3} y R^{Y4} se seleccionan cada uno de manera independiente de H, alquilo C₁₋₆ opcionalmente sustituido por 1 o más halo, y alcoxi C₁₋₆ opcionalmente sustituido por 0-3 R^P;

cada R^P es seleccionado de manera independiente de H, halo, -OH, alquilo C₁₋₃, y C=O;

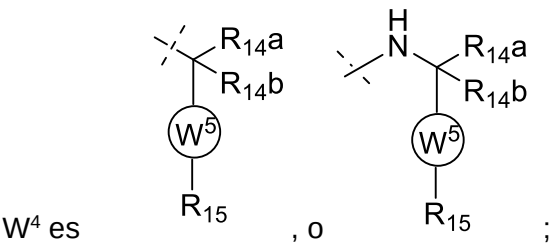
W³ se selecciona de entre W³ se selecciona de entre T opcionalmente sustituido, -T-N(R^{1a}R^{1b})X³ opcionalmente sustituido, -T-N(R^{1a}R^{1b}) opcionalmente sustituido, -T-Arilo opcionalmente sustituido, -T-Heteroarilo opcionalmente sustituido, T-biheteroarilo opcionalmente sustituido, -T- heterociclilo opcionalmente sustituido, -T-biheterociclilo opcionalmente sustituido, -NR¹-T-Arilo opcionalmente sustituido, -NR¹-T-Heteroarilo opcionalmente sustituido, y -NR¹-T- Heterociclilo opcionalmente sustituido;

X³ es C=O o R¹;

R¹, R^{1a}, y R^{1b} son cada uno independientemente seleccionados de entre H, alquilo C_{1-C6} opcionalmente sustituido por 1 o más halo u -OH, R^{Y3}C=O, R^{Y3}C=S, R^{Y3}SO, R^{Y3}SO₂, N(R^{Y3}R^{Y4})C=O, N(R^{Y3}R^{Y4})C=S, N(R^{Y3}R^{Y4})SO y N(R^{Y3}R^{Y4})SO₂;

T se selecciona de entre alquilo opcionalmente sustituido, -(CH₂)_n-, donde cada uno de los grupos metileno opcionalmente se sustituye con uno o dos sustituyentes seleccionados de entre halógeno, metilo, alcoxi opcionalmente sustituido, alquilo C1-C₆ opcionalmente sustituido por 1 o más sustituyentes independientemente seleccionados de entre halógeno, C(O) NR¹R^{1a}, y NR¹R^{1a}, o R¹ y R^{1a} se unen para formar un heterociclilo opcionalmente sustituido; y

n es de 0 a 6;

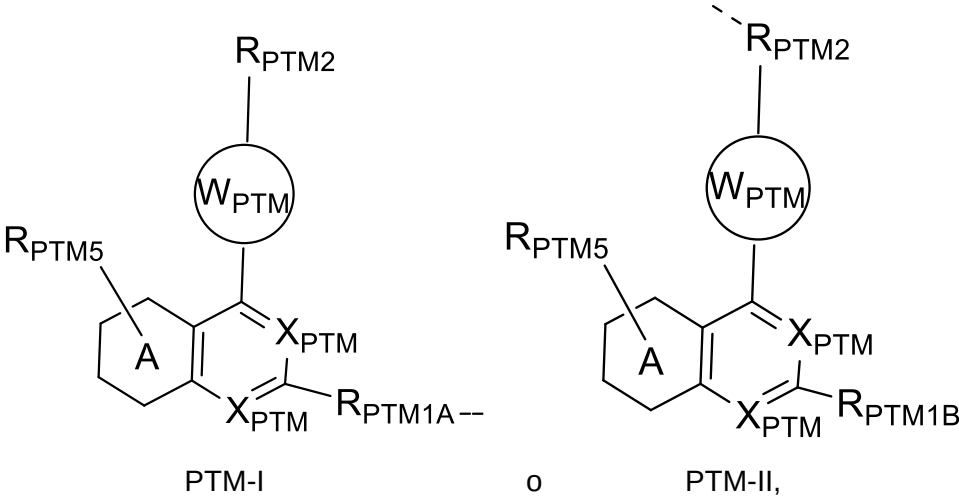


R_{14a} y R_{14b} son cada uno de manera independiente H o alquilo C₁₋₆ opcionalmente sustituido;

W⁵ es fenilo opcionalmente sustituido o heteroarilo de 5-10 miembros opcionalmente sustituido;

R₁₅ se selecciona de entre H, halógeno, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a} SO₂R_{14b}, alquilo C₁₋₆ opcionalmente sustituido, haloalquilo C₁₋₆ opcionalmente sustituido, haloalcoxi C₁₋₆ opcionalmente sustituido, arilo C₆₋₁₀ opcionalmente sustituido, heteroarilo de 5-10 miembros opcionalmente sustituido, cicloalquilo C₃₋₁₁ opcionalmente sustituido, y heterocicloalquilo de 3-11 miembros opcionalmente sustituido;

el PTM es:



en donde:

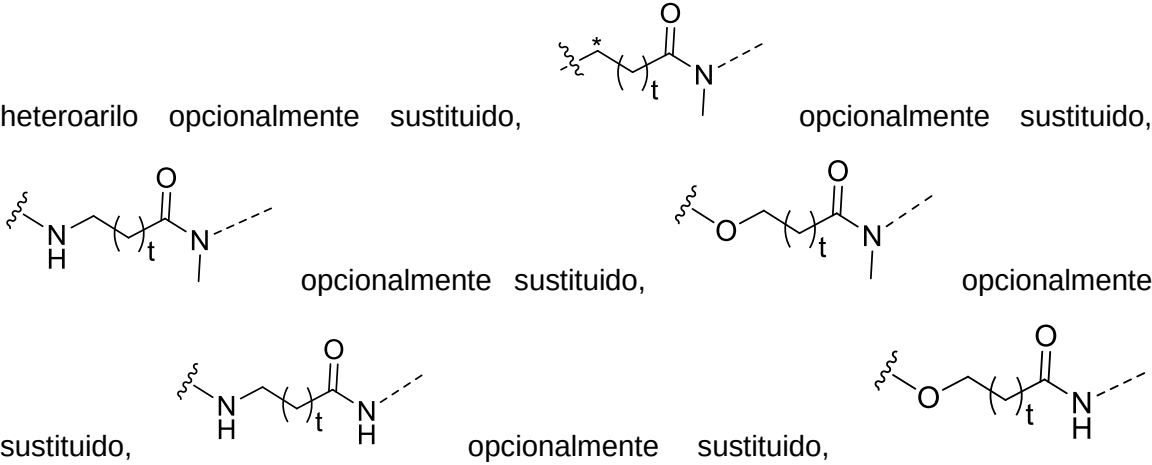


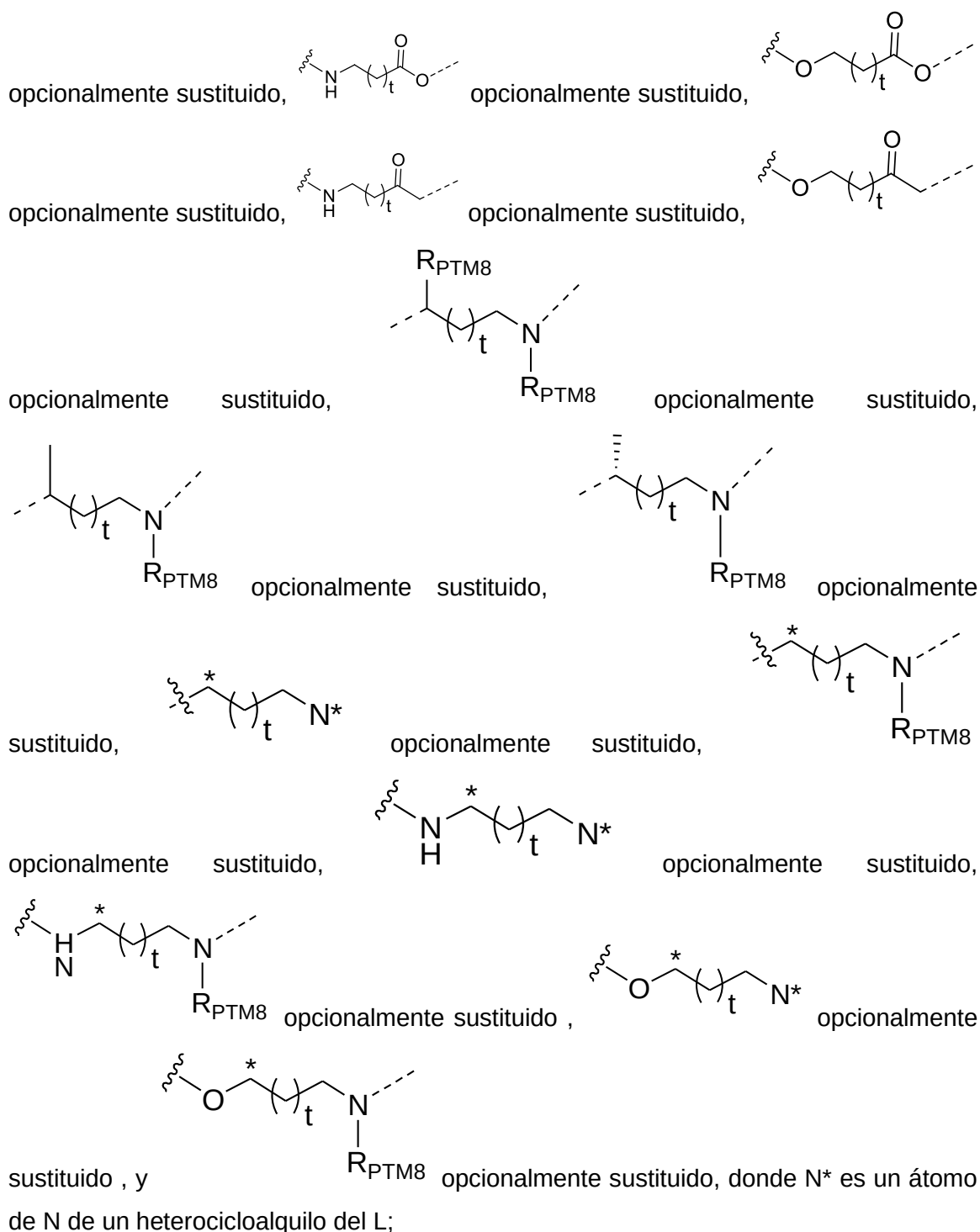
es fenilo, heteroarilo de 6 miembros, cicloalquilo de 6 miembros, o heterocicloalquilo de 6 miembros;

X_{PTM} es CH o N;

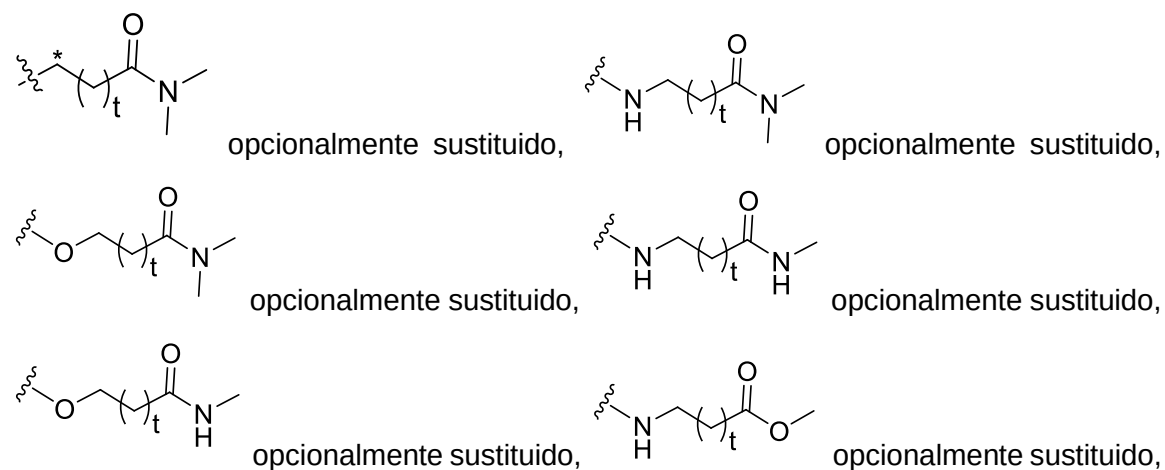
W_{PTM} se selecciona de entre cicloalquilo C₃₋₆ opcionalmente sustituido, heteroalquilo C₃₋₆ opcionalmente sustituido, heterocicloalquilo de 3-6 miembros opcionalmente sustituido, arilo opcionalmente sustituido, y heteroarilo opcionalmente sustituido;

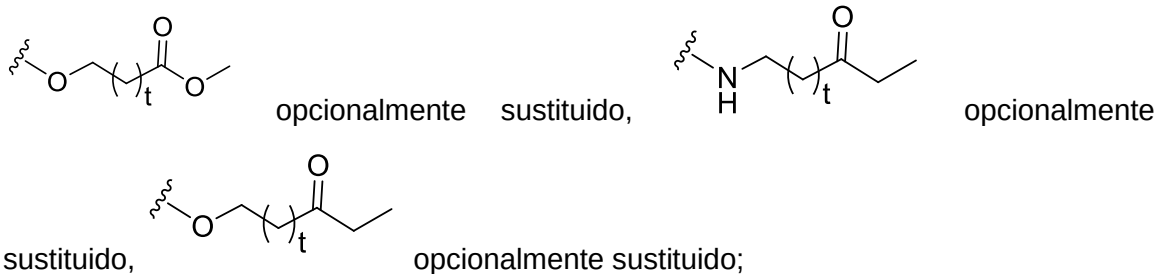
R_{PTM1A} se selecciona de entre NR_{PTM9}R_{PTM10}, OR_{PTM9}R_{PTM10}, H, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, cicloalquilo C₃₋₆ opcionalmente sustituido, O-(cicloalquilo C₃₋₆) opcionalmente sustituido, -O-alquilo C₁₋₄-cicloalquilo C₃₋₆ opcionalmente sustituido, heteroalquilo C₃₋₆ opcionalmente sustituido, O-(heteroalquilo C₃₋₆) opcionalmente sustituido, O-alquilo C₁₋₄-heteroalquilo C₃₋₆opcionalmente sustituido, O-alquilo C₁₋₄-heterocicloalquilo C₃₋₆ opcionalmente sustituido, arilo opcionalmente sustituido, O-arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, , O-





R_{PTM1B} se selecciona de entre $NR_{PTM9}R_{PTM10}$, $OR_{PTM9}R_{PTM10}$, H, alquilo opcionalmente sustituido, O-alquilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, O-(cicloalquilo C_{3-6}) opcionalmente sustituido, -O-alquilo C_{1-4} -cicloalquilo C_{3-6} opcionalmente sustituido, heteroalquilo C_{3-6} opcionalmente sustituido, O-(heteroalquilo C_{3-6}) opcionalmente sustituido, O-alquilo C_{1-4} -heteroalquilo C_{3-6} opcionalmente sustituido, arilo opcionalmente sustituido, O-arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, O-heteroarilo opcionalmente sustituido,





R_{PTM9} y R_{PTM10} son cada uno seleccionado de manera independiente de entre H, alquilo C_{1-6} opcionalmente sustituido, amino alifático opcionalmente sustituida, amido alifático opcionalmente sustituida y fenilo;

R_{PTM2} es H, $(C=O)R_{PTM2}'$, o alquilo opcionalmente sustituido;

R_{PTM2}' es alquilo opcionalmente sustituido, alquenilo opcionalmente sustituido, -N $(R_{PTM8})_2$ o $-C(OH)_2$;

R_{PTM3} es alquilo, alcoxi, fenilo o naftalenilo, cada uno opcionalmente sustituido con 1, 2, o 3 sustituyentes independientemente seleccionados de entre OH, H, y halógeno;

R_{PTM4A} es OH, H, halógeno, o alquilo C_{1-6} opcionalmente sustituido;

R_{PTM4B} es OH, H, $-CH_2CN$, halógeno, o alquilo C_{1-6} opcionalmente sustituido;

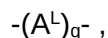
R_{PTM5} es 1, 2, o 3 sustituyentes independientemente seleccionados de entre arilo opcionalmente sustituido, biarilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, biheteroarilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, heterocicloalquilo de 3-6 miembros opcionalmente sustituido, halógeno, H, alquilo opcionalmente sustituido, OH y alcoxi;

R_{PTM8} es H o alquilo;

t es 0, 1, 2, 3, 4, 5, o 6; y

— indica el sitio de unión del L; y

el L es:



donde:

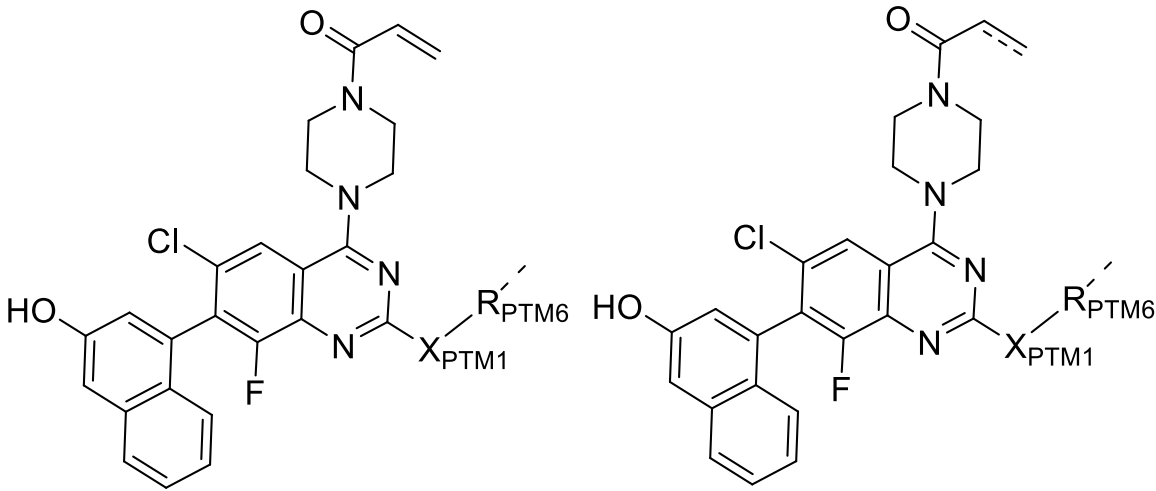
q es un número entero mayor o igual que 1;

cada A^L se selecciona de manera independiente de entre un enlace, $CR^{L1}R^{L2}$, O, S, SO, SO_2 , NR^{L3} , SO_2NR^{L3} , $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, $C\equiv C$, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, cicloalquilo C_{3-11} opcionalmente sustituido con 0-6 R^{L1} y/o R^{L2} , heterociclilo C_{3-11} opcionalmente sustituido con 0-6 R^{L1} y/o R^{L2} , arilo opcionalmente sustituido con 0-6 R^{L1} y/o R^{L2} , y heteroarilo opcionalmente sustituido con 0-6 R^{L1} y/o R^{L2} , donde R^{L1} o R^{L2} , cada uno de manera independiente se enlaza opcionalmente a otros grupos para formar cicloalquilo o heterociclilo, cada uno opcionalmente sustituido con 0-4 R^{L5} ; y

R^{L1} , R^{L2} , R^{L3} , R^{L4} y R^{L5} son, cada uno de manera independiente, seleccionados de entre H, halo, alquilo C_{1-8} , Oalquilo C_{1-8} , Salquilo C_{1-8} , NHalquilo C_{1-8} , N(alquilo C_{1-8})₂, cicloalquilo C_{3-11} , arilo, heteroarilo, heterociclilo C_{3-11} , Ocicloalquilo C_{1-8} , Scicloalquilo C_{1-8} , NHcicloalquilo C_{1-8} , N(cicloalquilo C_{1-8})₂, N(cicloalquilo C_{1-8})(alquilo C_{1-8}), OH, NH_2 , SH, SO_2 alquilo C_{1-8} , $P(O)$ (Oalquilo C_{1-8})(alquilo C_{1-8}), $P(O)$ (Oalquilo C_{1-8})₂, CC-alquilo C_{1-8} , CCH, $CH=CH$ (alquilo C_{1-8}), C (alquilo C_{1-8})= CH (alquilo C_{1-8}), C (alquilo C_{1-8})= C (alquilo C_{1-8})₂, $Si(OH)_3$, Si (alquilo C_{1-8})₃, $Si(OH)$ (alquilo C_{1-8})₂, COalquilo C_{1-8} , CO_2H , halógeno, CN, CF_3 , CHF_2 , CH_2F , NO_2 , SF_5 , SO_2N Halquilo C_{1-8} , SO_2N (alquilo C_{1-8})₂, SON Halquilo C_{1-8} ,

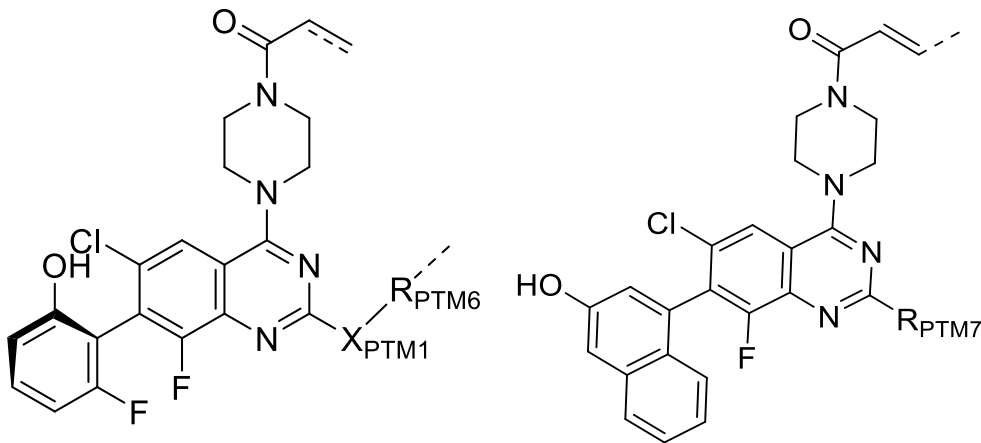
SON(alquilo C₁₋₈)₂, CONHalquilo C₁₋₈, CON(alquilo C₁₋₈)₂, N(alquilo C₁₋₈)CONH(alquilo C₁₋₈), N(alquilo C₁₋₈)CON(alquilo C₁₋₈)₂, NHCONH(alquilo C₁₋₈), NHCON(alquilo C₁₋₈)₂, NHCONH₂, N(alquilo C₁₋₈)SO₂NH(alquilo C₁₋₈), N(alquilo C₁₋₈) SO₂N(alquilo C₁₋₈)₂, NH SO₂NH(alquilo C₁₋₈), NH SO₂N(alquilo C₁₋₈)₂, y NH SO₂NH₂.

2. El compuesto de acuerdo con la reivindicación 1, donde el PTM se selecciona de entre:



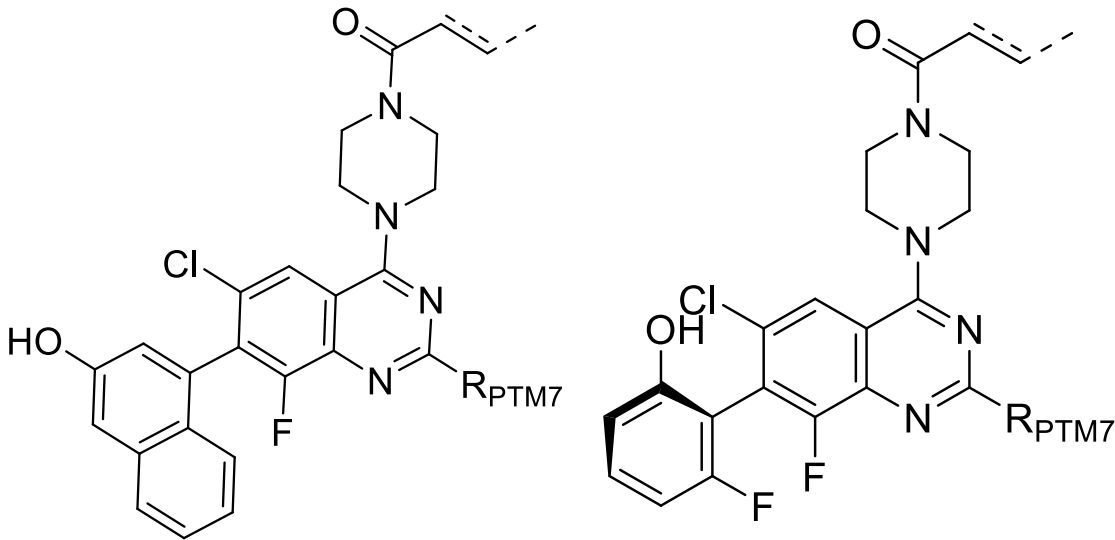
PTM-Va

PTM-Vb



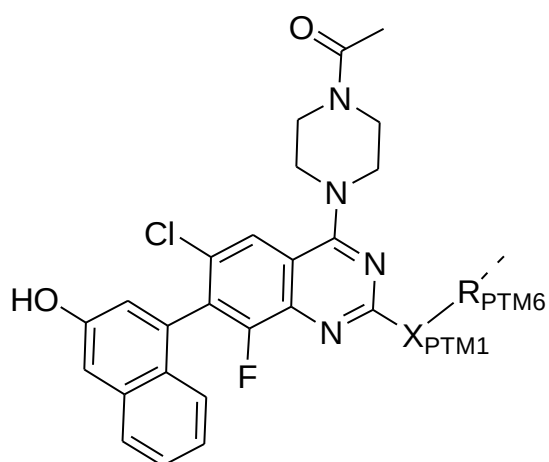
PTM-VI

PTM-VIIa

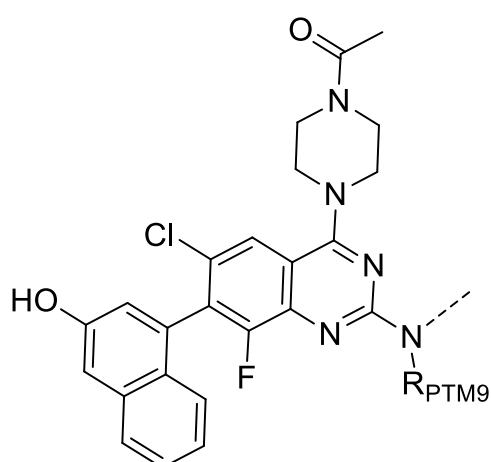


PTM-VIIb

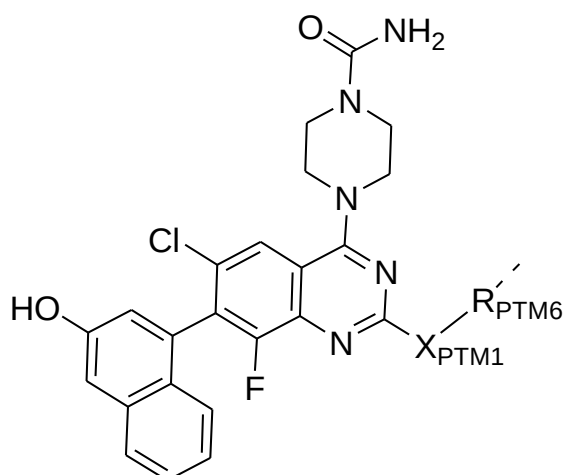
PTM-VIII



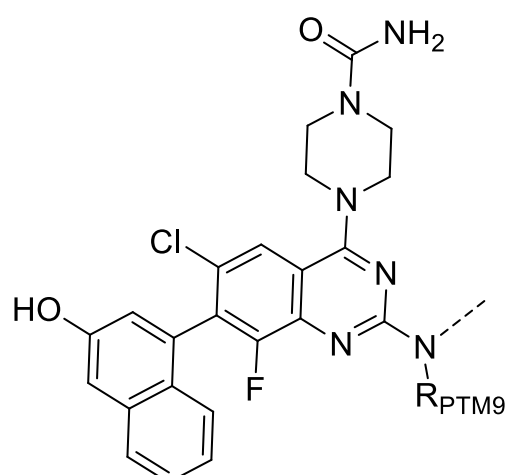
PTM-IXa



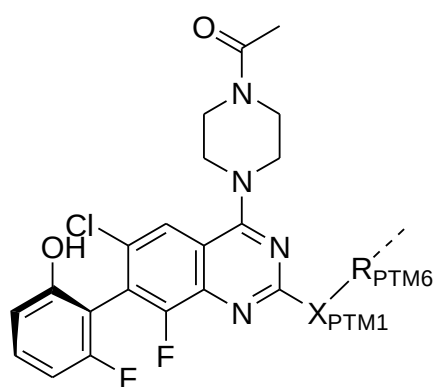
PTM-I-Xb



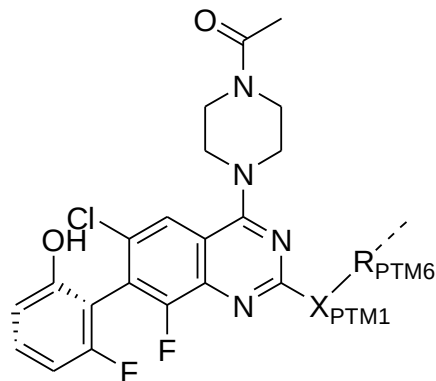
PTM-Xa



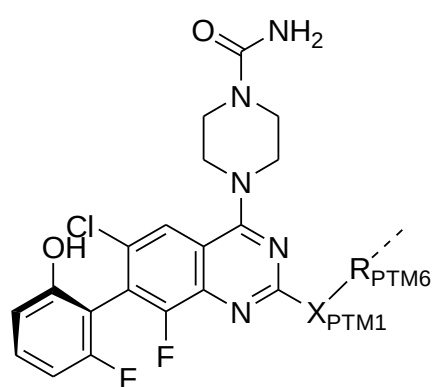
PTM-Xb



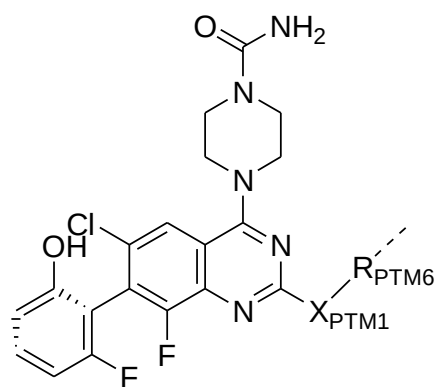
PTM-XI



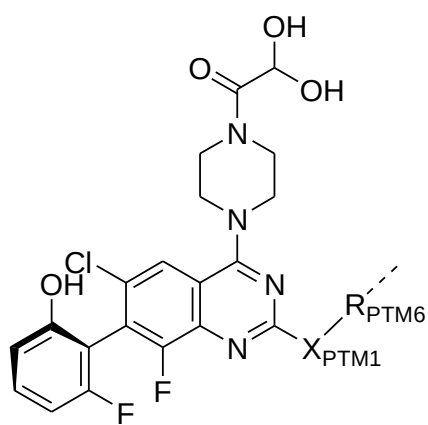
PTM-XII



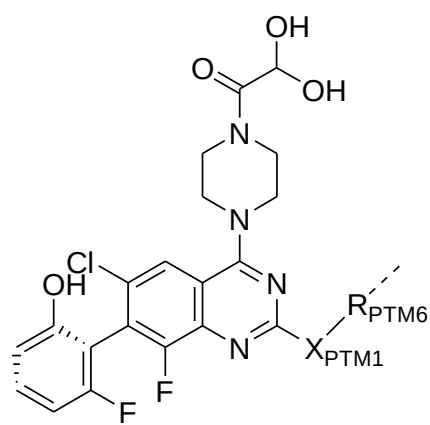
PTM-XIII



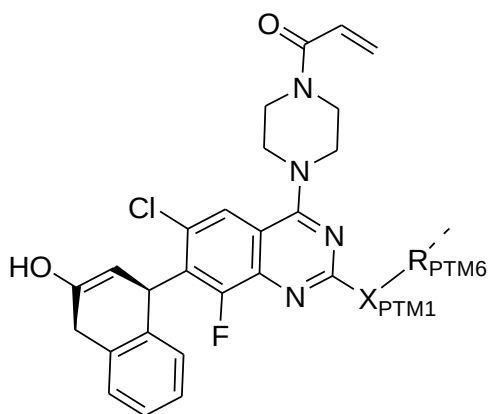
PTM-XIV



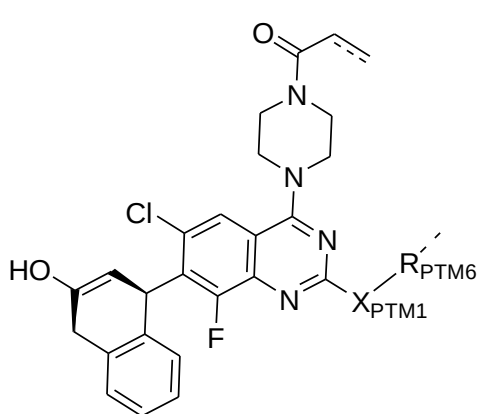
PTM-XV



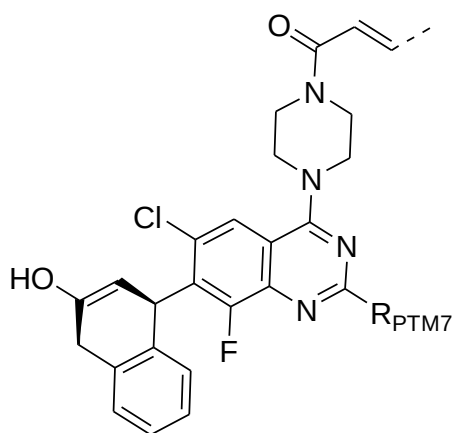
PTM-XVI



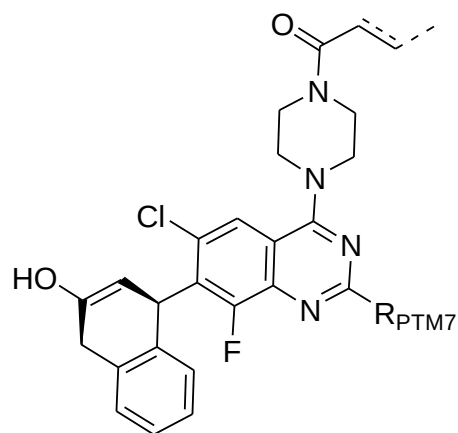
PTM-XVIIa



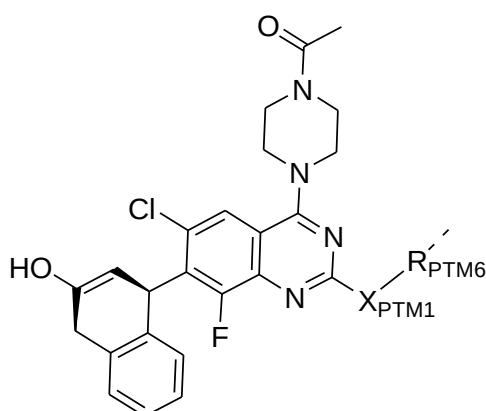
PTM-XVIIb



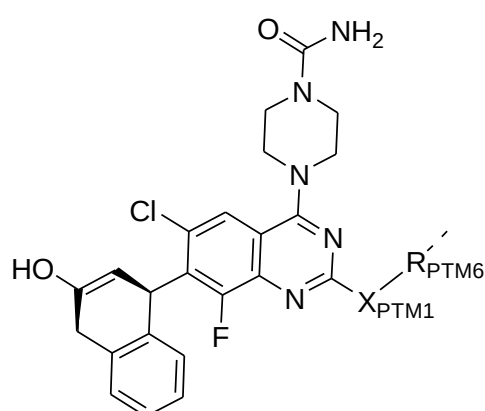
PTM-XVIII



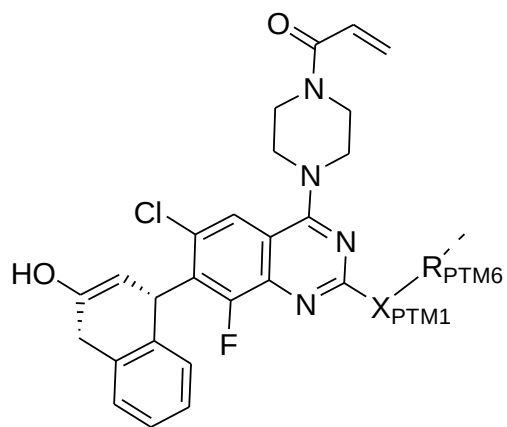
PTM-XIV



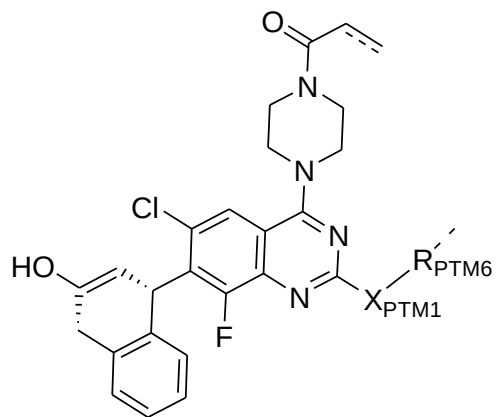
PTM-XV



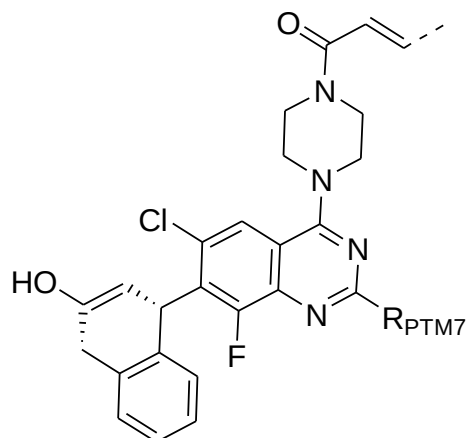
PTM-XVI



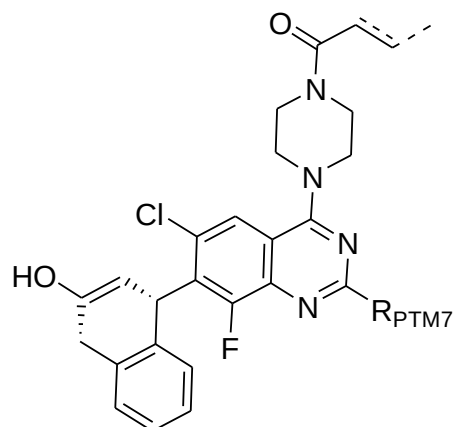
PTM-XVIIa



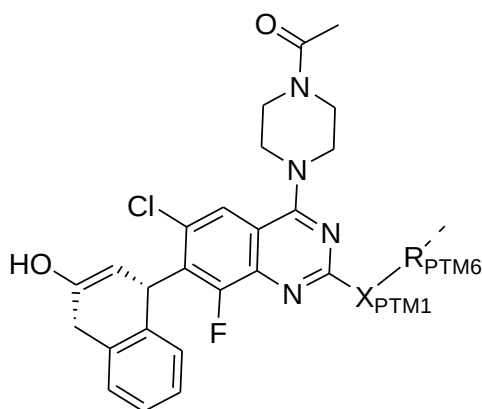
PTM-XVIIb



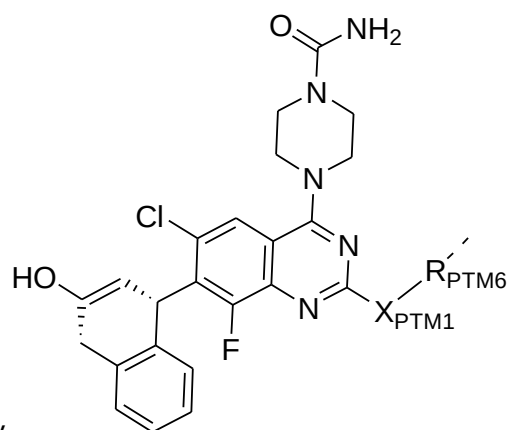
PTM-XVIII



PTM-XIX



PTM-XX

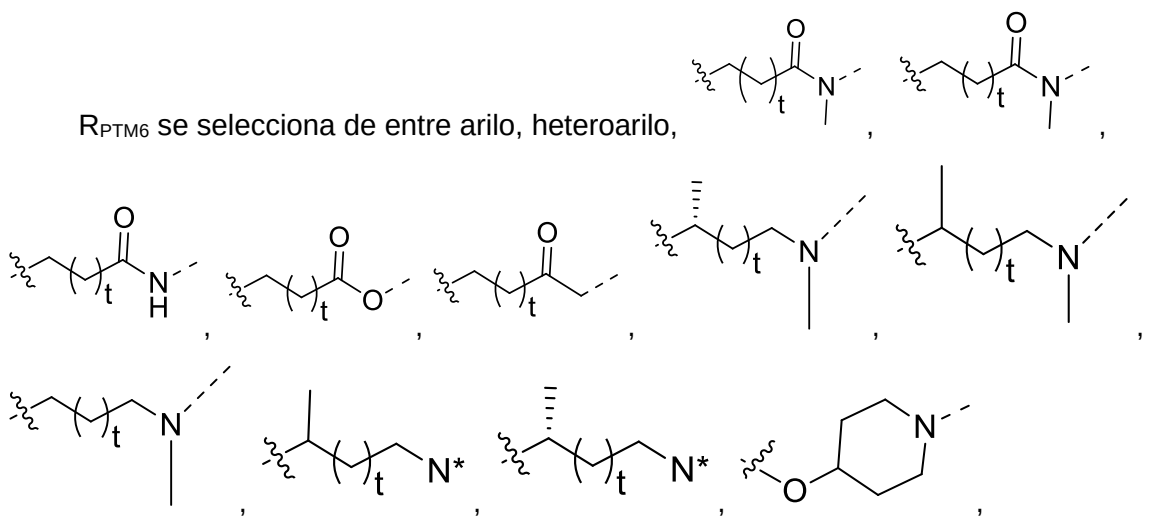


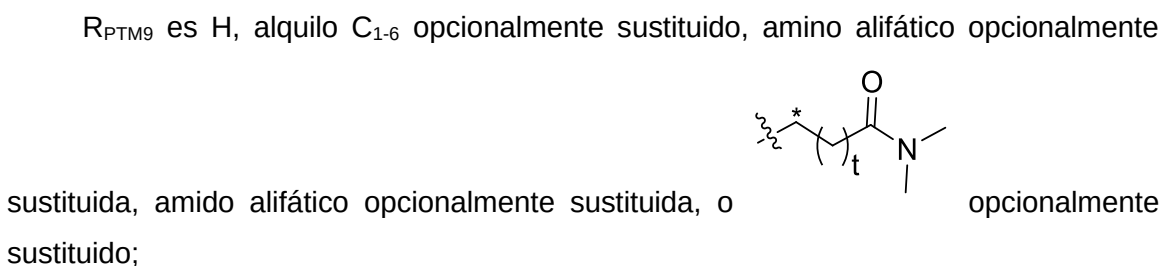
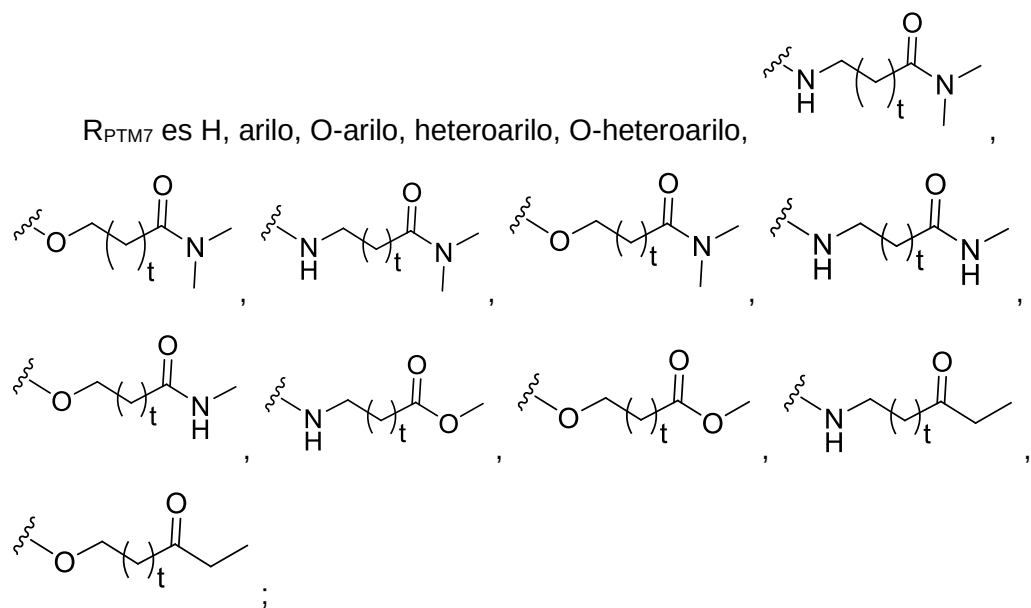
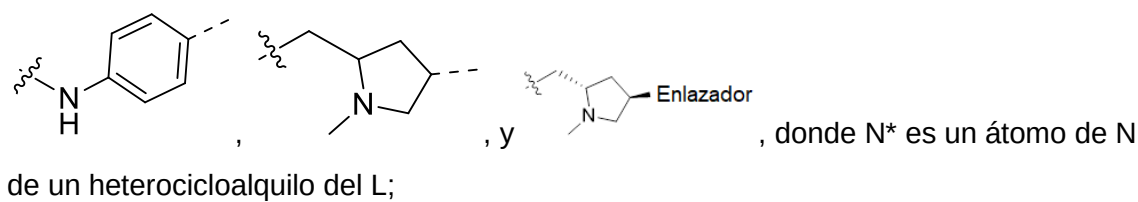
PTM-XXI

donde:

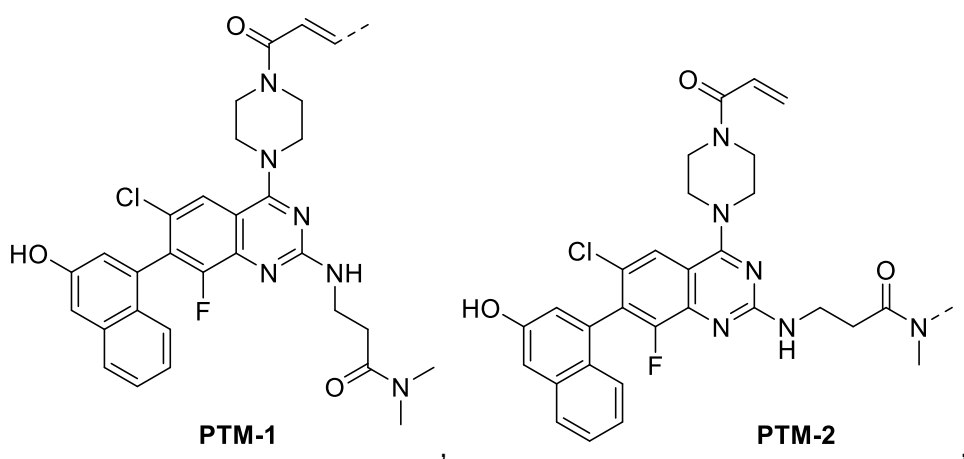
X_{PTM1} es NH u O;

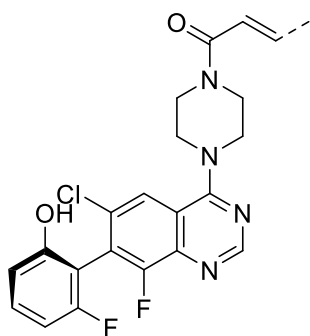
R_{PTM6} se selecciona de entre arilo, heteroarilo,





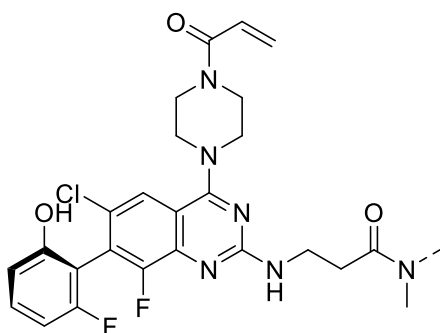
3. El compuesto de acuerdo con cualquiera de la reivindicación 1 o reivindicación 2, donde el PTM es representado por la estructura química seleccionada de entre:





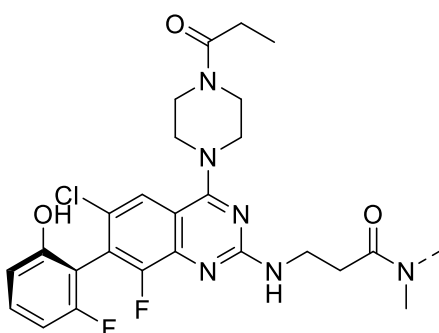
PTM-3

,



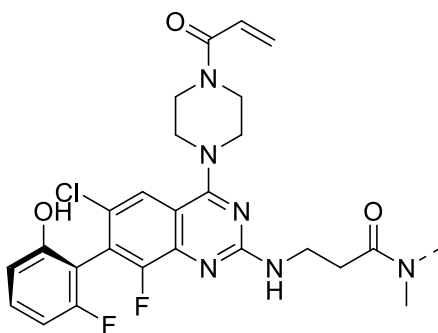
PTM-4

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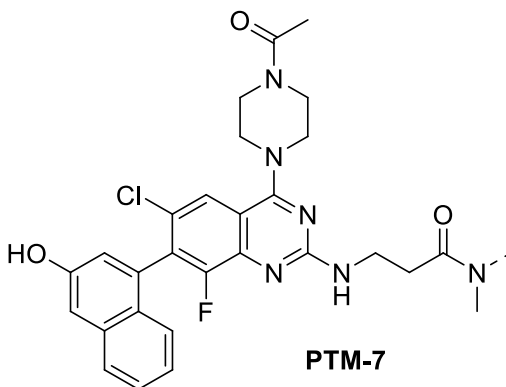
PTM-5

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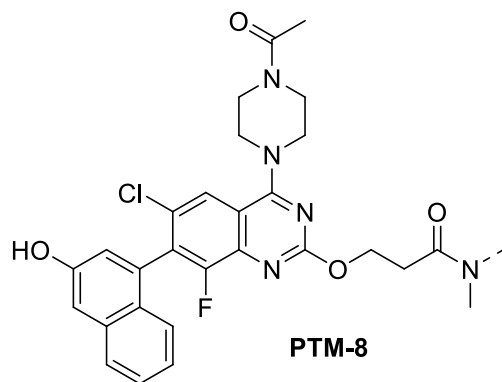
PTM-6

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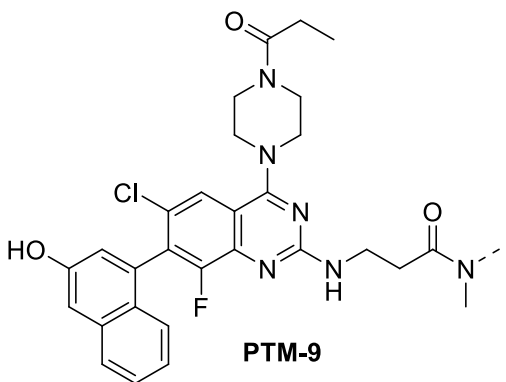
PTM-7

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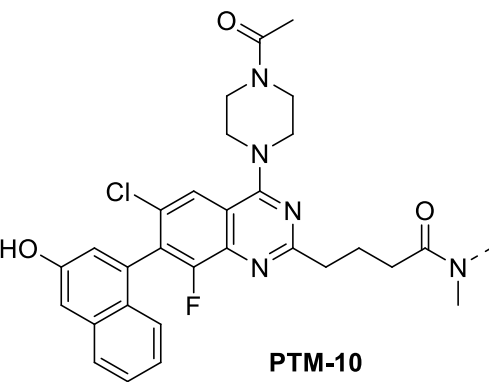
PTM-8

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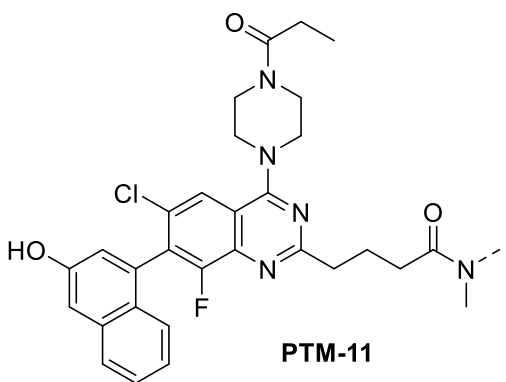
PTM-9

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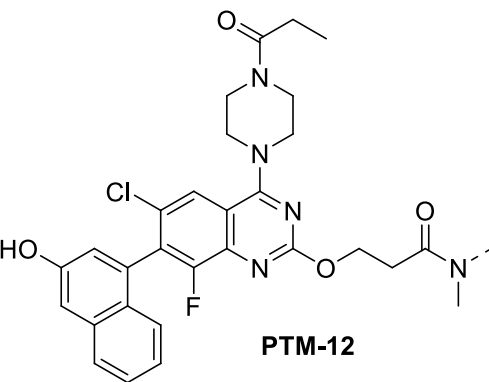
PTM-10

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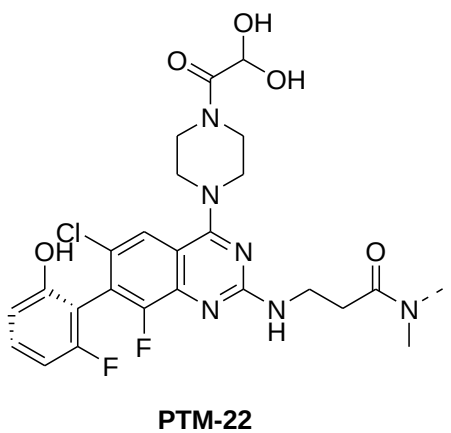
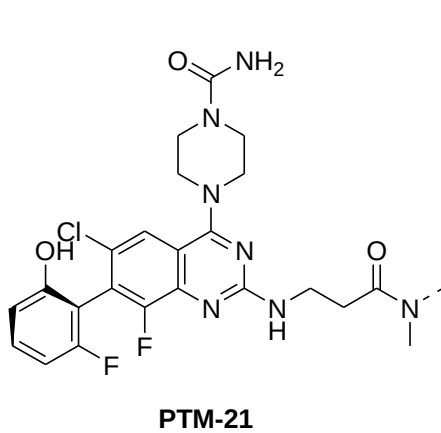
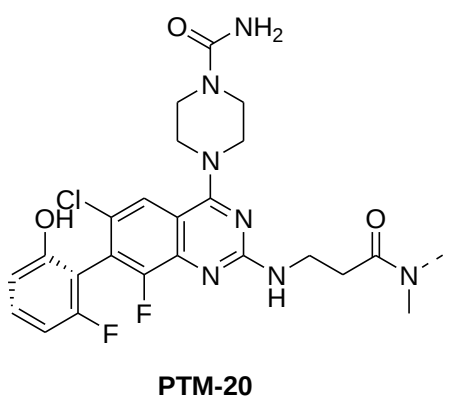
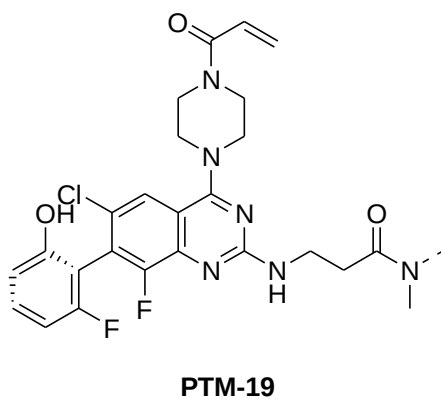
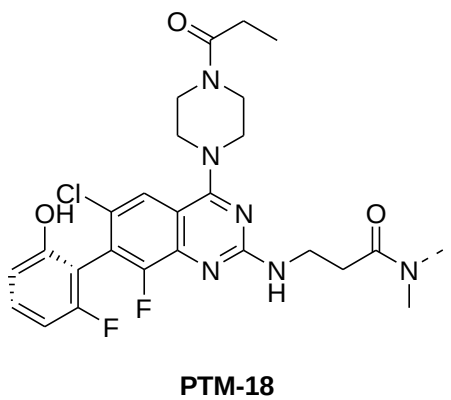
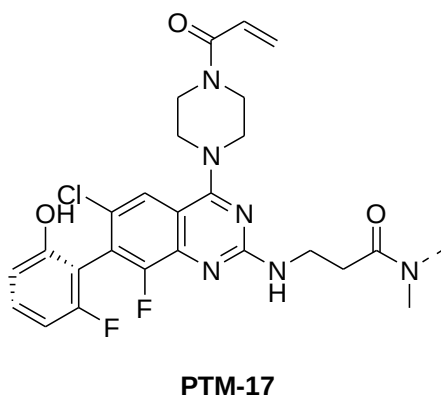
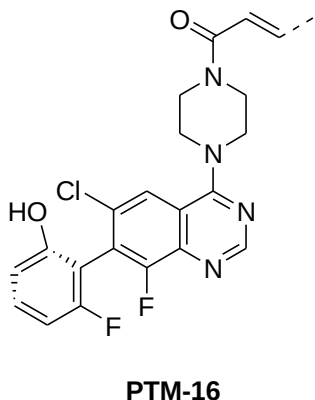
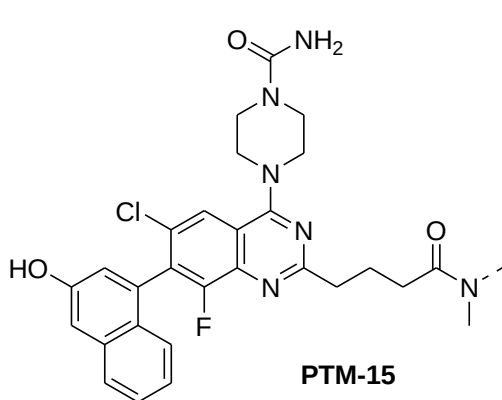
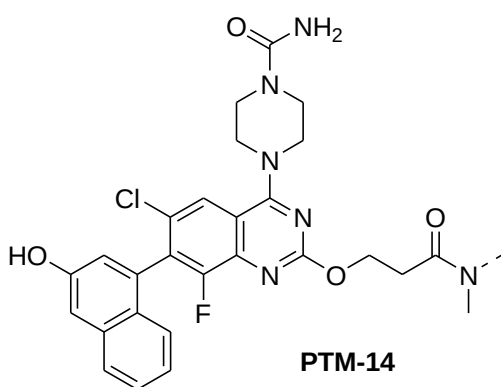
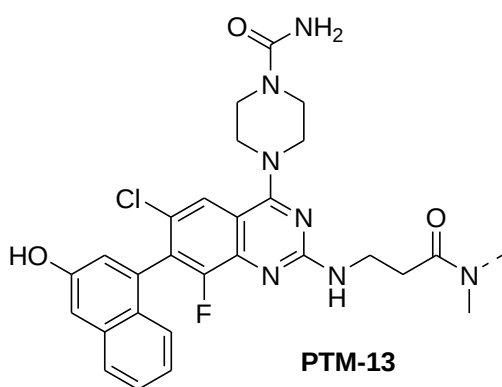
PTM-11

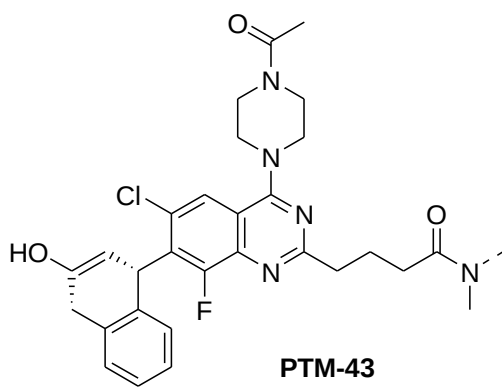
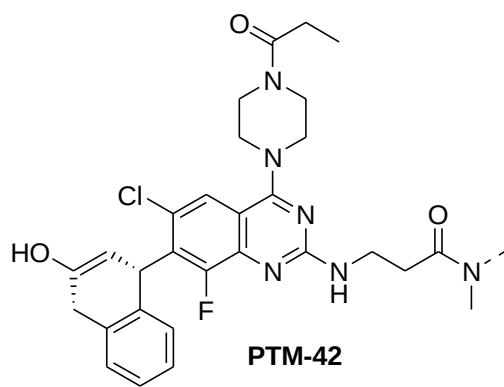
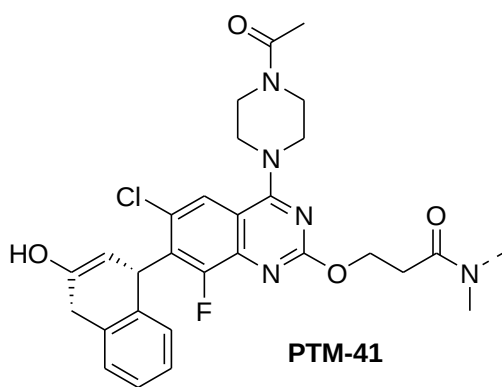
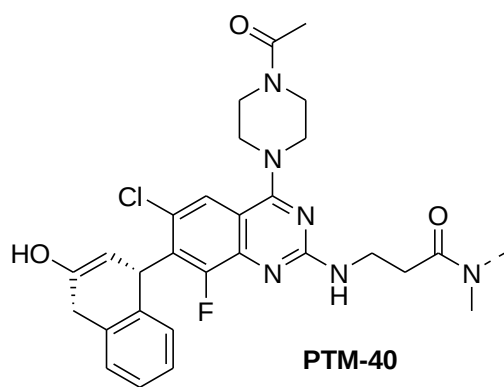
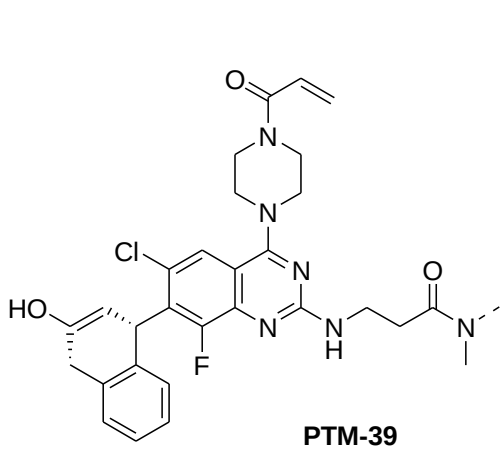
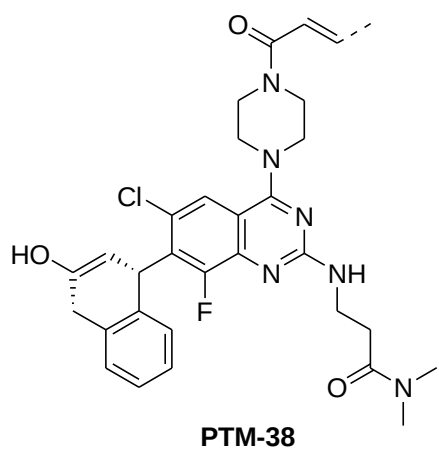
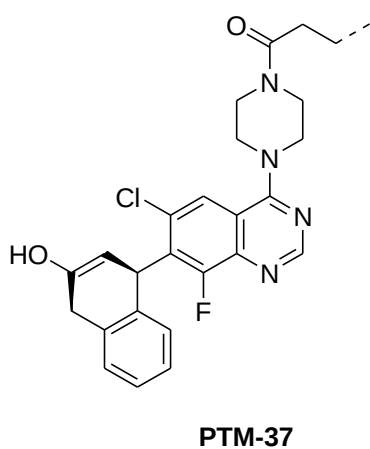
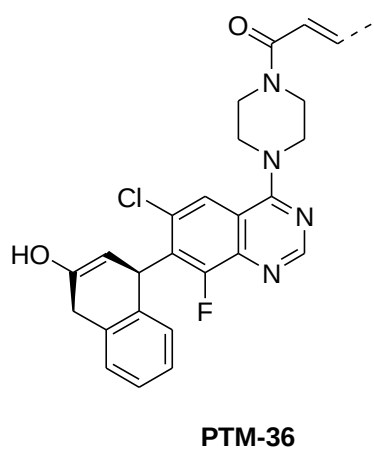
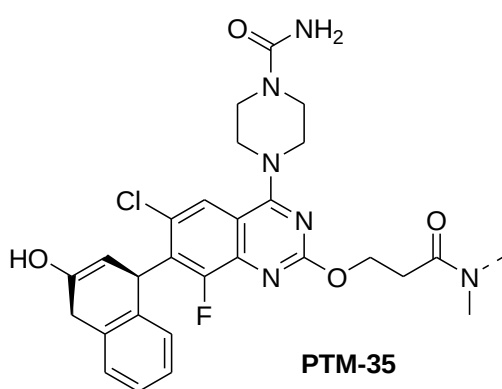
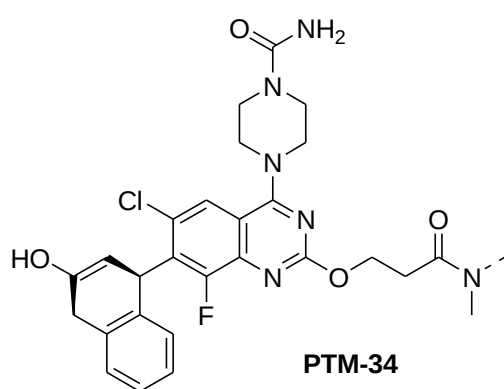
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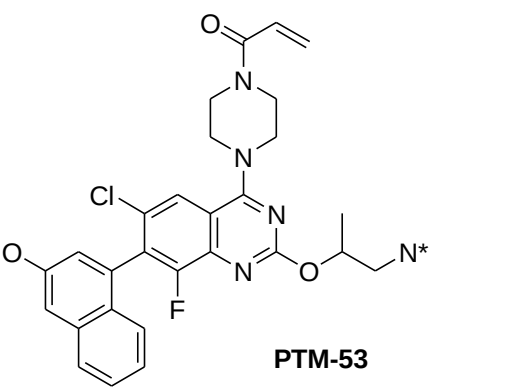
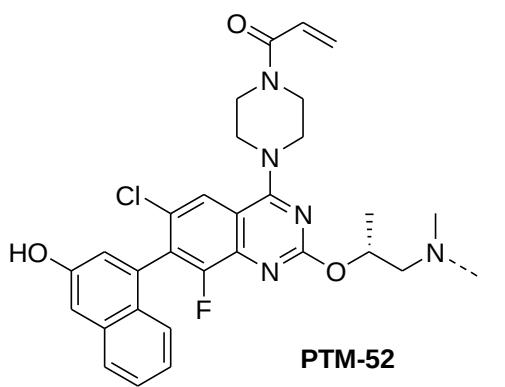
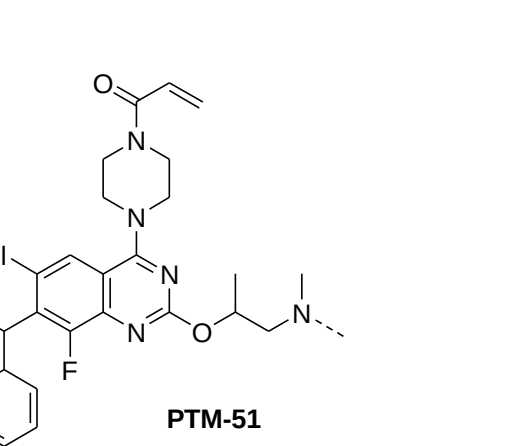
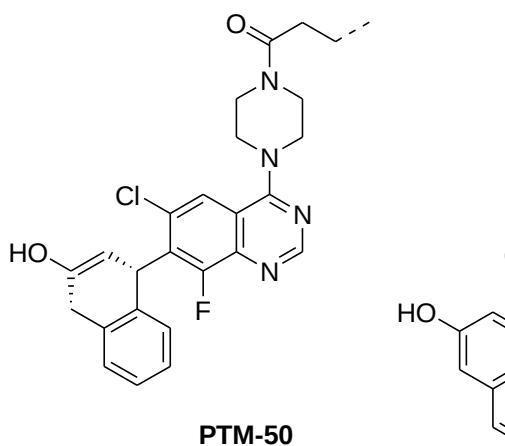
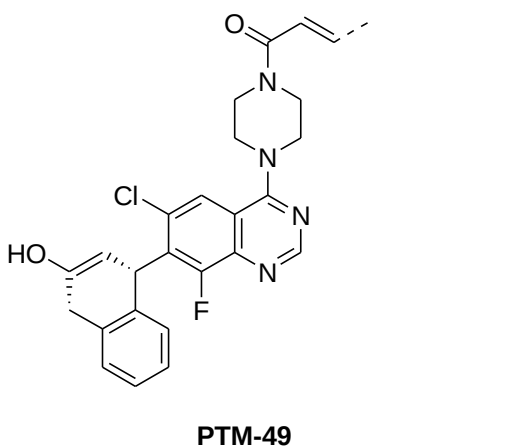
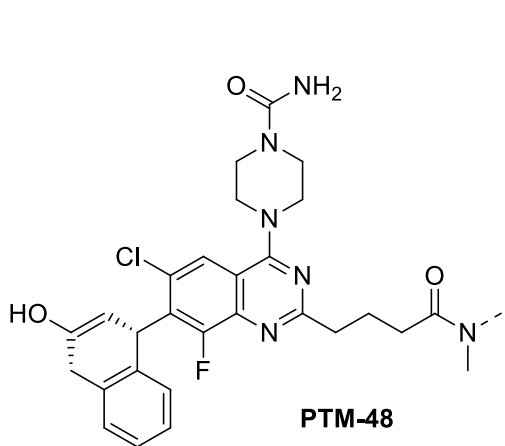
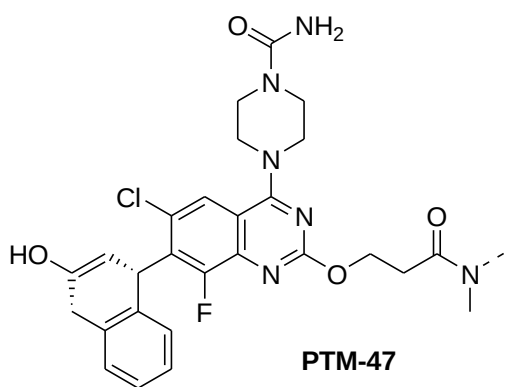
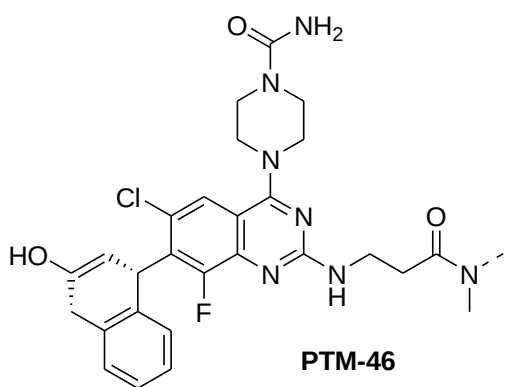
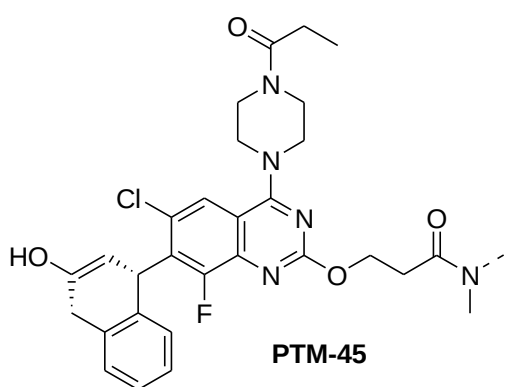
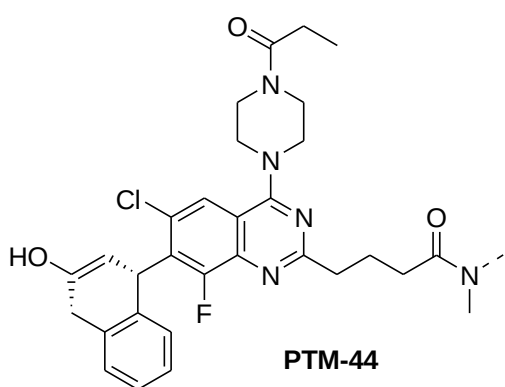


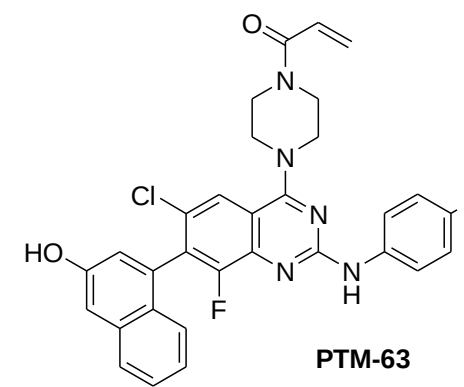
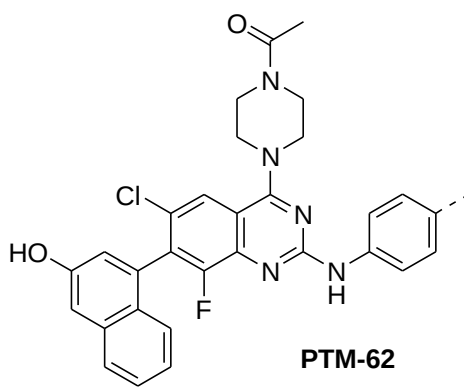
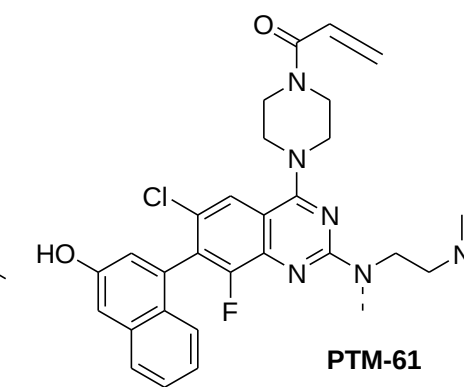
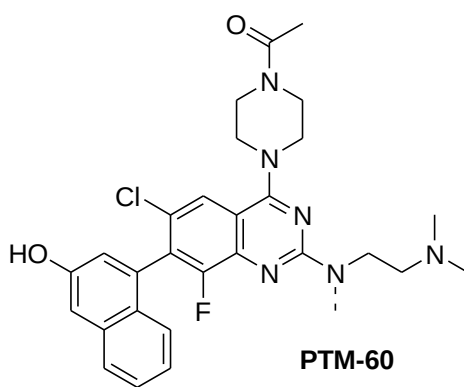
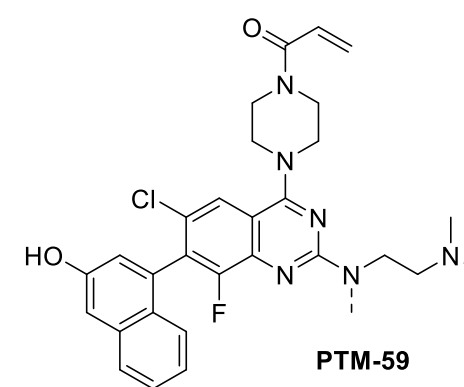
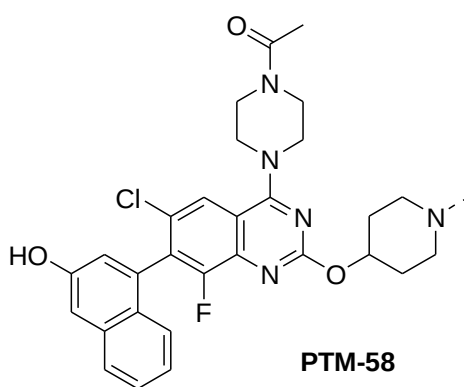
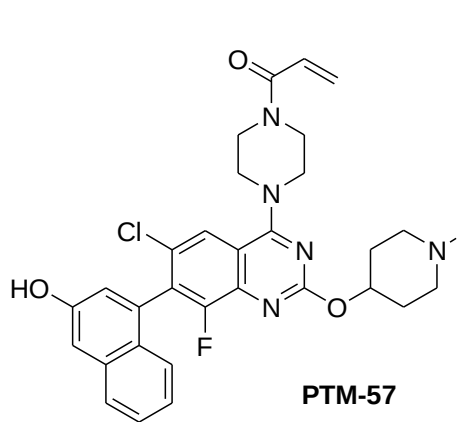
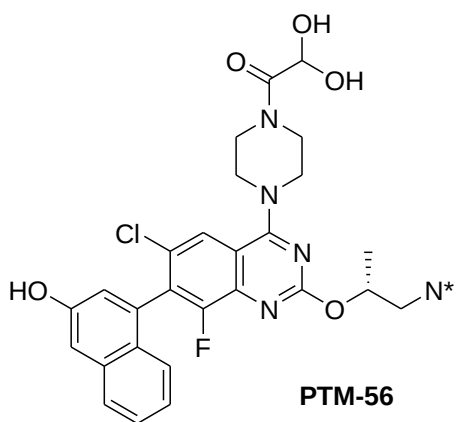
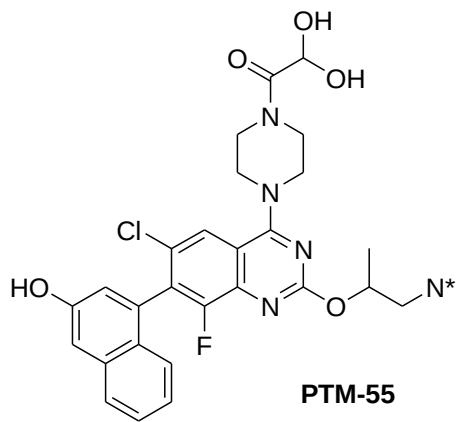
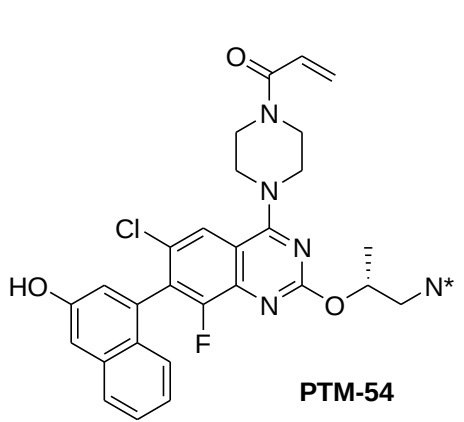
PTM-12

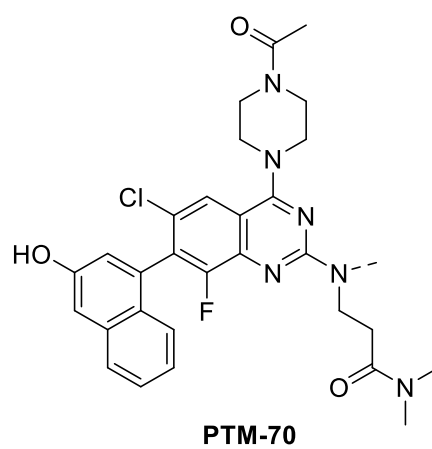
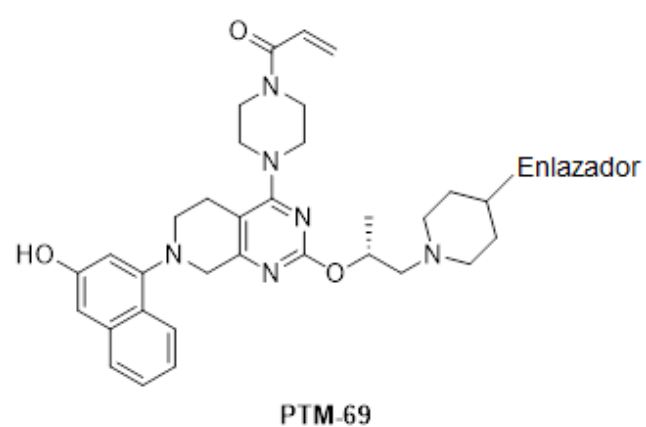
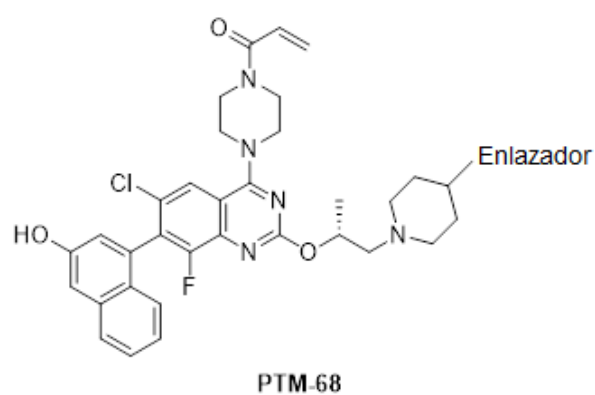
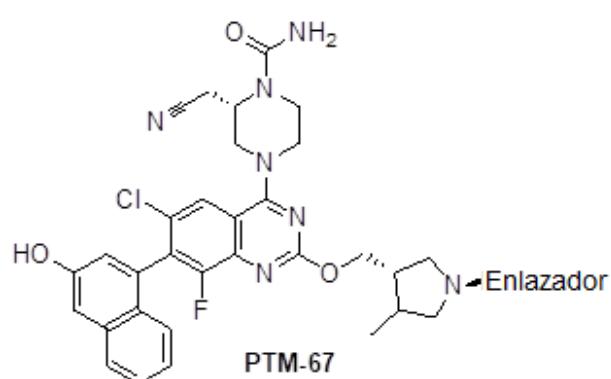
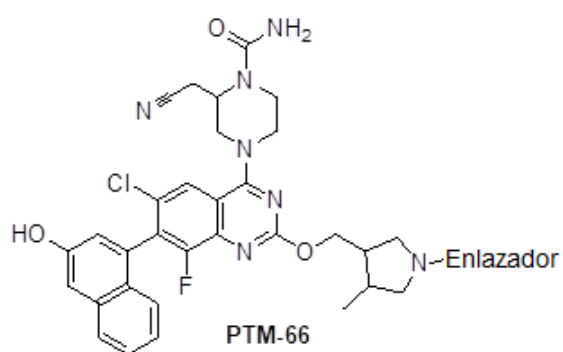
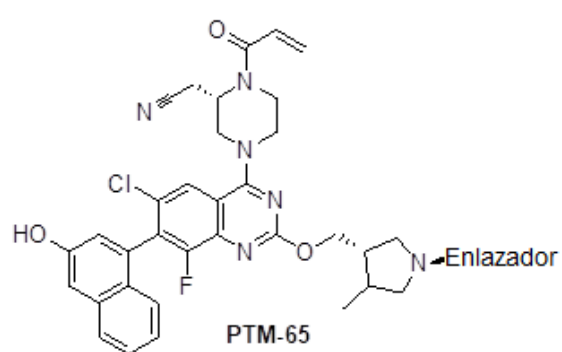
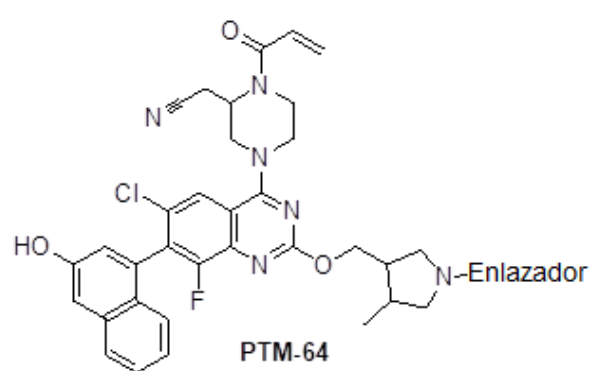
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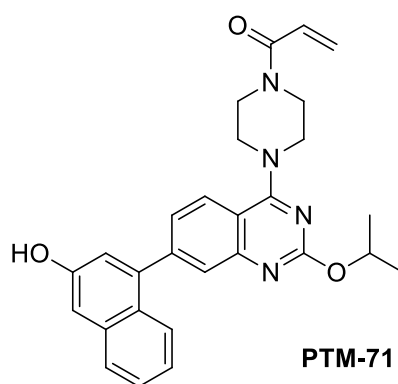




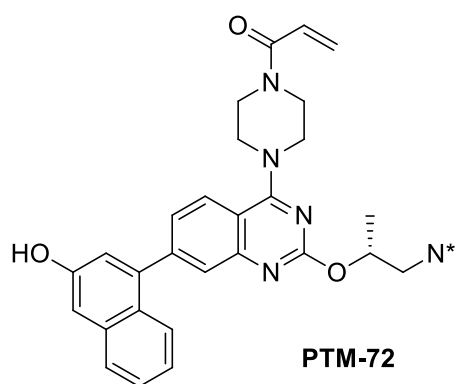




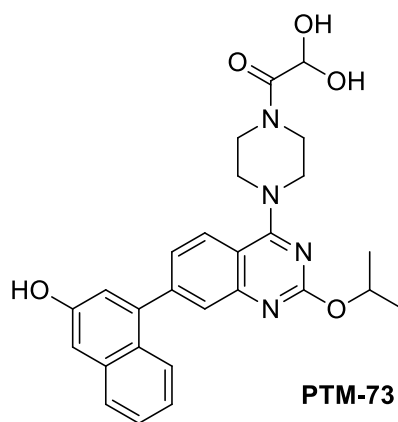




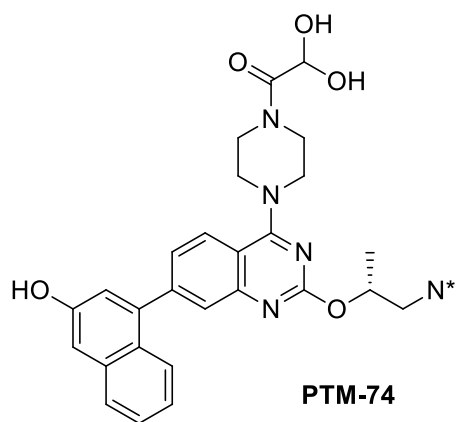
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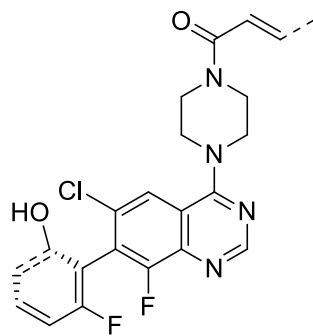
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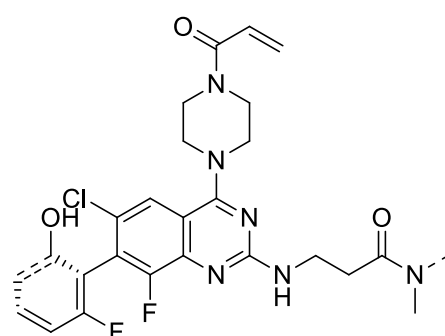
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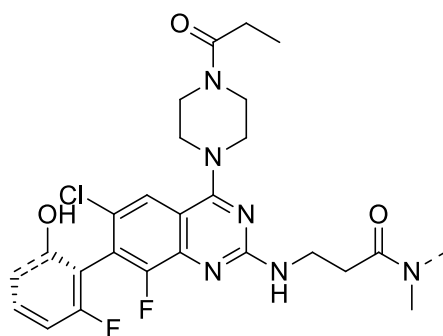
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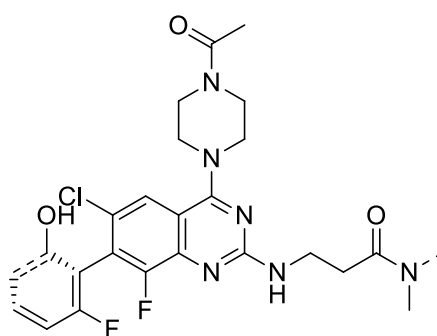
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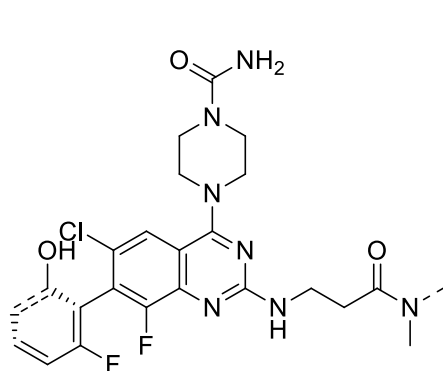
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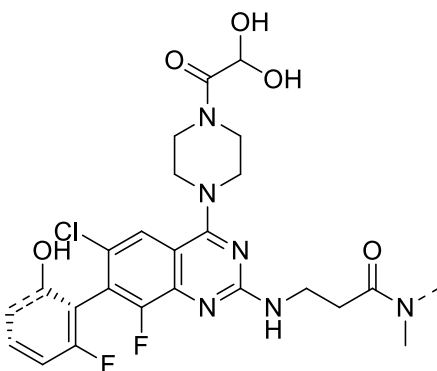
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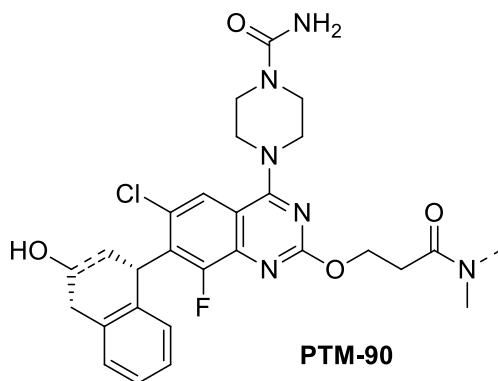
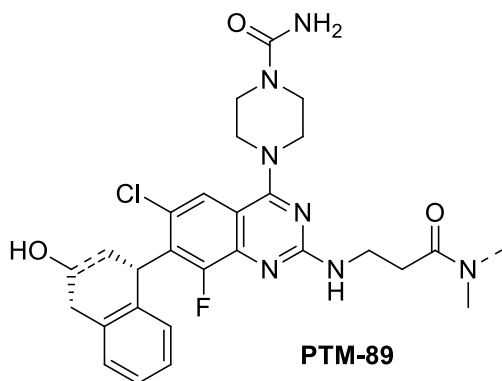
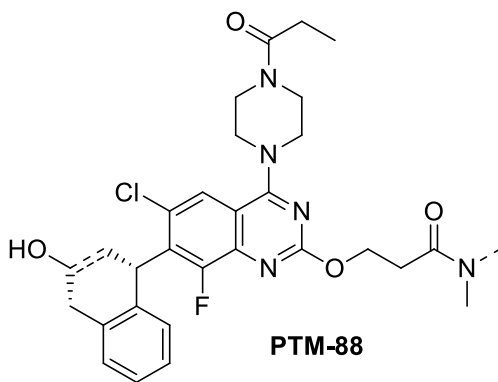
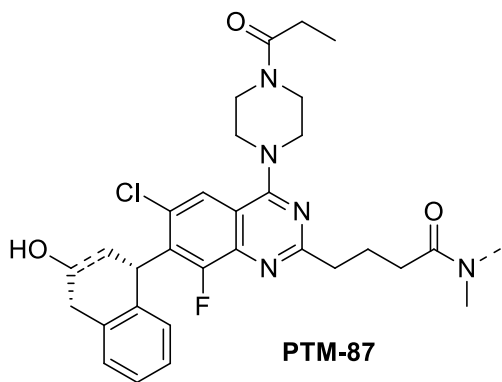
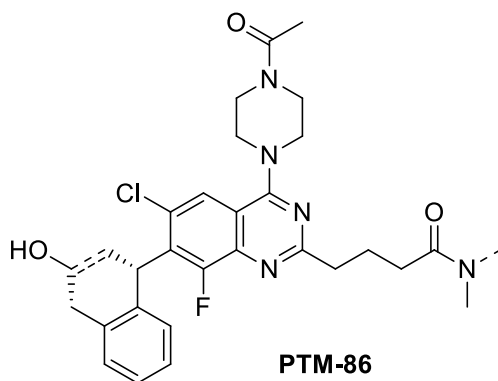
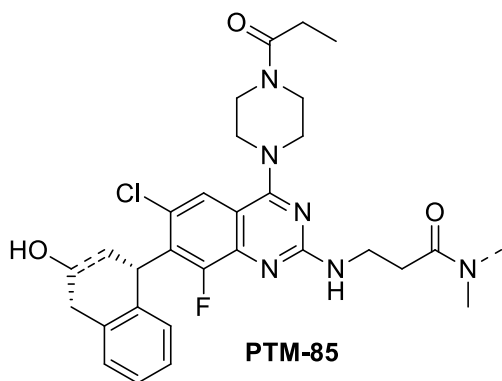
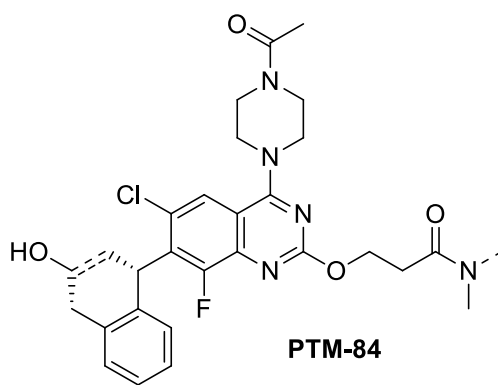
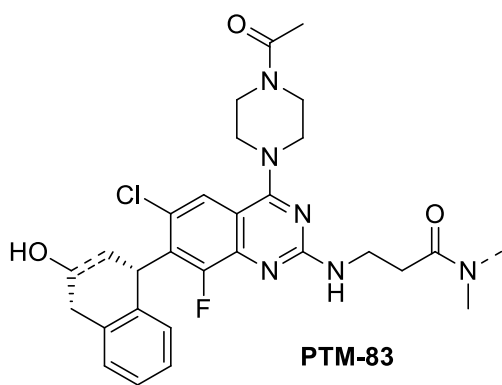
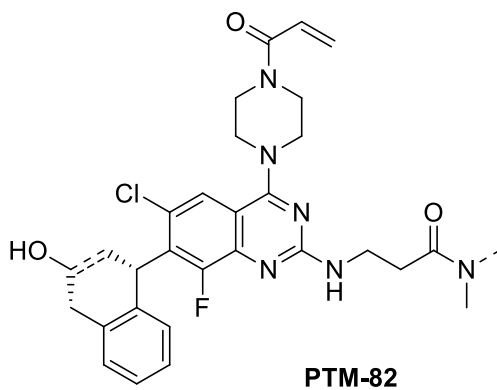
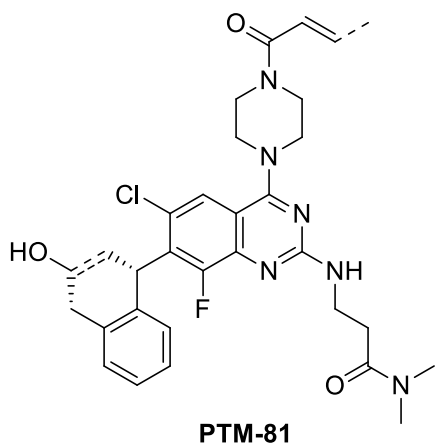
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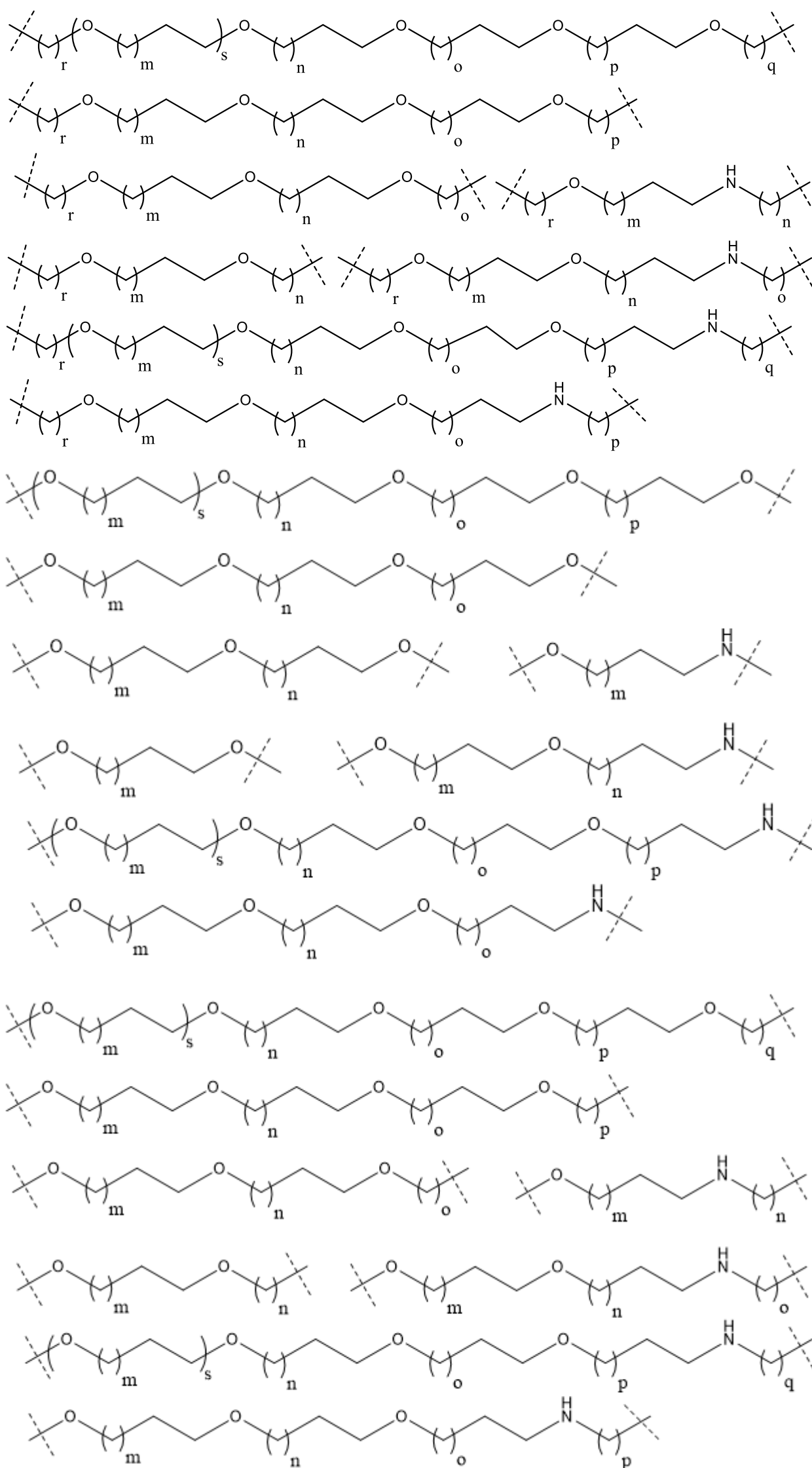


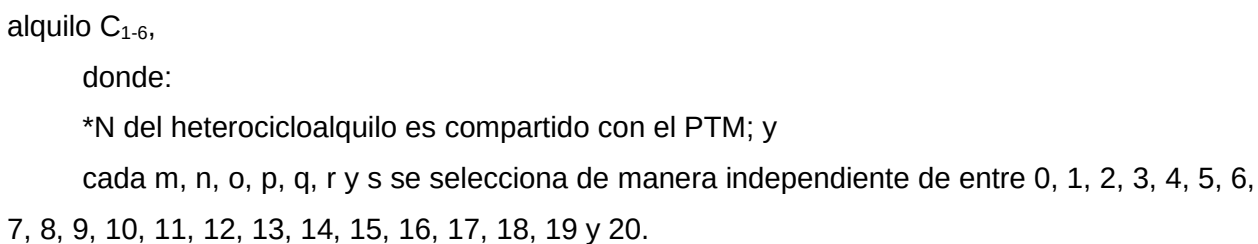
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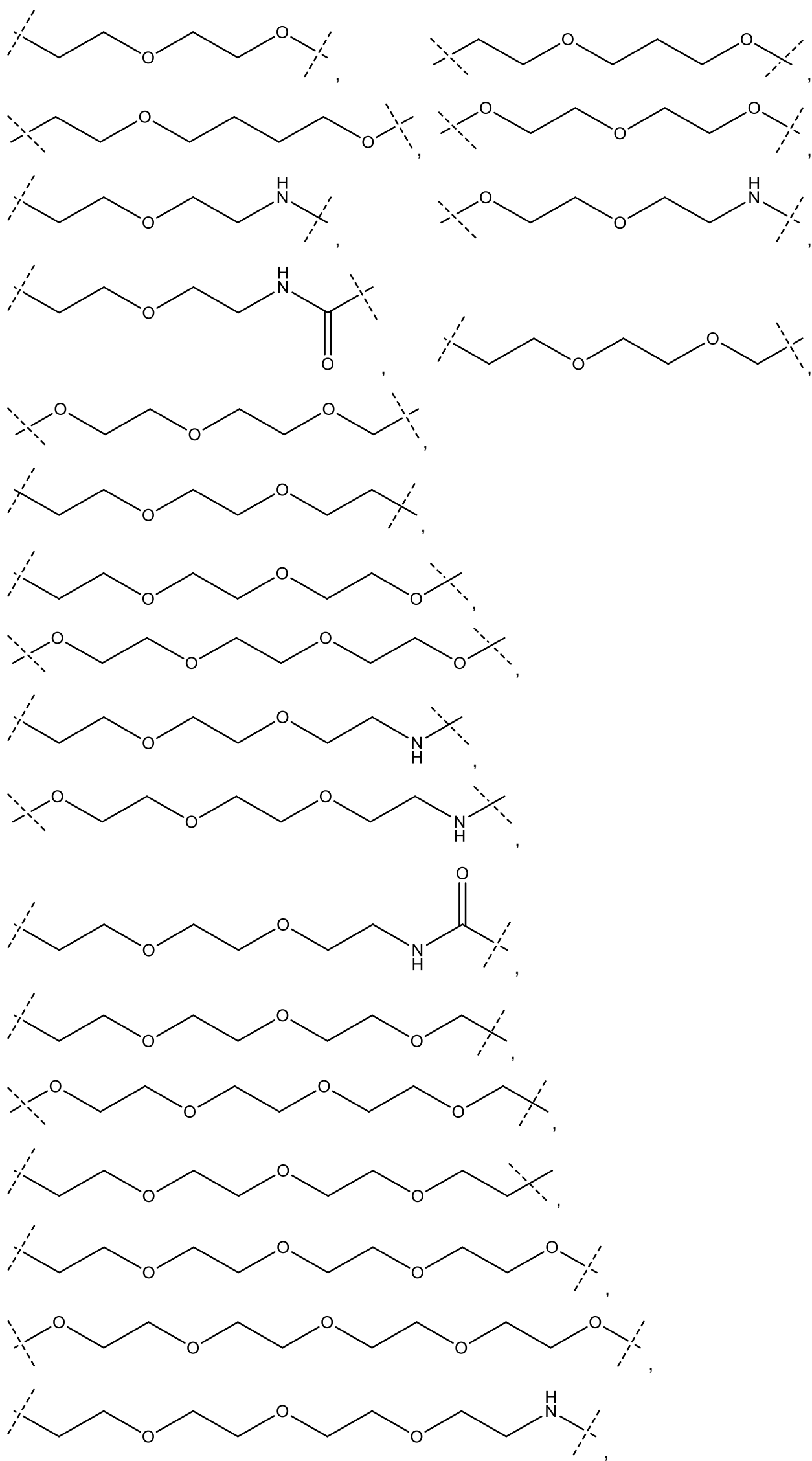


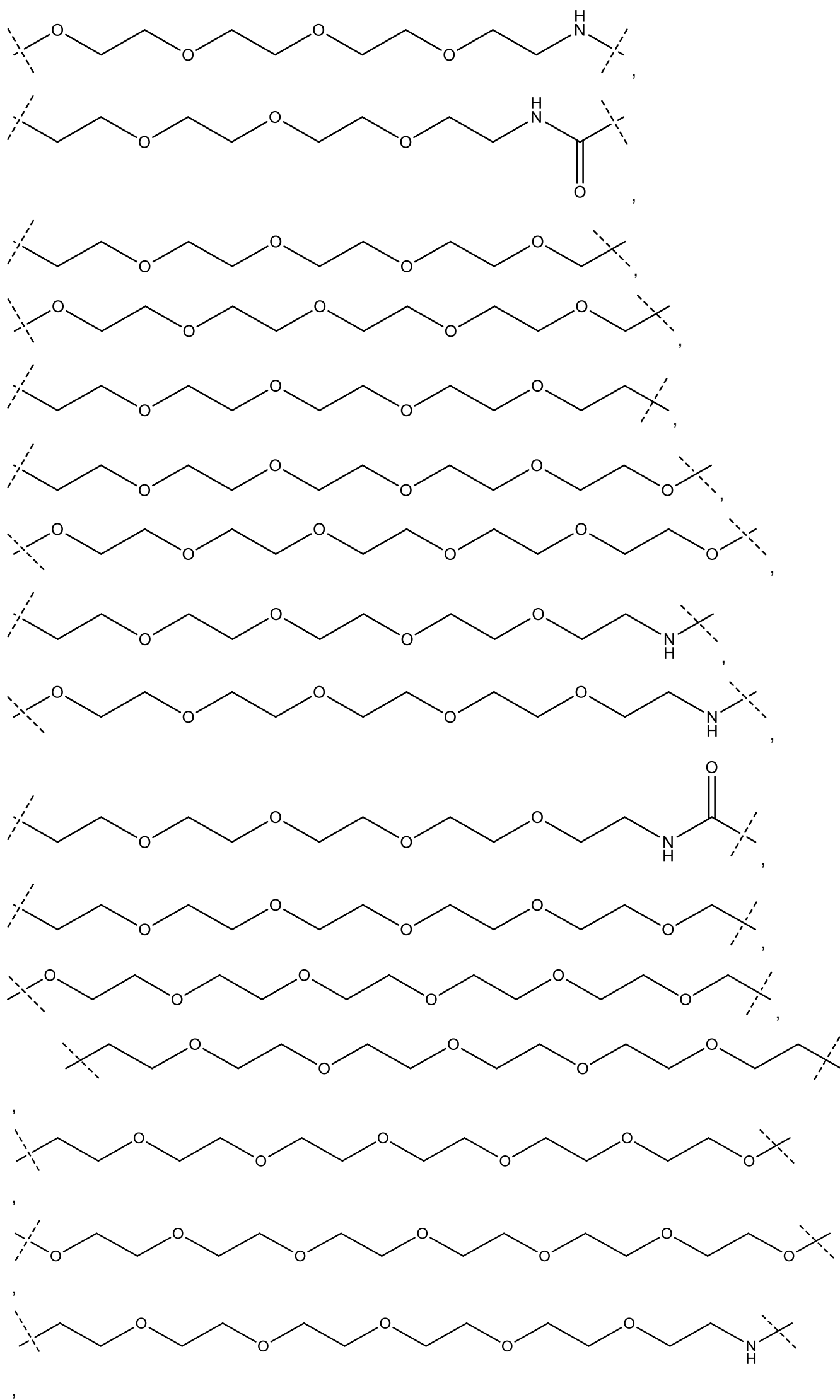
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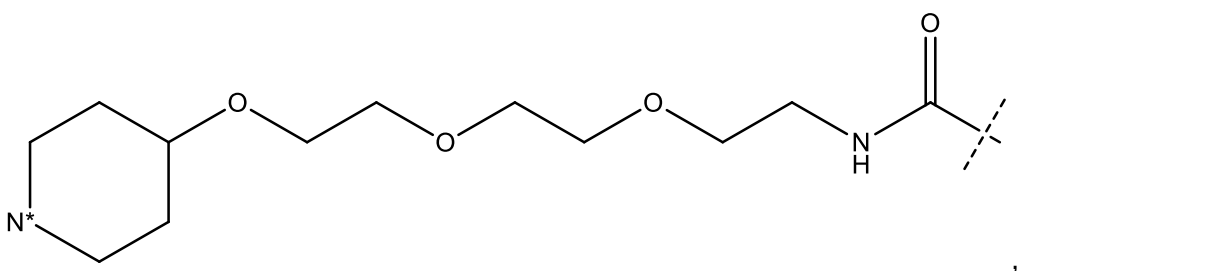
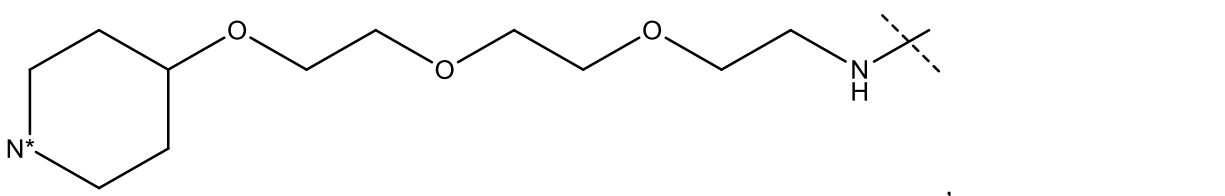
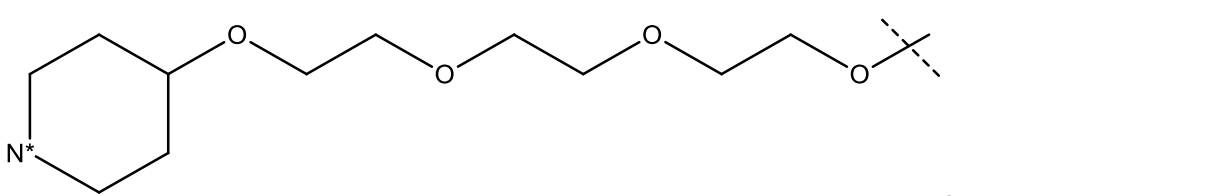
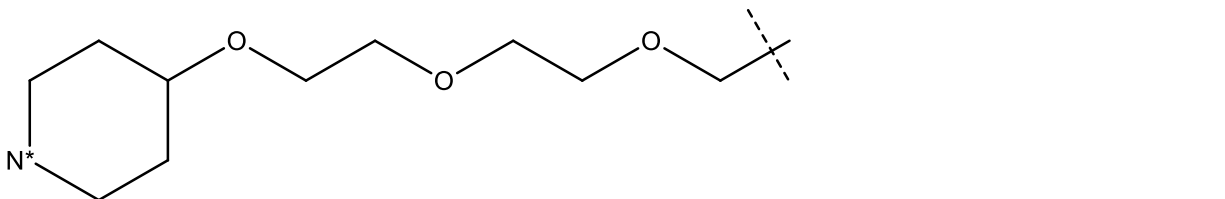
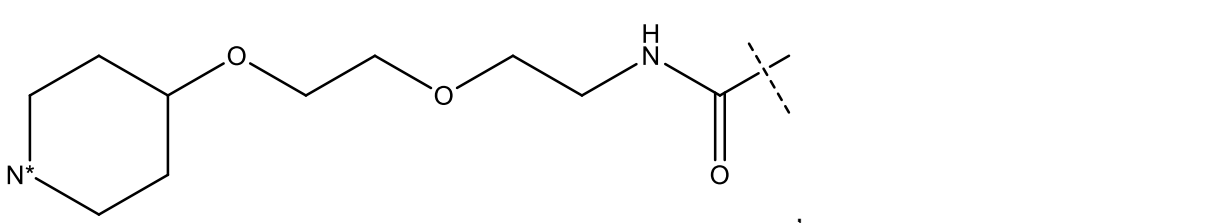
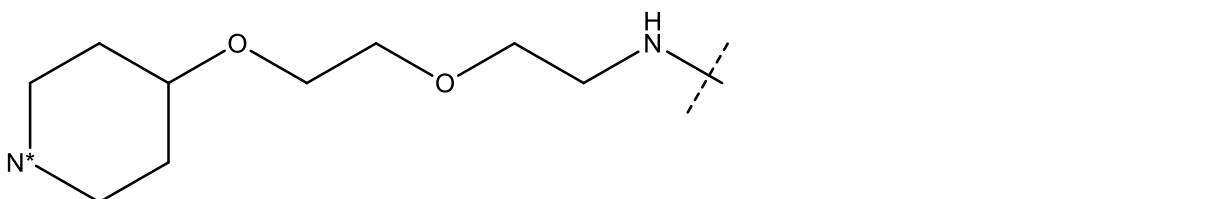
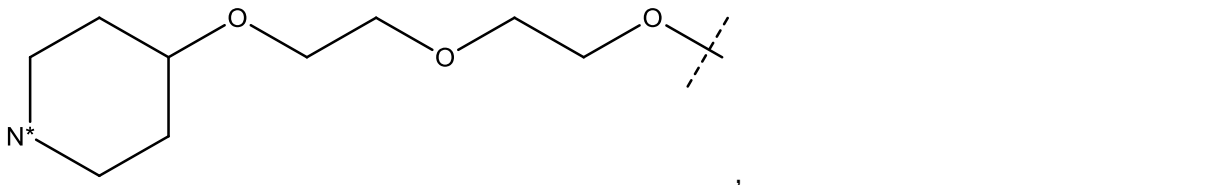
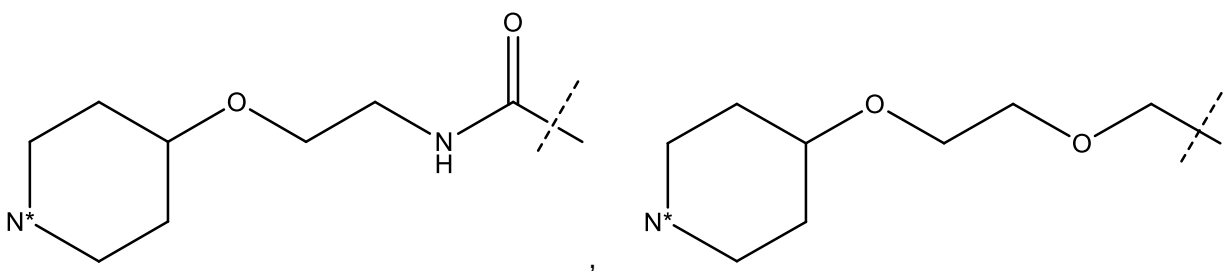
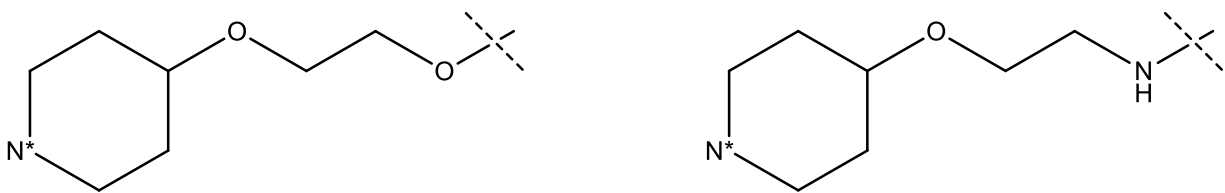
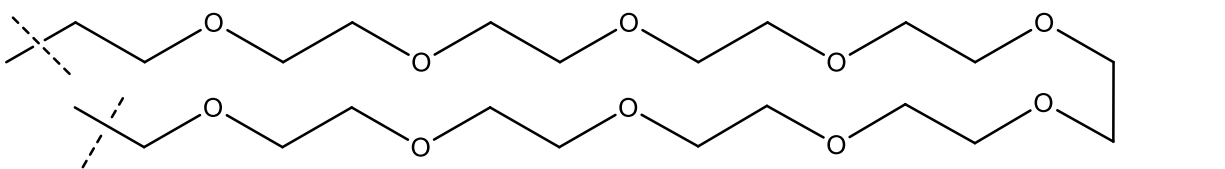


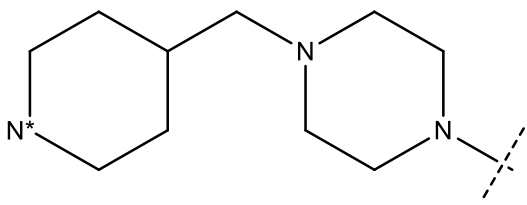
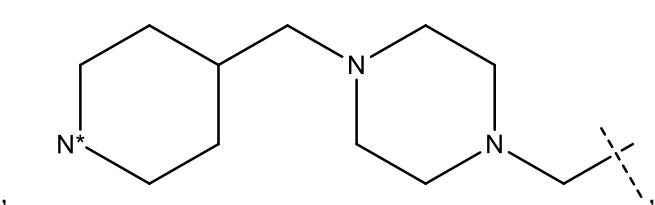
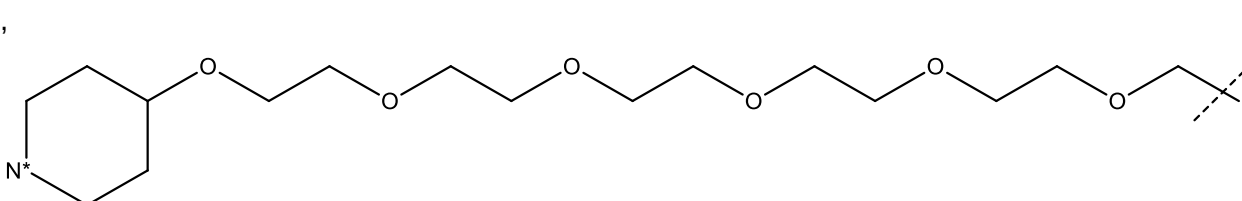
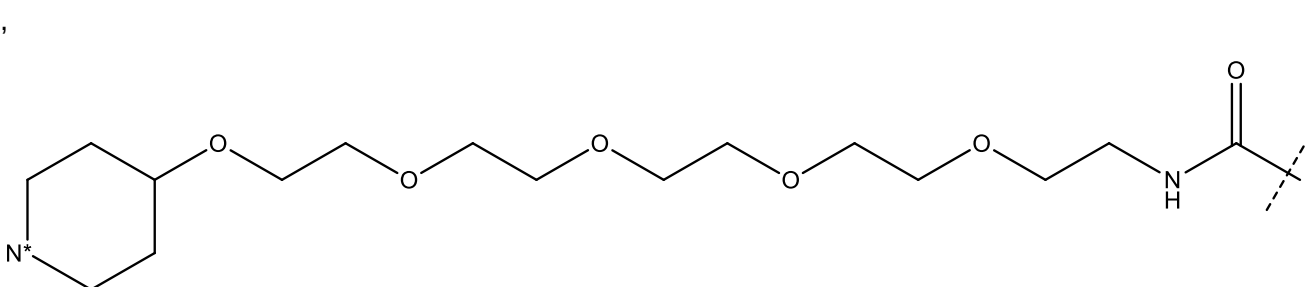
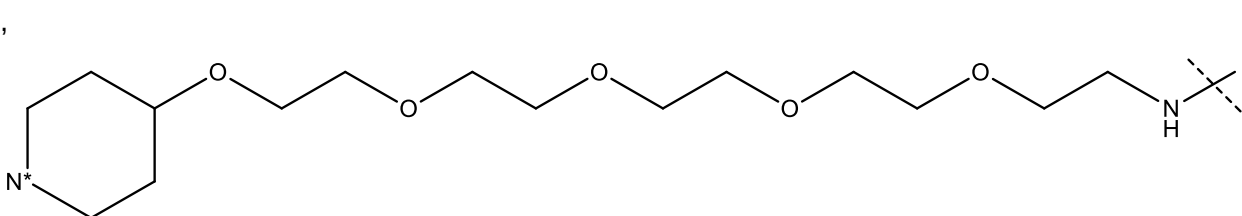
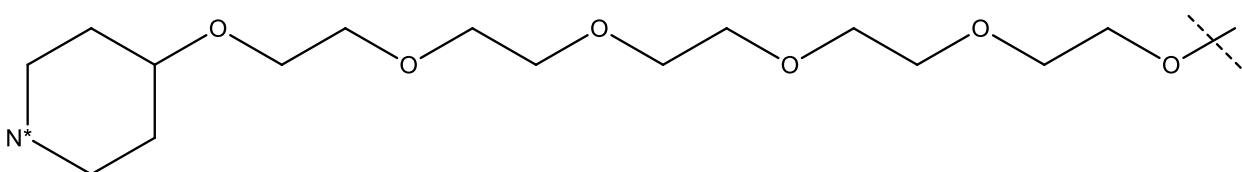
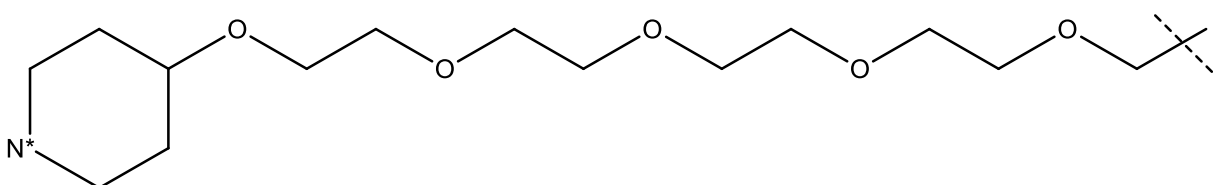
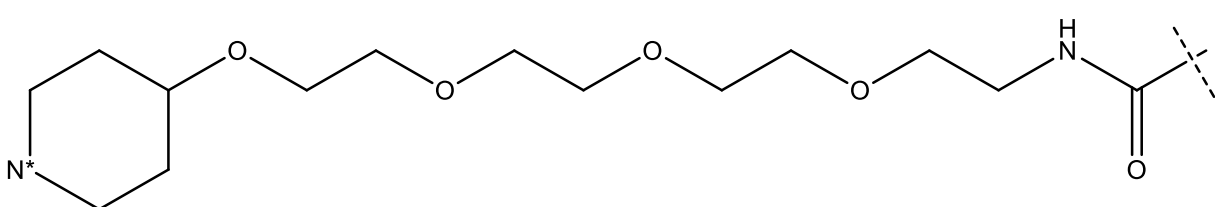
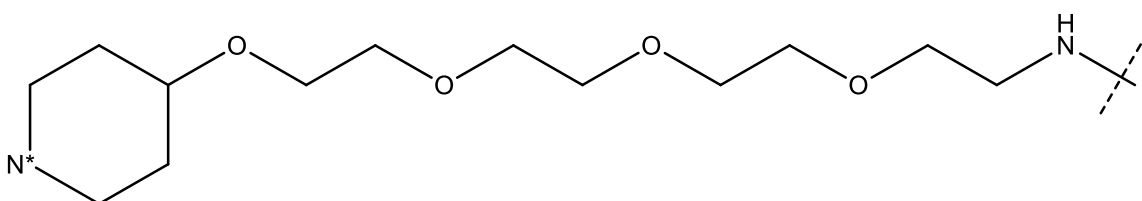
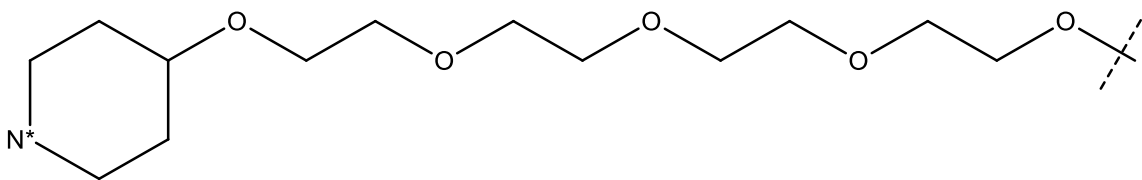
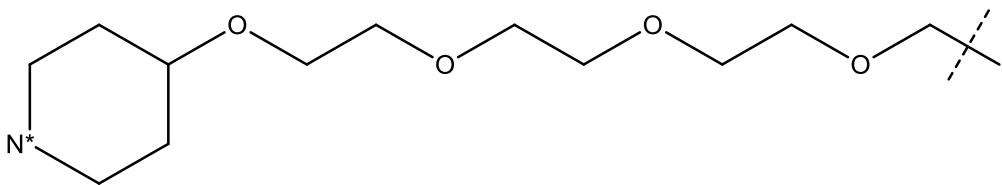


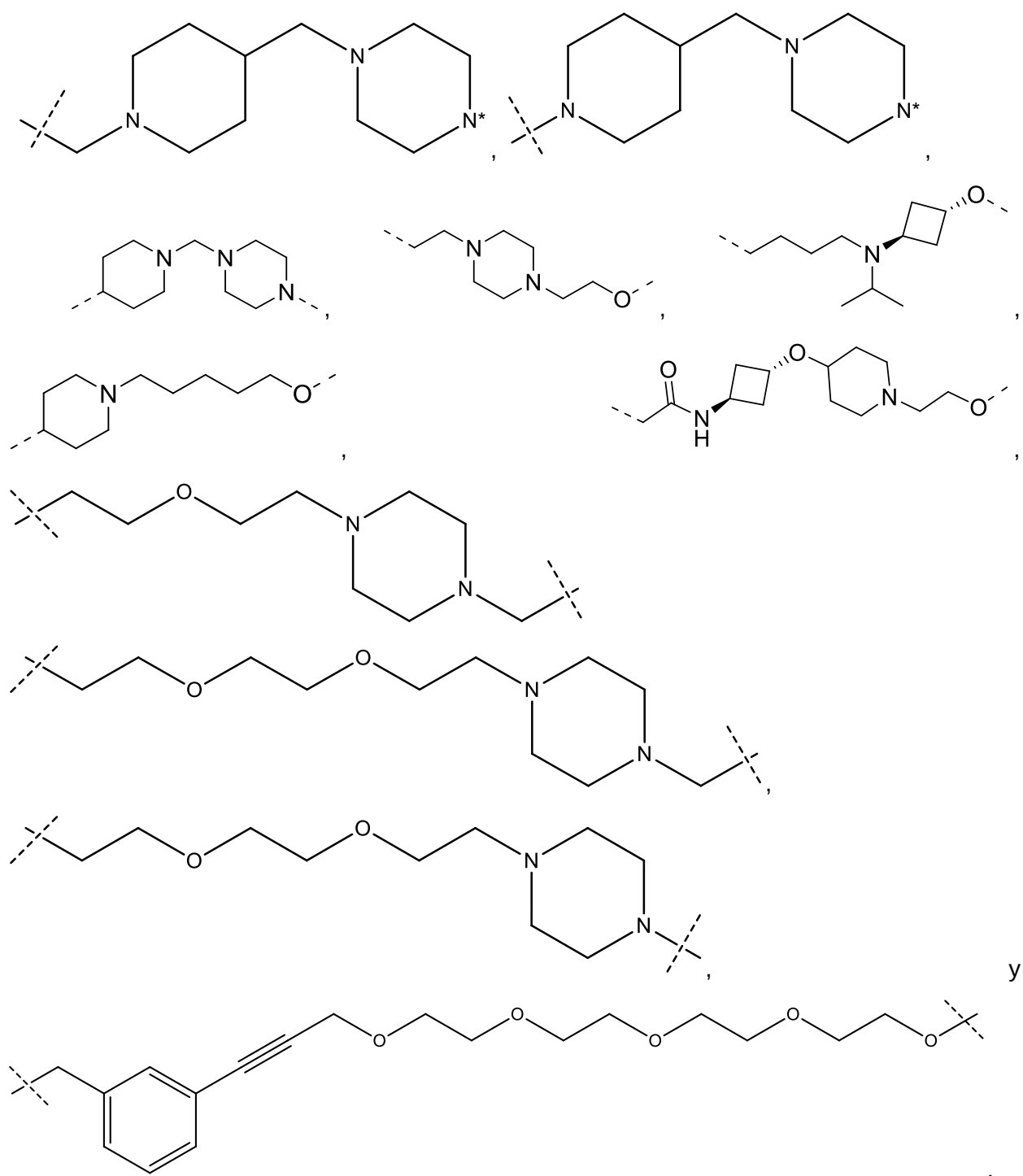
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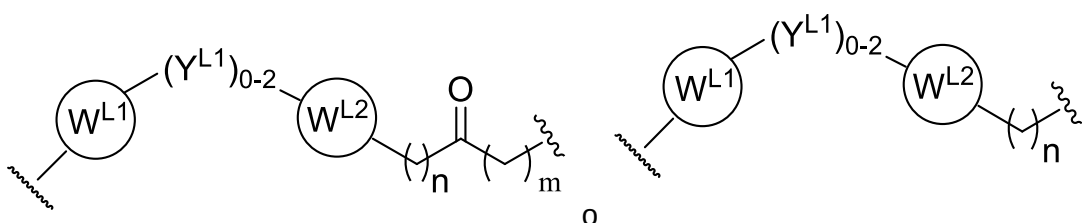


donde N* del heterocicloalquilo es compartido con el PTM.

6. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el L es polietilenglicol con 1 a 10 unidades de etilenglicol opcionalmente sustituido con arilo.

7. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el L es un alquilo C₁₋₅₀, donde cada carbono opcionalmente se sustituye con (1) un heteroátomo seleccionado de entre átomos de N, S, P o Si que tiene una cantidad adecuada de hidrógenos y/o sustituciones para completar la valencia, (2) un cicloalquilo o cicloalquilo bicíclico opcionalmente sustituido, (3) un heterocicloalquilo o heterocicloalquilo opcionalmente sustituido, (4) un arilo o arilo bicíclico opcionalmente sustituido, o (5) heteroarilo o heteroarilo bicíclico opcionalmente sustituido, con la condición de que no haya enlaces heteroátomo-heteroátomo.

8. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el L es:



donde:

cada uno de W^{L1} y W^{L2} de manera independiente está ausente o es un anillo de 4-8 miembros con 0-4 heteroátomos opcionalmente sustituido con R^Q ;

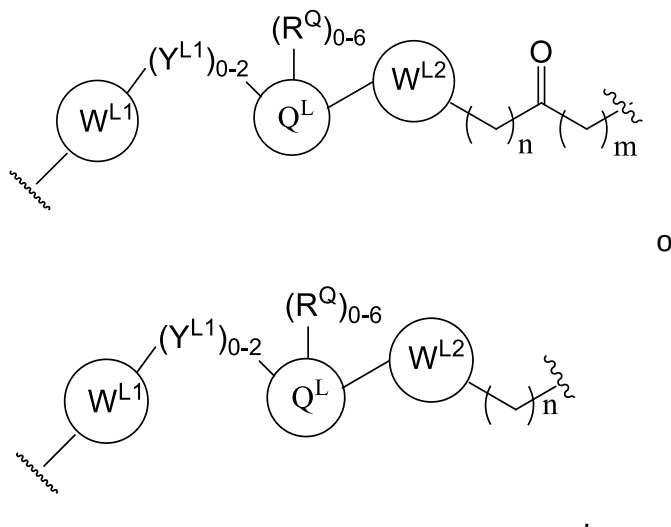
cada R^Q es de manera independiente H, halo, OH, CN, alquilo C_{1-6} opcionalmente sustituido, alcoxi C_{1-6} opcionalmente sustituido, o 2 R^Q tomados junto con el átomo al que se unen forman un sistema de anillo de 4-8 miembros que contiene 0-4 heteroátomos;

cada Y^{L1} es de manera independiente un enlace o alquilo C_{1-6} opcionalmente sustituido, en donde uno o más átomos de C se remplazan opcionalmente con O;

m y n son independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y

 indica el punto de unión al PTM o al ULM.

9. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el L es:



en donde:

cada uno de W^{L1} y W^{L2} de manera independiente está ausente o es arilo, heteroarilo, cíclico, heterocíclico, alquilo C_{1-6} , en donde uno o más átomos de C se remplazan opcionalmente con O o N, alquenilo C_{1-6} , en donde uno o más átomos de C se remplazan opcionalmente con O, alquinilo C_{1-6} , en donde uno o más átomos de C se remplazan opcionalmente con O, bicíclico, biarilo, biheteroarilo o biheterocíclico, cada uno opcionalmente sustituido con R^Q ;

cada R^Q es de manera independiente H, halo, OH, CN, CF_3 , hidroxilo, nitro, $C\equiv CH$, alquenilo C_{2-6} , alquinilo C_{2-6} , alquilo C_{1-6} opcionalmente sustituido, alcoxi C_{1-6} opcionalmente sustituido, Oalquilo C_{1-3} opcionalmente sustituido, OH, NH_2 , $NR^{Y1}R^{Y2}$, o CN, o 2 R^Q , tomados junto con el átomo al que se unen, forman un sistema de anillo de 4-8 miembros que contiene 0-4 heteroátomos;

cada Y^{L1} es de manera independiente un enlace, NR^{YL1} , O, S, NR^{YL2} , $CR^{YL1}R^{YL2}$, $C=O$, $C=S$, SO , SO_2 , alquilo C_{1-6} opcionalmente sustituido, en donde uno o más átomos de C se remplazan opcionalmente con O, o anillo alicíclico o aromático de 3-6 miembros con 0-4 heteroátomos;

Q^L es anillo alicíclico o aromático de 3-6 miembros con 0-4 heteroátomos, opcionalmente con puente, opcionalmente sustituido con 0-6 R^Q;

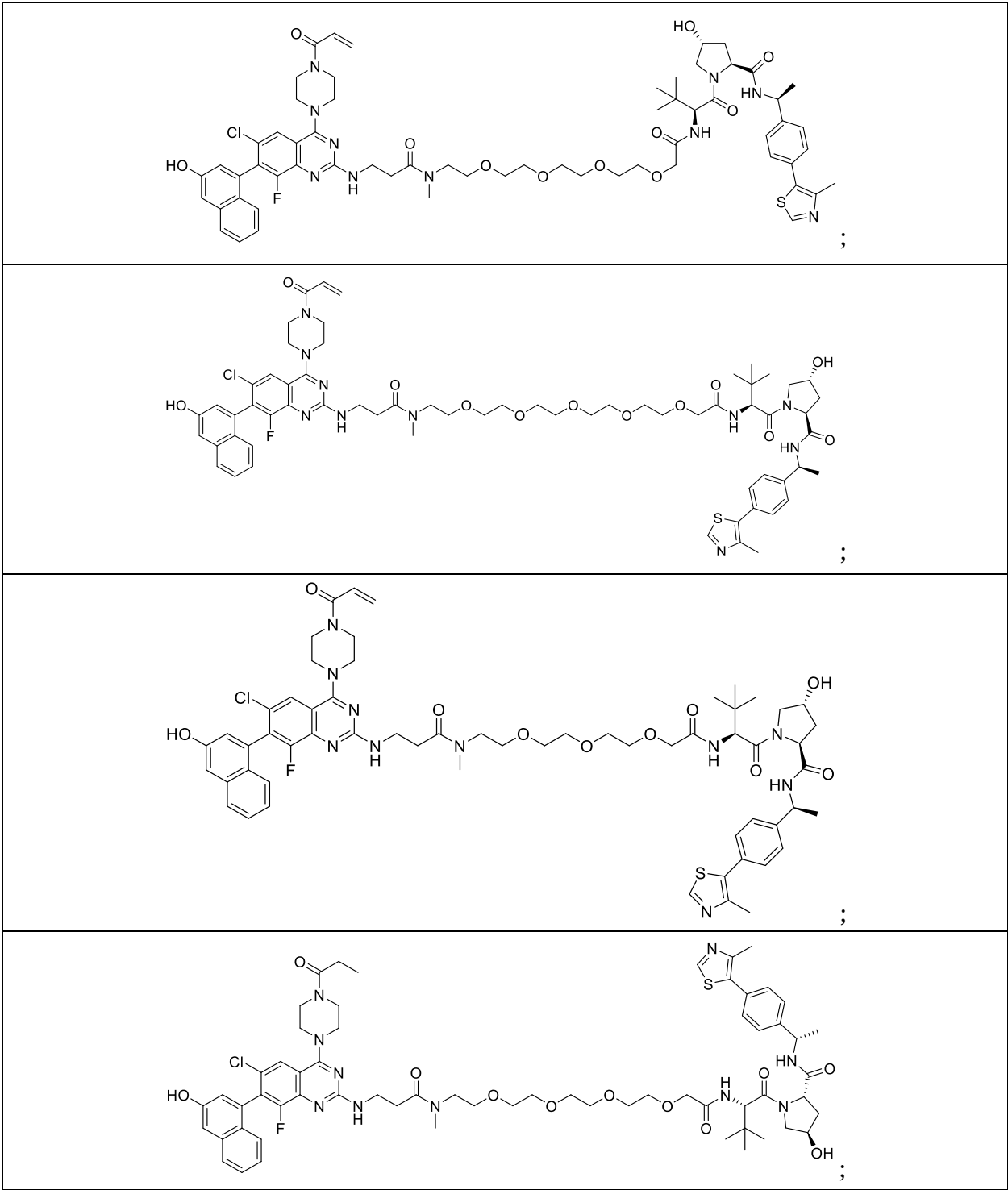
cada R^Q es de manera independiente H, alquilo C₁₋₆ opcionalmente sustituido, o 2 R^Q, tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

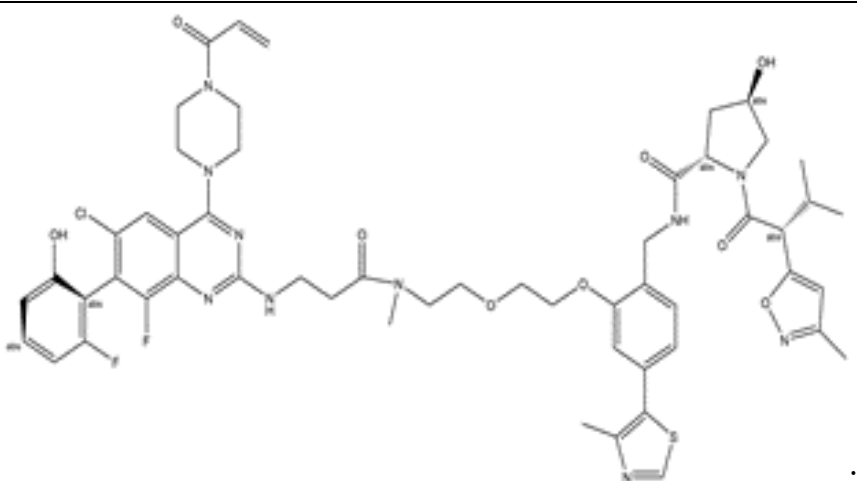
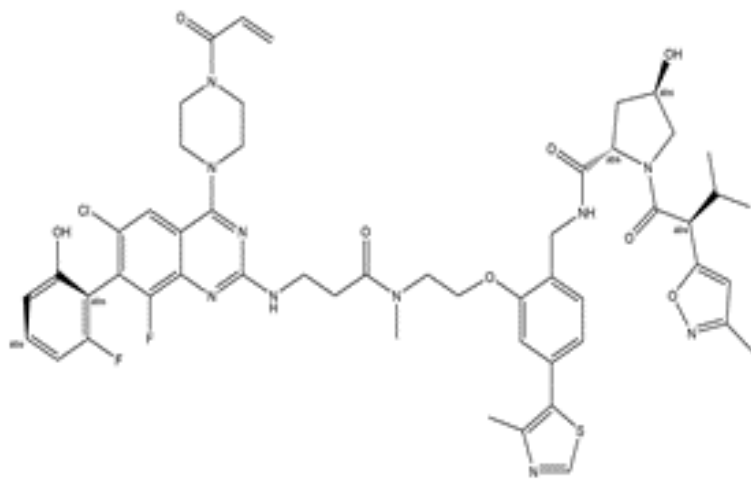
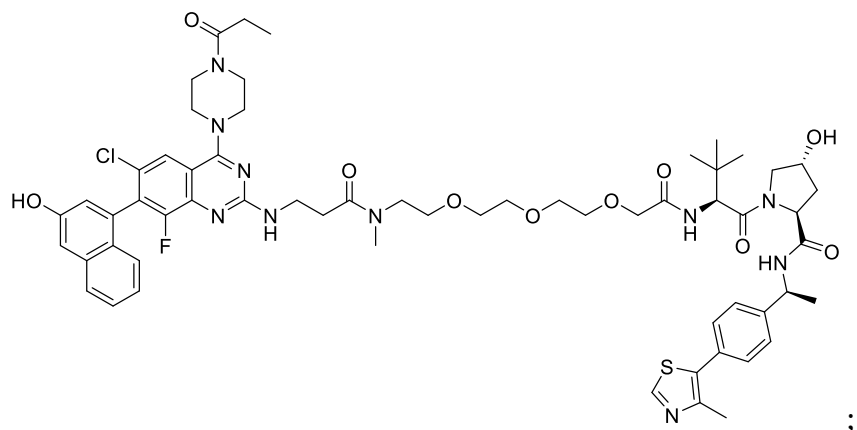
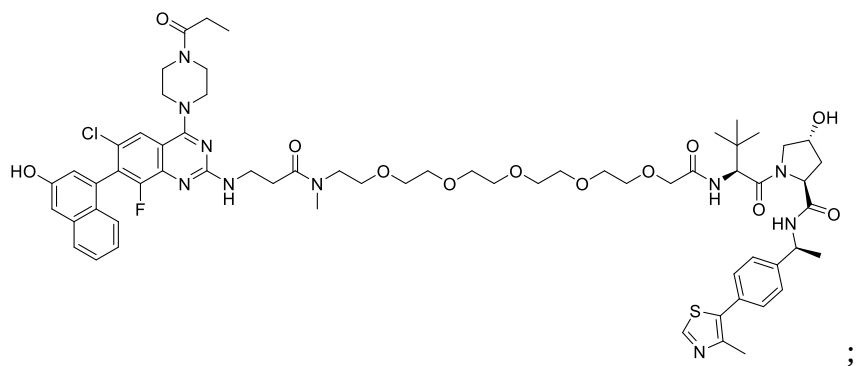
R^{YL1} y R^{YL2} son cada uno de manera independiente seleccionado de entre H, OH, y alquilo C₁₋₆ opcionalmente sustituido por 1 o más halo o alcoxi C₁₋₆, o R¹ y R² tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

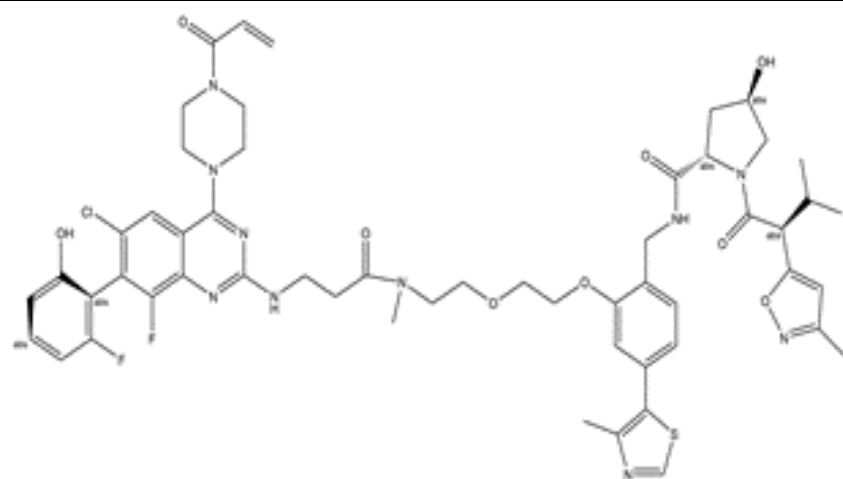
m y n son cada uno independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y

 indica el punto de unión al PTM o al ULM.

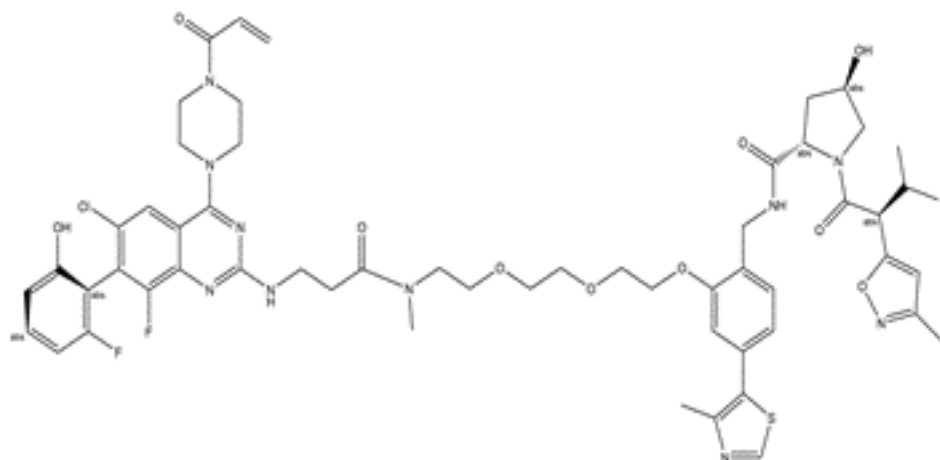
10. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, en donde el compuesto es seleccionado de entre:



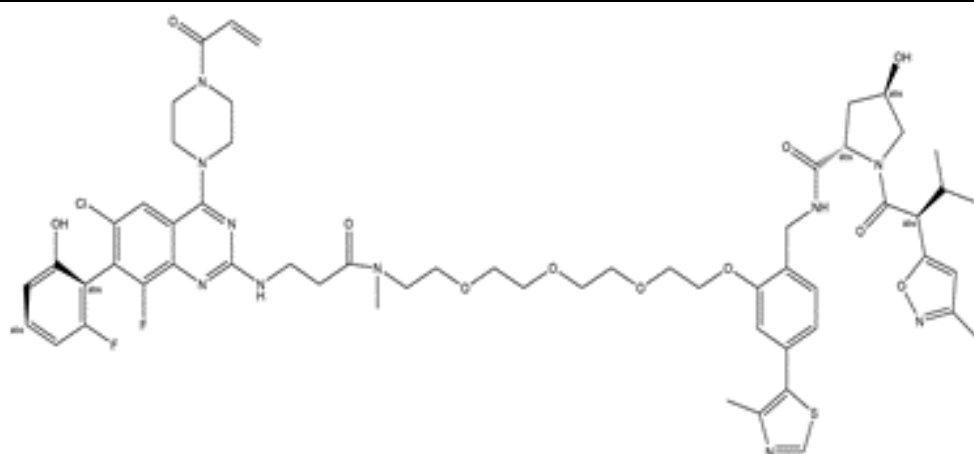




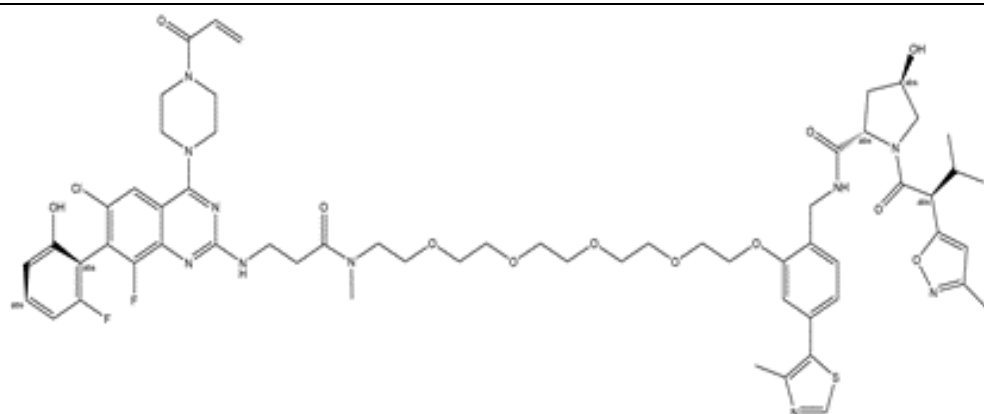
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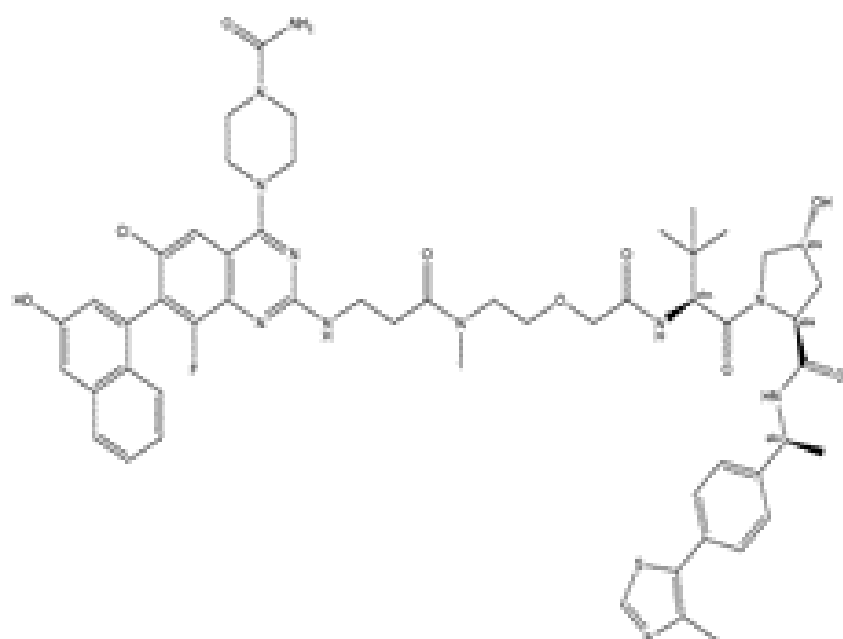
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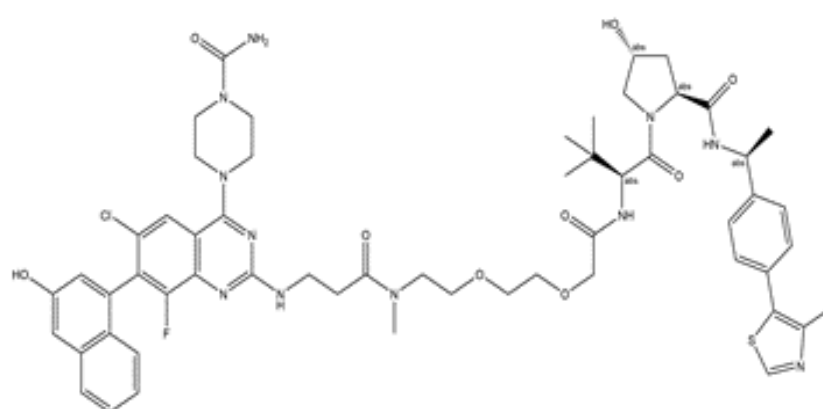
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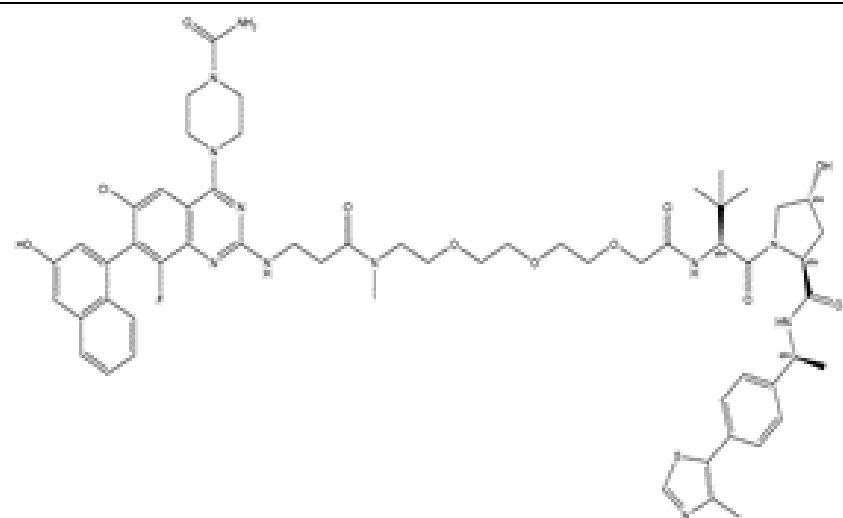
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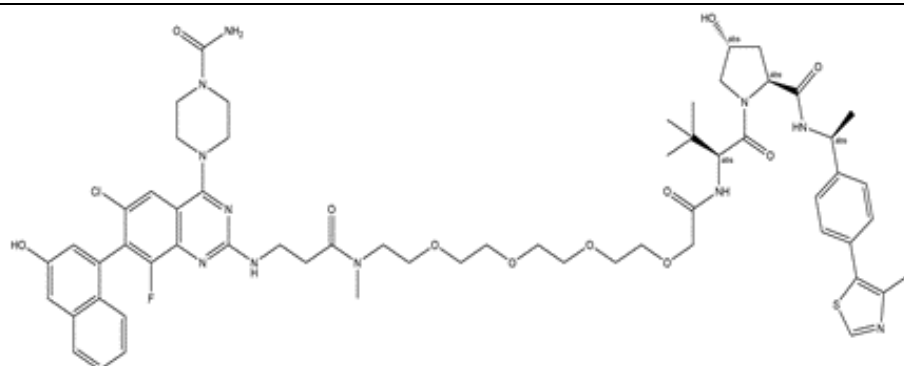
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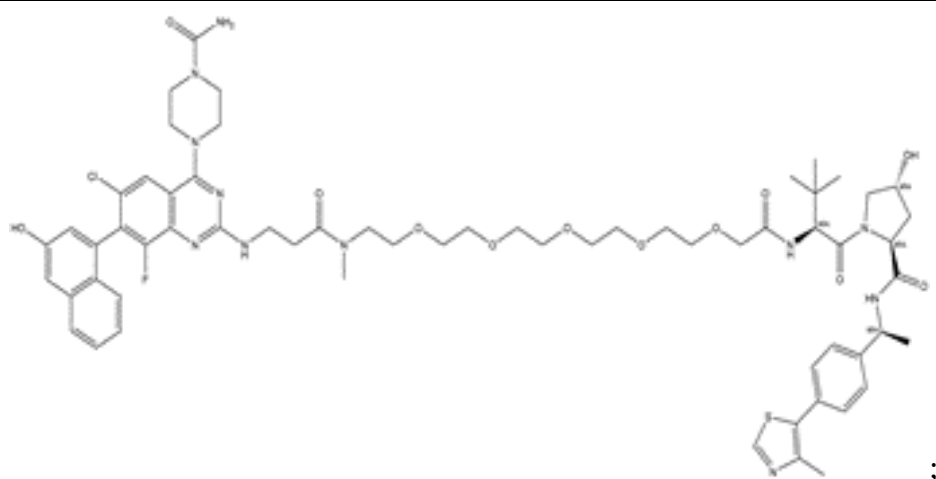
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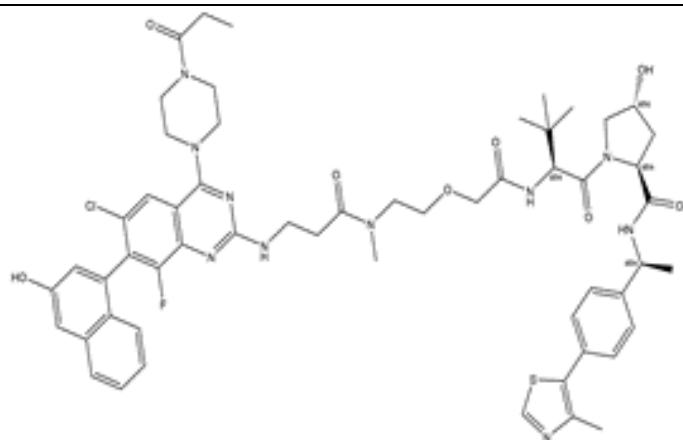
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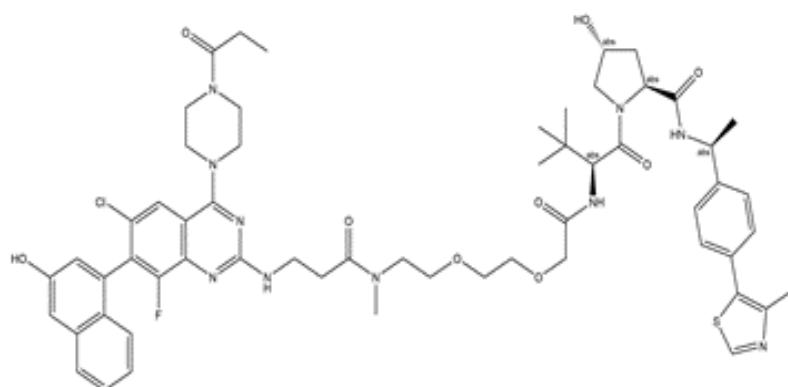
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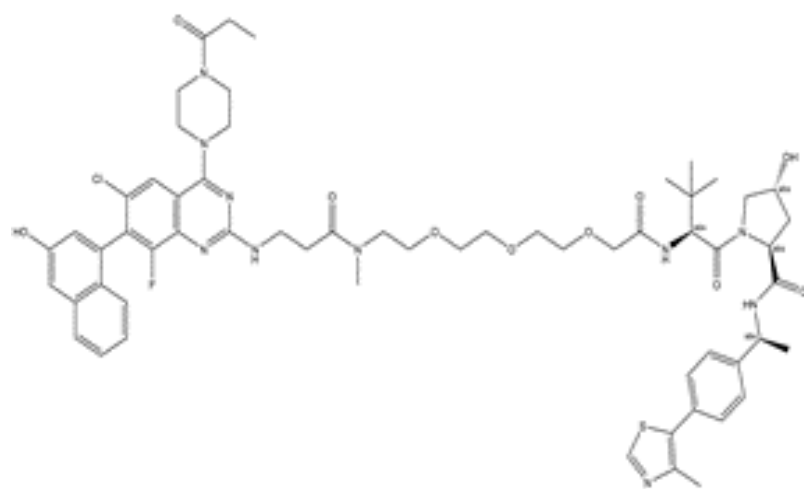
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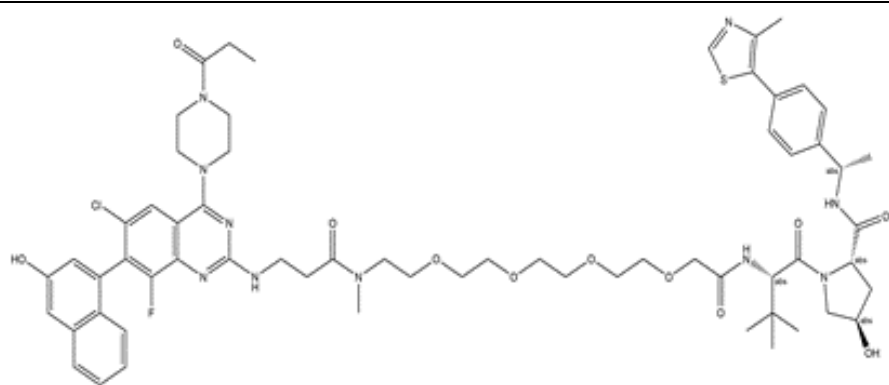
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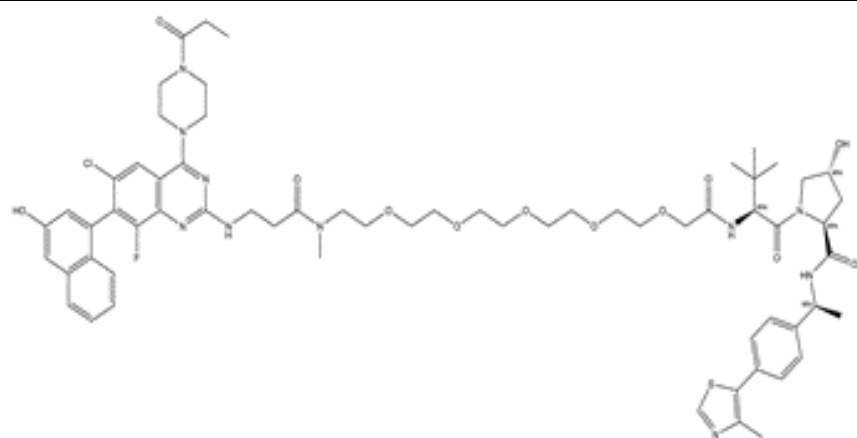
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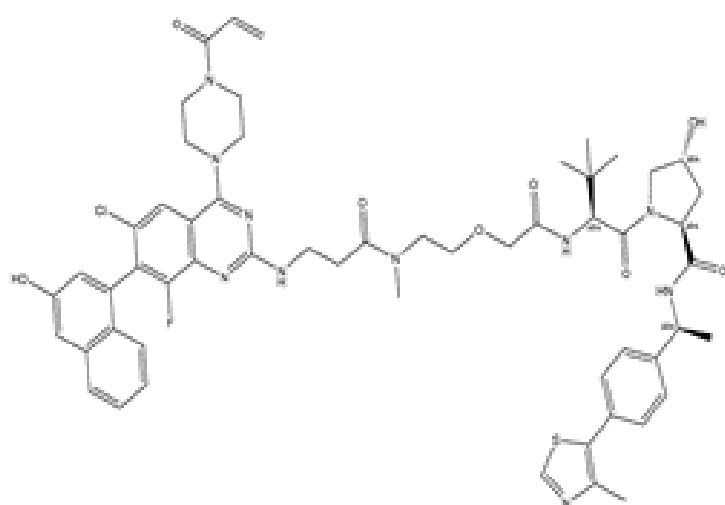
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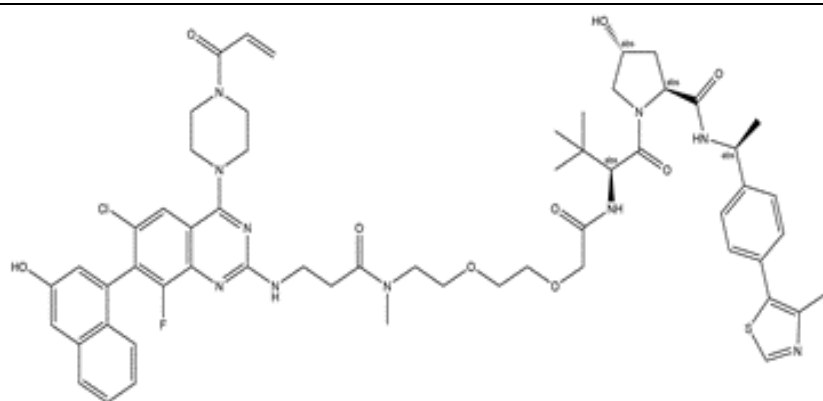
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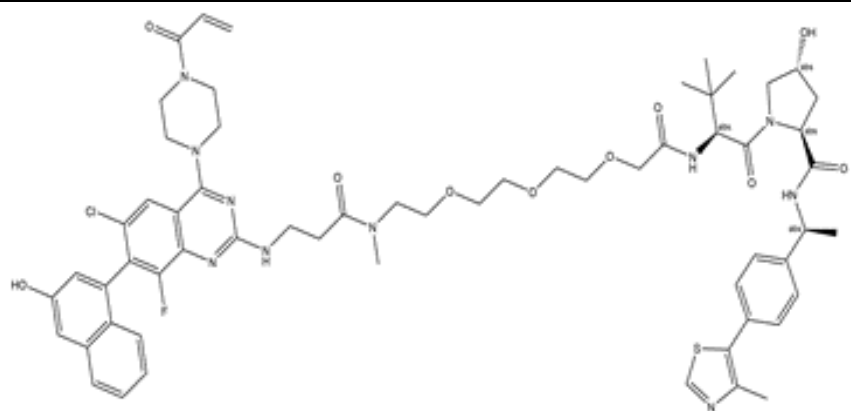
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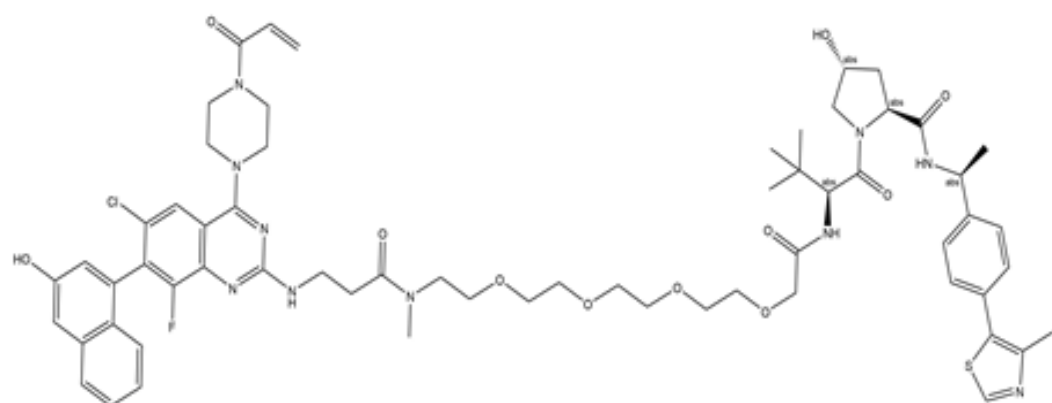
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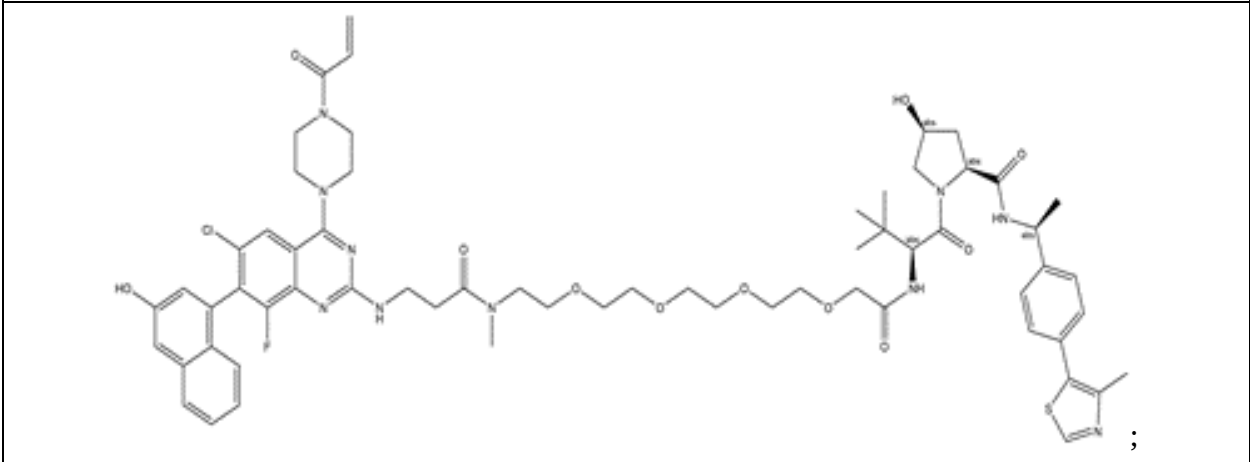
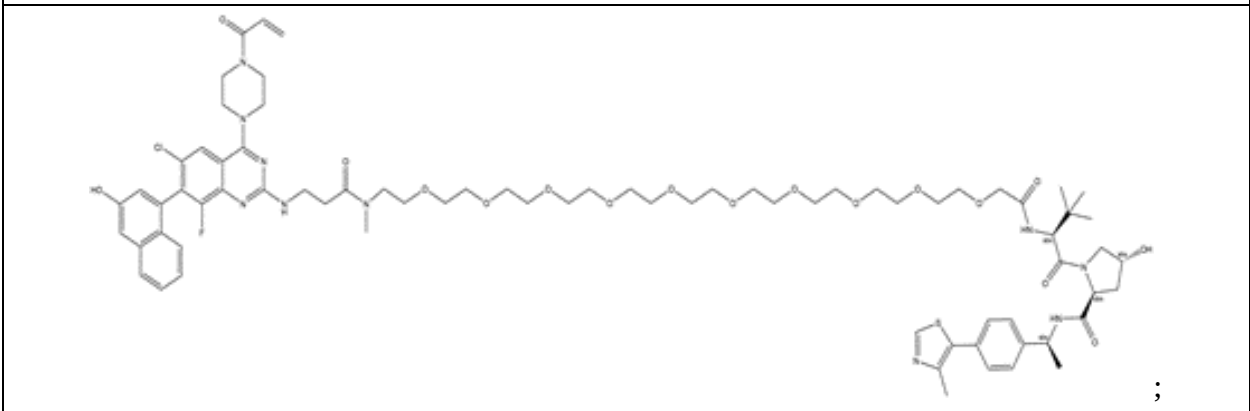
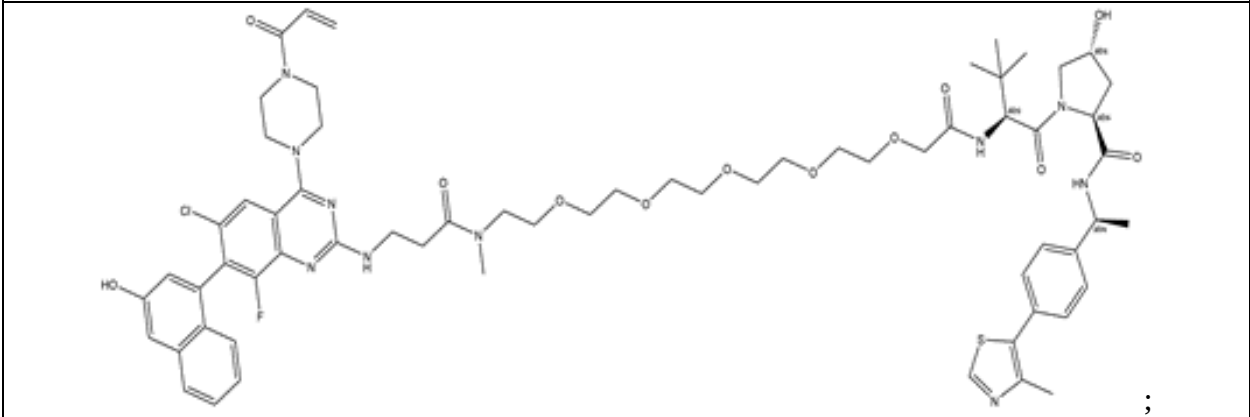
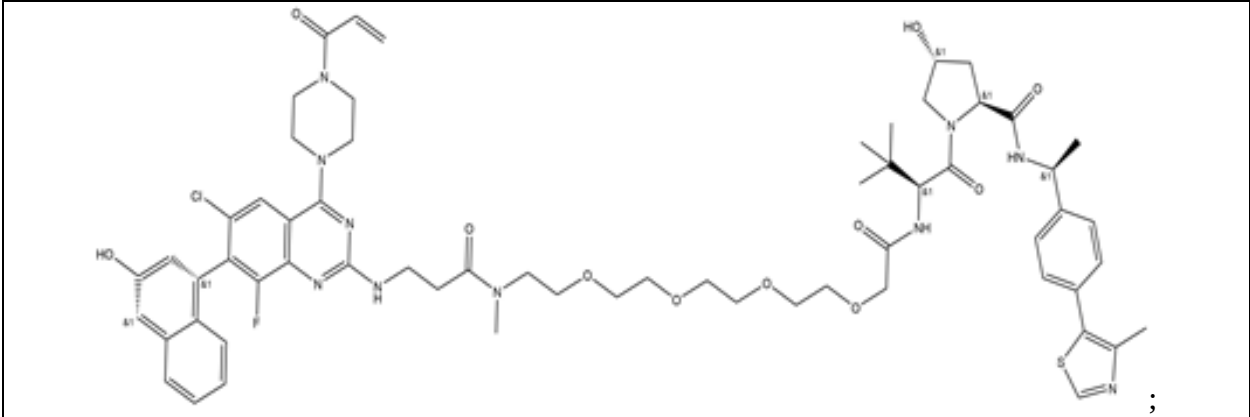
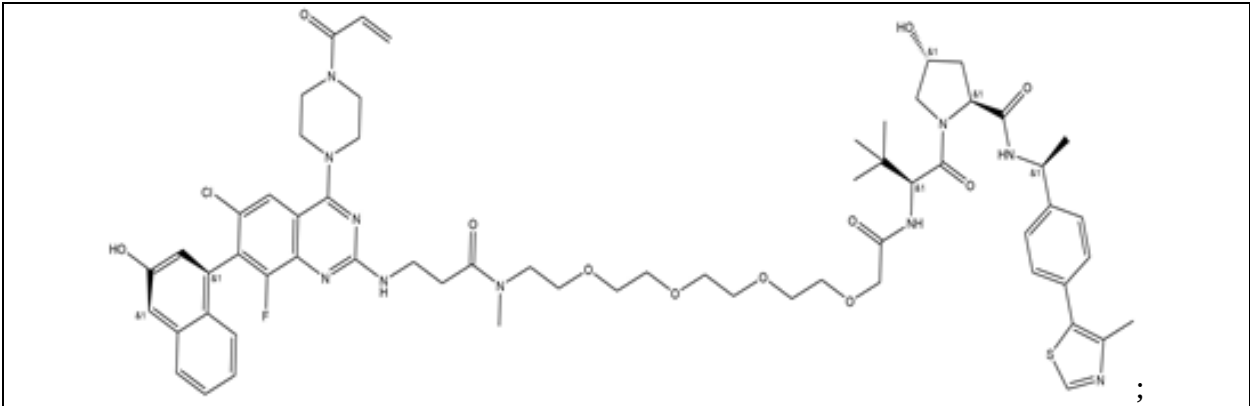
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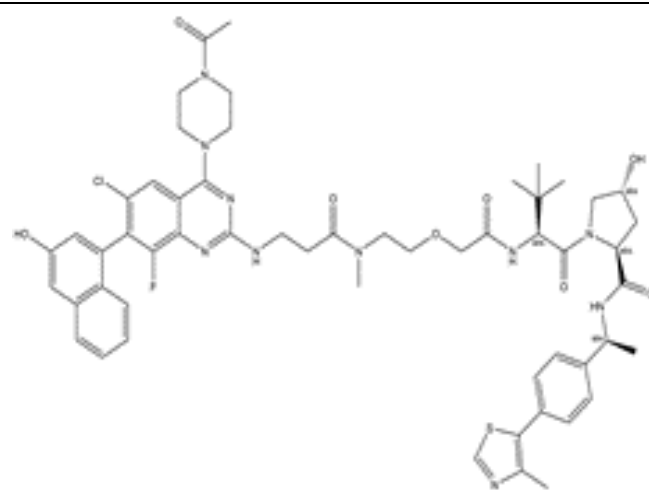


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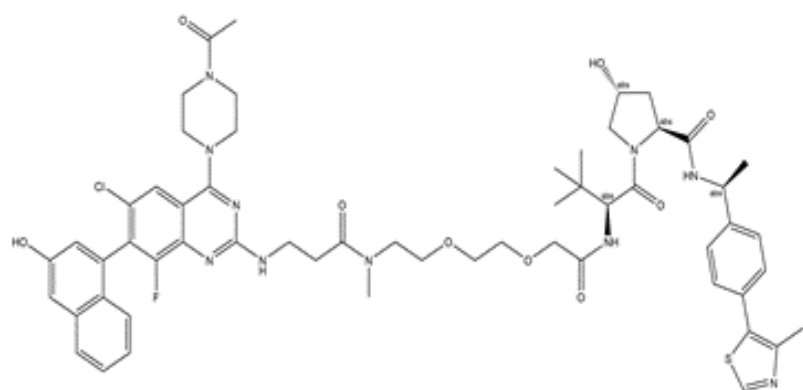


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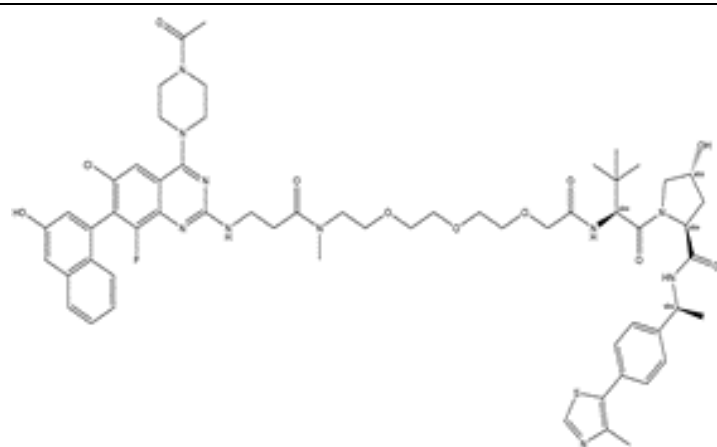




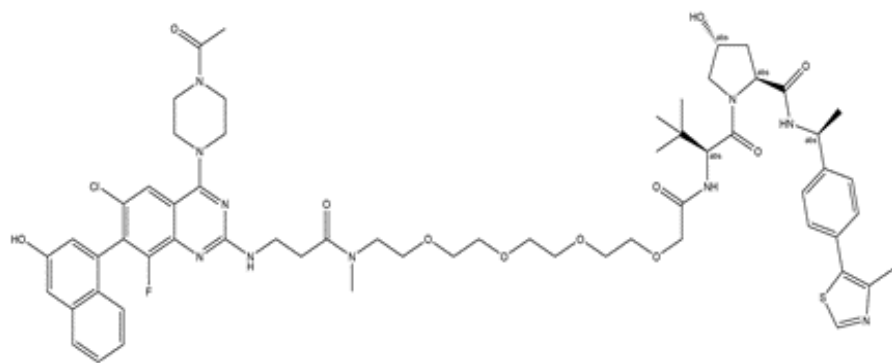
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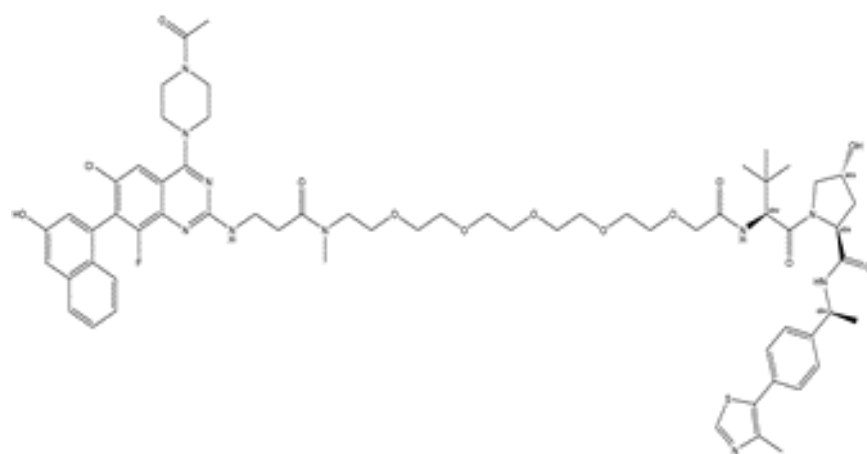
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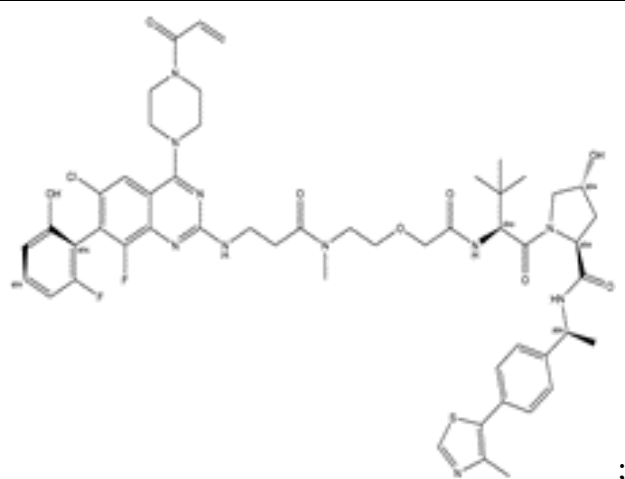
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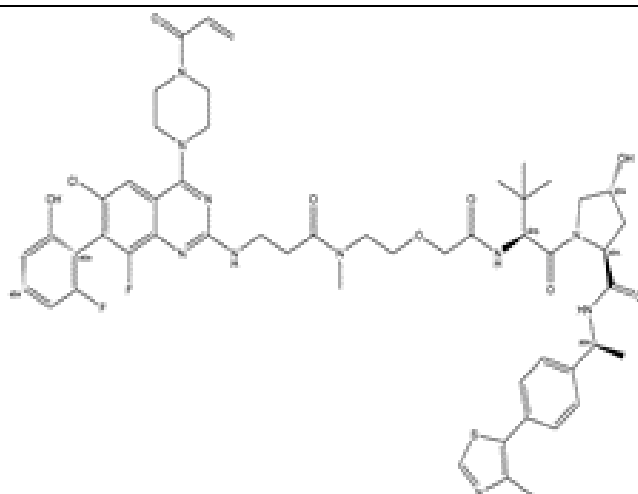
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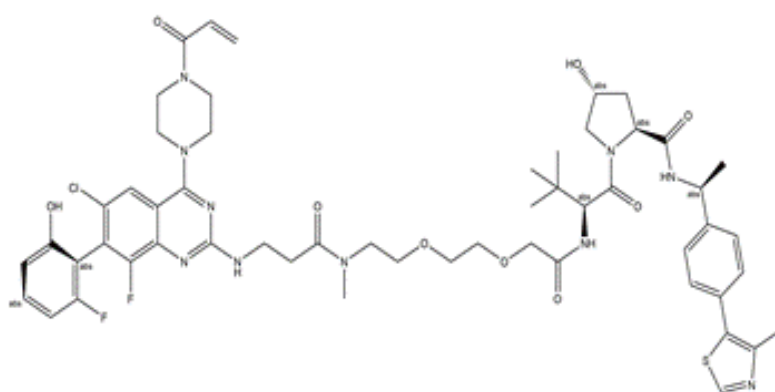
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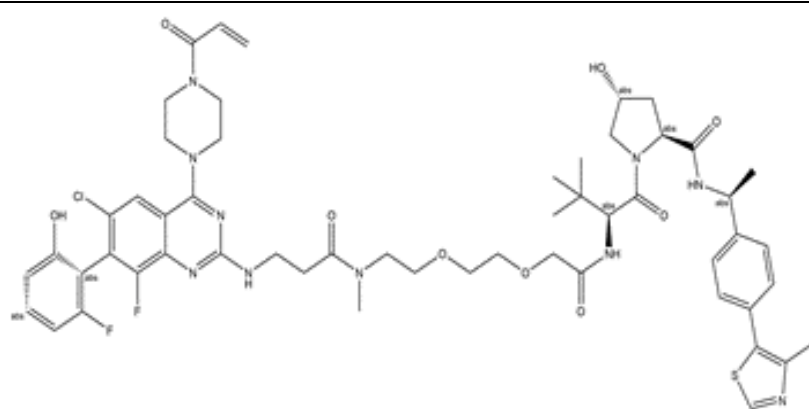
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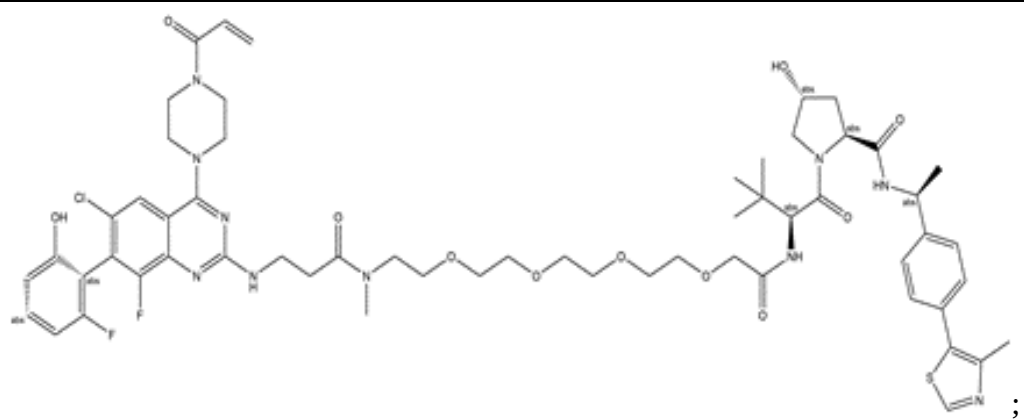
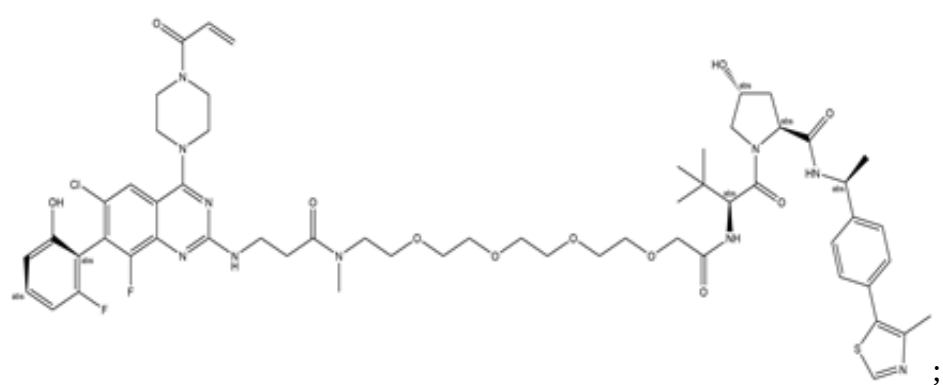
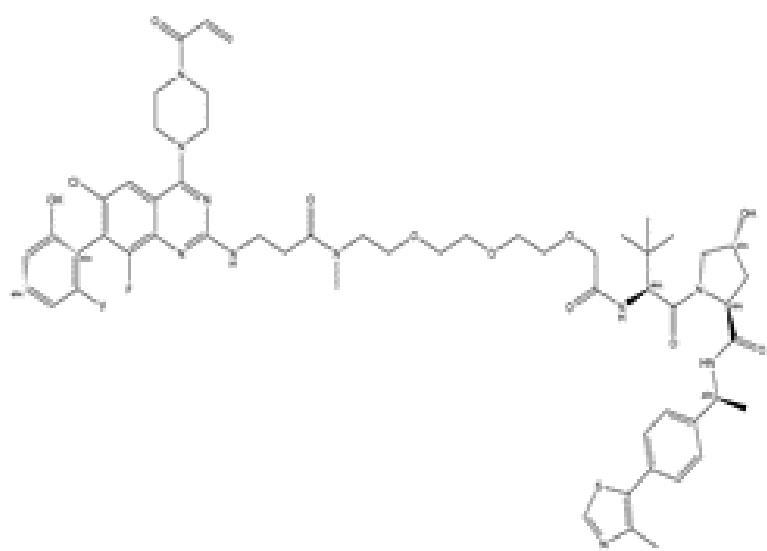
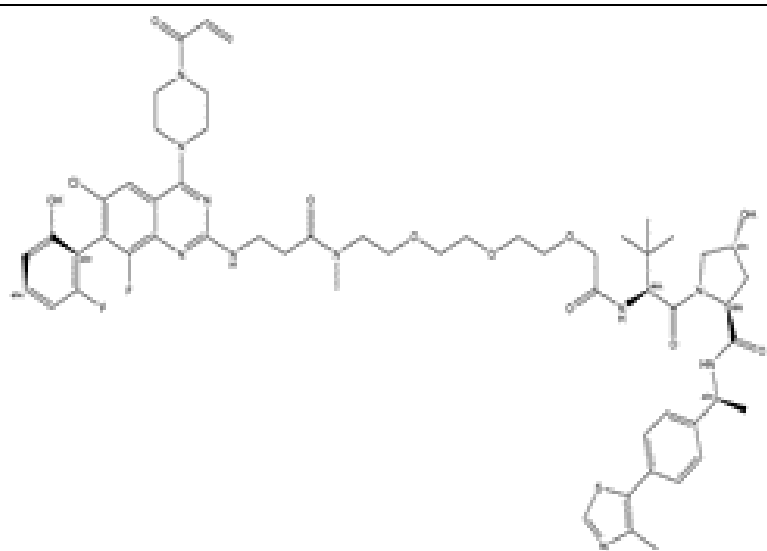
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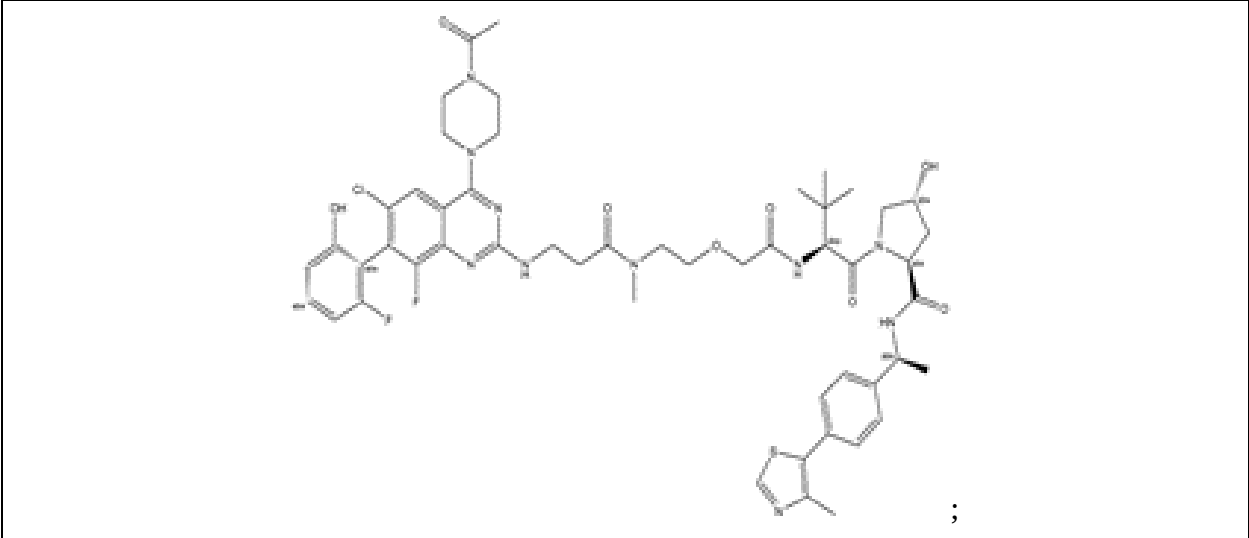
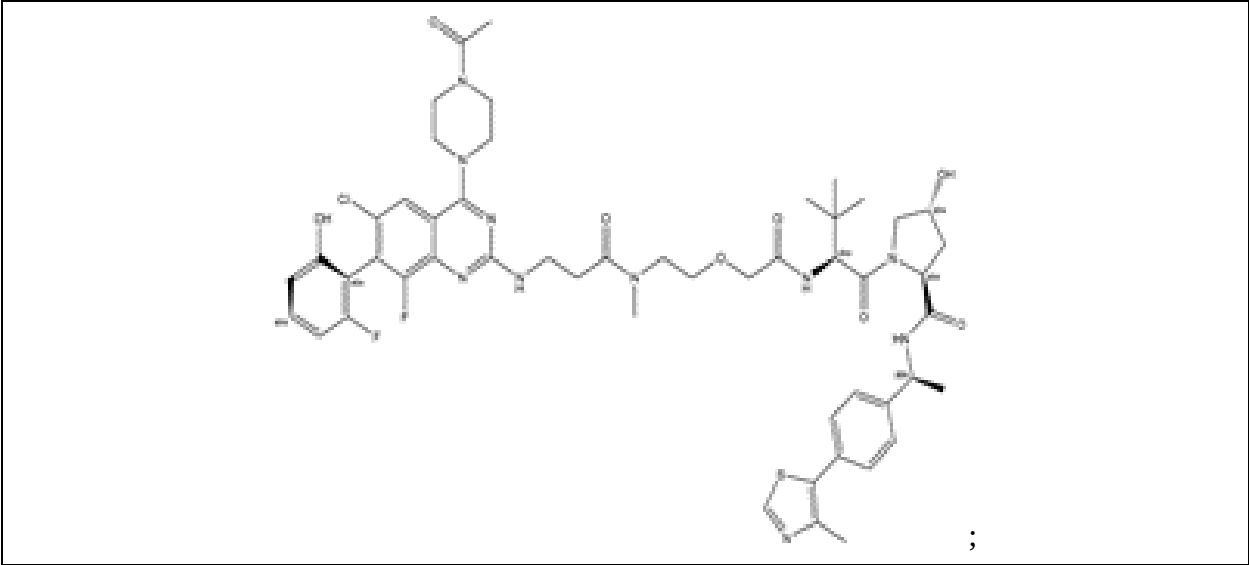
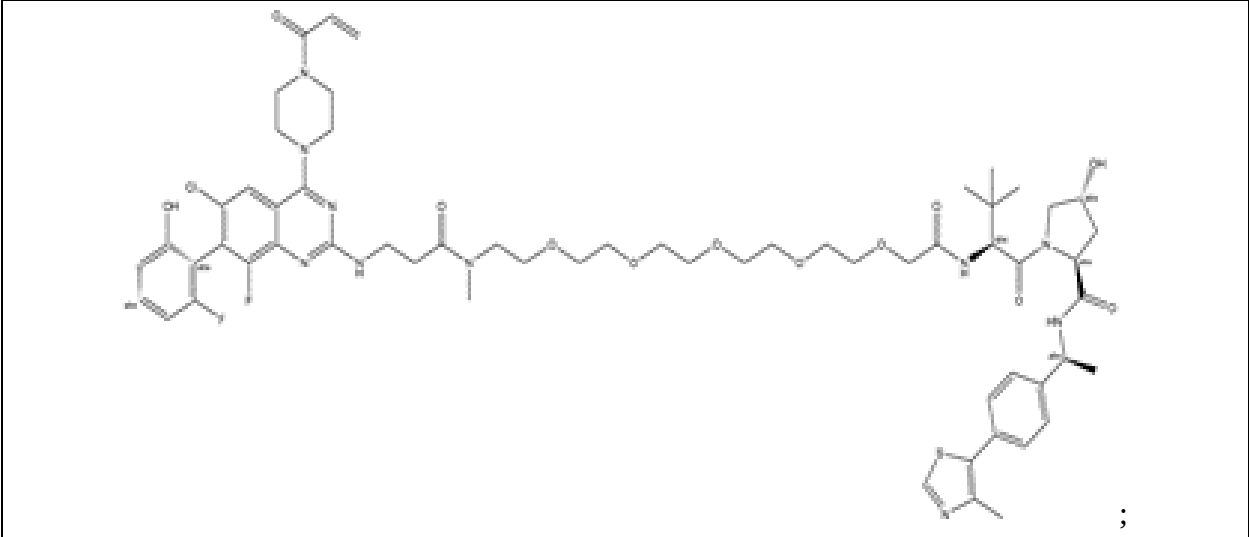
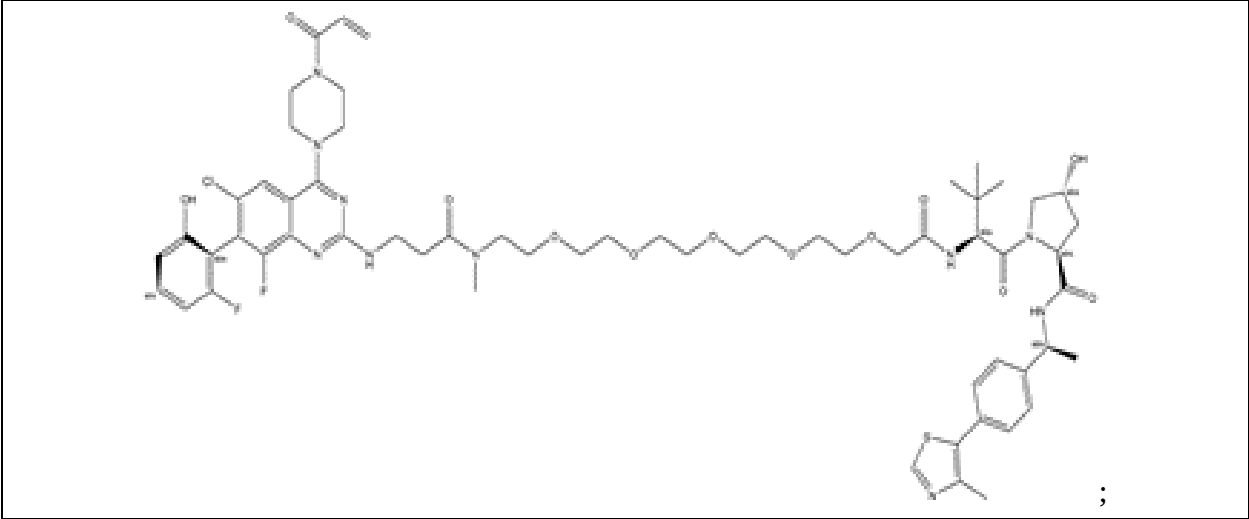


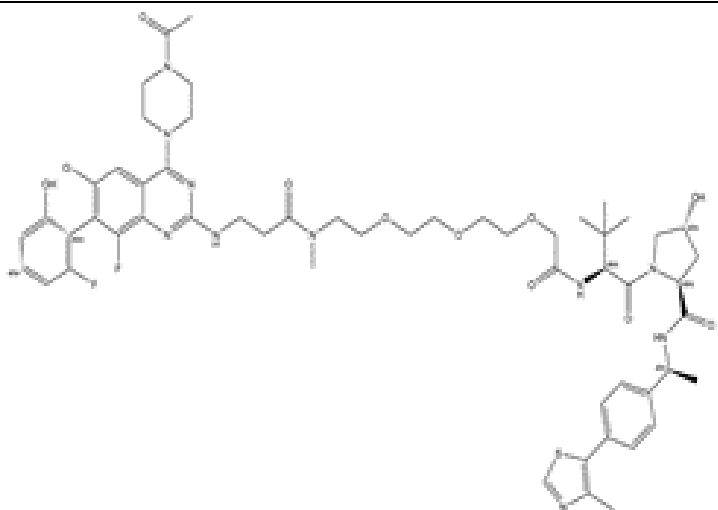
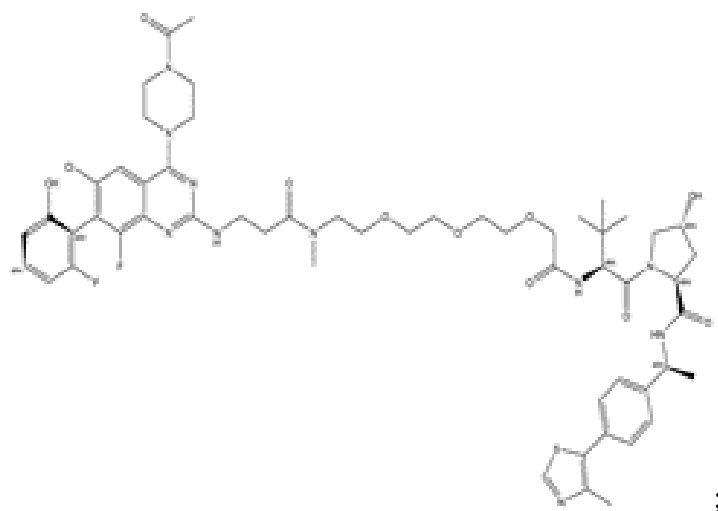
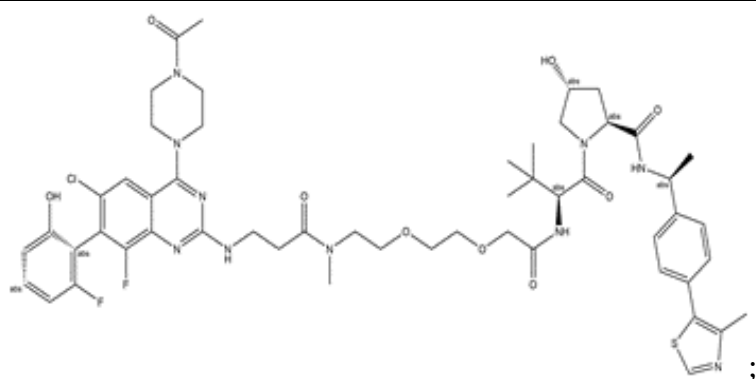
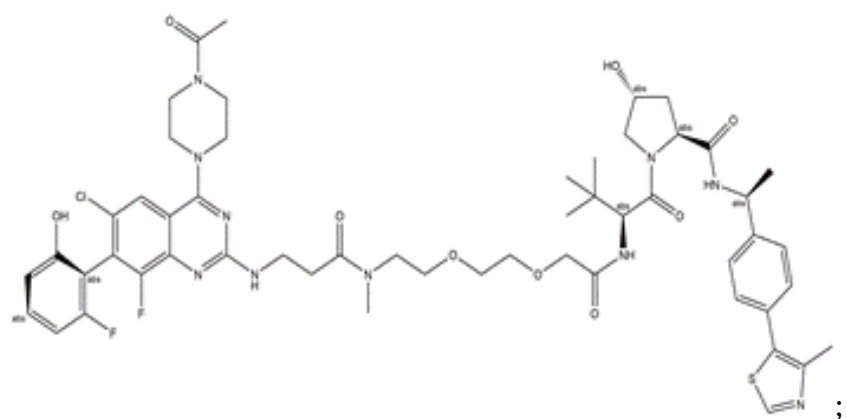
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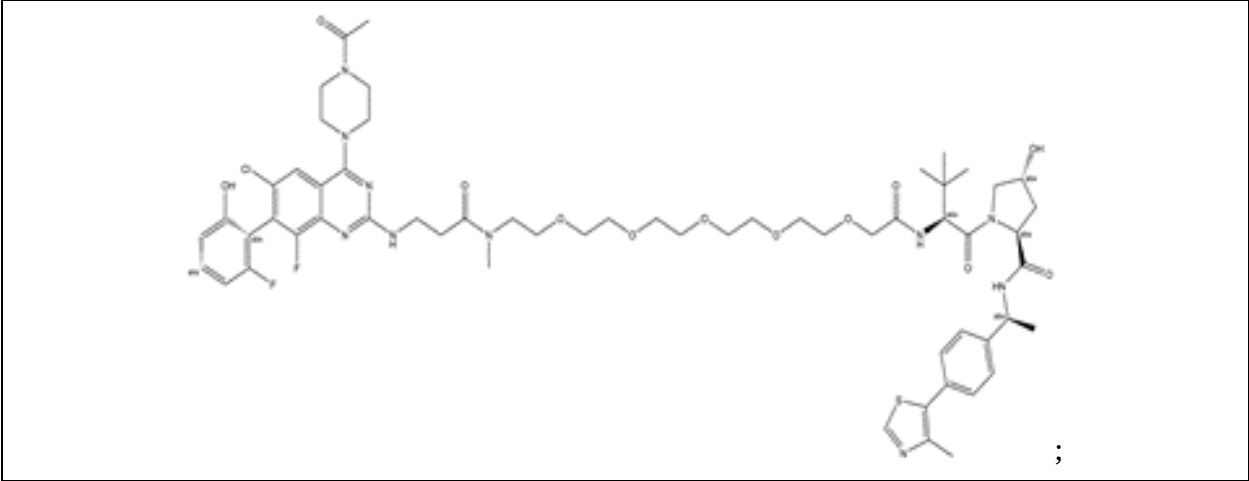
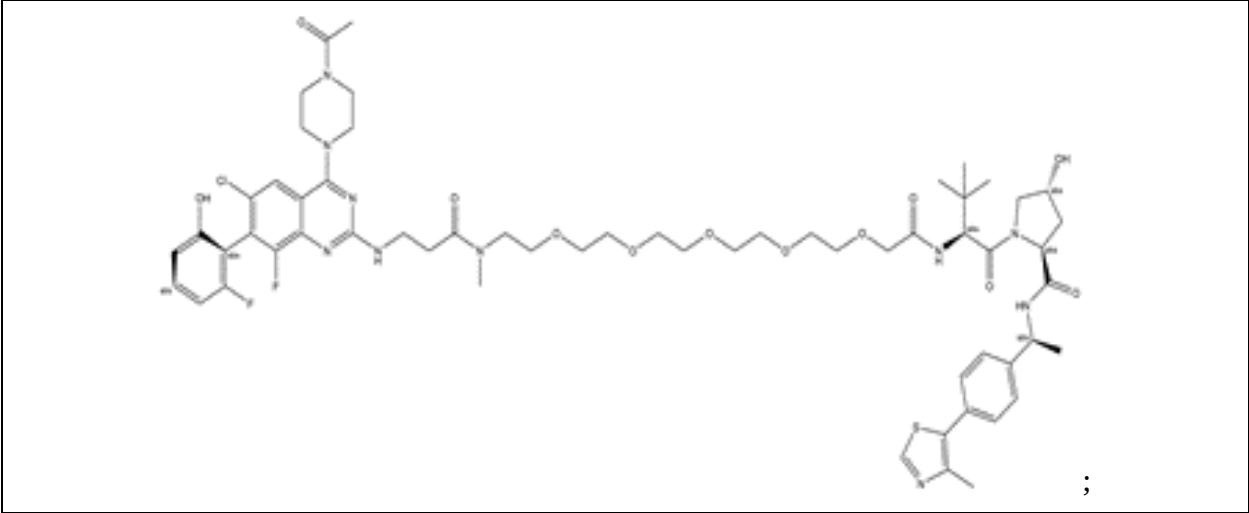
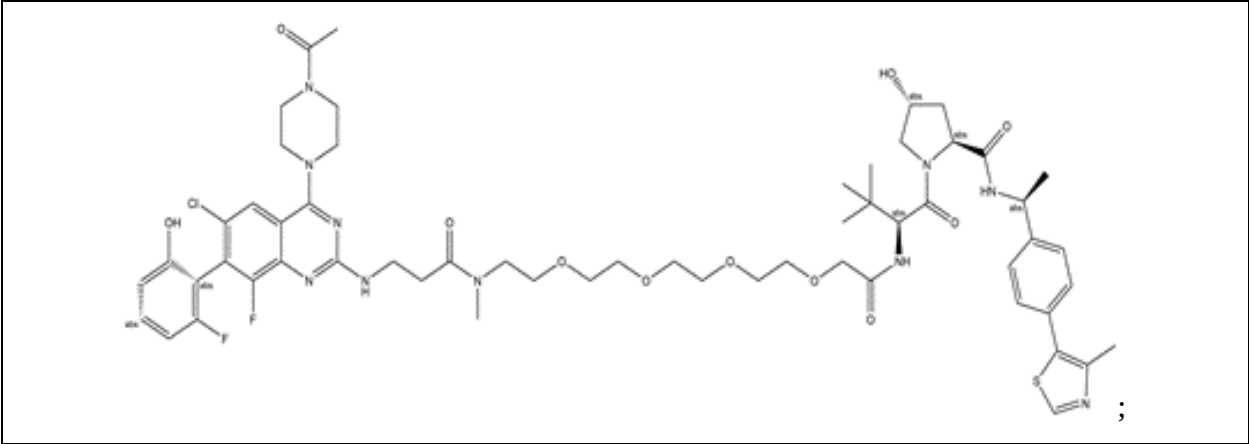
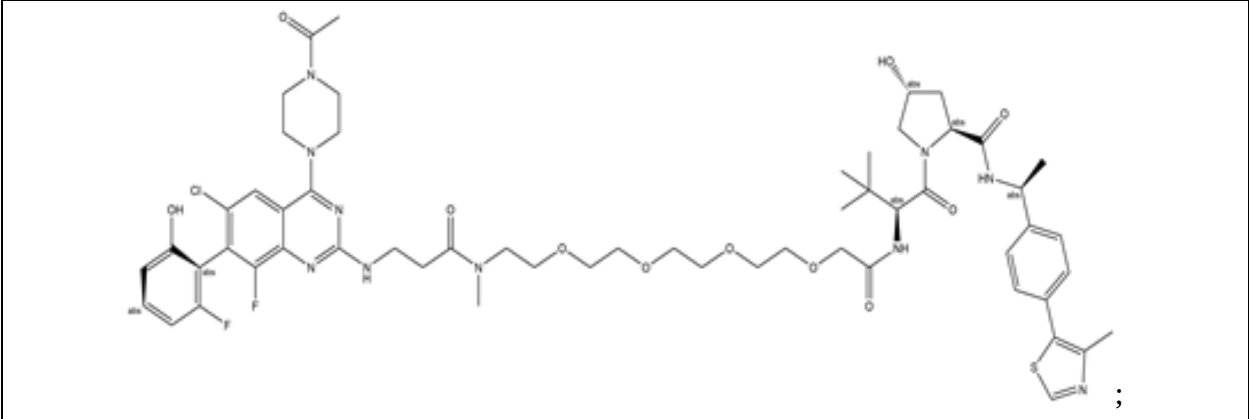


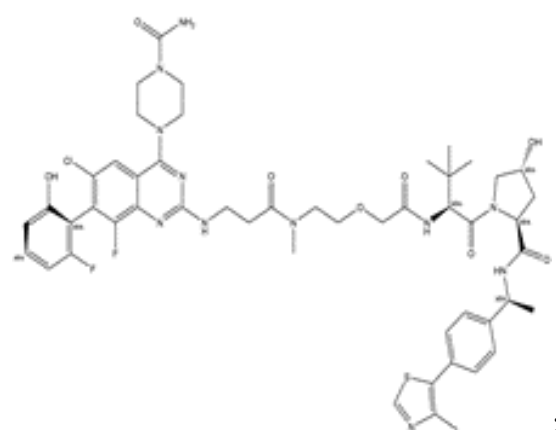
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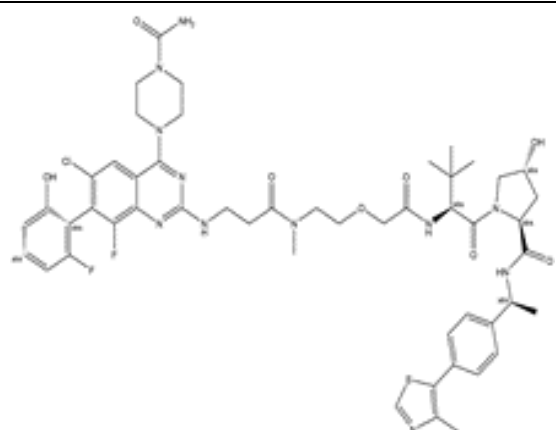




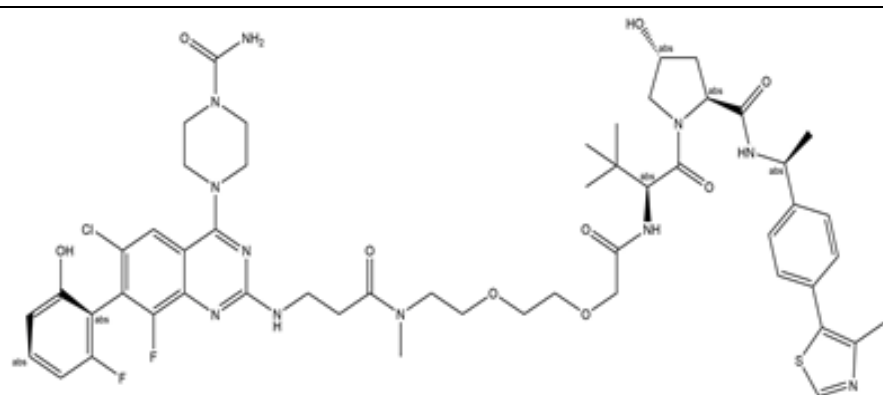




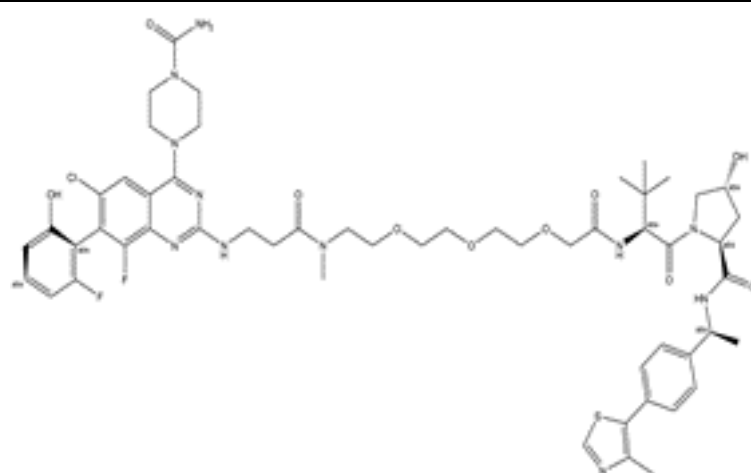
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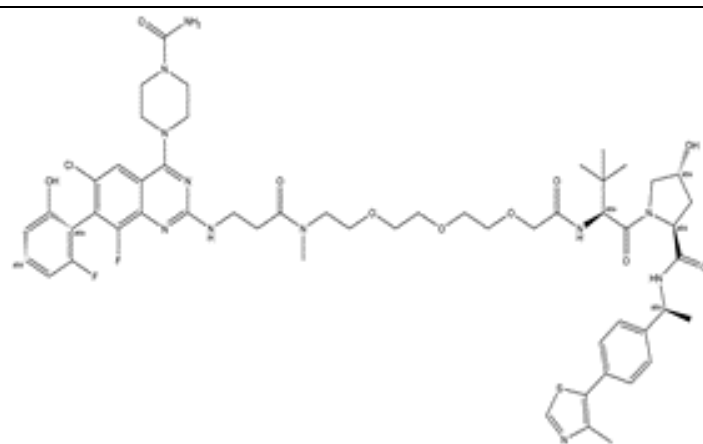
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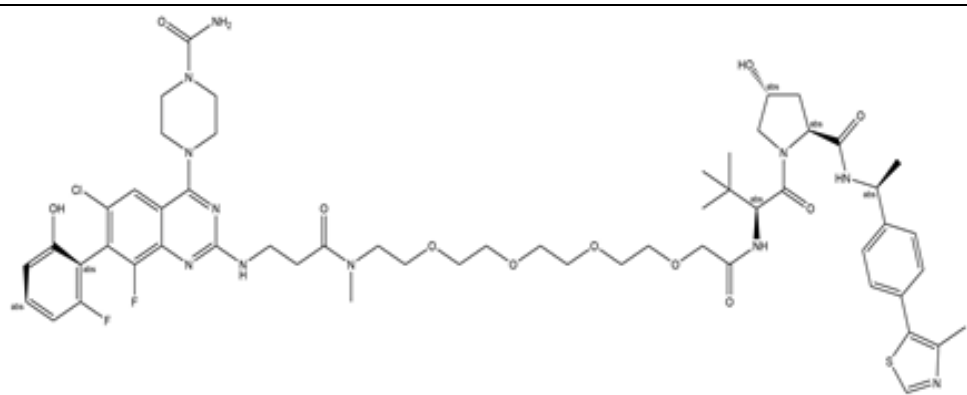
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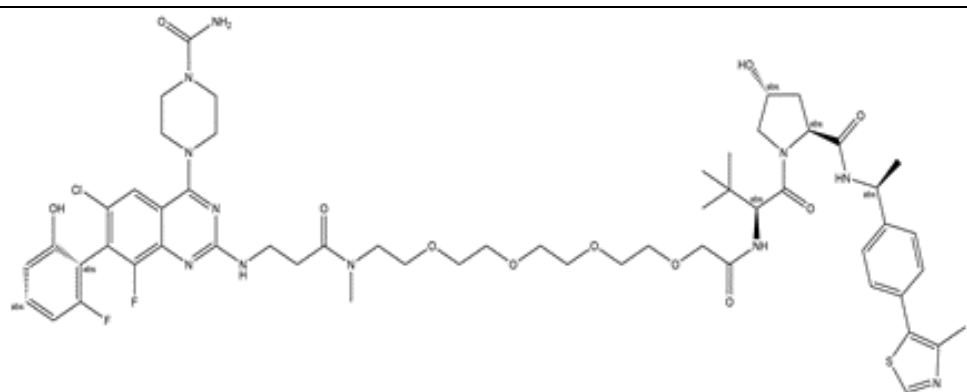
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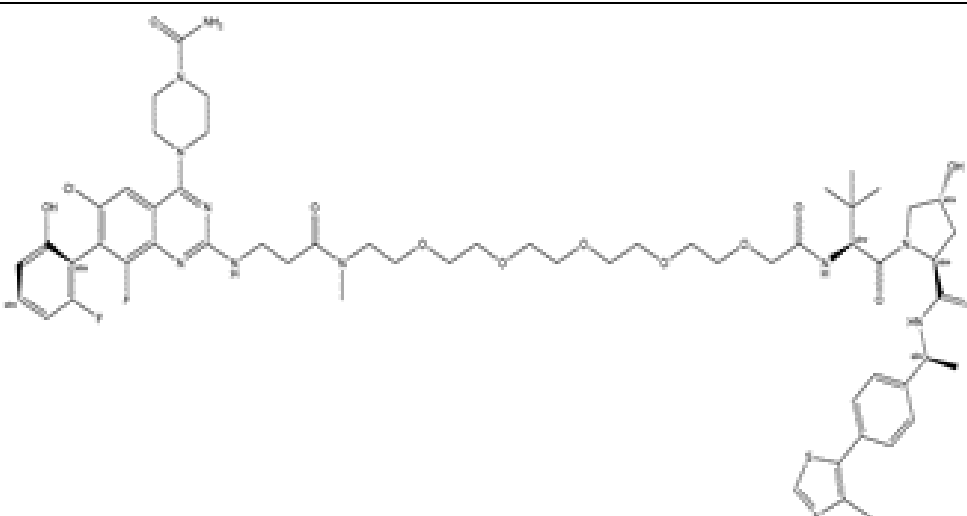
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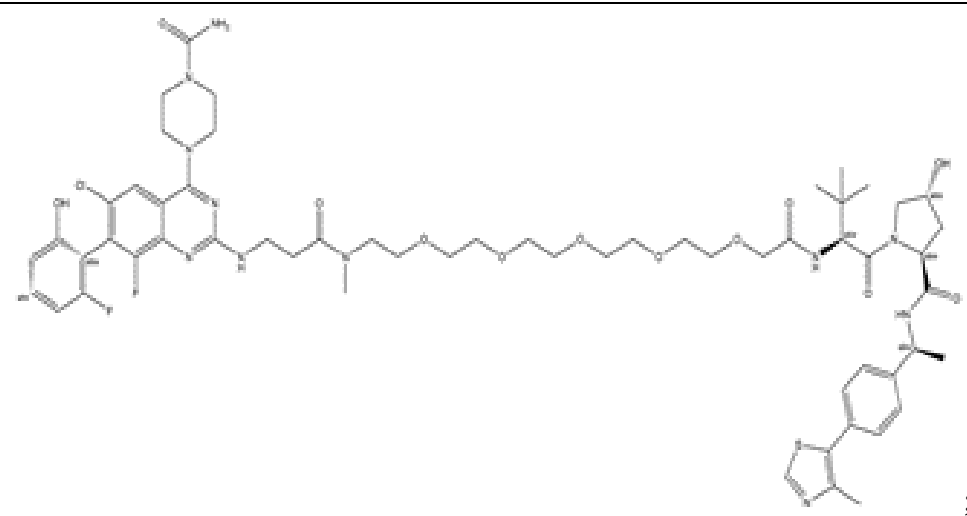
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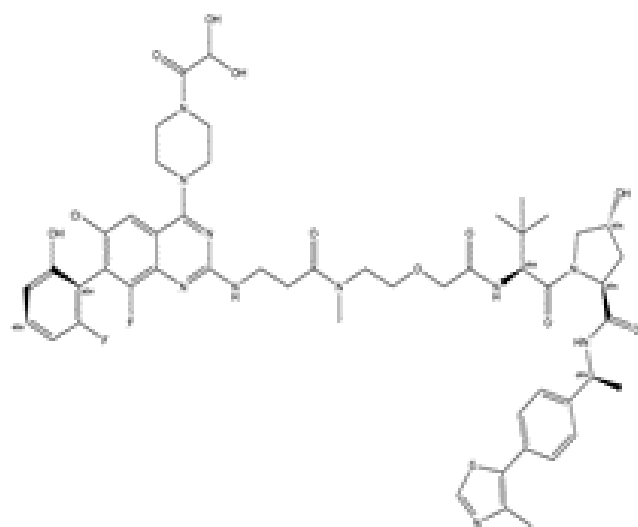
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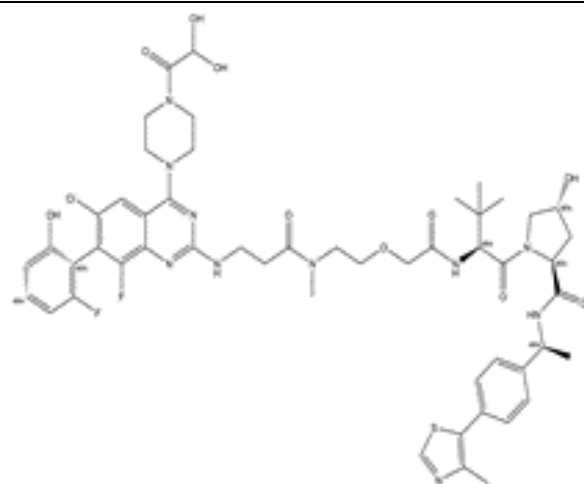
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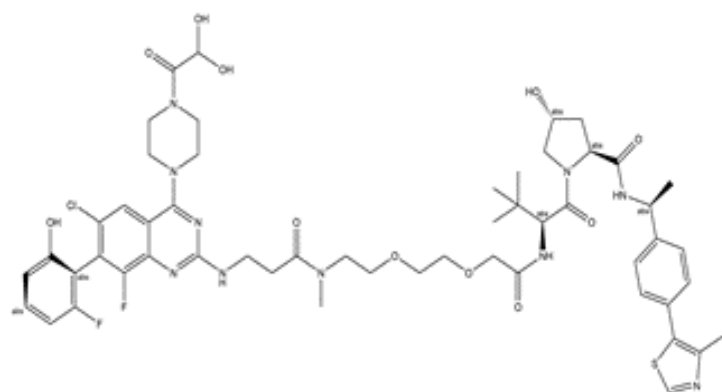
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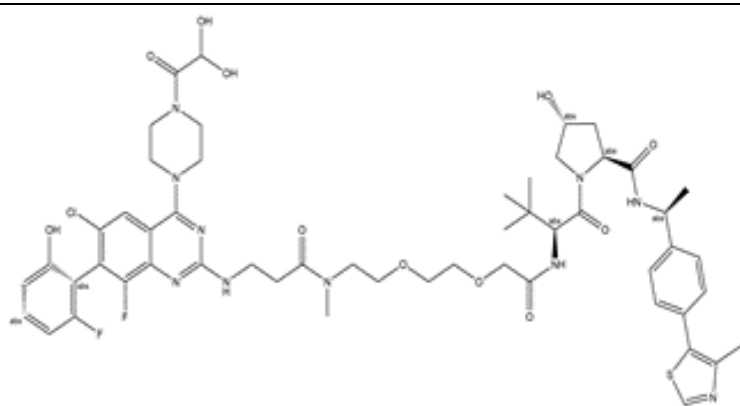
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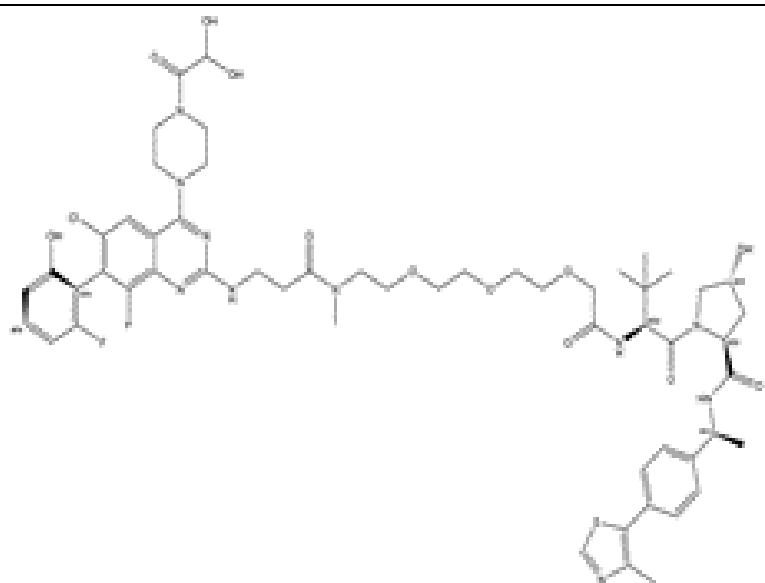
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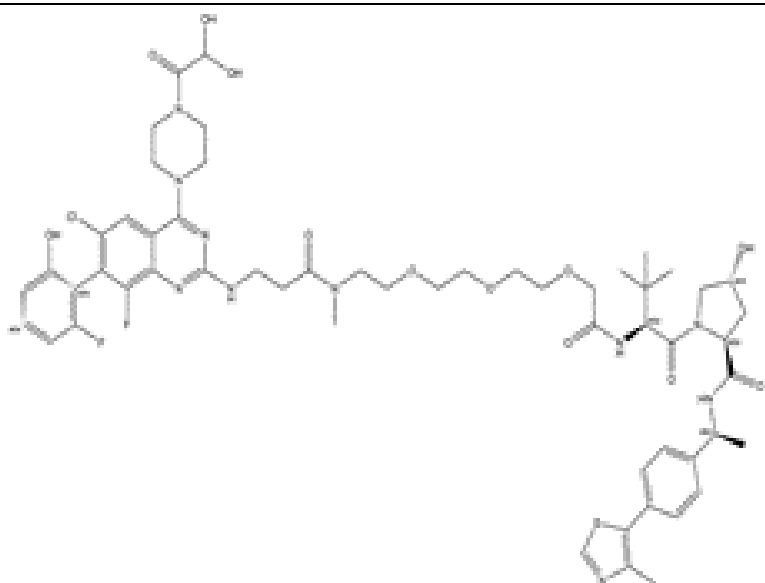
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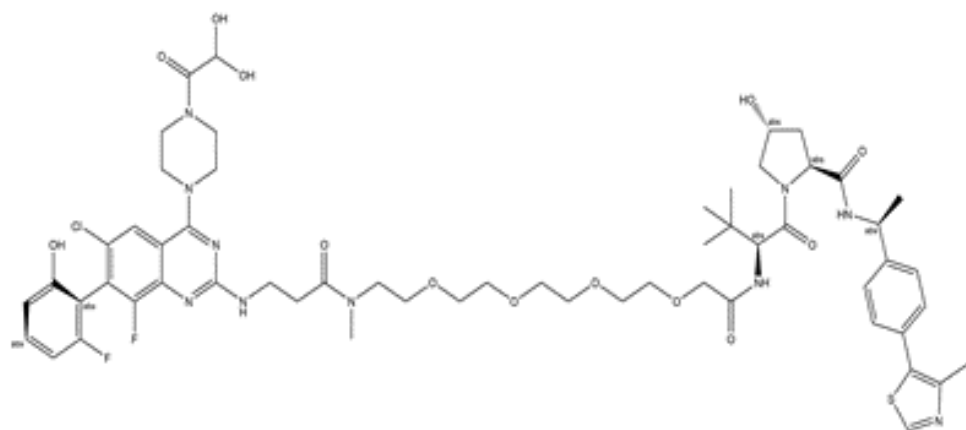
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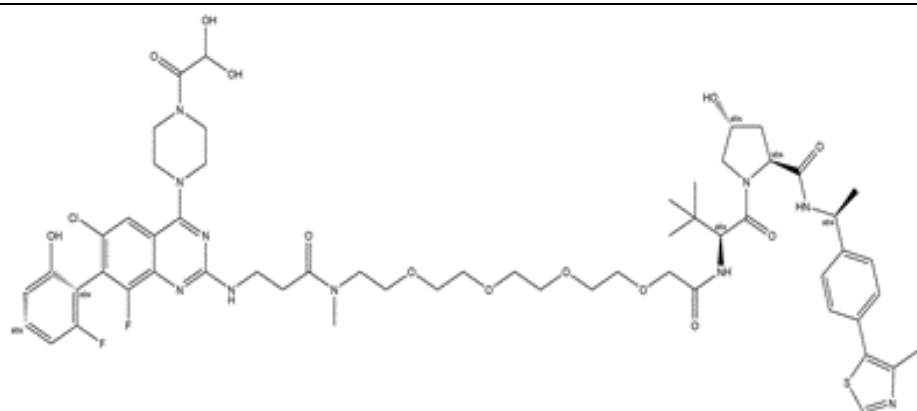
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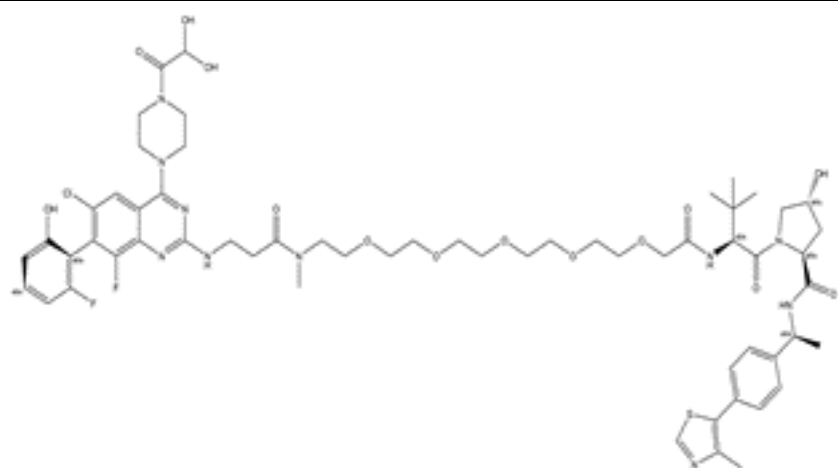
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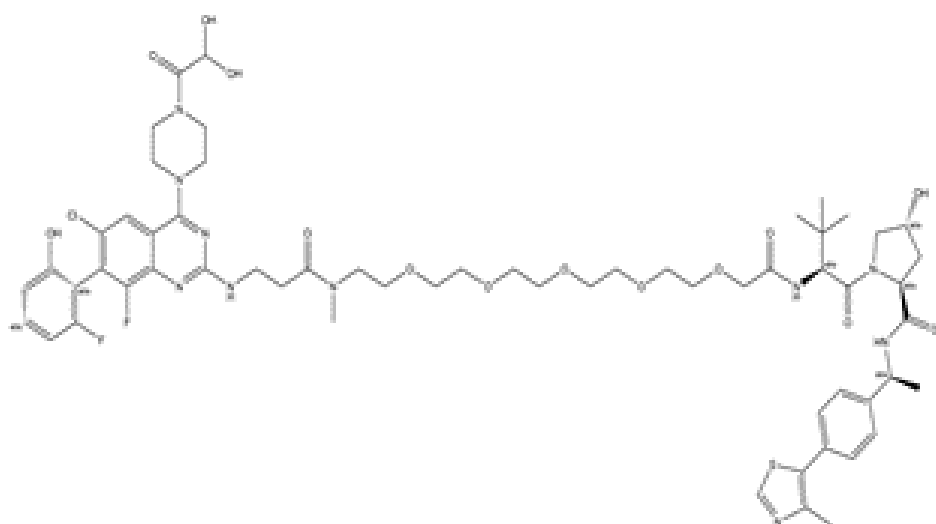
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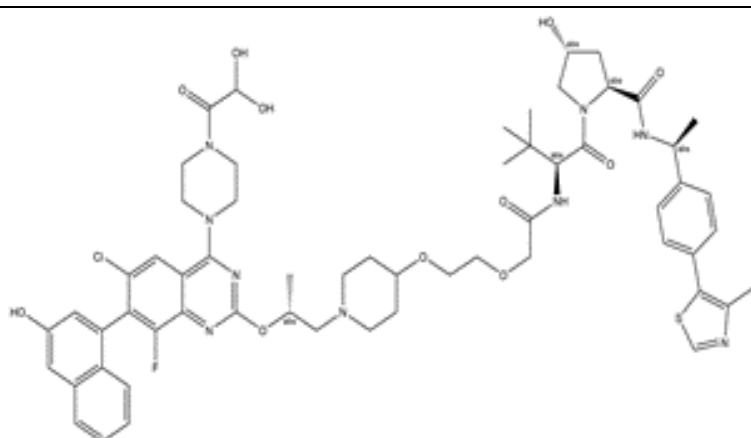
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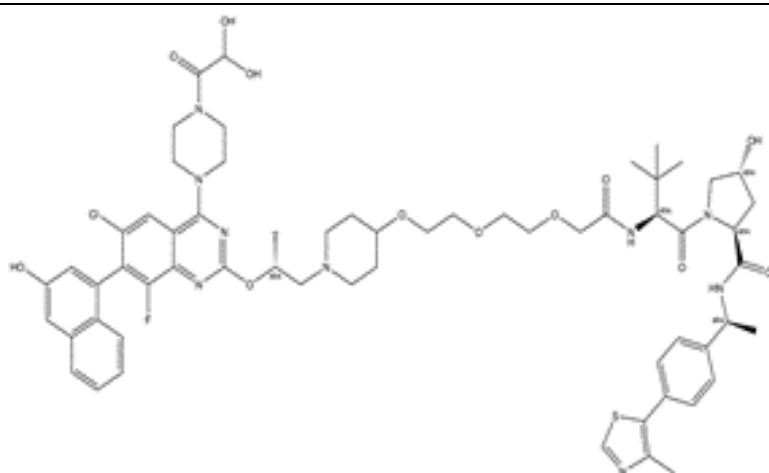
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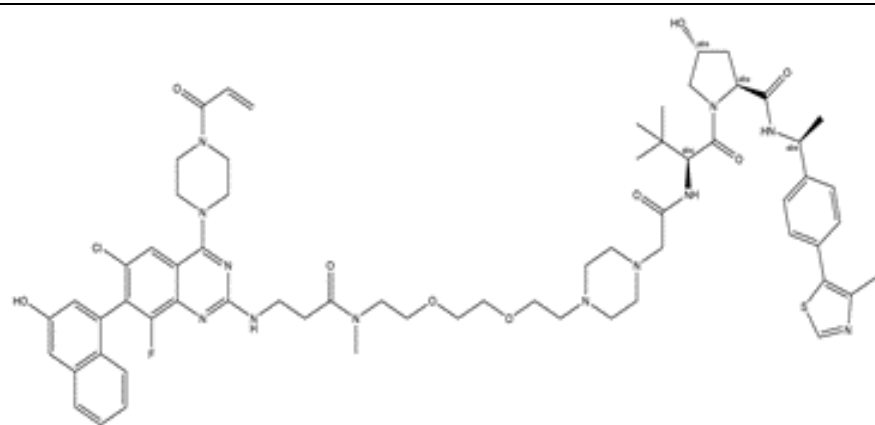
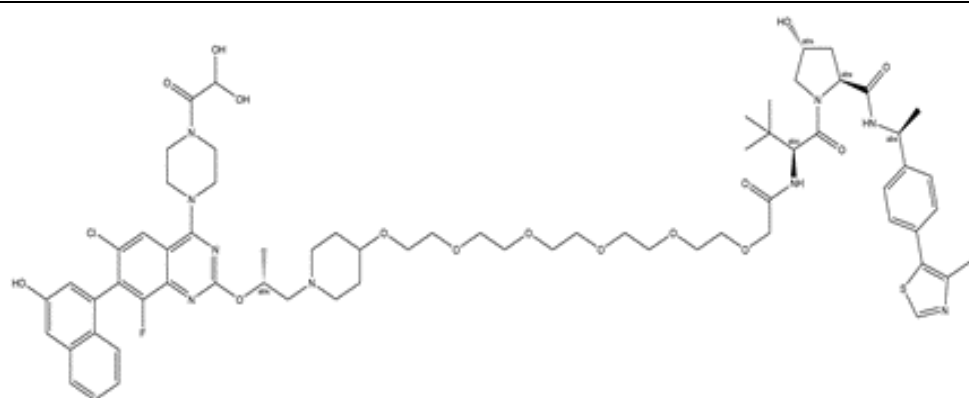
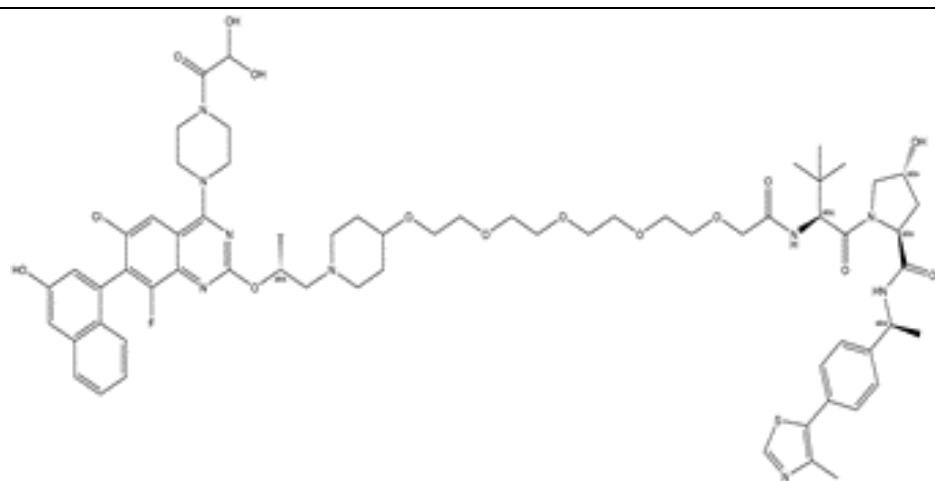
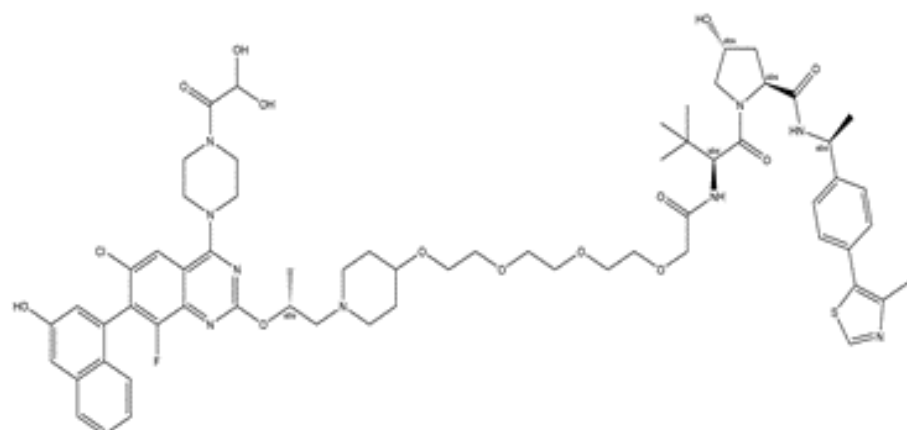
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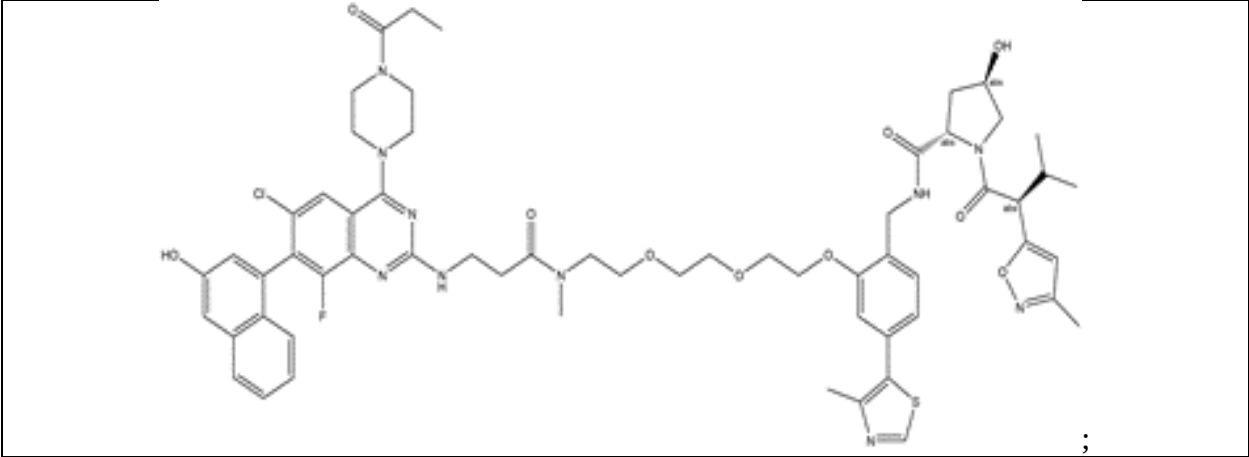
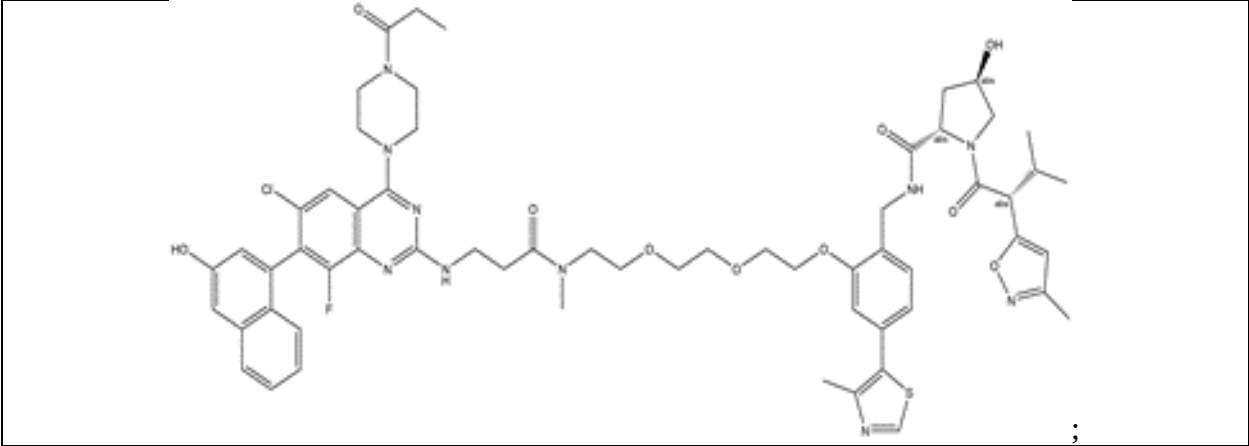
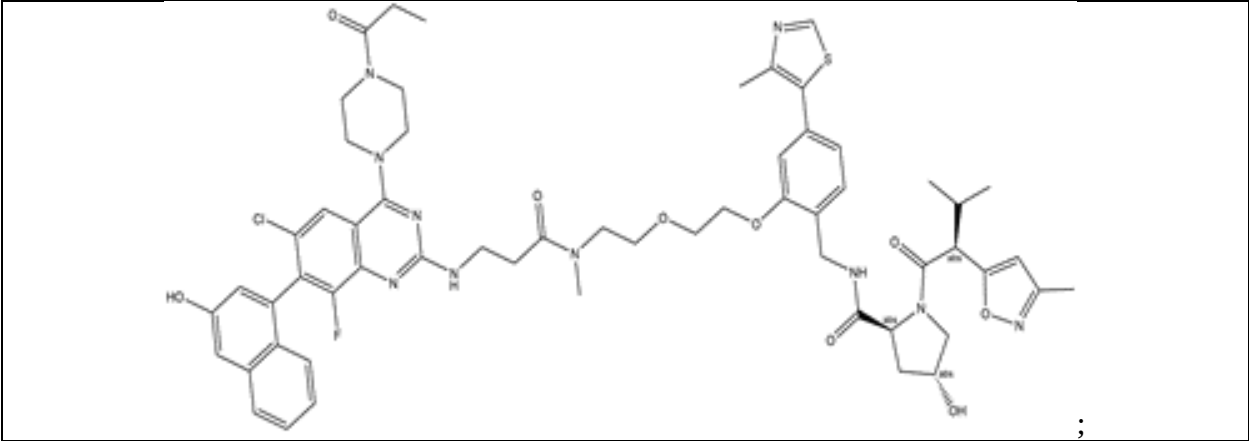
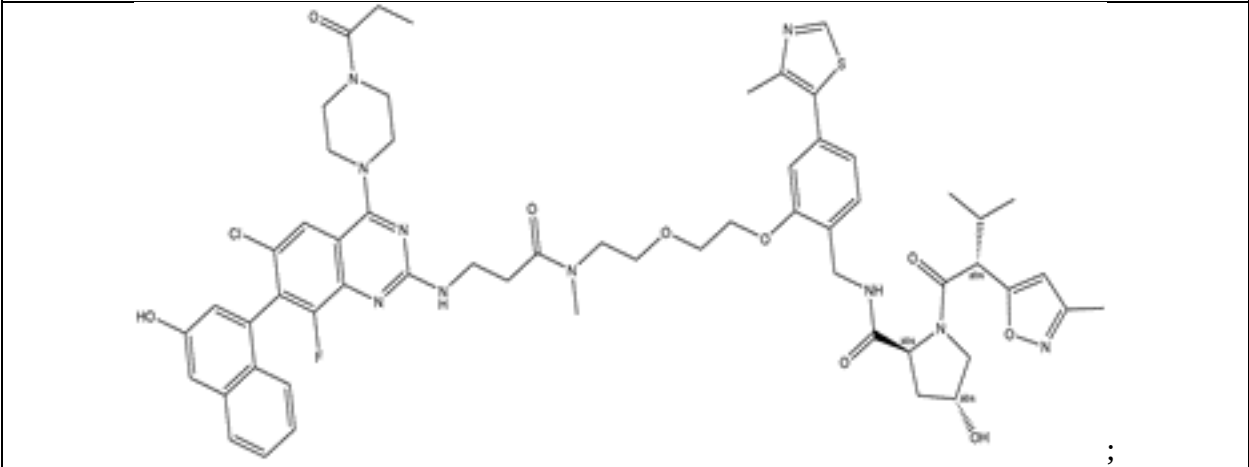
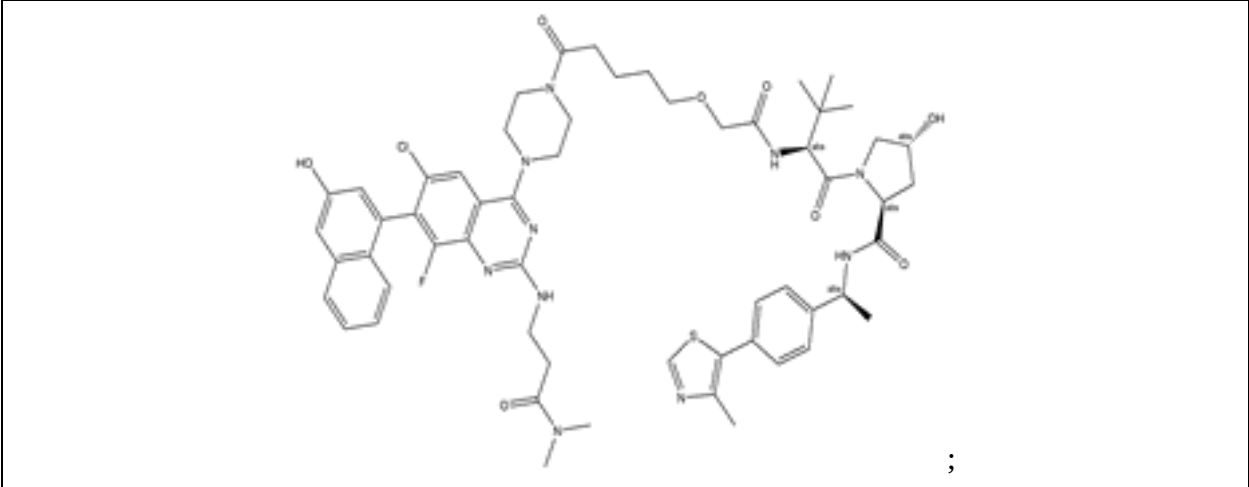


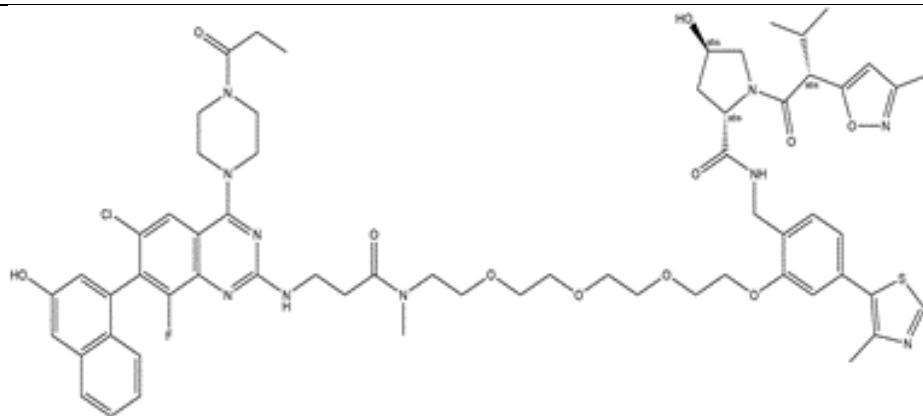
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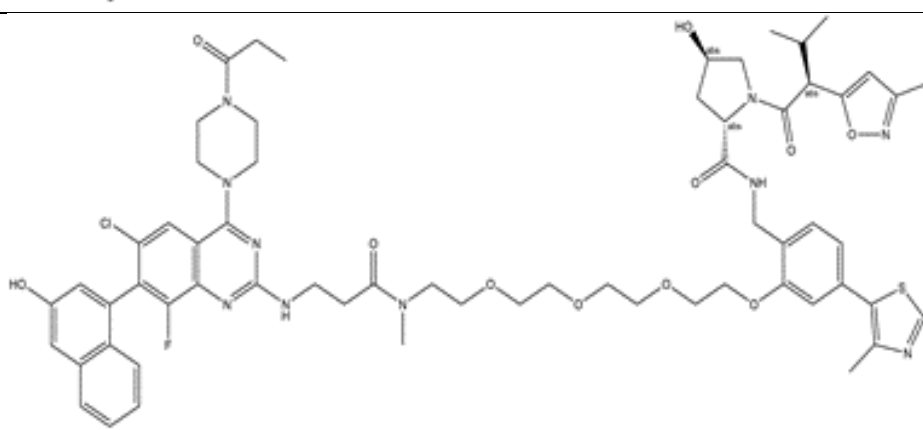
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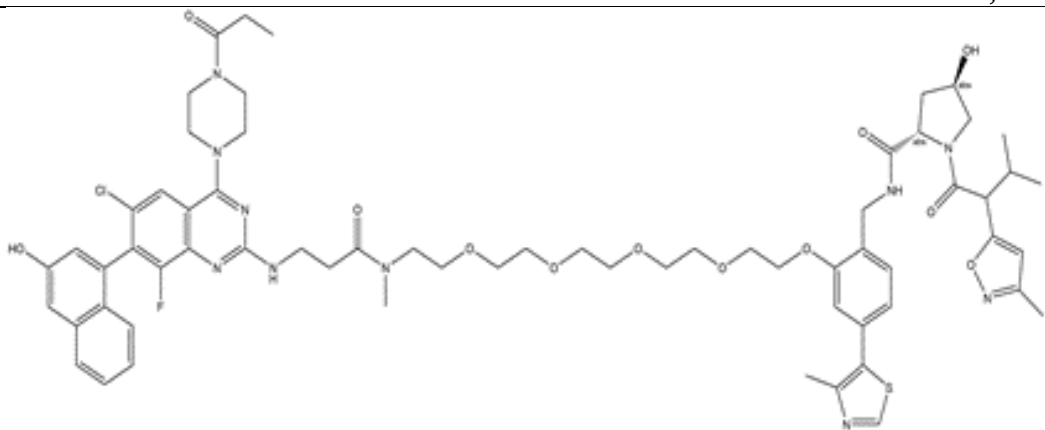




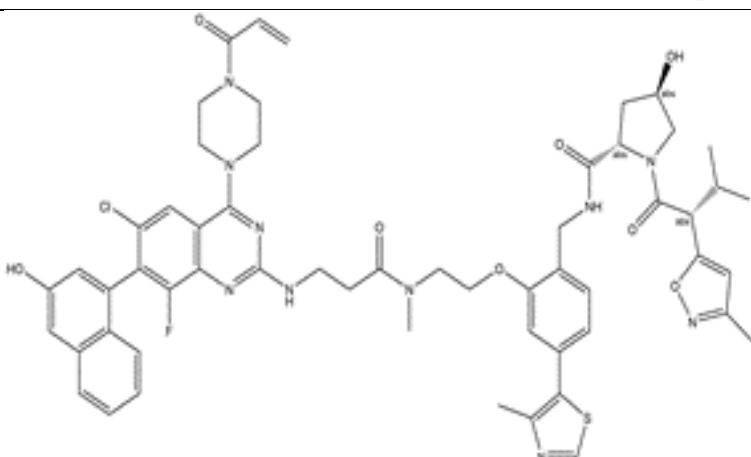
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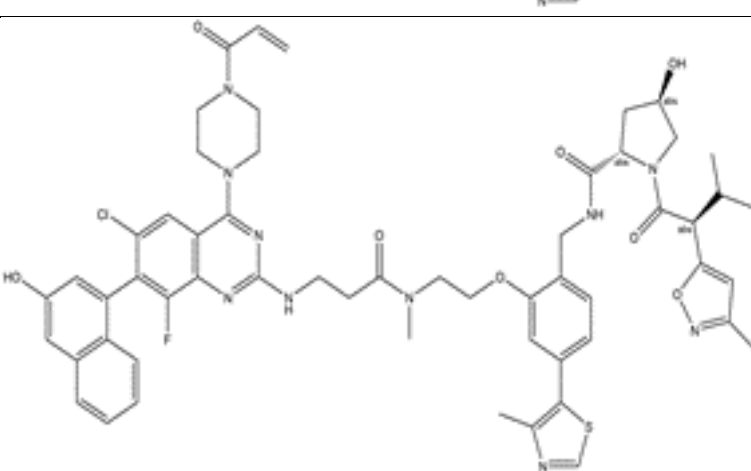
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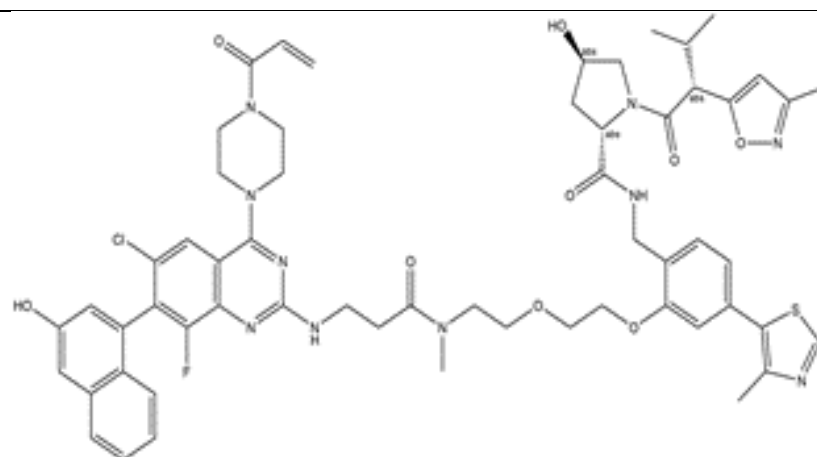
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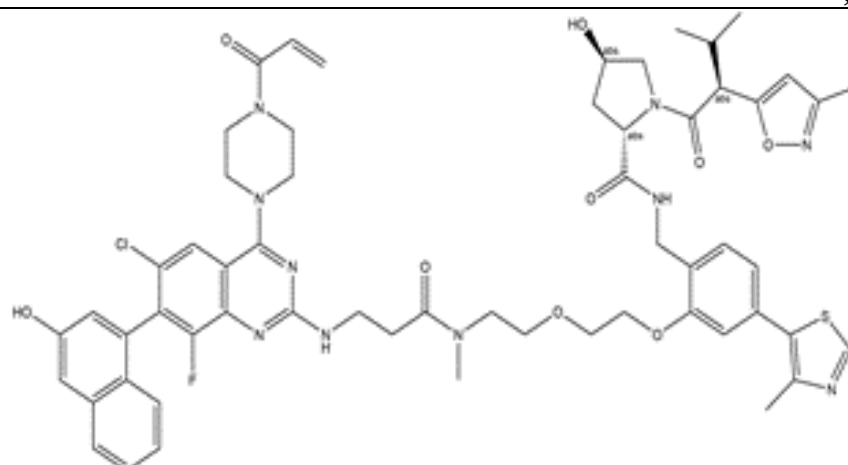
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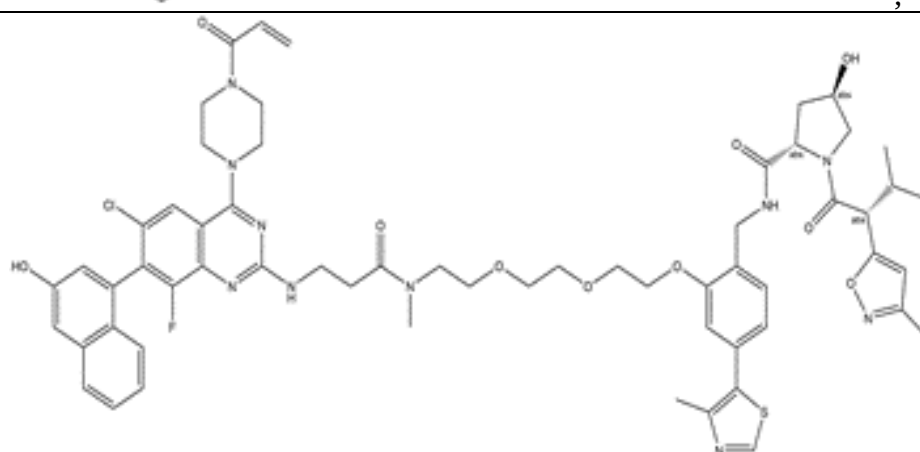
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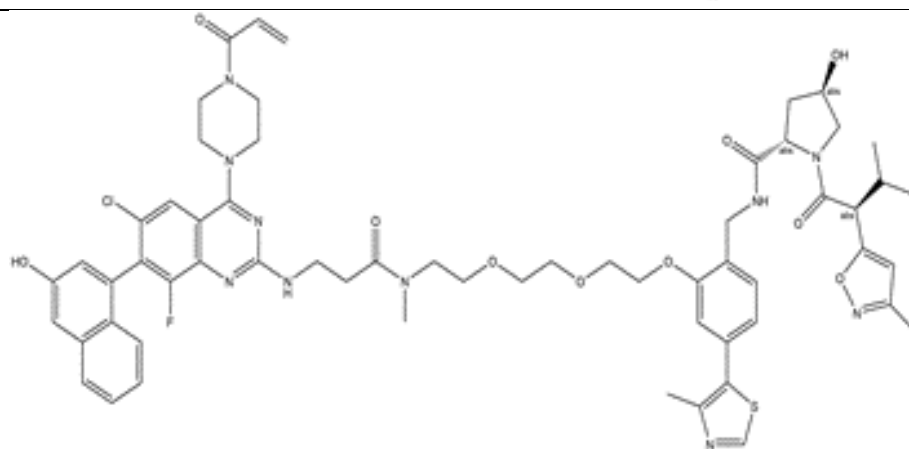
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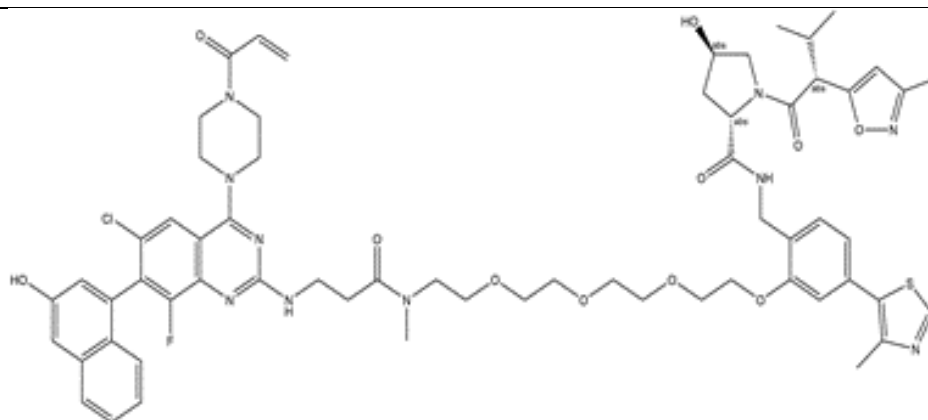
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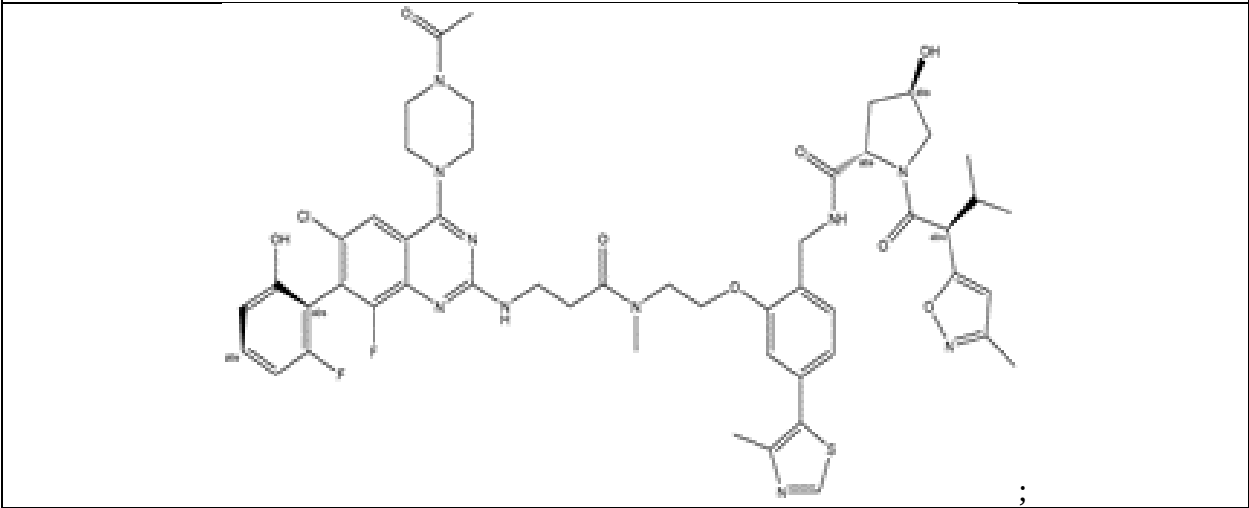
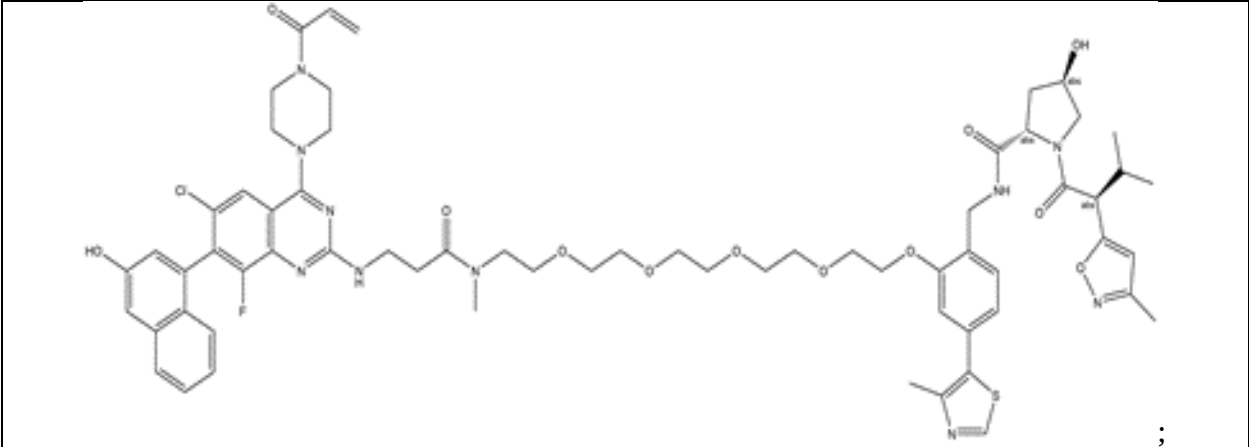
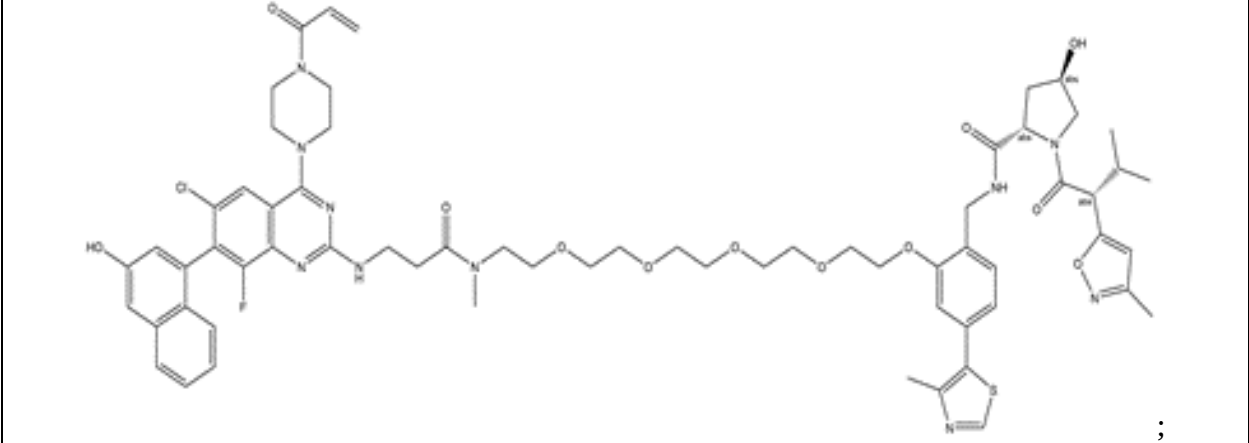
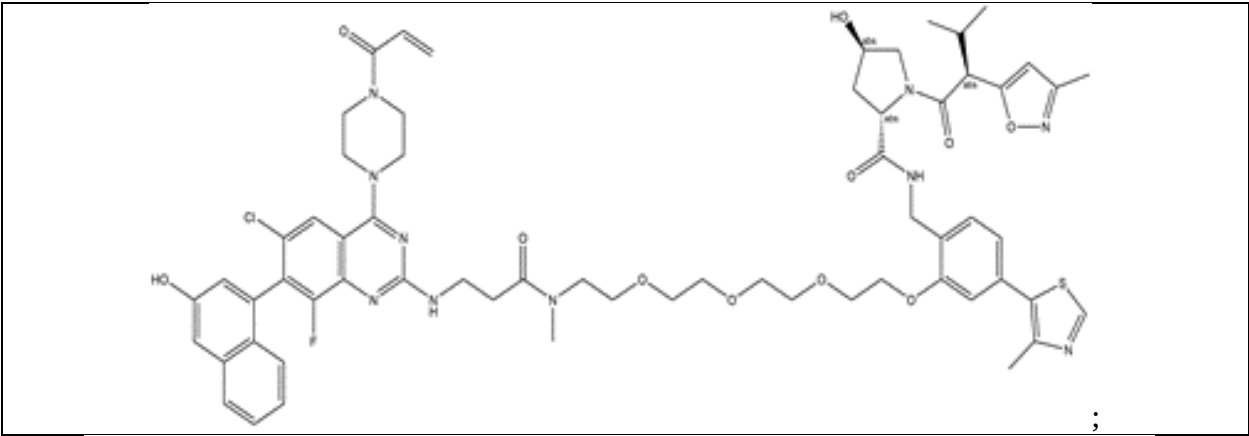
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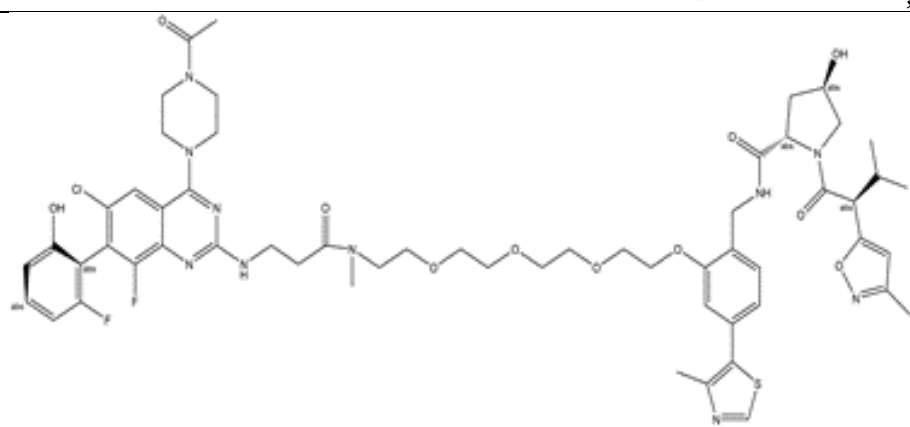
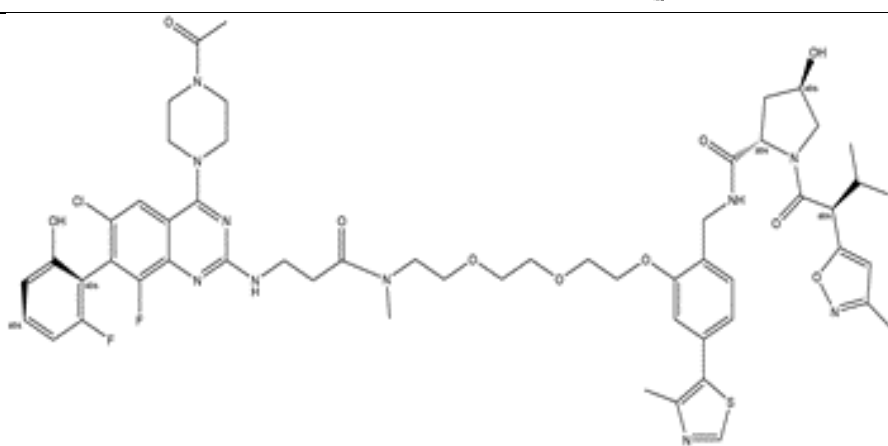
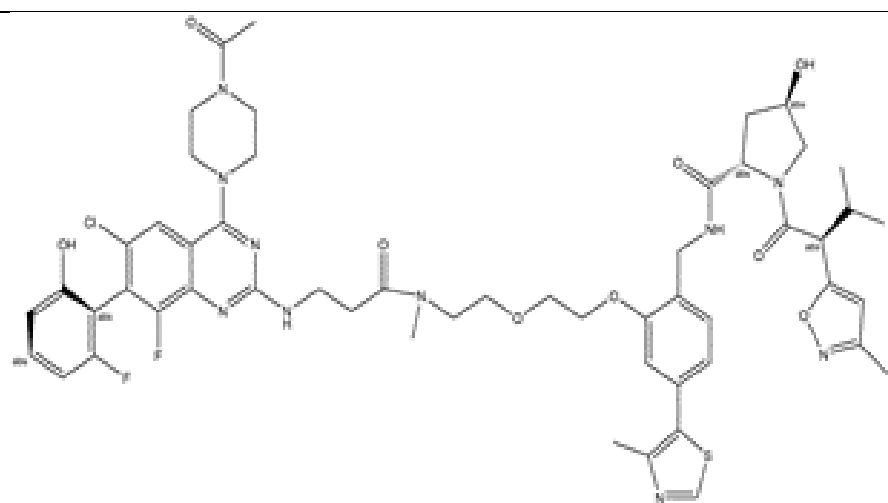
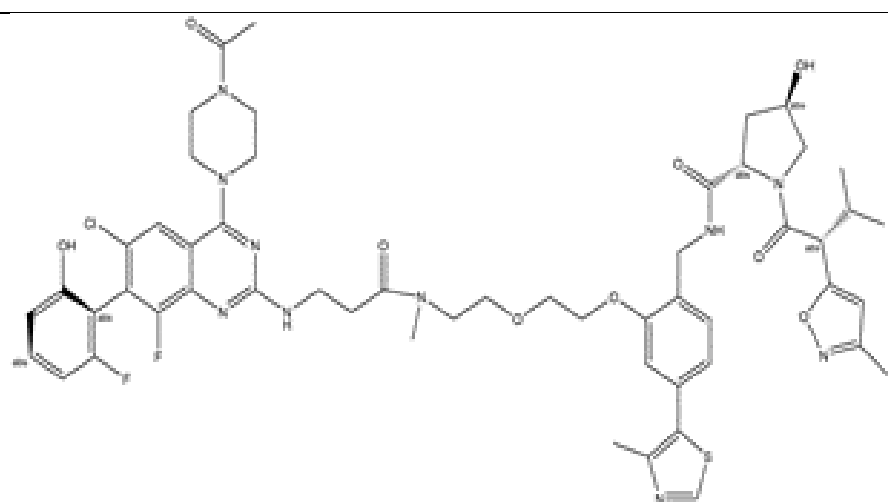


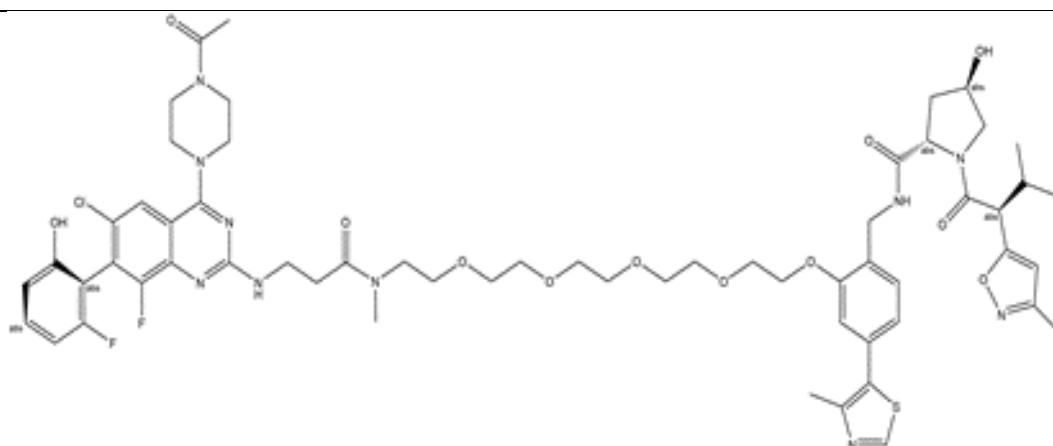
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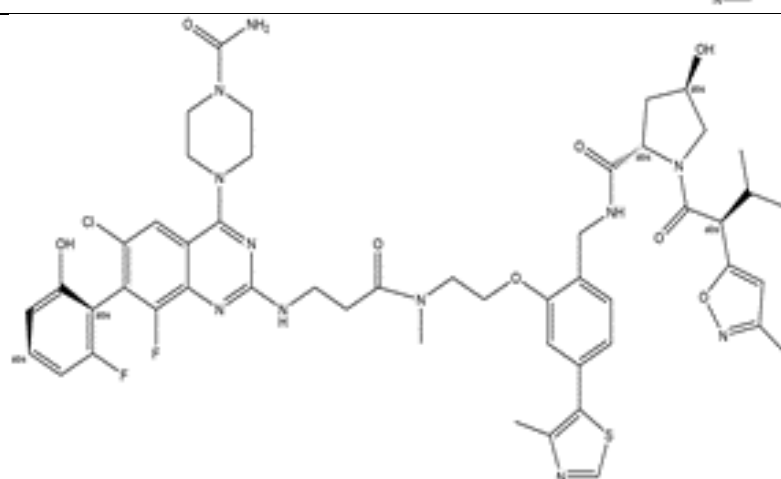
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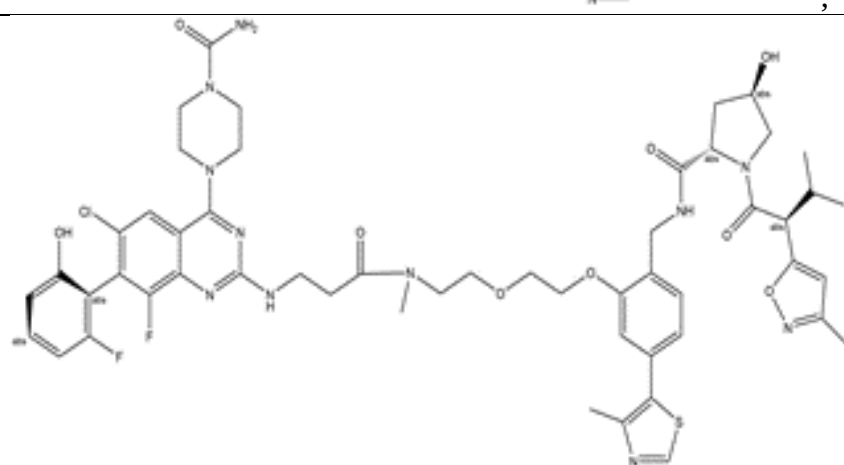




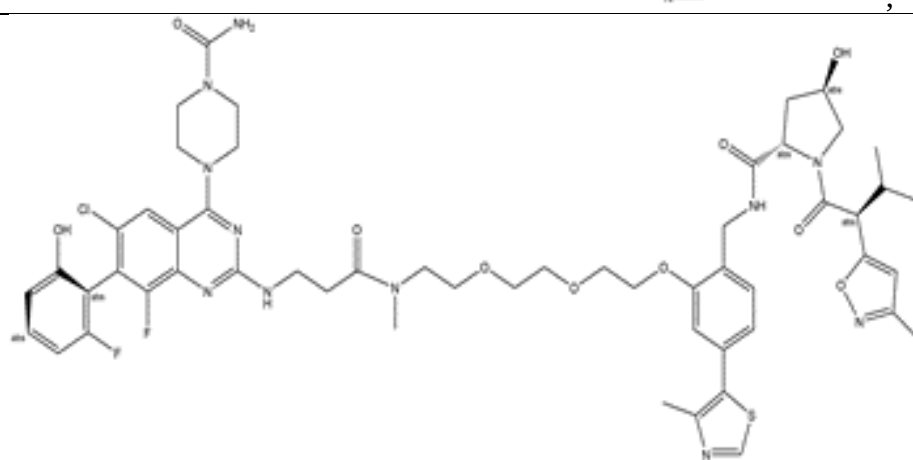
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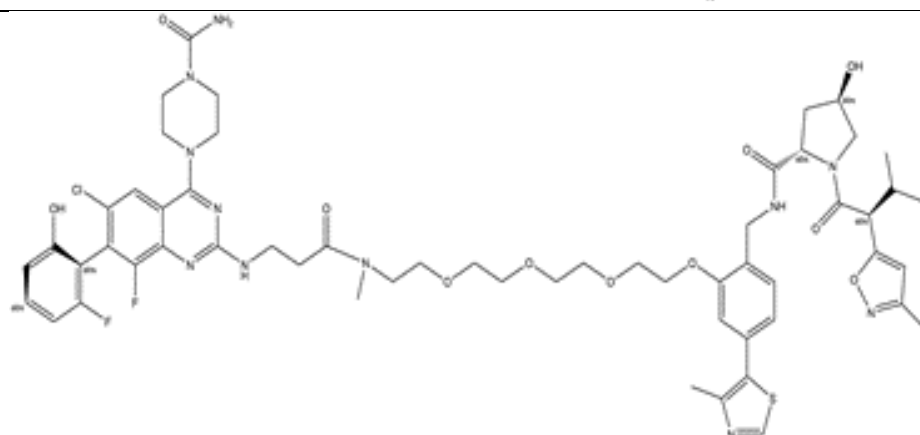
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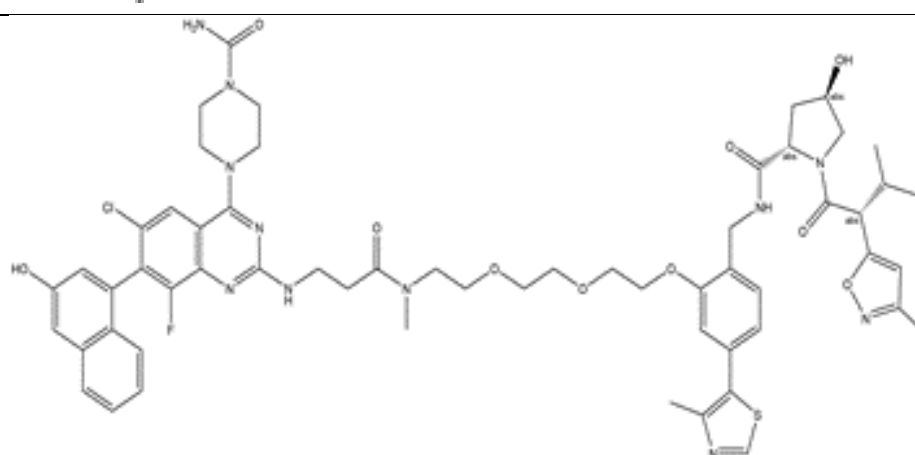
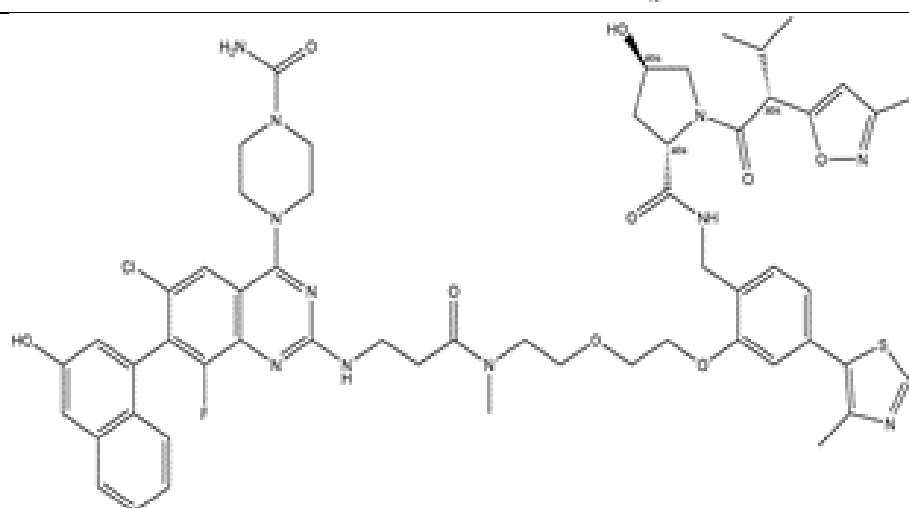
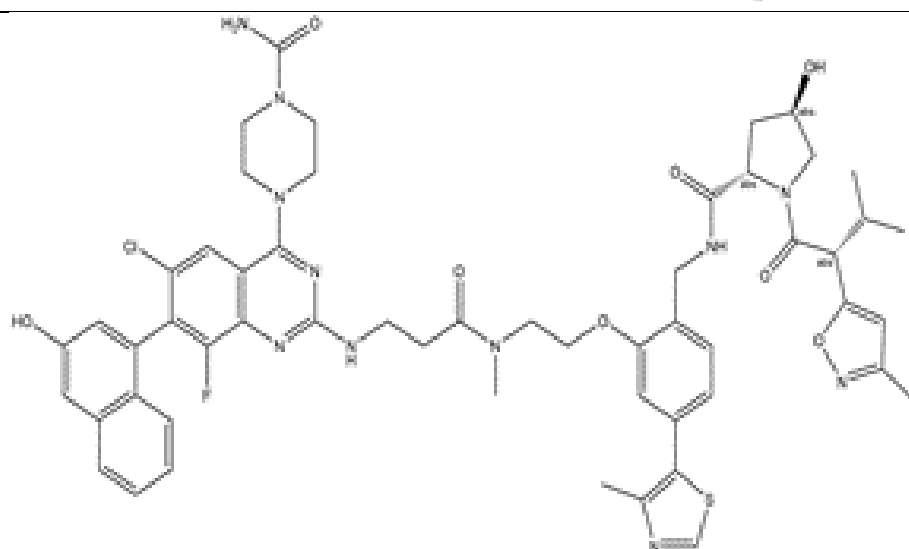
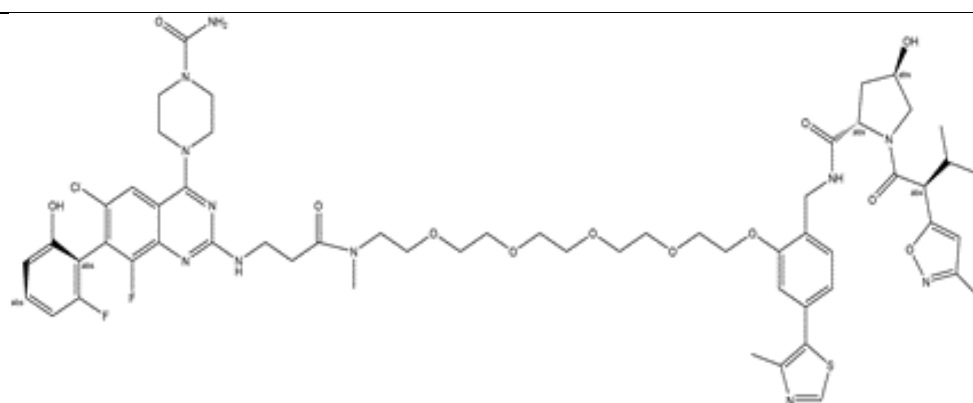
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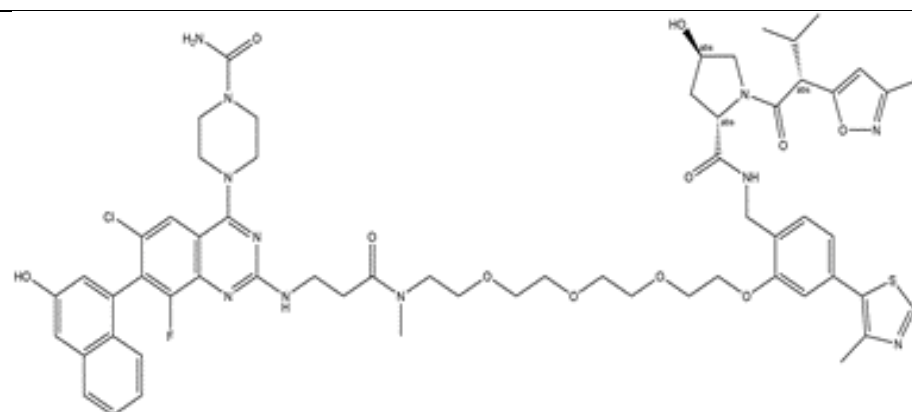


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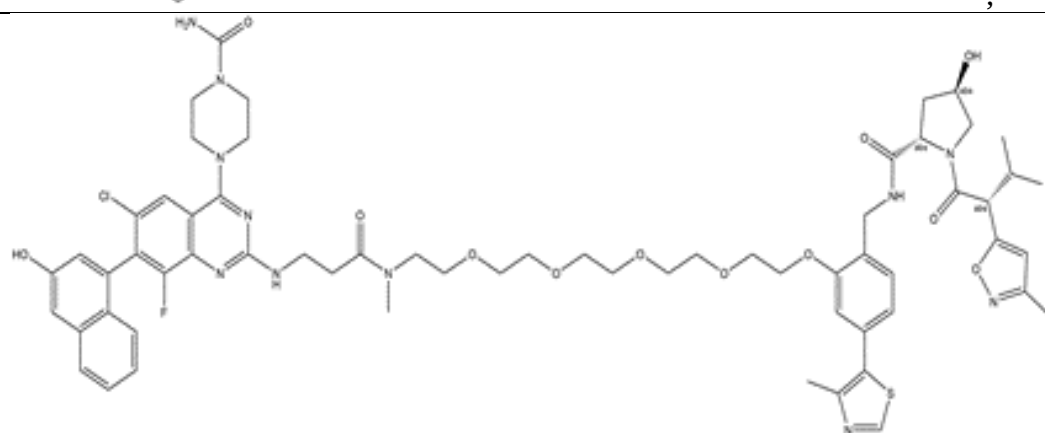


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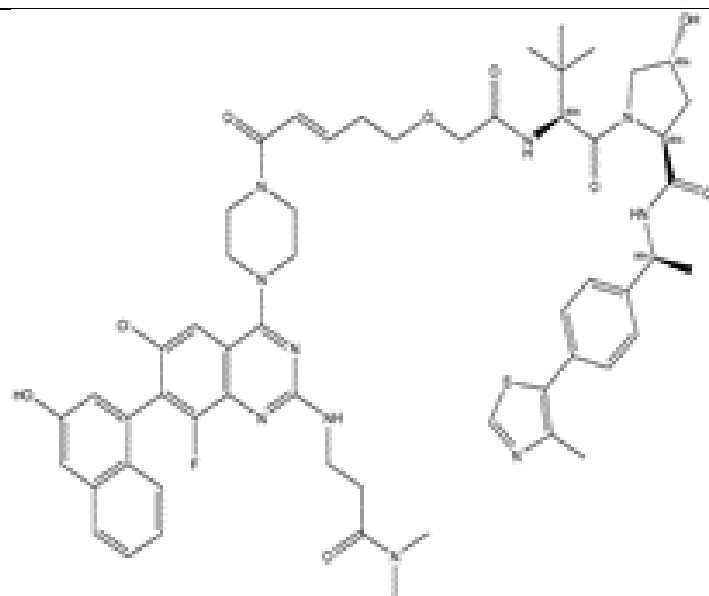




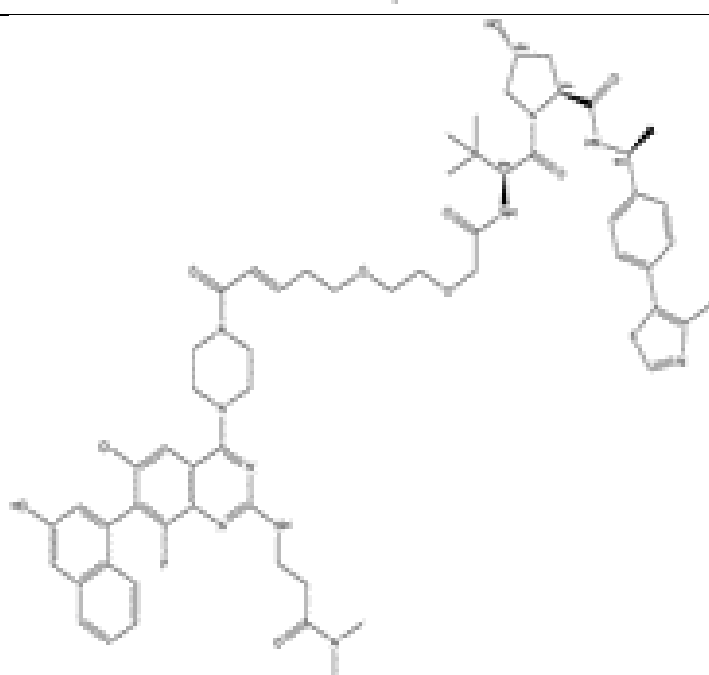
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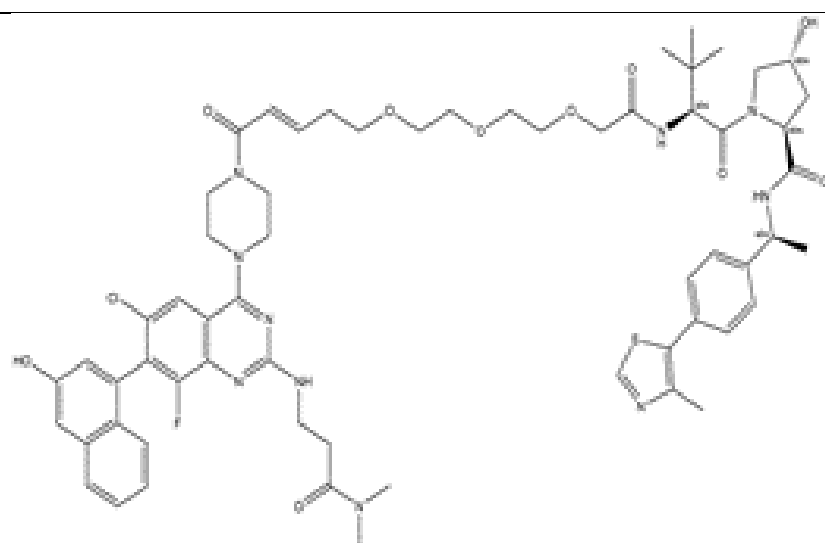
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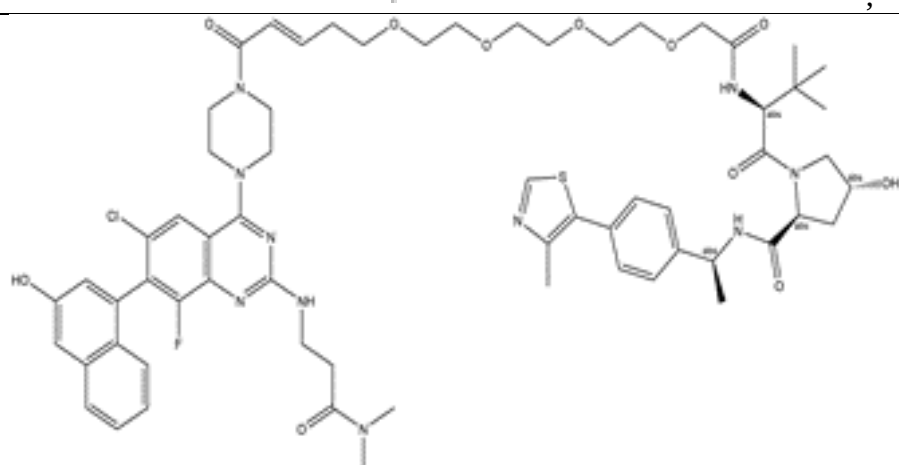
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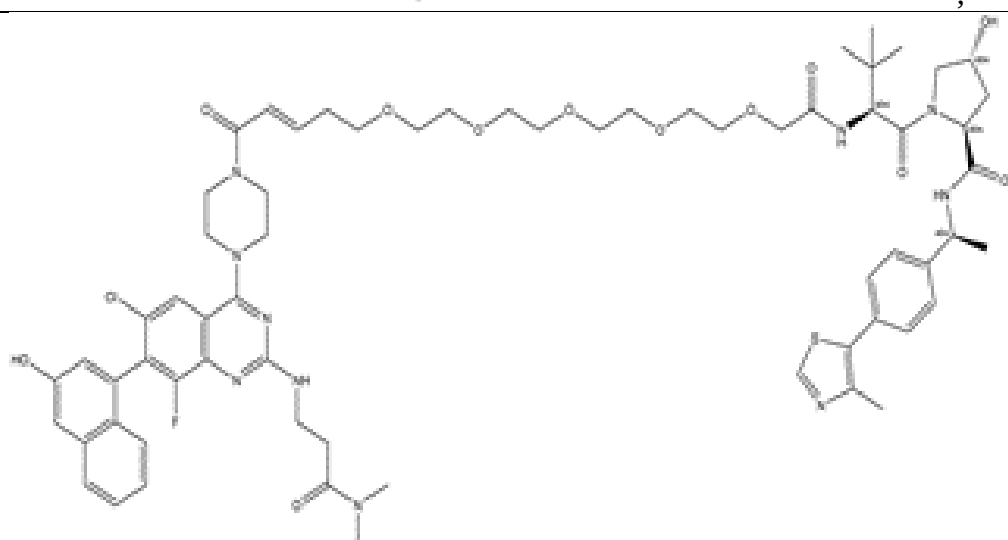
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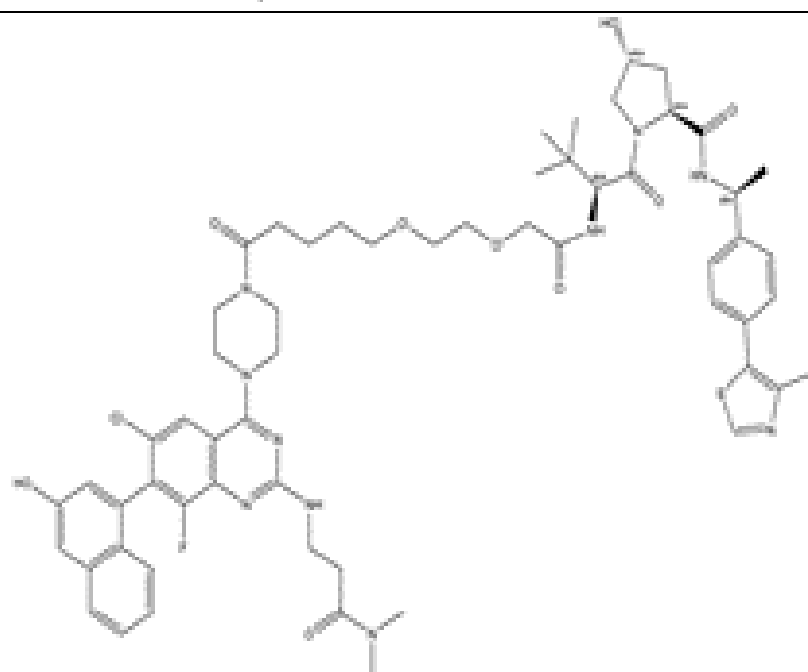
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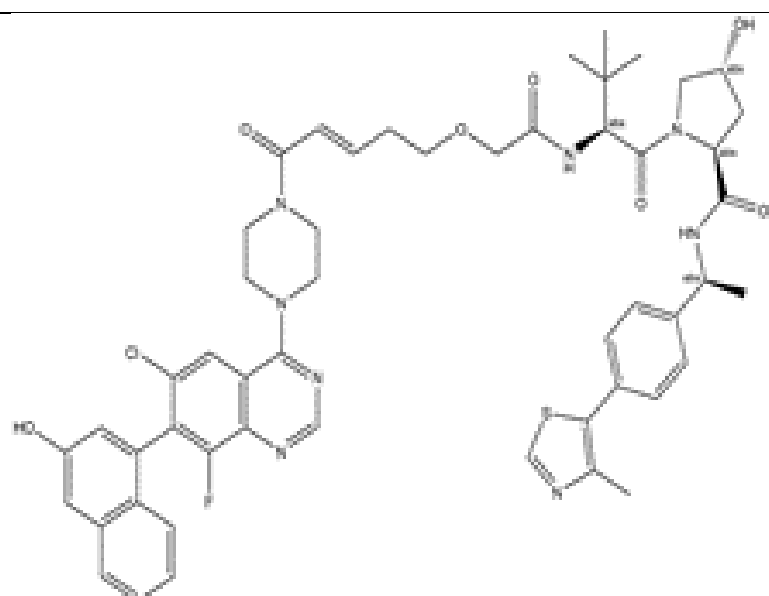
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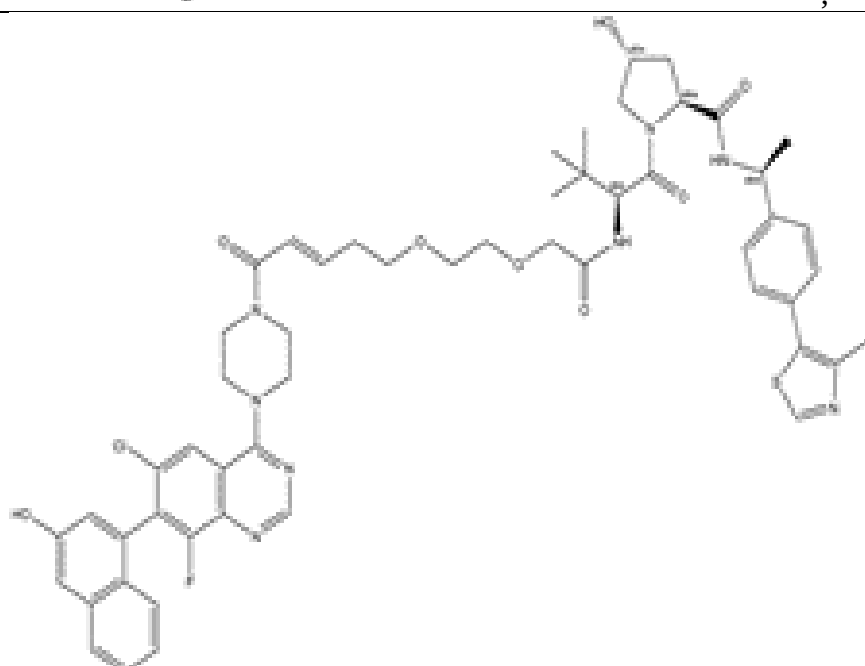
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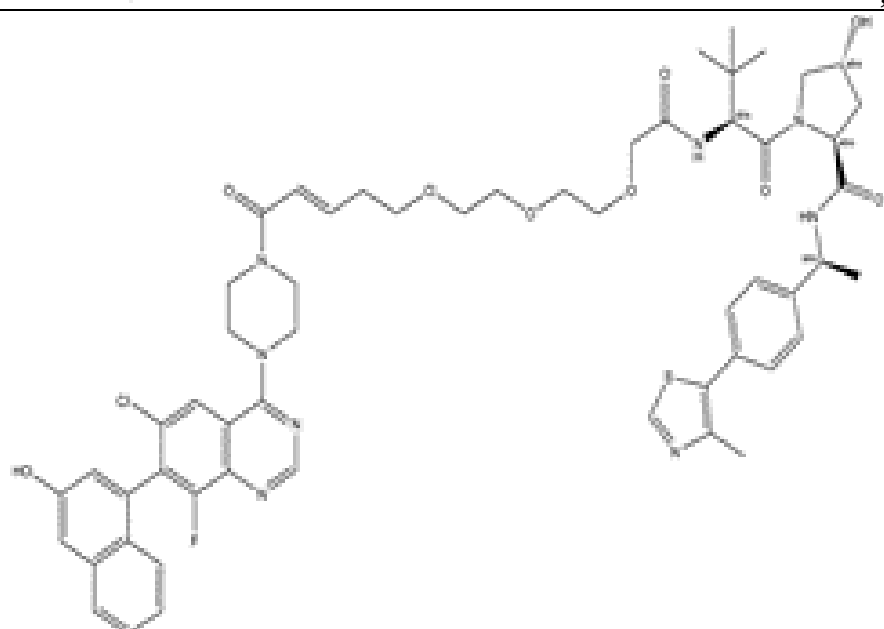
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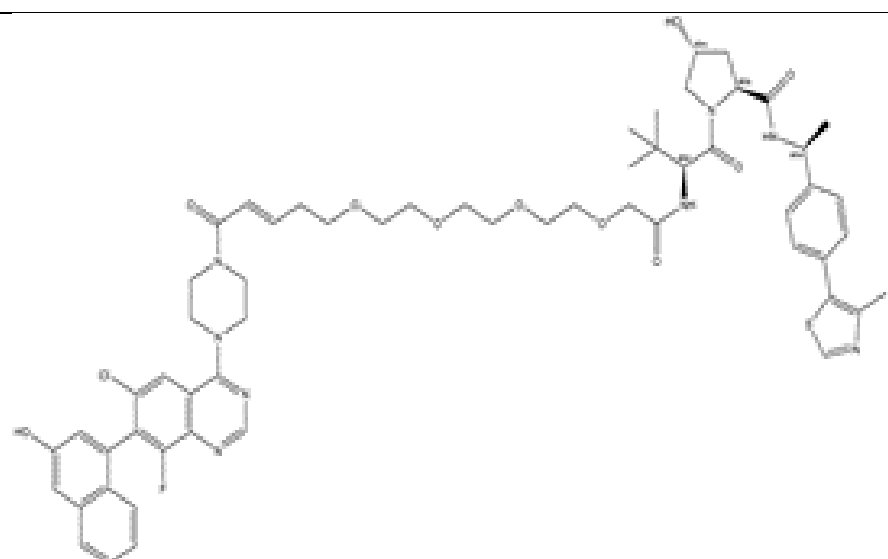
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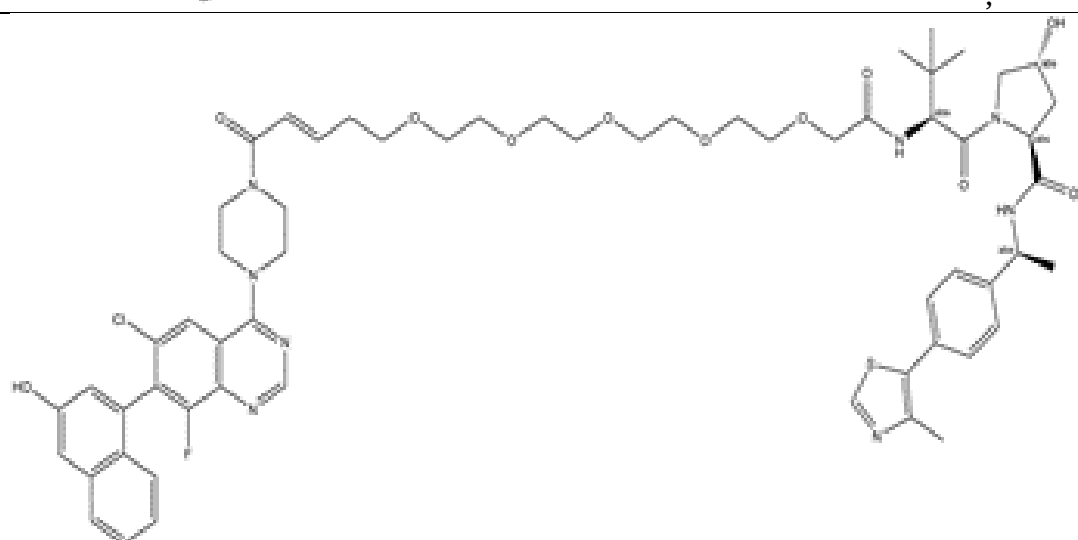
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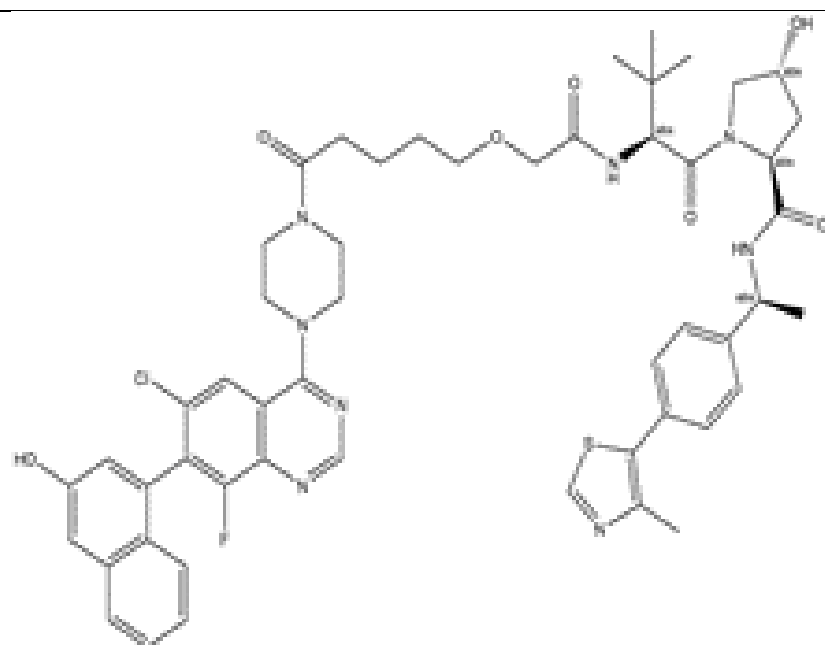
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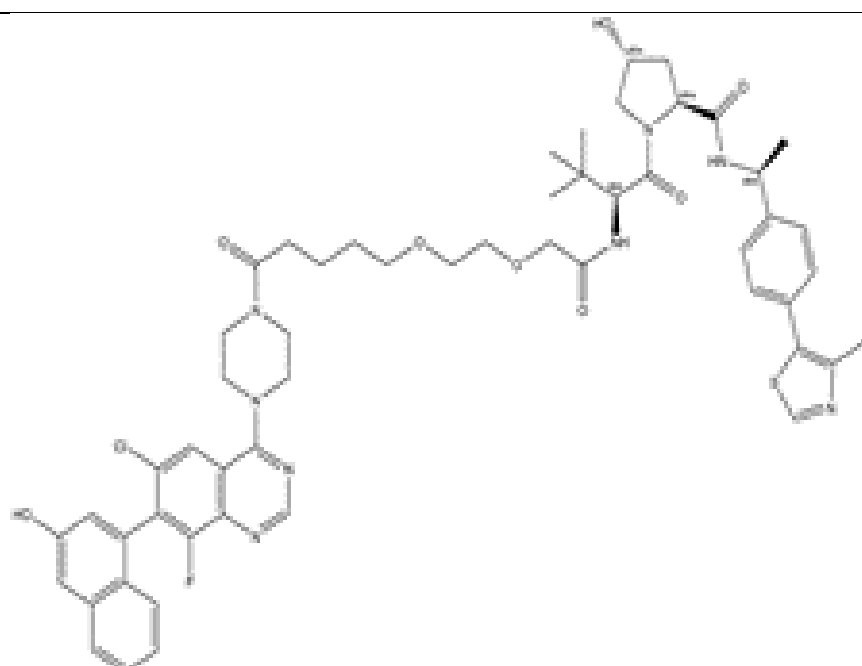
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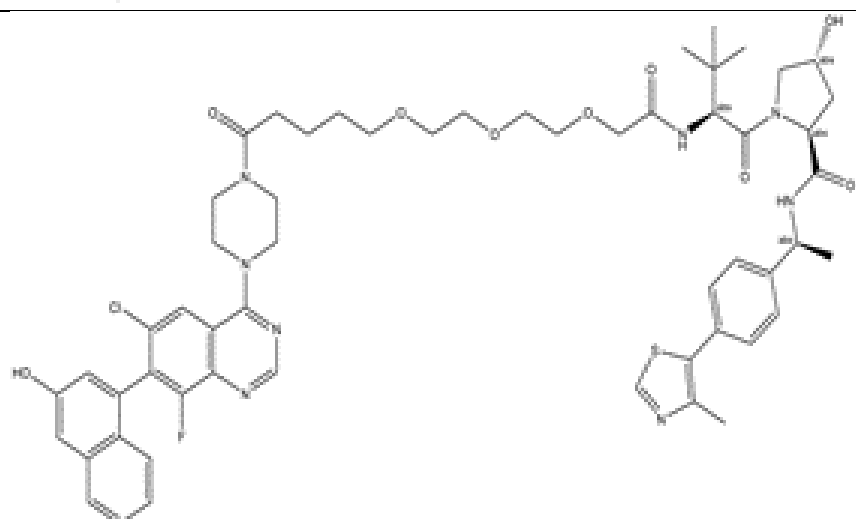
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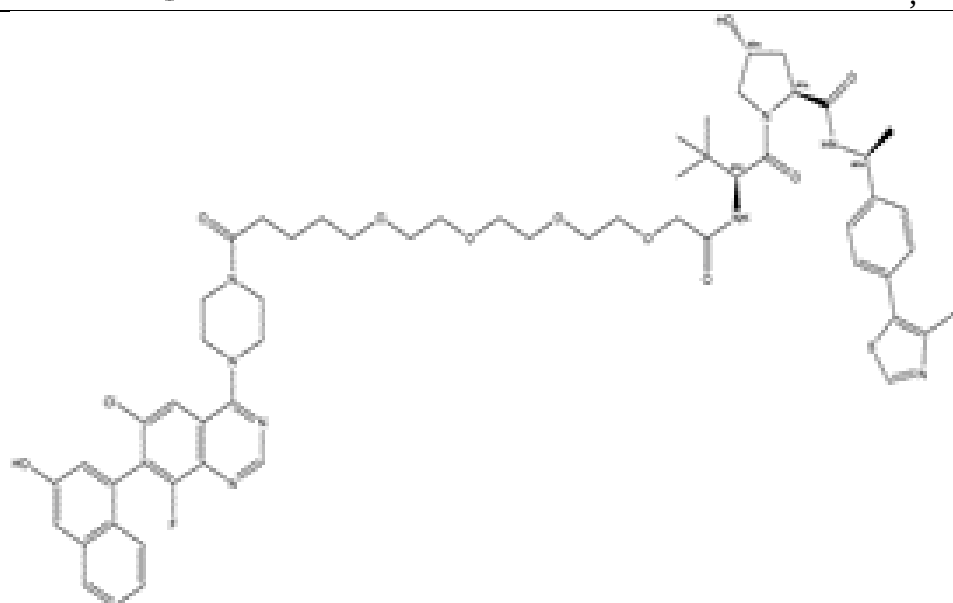
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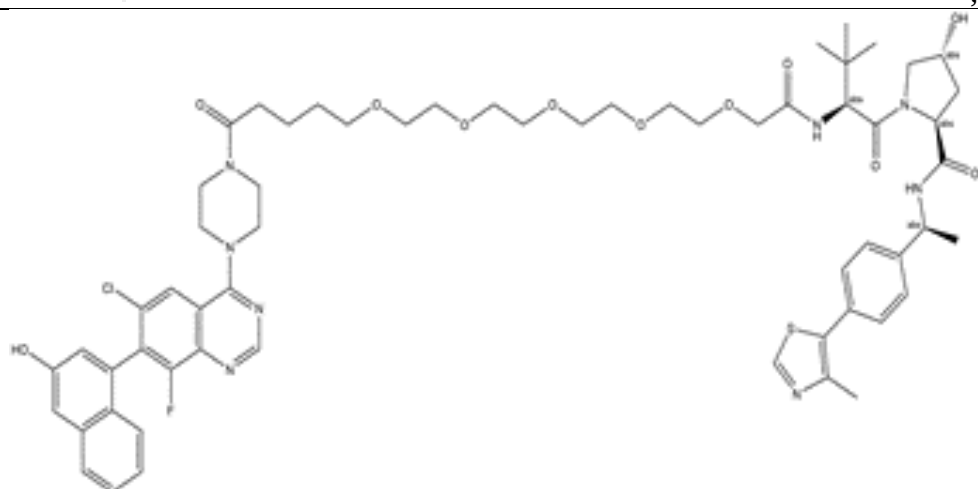
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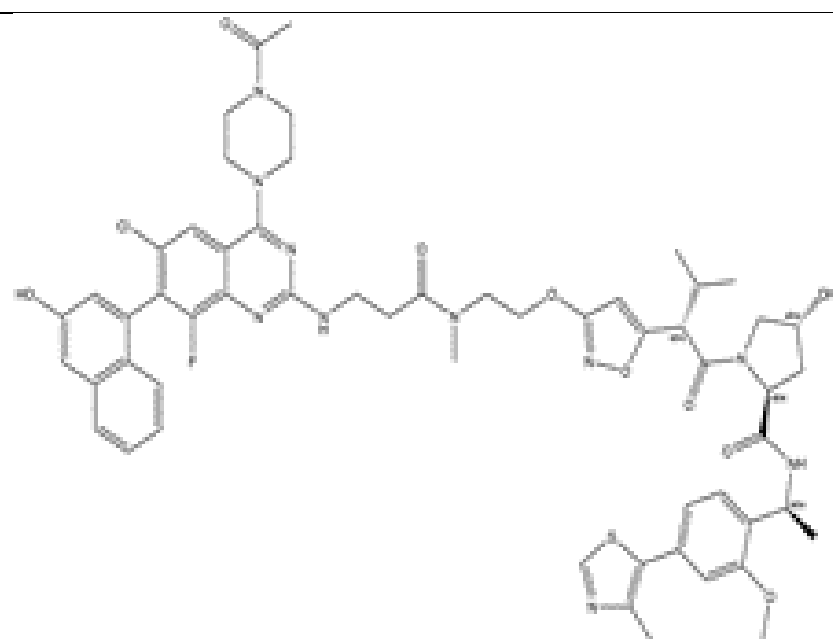
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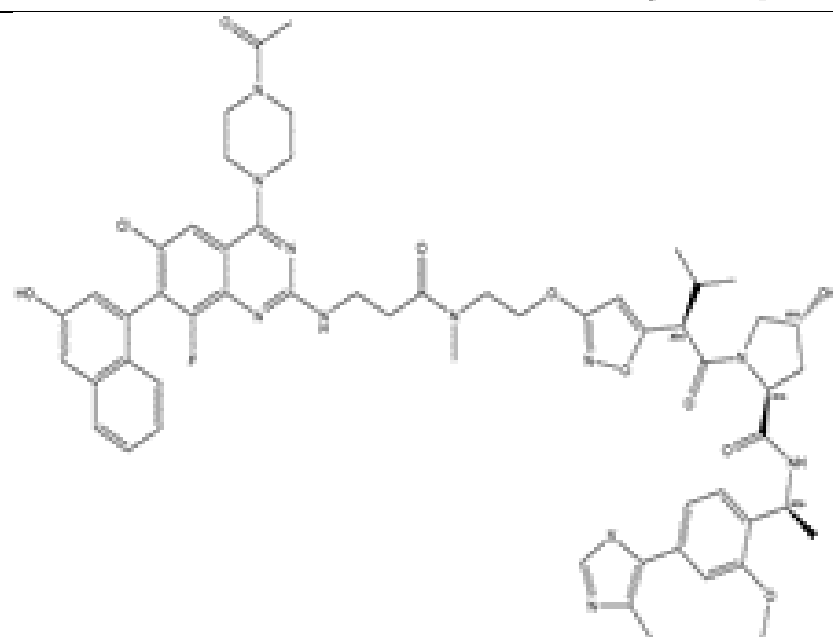
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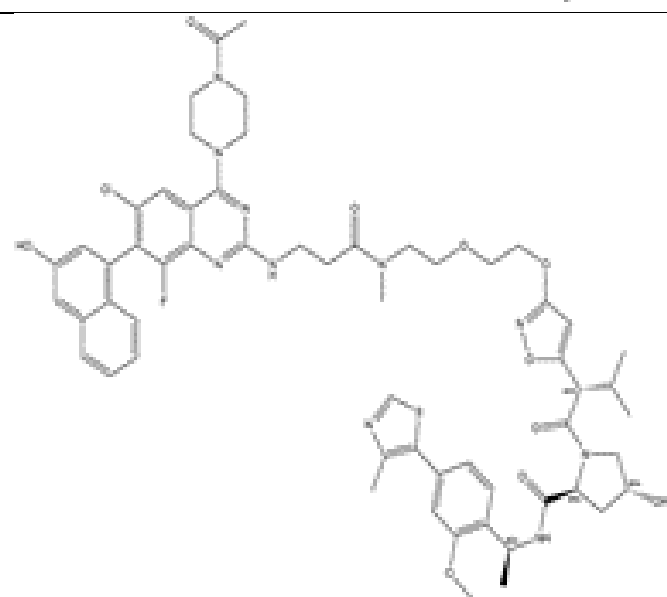
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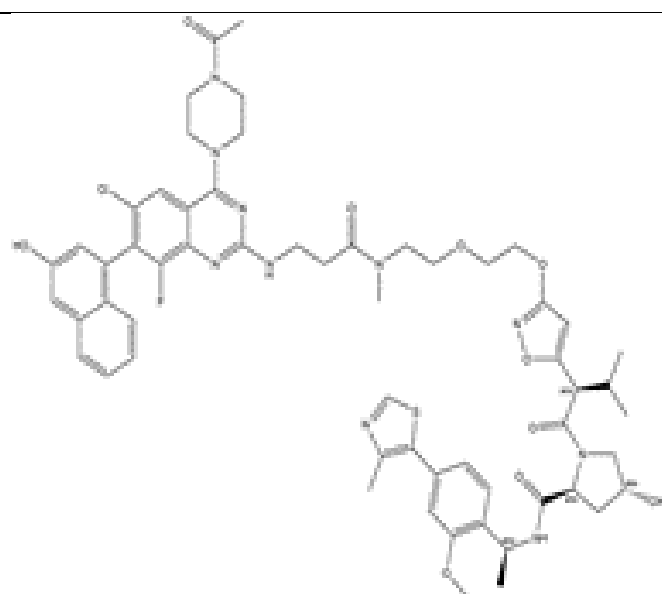
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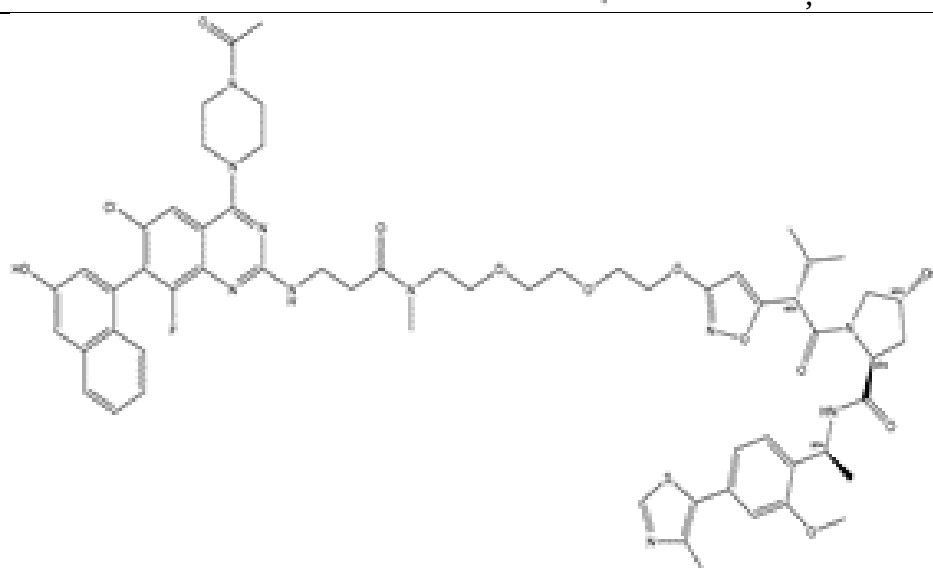
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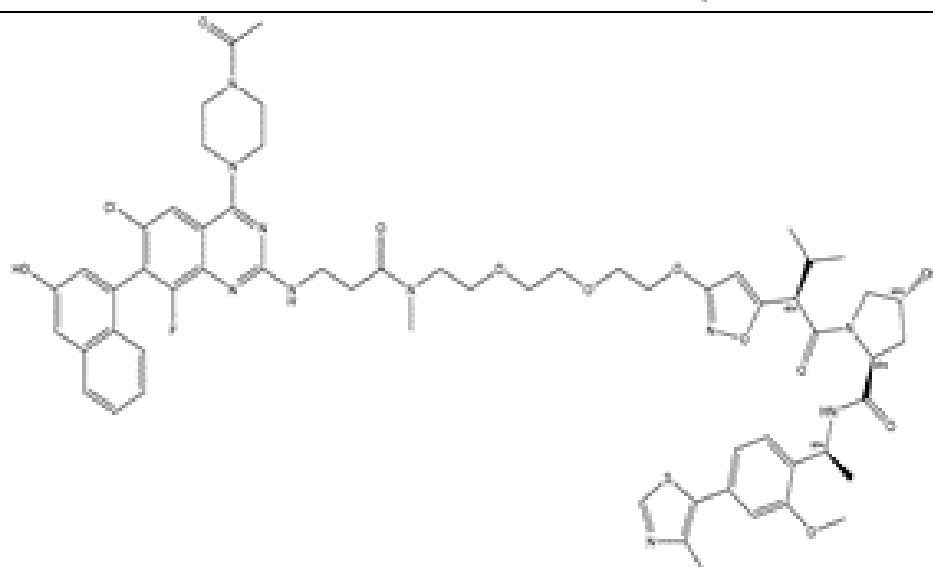
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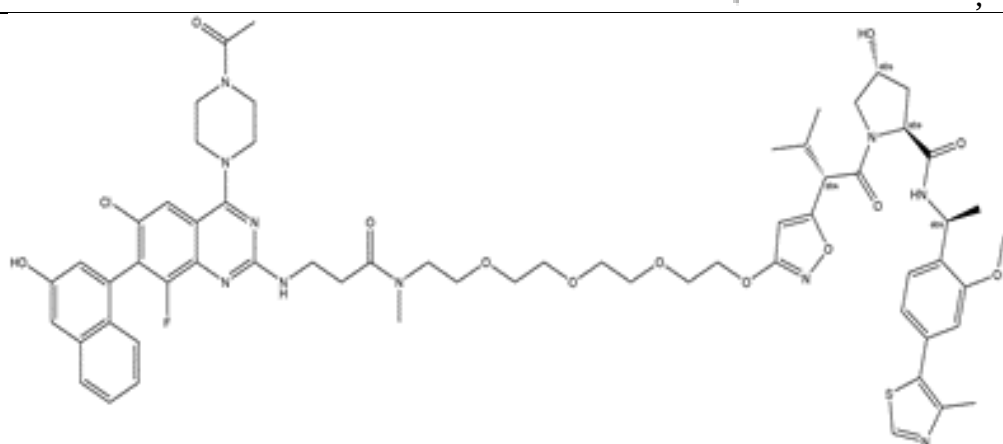
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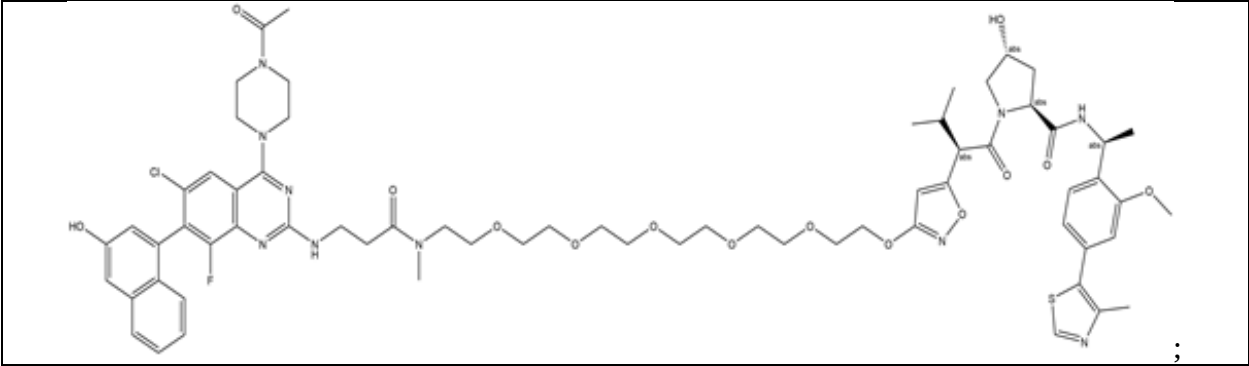
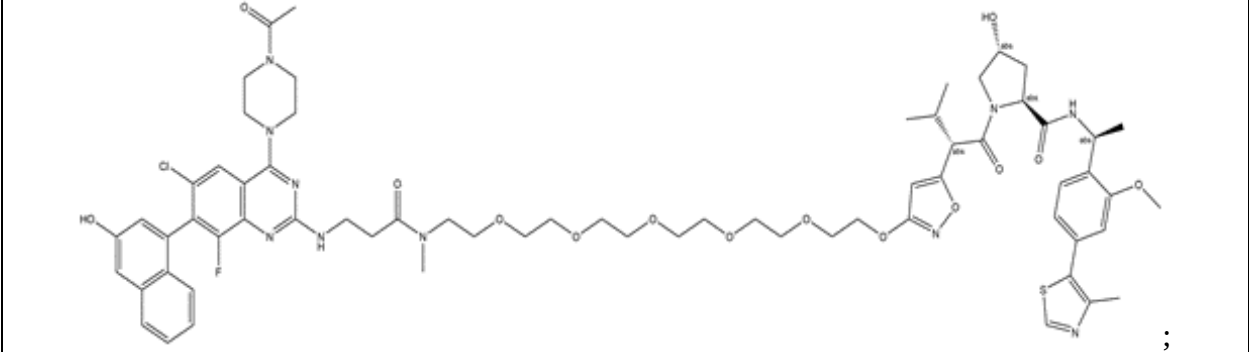
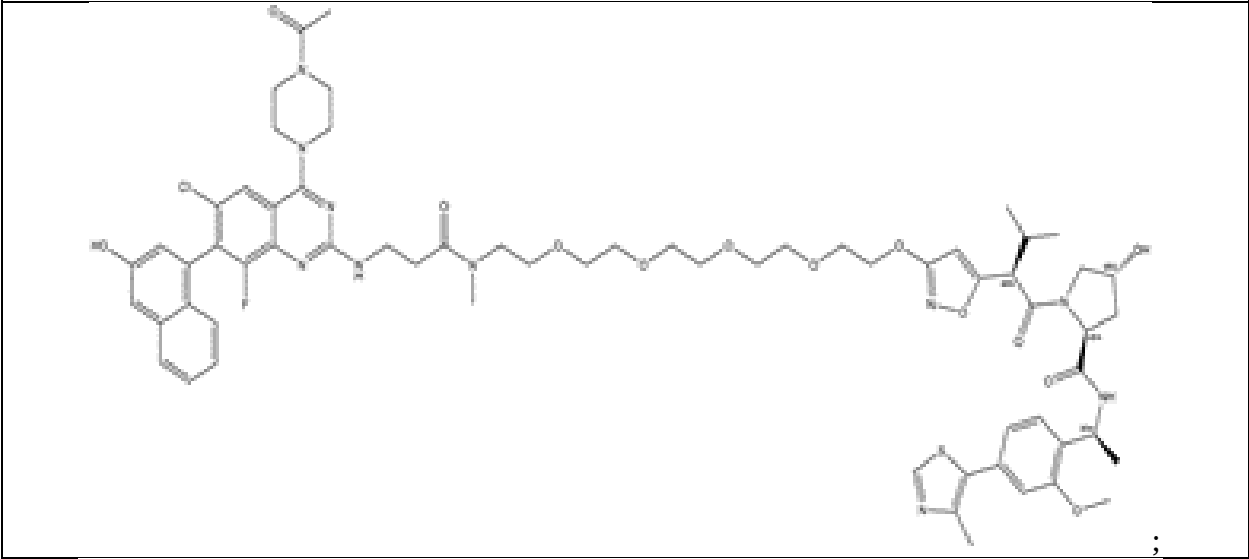
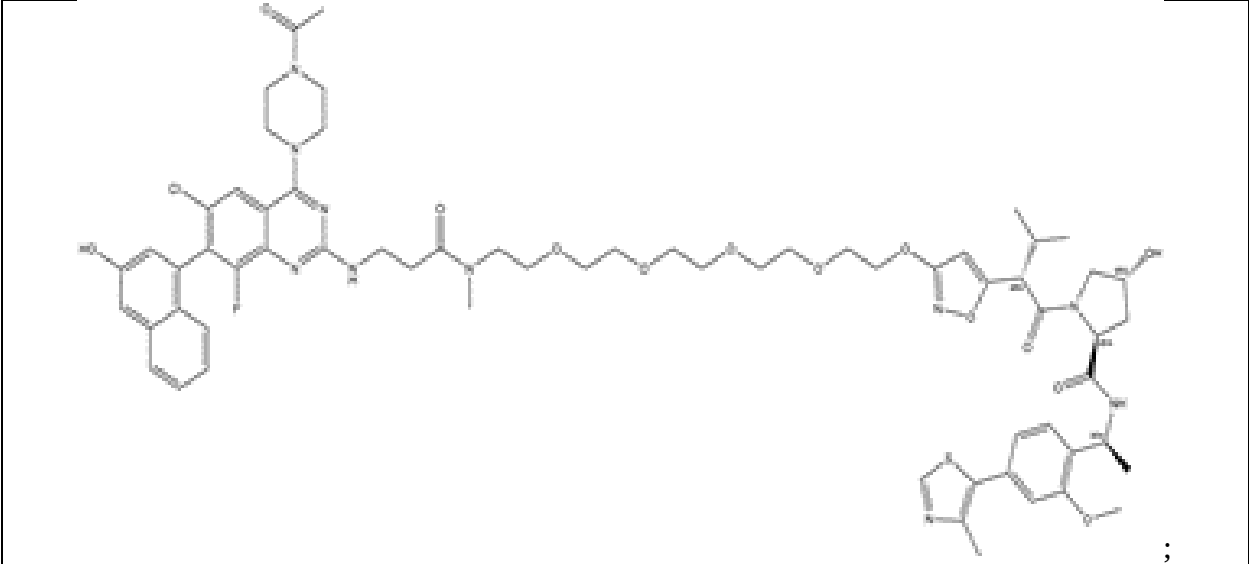
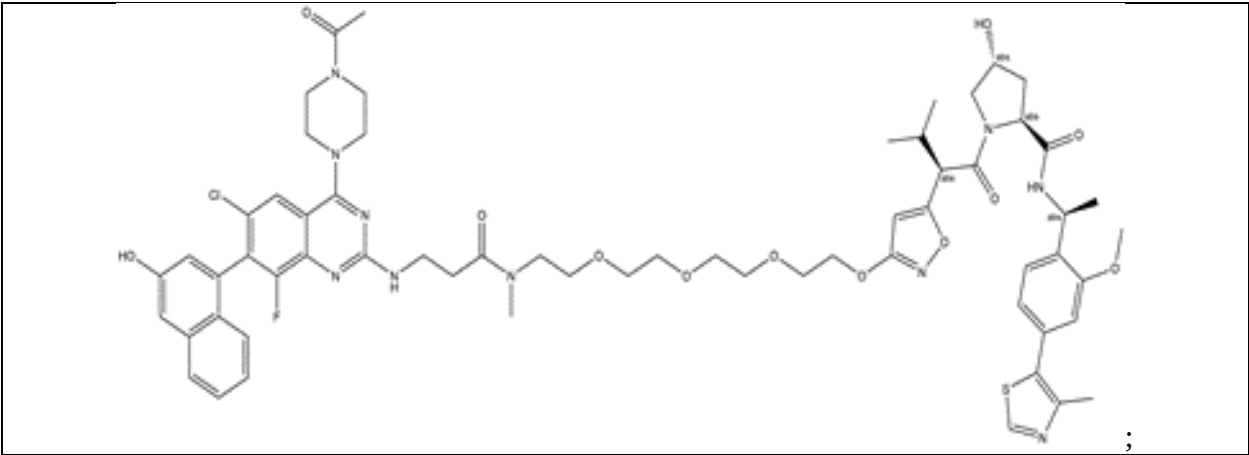
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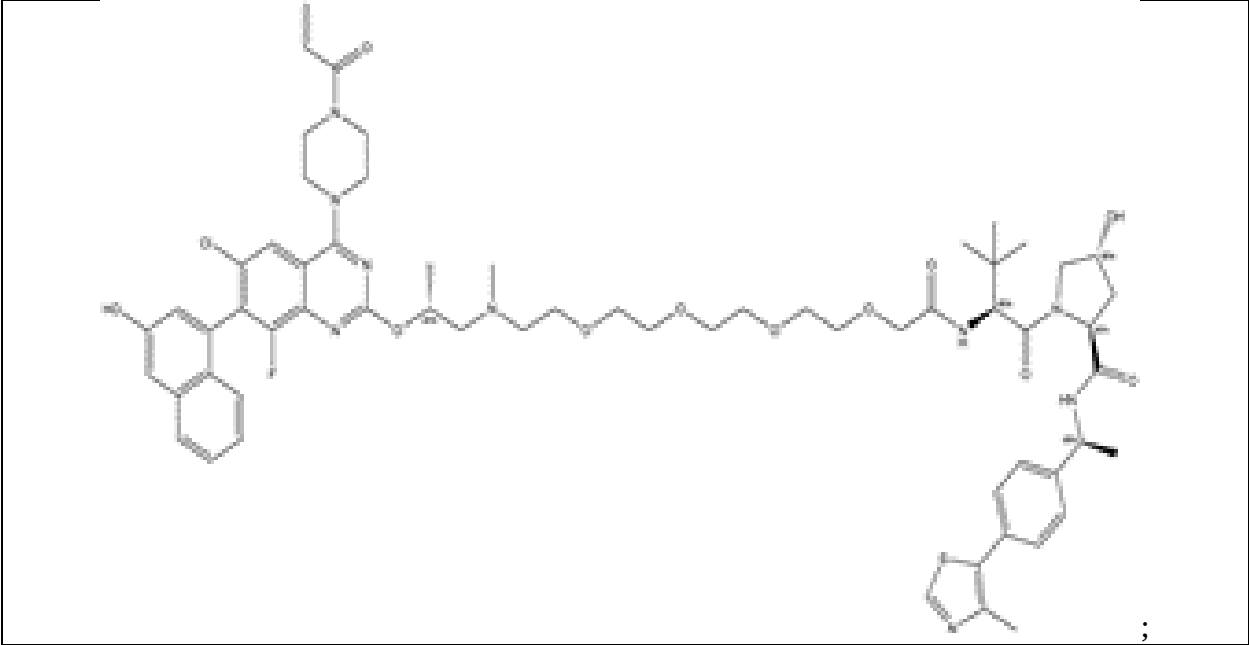
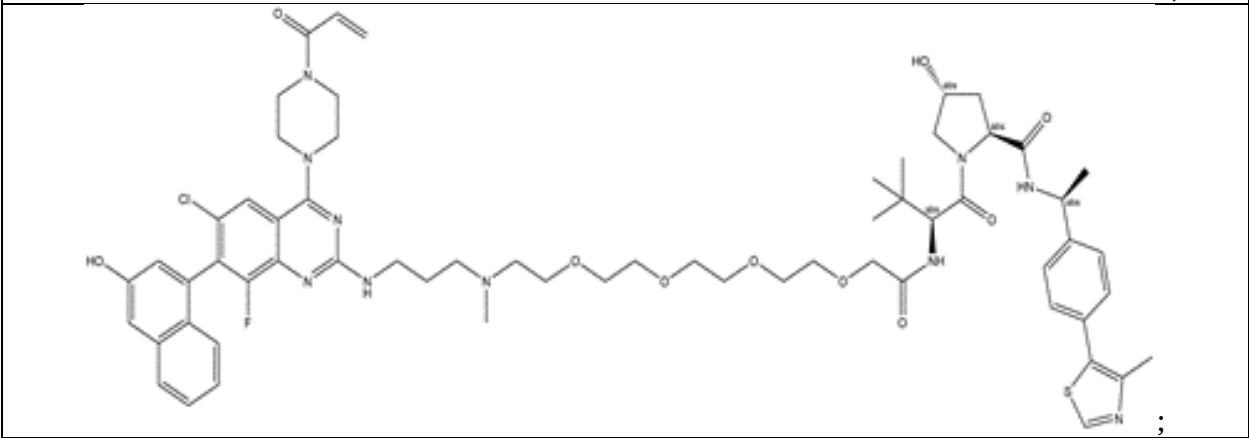
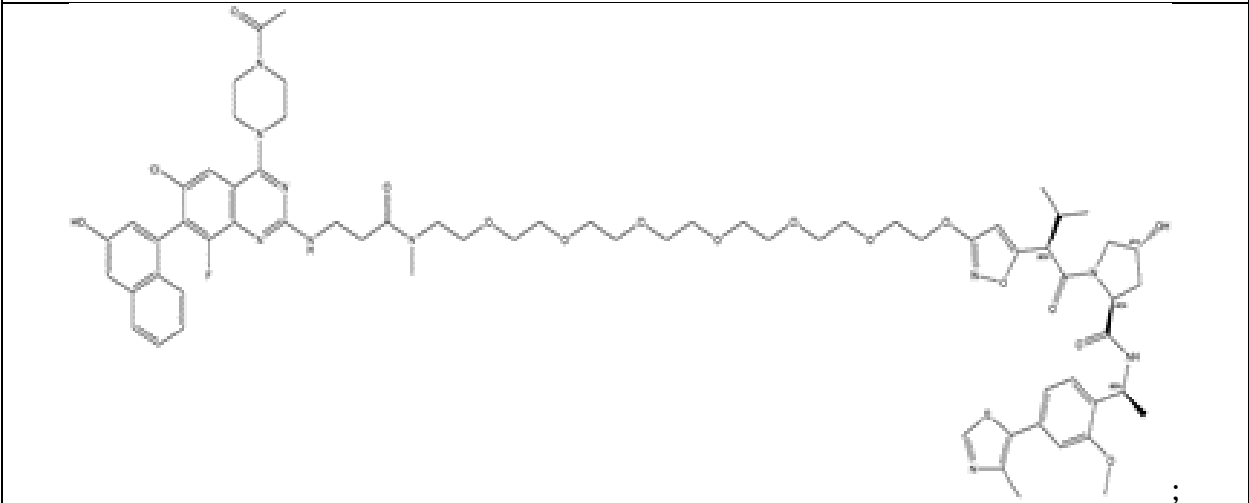
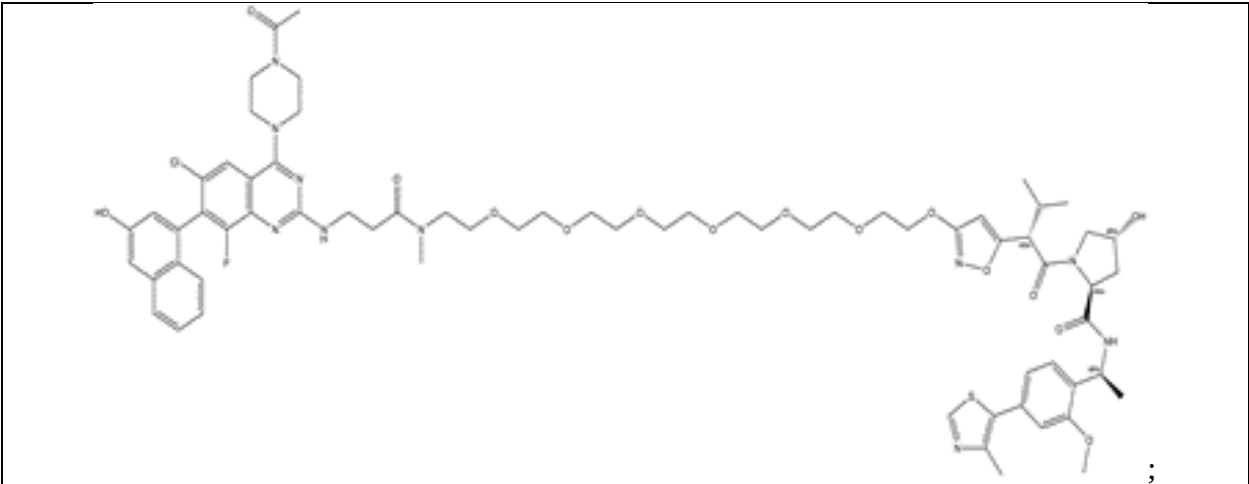


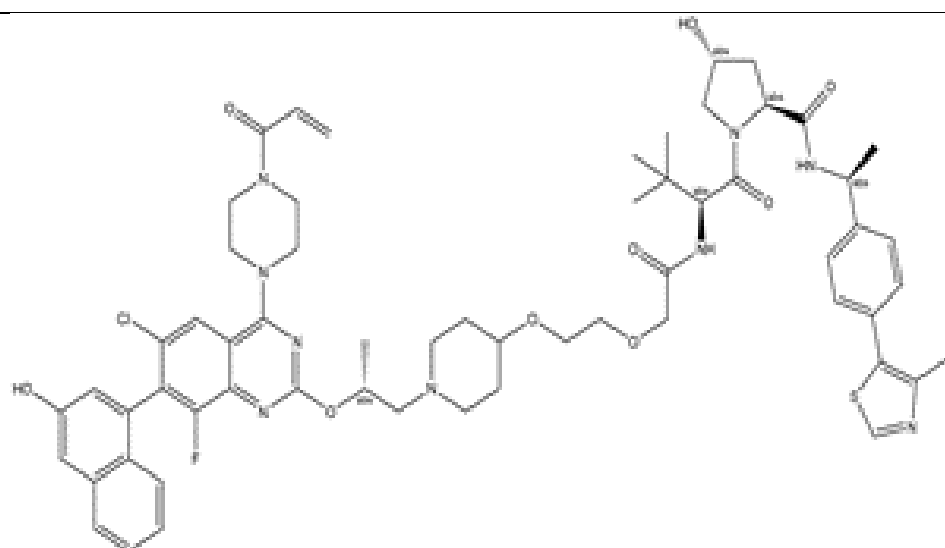
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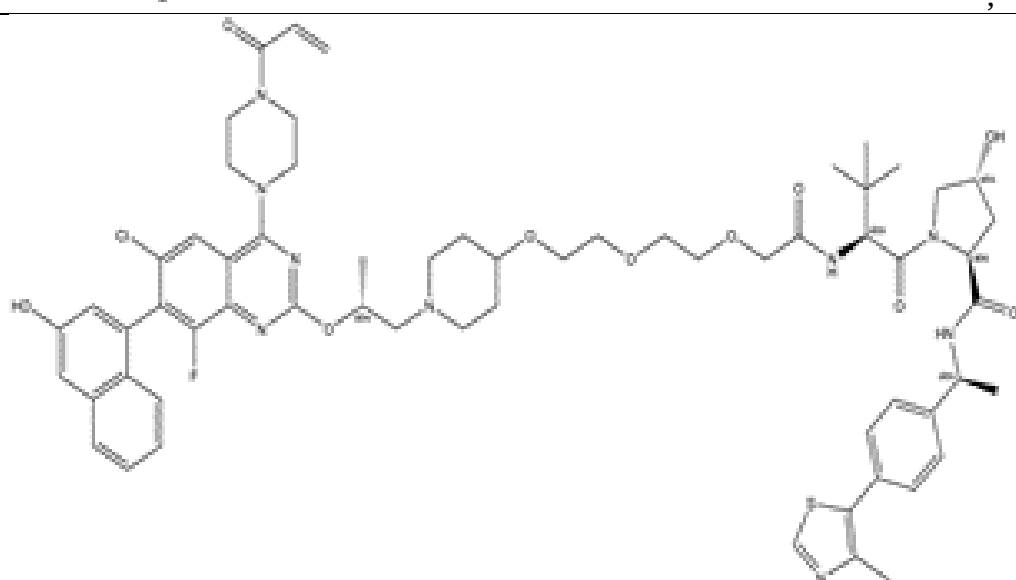
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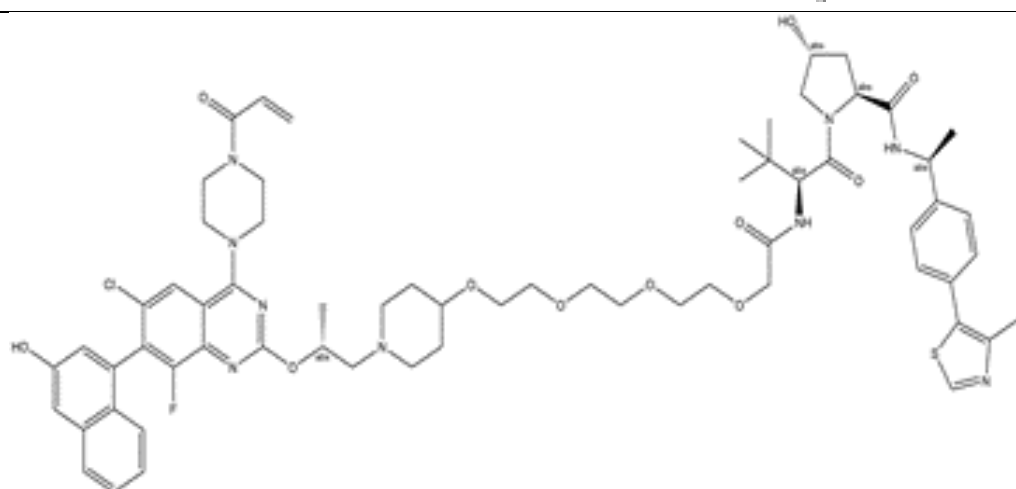




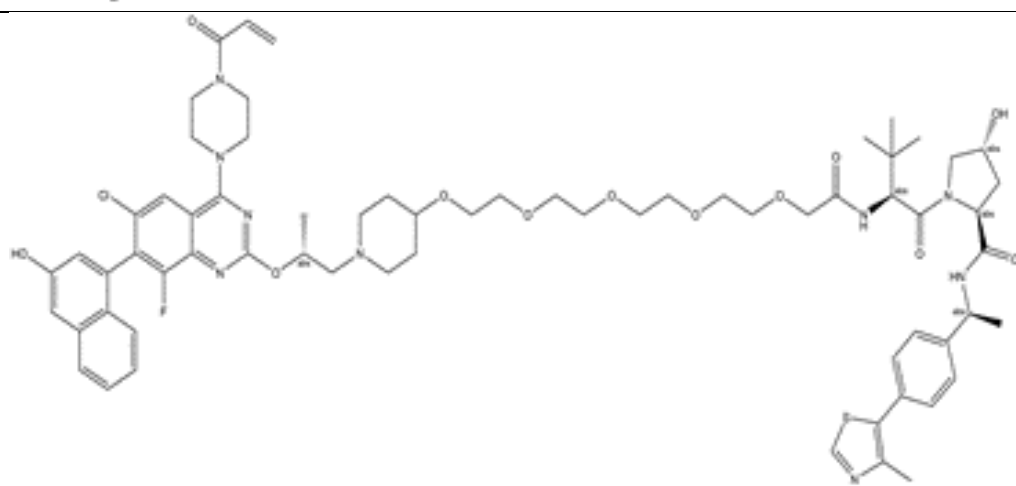
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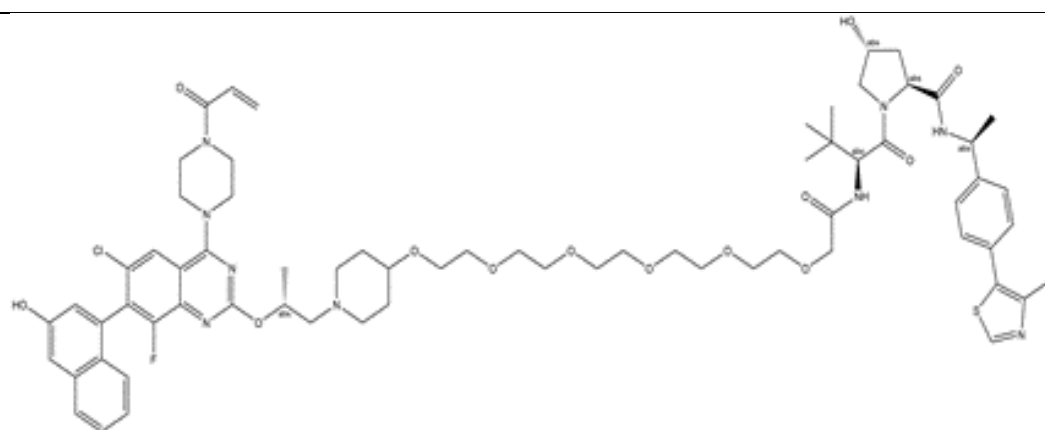
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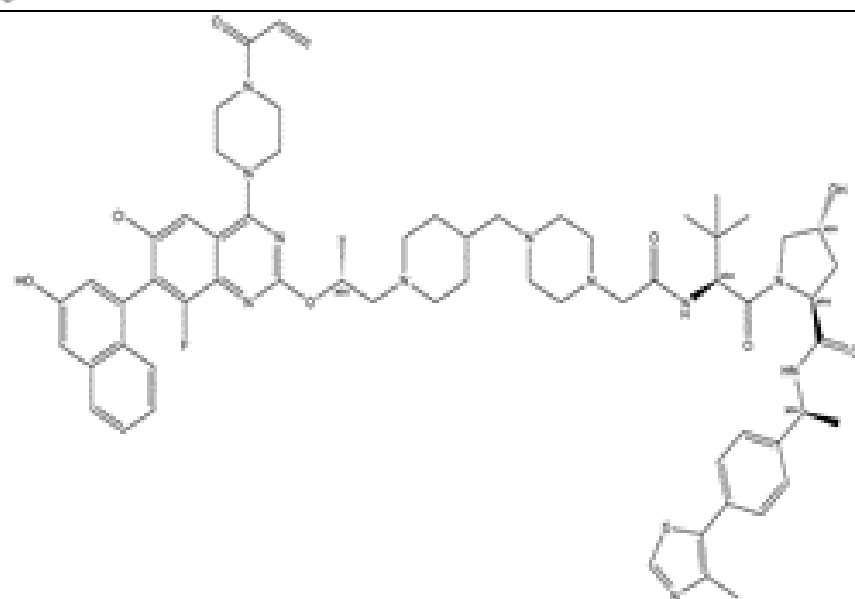
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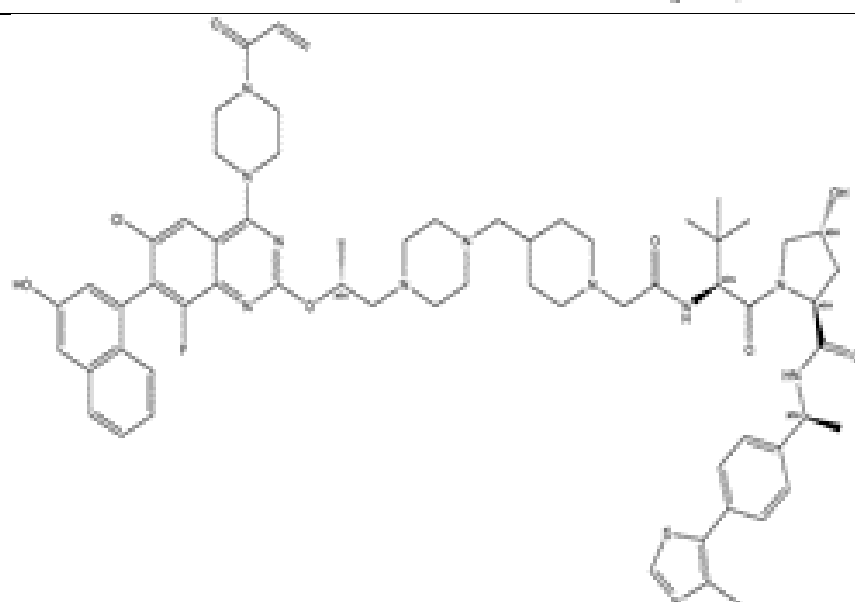
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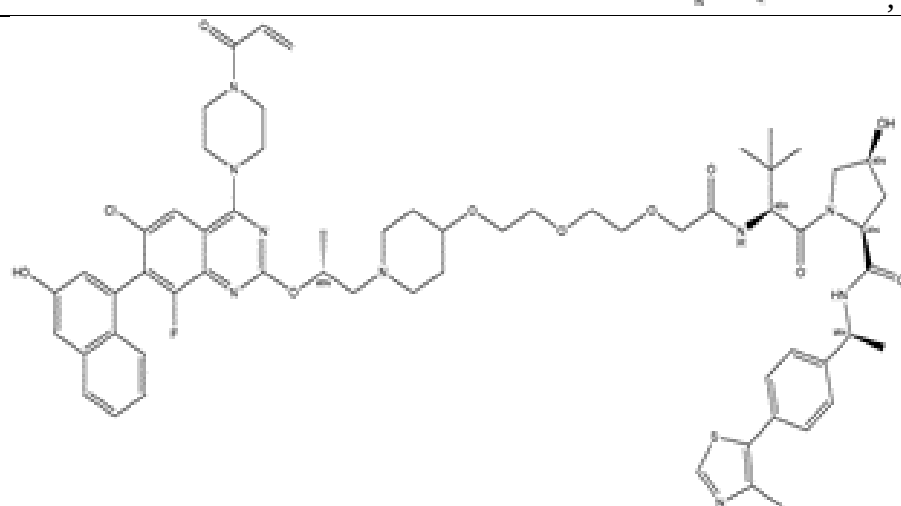
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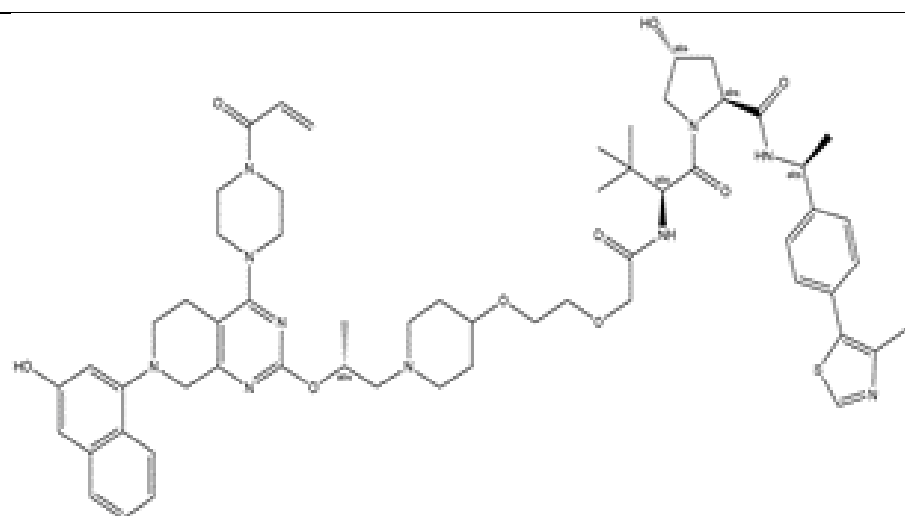
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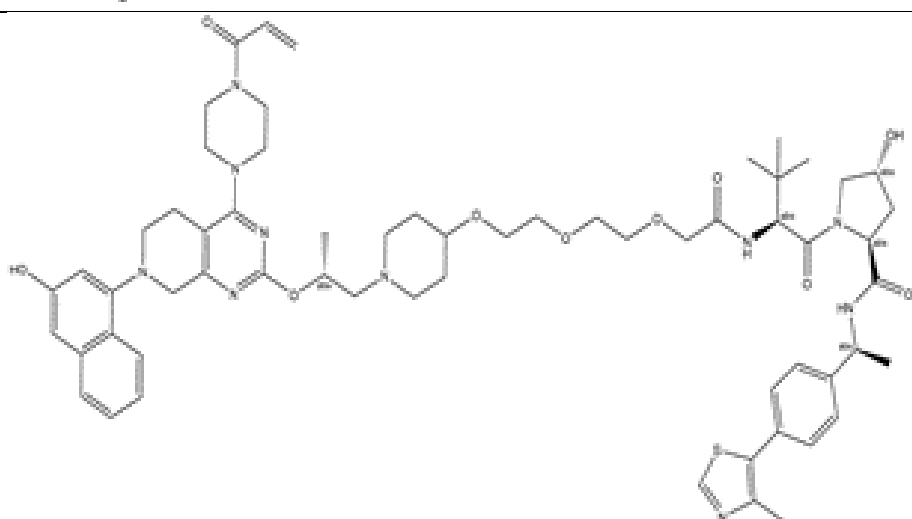
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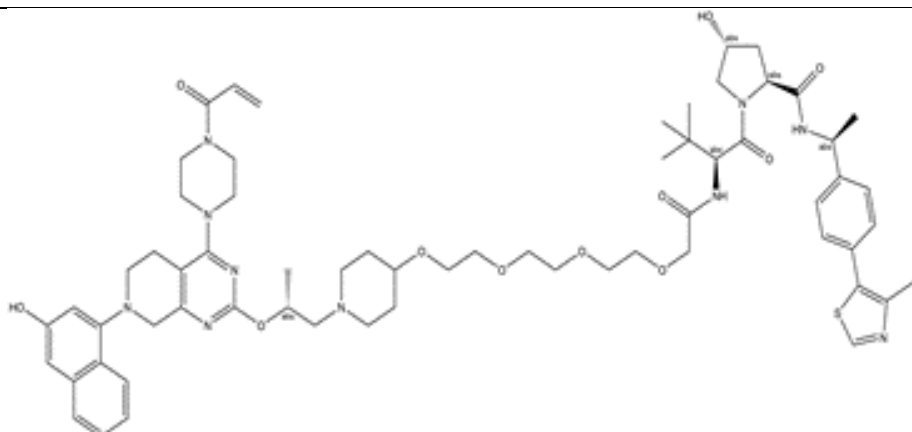
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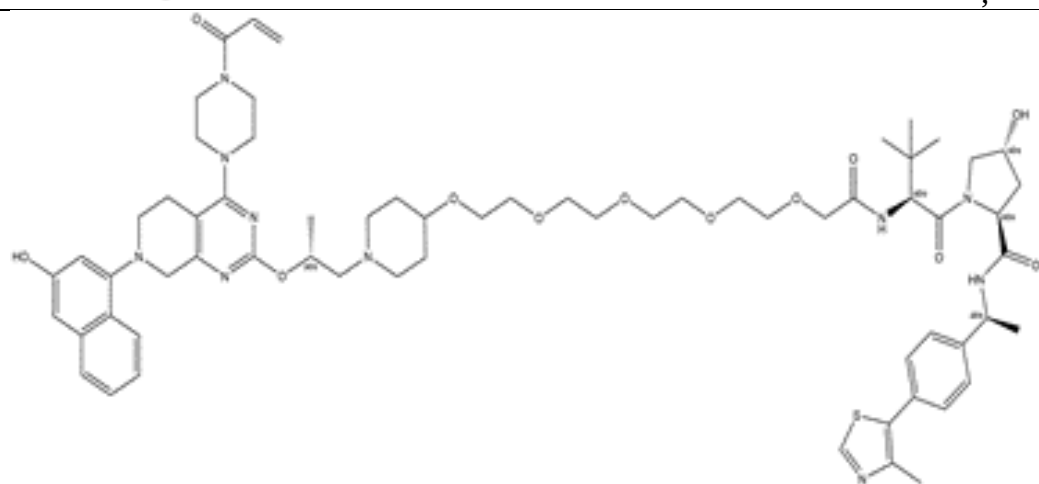
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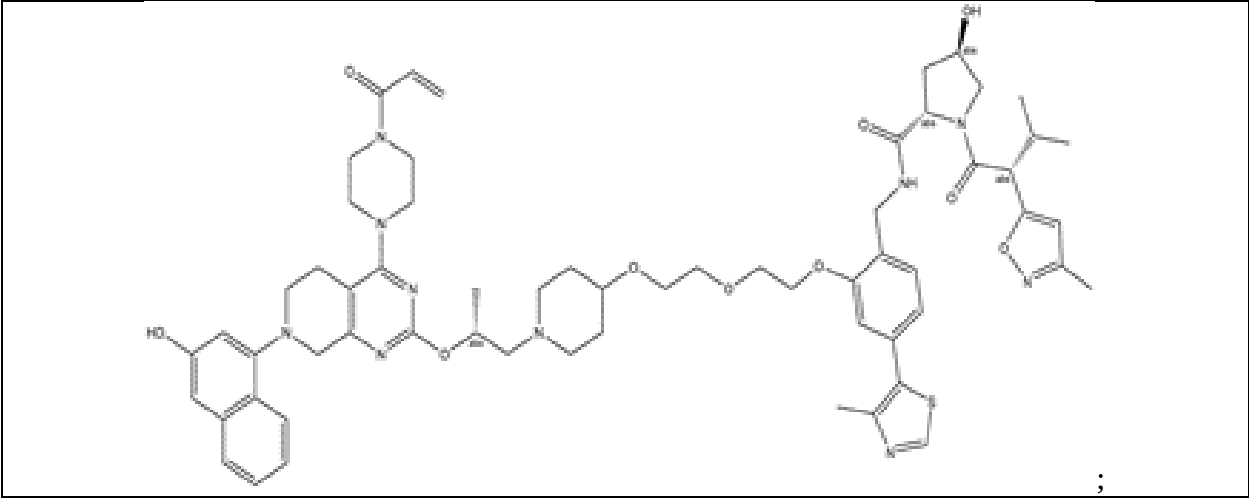
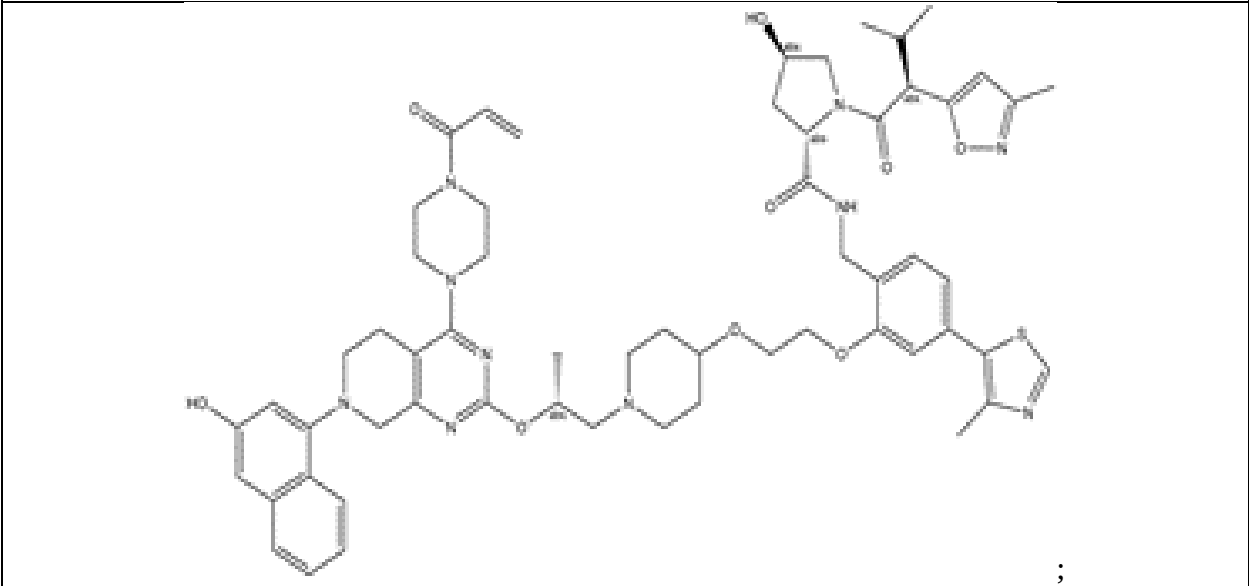
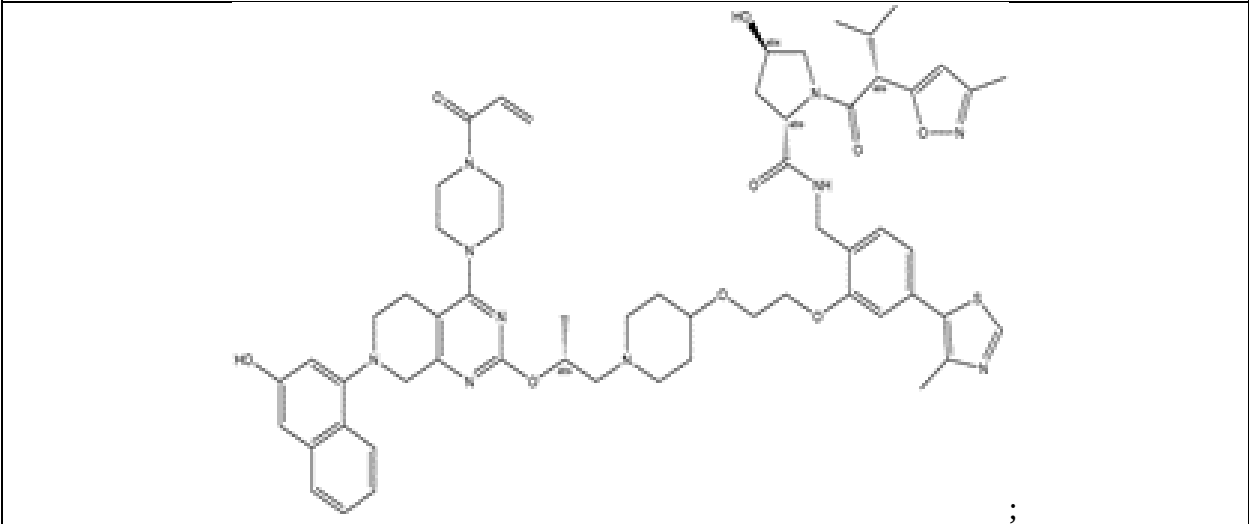
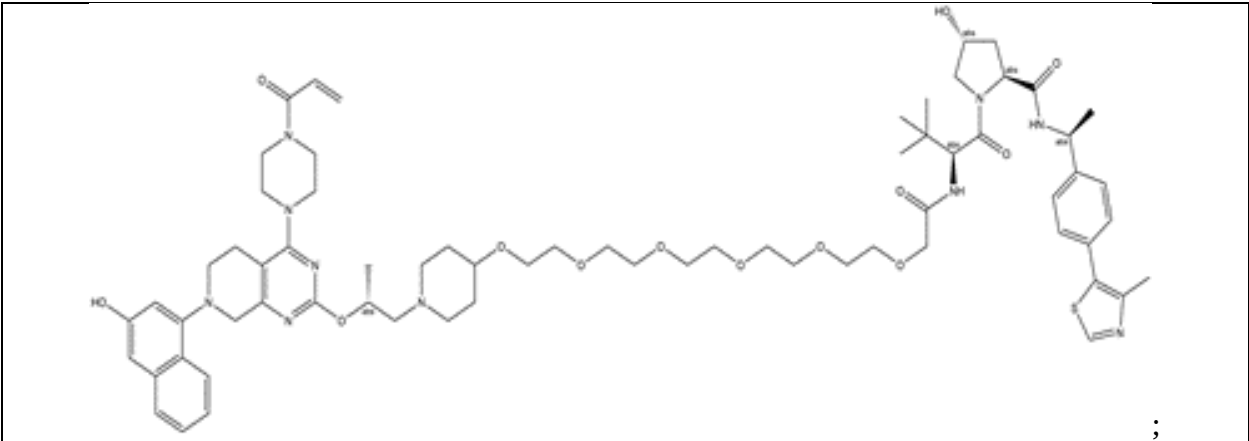
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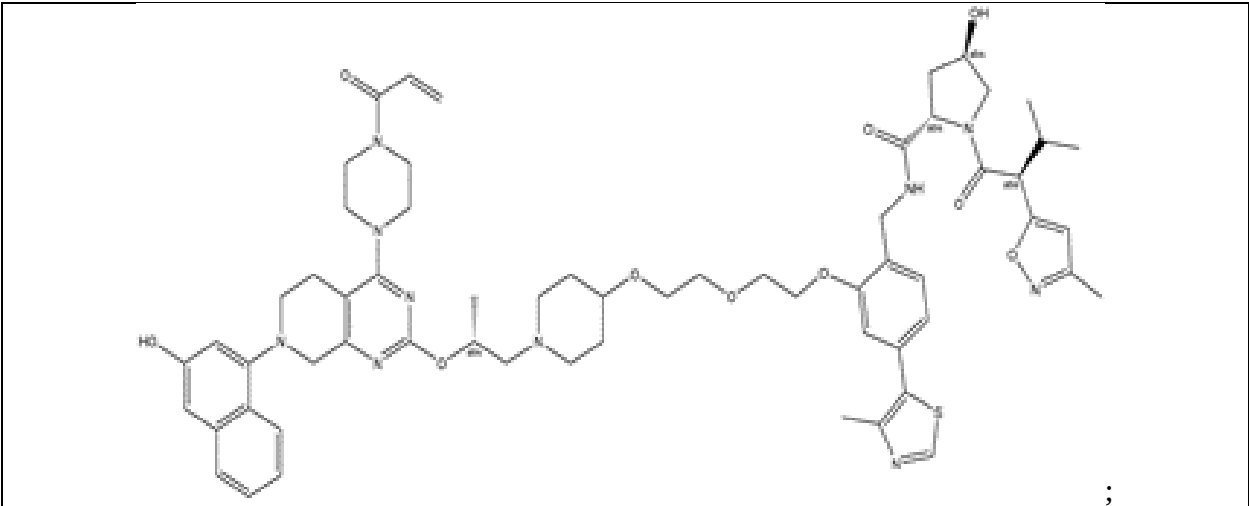


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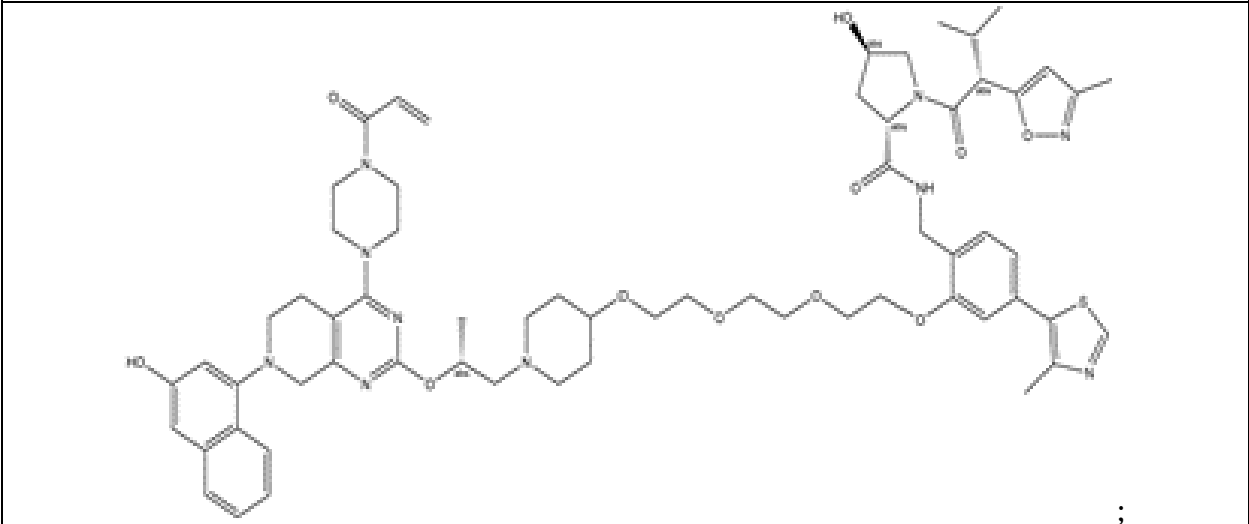


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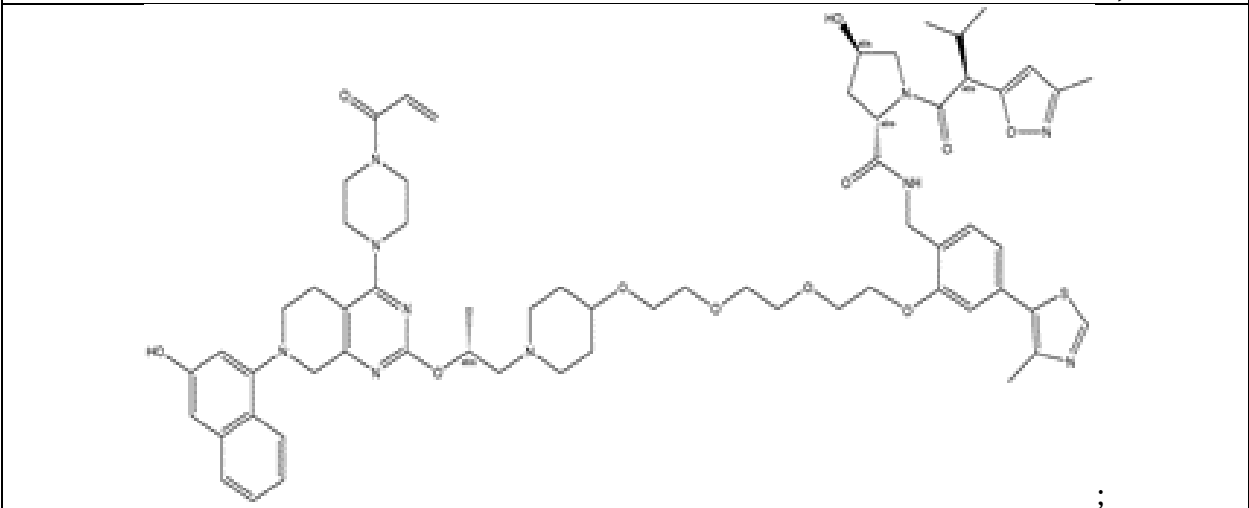




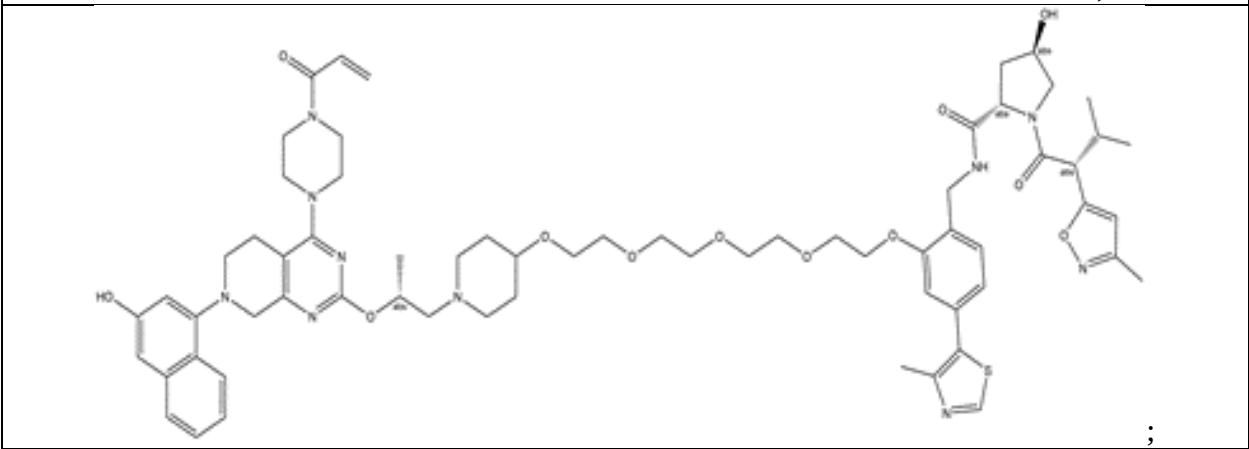
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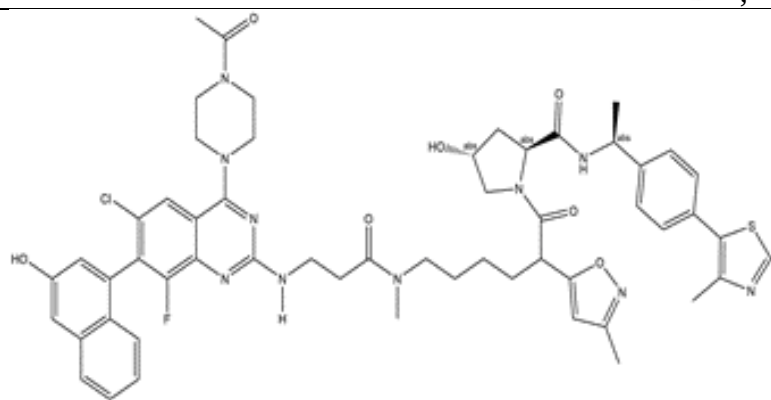
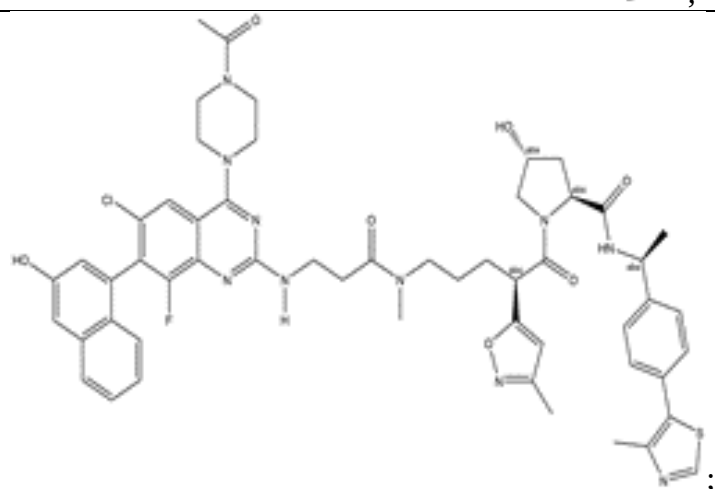
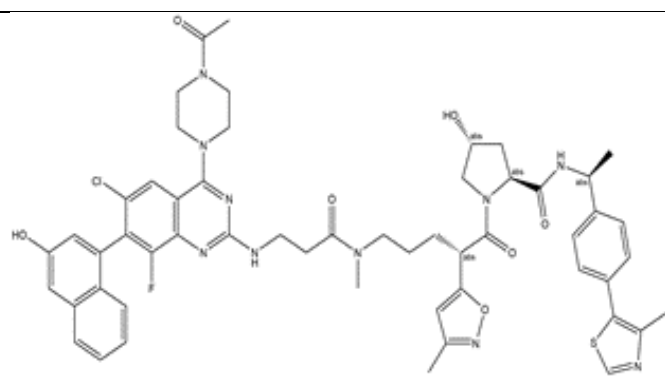
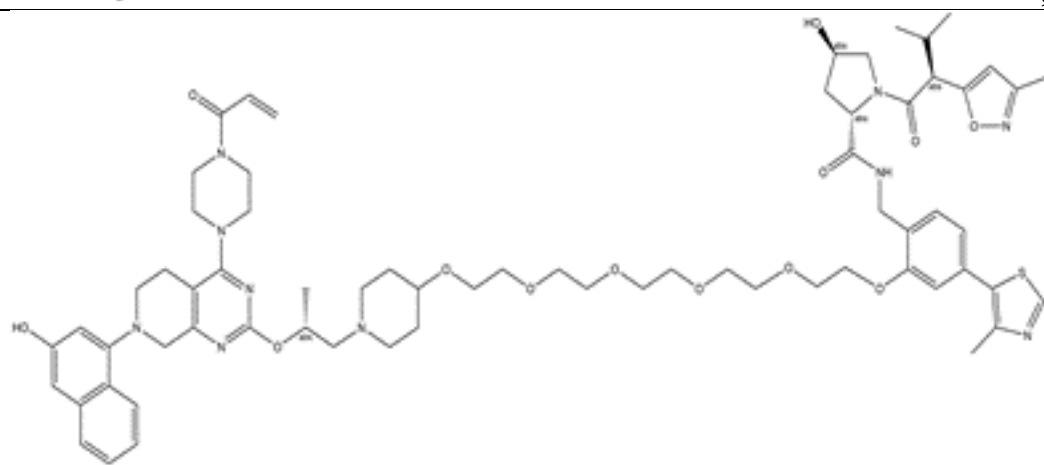
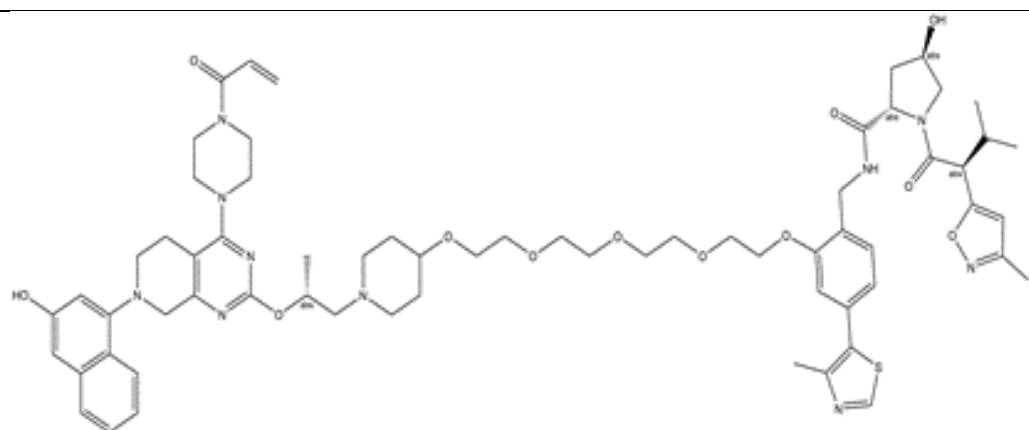
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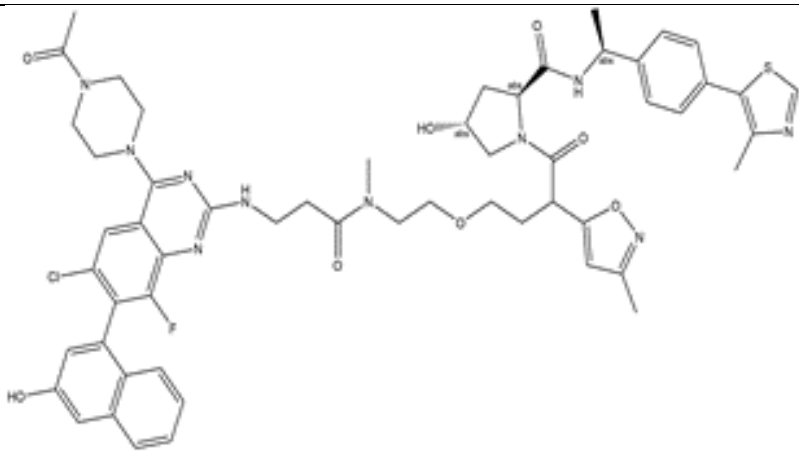


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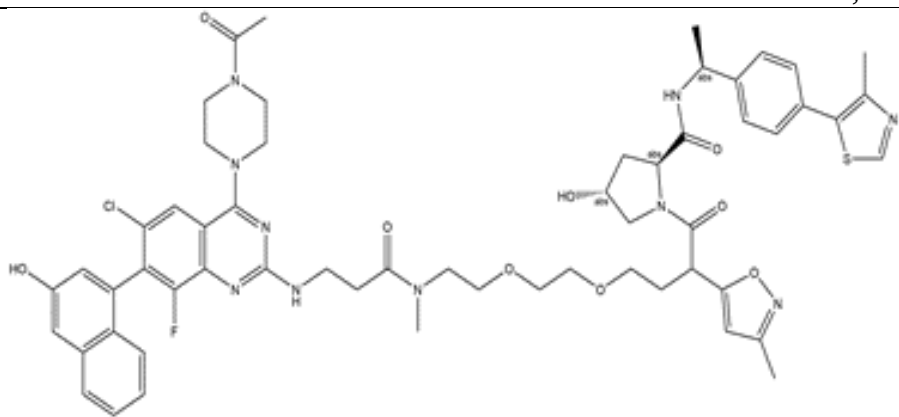


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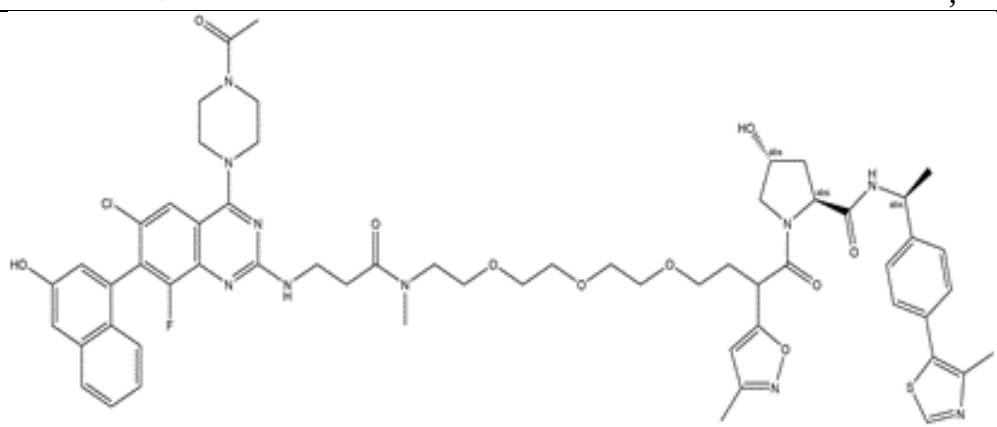




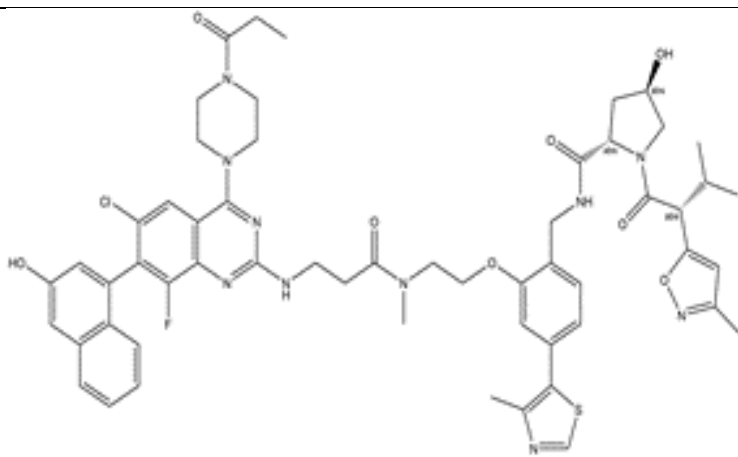
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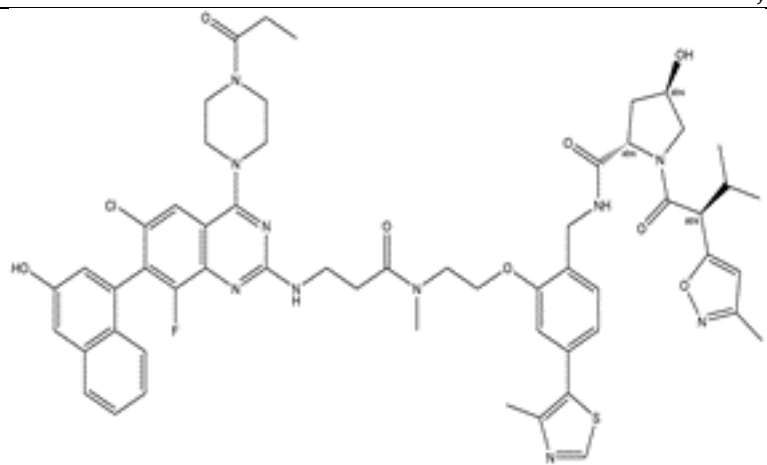
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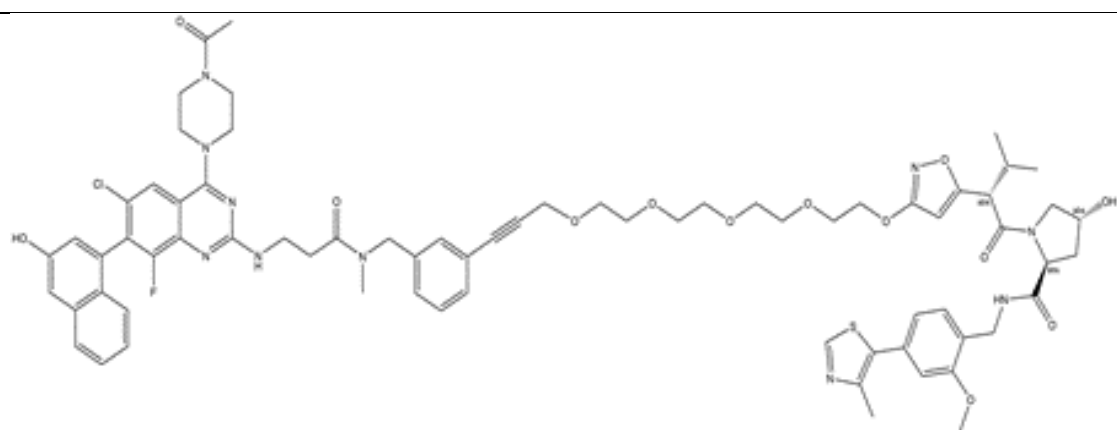
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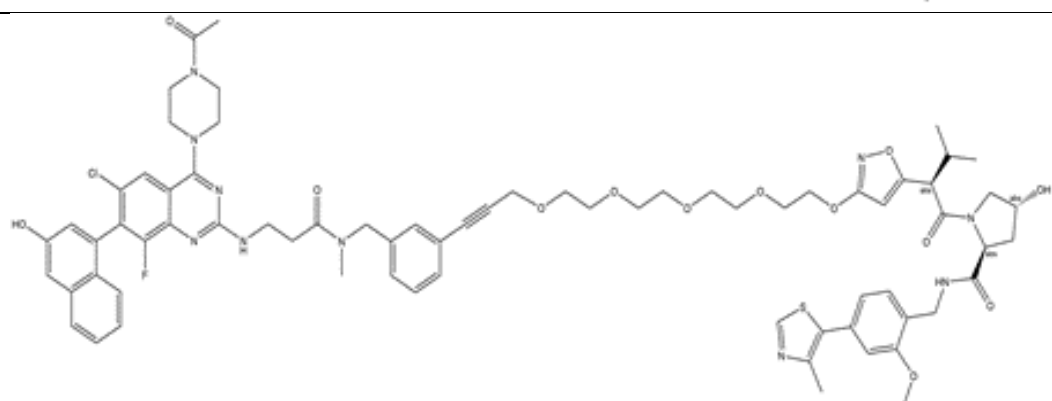
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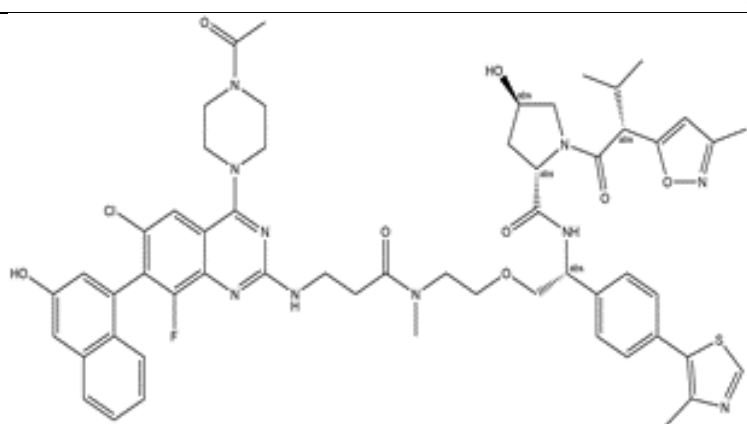
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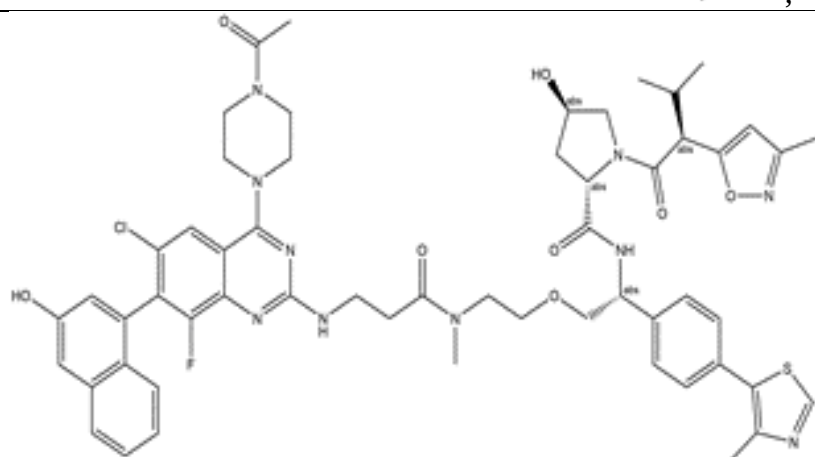
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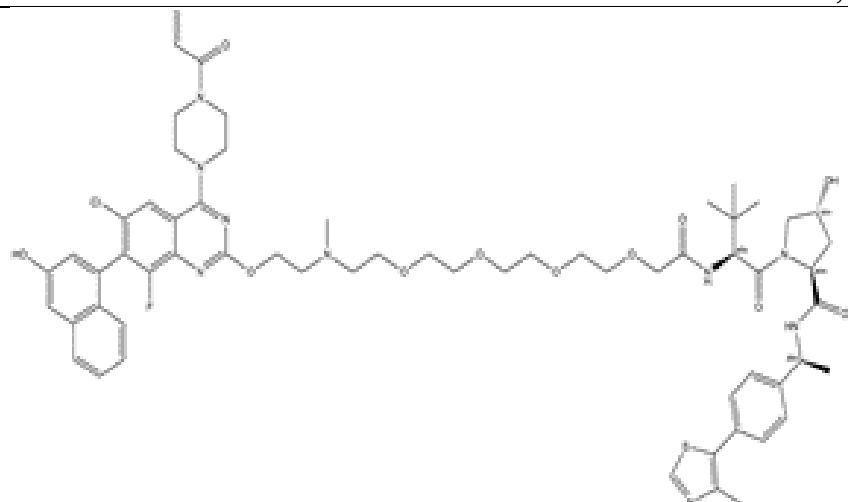
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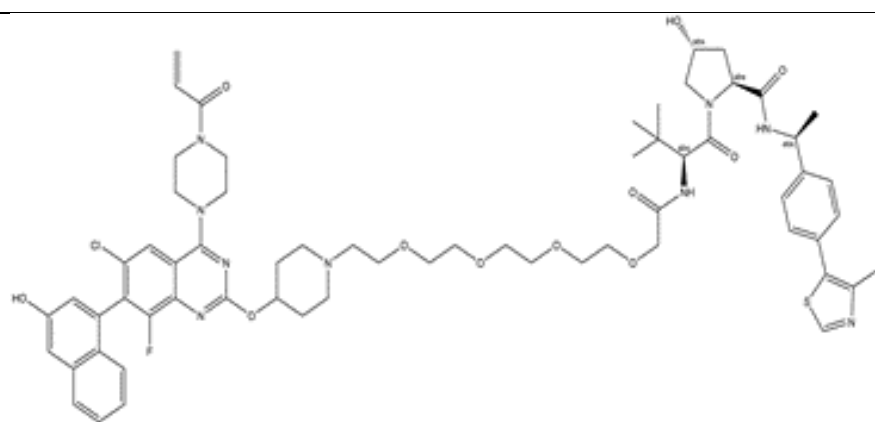
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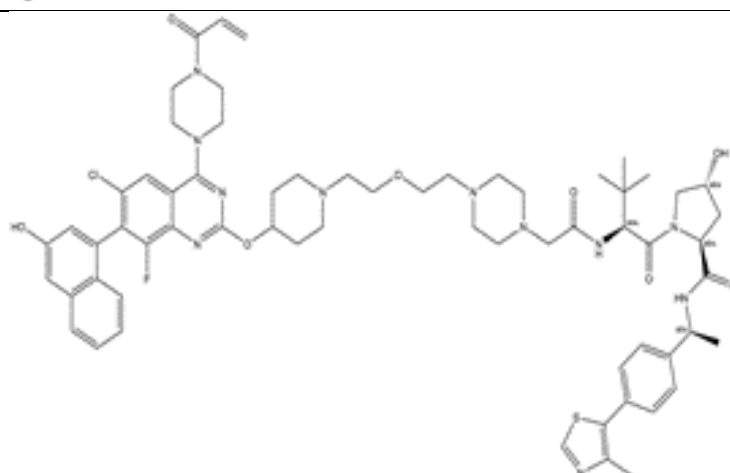
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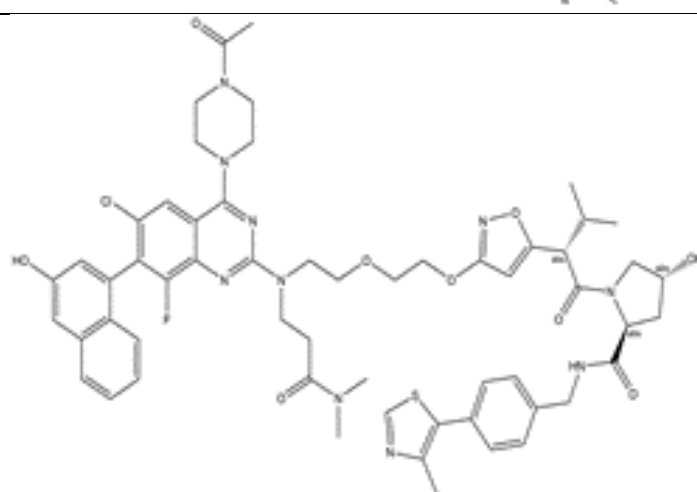
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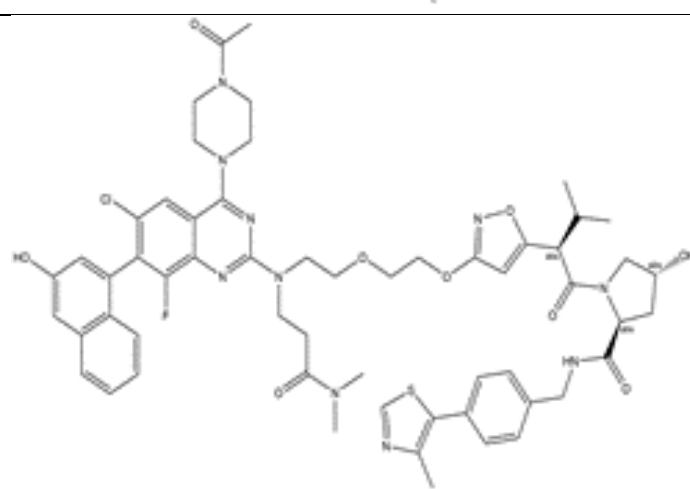
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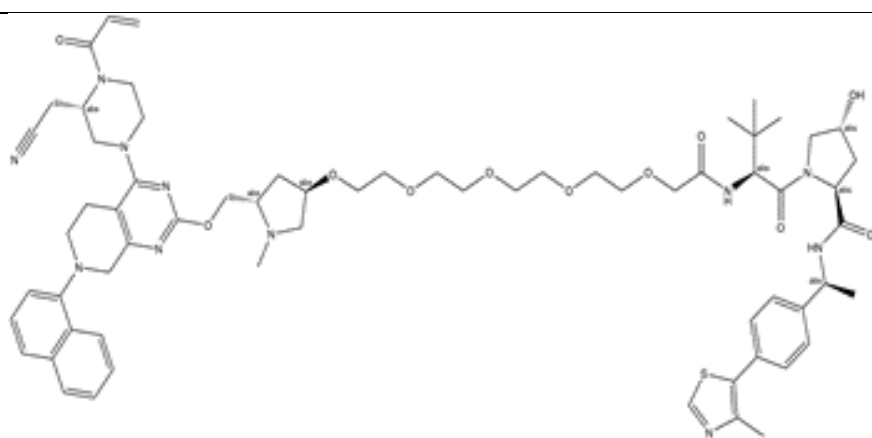
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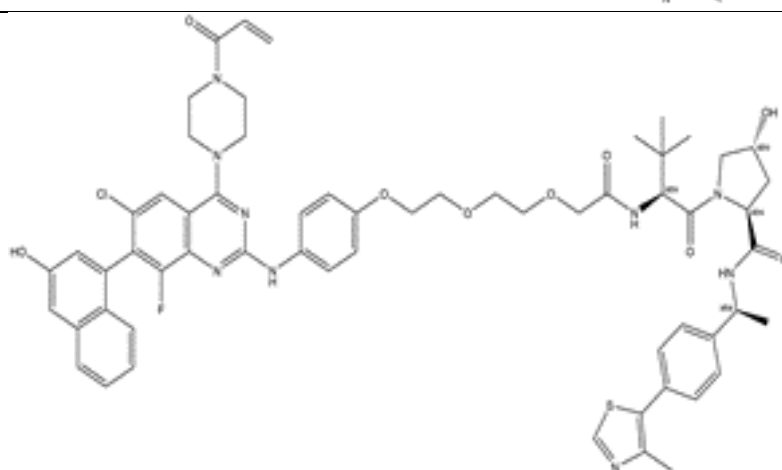
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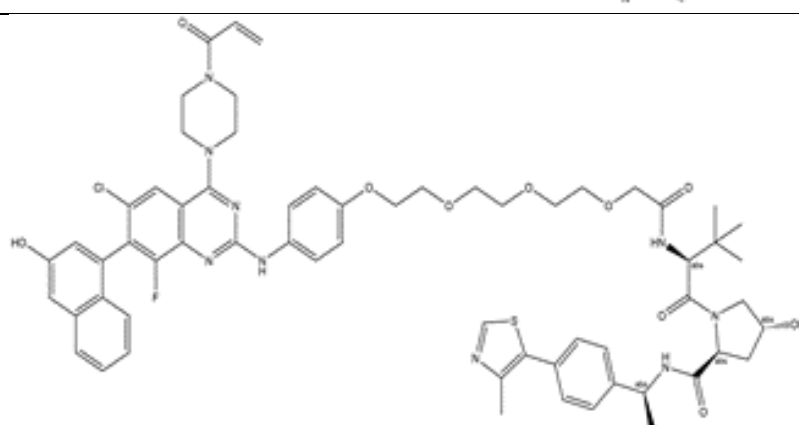
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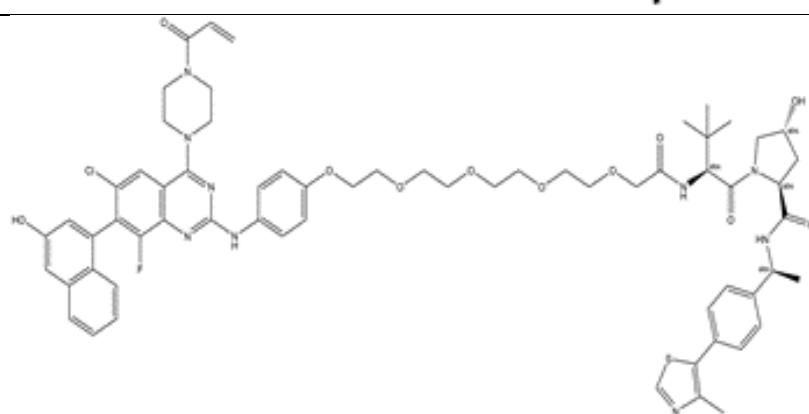
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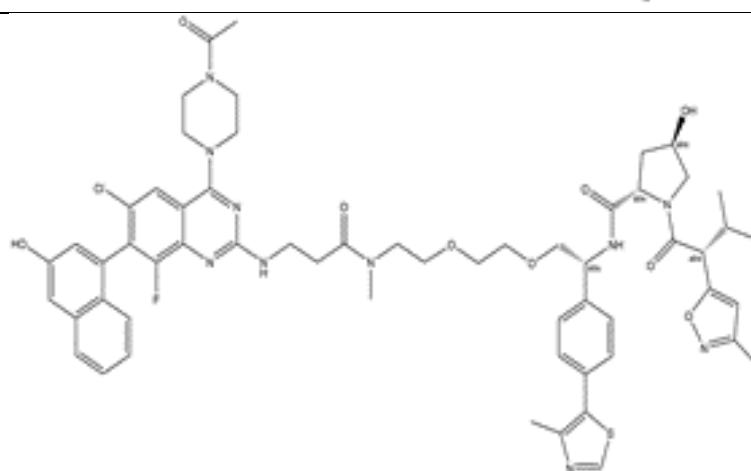
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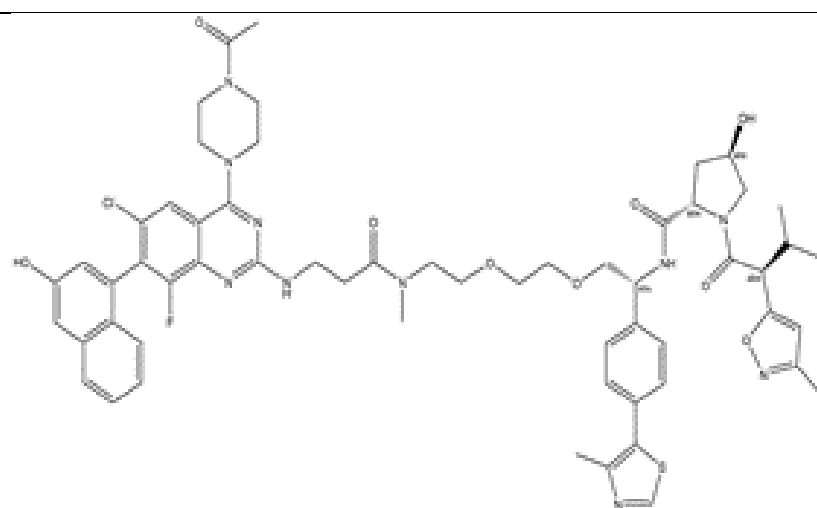
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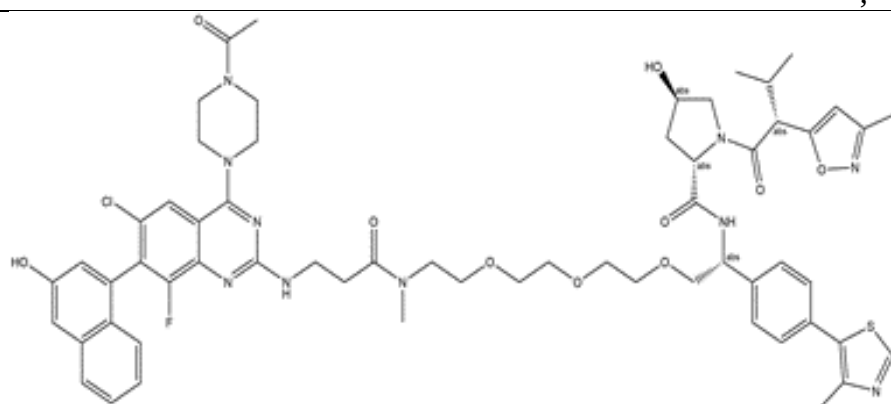
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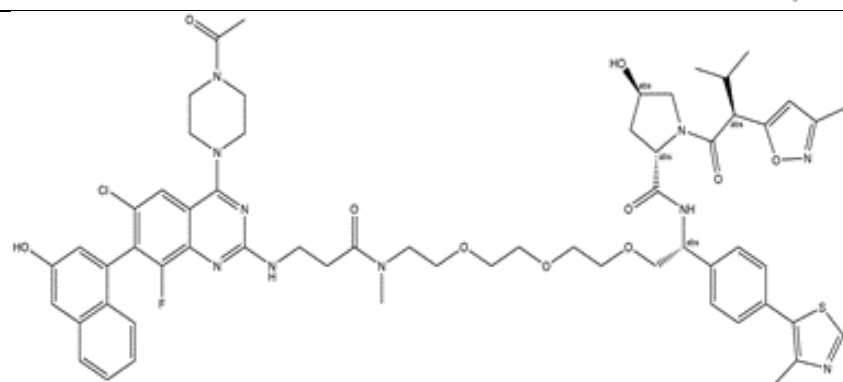
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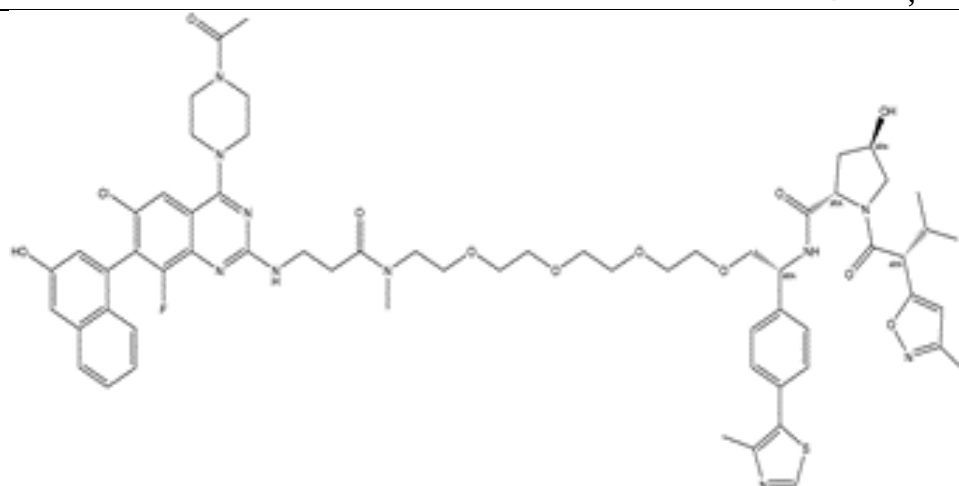
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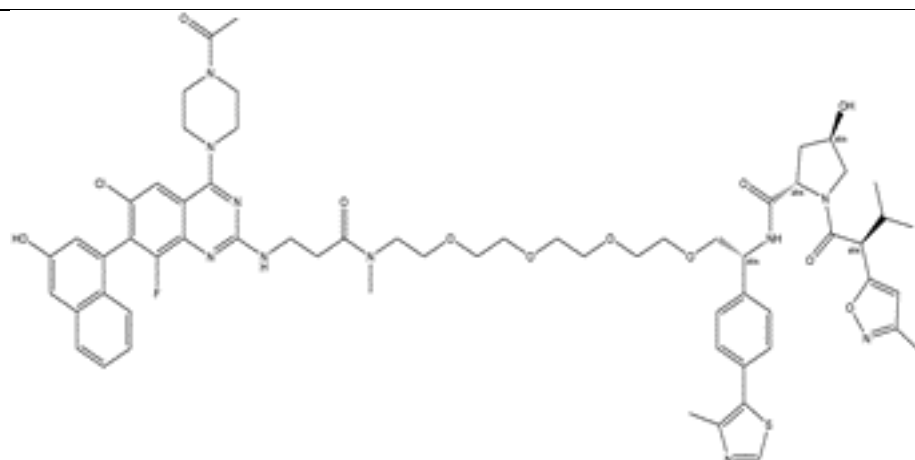
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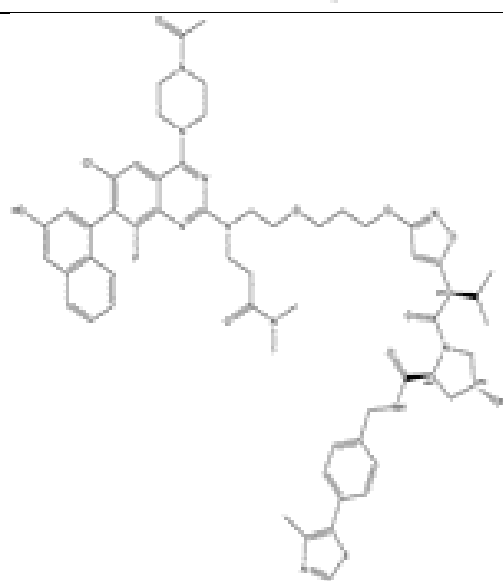
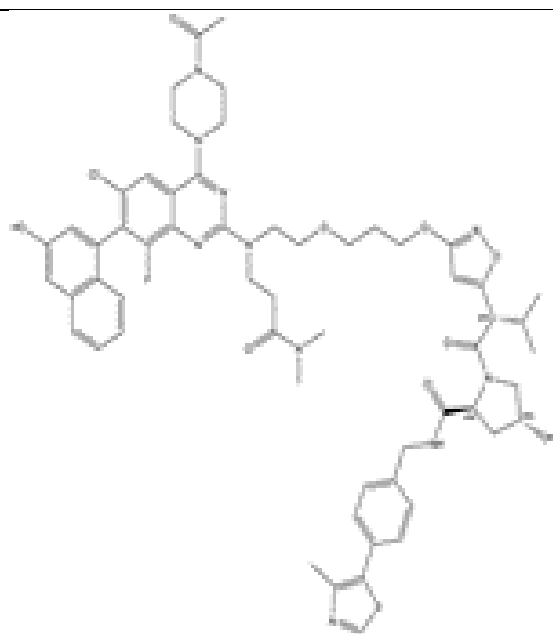
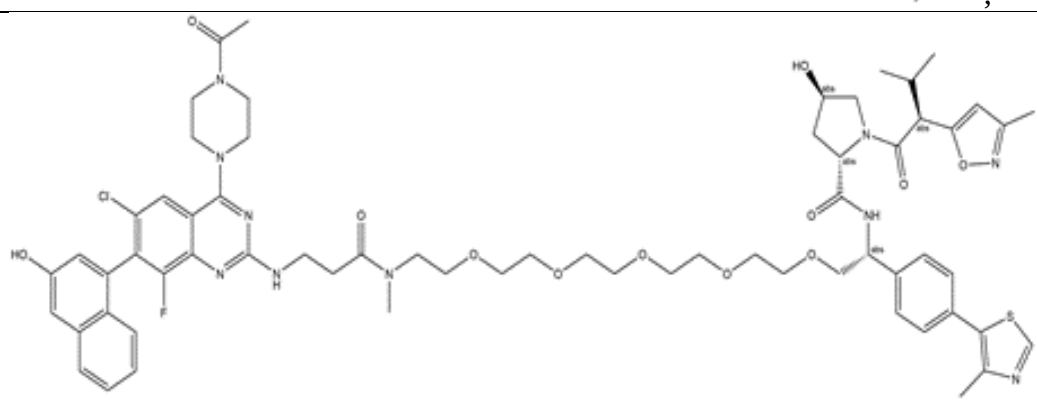
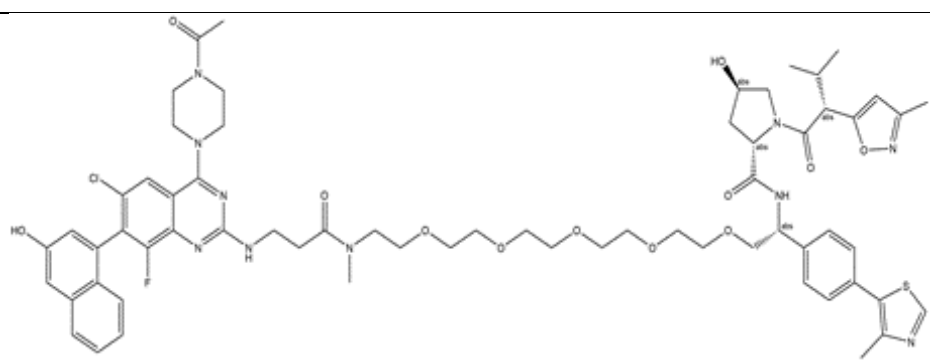
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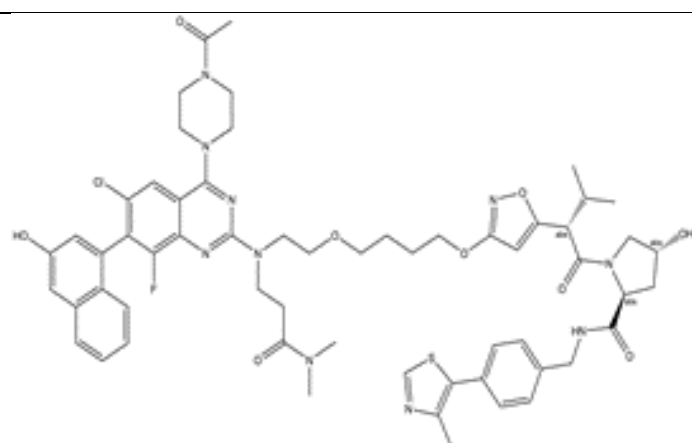


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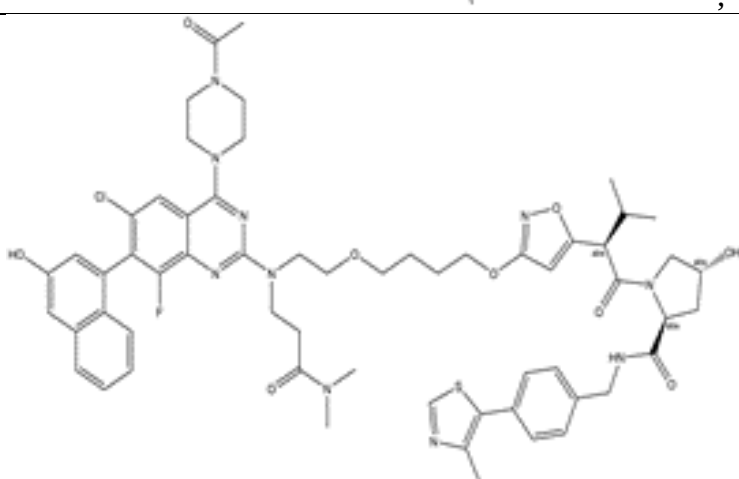


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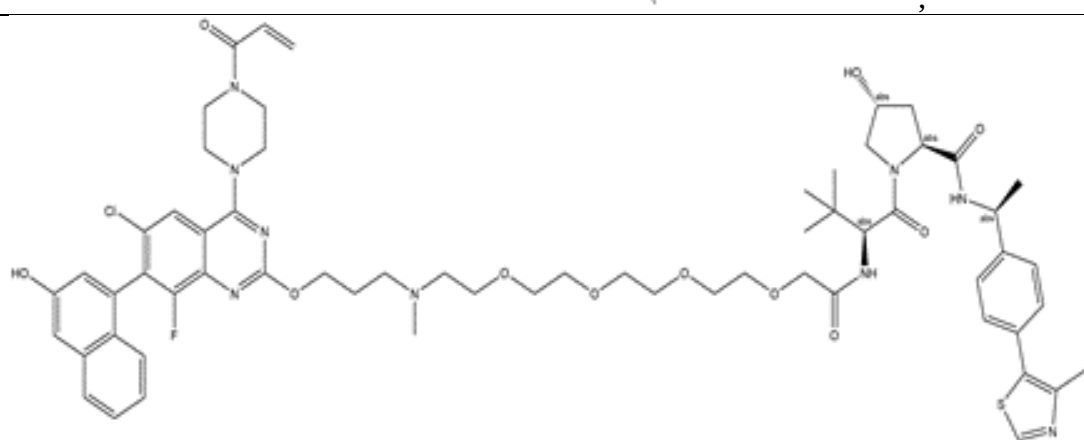




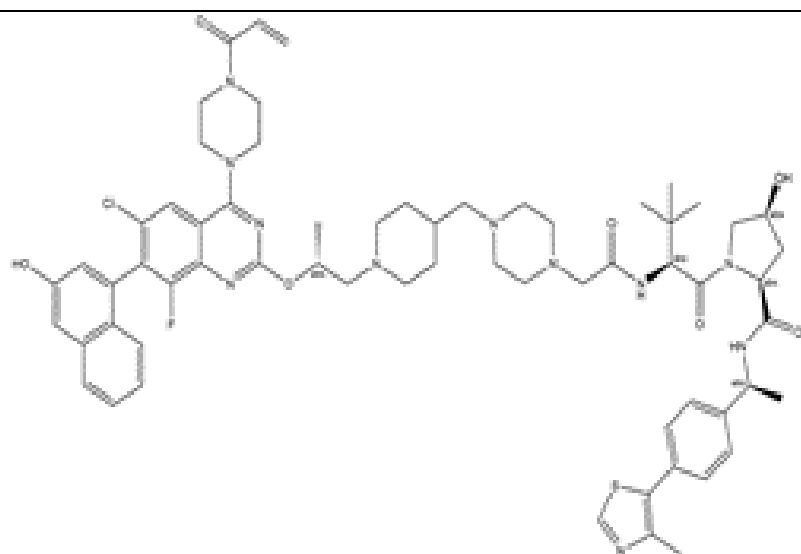
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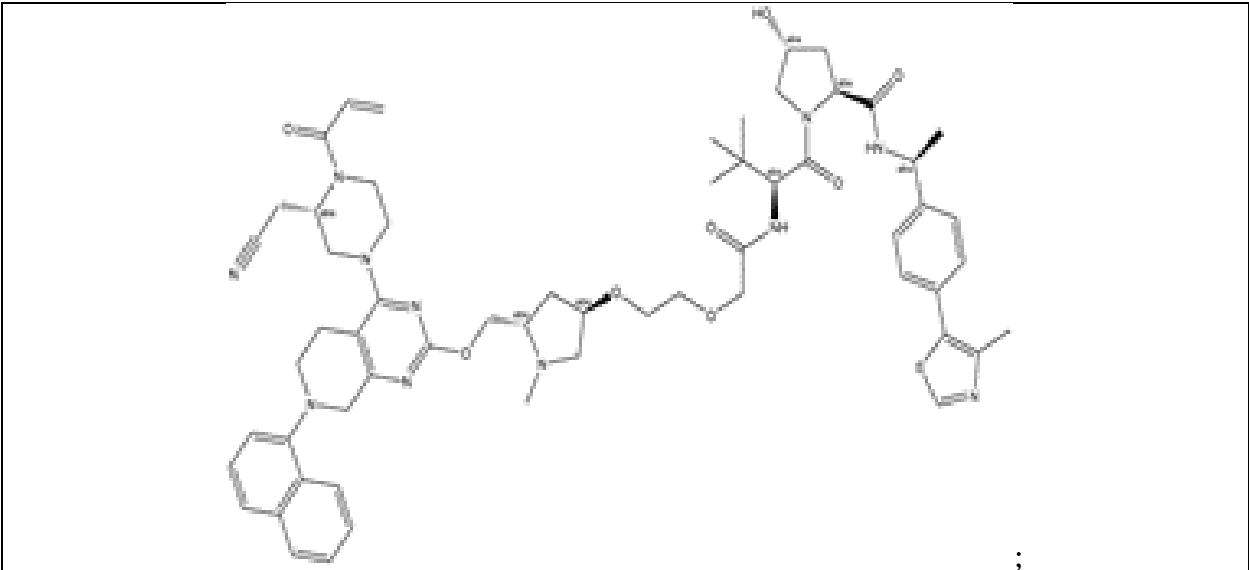
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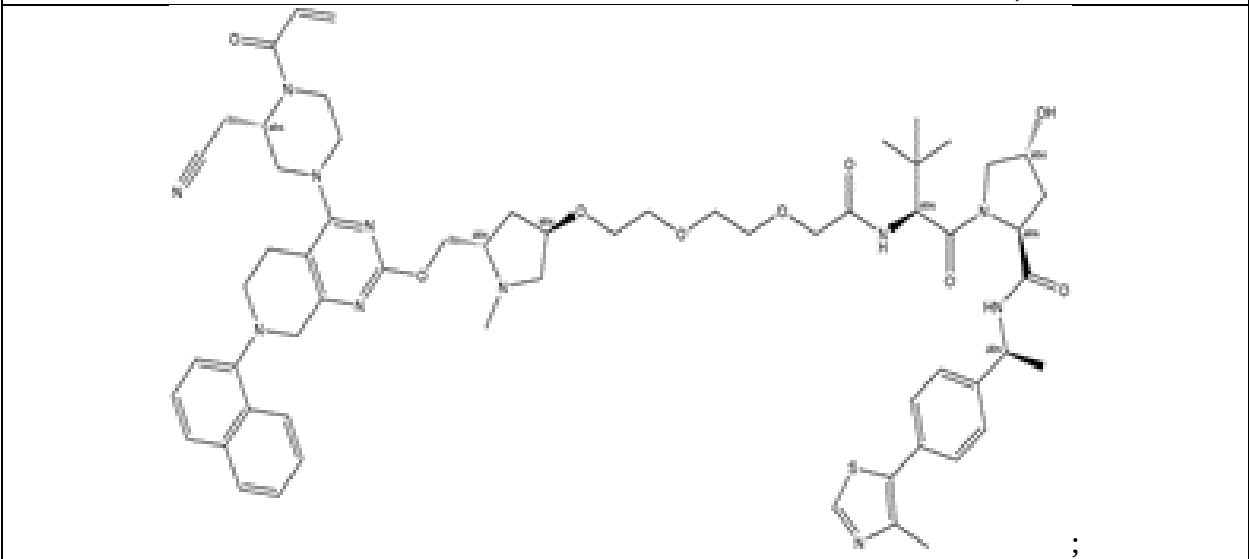
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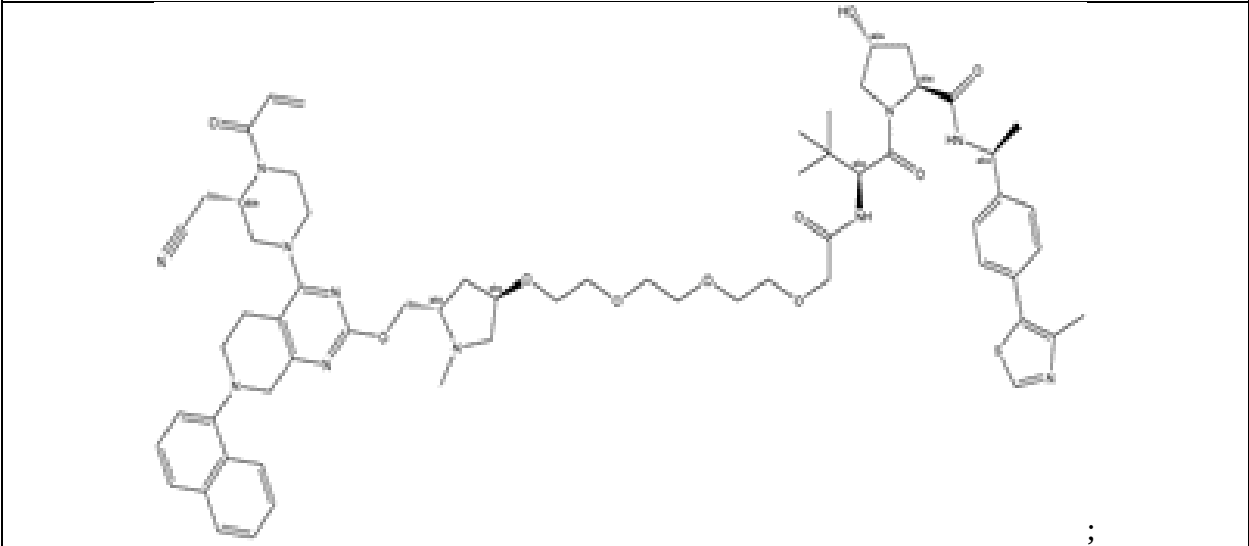
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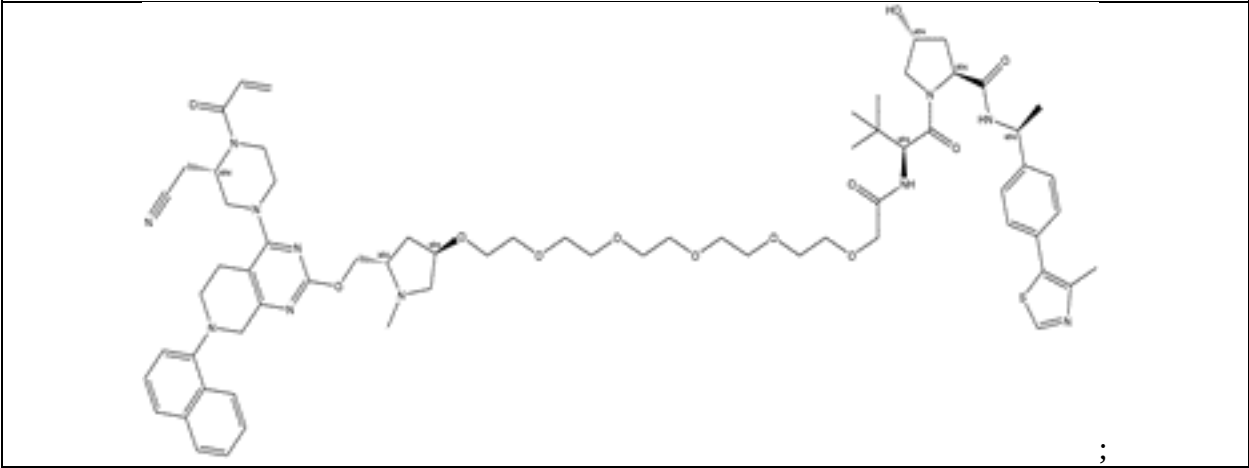
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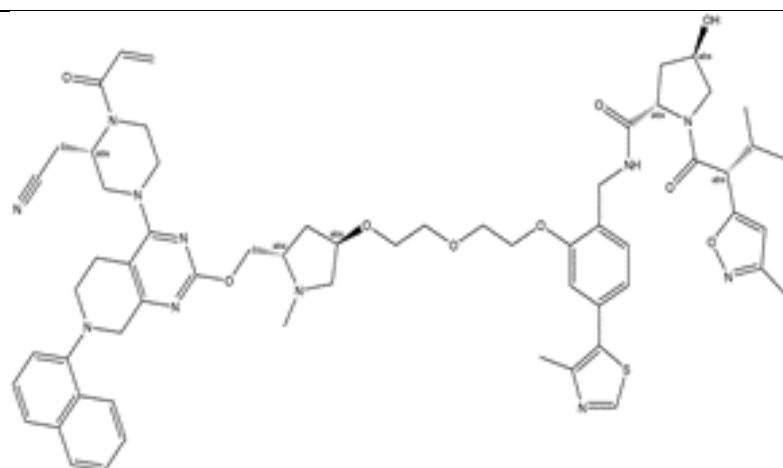
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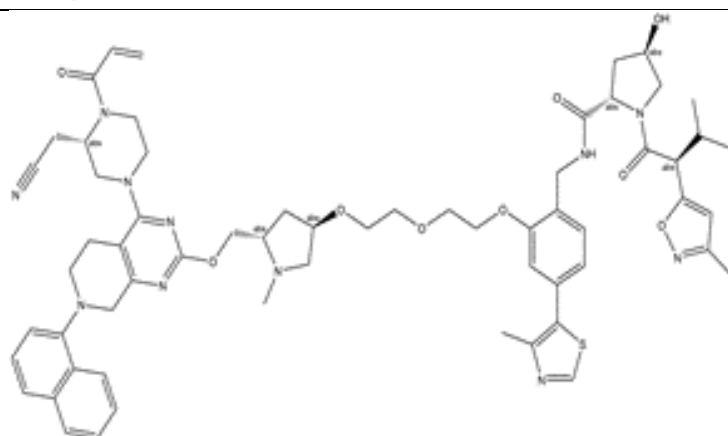
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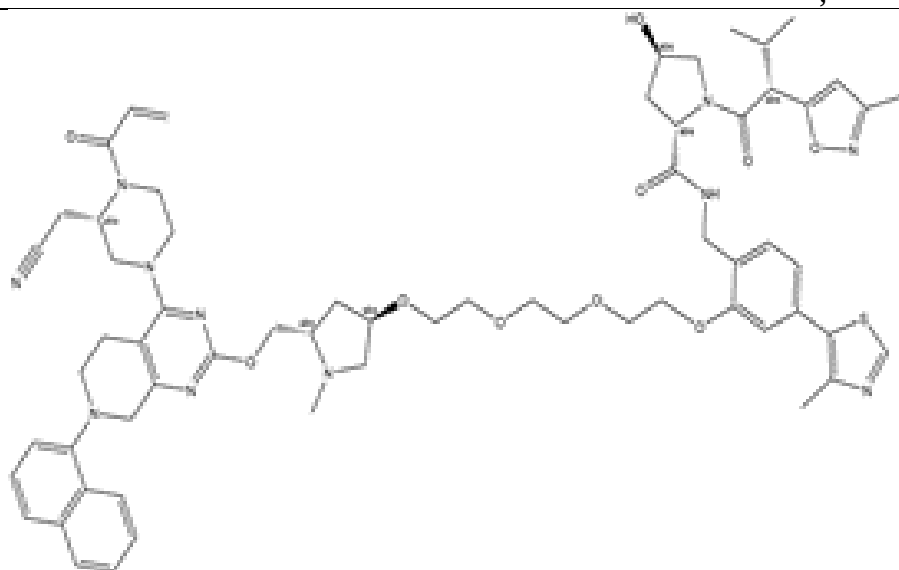
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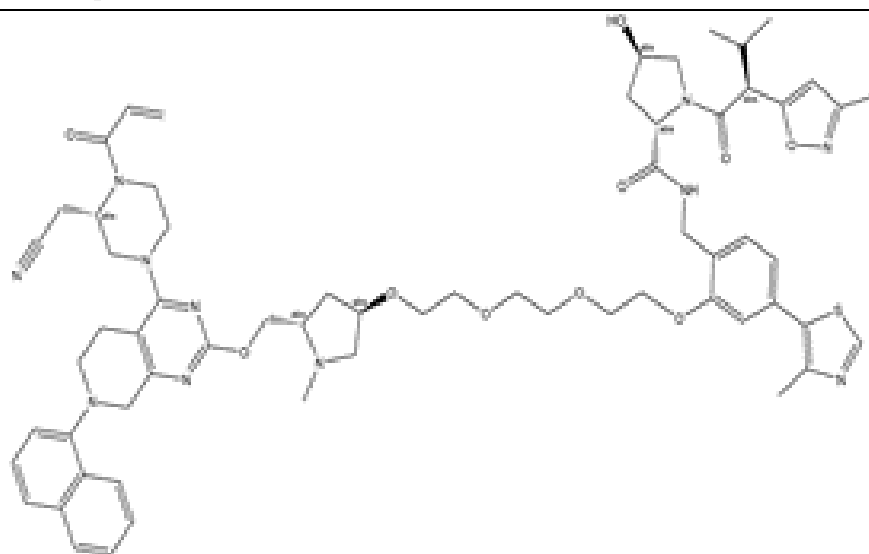
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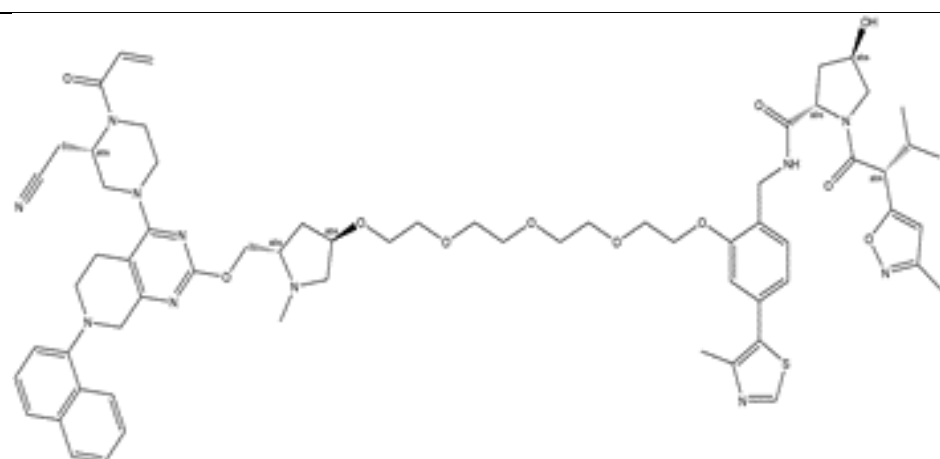
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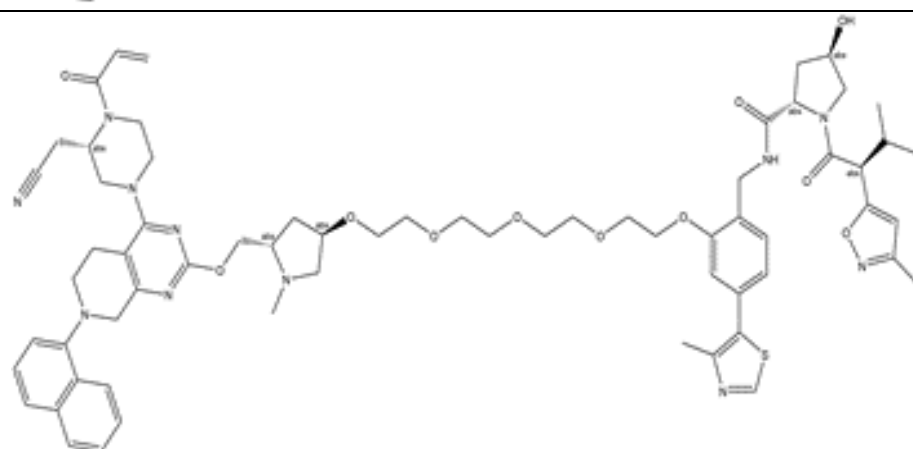
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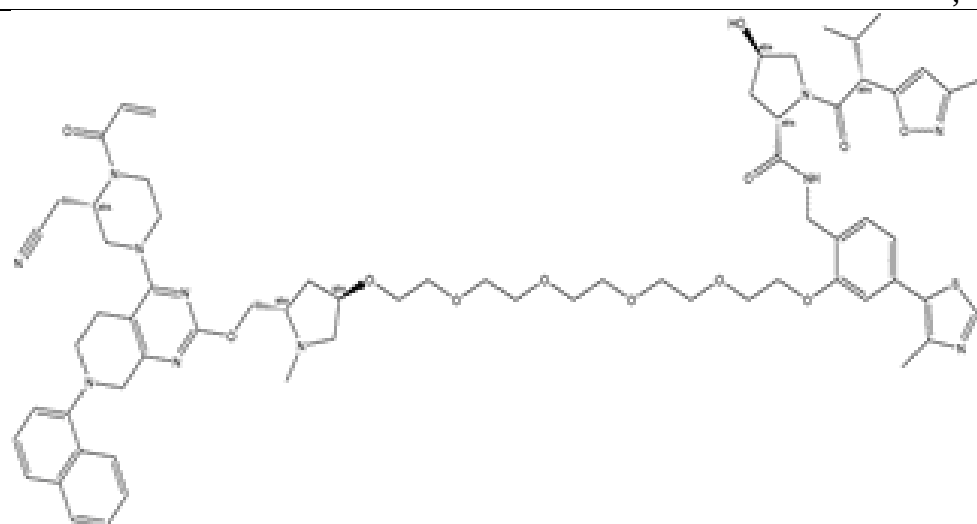
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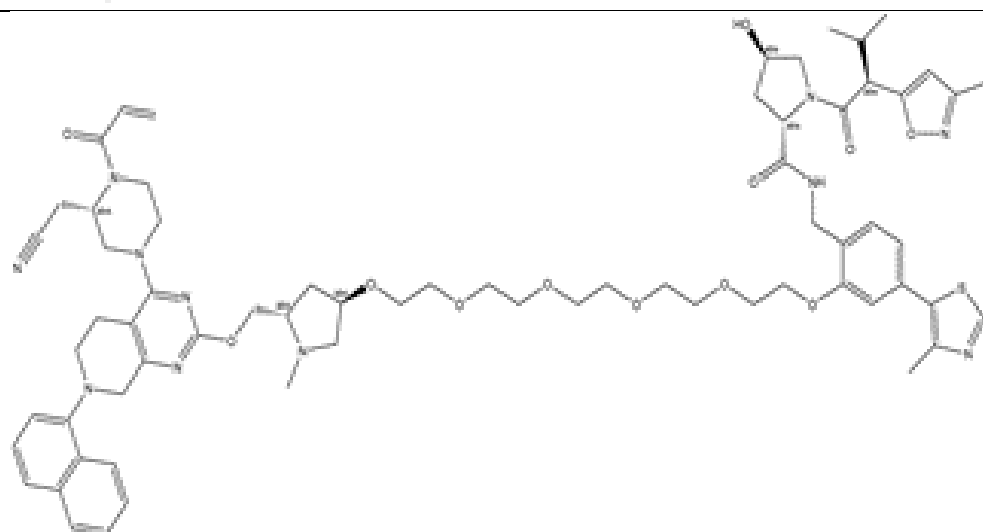
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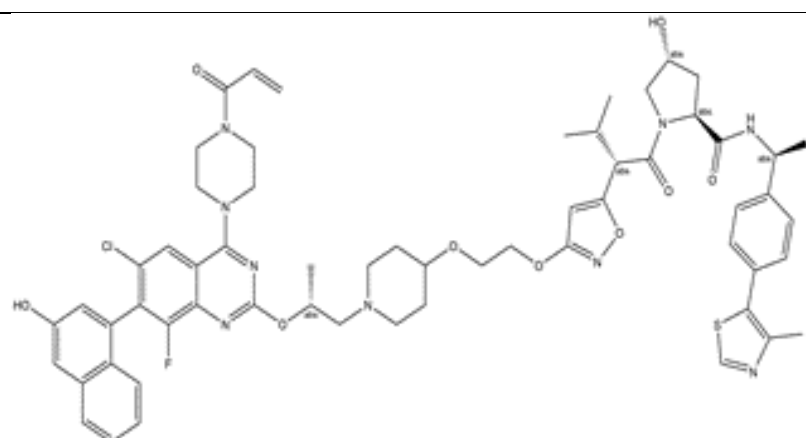
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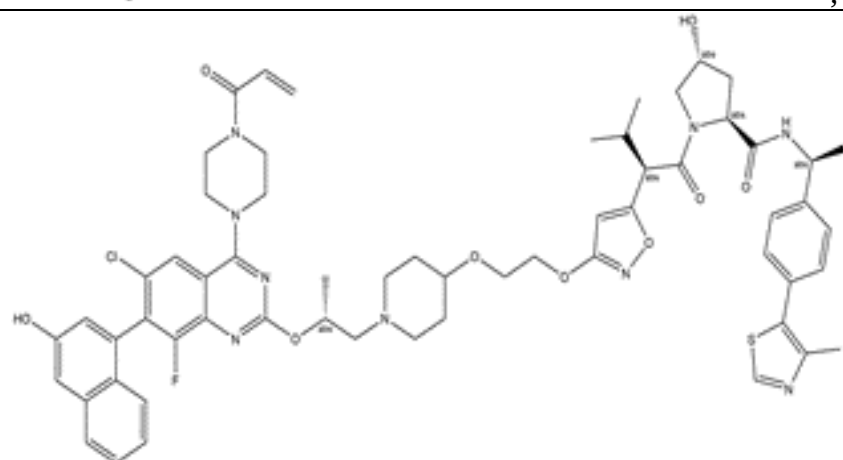
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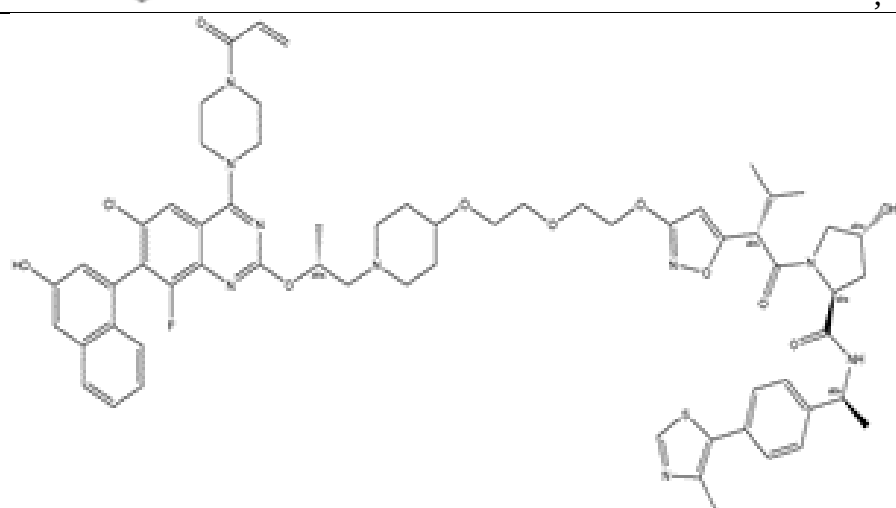
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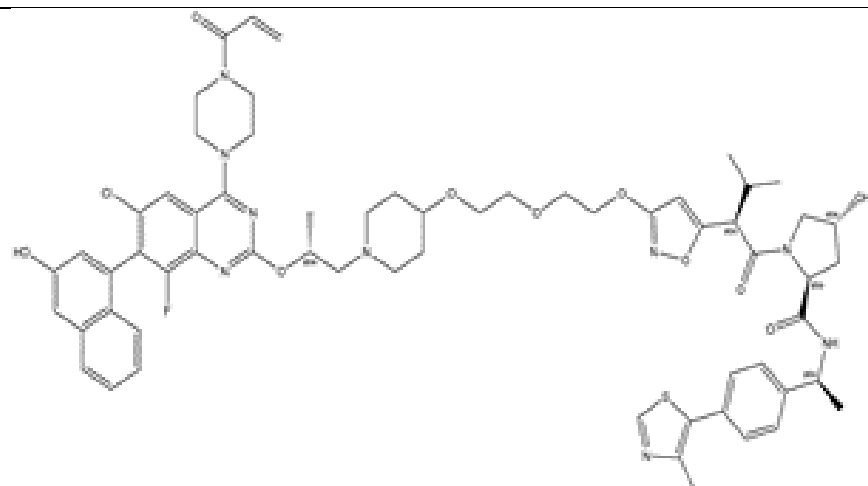
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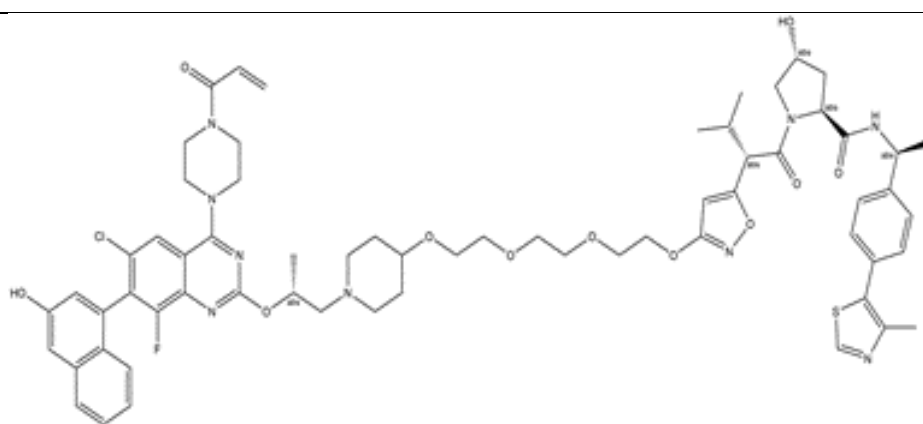
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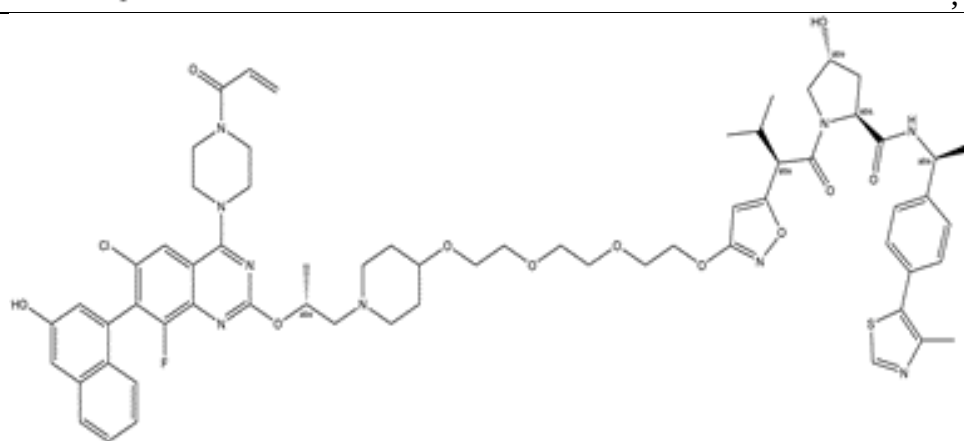
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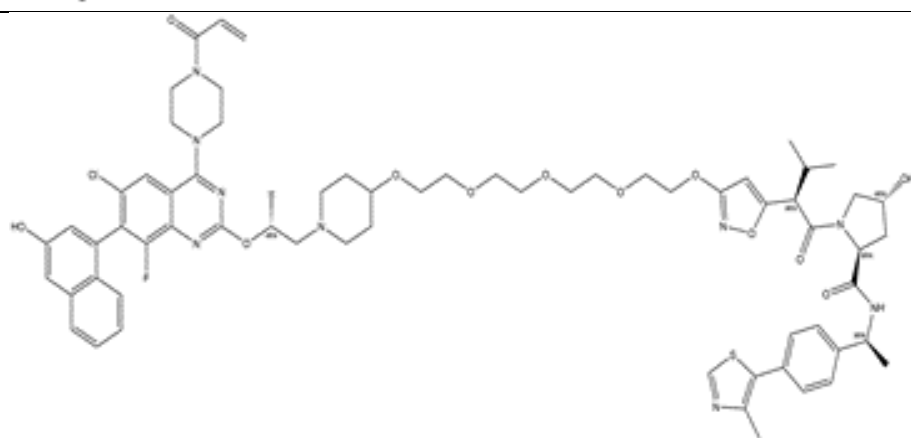
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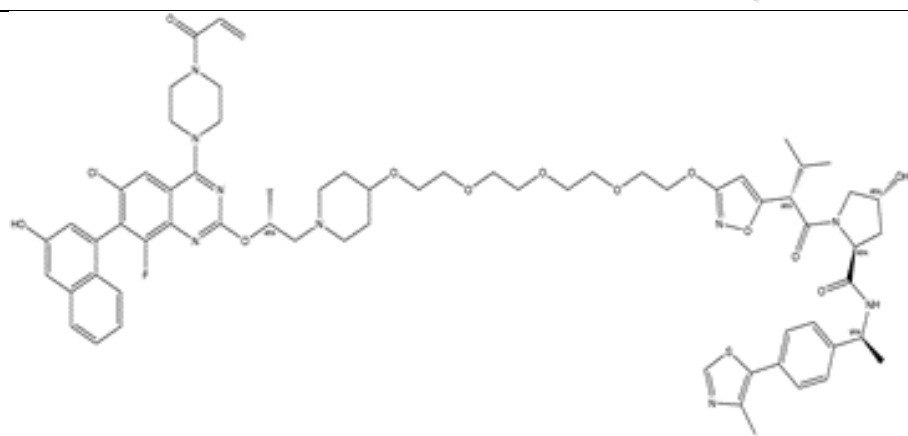
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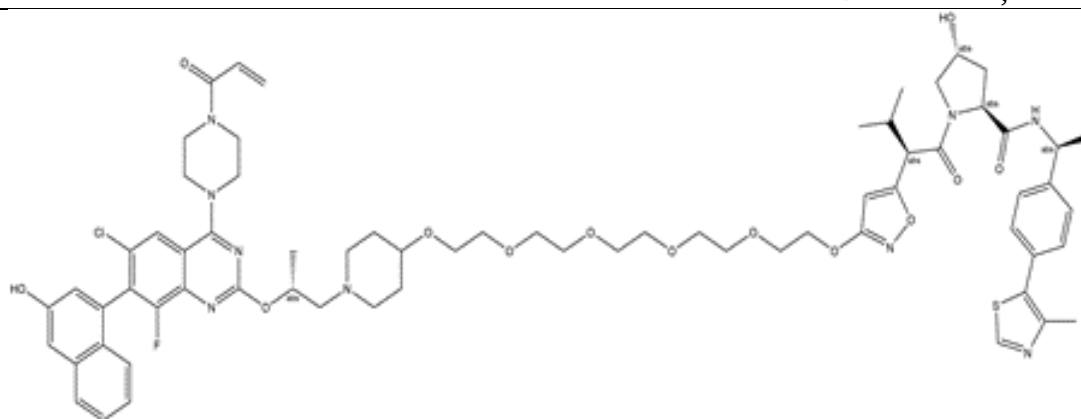
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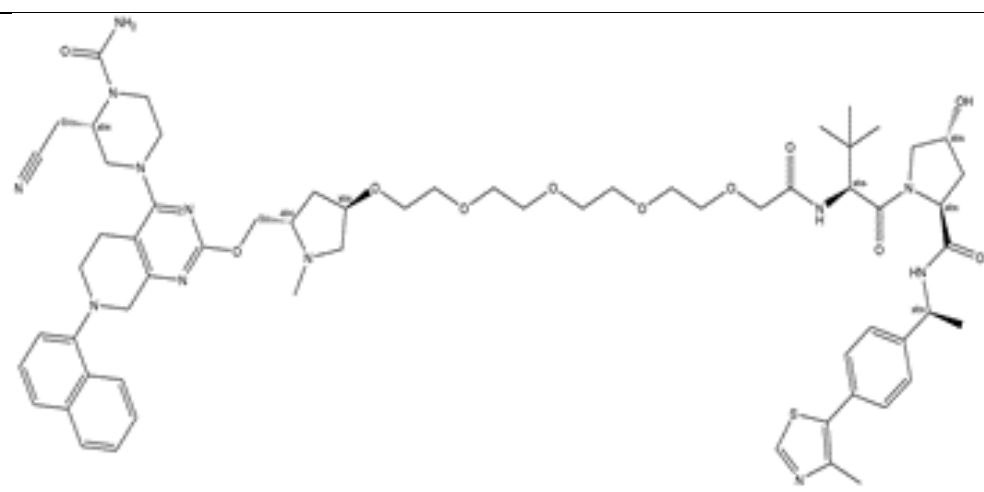
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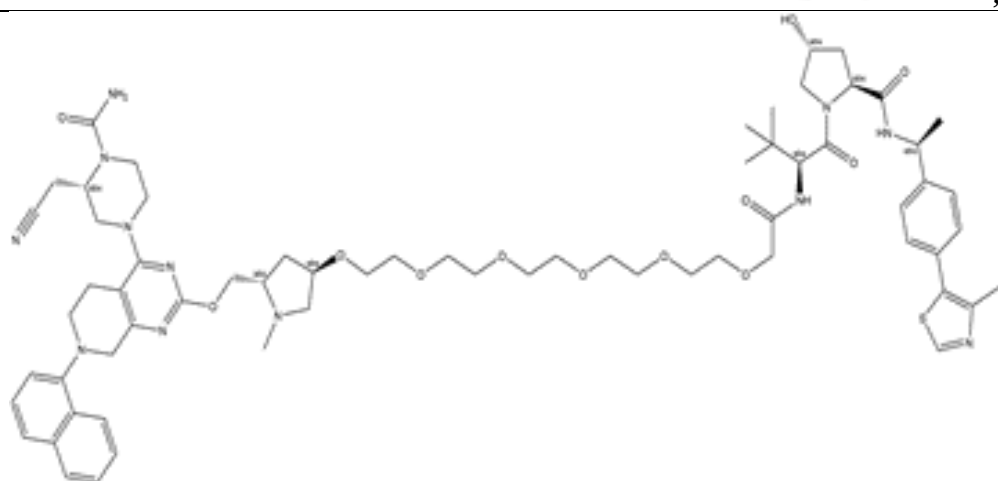
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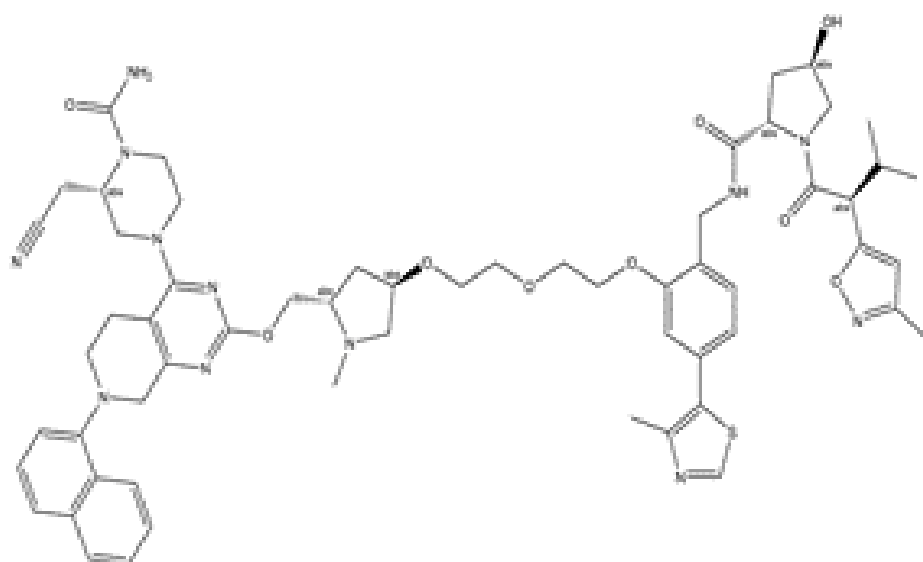
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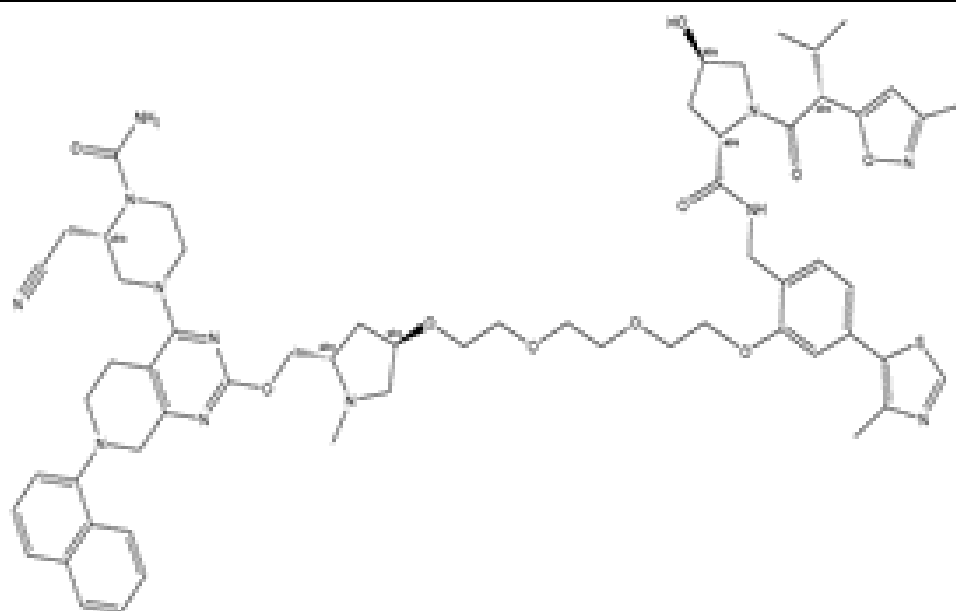
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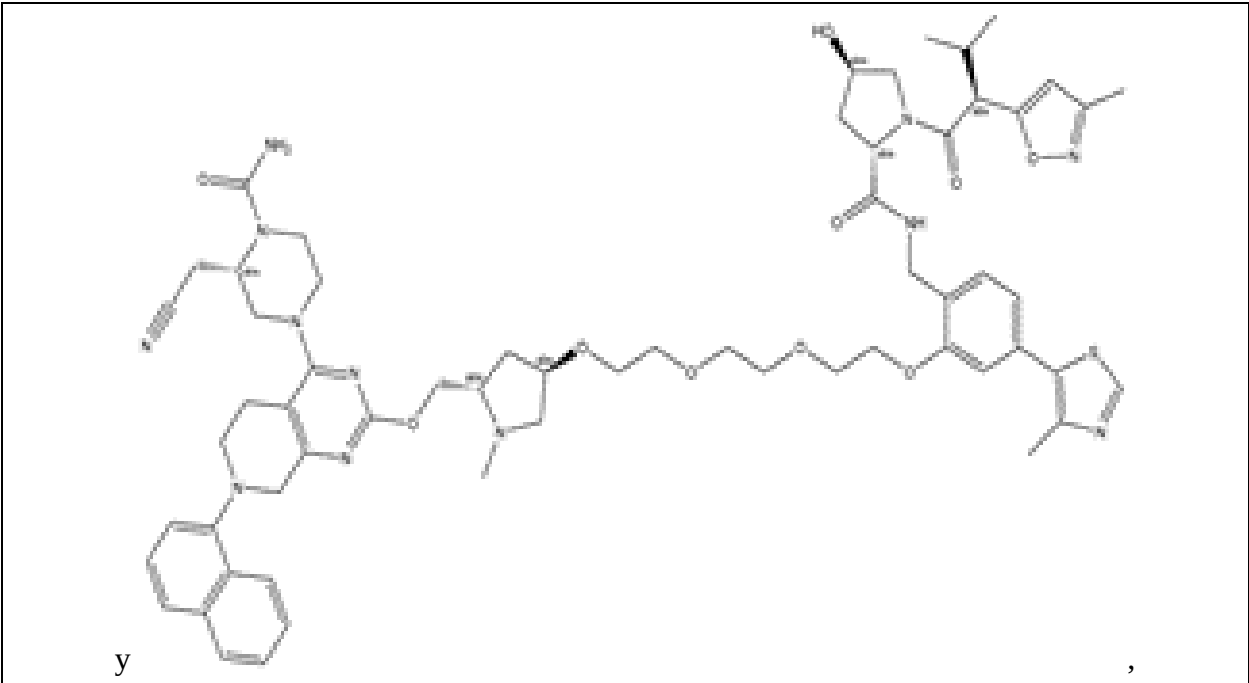
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o una sal farmacéuticamente aceptable de este.

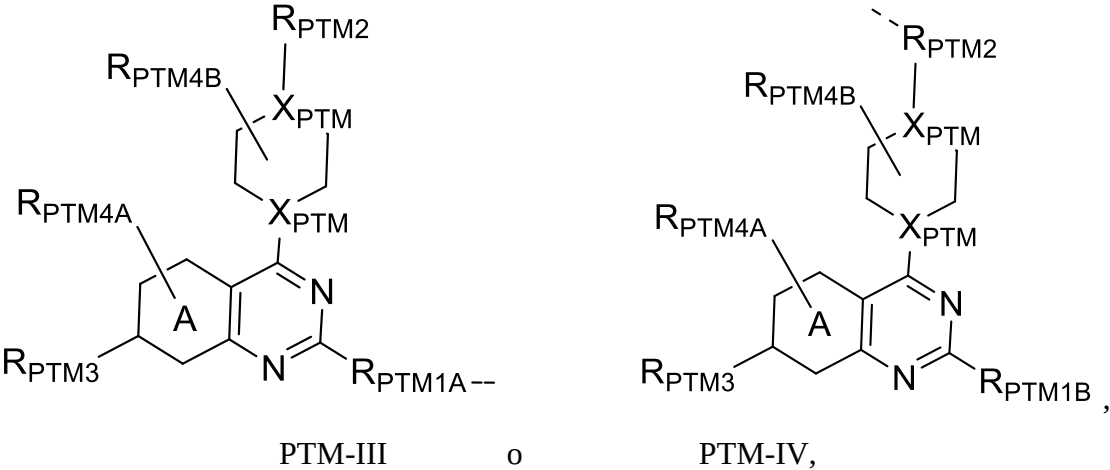
11. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1 a 10 y un portador farmacéuticamente aceptable.

12. La composición farmacéutica de acuerdo con la reivindicación 11, que comprende además un agente bioactivo adicional.

13. La composición farmacéutica de acuerdo con la reivindicación 12, en donde el agente bioactivo adicional es un agente contra el cáncer.

14. La composición farmacéutica de acuerdo con la reivindicación 13, en donde el agente contra el cáncer es un inhibidor de receptores del factor de crecimiento epidérmico.

15. El compuesto de acuerdo con la reivindicación 1, donde el PTM es:



donde:



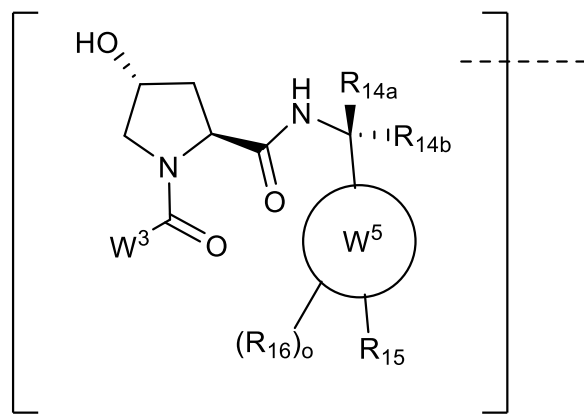
es fenilo, heteroarilo de 6 miembros, cicloalquilo de 6 miembros, o heterocicloalquilo de 6 miembros;

X_{PTM} es CH o N;

R_{PTM3} es alquilo, alcoxi, fenilo, o naftalenilo, cada uno opcionalmente sustituido de manera

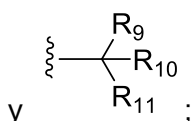
independiente con 1, 2 o 3 sustituyentes seleccionados de entre OH, H, y halógeno;
 R_{PTM4A} es OH, H, halógeno, o alquilo C_{1-6} opcionalmente sustituido; y
 R_{PTM4B} es OH, H, $-CH_2CN$, halógeno, o alquilo C_{1-6} opcionalmente sustituido.

16. El compuesto de acuerdo con la reivindicación 1 o 15, en donde el ULM es:



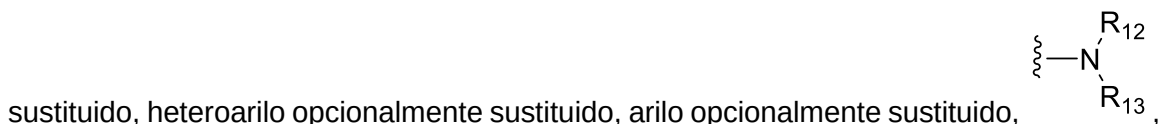
donde:

W^3 se selecciona de entre arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido

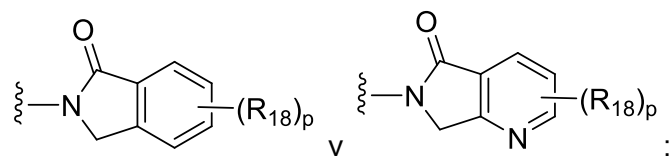


R_9 y R_{10} son cada uno de manera independiente seleccionados de entre hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, y heteroarilo opcionalmente sustituido, o R_9 , R_{10} , y el átomo de carbono al que se unen forma cicloalquilo opcionalmente sustituido;

R_{11} se selecciona de entre heterociclilo opcionalmente sustituido, alcoxi opcionalmente



sustituido, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido,



R_{12} es H o alquilo opcionalmente sustituido;

R_{13} se selecciona de entre H, alquilo opcionalmente sustituido, alquilcarbonilo opcionalmente sustituido, (cicloalquil)alquilcarbonilo opcionalmente sustituido, aralquilcarbonilo opcionalmente sustituido, arilcarbonilo opcionalmente sustituido, (heterociclil)carbonilo opcionalmente sustituido, y aralquilo opcionalmente sustituido;

R_{14a} y R_{14b} son cada uno de manera independiente H o alquilo opcionalmente sustituido;

W^5 es fenilo opcionalmente sustituido o un heteroarilo de 5-10 miembros opcionalmente sustituido;

R_{15} se selecciona de entre H, halógeno, CN, OH, NO_2 , N $R_{14a}R_{14b}$, OR_{14a} , $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, $NR_{14a}SO_2R_{14b}$, alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, haloalcoxi opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, y cicloheteroalquilo opcionalmente sustituido;

cada R_{16} se selecciona de manera independiente de entre halo, CN, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, e hidroxil;

o es 0, 1, 2, 3 o 4;

p es 0, 1, 2, 3 o 4, y indica el sitio de unión del L.

Chemical structures 1 and 2 are shown. Structure 1 is a 4-hydroxy-2-((R₁-CH₂-C(=O)-NH-)-C(=O)-NH-C(=O)-NH-)-5-((R_{14a}-CH₂-C(=O)-NH-)-C(=O)-NH-C(=O)-NH-)-1,3-dioxolane derivative. Structure 2 is a 4-hydroxy-2-((R₁-CH₂-C(=O)-NH-)-C(=O)-NH-C(=O)-NH-)-5-((R_{14a}-CH₂-C(=O)-NH-)-C(=O)-NH-C(=O)-NH-)-1,3-dioxolane derivative. Both structures are shown with a dashed line indicating a point of attachment.

R₁ se selecciona de entre H, alquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y heteroarilo opcionalmente sustituido;

R₁₅ se selecciona de entre H, halógeno, CN, OH, NO₂, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido; alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, haloalcoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, y heterocicloalquilo opcionalmente sustituido;

R₃ está ausente o es heteroarilo de 5 o 6 miembros opcionalmente sustituido; y

 indica el sitio de unión del L.