

Señores

Superintendencia de Industria y Comercio

Dirección de Nuevas Creaciones

E. S. D.

Ref: Expediente No. NC2020/0013864.

**Solicitud de registro 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. & YALE UNIVERSITY**, solicitante de la patente en referencia, a continuación, doy respuesta al Oficio **No. 524** del 16 de enero de 2023.

1. Respecto a la patentabilidad de la solicitud (Artículo 14 de la Decisión)

En el numeral 3 del Oficio No. **524**, se presentan las siguientes objeciones a la patentabilidad de las reivindicaciones 33 a 37:

«De conformidad con lo señalado en el artículo 14 de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina solo son patentables las invenciones de producto o de procedimiento.

En consecuencia las reivindicaciones 33-37 no se consideran patentables, teniendo en cuenta que reclaman el uso de los compuestos reclamados como medicamentos para el tratamiento del cáncer»

Las reivindicaciones 33 a 37 se rechazan por supuestamente no ser patentables. El solicitante respetuosamente no está de acuerdo con esta objeción. Sin embargo, únicamente con el propósito de un enjuiciamiento acelerado, y sin aceptar la validez del rechazo, se cancelan las reclamaciones 33 a 37. Por lo tanto, se solicita respetuosamente la reconsideración y el retiro de esta objeción.

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

En el numeral 4.1 del Oficio No. **524**, se presentan las siguientes objeciones a la claridad de las reivindicaciones:

- *Esta oficina informa que todo el capítulo reivindicatorio no es claro ni se puede comprender el alcance de la invención reclamada, debido a que los términos ULM y PTM no definen estructura química alguna, sino un resultado a obtener (el ULM es un resto de unión a la ubiquitina ligasa E3 de molécula pequeña que se une a una ubiquitina ligasa E3; el PTM es una molécula pequeña que comprende un resto de unión a la proteína de sarcoma de rata Kirsten (KRas)), por lo que no hay un elemento técnico real que defina debidamente la materia objeto de protección.*
- *De igual forma, el término “proteína pequeña” no define ninguna molécula específica ni el tamaño real de esta.*
- *Así las cosas no es posible realizar una búsqueda razonable de la materia reclamada, ya que no es posible determinar con certeza cuáles moléculas del estado de la técnica caen dentro de estas definiciones.*
- *Se recuerda que los compuestos químicos se deben caracterizar por su estructura química definida y/o su nombre químico, que es lo que permite diferenciarla claramente de lo conocido en el estado de la técnica y permitir apreciar si la estructura es inesperada o cuál parte de ella es la responsable de su efecto técnico.*
- *Así las cosas, es necesario que la solicitante reclame su invención en términos técnicos correctos como la estructura química bien definida para*

poder hacer un análisis de patentabilidad correcto que no entre en ambigüedades.

Con el fin de acelerar el enjuiciamiento de la presente solicitud respecto a la claridad y concisión de las reivindicaciones, sin que esto signifique que el solicitante acepta que las objeciones sean procedentes, **es deseo del solicitante presentar un nuevo capítulo reivindicatorio compuesto por 16 reivindicaciones**, que encuentran su debido sustento en las reivindicaciones y la descripción originalmente presentadas, sin que ello conlleve ampliación de la invención.

La reivindicación 1 se modificó incorporando materia de las reivindicaciones 3, 6, 7, 14, 17 y 20, y eliminado algunas expresiones que pueden ser interpretadas como poco claras.

Se objetan las reivindicaciones 1 a 37 porque supuestamente no son claras ni concisas en vista de las definiciones funcionales de PTM y ULM. En particular, este despacho alega que *“los compuestos químicos se deben caracterizar por su estructura química definida y/o su nombre químico”*. El solicitante respetuosamente no está de acuerdo con esto. Sin embargo, únicamente con el propósito de agilizar el enjuiciamiento, y sin consentir la validez de las objeciones, se modifica la presente reivindicación 1 para incorporar definiciones estructurales para las variables ULM, L y PTM. El solicitante afirma que lo anterior aclara aún más las presentes reivindicaciones.

Por lo tanto, ahora es más evidente que existe un elemento técnico real que define debidamente el producto que se reclama con características que evidentemente son diferentes de lo que existe en el estado de la técnica, sin que existan moléculas del estado de la técnica que caigan dentro de lo definido en el capítulo reivindicatorio que ahora se presenta y con efectos ventajosos frente a los productos de divulgaciones anteriores a la solicitud.

Por su parte, la expresión *«molécula pequeña»* se eliminó del capítulo reivindicatorio que ahora se presenta y la expresión *«proteína pequeña»* no aparece en dicho capítulo.

Por lo tanto, por lo anterior, se solicita respetuosamente la reconsideración y el retiro de las objeciones presentadas.

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

El Oficio No. **524** no presenta ninguna divulgación anterior a la fecha de prioridad de la presente solicitud y, por lo tanto, no existen razones de negar el privilegio de patente por falta de novedad o de nivel inventivo.

4. 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 los artículos 30 y 45 de la Decisión 486 según los requerimientos del Examinador.

De otra parte, lo revelado en las nuevas reivindicaciones de la presente solicitud resulta completamente novedoso e inventivo sobre el estado del arte anterior a la solicitud, toda vez que no se han citado documentos que anticipen la materia reclamada. Por consiguiente, no se puede derivar la inexistencia de los requisitos de ley para la concesión del privilegio de patente.

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 16 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 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.

5. Anexos

Junto con este escrito se incluye lo siguiente:

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

6. Pagos

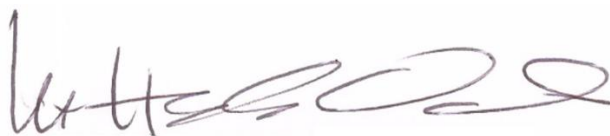
Junto con esta respuesta se paga la tasa correspondiente a la modificación del capítulo reivindicatorio.

7. 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.

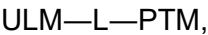
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REIVINDICACIONES (con marcas de modificación)

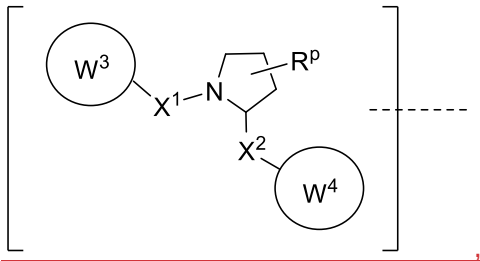
1. Un compuesto bifuncional que tiene la estructura química:



o una sal, ~~un enantiómero, un estereoisómero, un solvato, un polimorfo o un profármaco~~ farmacéuticamente aceptable de este,

donde:

~~el ULM es: un resto de unión a la ubiquitina ligasa E3 de molécula pequeña que se une a una ubiquitina ligasa E3;~~



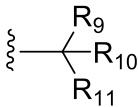
en donde

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;

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

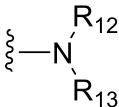
W³ se selecciona de entre fenilo opcionalmente sustituido con alquilo C₁₋₆, un



heteroarilo de 5-10 miembros opcionalmente sustituido con alquilo C₁₋₆, y

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

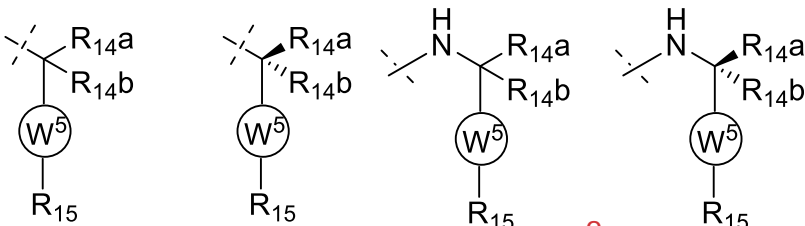


de 5-10 miembros, arilo C₆₋₁₀, y, en donde el heterociclilo, heteroarilo, y arilo son opcionalmente sustituidos con alquilo C₁₋₆;

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;



W⁴ es, o

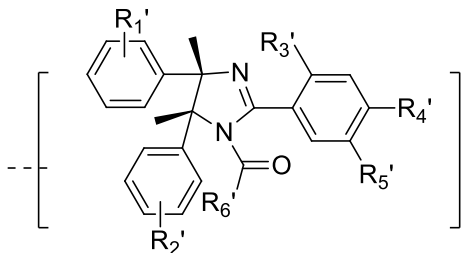
R_{14a} y R_{14b} se seleccionan cada uno de manera independiente de H, haloalquilo C₁₋

6 o alquilo C₁₋₆ opcionalmente sustituido;

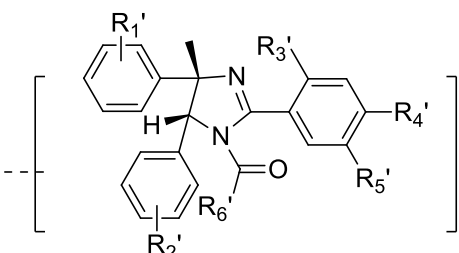
W⁵ es un fenilo opcionalmente sustituido o un heteroarilo de 5-10 miembros opcionalmente sustituido;

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 cicloheteroalquilo de 3-11 miembros opcionalmente sustituido;

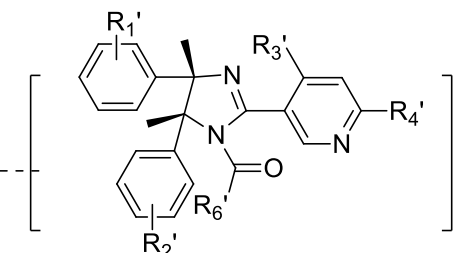
o ULM es



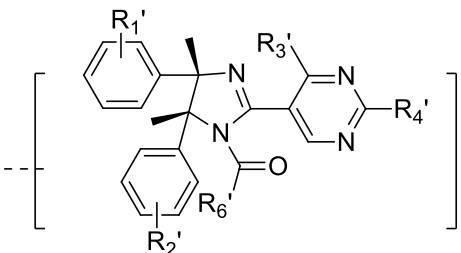
A-1-1



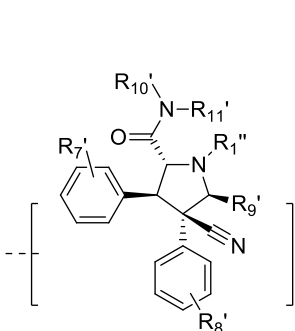
A-1-2



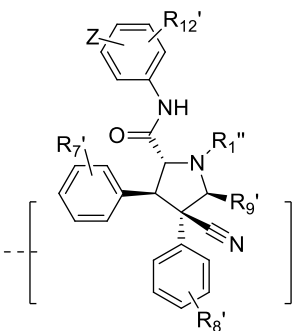
A-1-3



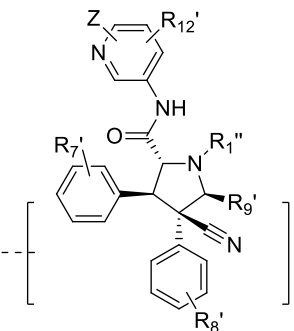
A-1-4



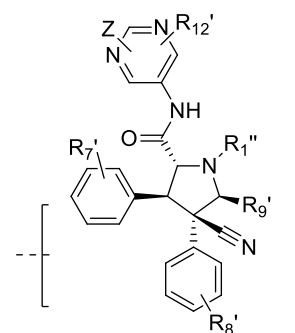
A-4-1



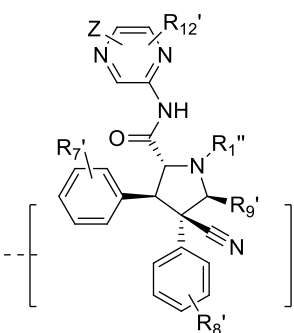
A-4-2



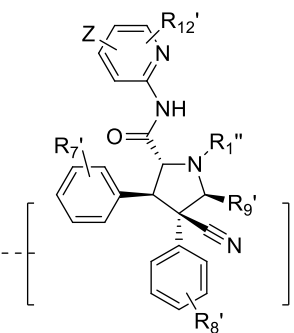
A-4-3



A-4-4



A-4-5



A-4-6

donde:

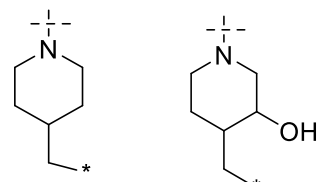
R₁' y R₂' de las Fórmulas A-1-1 a A-1-4 se seleccionan de manera independiente de F, Cl, Br, I, acetileno, CN, CF₃ y NO₂;

R₃' se selecciona de entre -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃ y -

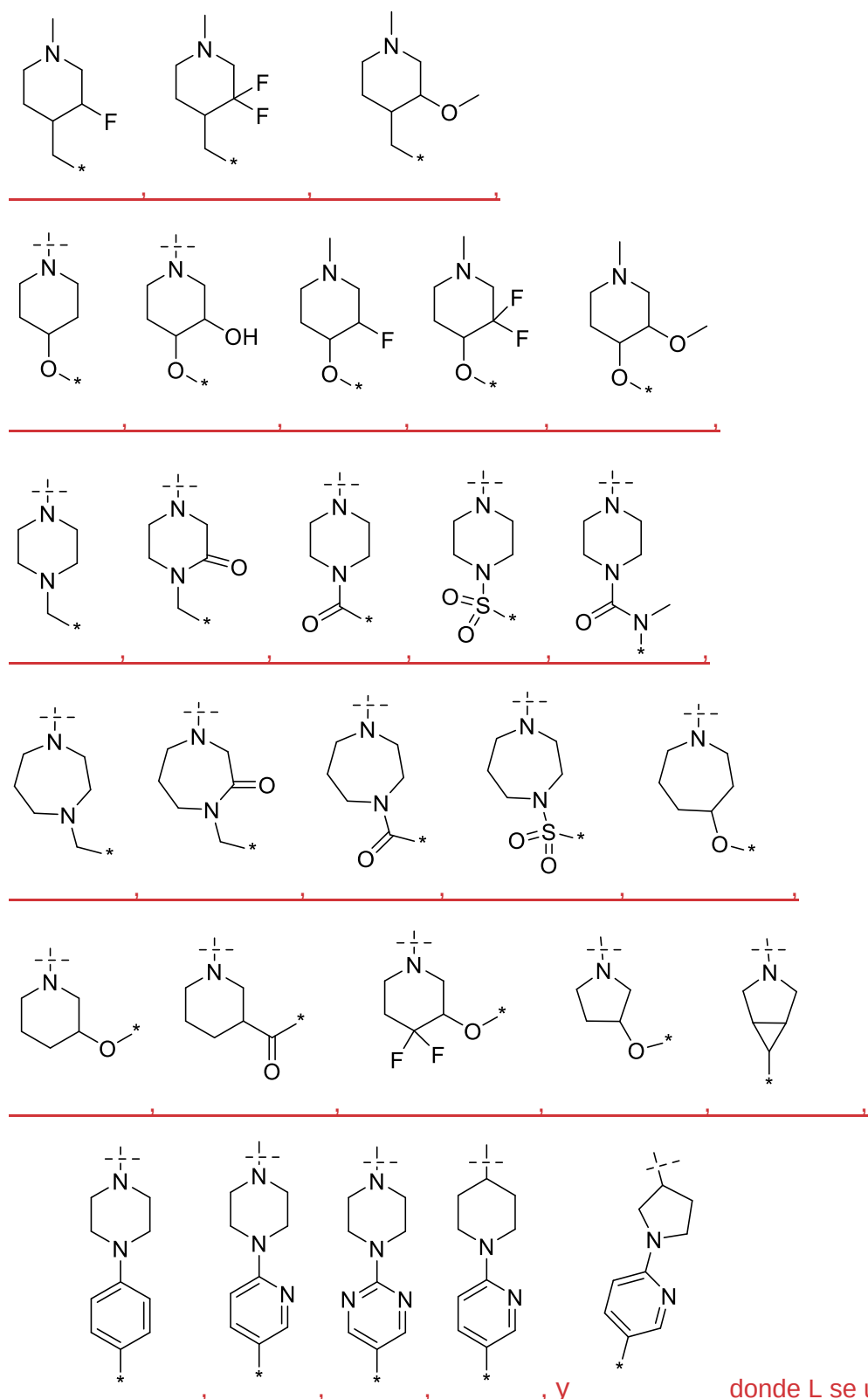
OCH(CH₃)₂:

R4' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre H, halógeno, -CH₃, -CF₃, -OCH₃, -C(CH₃)₃, -CH(CH₃)₂, -ciclopropilo, -CN, -C(CH₃)₂OH, -C(CH₃)₂OCH₂CH₃, -C(CH₃)₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₃, -C(CH₃)₂CH₂OCH₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₃, -C(CH₃)₂CN, -C(CH₃)₂C(O)CH₃, -C(CH₃)₂C(O)NHCH₃, -C(CH₃)₂C(O)N(CH₃)₂, -SCH₃, -SCH₂CH₃, -S(O)₂CH₃, -S(O)₂CH₂CH₃, -NHC(CH₃)₃, -N(CH₃)₂, pirrolidinilo y 4-morfolinilo;

R5' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre halógeno, -ciclopropilo, -S(O)₂CH₃, -S(O)₂CH₂CH₃, 1-pirrolidinilo, -NH₂, -N(CH₃)₂ y -NHC(CH₃)₃; y



R6' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre H, _____,



donde L se une al «*» de

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, heteroarilo, 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;

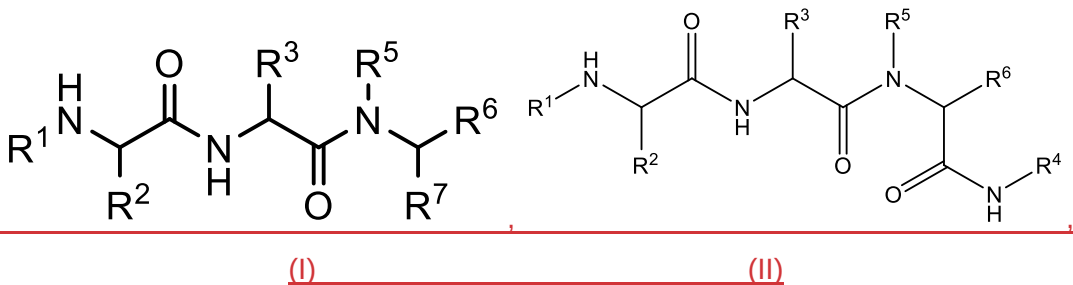
m, n y p son de manera independiente de 0 a 6;

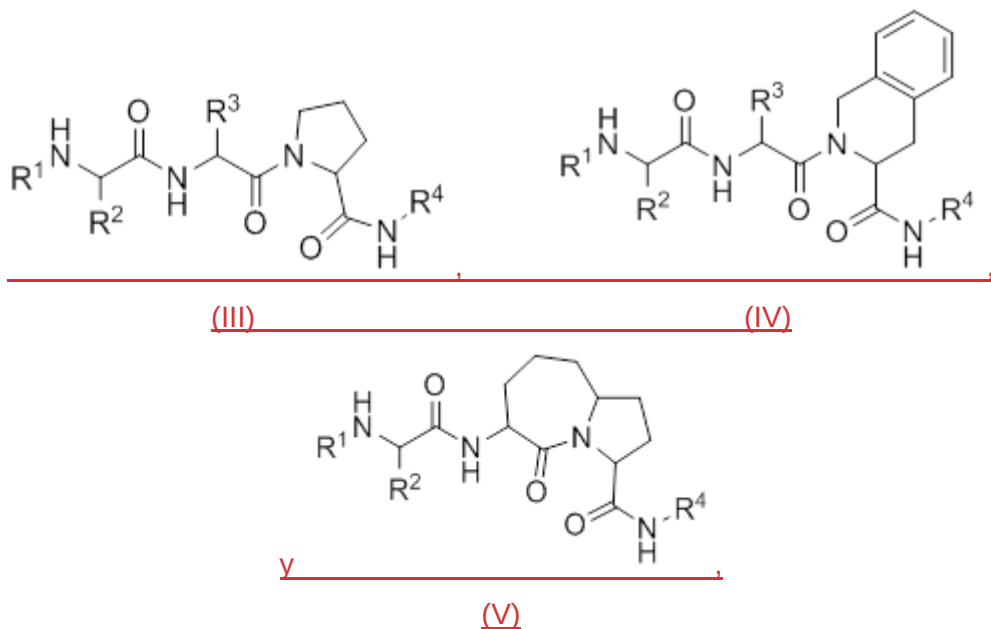
R12' de la Fórmula A-4-1 a A-4-6 se selecciona de entre -O-(alquilo), -O-(alquilo)-acoxi, -C(O)-(alquilo), -C(OH)-alquilo-alcoxi, -C(O)-NH-(alquilo), -C(O)-N-(alquilo)₂, -S(O)-(alquilo), S(O)₂-(alquilo), -C(O)-(amino cíclico) y -O-arilo-(alquilo), -O-arilo-(alcoxi);

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 aloxi, cicloalquilo, cicloalquilo sustituido con ari, y cicloalquilo sustituido con alcoxi; y

 indica conexión con L;

o ULM se selecciona de entre:





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;

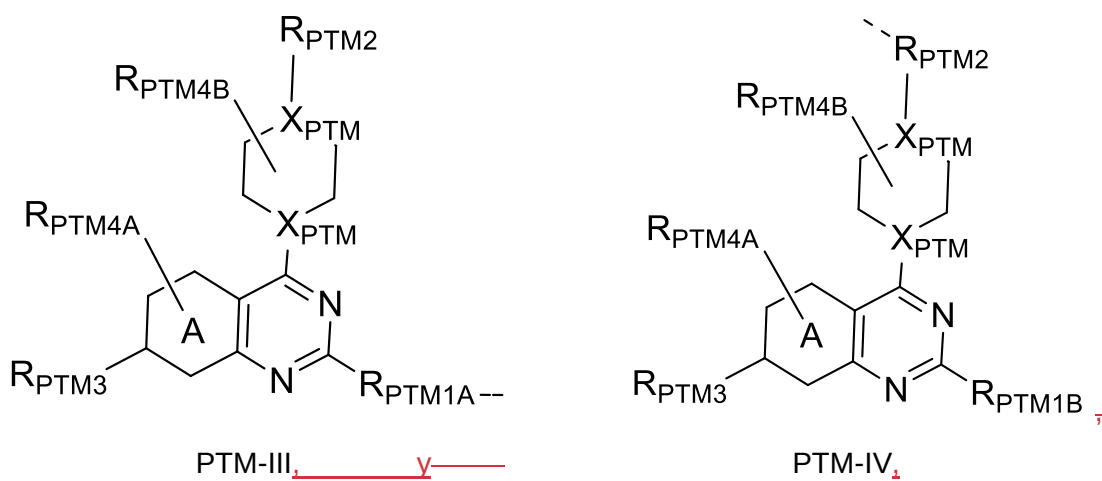
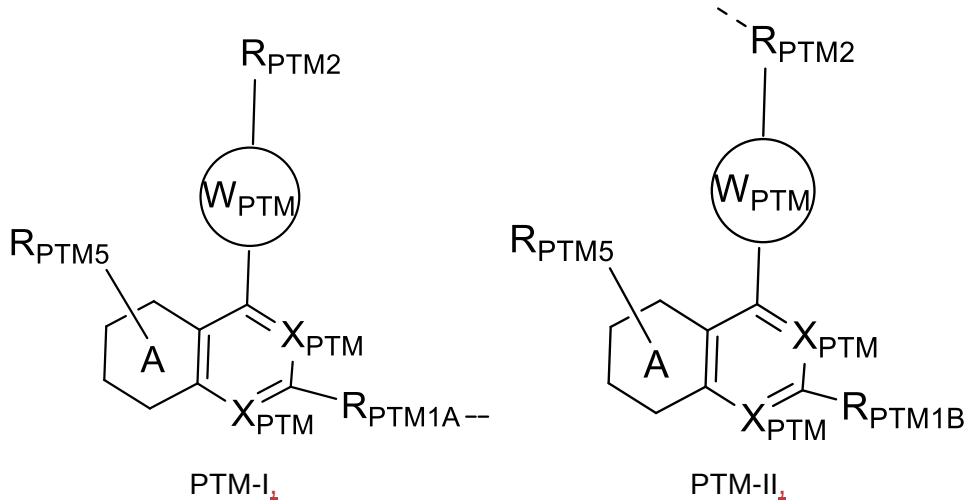
~~el PTM es una molécula pequeña que comprende un resto de unión a la proteína de sarcoma de rata Kirsten (KRas)~~se selecciona de entre:

÷y

L es un enlace o resto enlazador químico que conecta el ULM y el PTM.

2. ~~El compuesto bifuncional de acuerdo con la reivindicación 1, donde el resto de unión a la ubiquitina ligasa E3 que se dirige a una ubiquitina ligasa E3 se selecciona dentro del grupo que consiste en Von Hippel-Lindau (VLM), cereblon (CLM), homólogo diminuto doble de ratón (MLM) e IAP (ILM).~~

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



en donde:

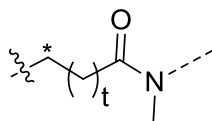


es un arilo, heteroarilo, cicloalquilo o heterocicloalquilo;

X_{PTM} es C o N;

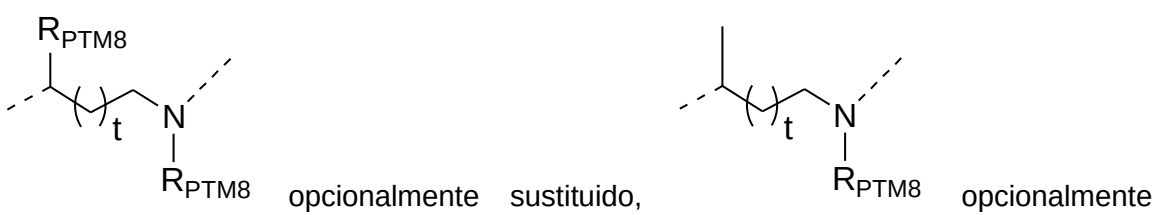
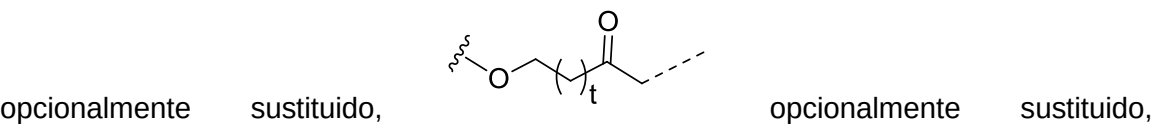
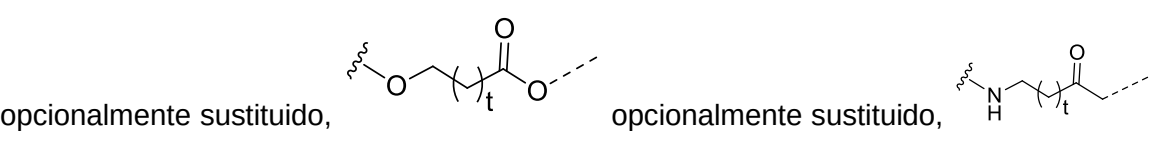
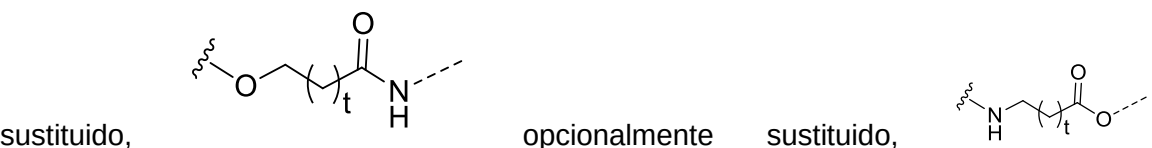
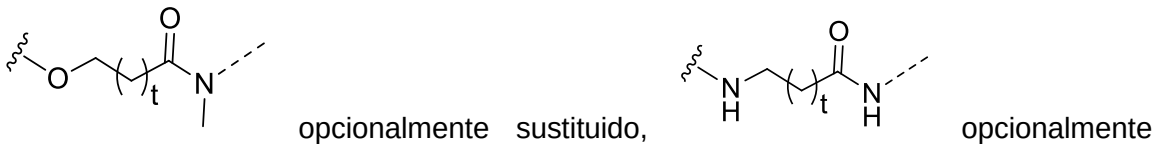
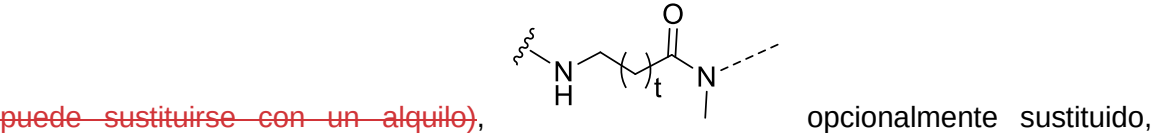
W_{PTM} se ~~elige dentro del grupo que consiste en~~ selecciona de entre cicloalquilo C₃₋₆ opcionalmente sustituido, y heteroalquilo C₃₋₆ opcionalmente sustituido, heterocicloalquilo de C₃₋₆ miembros opcionalmente sustituido, arilo opcionalmente sustituido ~~(p. ej., arilo C₅₋₇ opcionalmente sustituido)~~, heteroarilo opcionalmente sustituido ~~(p. ej., heteroarilo C₅₋₇ opcionalmente sustituido)~~;

R_{PTM1A} es 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 ~~(p. ej., arilo C₅₋₇ opcionalmente sustituido)~~, O-arilo opcionalmente sustituido ~~(p. ej., O-(arilo C₅₋₇) opcionalmente sustituido)~~, heteroarilo opcionalmente sustituido, ~~(p. ej., heteroarilo C₅₋₇ opcionalmente sustituido)~~, O-heteroarilo opcionalmente sustituido ~~(p. ej., O-(heteroarilo~~



~~C₅₋₇) opcionalmente sustituido)~~, opcionalmente sustituido ~~(p. ej.,~~

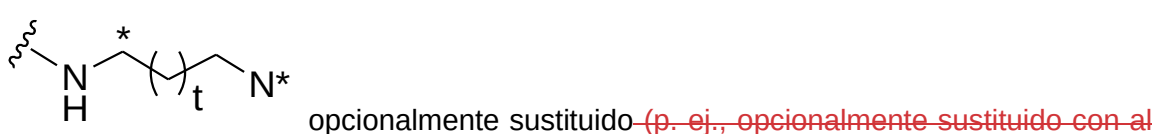
~~opcionalmente sustituido con al menos un alquilo, tal como el carbono * opcionalmente~~



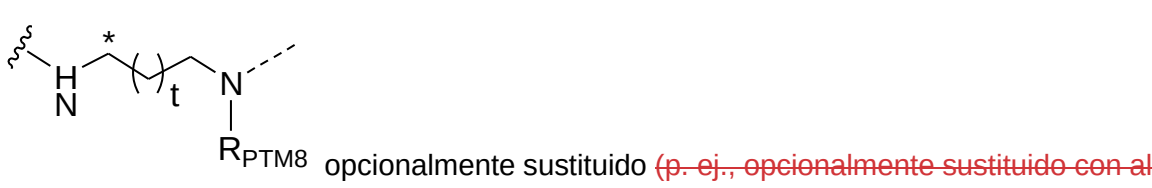
opcionalmente sustituido ~~(p. ej., opcionalmente sustituido con al menos un alquilo, tal~~



opcionalmente sustituido ~~(p. ej., opcionalmente sustituido con al menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un alquilo),~~



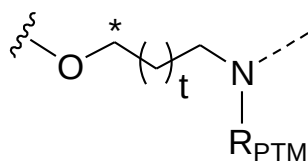
~~menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un alquilo),~~



~~menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un alquilo),~~

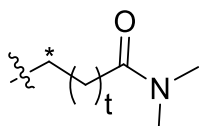


~~menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un alquilo),~~

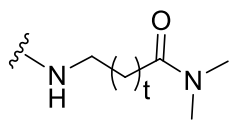


opcionalmente sustituido ~~(p. ej., opcionalmente sustituido con al menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un alquilo)~~, donde N* es un átomo de N de un heterocicloalquilo del ~~enlazador (L)~~;

R_{PTM1B} es NR_{PTM9}R_{PTM10}, OR_{PTM9}R_{PTM10}, H, alquilo opcionalmente sustituido, O-alquilo 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 C₃₋₆ opcionalmente sustituido, arilo opcionalmente sustituido ~~(p. ej., arilo C5-C7 opcionalmente sustituido)~~, O-arilo opcionalmente sustituido ~~(p. ej., O-(arilo C5-C7) opcionalmente sustituido)~~, heteroarilo opcionalmente sustituido ~~(p. ej., heteroarilo C5-C7 opcionalmente sustituido)~~, O-heteroarilo opcionalmente sustituido ~~(p. ej., O(heteroarilo C5-C7) opcionalmente~~

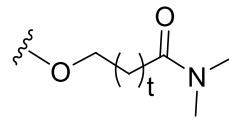


~~sustituido)~~, opcionalmente sustituido ~~(p. ej., opcionalmente sustituido con al menos un alquilo, tal como el carbono * opcionalmente puede sustituirse con un~~

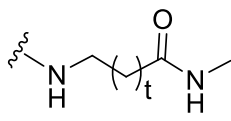


~~alquilo)~~,

opcionalmente sustituido,

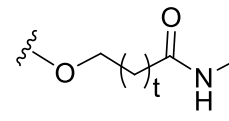


opcionalmente

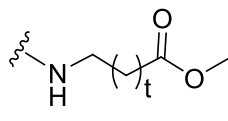


sustituido,

opcionalmente sustituido,

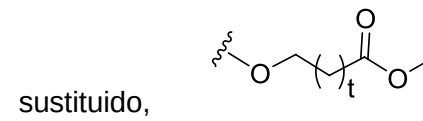


opcionalmente

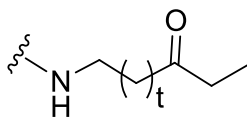


sustituido,

opcionalmente



sustituido,

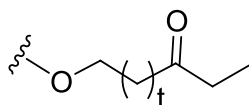


opcionalmente

sustituido,

opcionalmente

sustituido,



opcionalmente sustituido;

R_{PTM9} y R_{PTM10} son cada uno de manera independiente H, alquilo C₁₋₆ opcionalmente sustituido, ~~amina-amino alifática-alifático~~ opcionalmente sustituida, ~~amida-amido alifática-alifático~~ opcionalmente sustituida;

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

R_{PTM2'} es alquilo ~~lineal o ramificado~~ opcionalmente sustituido, alqueno opcionalmente sustituido, -N (R_{PTM8})₂ o -C(OH)₂;

R_{PTM3} es alquilo, alcoxi, fenilo o naftaleno, cada uno sustituido de manera independiente con OH, H, o halógeno;

R_{PTM4A} es OH, H, o halógeno, o alquilo C₁₋₆ ~~lineal o ramificado~~ opcionalmente sustituido;

R_{PTM4B} es OH, H, -CH₂CN, halógeno, alquilo C₁₋₆ ~~lineal o ramificado~~ opcionalmente

sustituido;

R_{PTM5} se ~~elige dentro del grupo que consiste en~~ selecciona de arilo opcionalmente sustituido, biarilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, biheteroarilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, cicloheteroalquilo de C_{3-6} miembros opcionalmente sustituido, halógeno, H, alquilo ~~lineal o ramificado~~ opcionalmente sustituido ~~(p. ej., alquilo C_{1-6} lineal o ramificado opcionalmente sustituido)~~, OH y alcoxi;

R_{PTM8} es un H o ~~un alquilo (p. ej., un alquilo C_1 , un alquilo C_2 , un alquilo C_3 o un alquilo C_4)~~;

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

 indica el sitio de unión ~~de L de al menos uno de un enlazador, ULM, ULM', CLM, CLM', VLM, VLM', ILM, ILM', MLM, MLM', o una combinación de estos; y~~

L es:



donde:

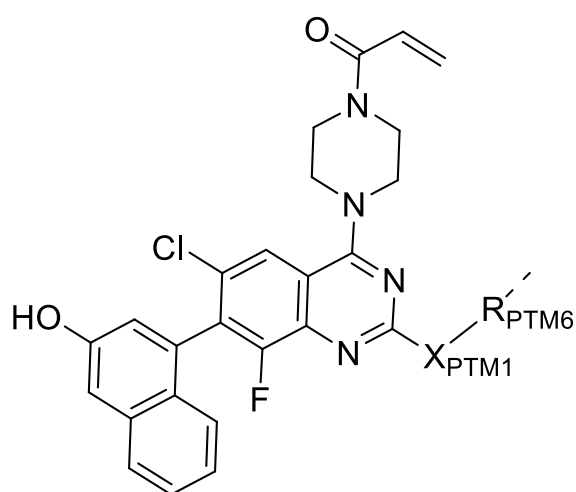
$(A^L)_g$ es un grupo que se conecta con al menos uno de un ULM, PTM, o ambos;

g es un número entero mayor o igual que 1;

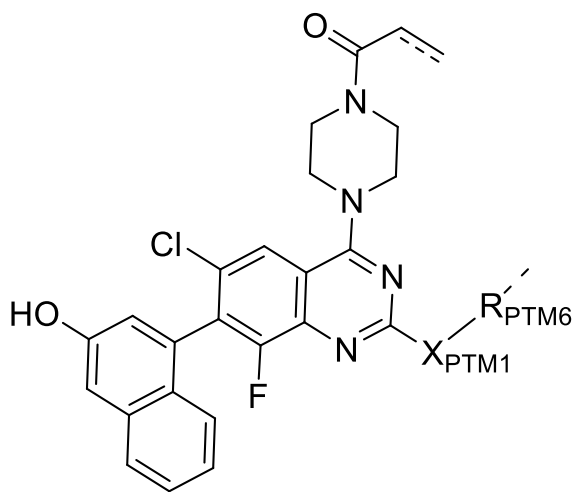
cada A^L se selecciona de manera independiente de entre un enlace, $CR^{L1}R^{L2}$, O, S, SO, SO_2 , NR^{L3} , SO_2NR^{L3} , $SONR^{L3}$, $CONR^{L3}$, $NR^{L3}CONR^{L4}$, $NR^{L3}SO_2NR^{L4}$, CO, $CR^{L1}=CR^{L2}$, $C\equiv C$, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, cicloalquilo C_{3-11} opcionalmente sustituido con 0-6 grupos R^{L1} y/o R^{L2} , heterociclilo C_{3-11} 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} , 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, 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, 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, NH₂, 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} , CO₂H, halógeno, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO_2 NHalquilo C_{1-8} , SO_2 N(alquilo C_{1-8})₂, SONHalquilo C_{1-8} , SON(alquilo C_{1-8})₂, CONHalquilo C_{1-8} , CON(alquilo C_{1-8})₂, N(alquilo C_{1-8})CONH(alquilo C_{1-8}), N(alquilo C_{1-8})CON(alquilo C_{1-8})₂, NHCONH(alquilo C_{1-8}), NHCON(alquilo C_{1-8})₂, NHCONH₂, N(alquilo C_{1-8})SO₂NH(alquilo C_{1-8}), N(alquilo C_{1-8})SO₂N(alquilo C_{1-8})₂, NH SO₂NH(alquilo C_{1-8}), NH SO₂N(alquilo C_{1-8})₂, y NH SO₂NH₂.

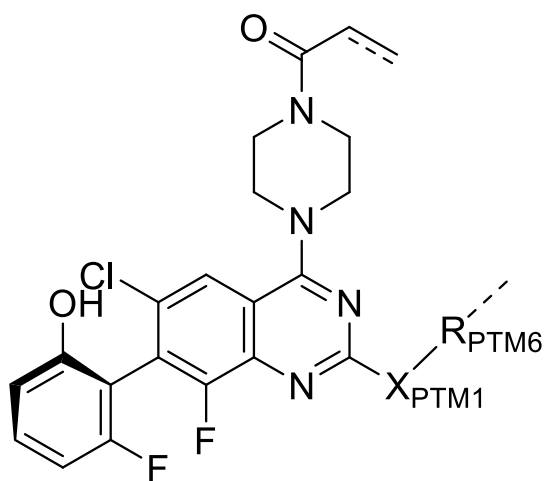
4.2. El compuesto bifuncional de acuerdo con ~~cualquiera de las reivindicaciones~~ reivindicación 1-3, donde el PTM es representado por:



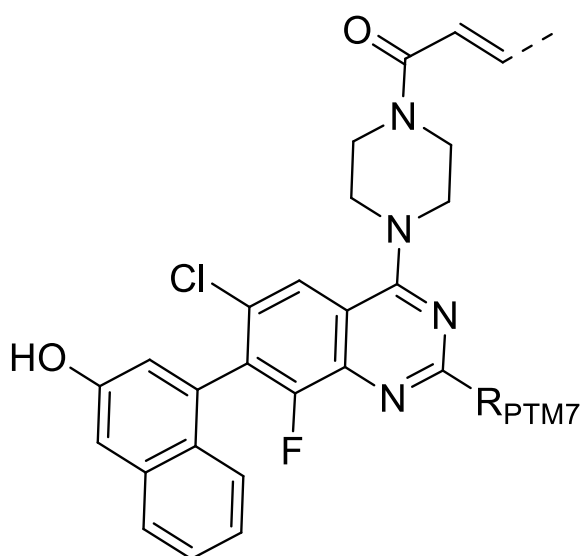
PTM-Va



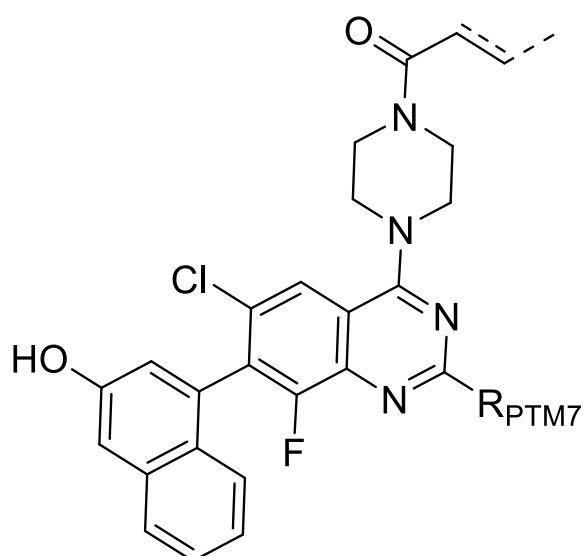
PTM-Vb



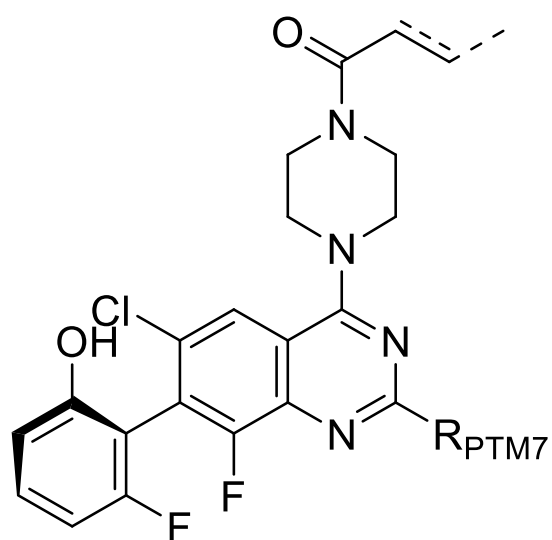
PTM-VI



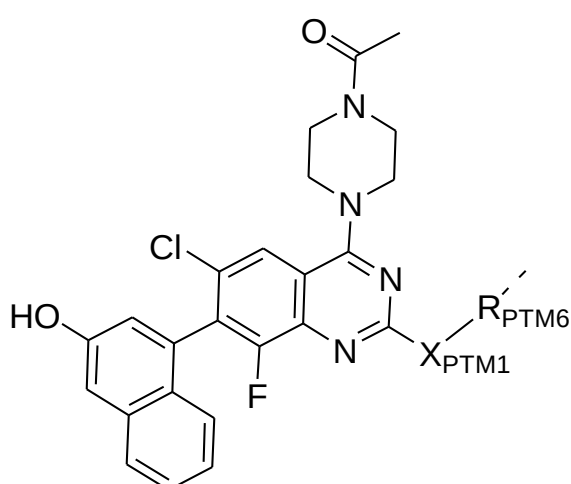
PTM-VIIa



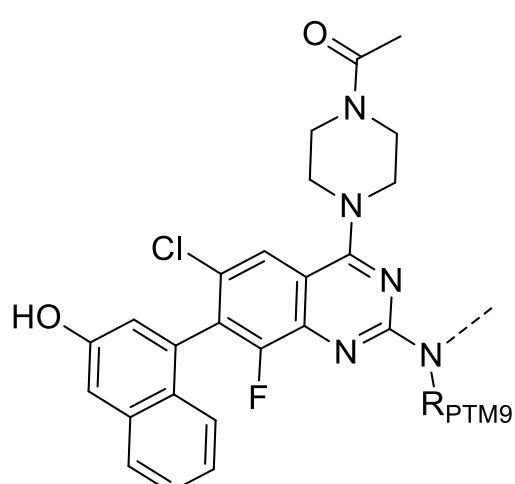
PTM-VIIb



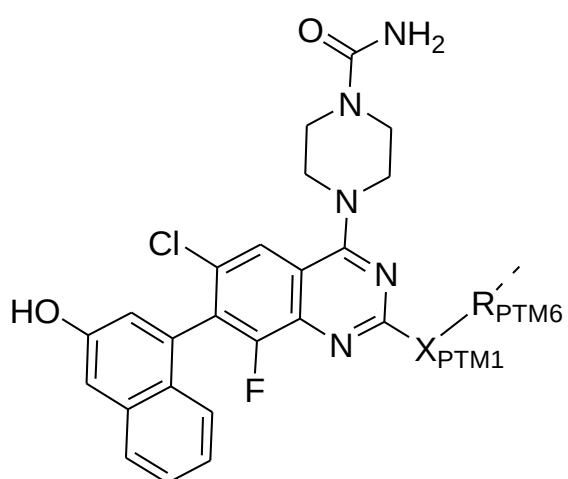
PTM-VIII



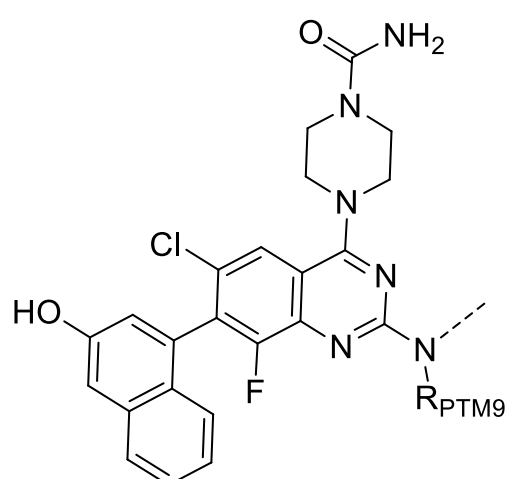
PTM-IXa



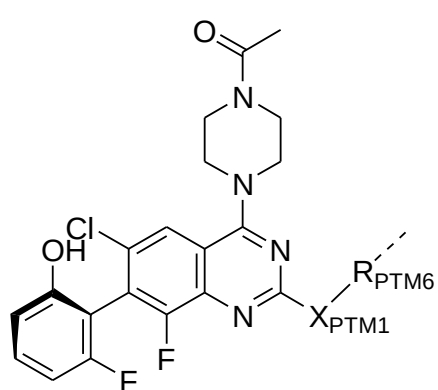
PTM-I-Xb



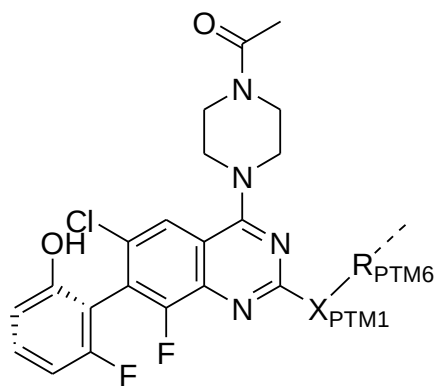
PTM-Xa



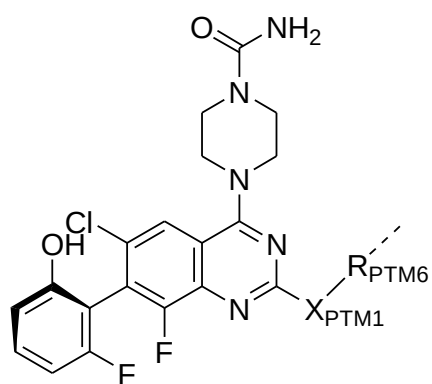
PTM-Xb



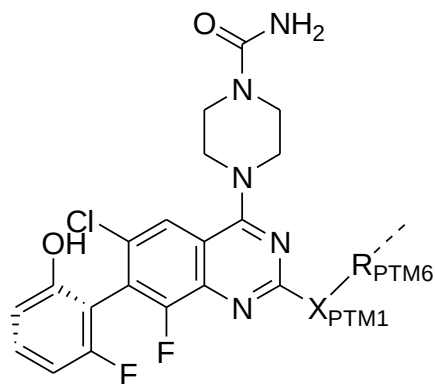
PTM-XI



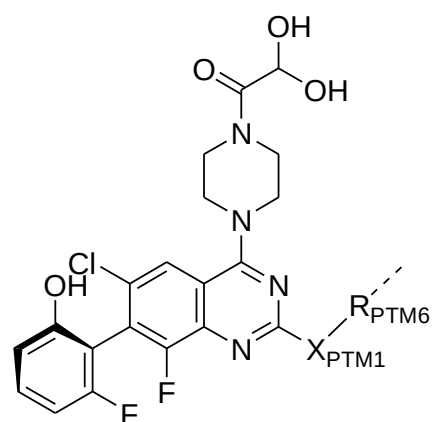
PTM-XII



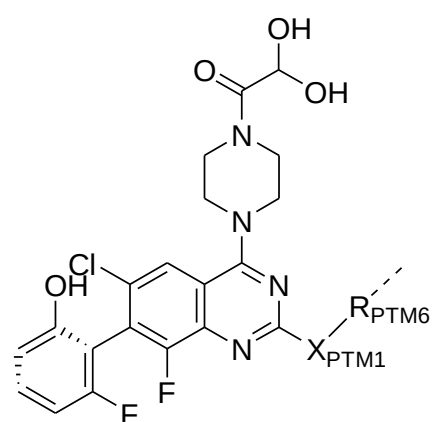
PTM-XIII



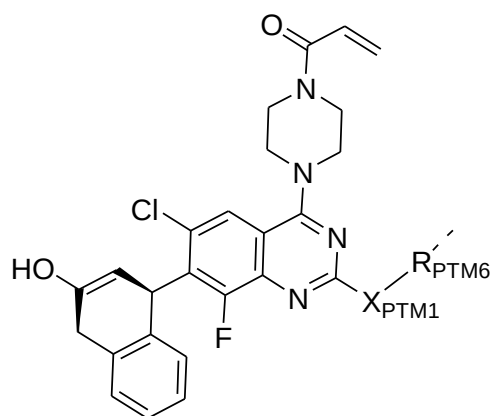
PTM-XIV



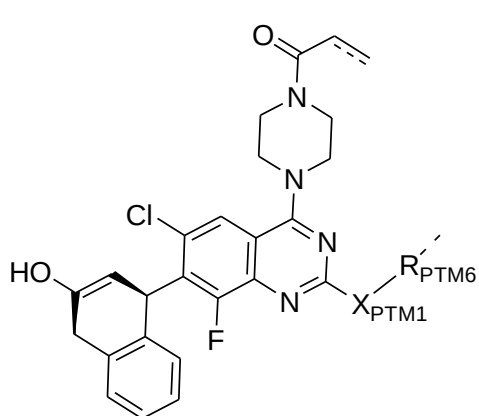
PTM-XV



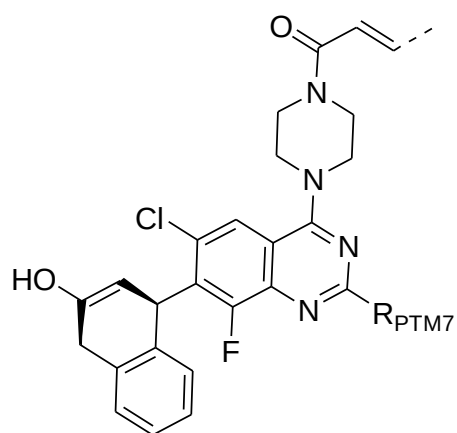
PTM-XVI



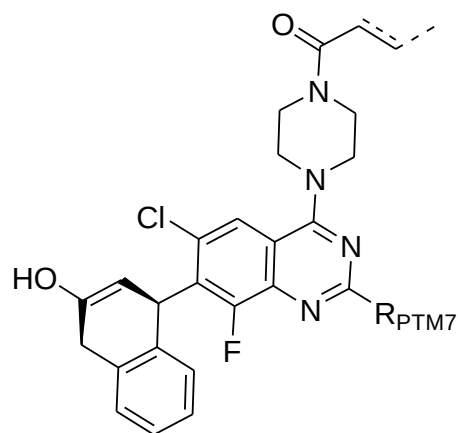
PTM-XVIIa



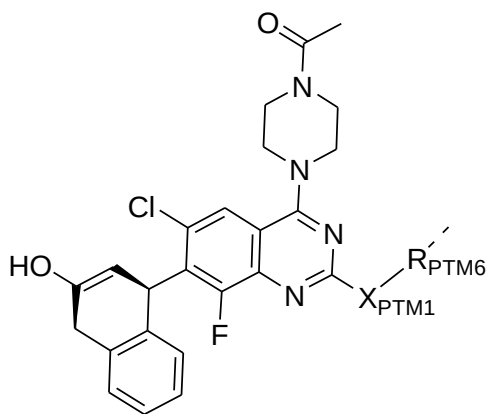
PTM-XVIIb



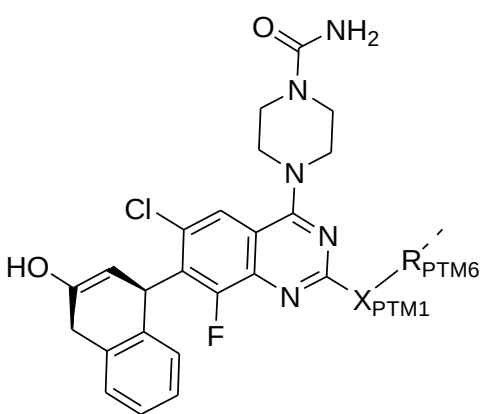
PTM-XVIII



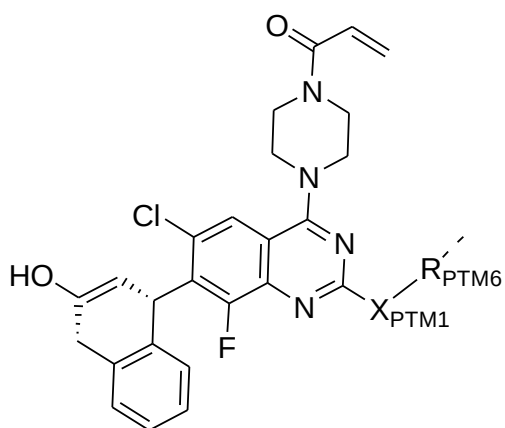
PTM-XIV



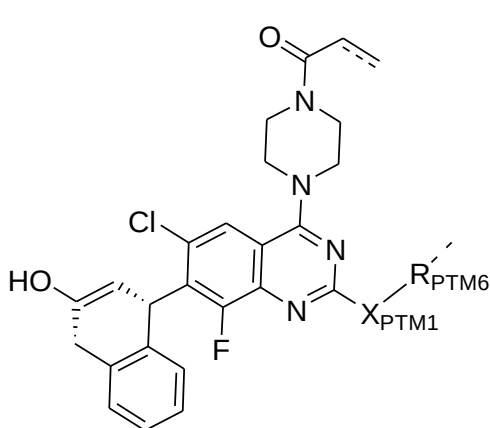
PTM-XV



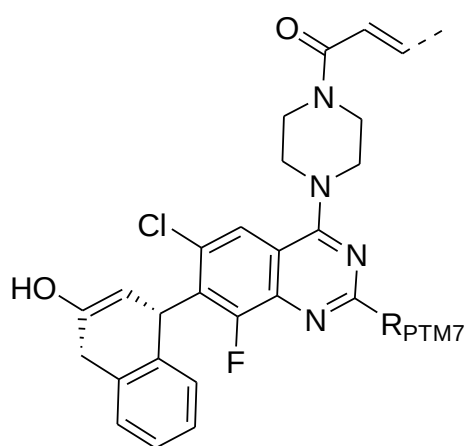
PTM-XVI



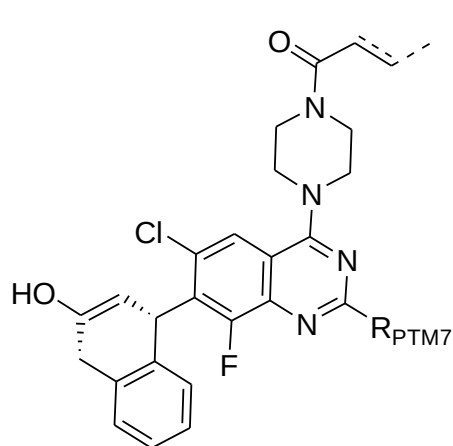
PTM-XVIIa



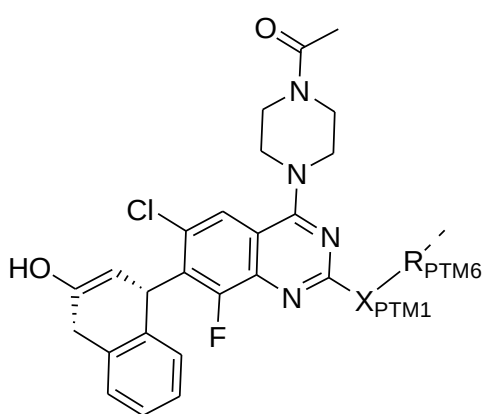
PTMXVIIb



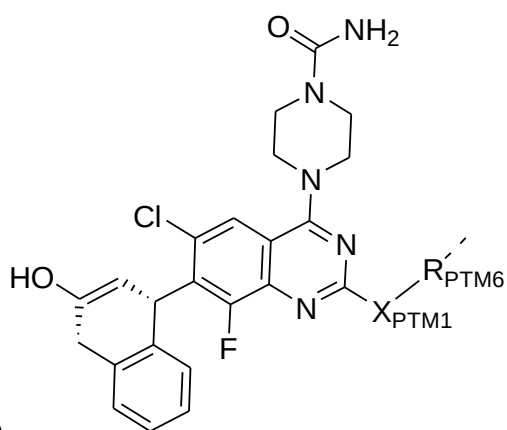
PTM-XVIII



PTM-XIX



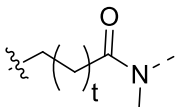
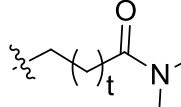
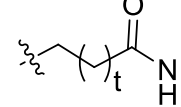
PTM-XX

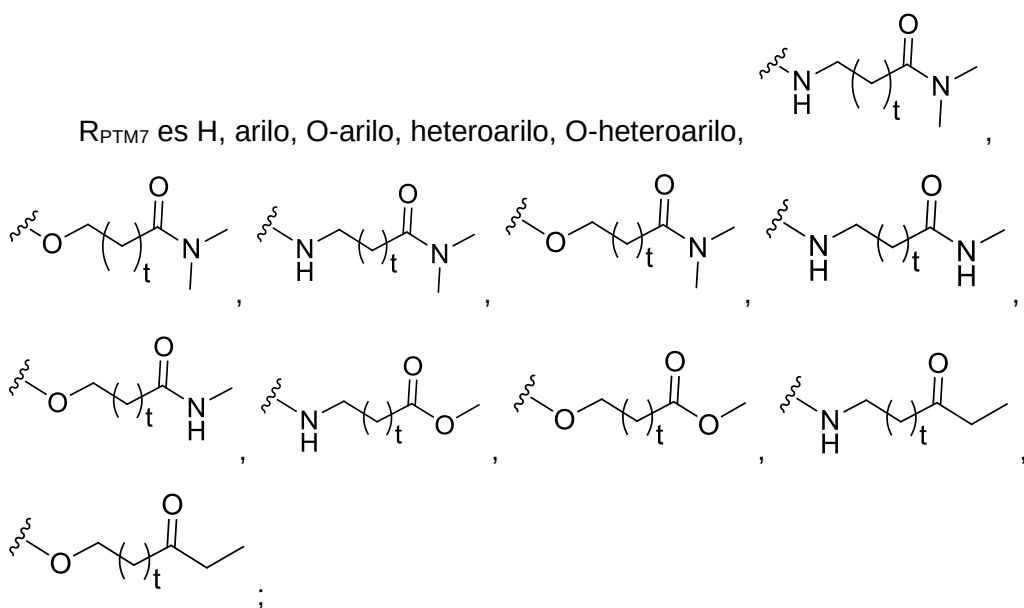
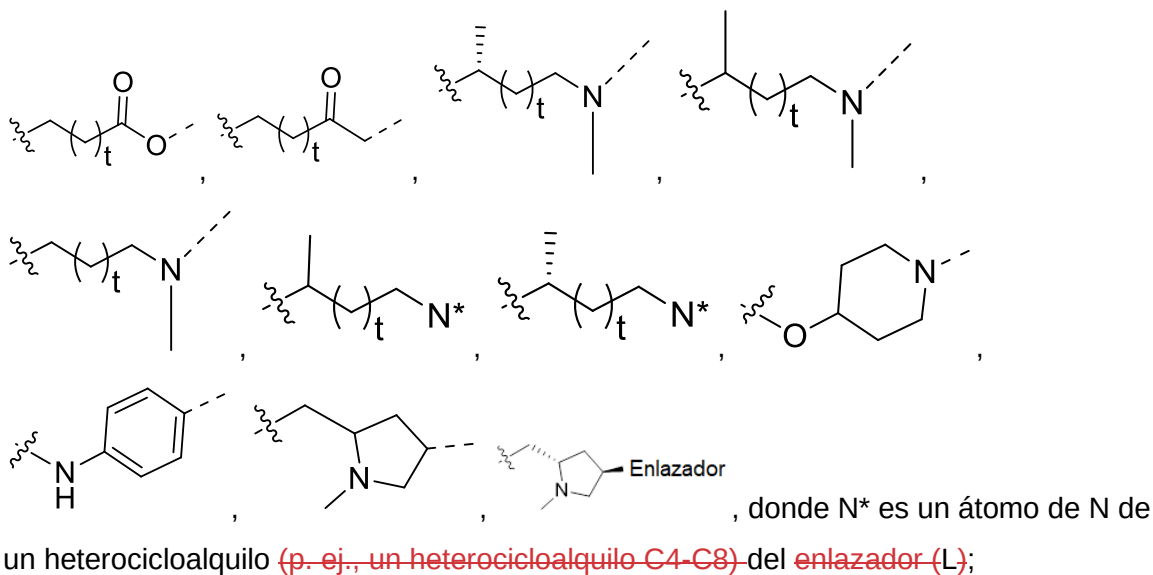


PTM-XXI

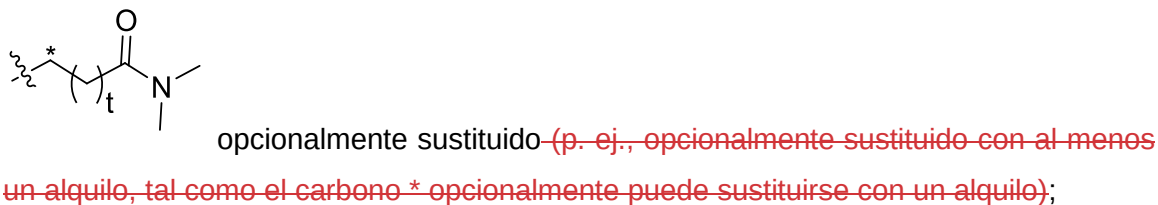
donde:

X_{PTM1} es NH u O;

R_{PTM6} es arilo, heteroarilo, , , ,



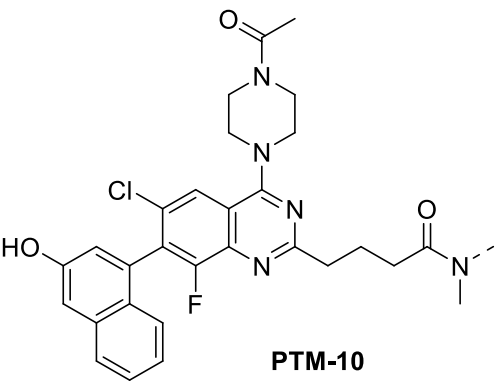
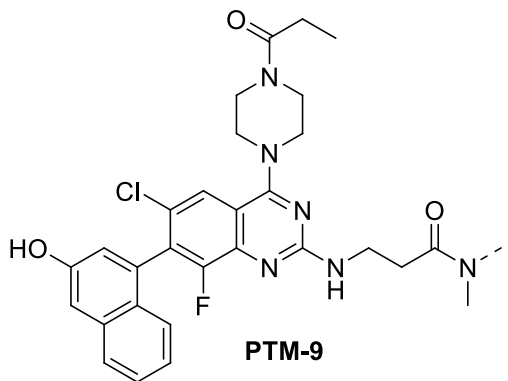
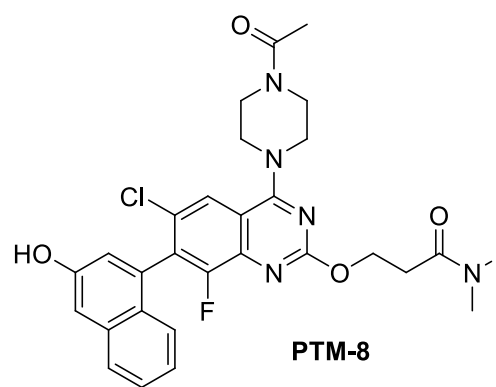
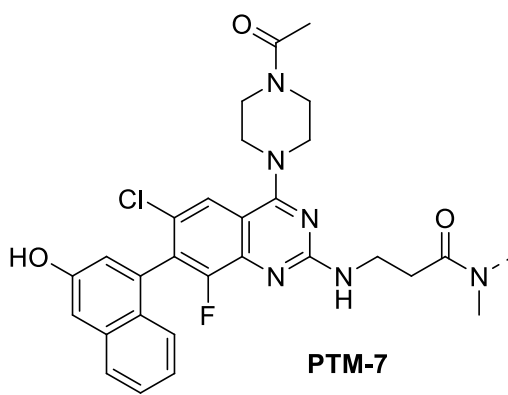
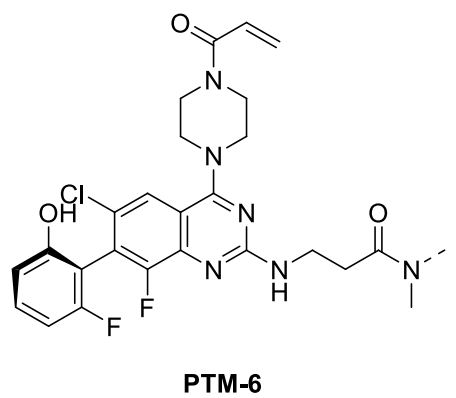
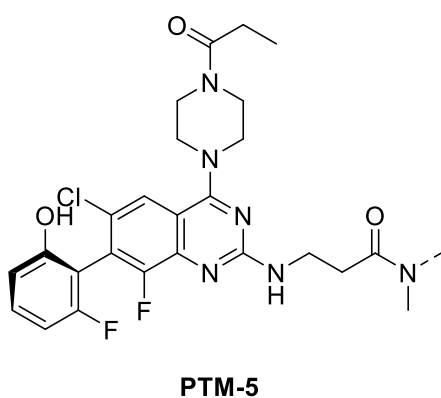
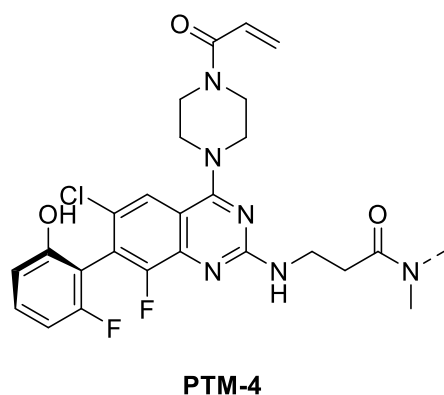
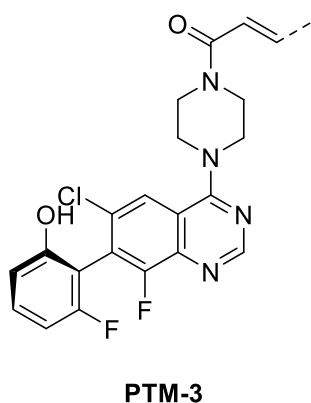
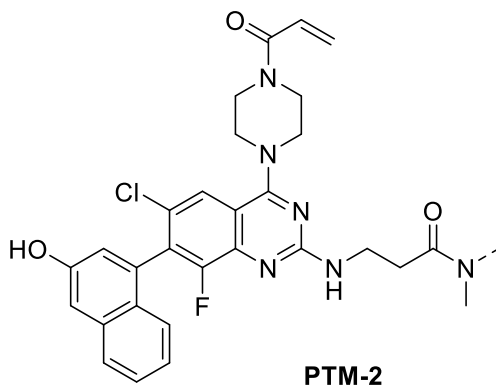
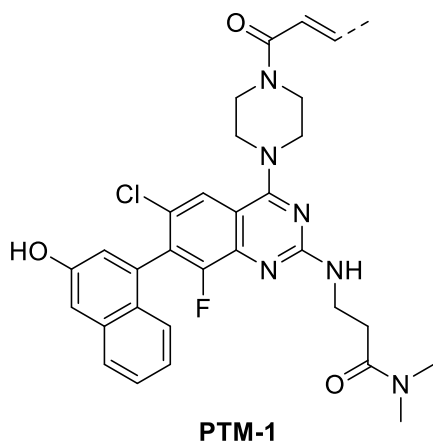
R_{PTM9} es H, alquilo C_{1-C6} opcionalmente sustituido, ~~amina-amino alifática-alifático~~ opcionalmente sustituida, ~~amida-amido alifática-alifático~~ opcionalmente sustituida, o

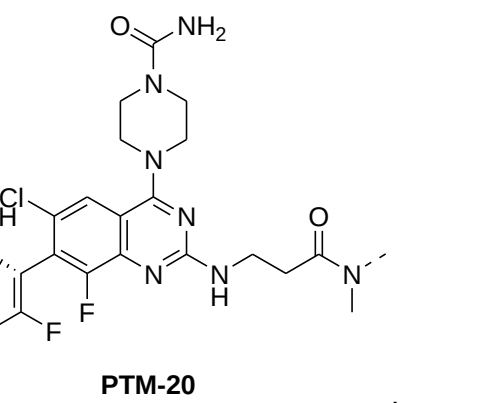
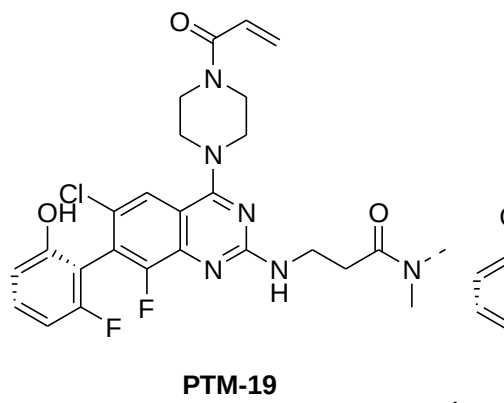
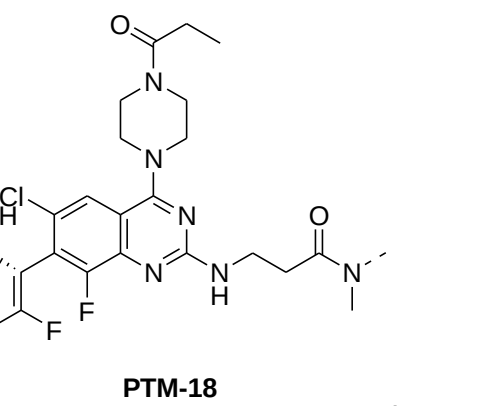
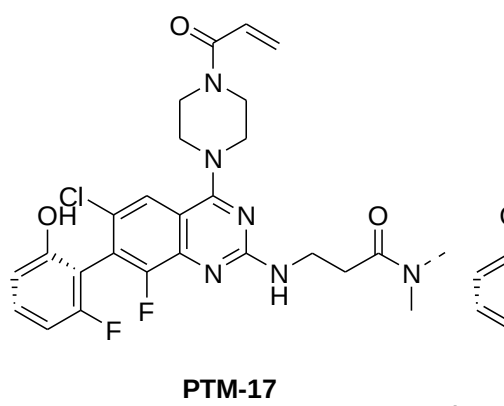
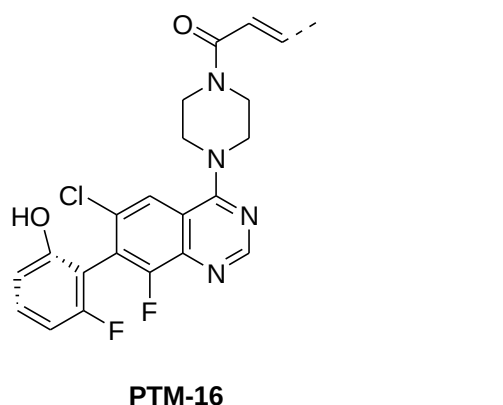
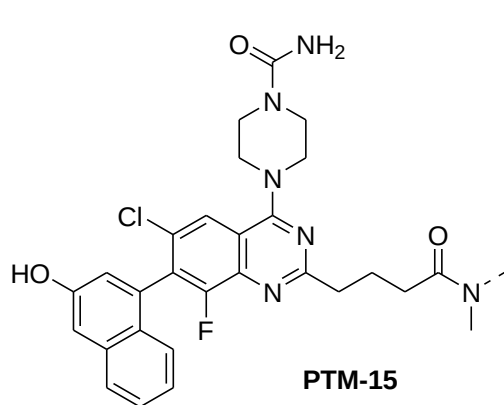
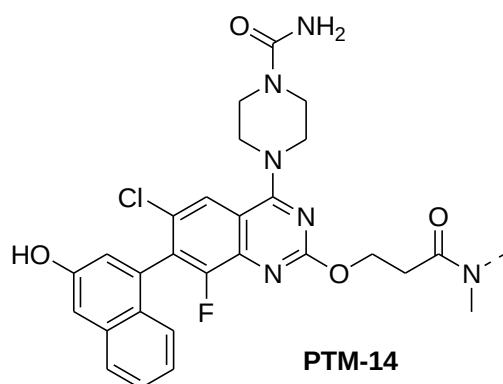
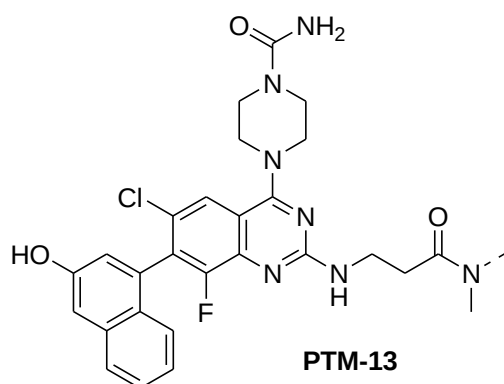
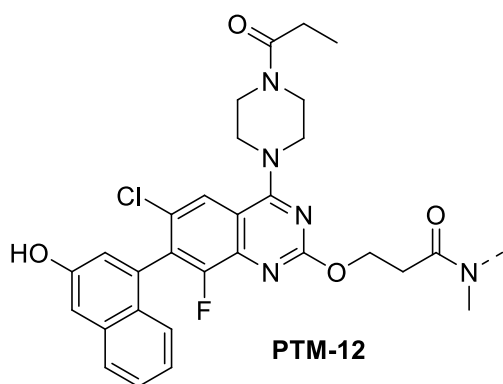
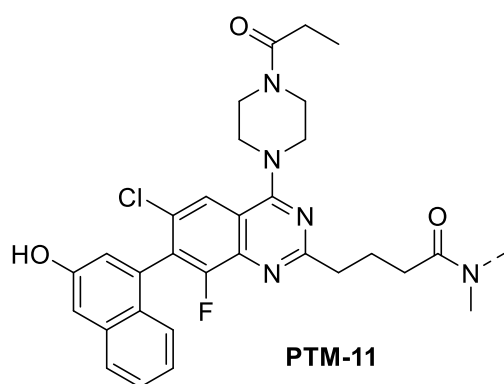


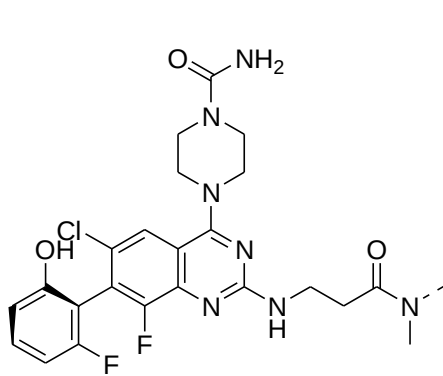
puede ser un enlace simple o un enlace doble; y

indica el sitio de unión del ~~L-al menos uno de un enlazador, ULM, ULM', CLM, CLM', VLM, VLM', ILM, ILM', MLM, MLM', o una combinación de estos.~~

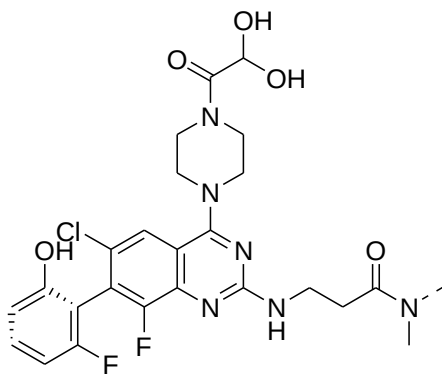
5.3. El compuesto bifuncional de acuerdo con cualquiera de las ~~reivindicaciones~~ reivindicación 1-4 o reivindicación 2, donde el PTM es representado por la estructura química:



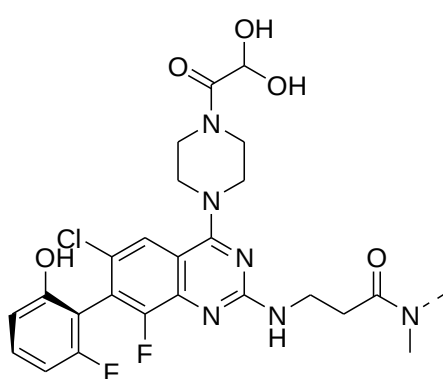




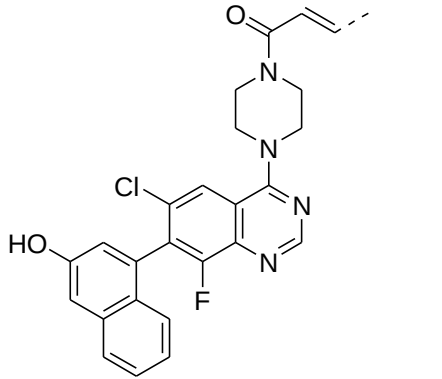
PTM-21



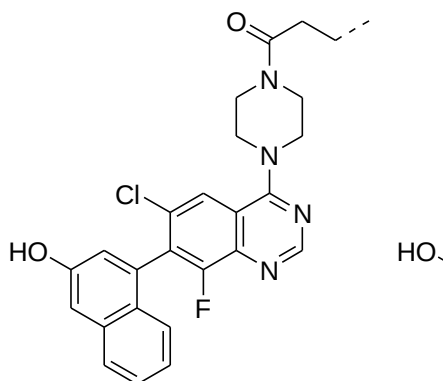
PTM-22



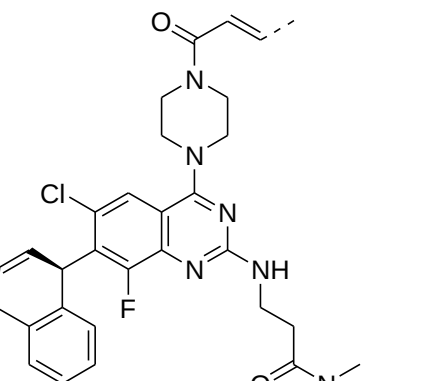
PTM-23



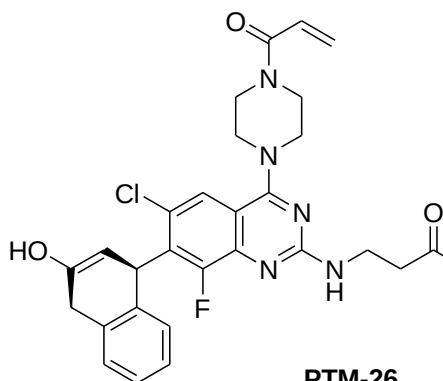
PTM-24



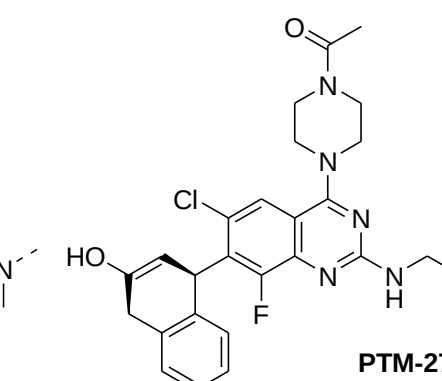
PTM-25



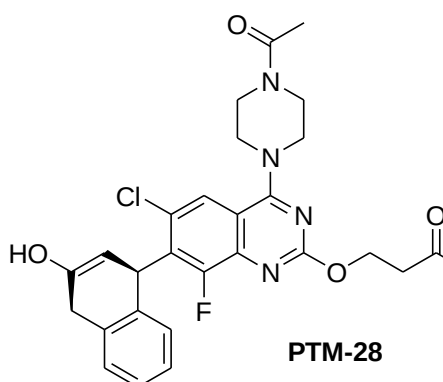
PTM-26



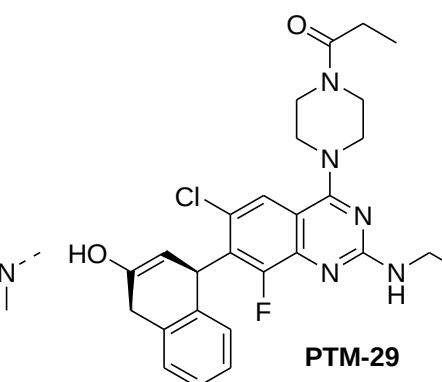
PTM-27



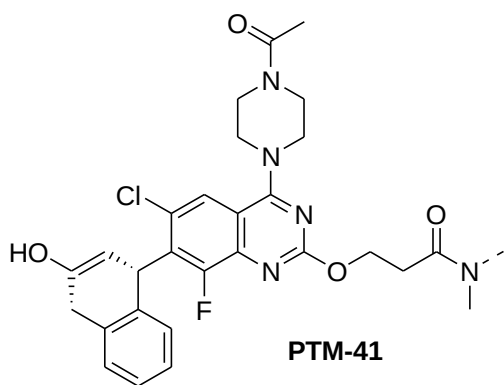
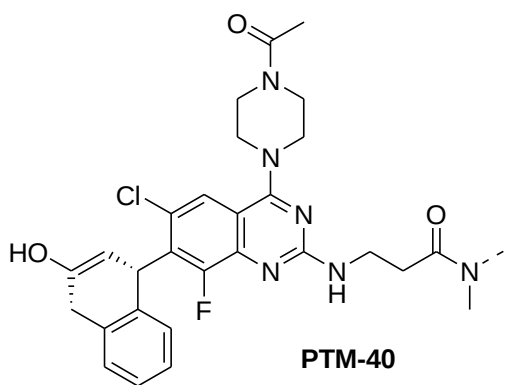
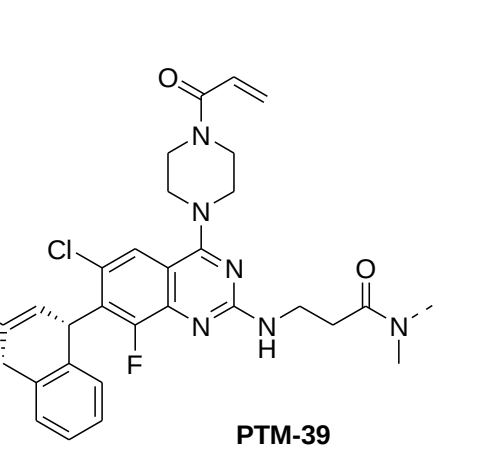
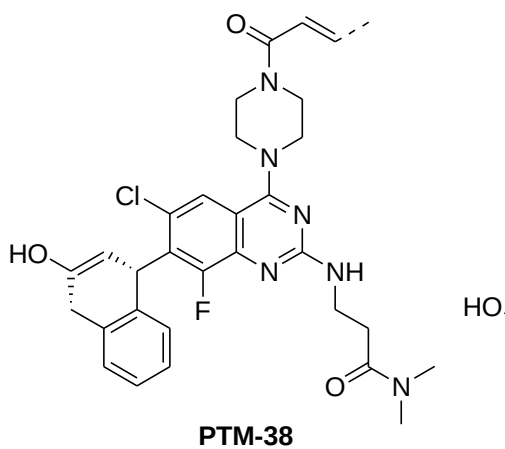
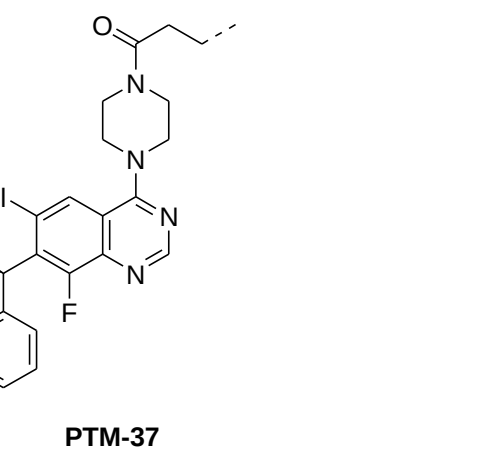
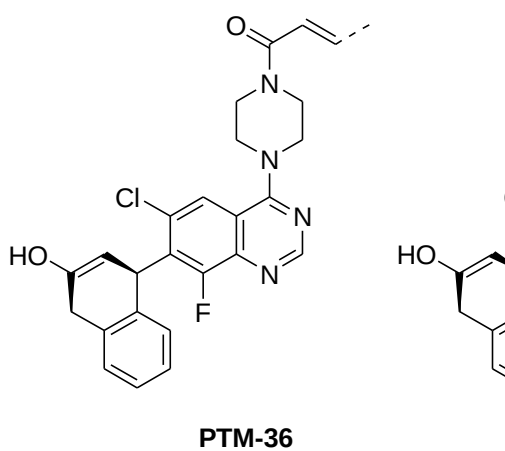
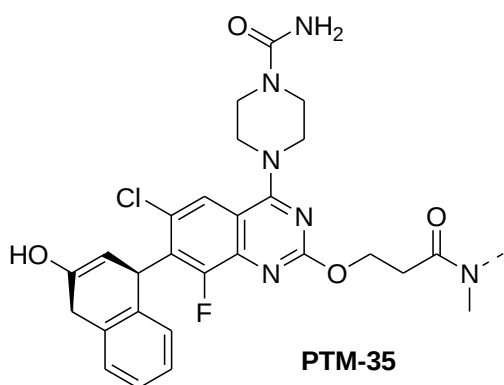
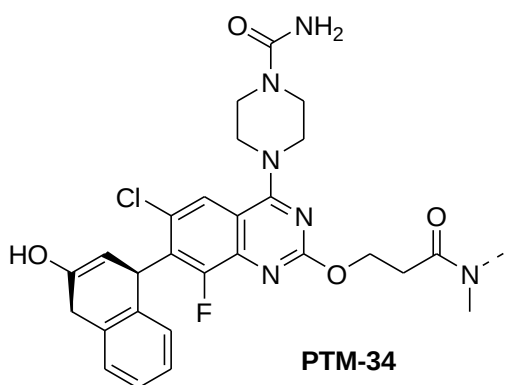
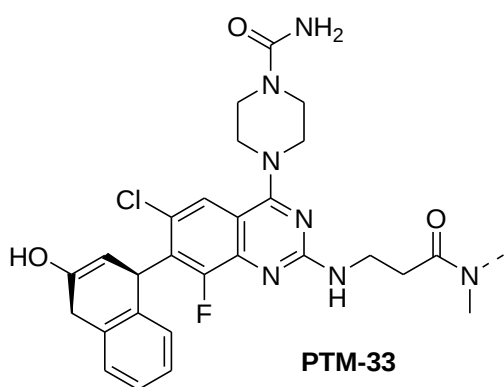
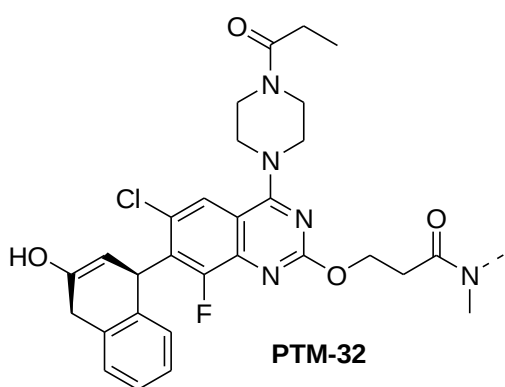
PTM-28

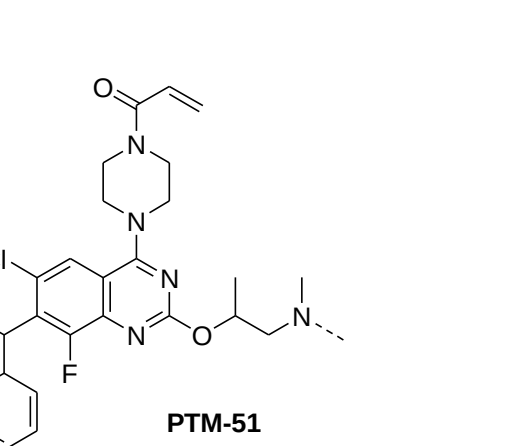
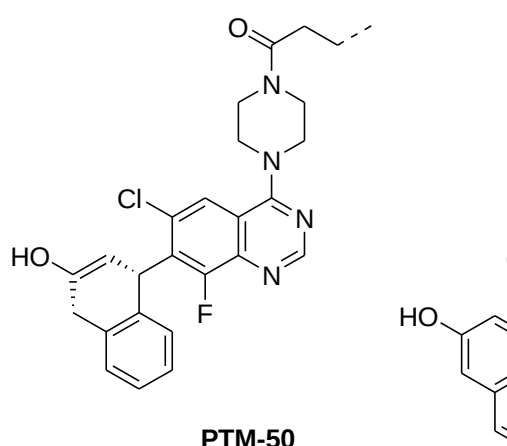
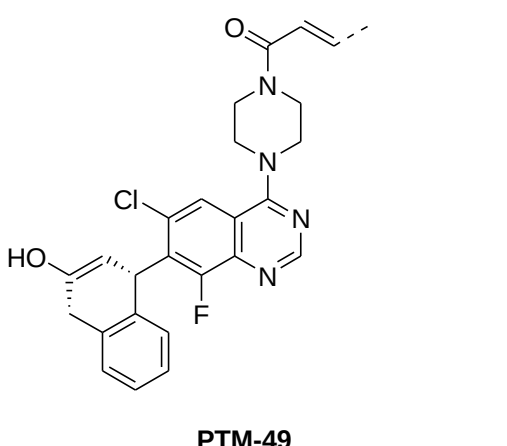
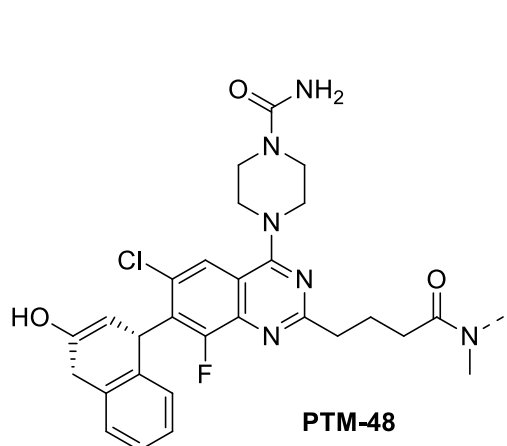
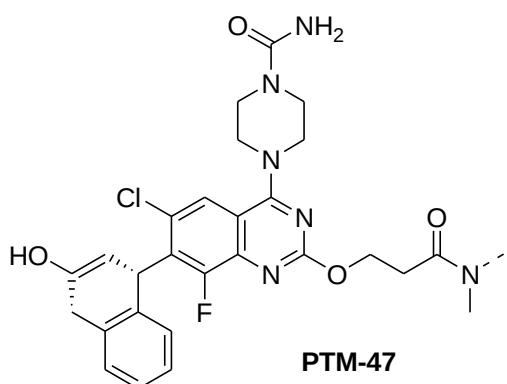
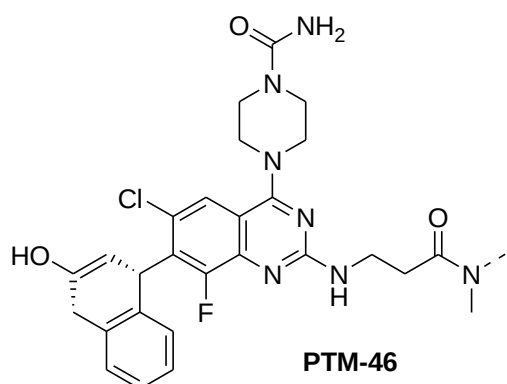
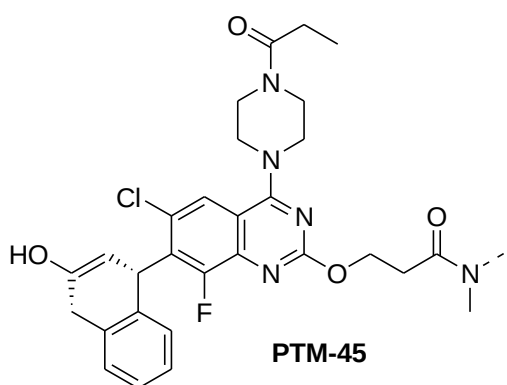
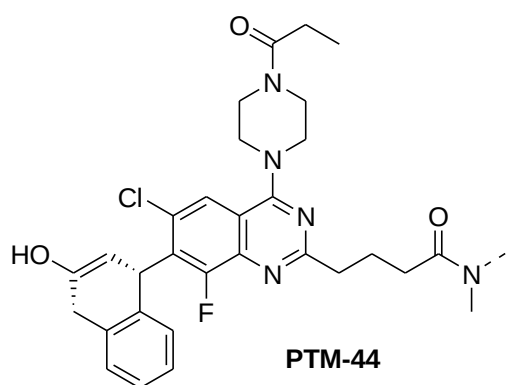
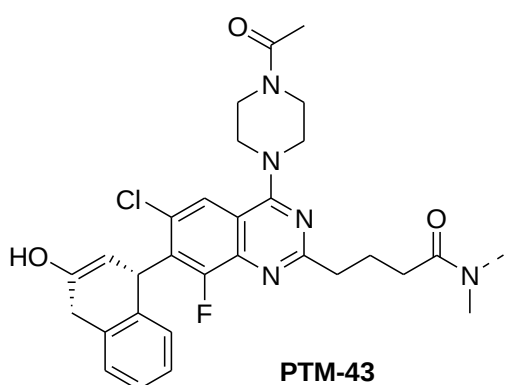
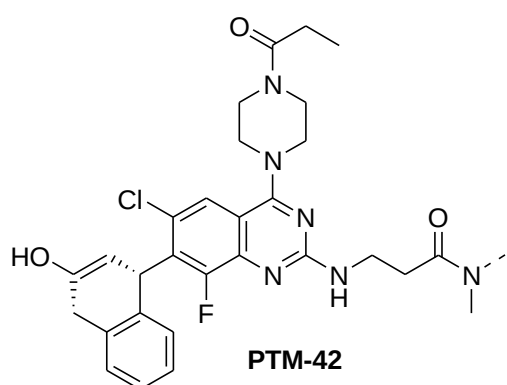


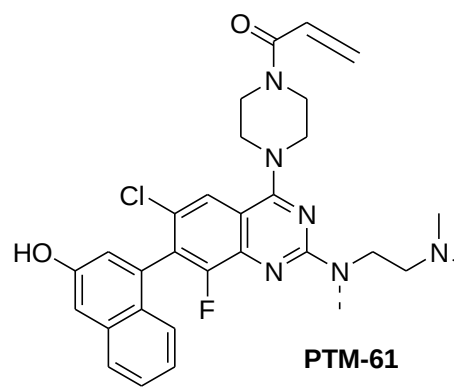
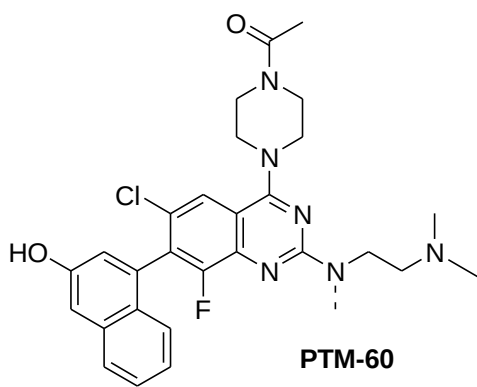
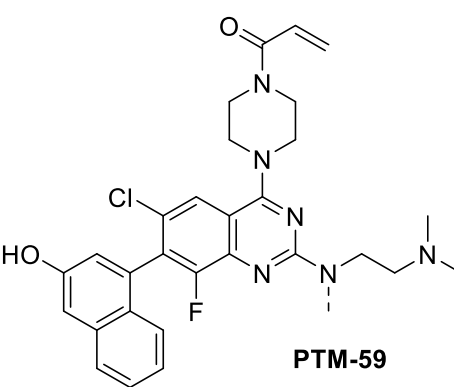
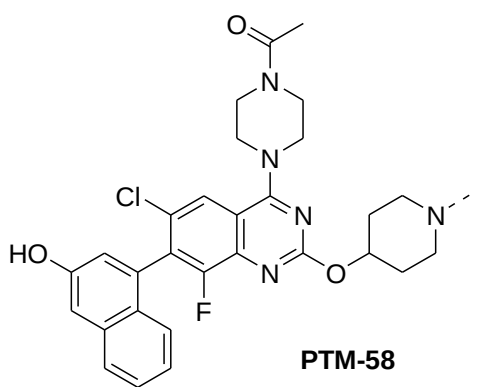
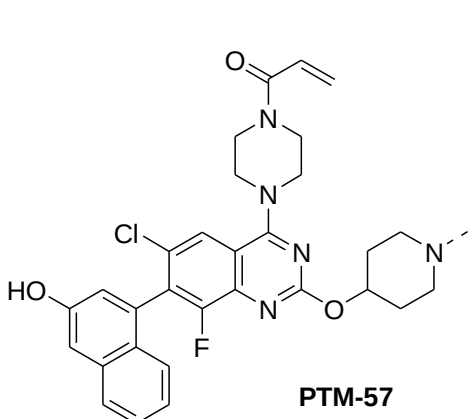
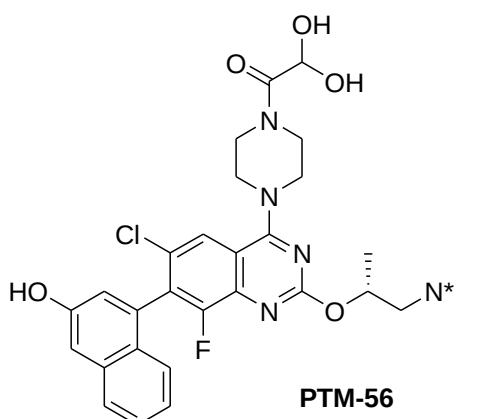
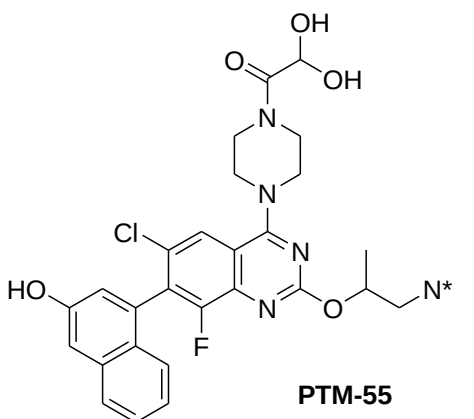
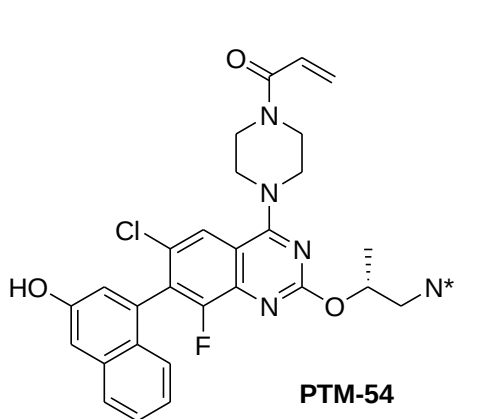
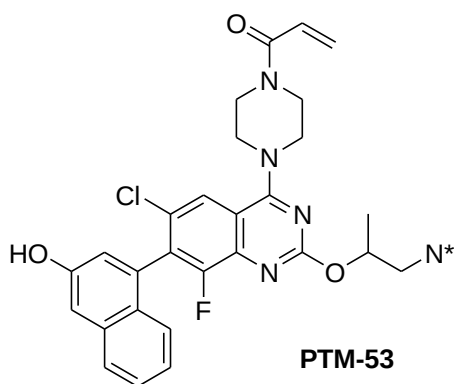
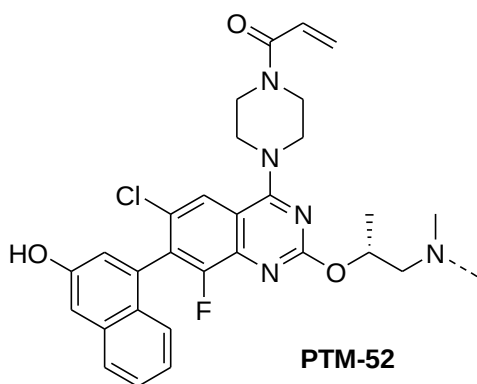
PTM-29

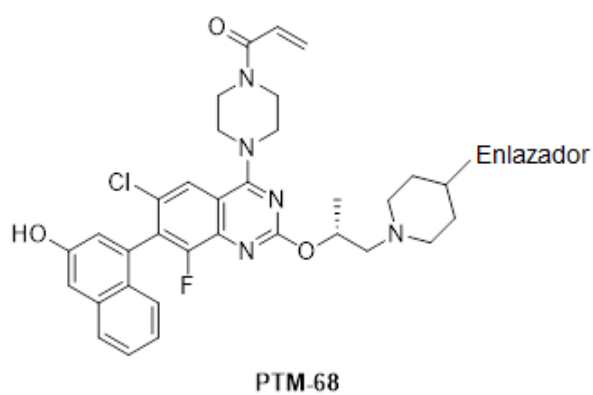
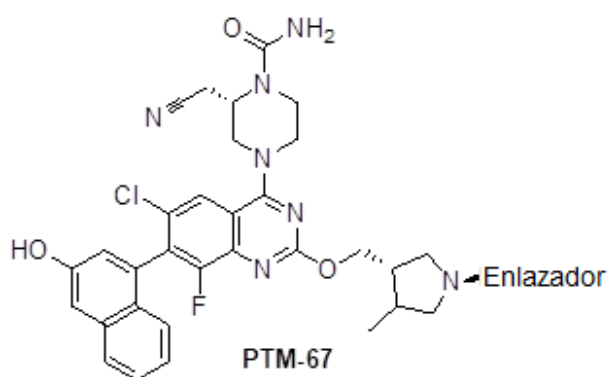
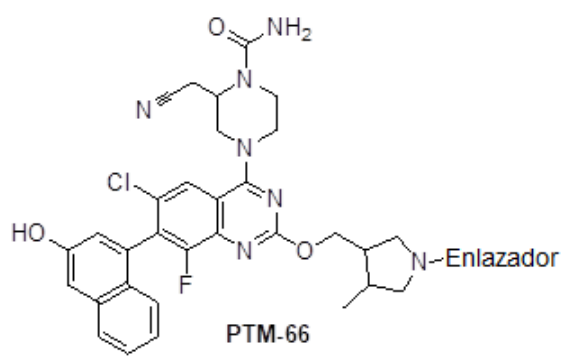
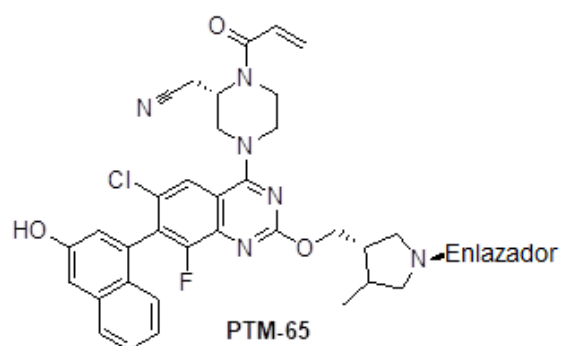
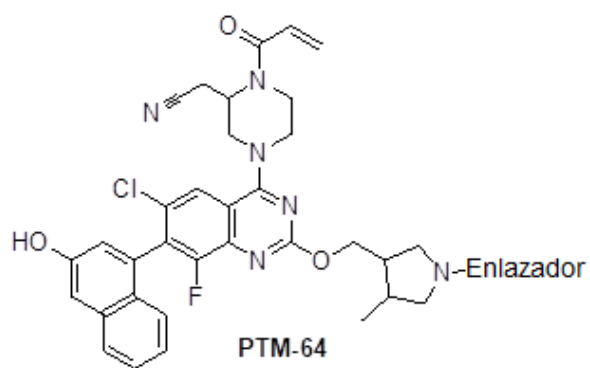
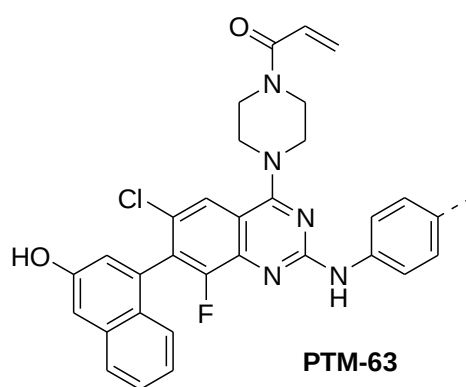
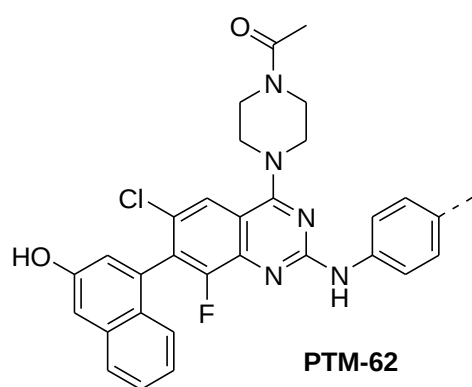


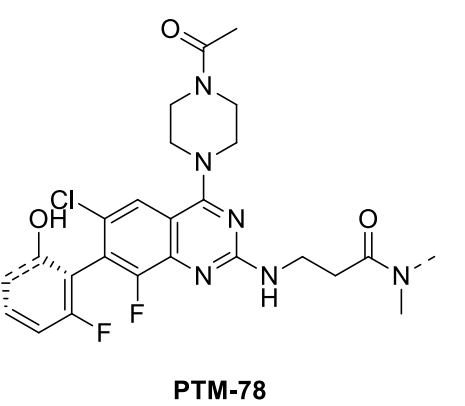
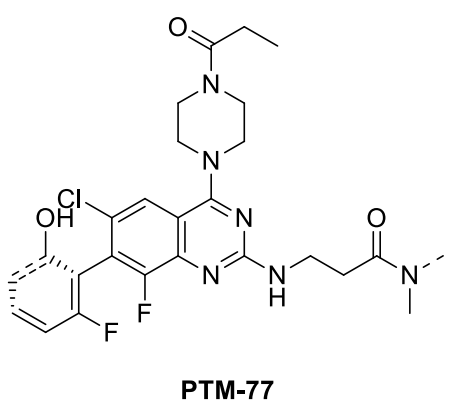
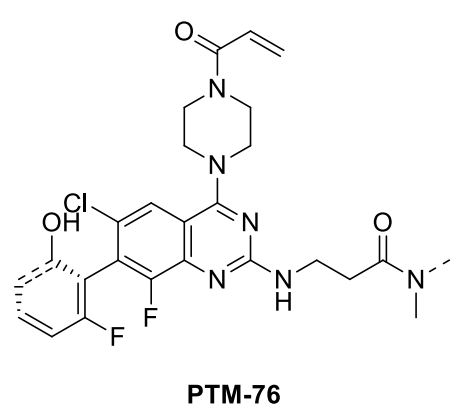
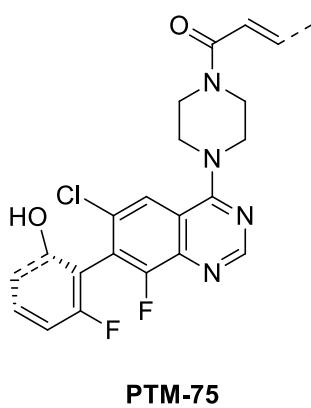
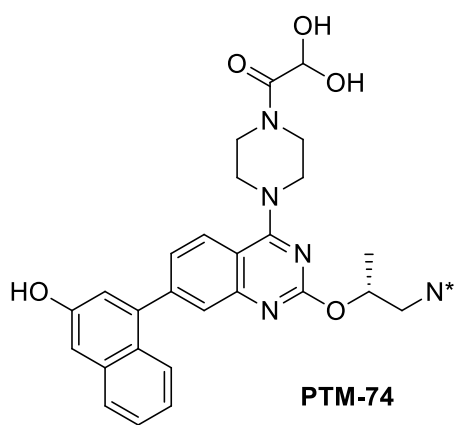
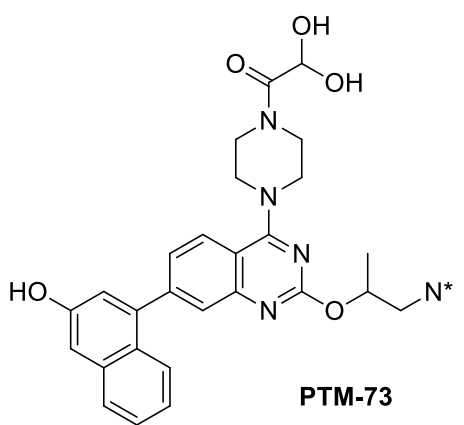
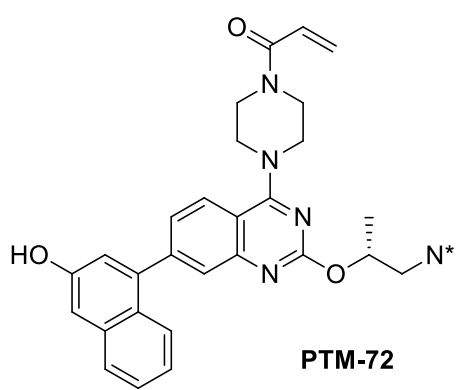
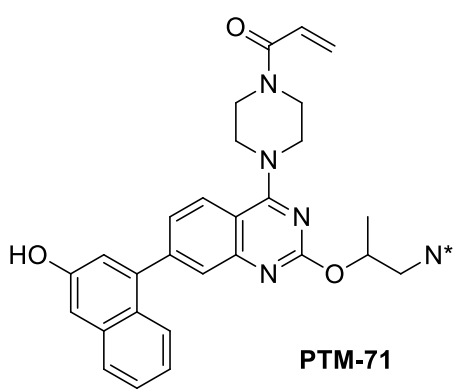
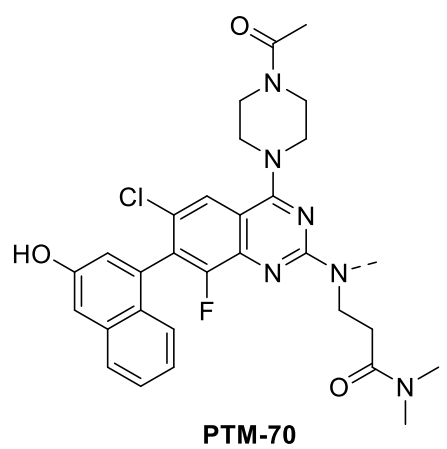
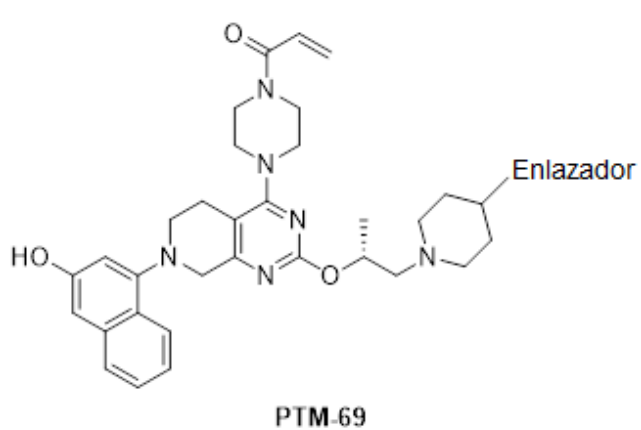
PTM-30

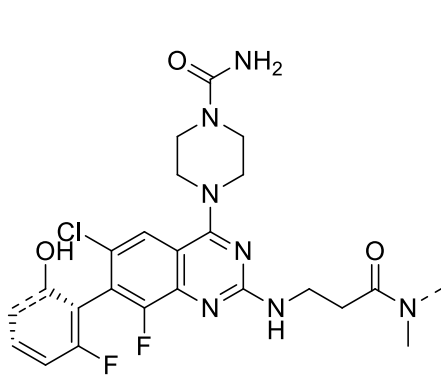




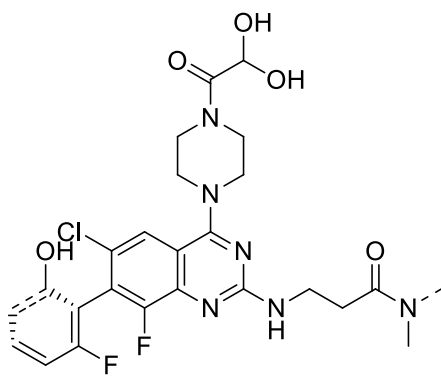




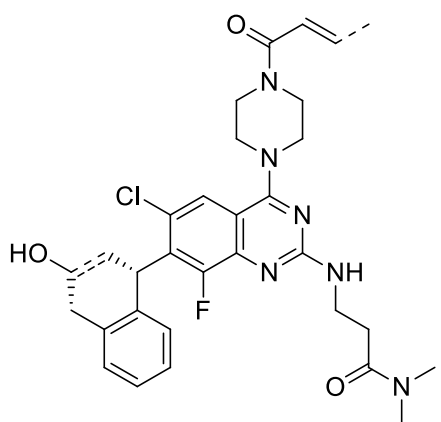




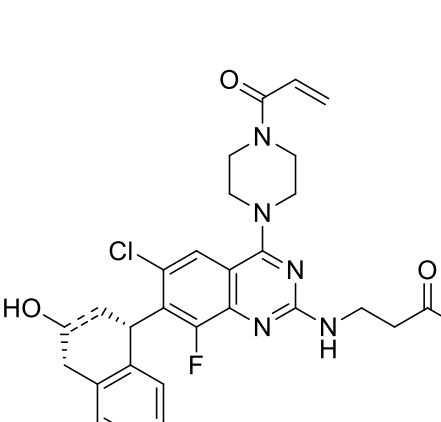
PTM-79



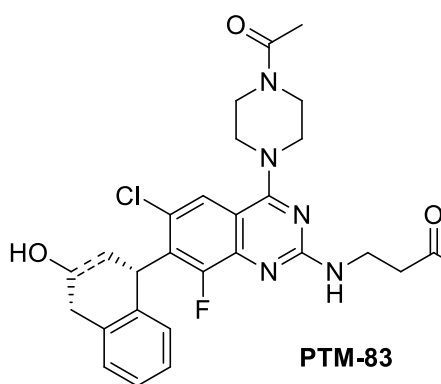
PTM-80



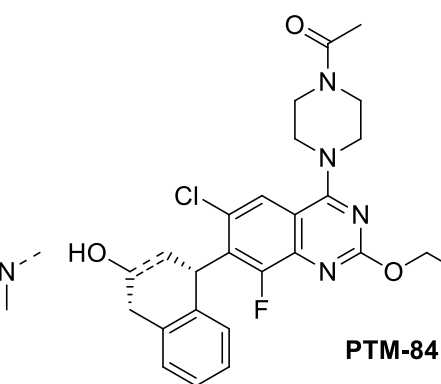
PTM-81



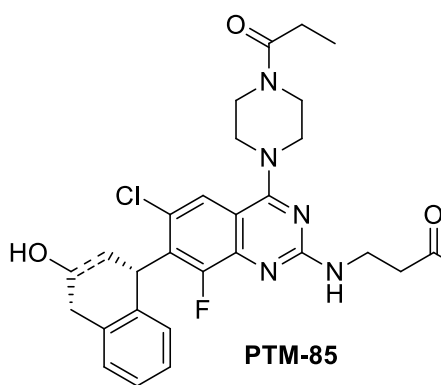
PTM-82



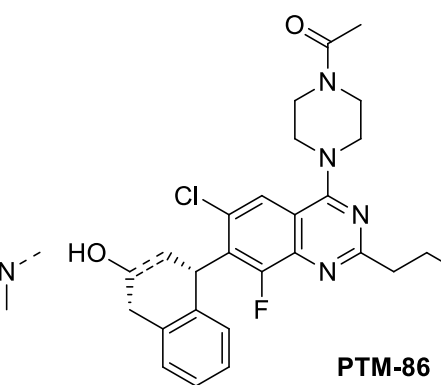
PTM-83



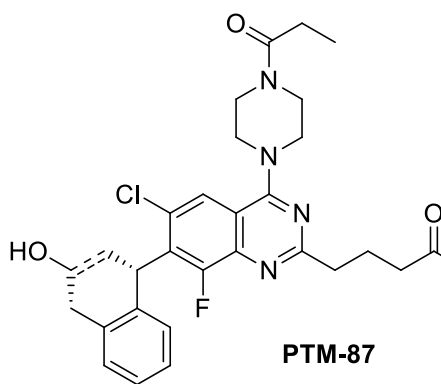
PTM-84



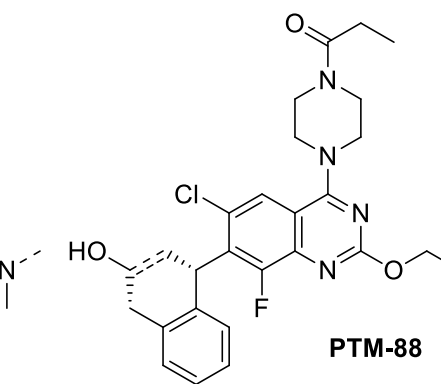
PTM-85



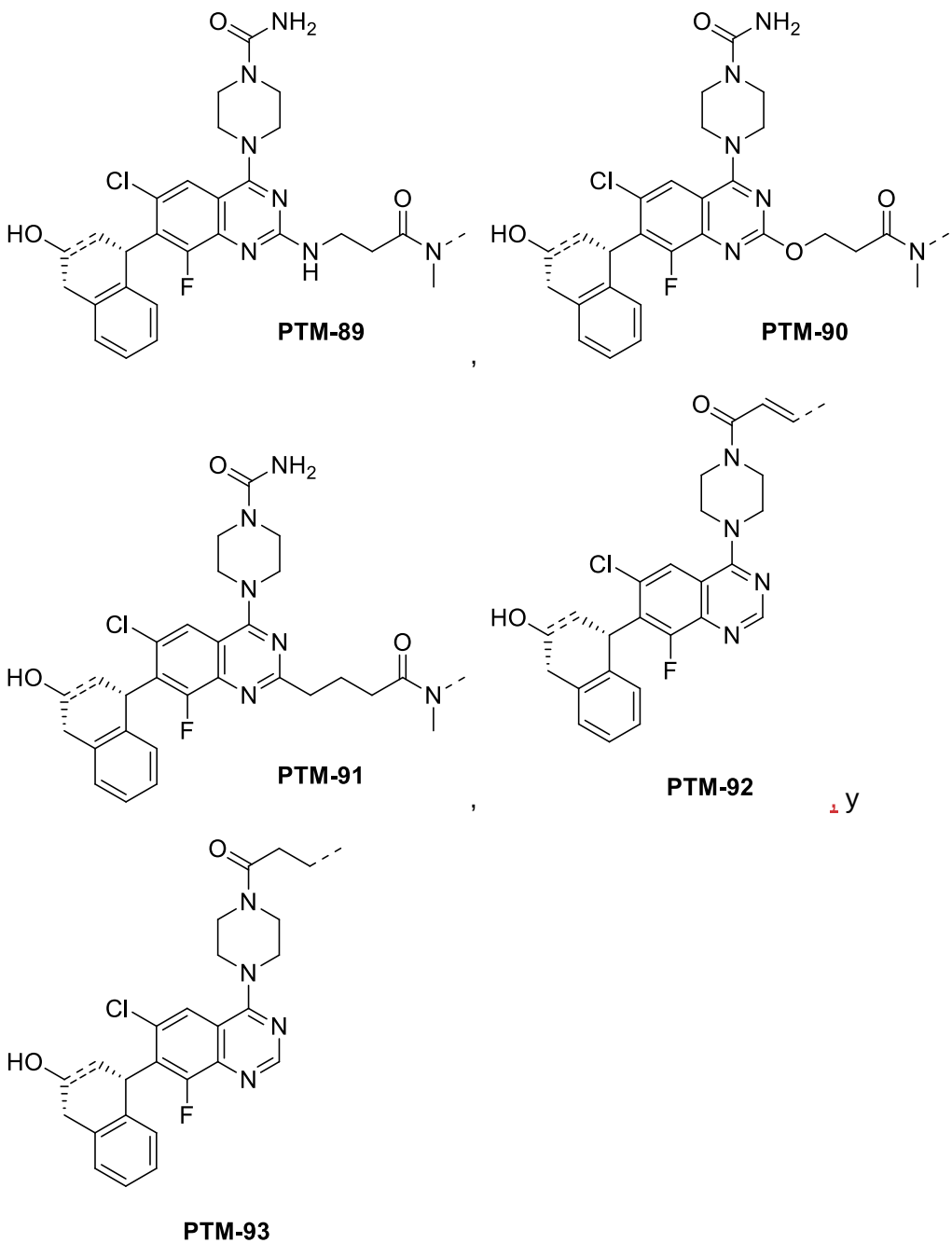
PTM-86



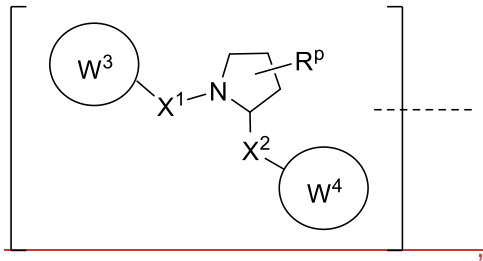
PTM-87



PTM-88



~~6. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5, donde ULM es un resto de unión a ligasa de Von Hippel-Lindau (VHL) (VLM) con una estructura química representada por:~~



~~donde:~~

- ~~X¹, X² se seleccionan cada uno de manera independiente dentro del grupo de un enlace, O, NR^{Y3}, CR^{Y3}R^{Y4}, C=O, C=S, SO y SO₂;~~
- ~~R^{Y3}, R^{Y4} se seleccionan cada uno de manera independiente dentro del grupo de H, alquilo C₁₋₆ lineal o ramificado, opcionalmente sustituido por 1 o más halo, alcoxilo C₁₋₆ opcionalmente sustituido por 0-3 grupos R^P;~~
- ~~R^P es 0, 1, 2 o 3 grupos, seleccionados de manera independiente dentro del grupo H, halo, -OH, alquilo C₁₋₃, C=O;~~
- ~~W³ se selecciona dentro del grupo de un T opcionalmente sustituido, un -T-~~

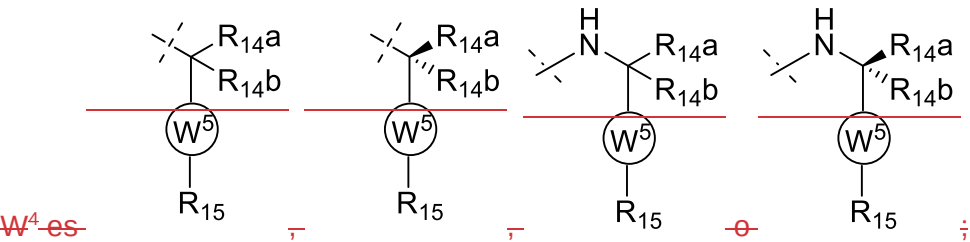
~~N(R^{1a}R^{1b})X³ opcionalmente sustituido, un T-N(R^{1a}R^{1b}) opcionalmente sustituido, un T-Arilo opcionalmente sustituido, un T-Heteroarilo opcionalmente sustituido, un T-biheteroarilo opcionalmente sustituido, un T-heterociclilo opcionalmente sustituido, un T-biheterociclilo opcionalmente sustituido, un NR¹-T-Arilo opcionalmente sustituido, un NR¹-T-Heteroarilo opcionalmente sustituido o un NR¹-T-Heterociclilo opcionalmente sustituido;~~

~~X³ es C=O, R¹, R^{1a}, R^{1b};~~

~~cada uno de R¹, R^{1a}, R^{1b} se selecciona dentro del grupo que consiste en H, grupo alquilo C₁-C₆ lineal o ramificado opcionalmente sustituido por 1 o más grupos 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 dentro del grupo de un alquilo opcionalmente sustituido, grupo (CH₂)_n, donde cada uno de los grupos metileno opcionalmente se sustituye con uno o dos sustituyentes seleccionados dentro del grupo de halógeno, metilo, alcoxi opcionalmente sustituido, un grupo alquilo C₁-C₆ lineal o ramificado opcionalmente sustituido por 1 o más halógenos, C(O)-NR¹R^{1a}, o NR¹R^{1a} o R¹ y R^{1a} se unen para formar un heterociclilo opcionalmente sustituido, o grupos -OH groups o una cadena lateral de aminoácidos opcionalmente sustituida; y~~

~~n es de 0 a 6,~~



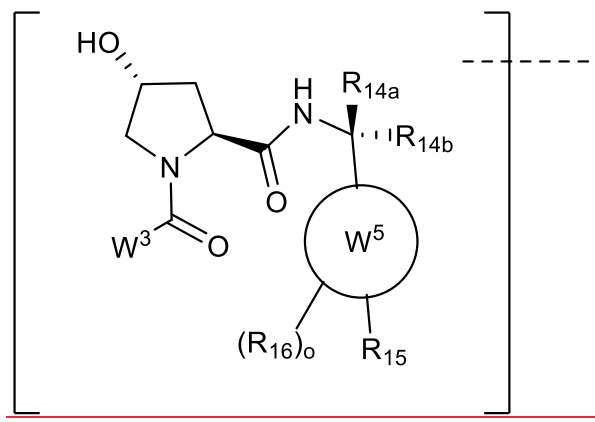
~~R_{14a}, R_{14b} se seleccionan cada uno de manera independiente dentro del grupo de H, haloalquilo o alquilo opcionalmente sustituido;~~

~~W⁵ se selecciona dentro del grupo de un fenilo opcionalmente sustituido o un heteroarilo de 5-10 miembros opcionalmente sustituido;~~

~~R₁₅ se selecciona dentro del grupo de H, halógeno, CN, OH, NO₂, NR^{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 o cicloheteroalquilo opcionalmente sustituido;~~

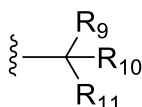
~~y donde la línea discontinua indica el sitio de unión de al menos un PTM, otro ULM (ULM') o un resto enlazador químico que acopla al menos un PTM o un ULM' o ambos a ULM.~~

7. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5, donde ULM es un resto de unión a ligasa de Von Hippel-Lindau (VHL) (VLM) con una estructura química representada por:



donde:

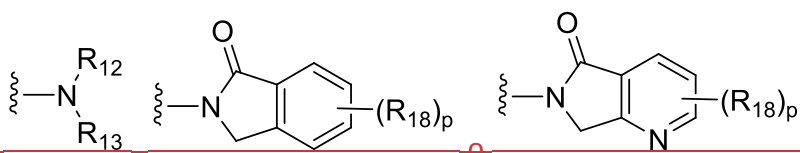
~~W³ se selecciona dentro del grupo de un arilo opcionalmente sustituido, heteroarilo~~



~~opcionalmente sustituido o~~;

~~R₉ y R₁₀ son de manera independiente hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o haloalquilo, o R₉, R₁₀, y el átomo de carbono al que se unen forma un cicloalquilo opcionalmente sustituido;~~

~~R₁₁ se selecciona dentro del grupo de un heterociclilo opcionalmente sustituido, alcoxi opcionalmente sustituido, heteroarilo opcionalmente sustituido, arilo opcionalmente~~



~~sustituido, o~~;

~~R₁₂ se selecciona dentro del grupo de H o alquilo opcionalmente sustituido;~~

~~R₁₃ se selecciona dentro del grupo de H, alquilo opcionalmente sustituido, alquilcarbonilo opcionalmente sustituido, (cicloalquil)alquilcarbonilo opcionalmente sustituido, aralquilcarbonilo opcionalmente sustituido, arilcarbonilo opcionalmente sustituido, (heterociclil)carbonilo opcionalmente sustituido o aralquilo opcionalmente sustituido;~~

~~R_{14a}, R_{14b} se seleccionan cada uno de manera independiente dentro del grupo de H, haloalquilo o alquilo opcionalmente sustituido;~~

~~W⁵ se selecciona dentro del grupo de un fenilo opcionalmente sustituido o un heteroarilo de 5-10 miembros opcionalmente sustituido;~~

~~R₁₅ se selecciona dentro del grupo de 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 o cicloheteroalquilo opcionalmente sustituido;~~

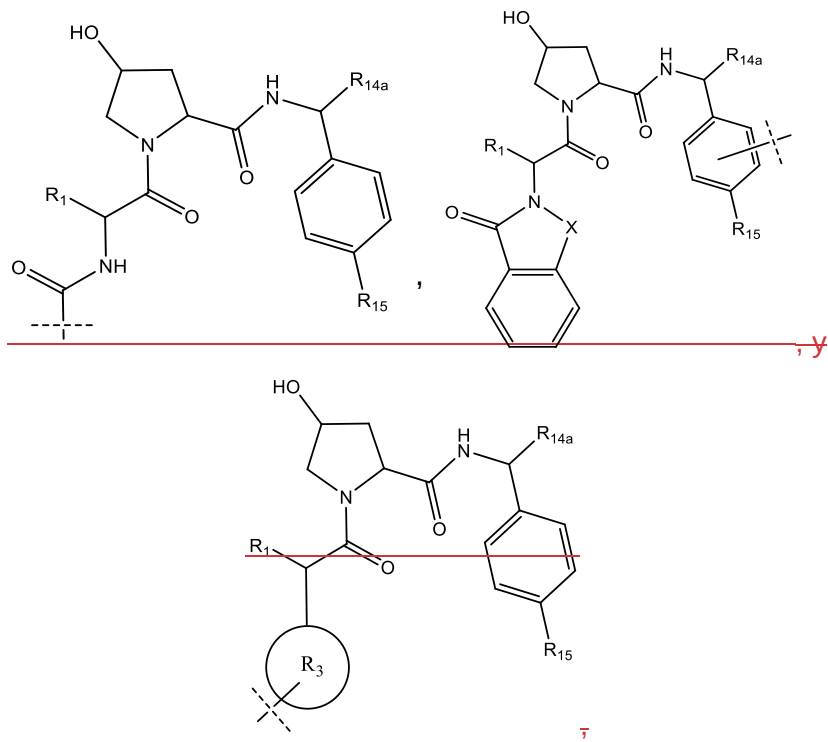
~~cada R₁₆ se selecciona de manera independiente dentro del grupo de halo, CN, alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, hidroxi o haloalcoxi opcionalmente sustituido;~~

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

~~R₁₈ se selecciona de manera independiente dentro del grupo de halo, alcoxi opcionalmente sustituido, ciano, alquilo opcionalmente sustituido, haloalquilo, haloalcoxi o un enlazador; y~~

~~p es 0, 1, 2, 3 o 4, y donde la línea discontinua indica el sitio de unión de al menos un PTM, otro ULM (ULM') o un resto enlazador químico que acopla al menos un PTM o un ULM' o ambos a ULM.~~

~~8. — El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-7, donde el ULM tiene una estructura química seleccionada dentro del grupo de:~~



~~donde:~~

~~R₁ es H, etilo, isopropilo, terc-butilo, sec-butilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo; alquilo opcionalmente sustituido, hidroxialquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o haloalquilo;~~

~~R_{14a} es H, haloalquilo, alquilo opcionalmente sustituido, metilo, fluorometilo, hidroximetilo, etilo, isopropilo o ciclopropilo;~~

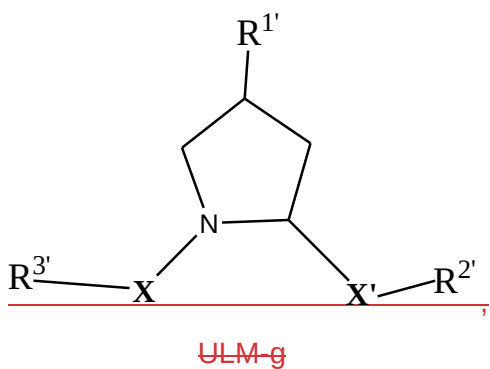
~~R₁₅ se selecciona dentro del grupo que consiste en H, halógeno, CN, OH, NO₂, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido; alquilo opcionalmente sustituido, haloalquilo opcionalmente sustituido, haloalcoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido o cicloheteroalquilo opcionalmente sustituido;~~

~~X es C, CH₂ o C=O~~

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

~~donde la línea discontinua indica el sitio de unión de al menos un PTM, otro ULM (ULM') o un resto enlazador químico que acopla al menos un PTM o un ULM' o ambos al ULM.~~

~~9. — El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5, donde el ULM comprende un grupo de acuerdo con la estructura química:~~



donde:

~~R¹ de ULM-g es un grupo alquilo C₁-C₆ opcionalmente sustituido, un -(CH₂)ₙOH opcionalmente sustituido, un -(CH₂)ₙSH opcionalmente sustituido, un grupo (CH₂)ₙ-O alquilo(C₁-C₆) opcionalmente sustituido, un grupo (CH₂)ₙ-WCOCW alquilo(C₀-C₆) opcionalmente sustituido que contiene un resto epóxido WCOCW donde cada W es de manera independiente H o un grupo alquilo C₁-C₃, un -(CH₂)ₙCOOH opcionalmente sustituido, un -(CH₂)ₙC(O)-(alquilo C₁-C₆) opcionalmente sustituido, un -(CH₂)ₙNHC(O)-R₁ opcionalmente sustituido, un -(CH₂)ₙC(O)-NR₁R₂ opcionalmente sustituido, un -(CH₂)ₙOC(O)-NR₁R₂ opcionalmente sustituido, (CH₂O)ₙH, un -(CH₂)ₙOC(O)-(alquilo C₁-C₆) opcionalmente sustituido, un -(CH₂)ₙC(O)-O-(alquilo C₁-C₆) opcionalmente sustituido, un -(CH₂O)ₙ opcionalmente sustituido, un -(OCH₂)ₙO-(alquilo C₁-C₆) opcionalmente sustituido, un -(CH₂O)ₙC(O)-(alquilo C₁-C₆) opcionalmente sustituido, un -(OCH₂)ₙNHC(O)-R₁ opcionalmente sustituido, un -(CH₂O)ₙC(O)-NR₁R₂, -(CH₂CH₂O)ₙH opcionalmente sustituido, un -(CH₂CH₂O)ₙCOOH opcionalmente sustituido, un -(OCH₂CH₂)ₙO-(alquilo C₁-C₆) opcionalmente sustituido, un -(CH₂CH₂O)ₙC(O)-(alquilo C₁-C₆) opcionalmente sustituido, un -(OCH₂CH₂)ₙNHC(O)-R₁ opcionalmente sustituido, un -(CH₂CH₂O)ₙC(O)-NR₁R₂ opcionalmente sustituido, un -SO₂Rₛ opcionalmente sustituido, un S(O)Rₛ, NO₂ opcionalmente sustituido, CN o halógeno (F, Cl, Br, I, preferentemente F o Cl);~~

~~R₁ y R₂ de ULM-g son cada uno de manera independiente H o un grupo alquilo C₁-C₆, que opcionalmente puede sustituirse con uno o dos grupos hidroxilo o hasta tres grupos halógeno (preferentemente flúor);~~

~~Rₛ de ULM-g es un grupo alquilo C₁-C₆, un grupo arilo, heteroarilo o heterociclo opcionalmente sustituido o un grupo -(CH₂)ₘNR₁R₂;~~

~~X y X' de ULM-g son cada uno de manera independiente C=O, C=S, S(O), S(O)₂, (preferentemente X y X' son ambos C=O);~~

~~R² de ULM-g es un grupo -(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂ alquilo opcionalmente sustituido, un grupo -(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂNR₁NR₂N opcionalmente sustituido, un -(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂArilo opcionalmente sustituido, un -(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂHeteroarilo opcionalmente sustituido, un -(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂHeterociclo opcionalmente sustituido, un -NR¹-(CH₂)ₙ-C(O)ᵤ(NR₁)ᵥ(SO₂)ᵂ alquilo opcionalmente sustituido, un -NR¹-(CH₂)ₙ-C(O)ᵤ(NR₁)ᵥ(SO₂)ᵂ-NR₁NR₂N opcionalmente sustituido, un -NR¹-(CH₂)ₙ-C(O)ᵤ(NR₁)ᵥ(SO₂)ᵂ-NR₁C(O)R₁N opcionalmente sustituido, un -NR¹-(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂArilo opcionalmente sustituido, un -NR¹-(CH₂)ₙ-Arilo Heteroarilo opcionalmente sustituido, un -NR¹-(CH₂)ₙ-(C=O)ᵤ(NR₁)ᵥ(SO₂)ᵂHeteroarilo opcionalmente sustituido o un -NR¹-(CH₂)ₙ-(C=O)ᵤNR₁(SO₂)ᵂHeterociclo opcionalmente sustituido, un grupo -X^{R2'}-alquilo opcionalmente sustituido; un grupo -X^{R2'}-Arilo opcionalmente sustituido; un grupo -X^{R2'}-Heteroarilo opcionalmente sustituido; un grupo~~

~~-X^{R2'}-Heterociclo opcionalmente sustituido; un opcionalmente sustituido;~~

~~R^{3'} de ULM-g es un alquilo opcionalmente sustituido, un -(CH₂)_n-(O)_u(NR₁)_v(SO₂)_w- alquilo opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-NR_{1N}R_{2N}-opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-NR₁C(O)R_{1N}-opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-C(O)NR₁R₂- opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Arilo opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Heteroarilo opcionalmente sustituido, un -(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Heterociclo opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-alquilo opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-NR_{1N}R_{2N}-opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-NR₁C(O)R_{1N}-opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Arilo opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Heteroarilo opcionalmente sustituido, un -NR¹-(CH₂)_n-C(O)_u(NR₁)_v(SO₂)_w-Heterociclo opcionalmente sustituido, un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-alquilo opcionalmente sustituido, un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-NR_{1N}R_{2N}-opcionalmente sustituido, un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-NR₁C(O)R_{1N}-opcionalmente sustituido, un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-Arilo opcionalmente sustituido, un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-Heteroarilo opcionalmente sustituido o un -O-(CH₂)_n-(C=O)_u(NR₁)_v(SO₂)_w-Heterociclo opcionalmente sustituido; grupo -(CH₂)_n-(V)_{n'}-(CH₂)_n-(V)_{n'}-alquilo, un grupo -(CH₂)_n-(V)_{n'}-(CH₂)_n-(V)_{n'}-Arilo opcionalmente sustituido, un grupo -(CH₂)_n-(V)_{n'}-(CH₂)_n-(V)_{n'}-Heteroarilo opcionalmente sustituido, un grupo -(CH₂)_n-(V)_{n'}-(CH₂)_n-(V)_{n'}-Heterociclo' opcionalmente sustituido, un grupo -(CH₂)_n-N(R₁')-(C=O)_{m'}-(V)_{n'}-alquilo opcionalmente sustituido, un grupo -(CH₂)_n-N(R₁')-(C=O)_{m'}-(V)_{n'}-Arilo opcionalmente sustituido, un grupo -(CH₂)_n-N(R₁')-(C=O)_{m'}-(V)_{n'}-Heteroarilo opcionalmente sustituido, un grupo -(CH₂)_n-N(R₁')-(C=O)_{m'}-(V)_{n'}-Heterociclo opcionalmente sustituido, un grupo alquilo -X^{R3'}- opcionalmente sustituido; un grupo -X^{R3'}-Arilo opcionalmente sustituido; un grupo -X^{R3'}-Heteroarilo opcionalmente sustituido; un grupo -X^{R3'}-Heterociclo opcionalmente sustituido;~~

~~R_{1N} y R_{2N} de ULM-g son cada uno de manera independiente H, alquilo C₁-C₆ que opcionalmente se sustituye con uno o dos grupos hidroxilo y hasta tres grupos halógeno o un grupo -(CH₂)_n-Arilo, -(CH₂)_n-Heteroarilo o -(CH₂)_n-Heterociclo opcionalmente sustituido;~~

~~V de ULM-g es O, S o NR₁;~~

~~R₁ de ULM-g es igual que anteriormente;~~

~~R¹ y R₁' de ULM-g son cada uno de manera independiente H o un grupo alquilo C₁-C₃;~~

~~X^{R2'} y X^{R3'} de ULM-g son cada uno de manera independiente un -(CH₂)_n, -(CH₂)_n-CH(X_v)=CH(X_v)- (cis o trans), -(CH₂)_n-CH=CH-, -(CH₂CH₂O)_n o un grupo cicloalquilo C₃-C₆ opcionalmente sustituidos, donde X_v es H, un halo o un grupo alquilo C₁-C₃ opcionalmente sustituido;~~

~~cada m de ULM-g es de manera independiente 0, 1, 2, 3, 4, 5 o 6;~~

~~cada m' de ULM-g es de manera independiente 0 o 1;~~

~~cada n de ULM-g es de manera independiente 0, 1, 2, 3, 4, 5, 6;~~

~~cada n' de ULM-g es de manera independiente 0 o 1;~~

~~cada u de ULM-g es de manera independiente 0 o 1;~~

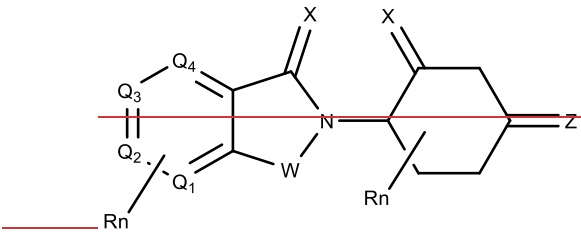
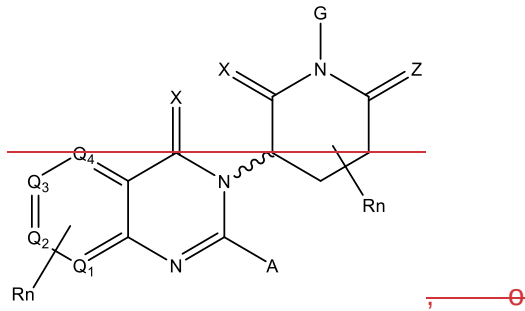
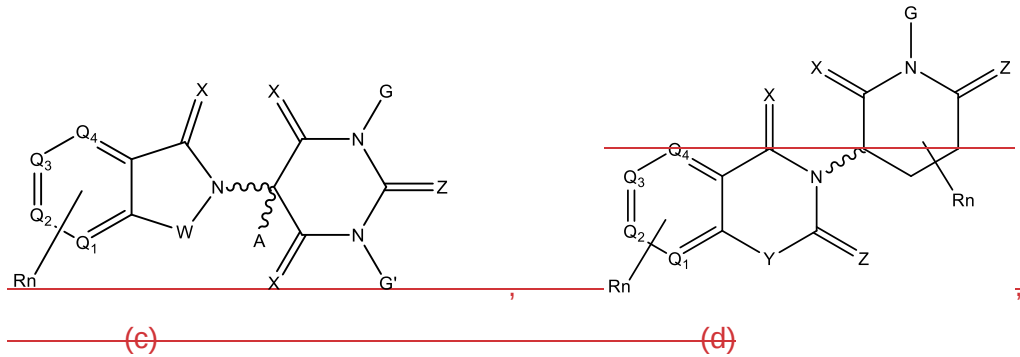
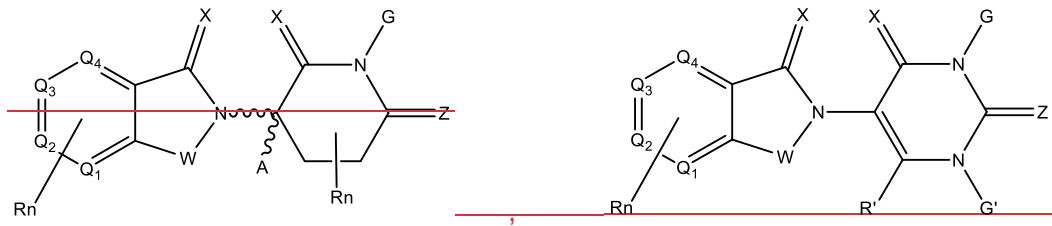
~~cada v de ULM-g es de manera independiente 0 o 1;~~

~~cada w de ULM-g es de manera independiente 0 o 1; y~~

~~uno o más cualesquiera de $R^{1'}$, $R^{2'}$, $R^{3'}$, X y X' de ULM-g opcionalmente se modifican para enlazarse de manera covalente al grupo PTM a través de un grupo enlazador cuando PTM no es ULM', o cuando PTM es ULM', uno o más cualesquiera de $R^{1'}$, $R^{2'}$, $R^{3'}$, X y X' de cada uno de ULM y ULM' opcionalmente se modifican para enlazarse de manera covalente entre sí directamente o a través de un grupo enlazador, o una sal, un estereoisómero, un solvato o un polimorfo farmacéuticamente aceptable de estos.~~

~~10. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5, donde el ULM es un resto de unión a la ligasa E3 de cereblon (CLM) seleccionado dentro del grupo que consiste en una talidomida, lenalidomida, pomalidomida, análogos de estas, isómeros de estas, o derivados de estas.~~

~~11. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5 y 10, donde el CLM tiene una estructura química representada por:~~



donde:

~~W se selecciona del grupo que consta de CH_2 , CHR , $C=O$, SO_2 , NH y N-alquilo;~~

~~cada X se selecciona independientemente del grupo que consta de O, S y H_2 ;~~

~~Y se selecciona dentro del grupo que consiste en CH_2 , $C=CR'$, NH , N-alquilo, N-arilo, N-hetarilo, N-cicloalquilo, N-heterociclilo, O y S;~~

~~Z se selecciona del grupo que consta de O, S y H₂;~~

~~G y G' se seleccionan de manera independiente dentro del grupo que consiste en H, alquilo lineal o ramificado opcionalmente sustituido, OH, R'OCOOR, R'OCONR'', CH₂-heterociclilo opcionalmente sustituido con R', y bencilo opcionalmente sustituido con R';~~

~~Q₁, Q₂, Q₃ y Q₄ representan un carbono C sustituido con un grupo que se selecciona independientemente de R', N o N-óxido;~~

~~A se selecciona de manera independiente dentro del grupo H, alquilo lineal o ramificado opcionalmente sustituido, cicloalquilo, Cl y F;~~

~~R comprende CONR'R'', OR', NR'R'', SR', SO₂R', SO₂NR'R'', CR'R'', CR'NR'R'', (-CR'O)_nR'', arilo, hetarilo, alquilo lineal o ramificado opcionalmente sustituido, cicloalquilo, heterociclilo, P(O)(OR')R'', P(O)R'R'', OP(O)(OR')R'', OP(O)R'R'', Cl, F, Br, I, CF₃, CN, NR'SO₂NR'R'', NR'CONR'R'', CONR'COR'', NR'C(=N-CN)NR'R'', C(=N-CN)NR'R'', NR'C(=N-CN)R'', NR'C(=C-NO₂)NR'R'', SO₂NR'COR'', NO₂, CO₂R', C(C=N-OR')R'', CR'=CR'R'', CCR', S(C=O)(C=N-R')R'', SF₅ y OCF₃;~~

~~R' y R'' se seleccionan de manera independiente dentro del grupo que consiste en un enlace, H, alquilo, cicloalquilo, arilo, heteroarilo, heterocíclico, C(=O)R, heterociclilo, cada uno de los cuales opcionalmente se sustituye;~~

~~n' es un número entero de entre 1-10;~~

~~ representa un enlace que puede ser estereoespecífico ((R) o (S)) o no estereoespecífico; y~~

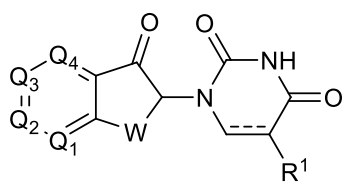
~~R_n comprende de 1 a 4 átomos o grupos funcionales seleccionados de manera independiente, por ejemplo, O, OH, N, alquilo C1-C6, alcoxi C1-C6, alquilo-arilo (p. ej., un alquilo-arilo que comprende al menos uno de alquilo C1-C6, arilo C4-C7, o una combinación de estos), arilo (p. ej., arilo C5-C7), amina, amida o carboxi,~~

~~donde:~~

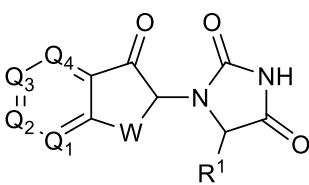
~~cuando n es 1, R_n se modifica para unirse de forma covalente al grupo enlazador (L), y~~

~~cuando n es 2, 3 o 4, entonces un R_n se modifica para unirse de forma covalente al grupo enlazador (L), y cualquier otro R_n se modifica de forma opcional para unirse de forma covalente a un PTM, un CLM, un segundo CLM con la misma estructura química que el CLM, un CLM', un segundo enlazador o cualquier múltiplo o combinación de estos.~~

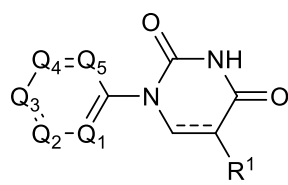
~~12. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5 o 10, donde el CLM tiene una estructura química representada por:~~



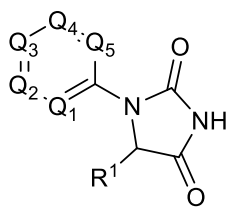
(h)



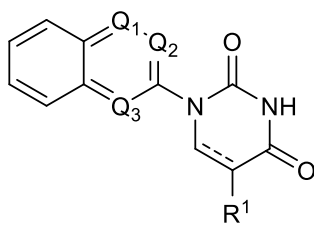
(i)



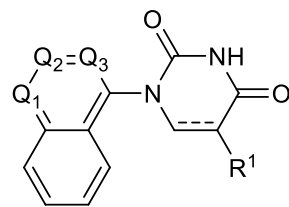
(j)



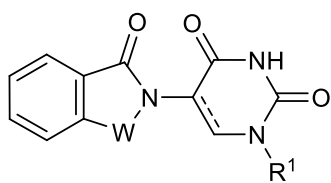
(k)



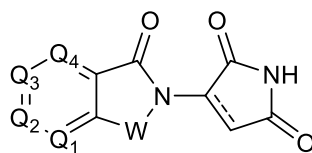
(l)



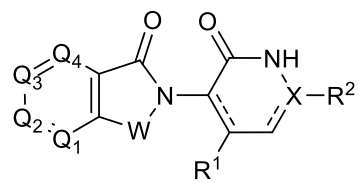
(m)



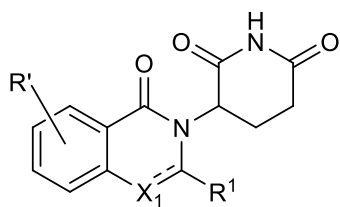
(n)



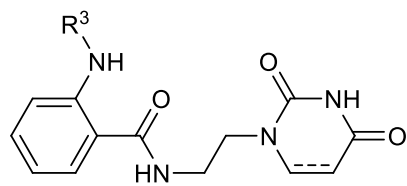
(o)



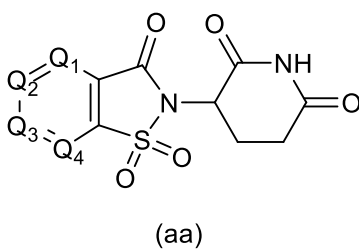
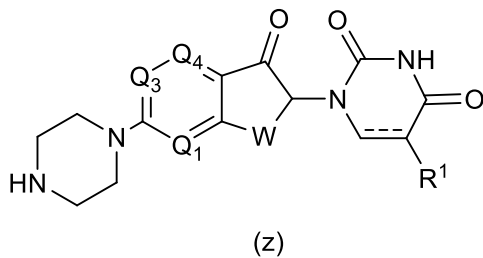
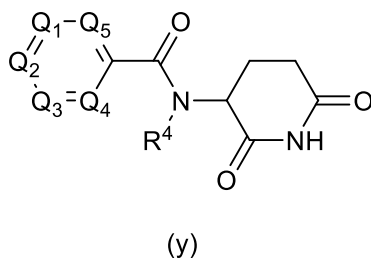
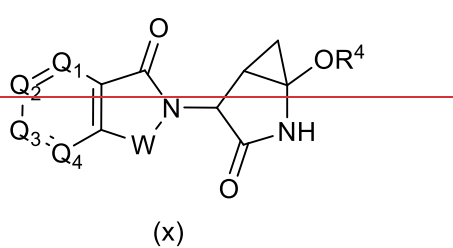
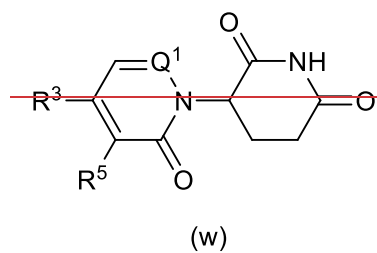
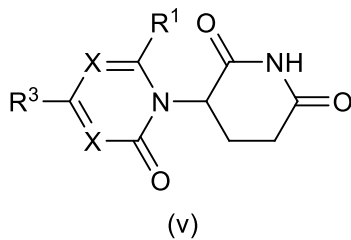
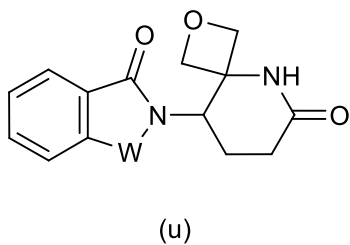
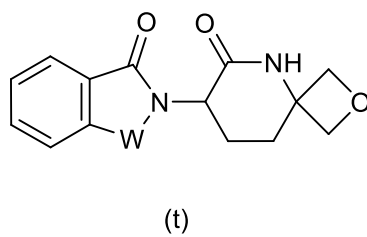
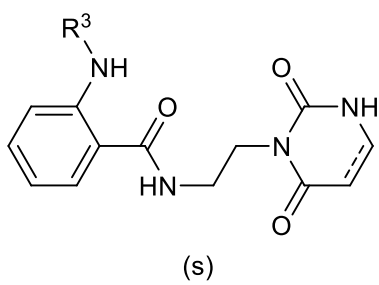
(p)

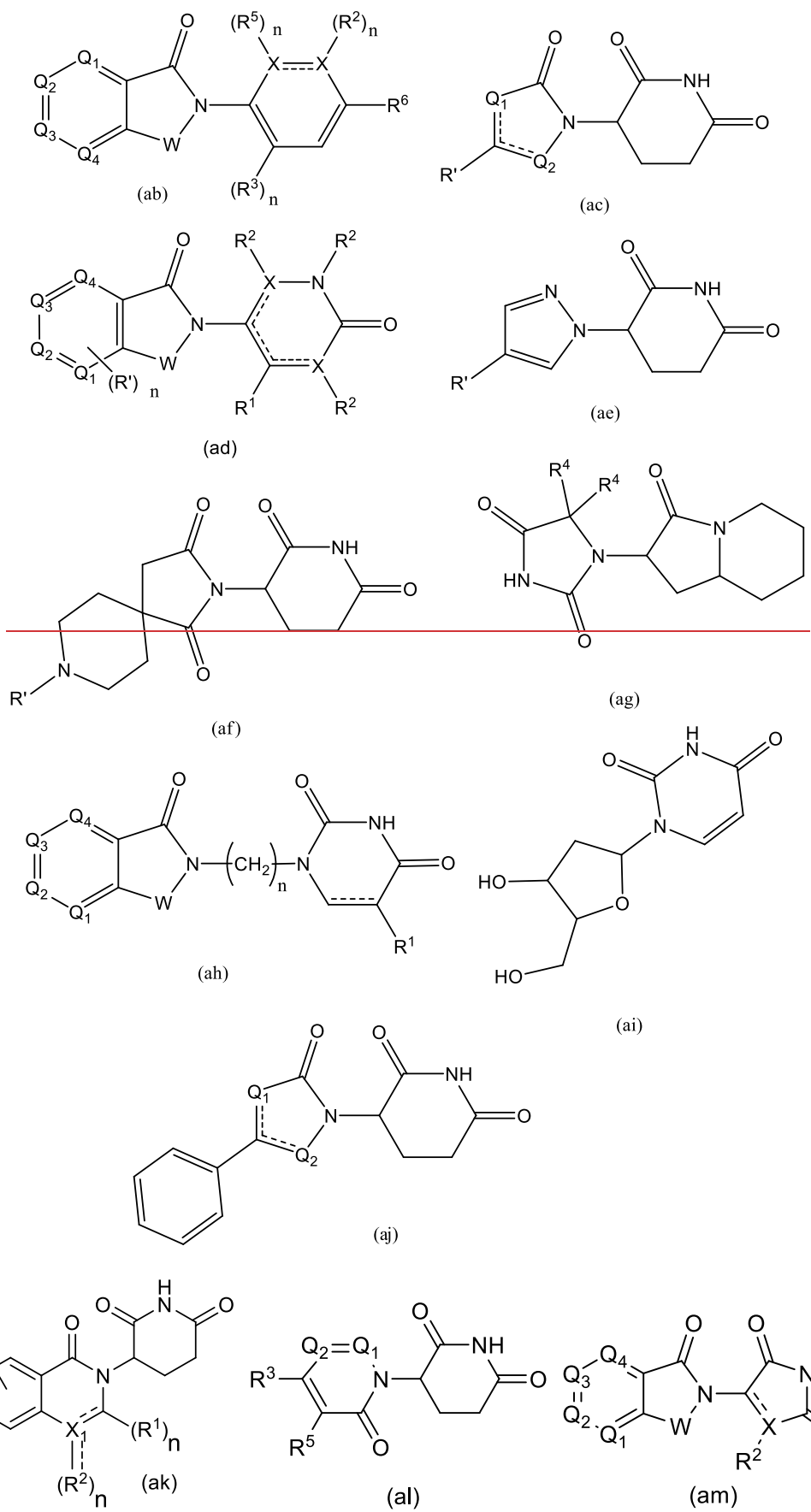


(q)



(r)





donde:

~~W se selecciona de manera independiente de entre CH₂, CHR, C=O, SO₂, NH y N-~~
~~alquilo;~~

~~Q₁, Q₂, Q₃, Q₄, Q₅ son cada uno de manera independiente un carbono C o N~~
~~sustituido con un grupo seleccionado de manera independiente de entre R', N o N-óxido;~~

~~R¹ se selecciona de entre ausente, H, OH, CN, alquilo C1-C3, C=O;~~

~~R² se selecciona dentro del grupo ausente, H, OH, CN, alquilo C1-C3, CHF₂, CF₃,~~
~~CHO, C(=O)NH₂;~~

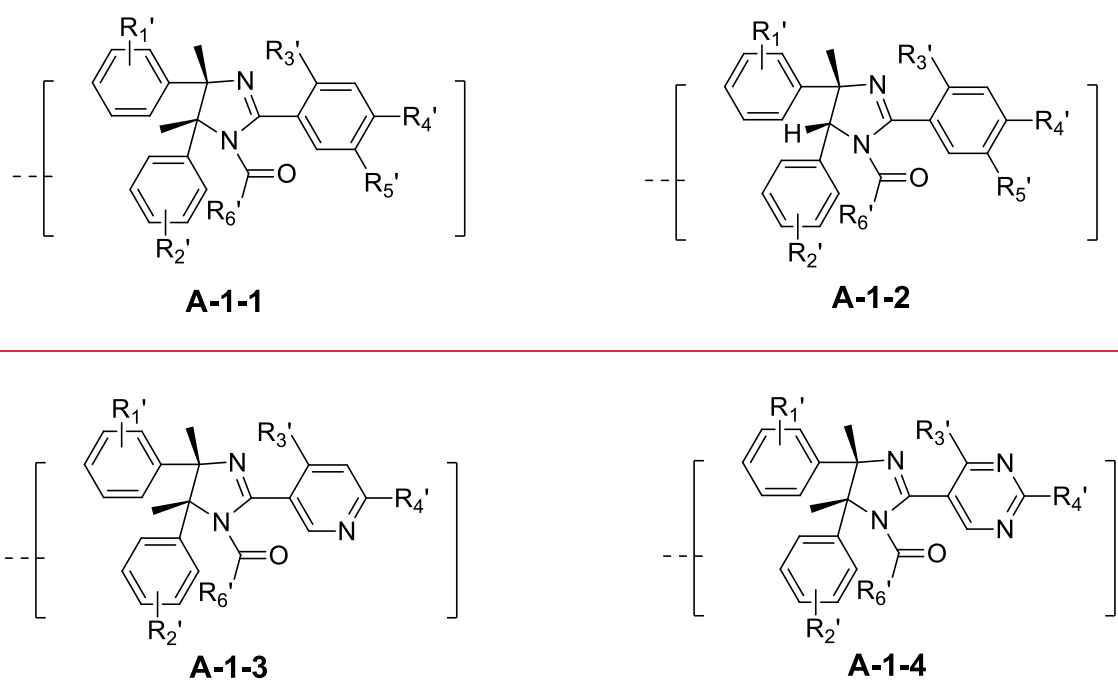
~~R³ se selecciona de entre H, alquilo (p. ej., alquilo C1-C6 o C1-C3), alquilo sustituido~~
~~(p. ej., alquilo C1-C6 o C1-C3 sustituido), alcoxi (p. ej., alcóxido C1-C6 o C1-C3), alcoxi~~

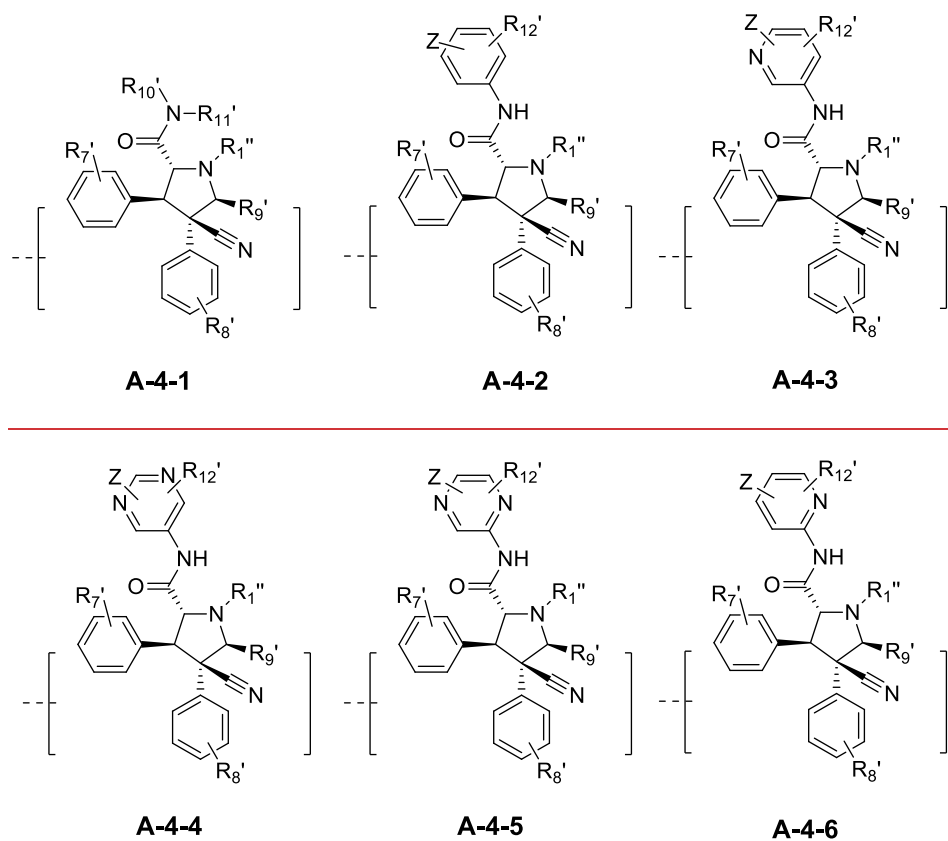
~~sustituido (p. ej., alcoxilo C1-C6 o C1-C3-sustituido);~~
~~R⁴ se selecciona de entre H, alquilo, alquilo sustituido;~~
~~R⁵ y R⁶ son cada uno de manera independiente H, halógeno, C(=O)R', CN, OH,~~
~~CF₃;~~
~~X es C, CH, C=O o N;~~
~~X₁ es C=O, N, CH o CH₂;~~
~~R' se selecciona de entre H, halógeno, amina, alquilo (p. ej., alquilo C1-C3), alquilo~~
~~sustituido (p. ej., alquilo C1-C3 sustituido), alcoxi (p. ej., alcoxilo C1-C3), alcoxi sustituido~~
~~(p. ej., alcoxilo C1-C3 sustituido), NR²R³, C(=O)OR², fenilo opcionalmente sustituido;~~
~~n es 0-4;~~

~~ es un enlace simple o doble; y~~
~~el CLM se une de manera covalente a un PTM, un grupo enlazador químico (L), un~~
~~ULM, CLM, CLM', o combinaciones de estos.~~

~~13. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5,~~
~~donde el ULM es un resto de unión a (MDM2) (MLM) con un resto químico seleccionado dentro~~
~~del grupo que consiste en imidazolinonas sustituidas, espiroindolinonas sustituidas, pirrolidinas~~
~~sustituidas, piperidinonas sustituidas, morfolinonas sustituidas, pirrolopirimidinas sustituidas,~~
~~imidazolopiridinas sustituidas, una tiazoloimidazolina sustituida, pirrolopirrolidinonas sustituidas~~
~~e isoquinolinonas sustituidas.~~

~~14. El compuesto bifuncional asociado a la reivindicación 13, donde el MLM se~~
~~selecciona de entre:~~





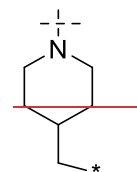
donde:

~~R1' y R2' de las Fórmulas A-1-1 a A-1-4 (es decir, A-1-1, A-1-2, A-1-3 y A-1-4) se seleccionan de manera independiente dentro del grupo que consiste en F, Cl, Br, I, acetileno, CN, CF₃ y NO₂;~~

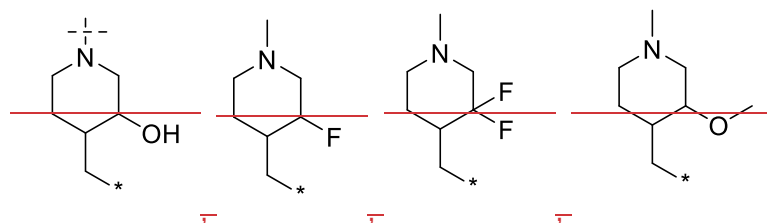
~~R3' se selecciona dentro del grupo que consiste en -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃ y -OCH(CH₃)₂;~~

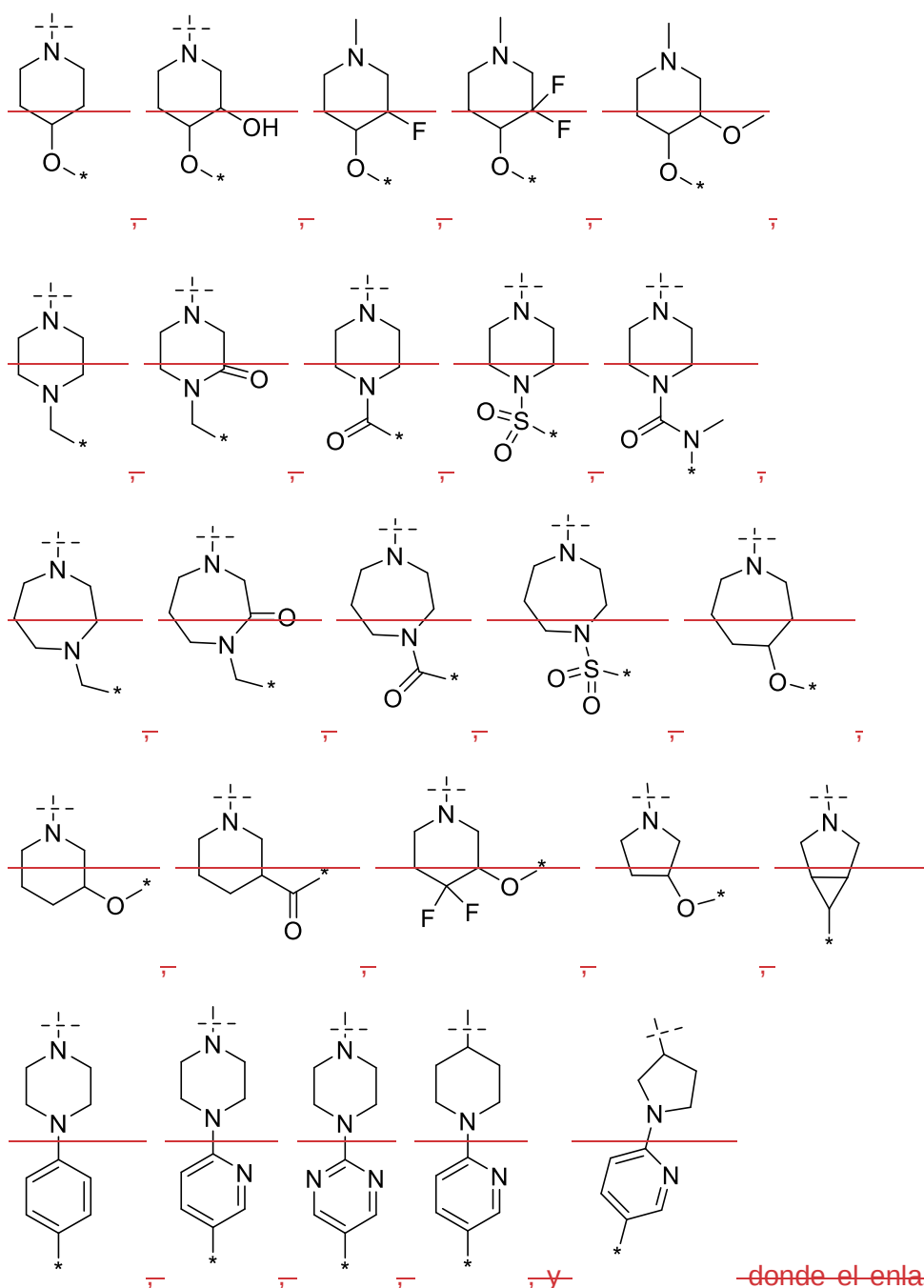
~~R4' de las Fórmulas A-1-1 a A-1-4 se selecciona dentro del grupo que consiste en H, halógeno, -CH₃, -CF₃, -OCH₃, -C(CH₃)₃, -CH(CH₃)₂, -ciclopropilo, -CN, -C(CH₃)₂OH, -C(CH₃)₂OCH₂CH₃, -C(CH₃)₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₃, -C(CH₃)₂CH₂OCH₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₂CH₃, -C(CH₃)₂CN, -C(CH₃)₂C(O)CH₃, -C(CH₃)₂C(O)NHCH₃, -C(CH₃)₂C(O)N(CH₃)₂, -SCH₃, -SCH₂CH₃, -S(O)₂CH₃, -S(O)₂CH₂CH₃, -NHC(CH₃)₃, -N(CH₃)₂, pirrolidinilo y 4-morfolinilo;~~

~~R5' de las Fórmulas A-1-1 a A-1-4 se selecciona dentro del grupo que consiste en halógeno, -ciclopropilo, -S(O)₂CH₃, -S(O)₂CH₂CH₃, 1-pirrolidinilo, -NH₂, -N(CH₃)₂ y -NHC(CH₃)₃; y~~



~~R6' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre H,~~





~~donde el enlazador se une al «*» de R⁶ o al átomo del extremo de R⁴;~~

~~R7' de la Fórmula A-4-1 a A-4-6 es uno o más (p. ej., 1, 2, 3, 4) halógenos;~~

~~R8' de la Fórmula A-4-1 a A-4-6 es uno o más grupos (p. ej., 1, 2, 3 o 4 grupos) seleccionados dentro del grupo que consiste en H, F, Cl, Br, I, CN, NO₂, etinilo, ciclopropilo, metilo, etilo, isopropilo, vinilo, metoxi, etoxi, isopropoxi, OH, otro alquilo C1-6, otro alqueno C1-6 y alquino C1-6, mono, di o trisustituido;~~

~~R9' de la Fórmula A-4-1 a A-4-6 se selecciona dentro del grupo que consiste en alquilo, alquilo sustituido, alqueno, alqueno sustituido, alquino, alquino sustituido, arilo, arilo sustituido, hetero arilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, alqueno y cicloalqueno sustituido;~~

~~Z de la Fórmula A-4-1 a A-4-6 se selecciona dentro del grupo que consiste en 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 dentro del grupo que consiste en 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 puede sustituirse con OR' y heteroarilo-(CH₂)_n-heterociclo donde el heterociclo opcionalmente puede sustituirse 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;~~

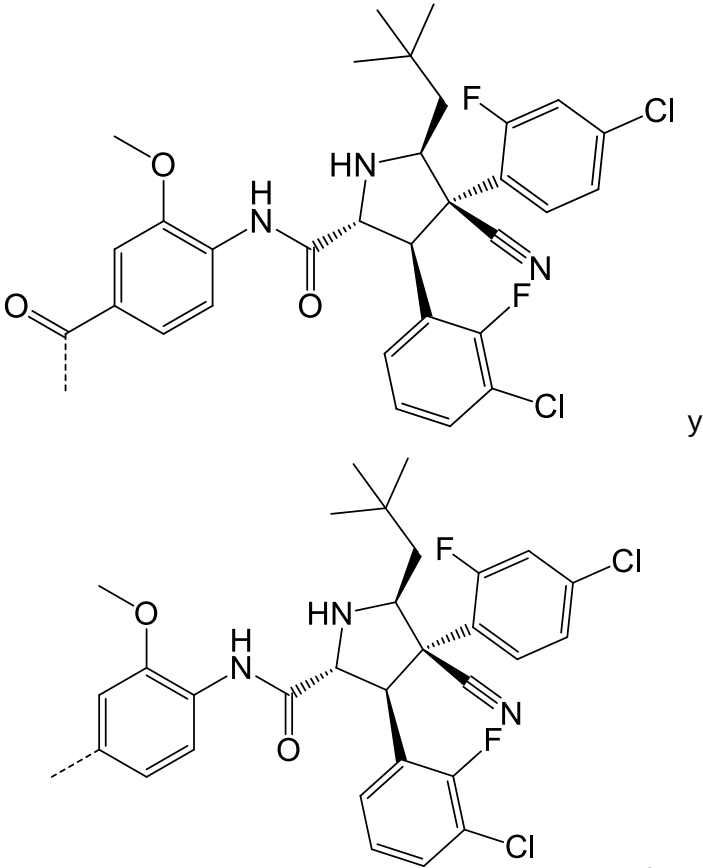
~~m, n y p son de manera independiente de 0 a 6;~~

~~R12' de la Fórmula A-4-1 a A-4-6 se selecciona dentro del grupo que consiste en -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)-(amina cíclica) 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 aloxi, cicloalquilo, cicloalquilo sustituido con ari, y cicloalquilo sustituido con alcoxi; y~~

~~ indica conexión con L.~~

15.4. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 3 o 14, donde el MLM se selecciona de entre:

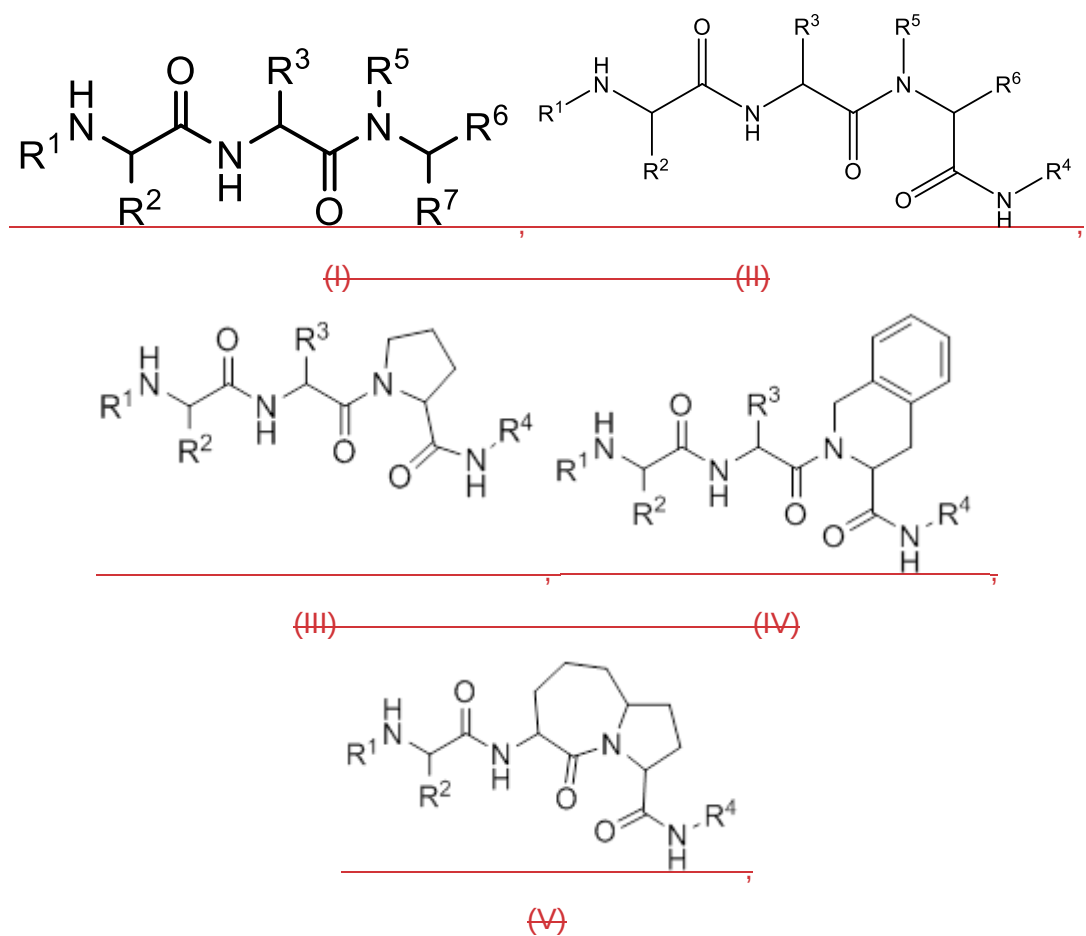


~~16. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5,~~

~~donde el ULM es un resto de unión a la ubiquitina ligasa E3 de IAP (ILM) que comprende los aminoácidos alanina (A), valina (V), prolina (P) e isoleucina (I) o sus miméticos no naturales.~~

~~17. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-5 o 16, donde el ULM es un resto de unión a la ubiquitina ligasa E3 de IAP (ILM) que comprende un fragmento de tetrapéptido de AVPI o derivado de este.~~

~~18. El compuesto bifuncional de acuerdo con la reivindicación 16 o 17, donde el ILM se selecciona dentro del grupo que consiste en las estructuras químicas representadas por las Fórmulas (I), (II), (III), (IV) y (V):~~



~~donde:~~

~~R¹ para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre H o alquilo;~~

~~R² para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre 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, más preferentemente, 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;~~

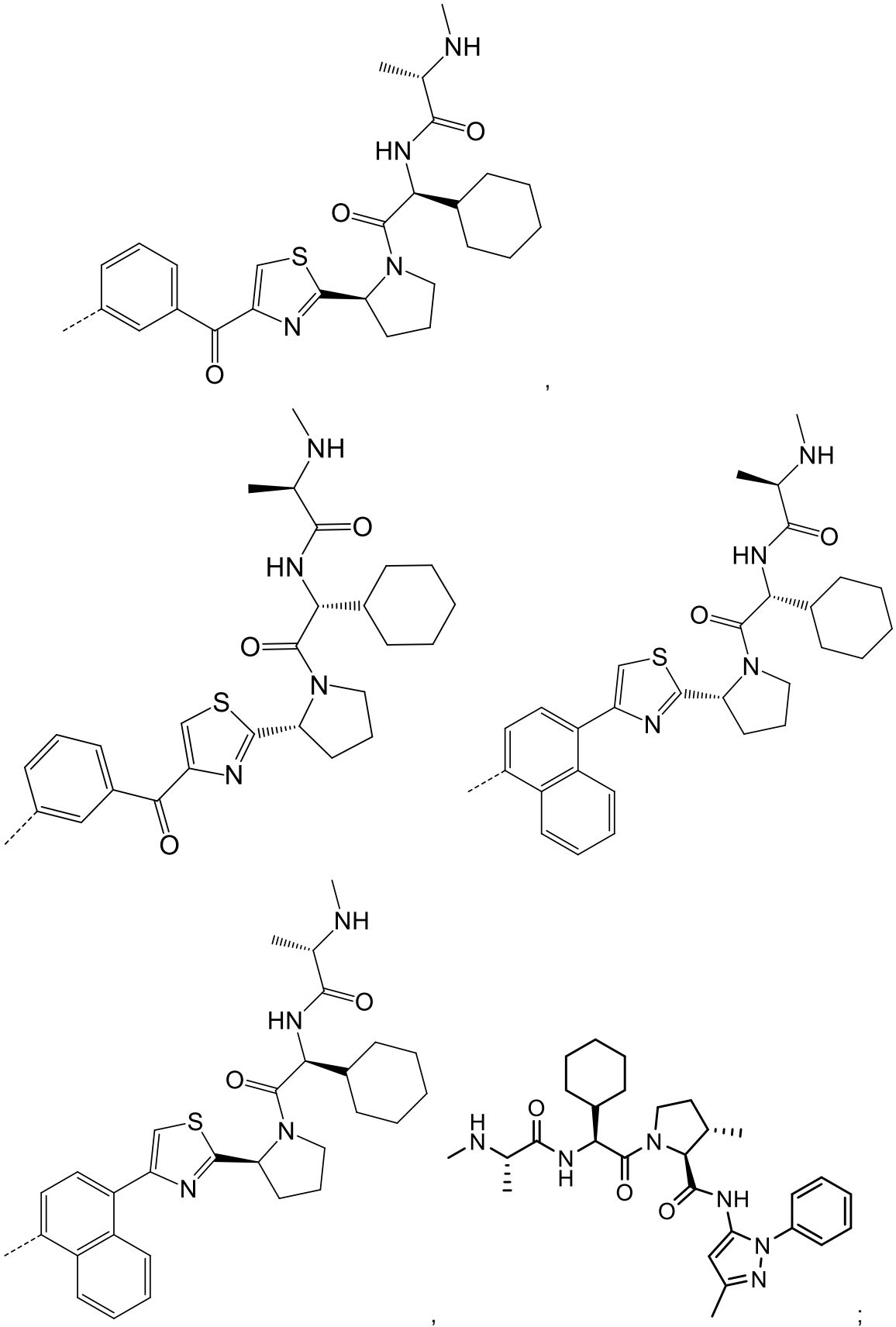
~~R³ y R⁵ para las Fórmulas (I), (II), (III), (IV) y (V) tomados juntos pueden formar un anillo de 5-8 miembros opcionalmente fusionado de manera adicional a 1-2 anillos cicloalquilo, heterocicloalquilo, arilo o heteroarilo;~~

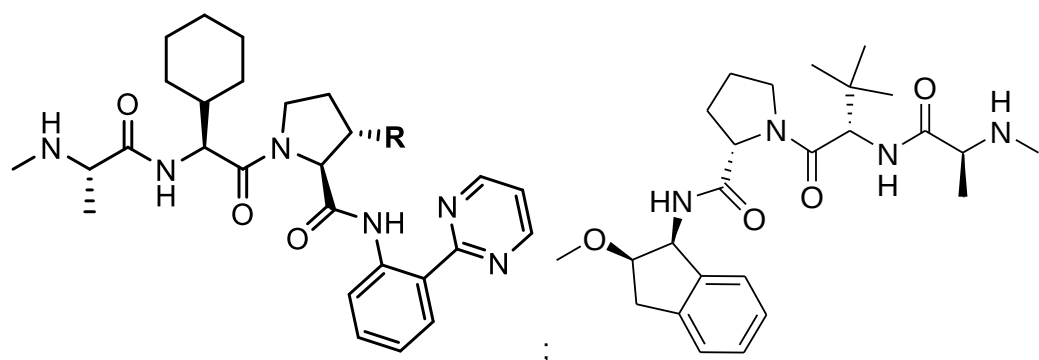
~~R⁷ para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilo-C(O)-R⁴, arilalquilo, heteroarilo, heteroarilo-C(O)-R⁴, heteroarilo-R⁴, heteroarilo-naftaleno,~~

~~heteroarilalquilo o C(O)NH-R^4 , 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-R^4 o C(O)-R^4 ; y~~

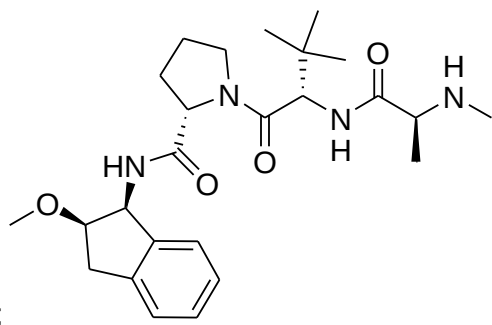
~~R^4 se selecciona de entre alquilo, cicloalquilo, heterocicloalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilo o arilo bicíclico, arilalquilo, heteroarilo o heteroarilo bicíclico, heteroarilalquilo, opcionalmente sustituido de manera adicional con 1-3 sustituyentes tal como se describió anteriormente.~~

19.5. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 36-18, donde el ILM se selecciona de ~~entro del grupo que consiste~~ entre:

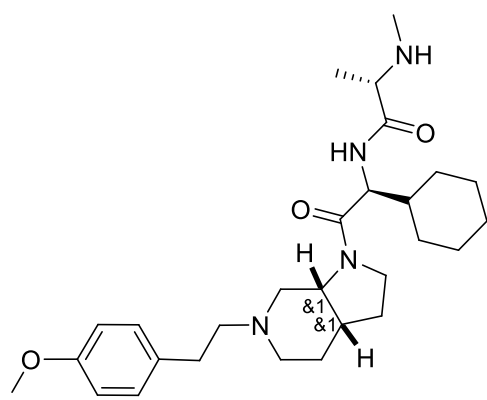




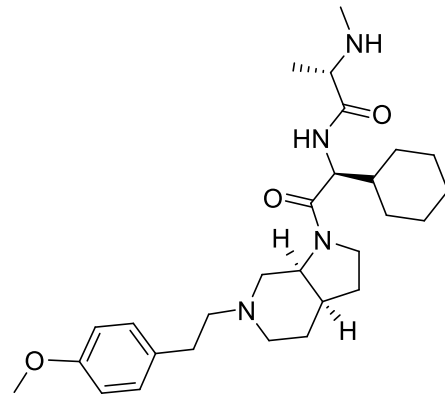
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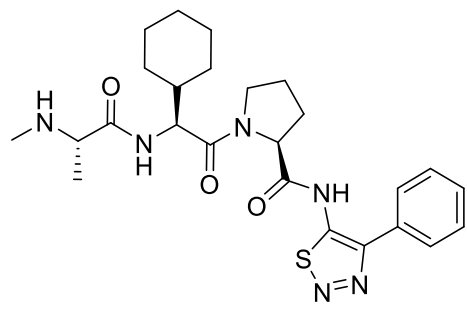
;



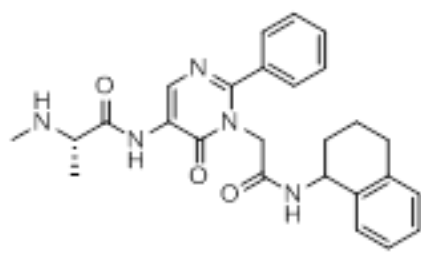
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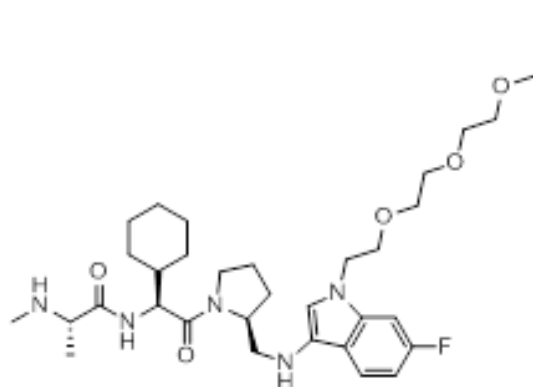
;



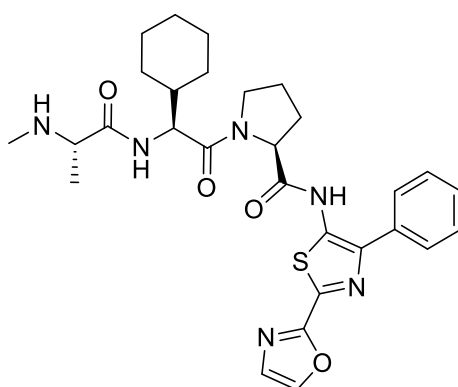
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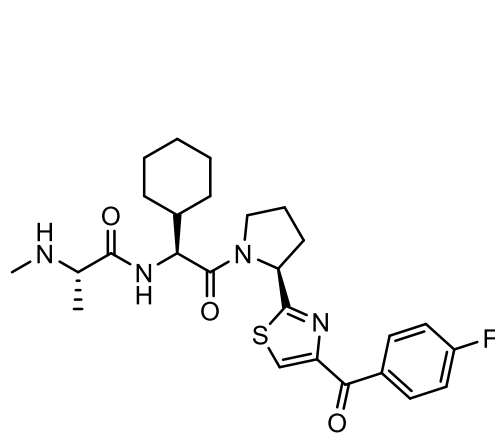
;



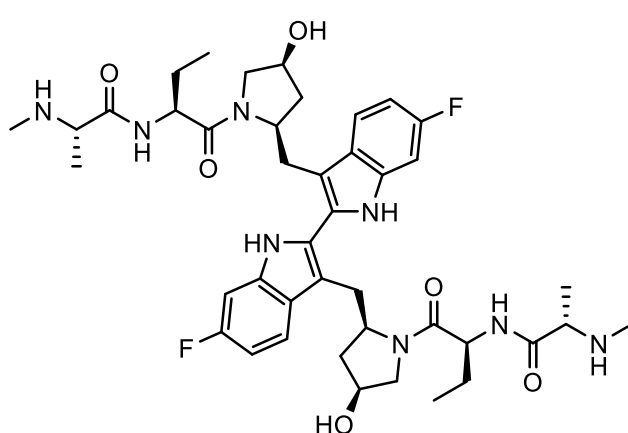
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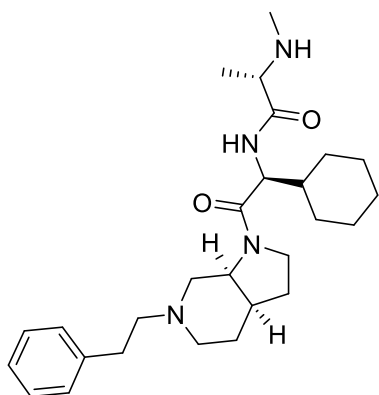
;



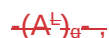
;



y



~~20. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-19, donde el enlazador (L) comprende una unidad estructural química representada por la fórmula:~~



~~donde:~~

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

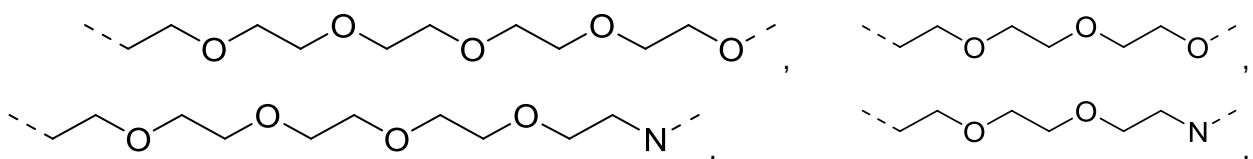
~~q es un número entero mayor o igual que 1;~~

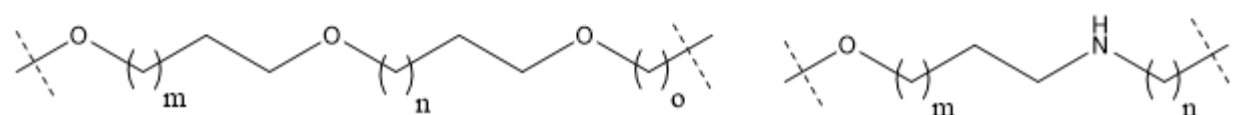
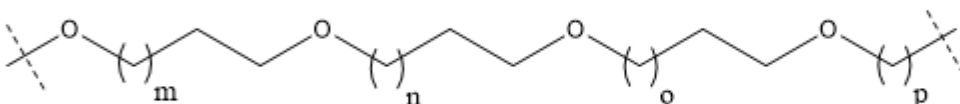
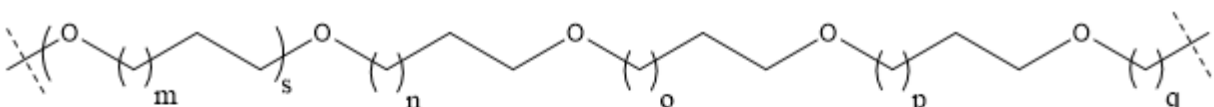
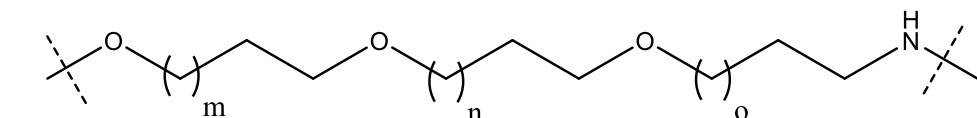
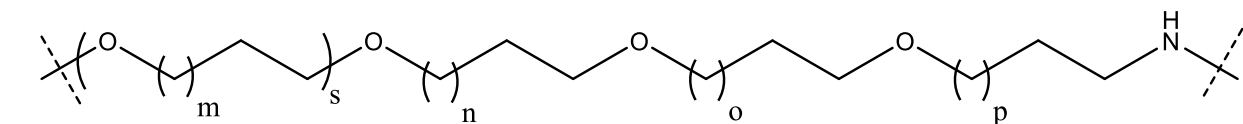
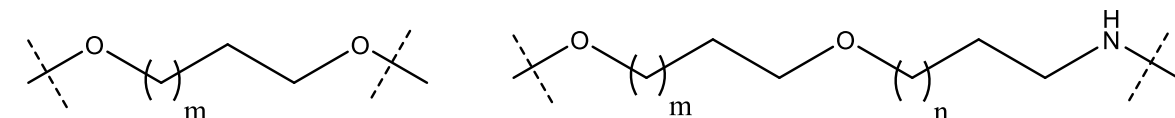
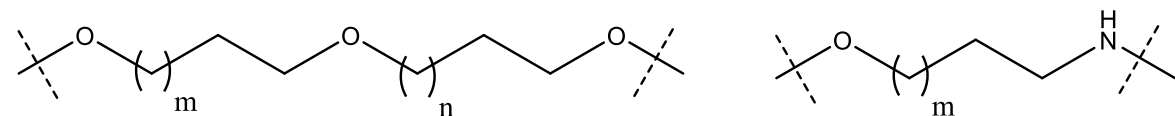
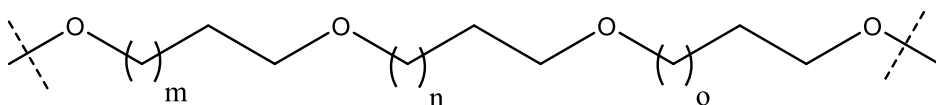
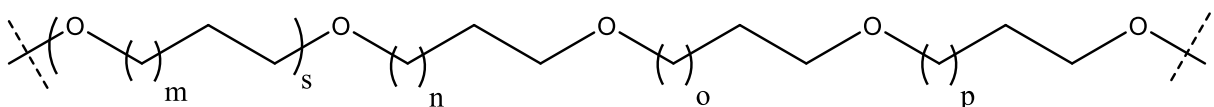
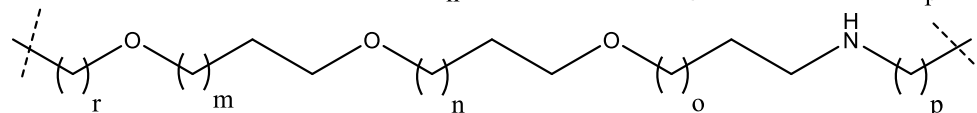
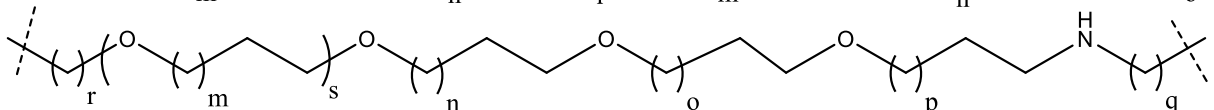
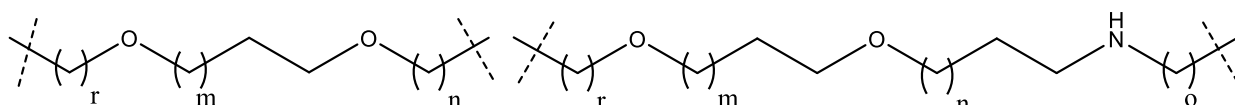
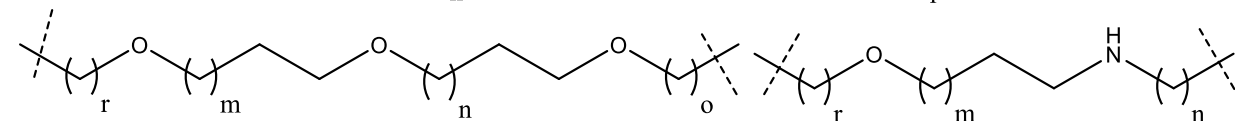
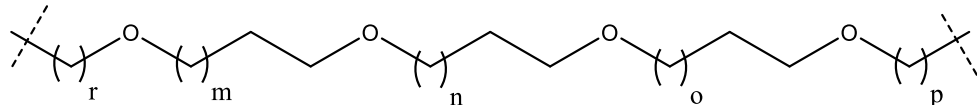
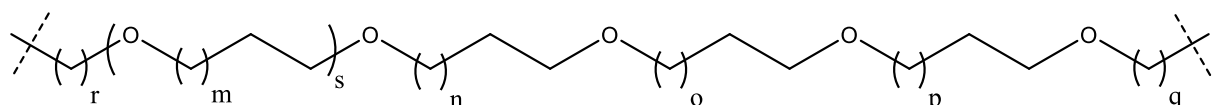
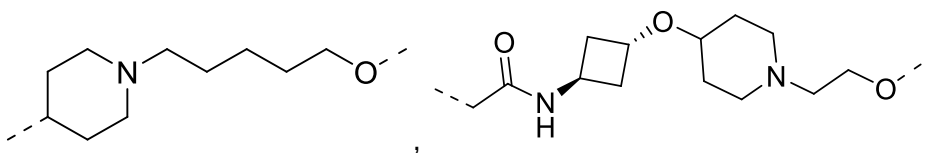
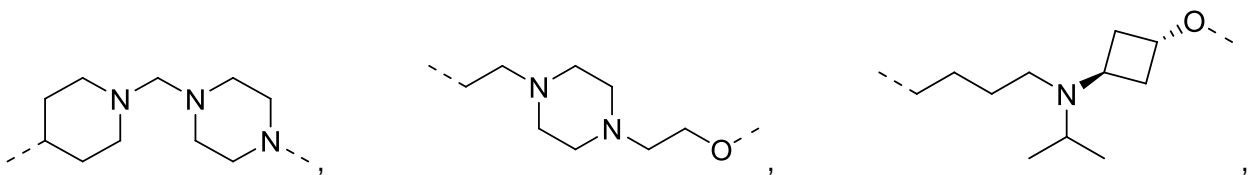
~~cada A^L se selecciona de manera independiente dentro del grupo que consiste en un enlace, CR^{L1}R^{L2}, O, S, SO, SO₂, NR^{L3}, SO₂NR^{L3}, SONR^{L3}, CONR^{L3}, NR^{L3}CONR^{L4}, NR^{L3}SO₂NR^{L4}, CO, CR^{L1}=CR^{L2}, C=C, SiR^{L1}R^{L2}, P(O)R^{L1}, P(O)OR^{L1}, NR^{L3}C(=NCN)NR^{L4}, NR^{L3}C(=NCN), 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}, 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, opcionalmente sustituido con 0-4 grupos R^{L5}; y~~

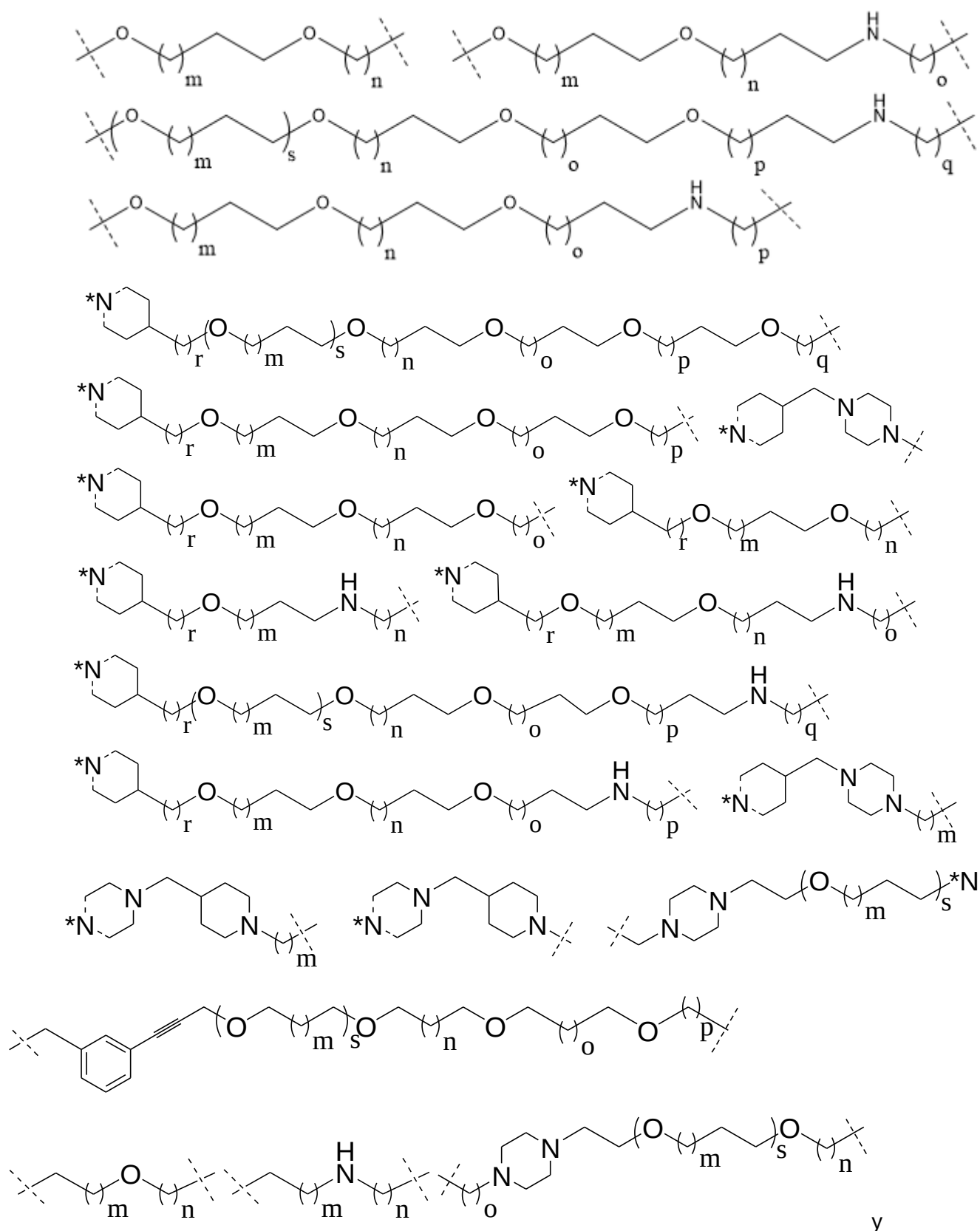
~~R^{L1}, R^{L2}, R^{L3}, R^{L4} y R^{L5} son, cada uno de manera independiente, H, halo, alquilo C₁₋₈, Oalquilo C₁₋₈, Salquilo C₁₋₈, NHalquilo C₁₋₈, N(alquilo C₁₋₈)₂, cicloalquilo C₃₋₁₁, arilo, heteroarilo, heterociclilo C₃₋₁₁, Ocicloalquilo C₁₋₈, Scicloalquilo C₁₋₈, NHcicloalquilo C₁₋₈, N(cicloalquilo 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, NH SO₂NH₂.~~

~~21. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-20, donde L es un medio para el acoplamiento covalente del PTM con el ULM.~~

22.6. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5-20, en donde ~~la unidad A^L del enlazador (L)~~ se selecciona dentro entre ~~del grupo que consiste en:~~







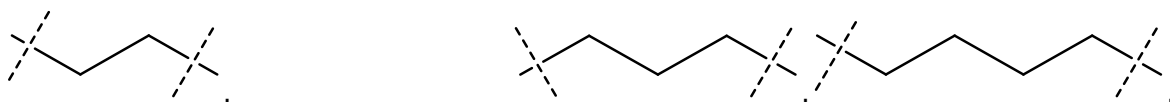
alquilo C₁₋₆; o

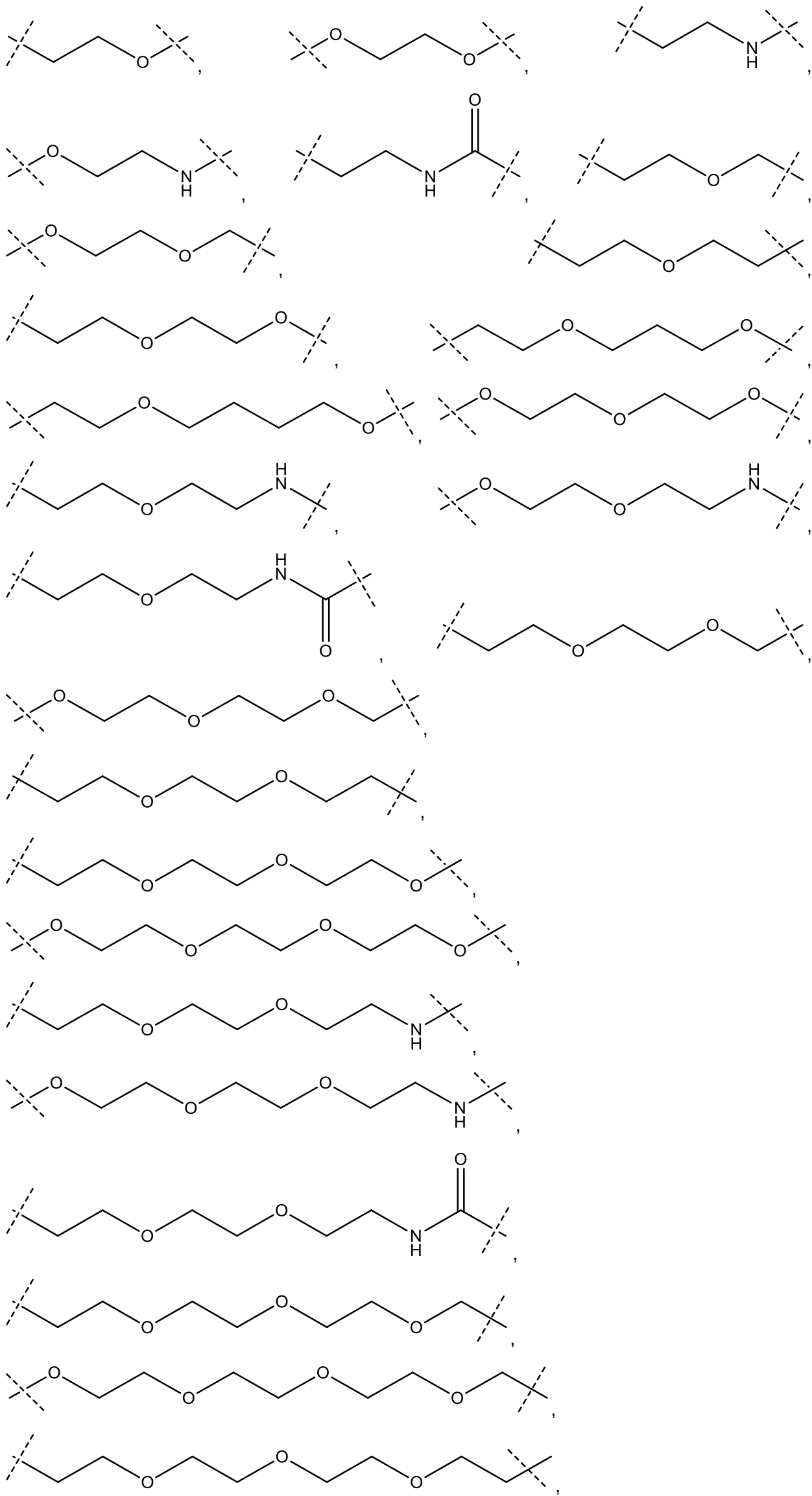
donde:

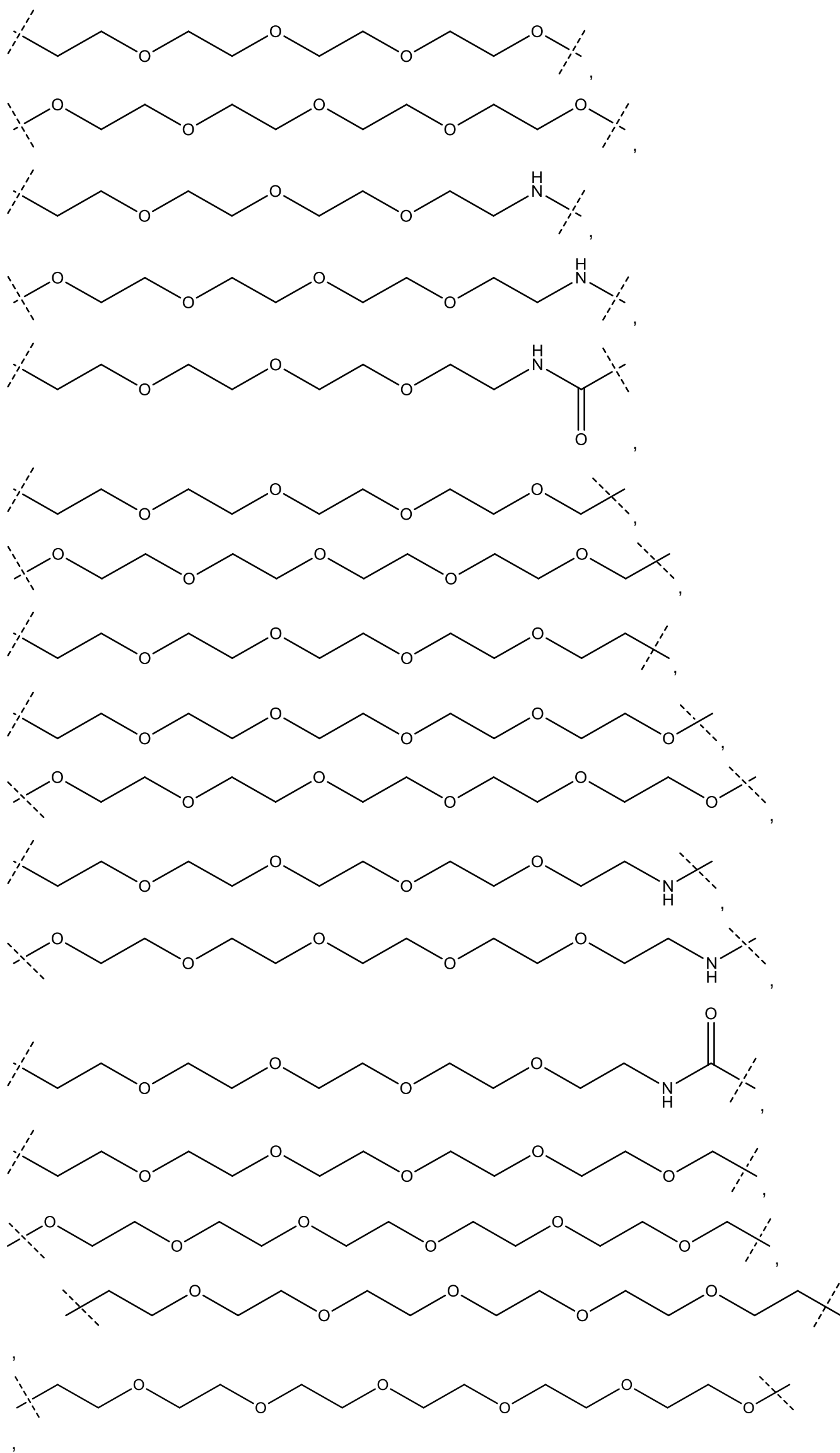
*N del heterocicloalquilo es compartido con el PTM; y

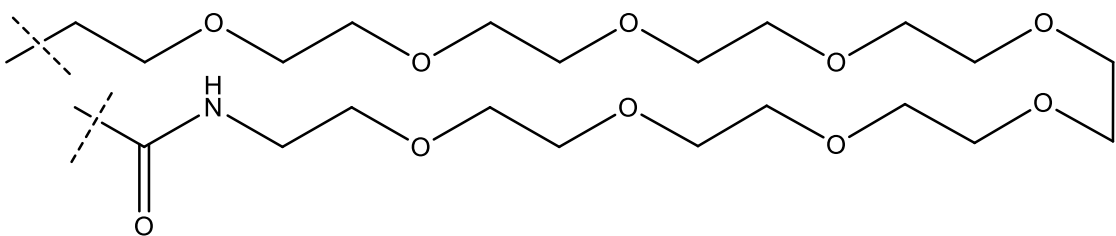
cada m, n, o, p, q, r y s se selecciona de manera independiente de entre 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 y 20.

23-7. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1- a 520, en donde la unidad A^L del enlazador (L) se selecciona dentro entre del grupo que consiste en:

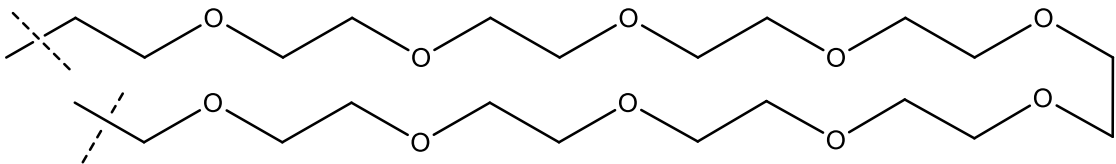




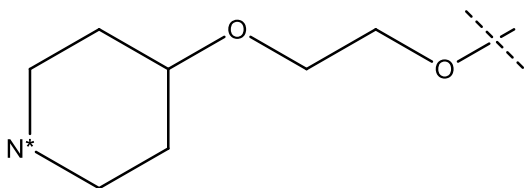




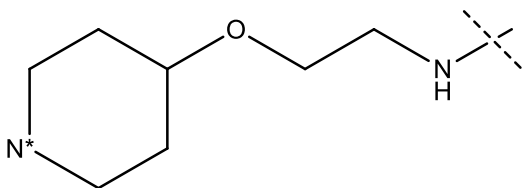
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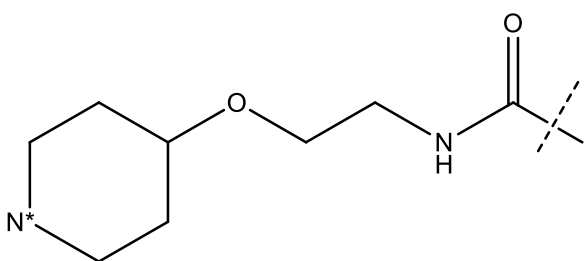
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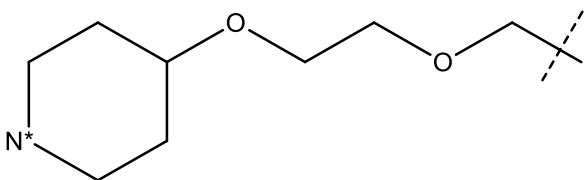
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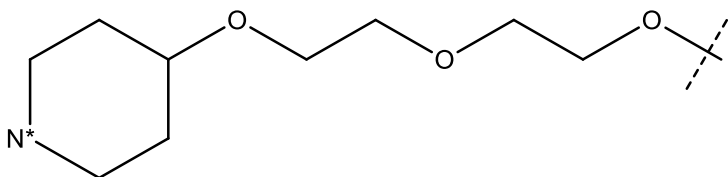
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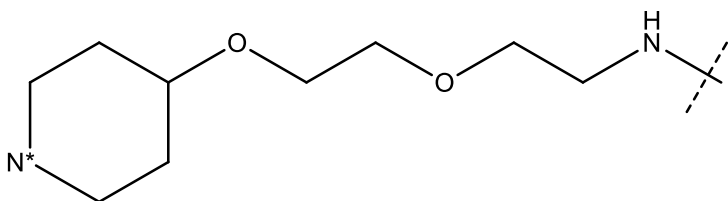
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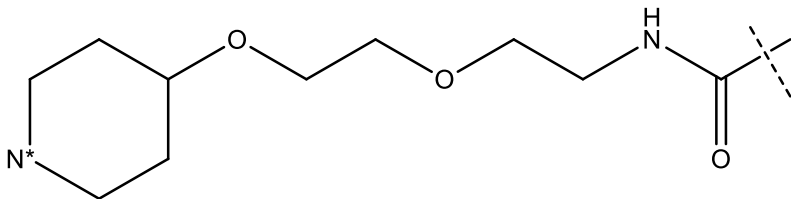
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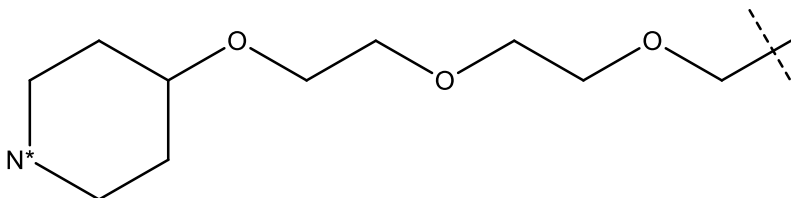
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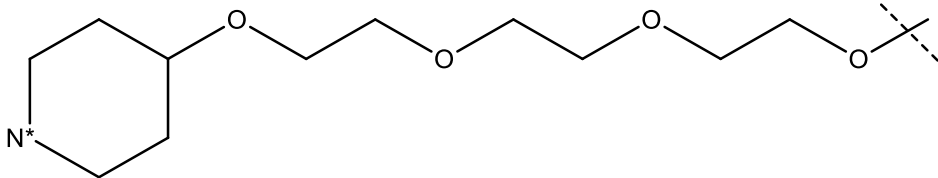
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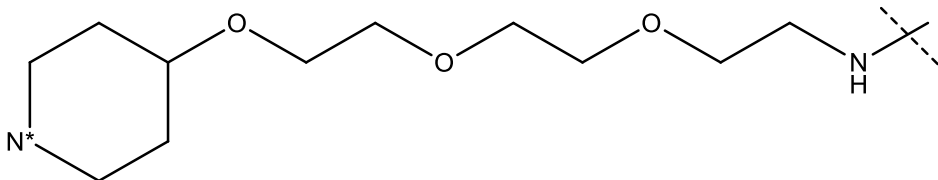
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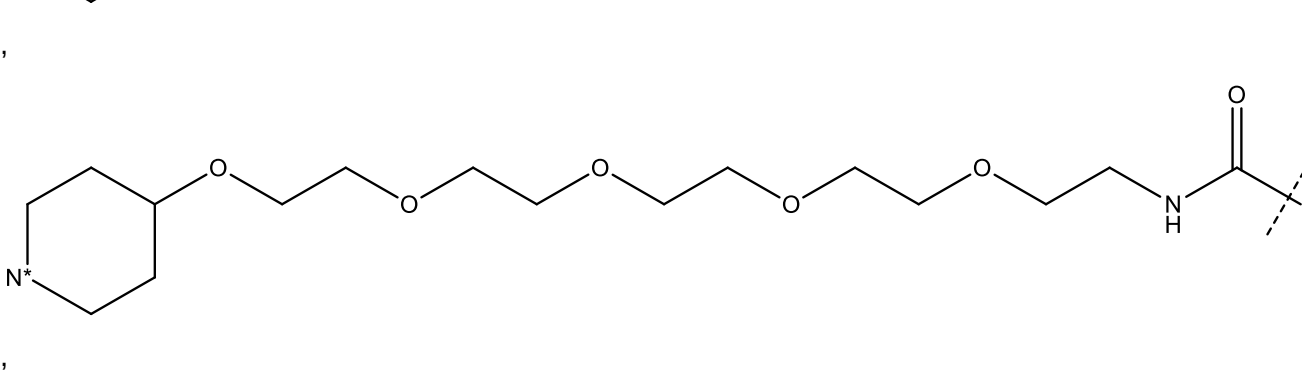
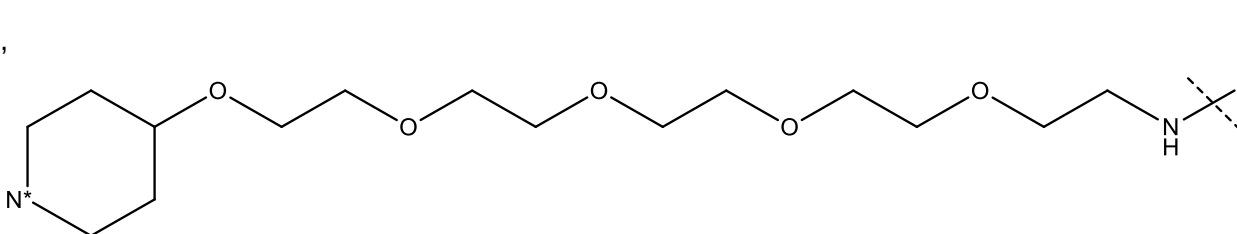
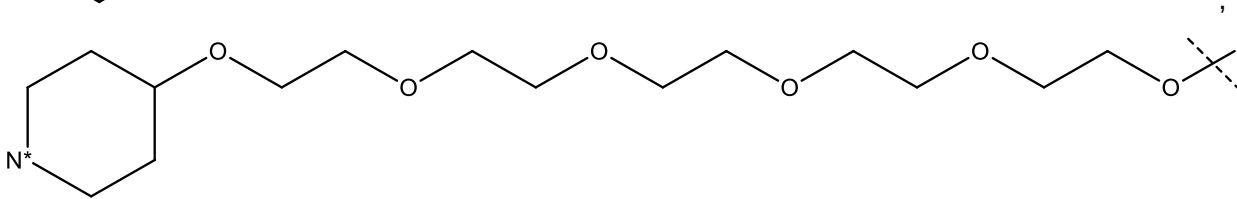
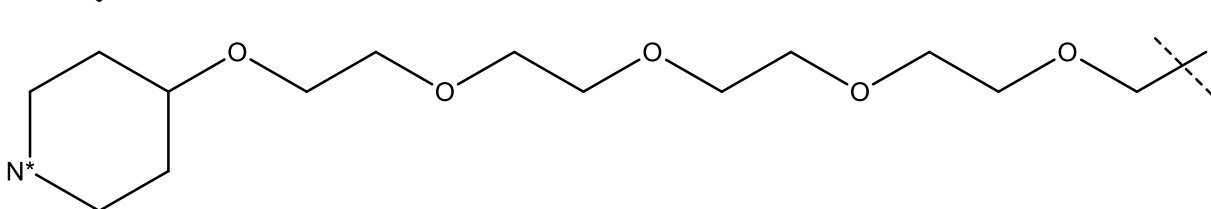
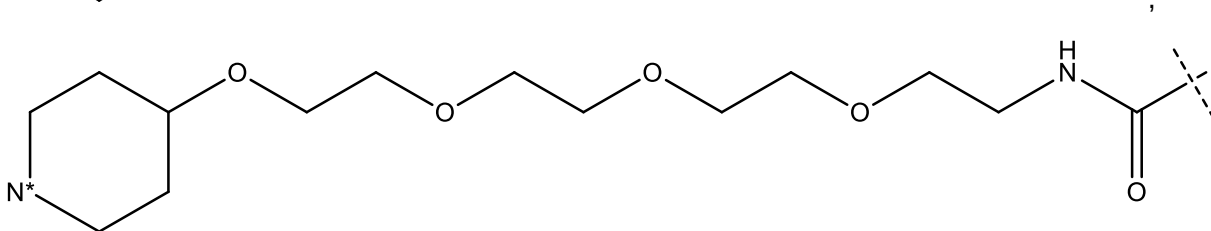
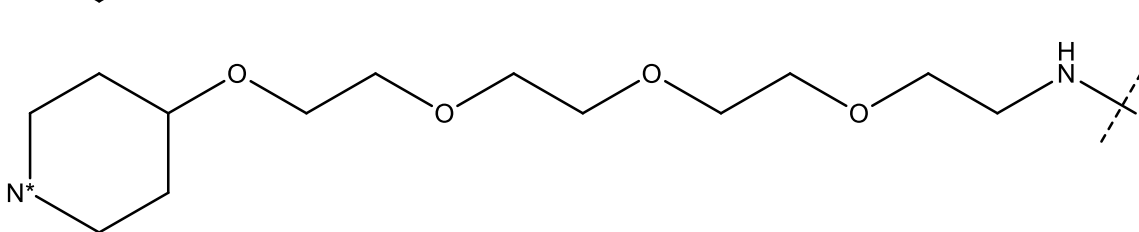
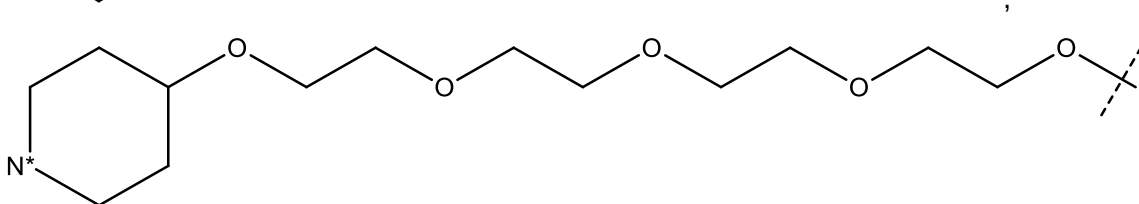
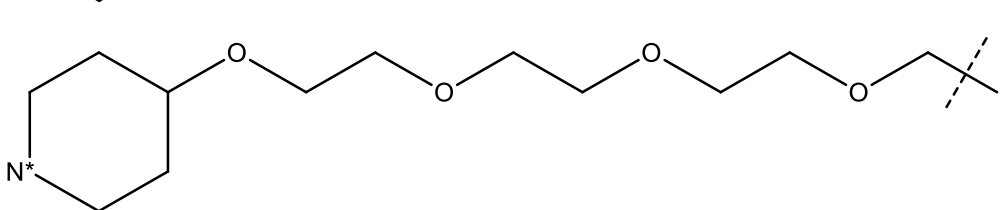
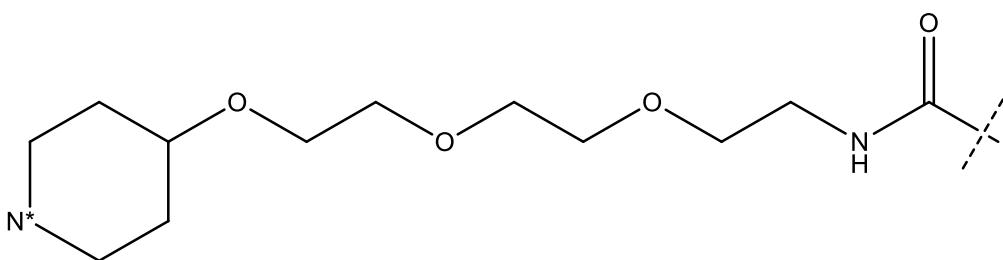
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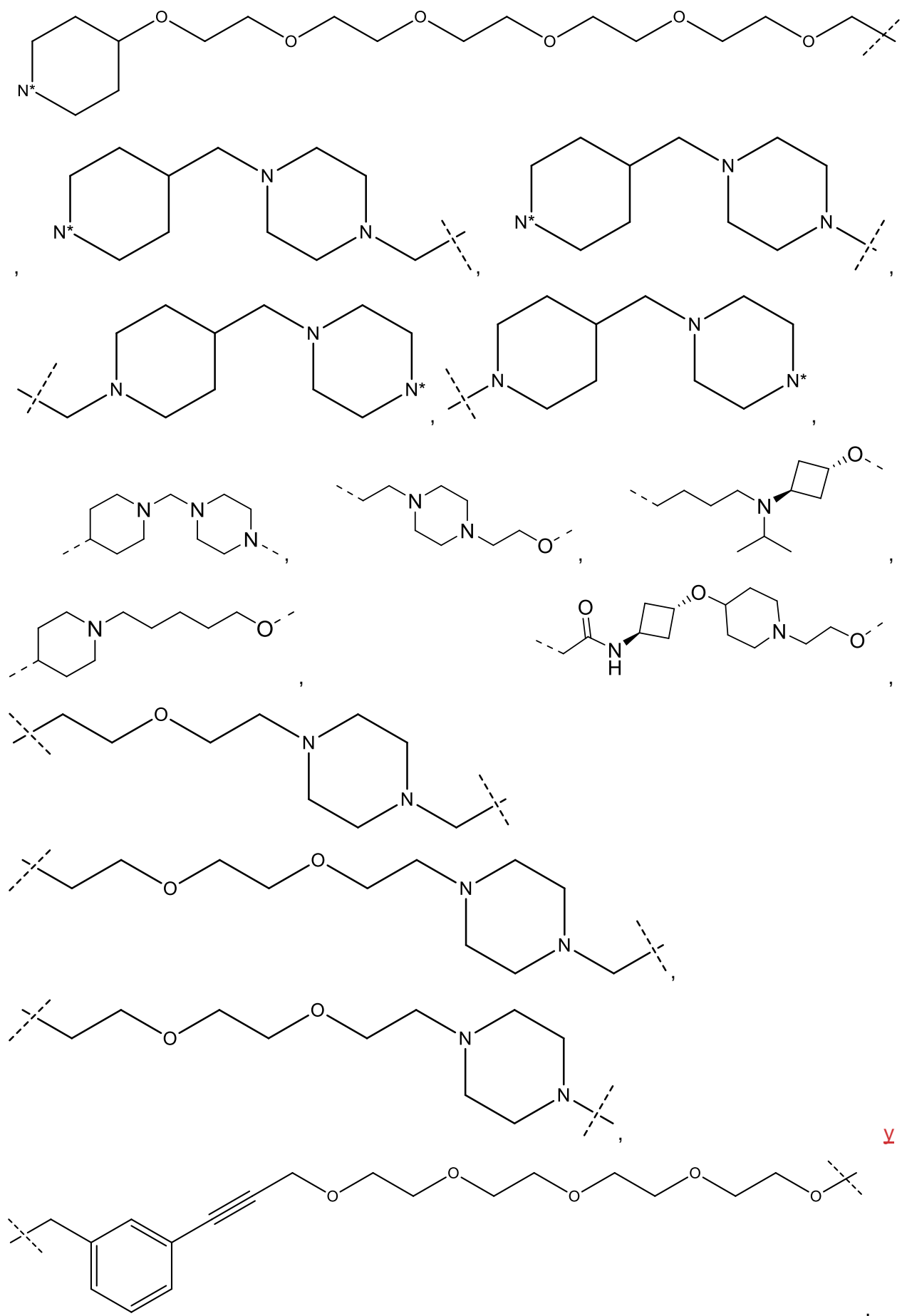


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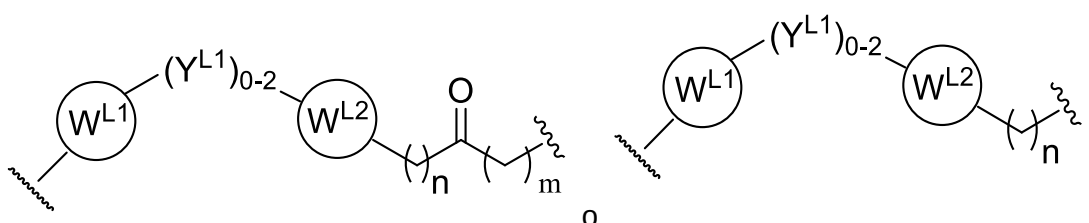
donde N* del heterocicloalquilo es compartido con el PTM.

24.8. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-20 a 5, en donde ~~el enlazador (L)~~ es un grupo polietileno oxi con 1 a 10 unidades de etilenglicol opcionalmente sustituido con arilo ~~o fenilo que comprende de 1 a 10 unidades de etilenglicol~~.

25.9. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-20 a 5, donde ~~el enlazador~~ es un alquilo C₁-C₅₀, 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 ~~(p. ej., sin heteroátomos enlazados de manera covalente o ubicados en adyacencia).~~

26.10. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-19 a 5, en donde ~~el enlazador (L) es~~ comprende la siguiente estructura química:



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 un H, halo, OH, CN, CF_3 , alquilo C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido, alcoxi C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido, 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;

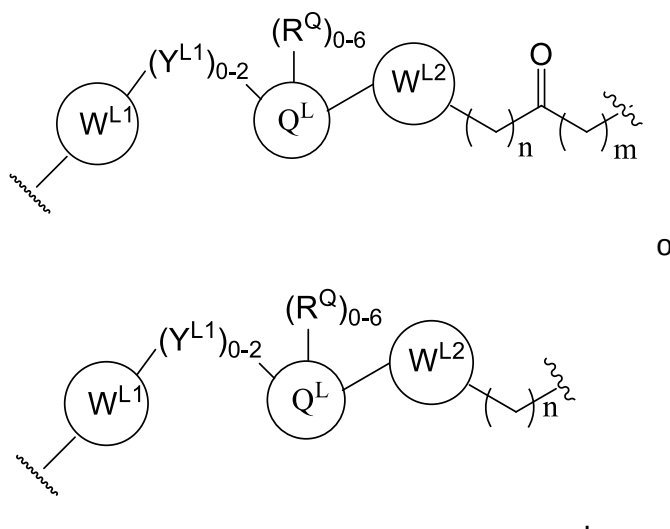
Y^{L1} es cada uno de manera independiente un enlace, alquilo C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido, y opcionalmente uno o más átomos de C se remplazan con O; o alcoxi C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido;

n es 0-10; y



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

27.11. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-19 a 5, donde ~~el enlazador (L) comprende la siguiente estructura química 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 uno o más átomos de C se remplazan con O o N, alqueno C_{1-6} y opcionalmente uno o más átomos de C se remplazan con O, alquino C_{1-6} y opcionalmente uno o más átomos de C se remplazan con O, bicíclico,

biarilo, biheteroarilo o biheterocíclico, cada uno opcionalmente sustituido con R^Q , 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} ~~lineal o ramificado~~ opcionalmente sustituido, alcoxi C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido, Oalquilo C_{1-3} opcionalmente sustituido ~~(p-ej., opcionalmente sustituido por 1 o más F)~~, OH, NH_2 , $NR^{Y1}R^{Y2}$, 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^{YL1} , O, S, NR^{YL2} , $CR^{YL1}R^{YL2}$, C=O, C=S, SO, SO_2 , alquilo C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido y opcionalmente uno o más átomos de C se remplazan con O; alcoxi C_{1-6} ~~(lineal, ramificado, 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 , cada R^Q es de manera independiente H, alquilo C_{1-6} ~~(lineal, ramificado, opcionalmente sustituido, por 1 o más halo, alcoxi C_{1-6})~~, 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^{YL1} , y R^{YL2} son cada uno de manera independiente H, OH, alquilo C_{1-6} ~~lineal o ramificado~~ opcionalmente sustituido por 1 o más halo o alcoxi C_{1-6} , o R^1 , tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

n es 0, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y



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

~~28. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1-20, donde al menos uno de:~~

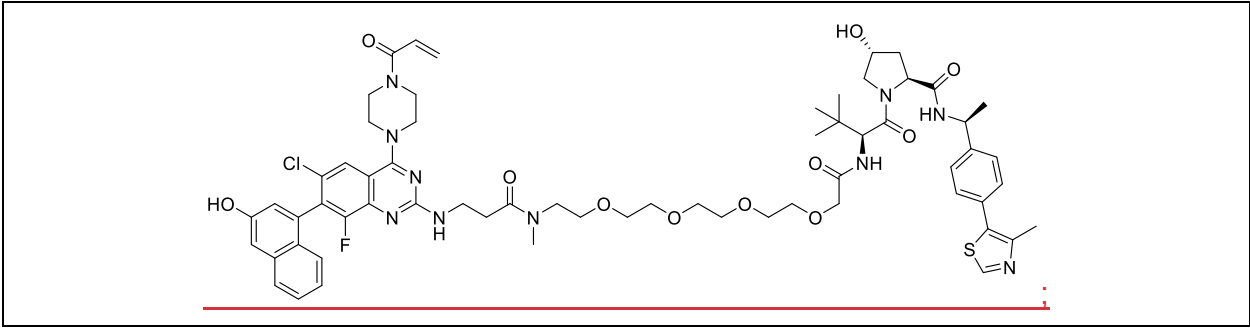
~~(a) el PTM se selecciona de entre un compuesto de la Tabla 4, 6, 8, 10 o 12, o un PTM de la Tabla 1;~~

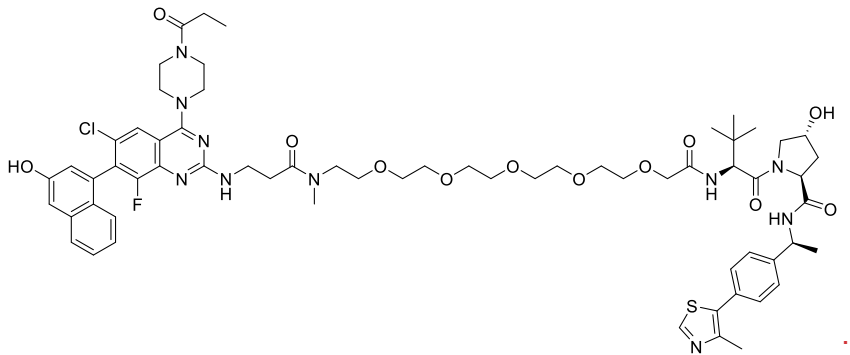
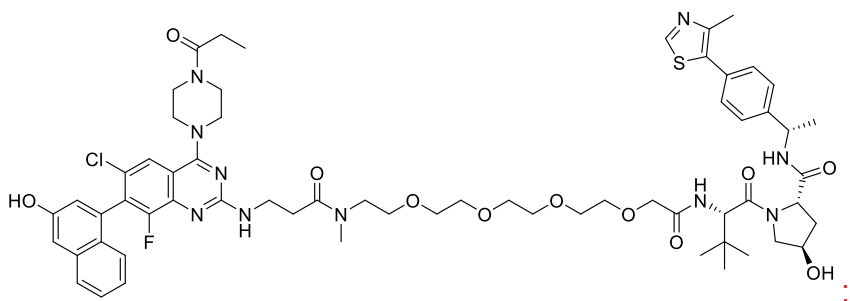
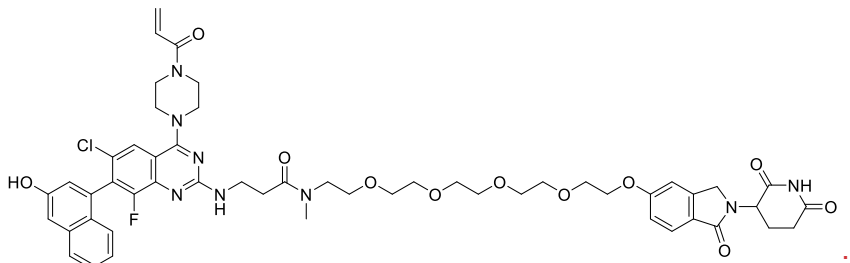
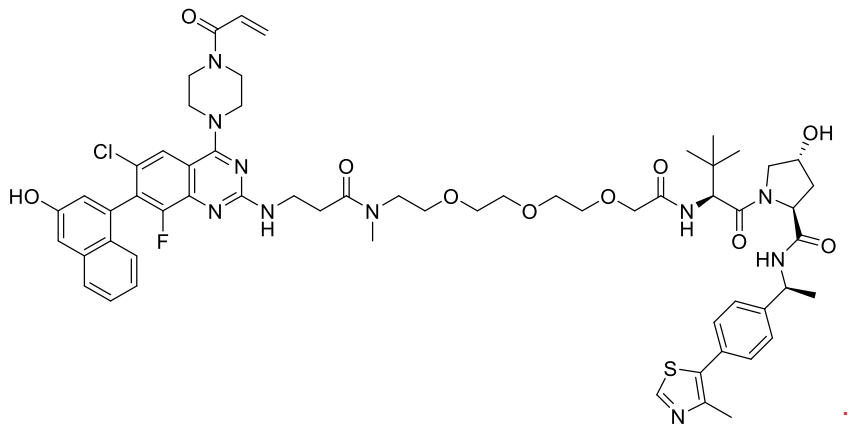
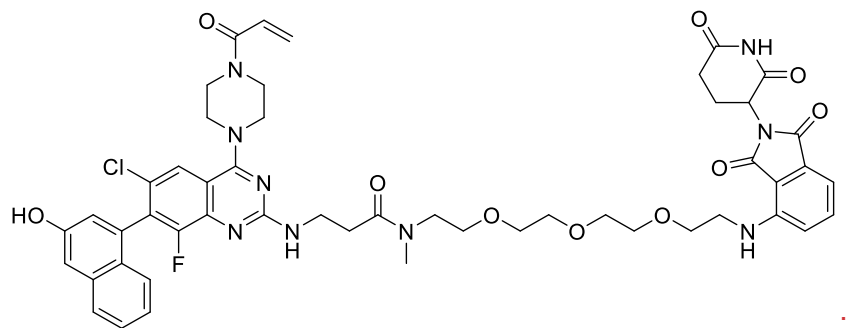
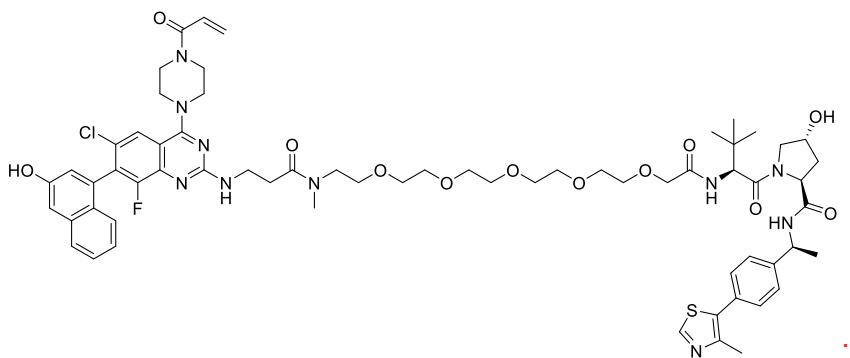
~~(b) el ULM se selecciona de entre un compuesto de las Tablas 4, 6, 8, 10 y 12 o un ULM de la Tabla 3;~~

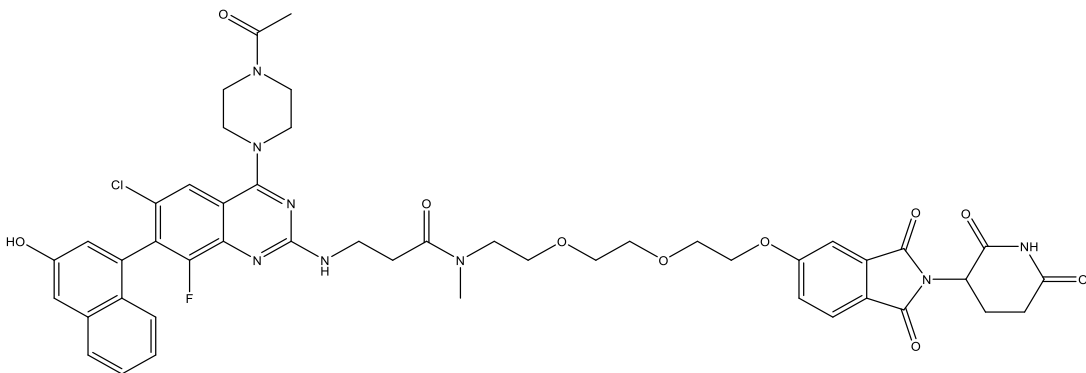
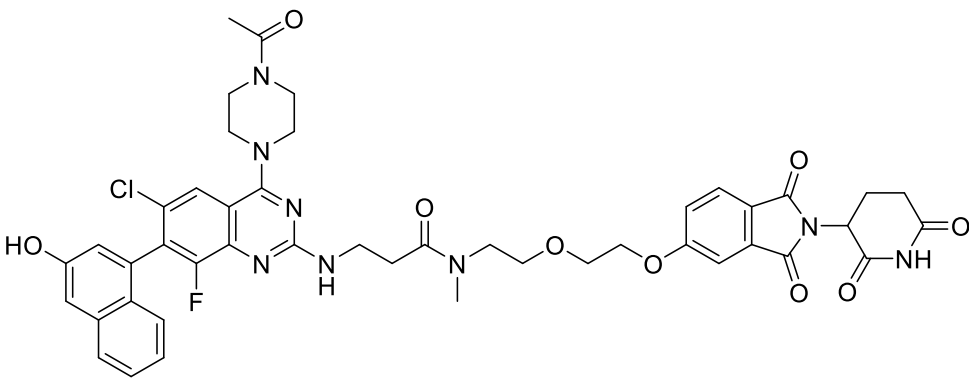
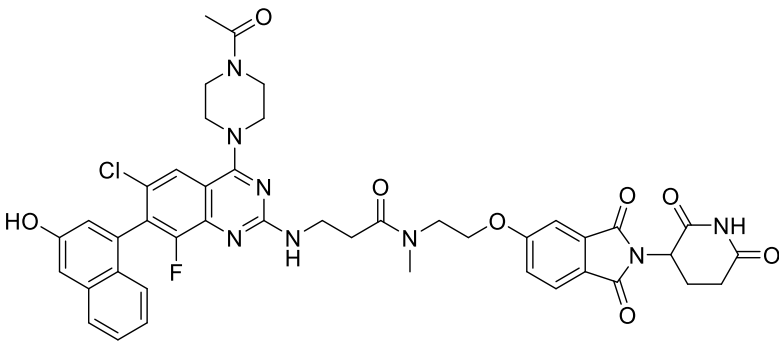
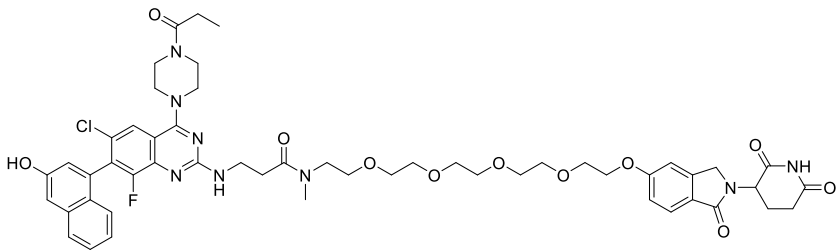
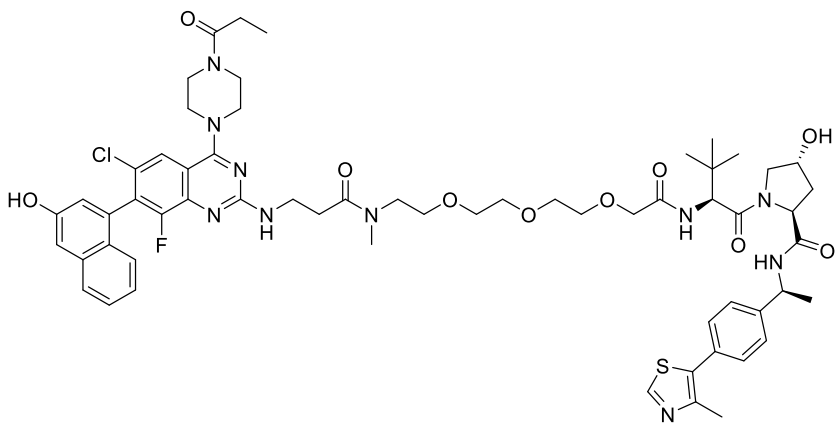
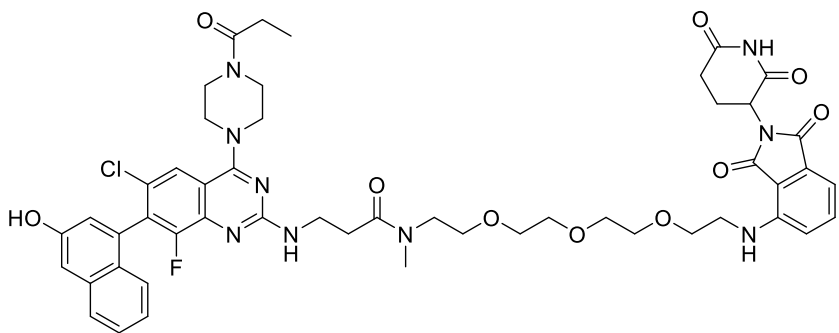
~~(c) la unidad A^L del enlazador (L) se selecciona de entre un compuesto de las Tablas 4, 6, 8, 10 y/o un L de la Tabla 2; o~~

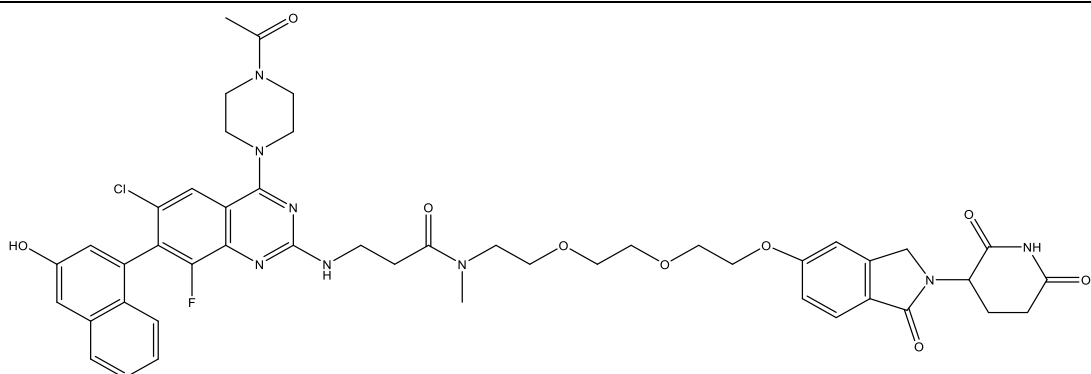
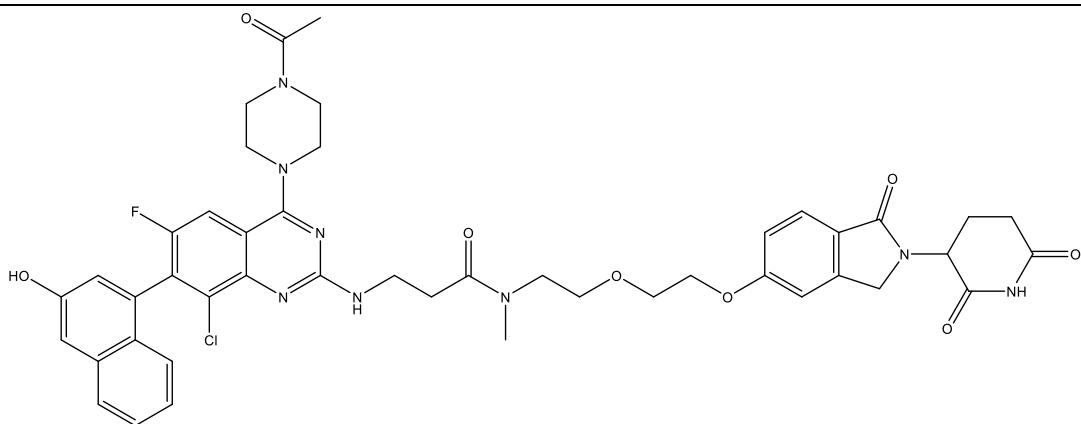
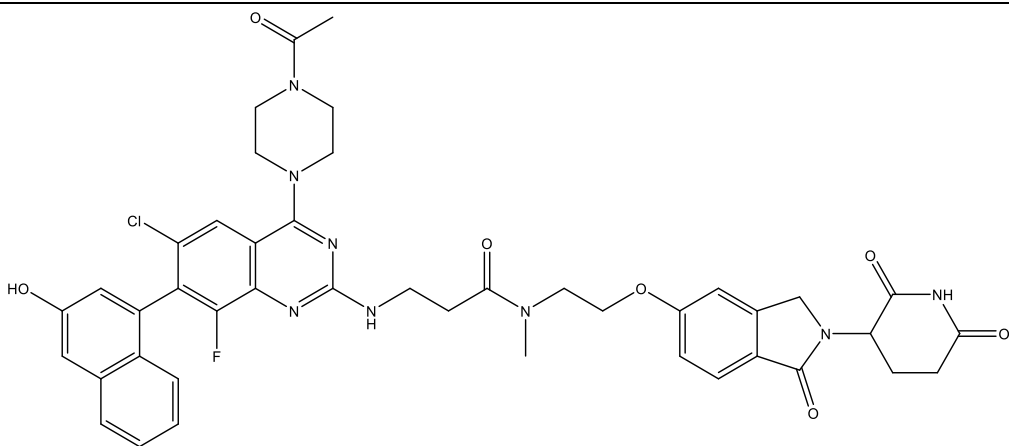
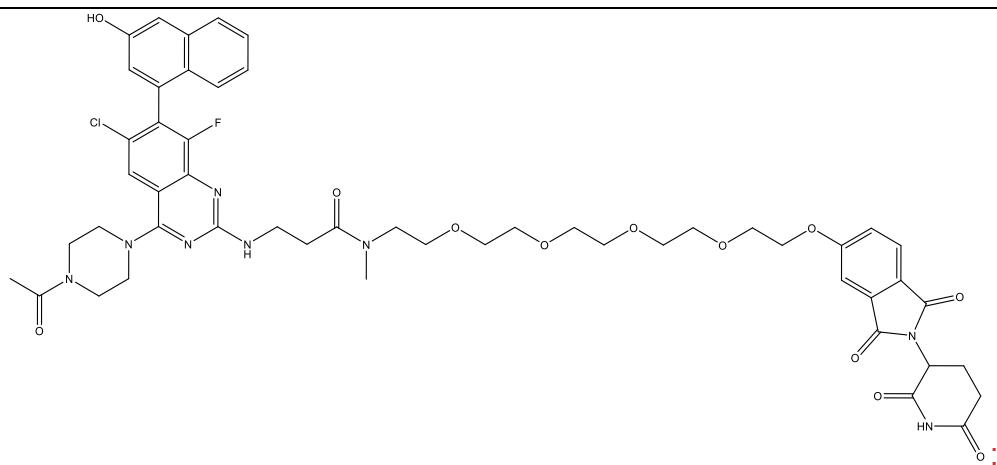
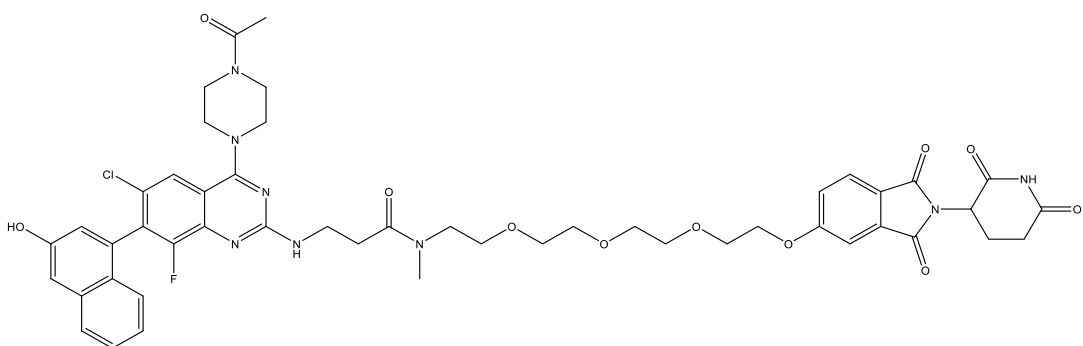
~~(d) combinaciones de estos.~~

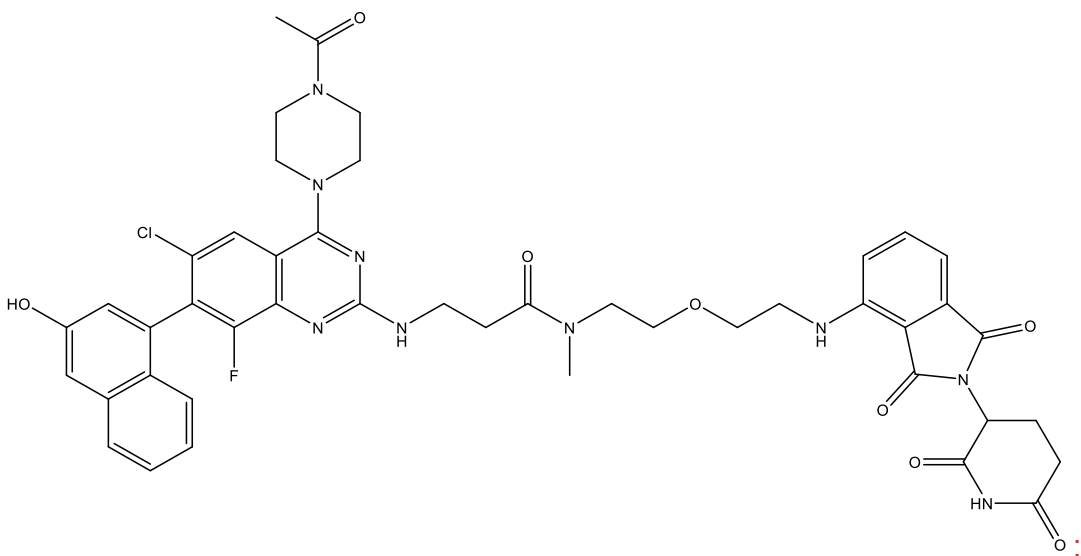
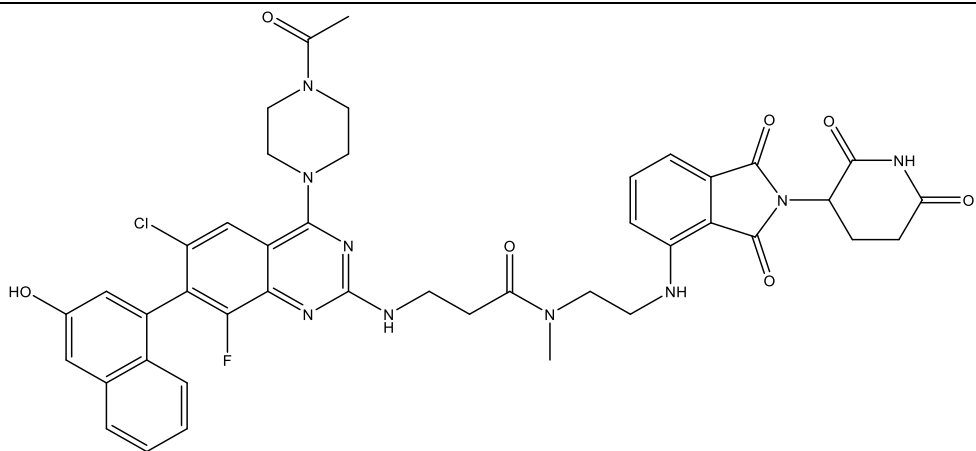
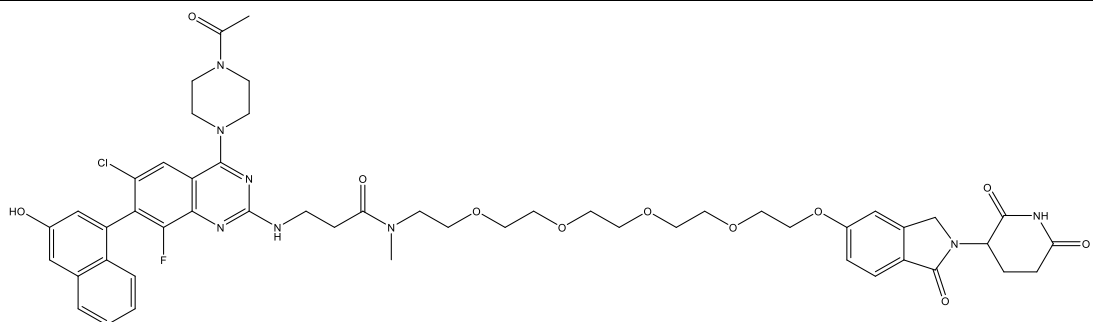
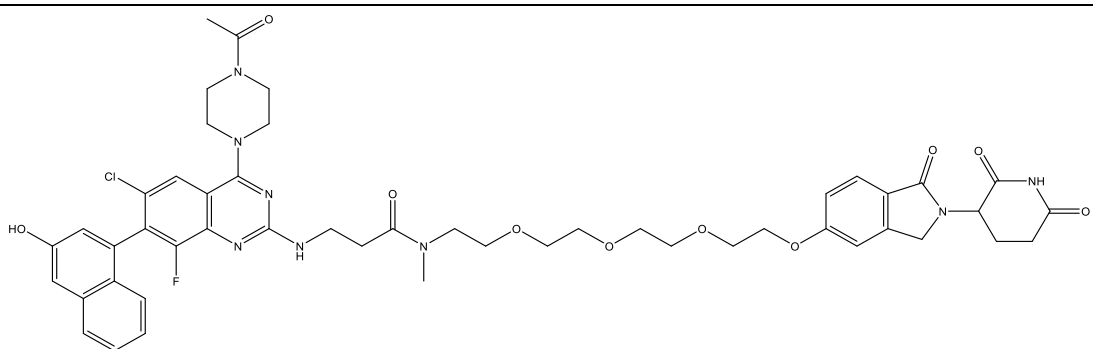
29.12. El Un compuesto bifuncional ~~de la reivindicación 1, donde el compuesto se selecciona~~ do ~~dentro del grupo que consiste en~~ re: ~~los ejemplos de compuestos 1-249, 254-454 y 458-573~~

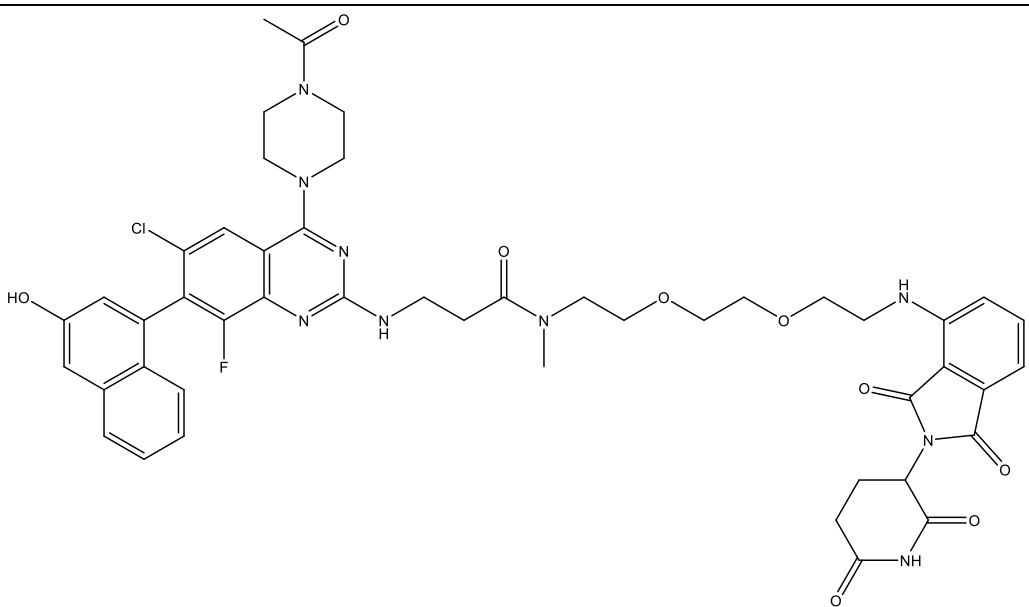




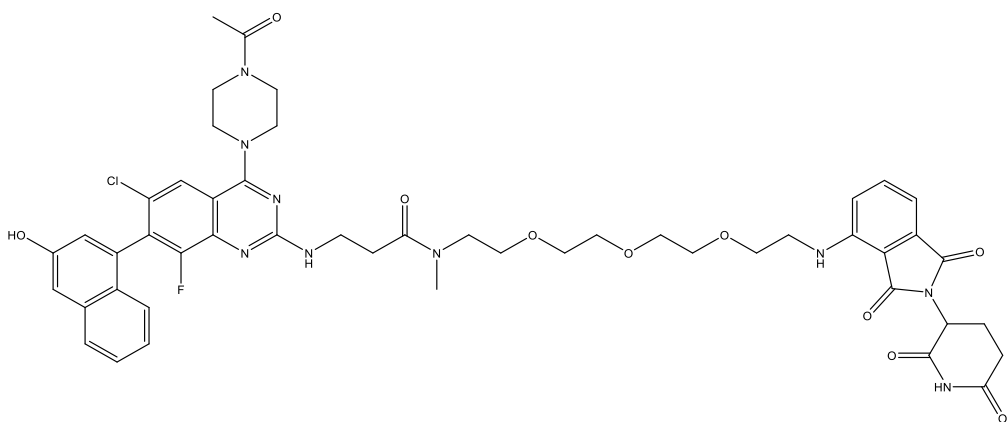




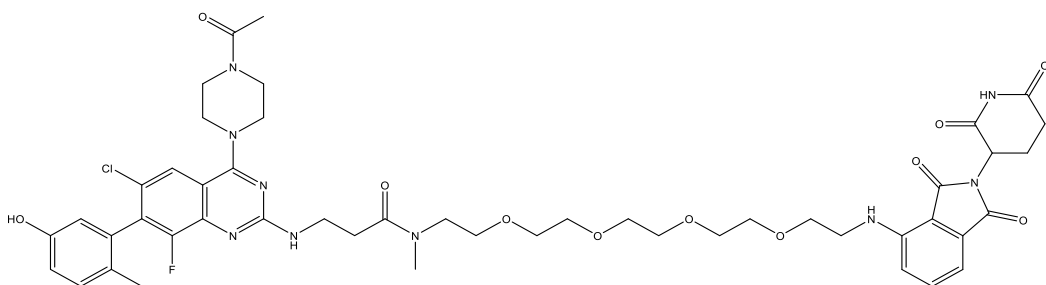




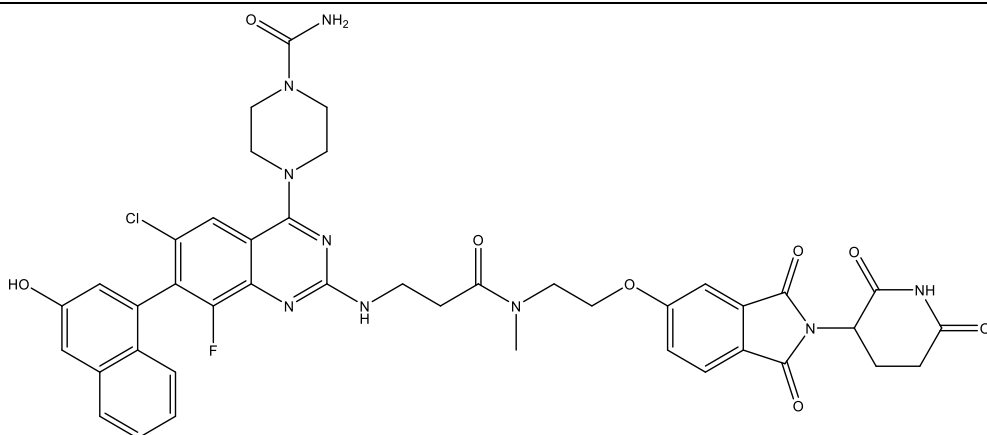
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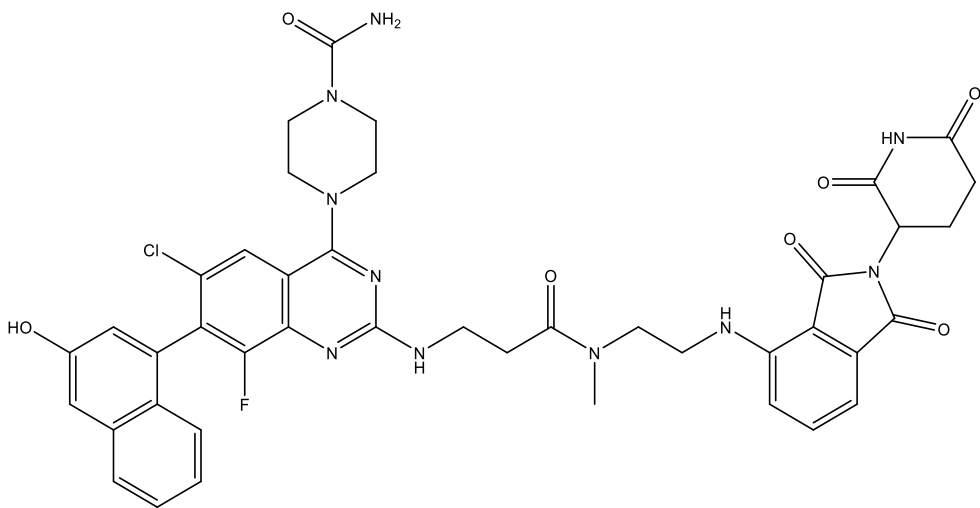
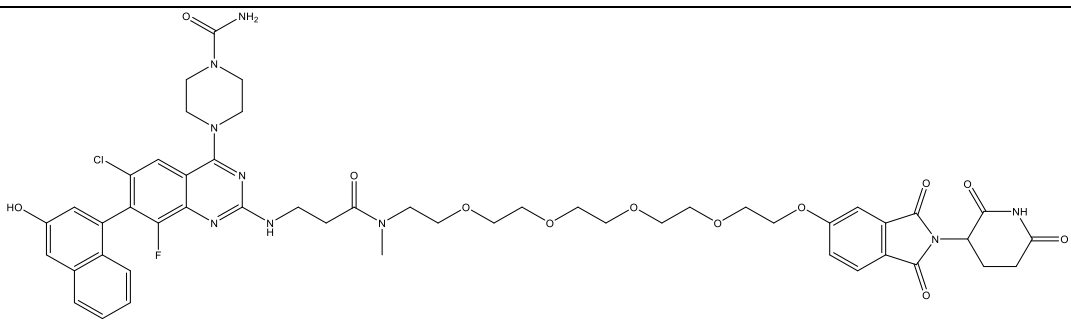
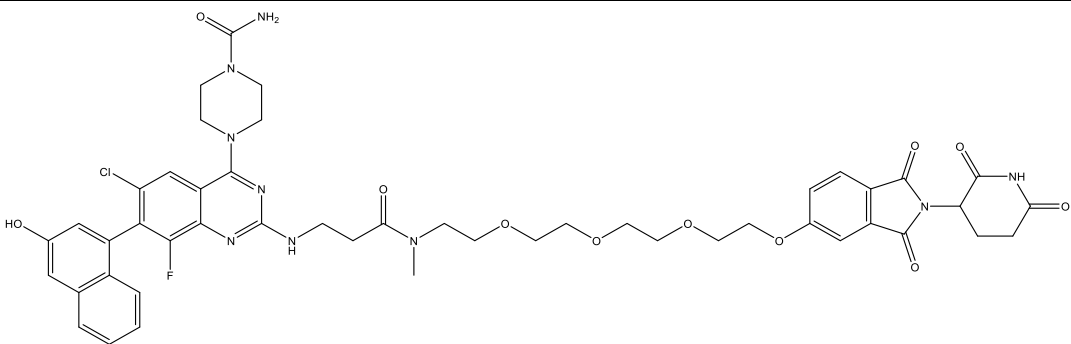
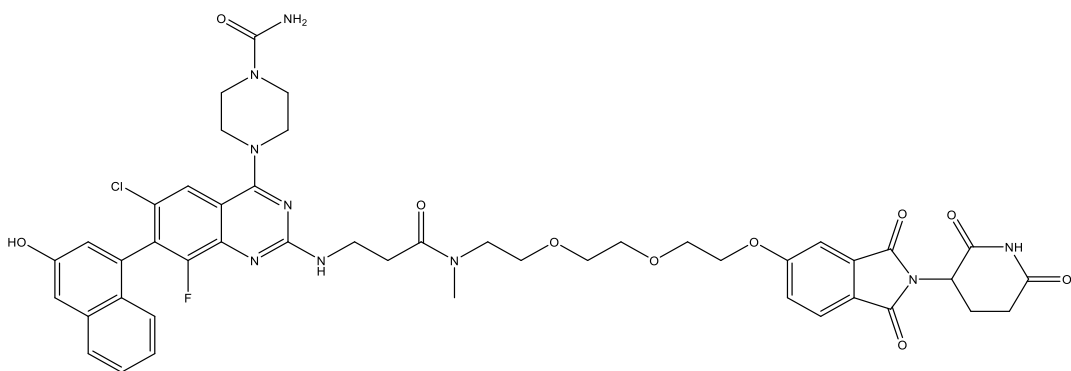
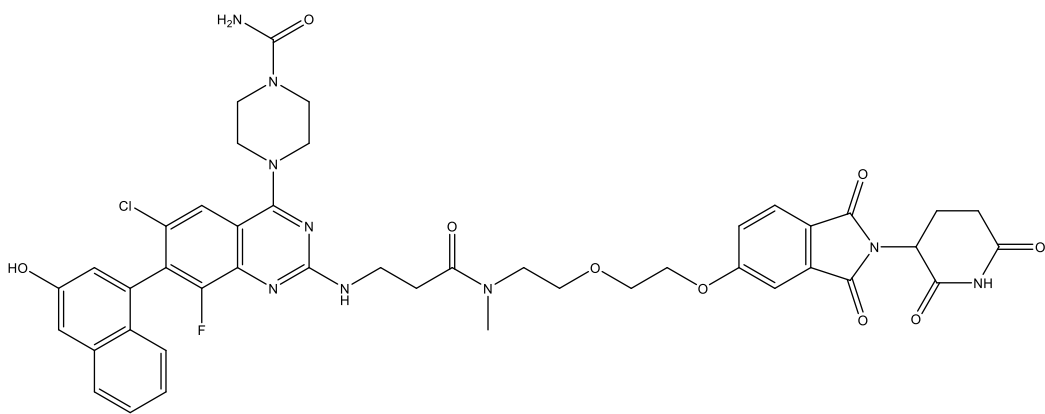
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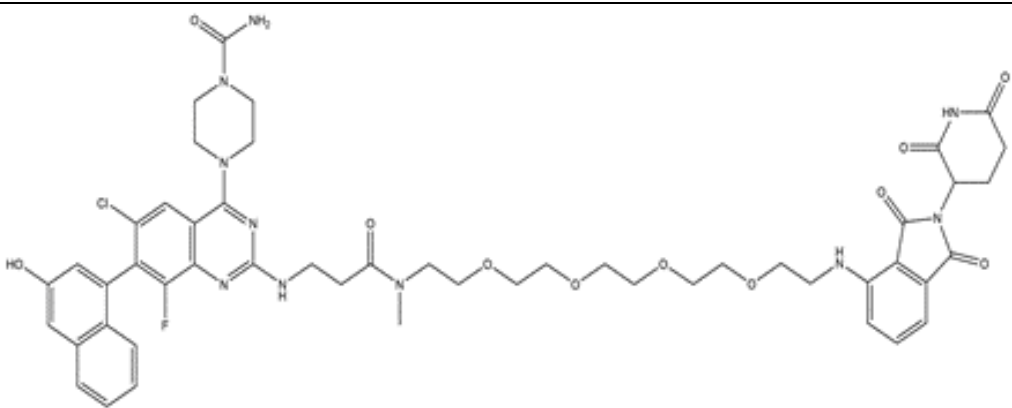
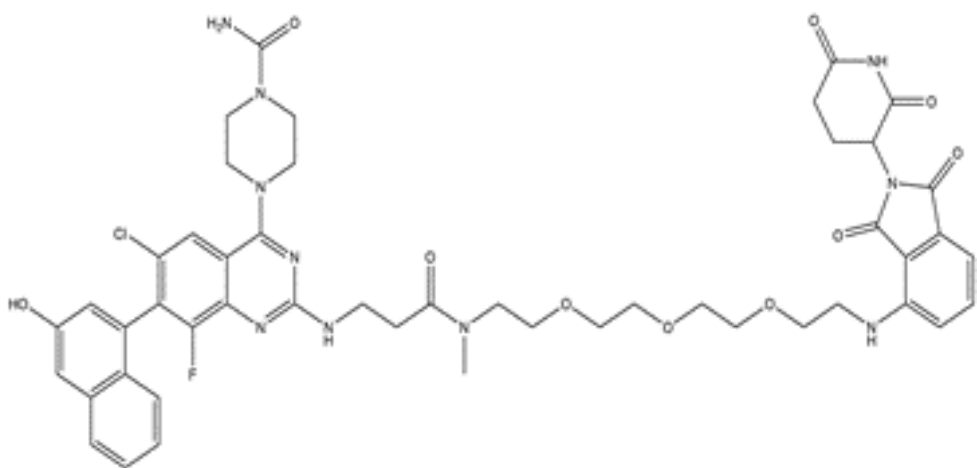
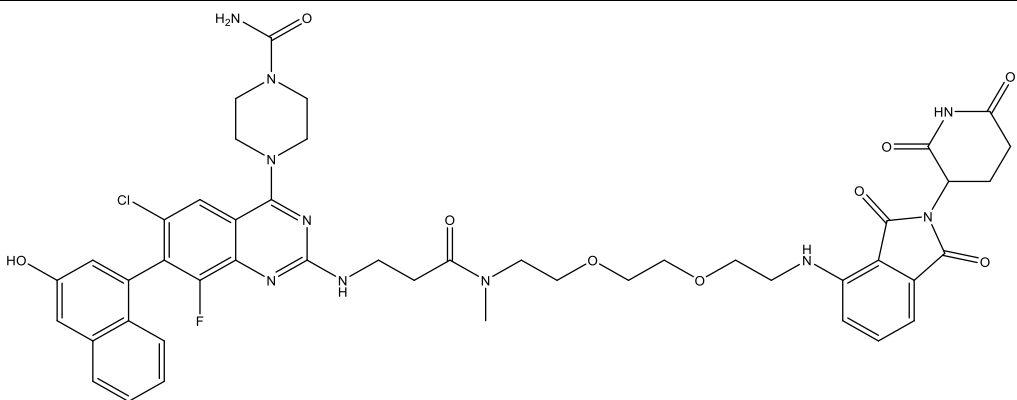
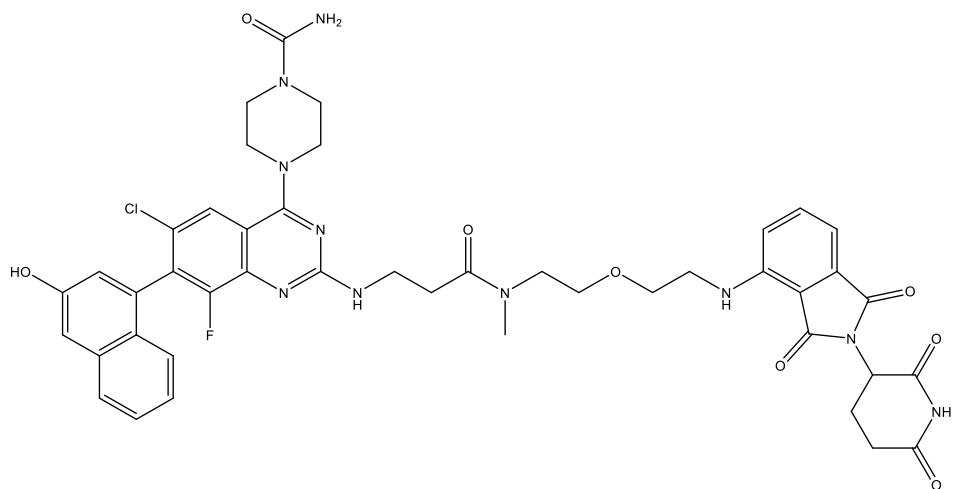


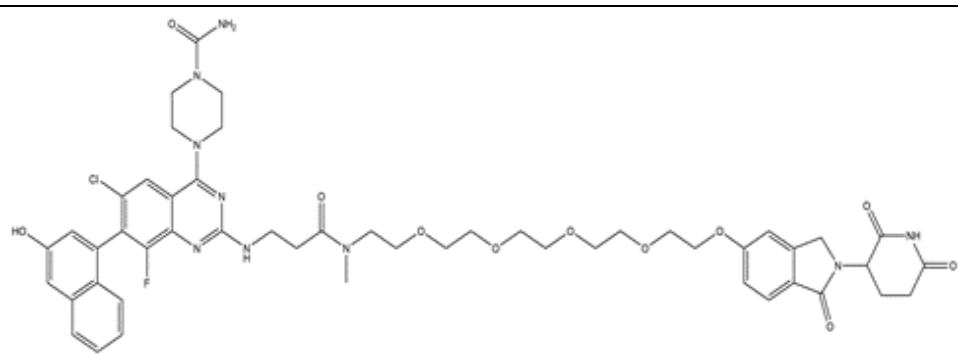
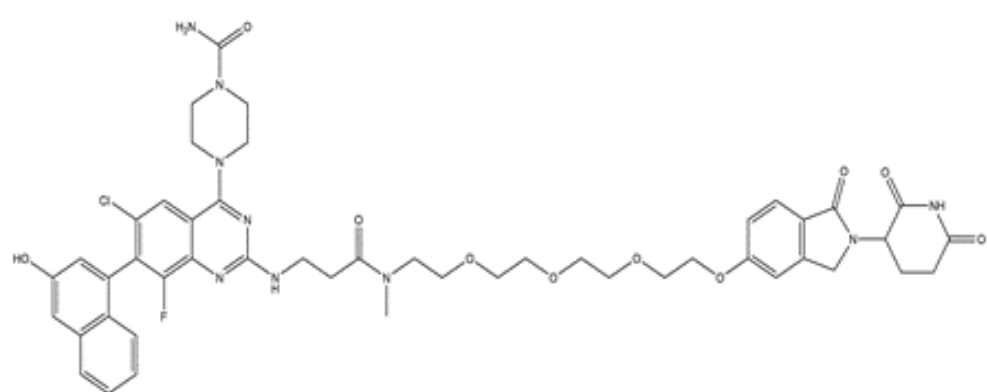
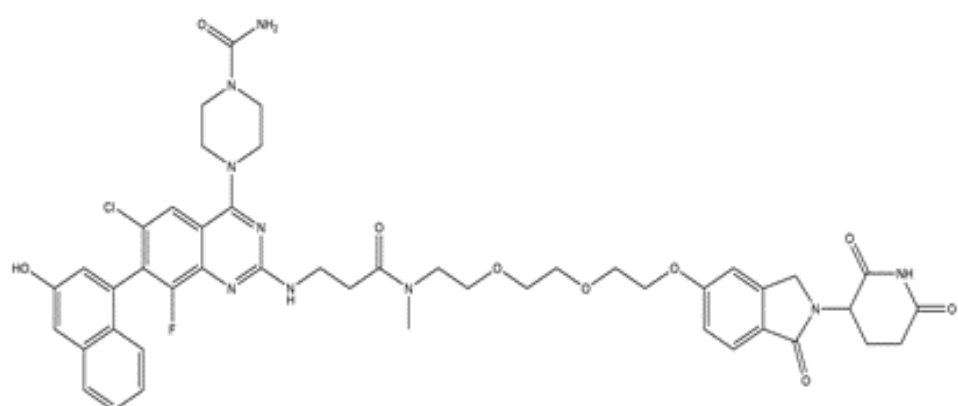
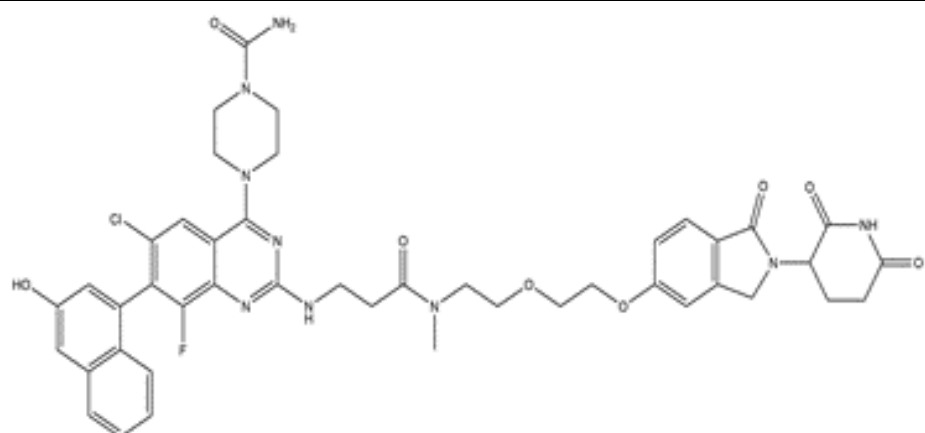
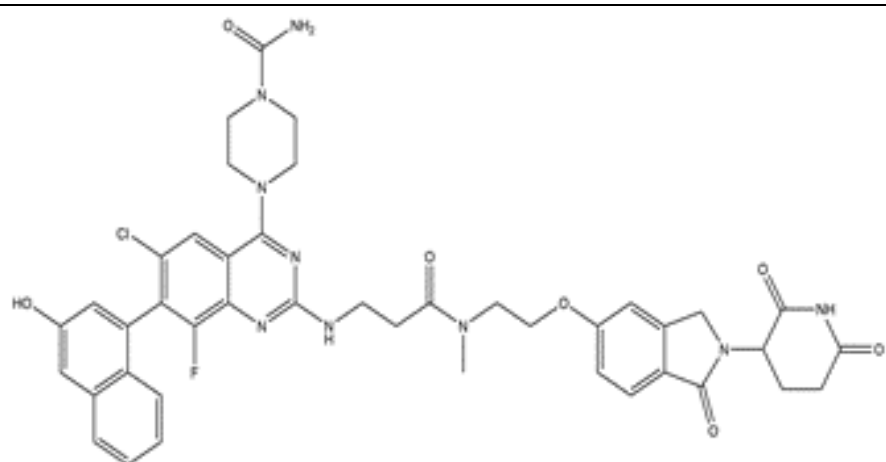
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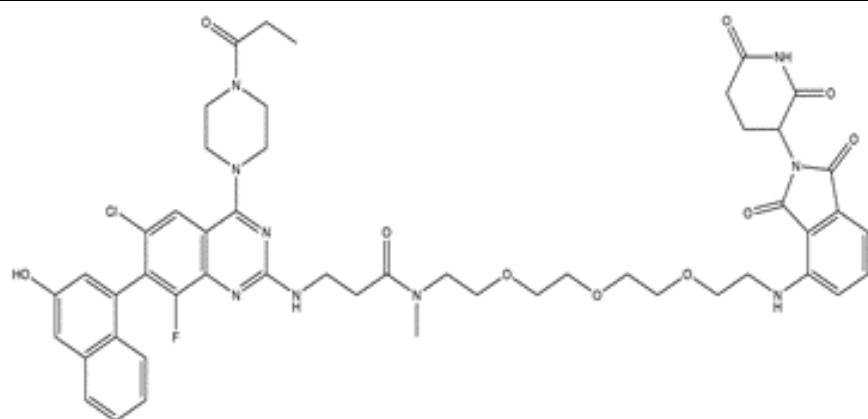
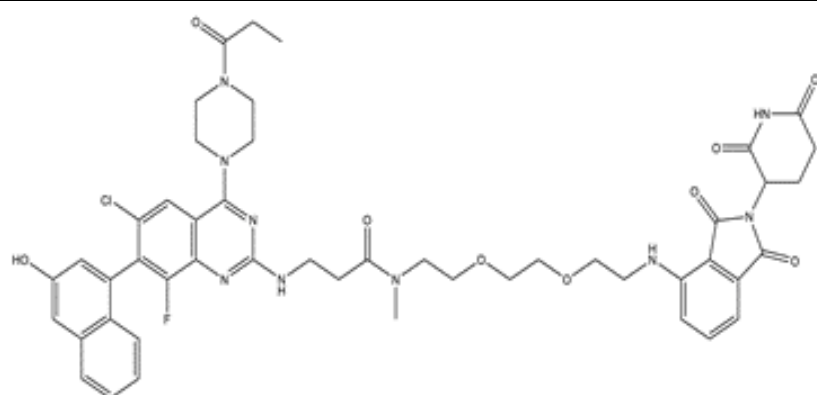
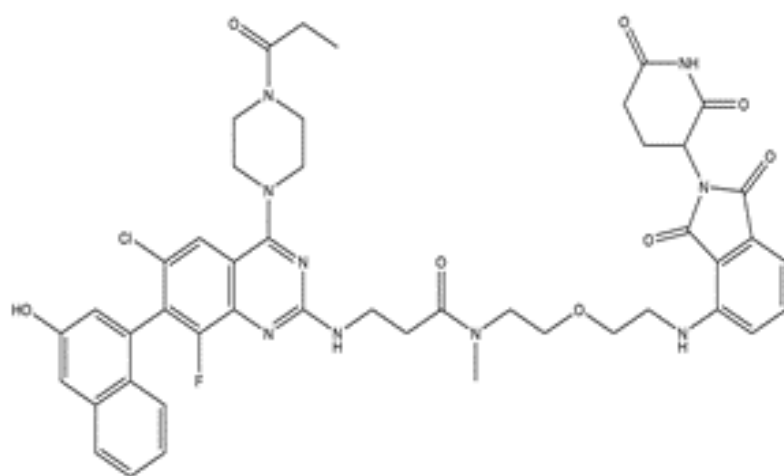
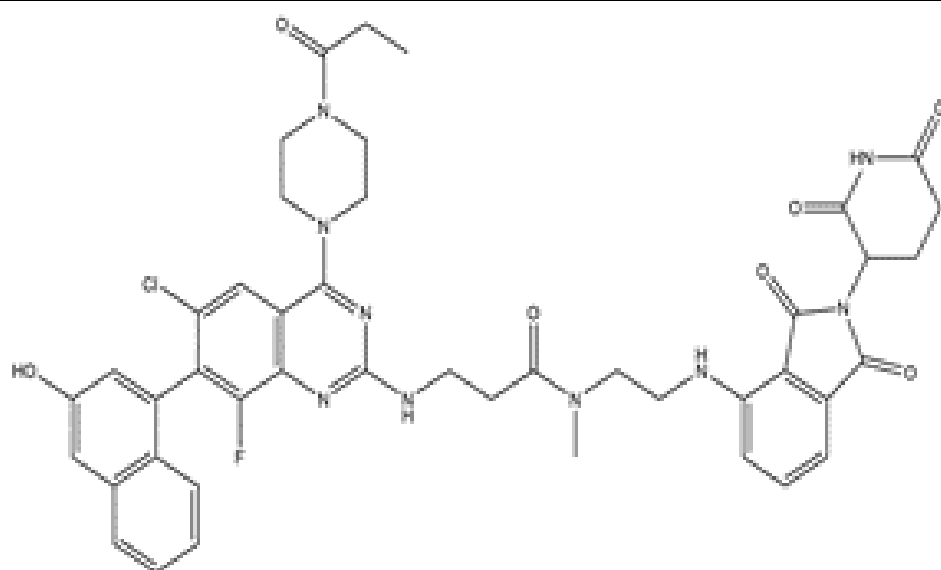


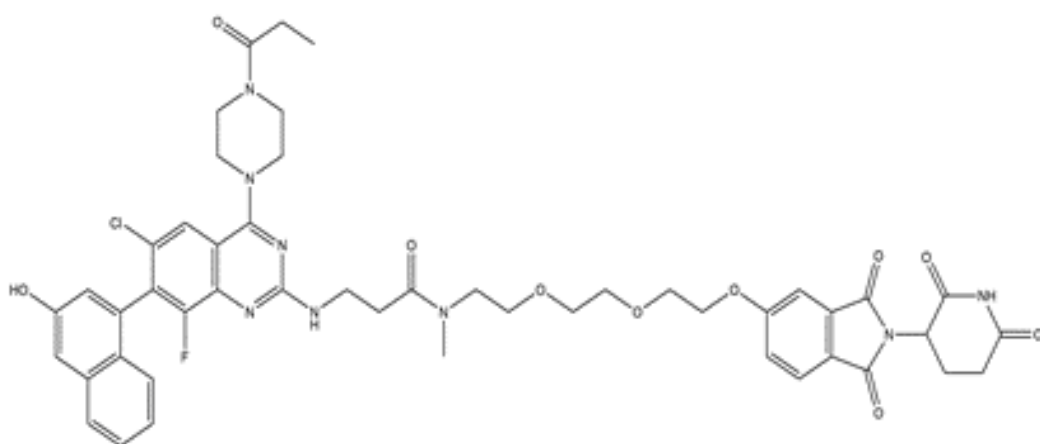
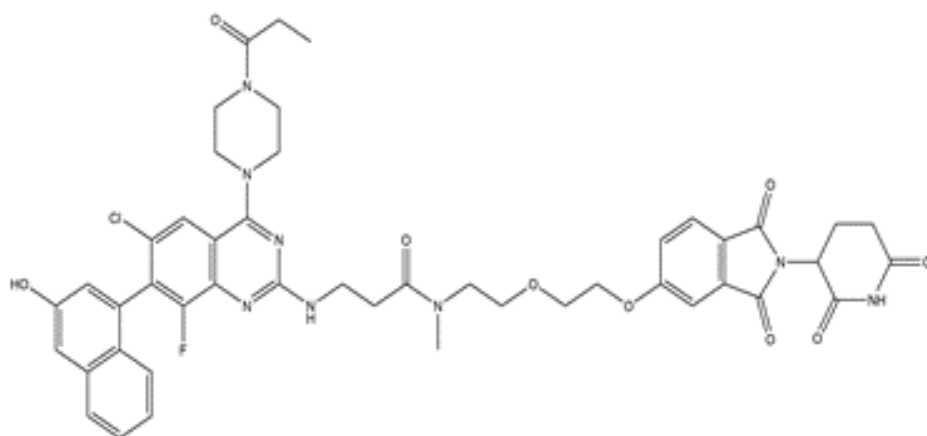
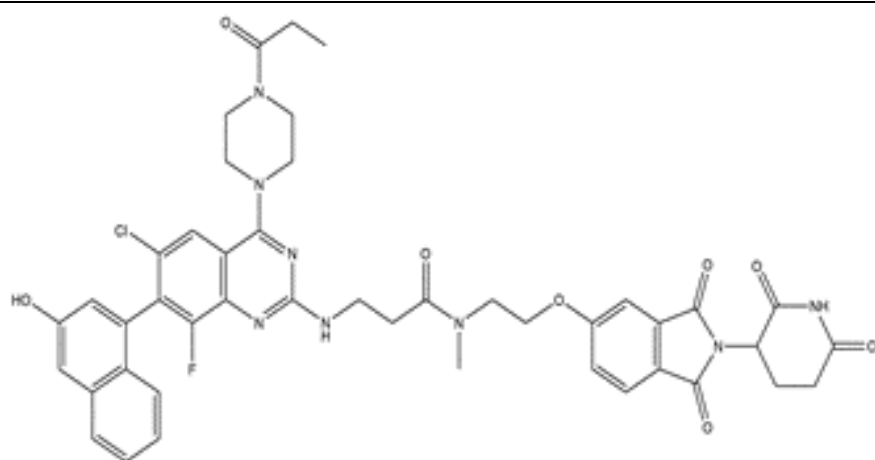
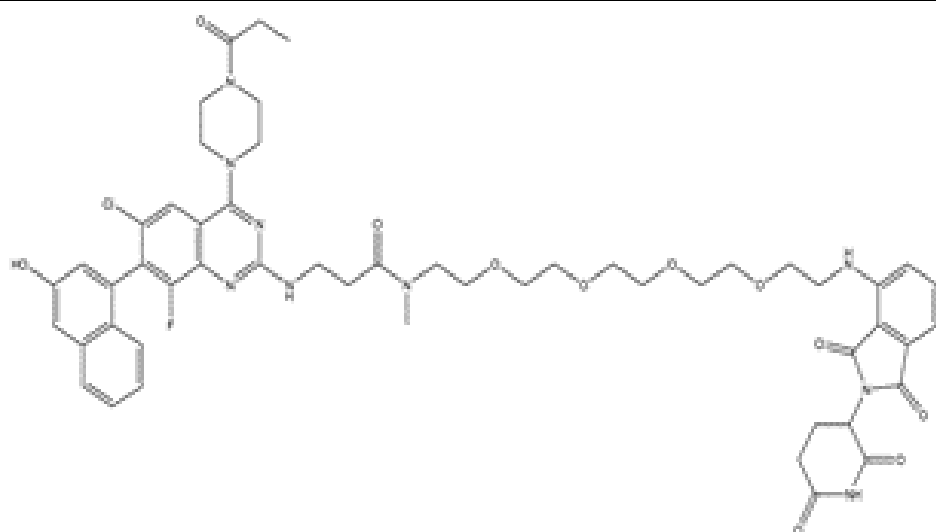
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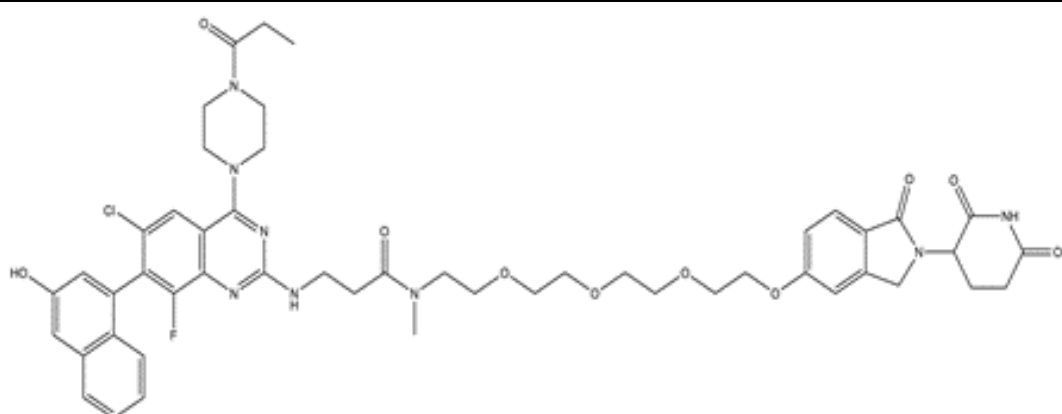
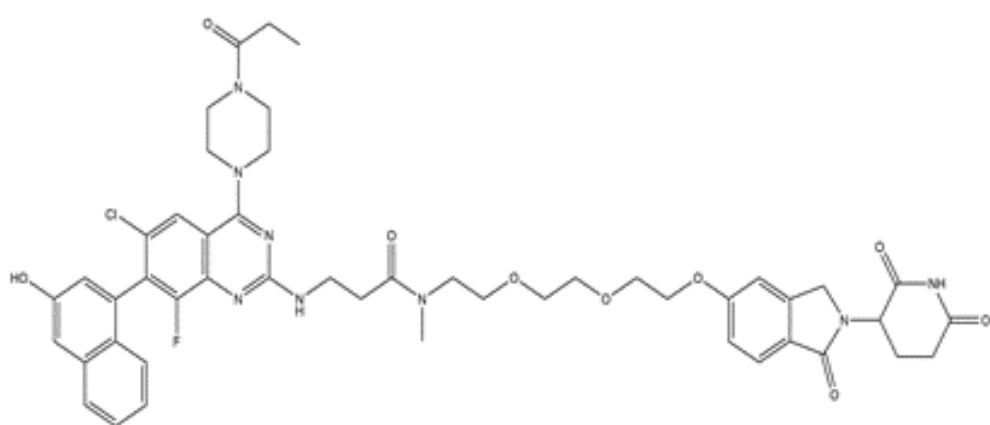
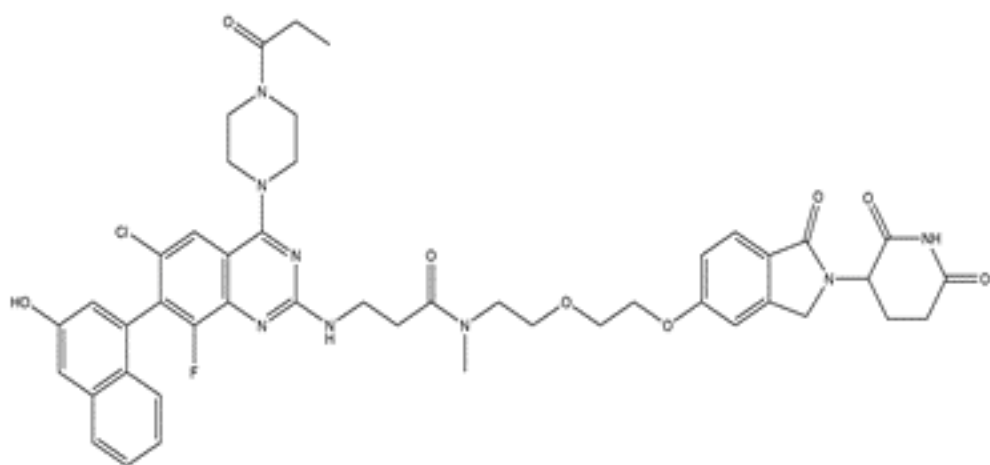
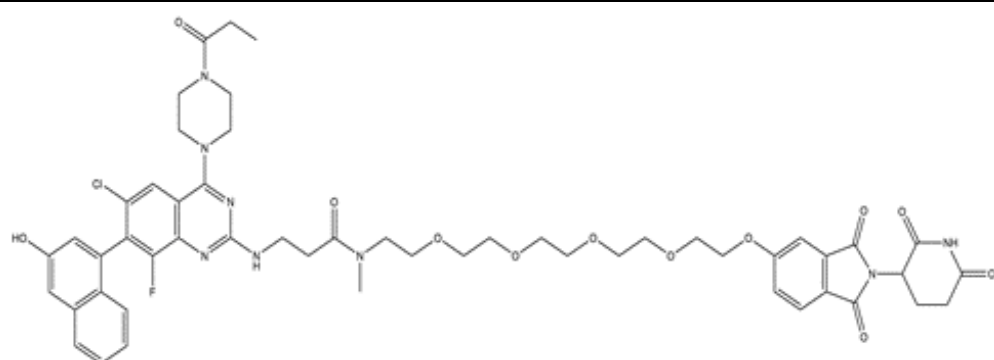
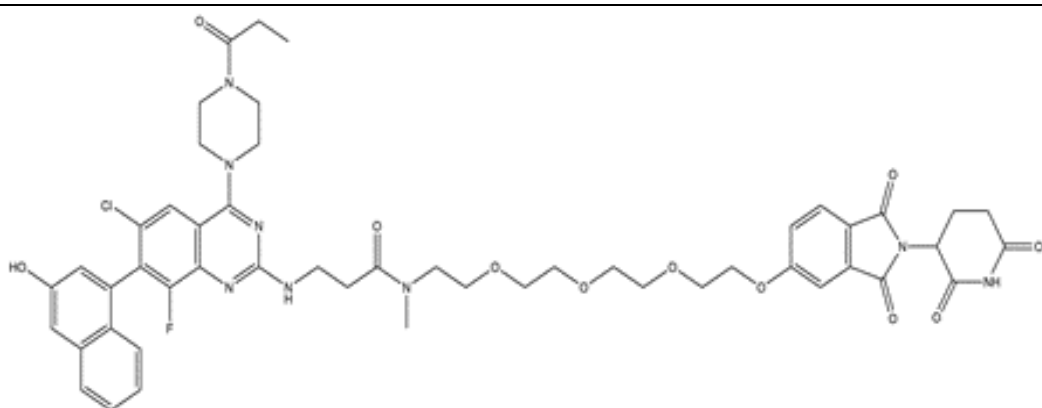


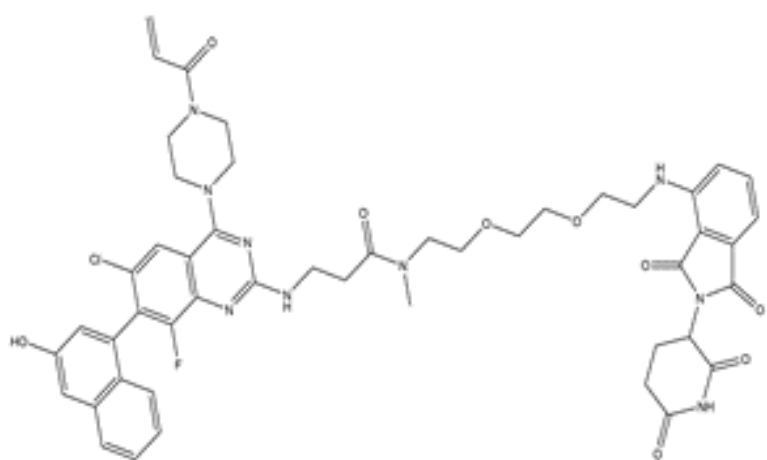
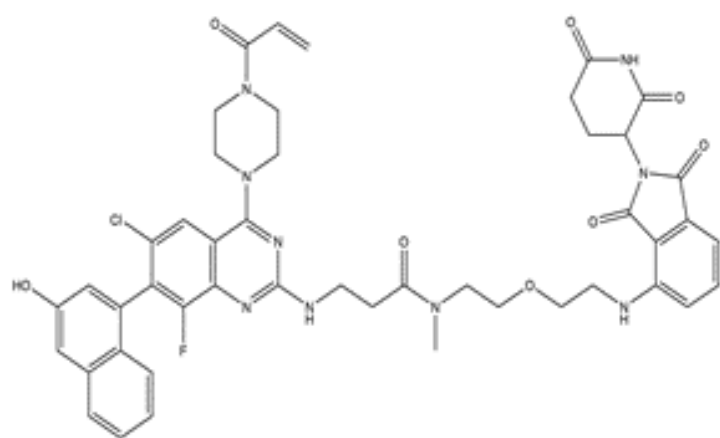
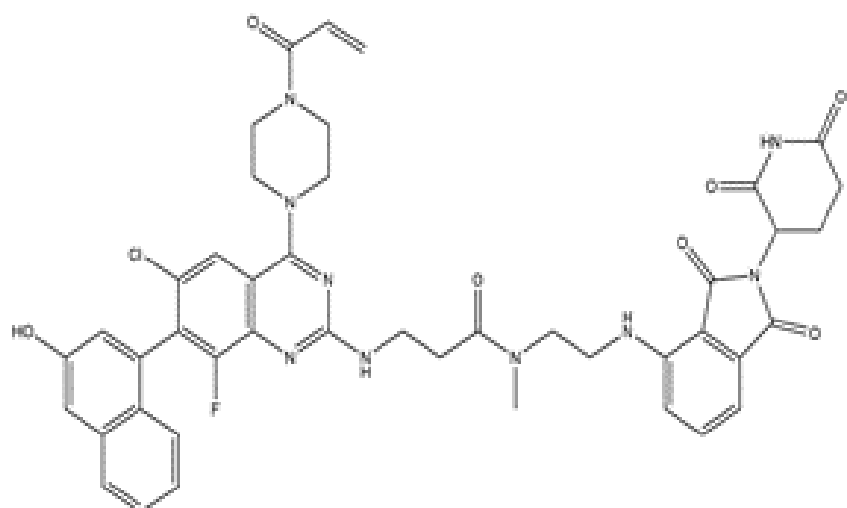
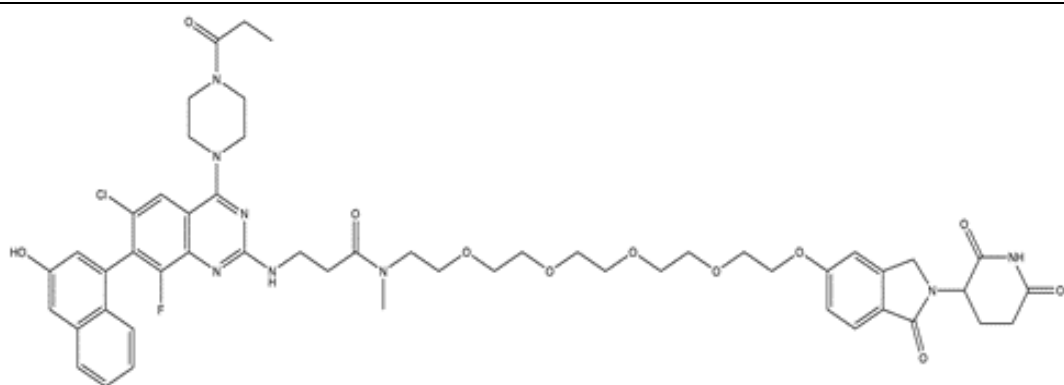


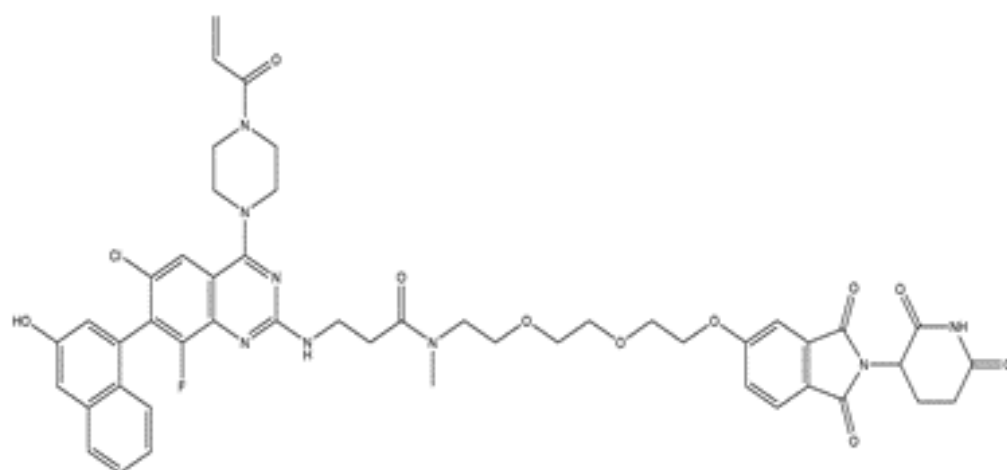
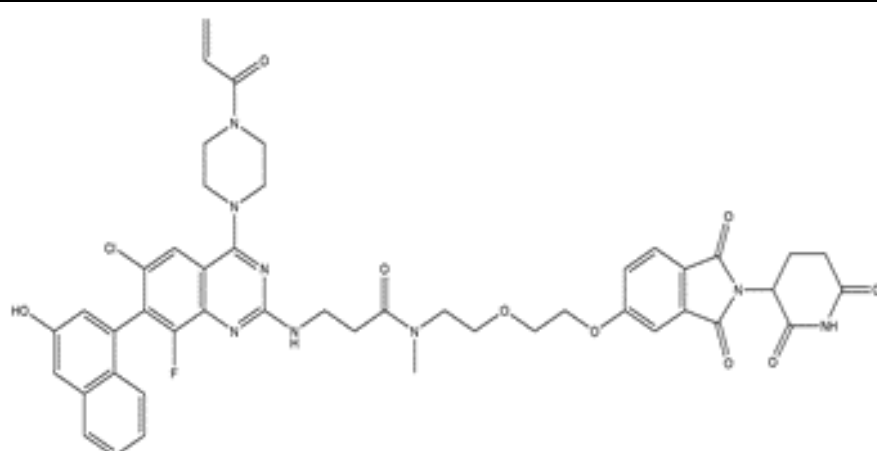
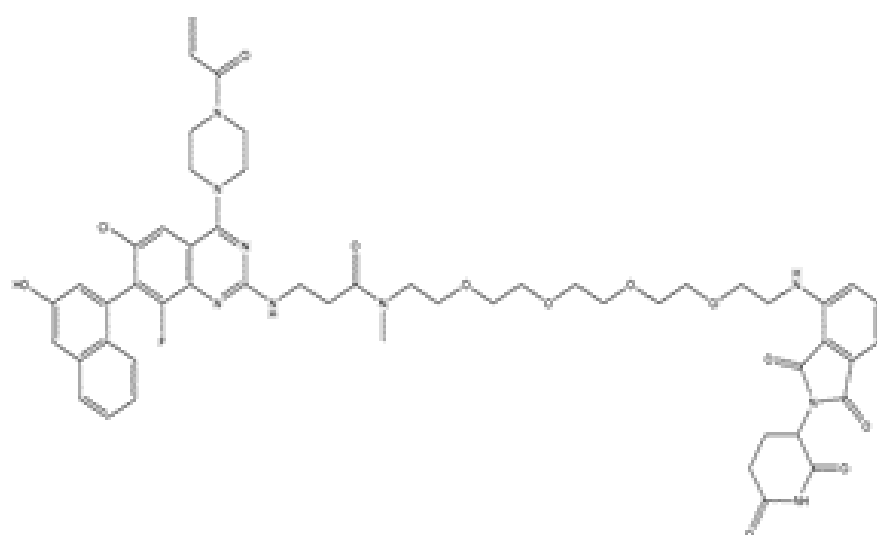
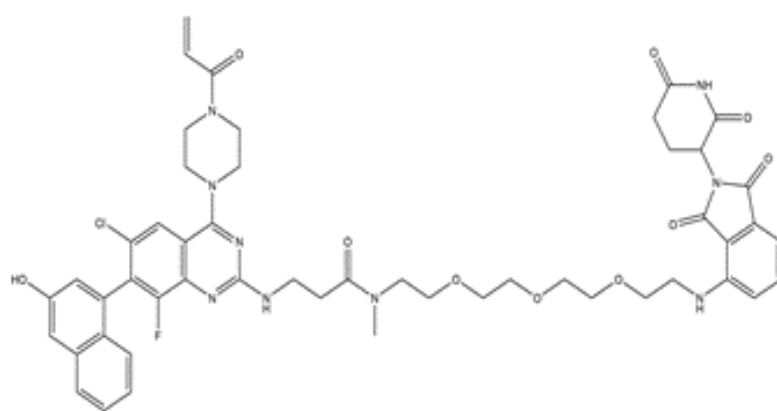


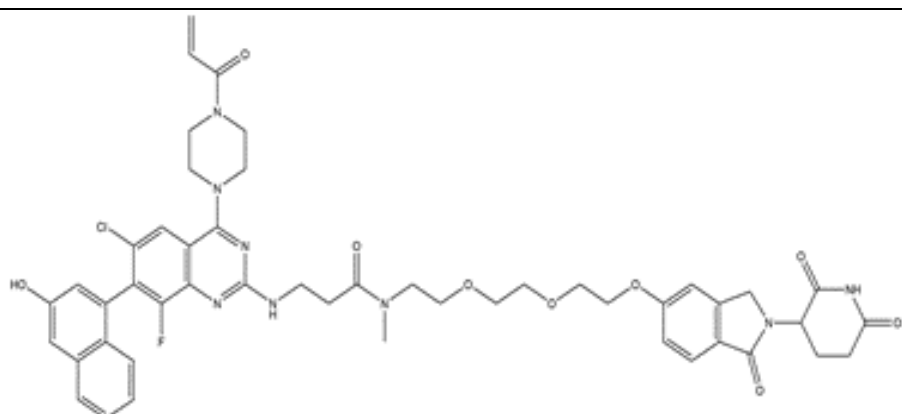
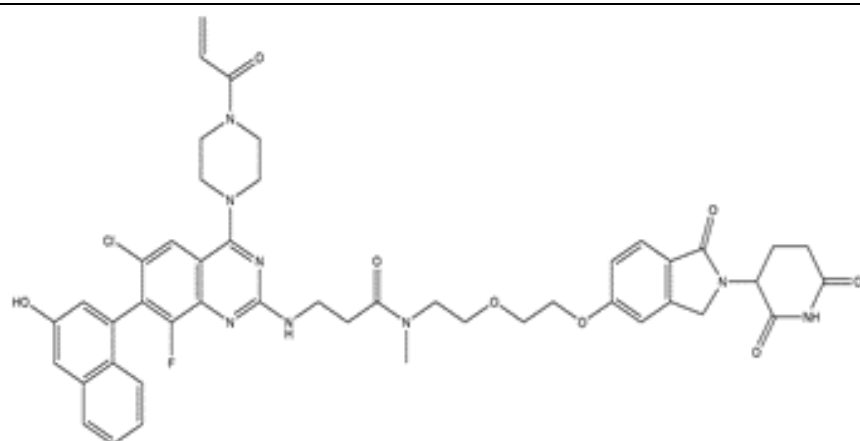
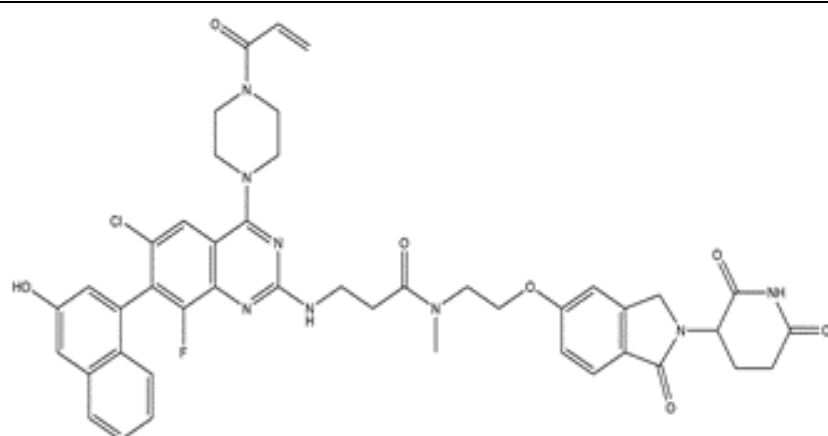
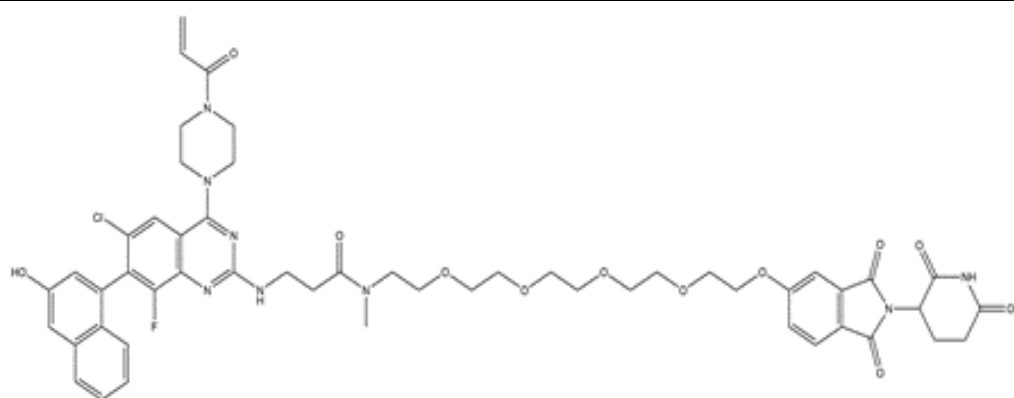
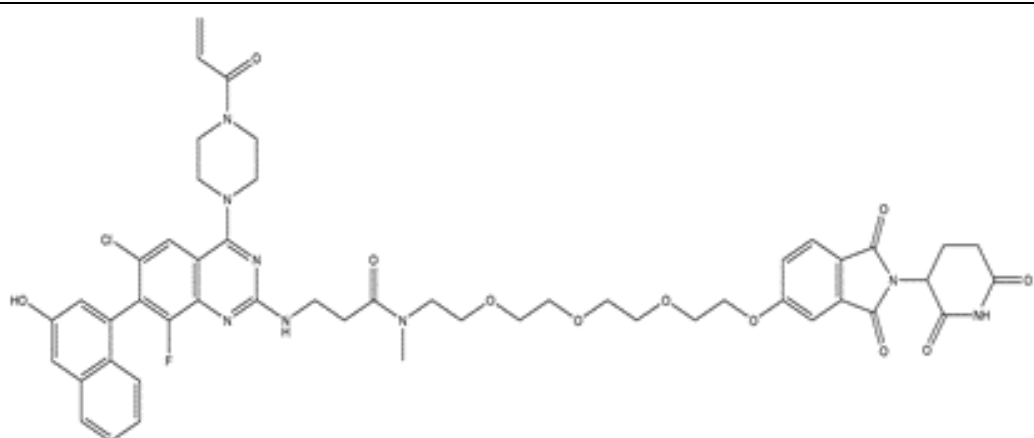


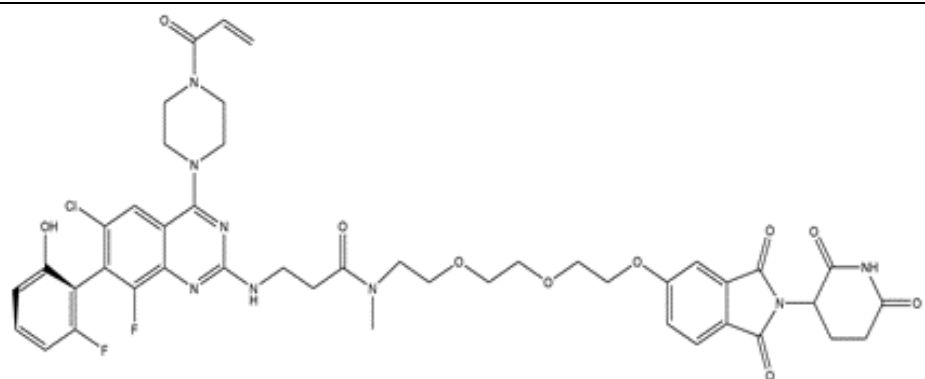
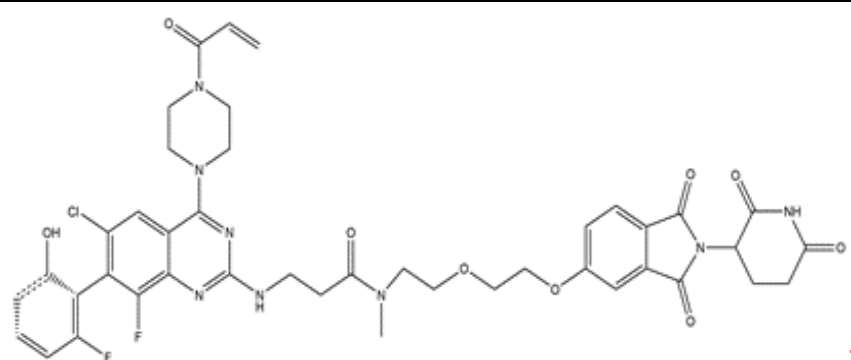
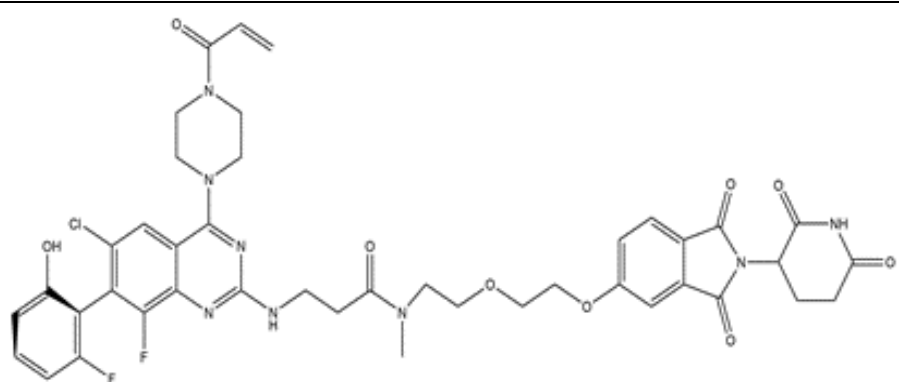
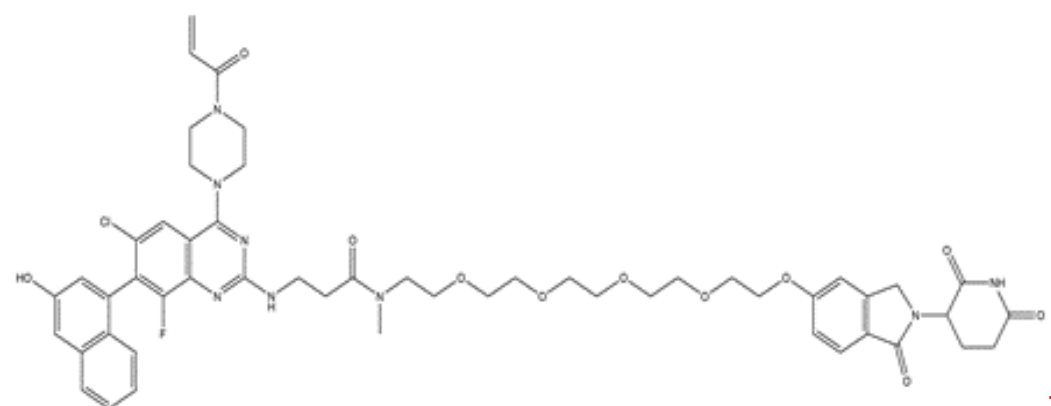
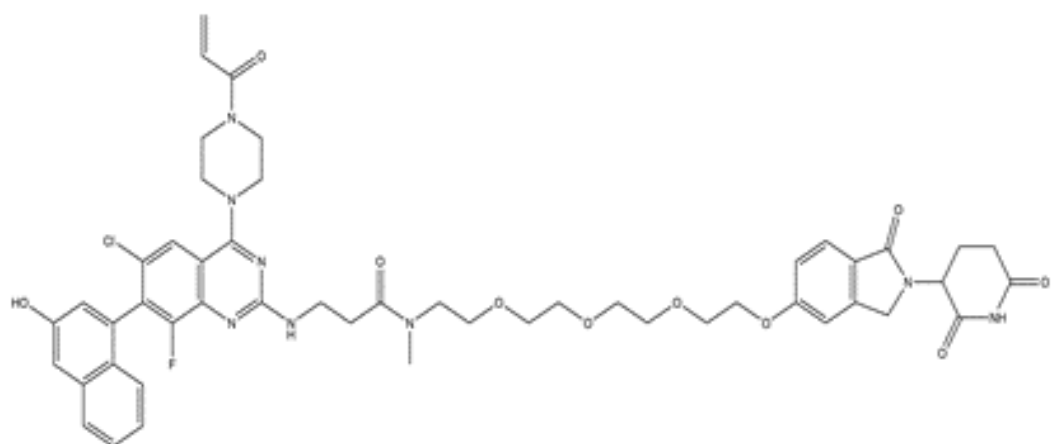


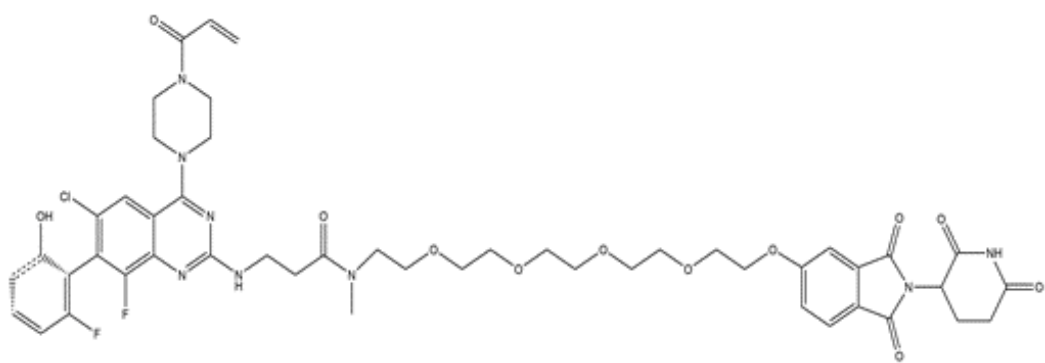
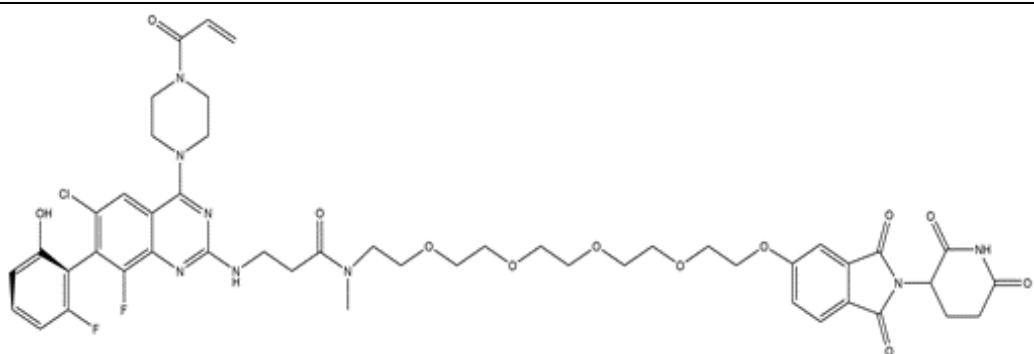
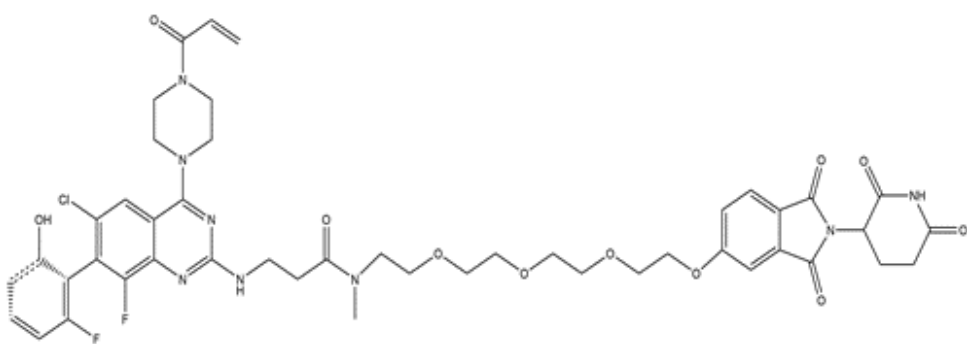
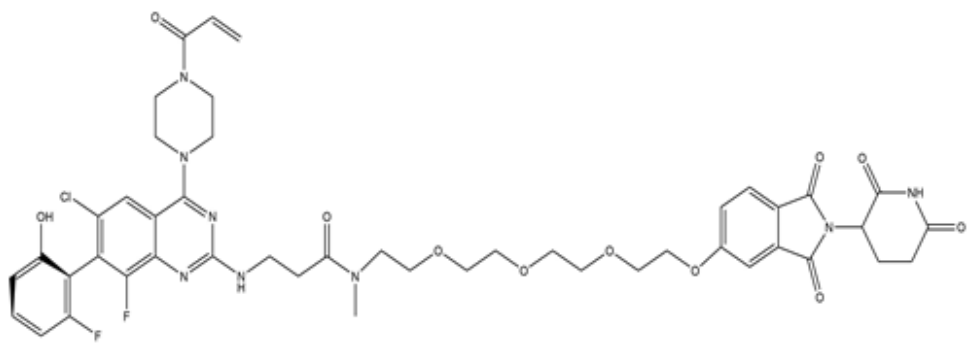
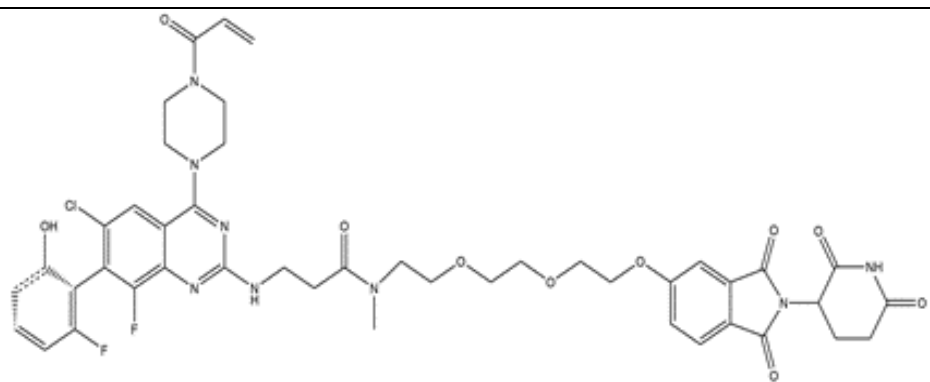


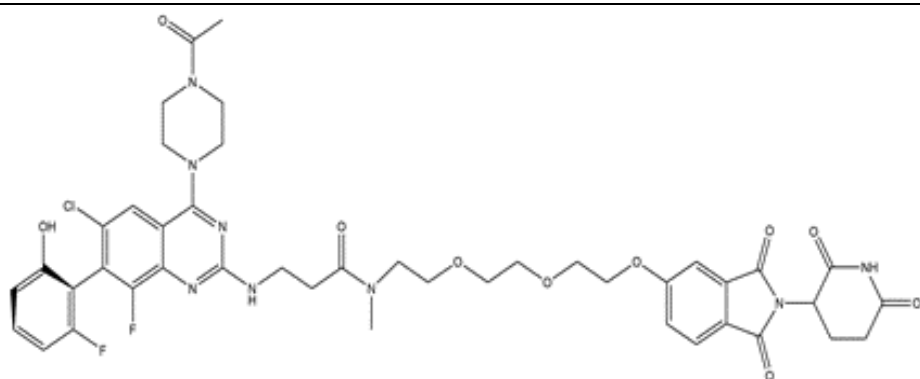
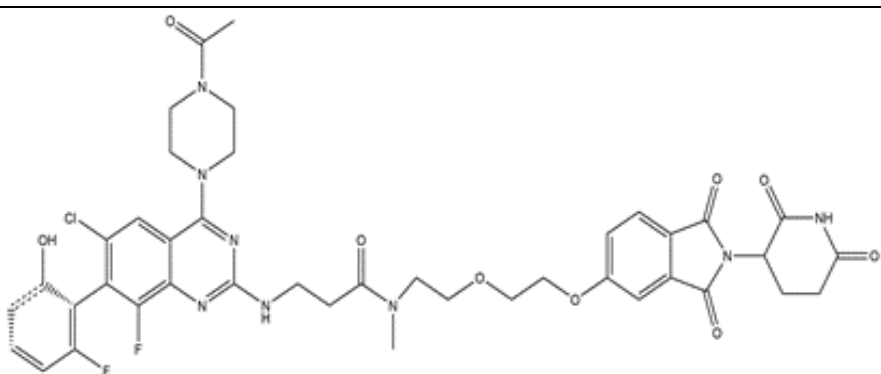
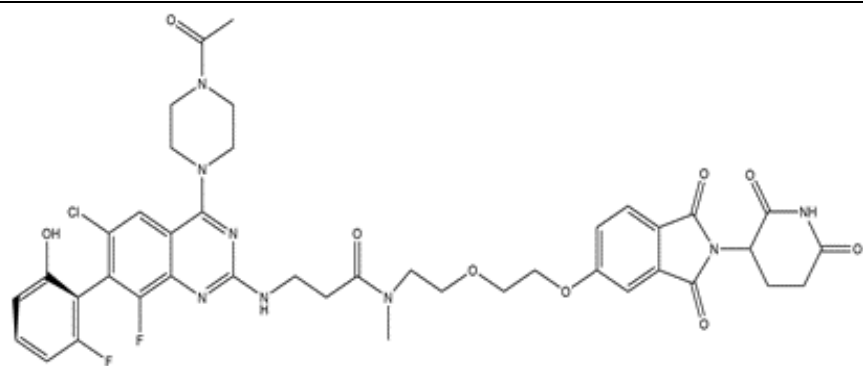
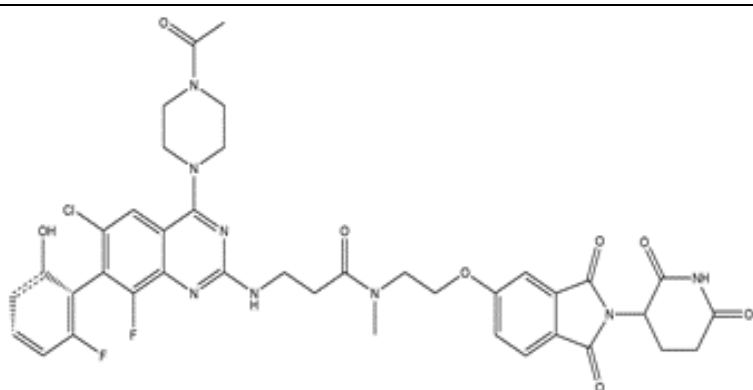
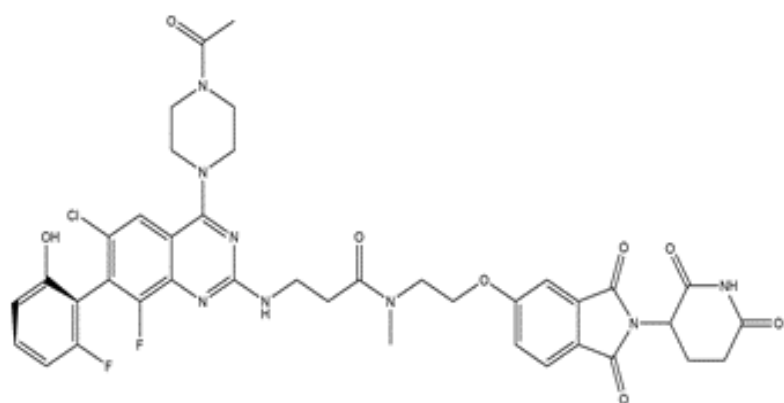


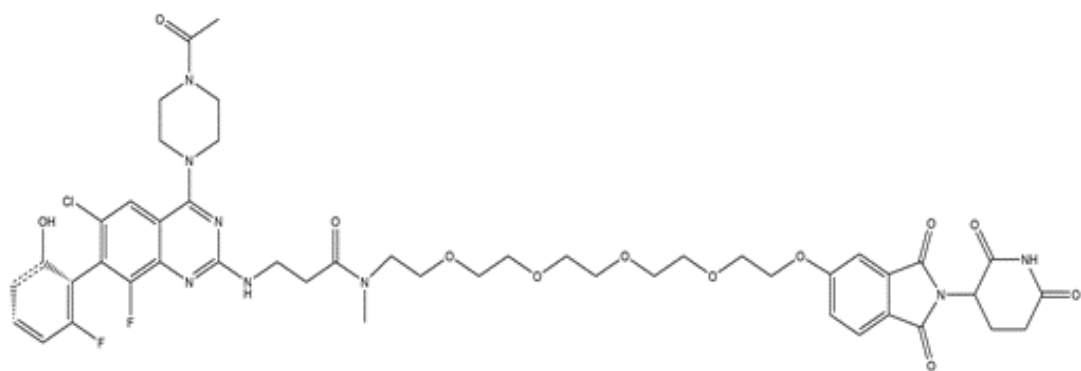
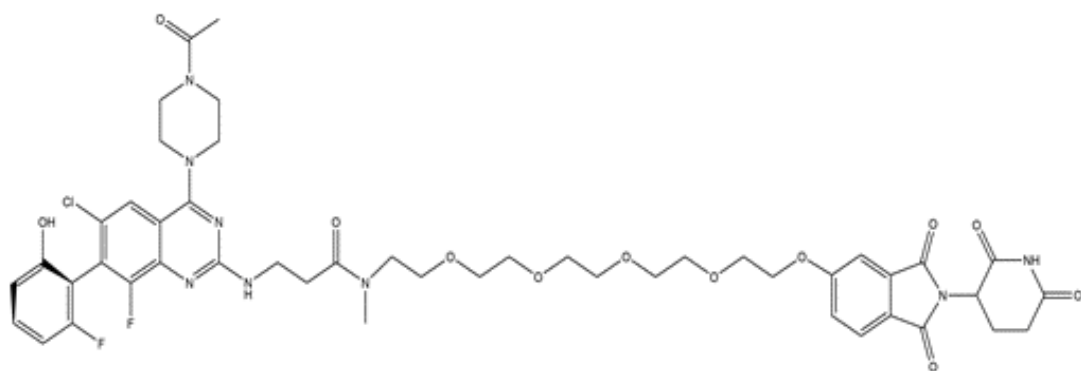
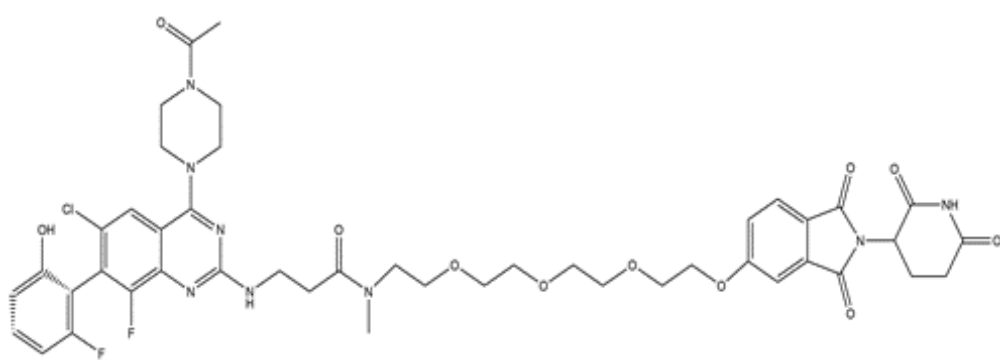
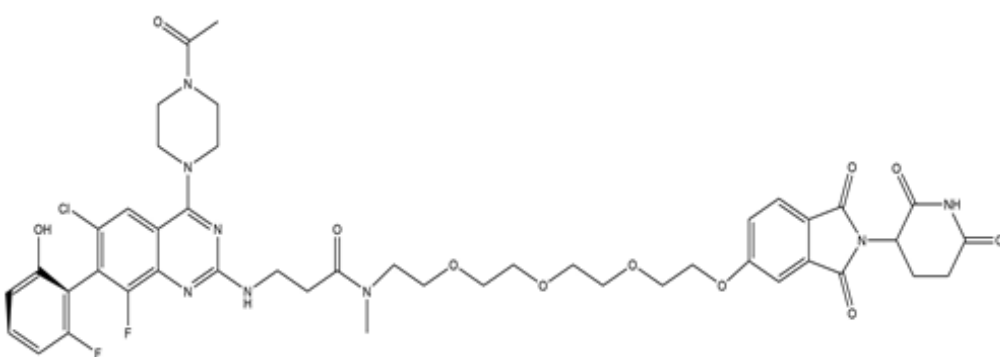
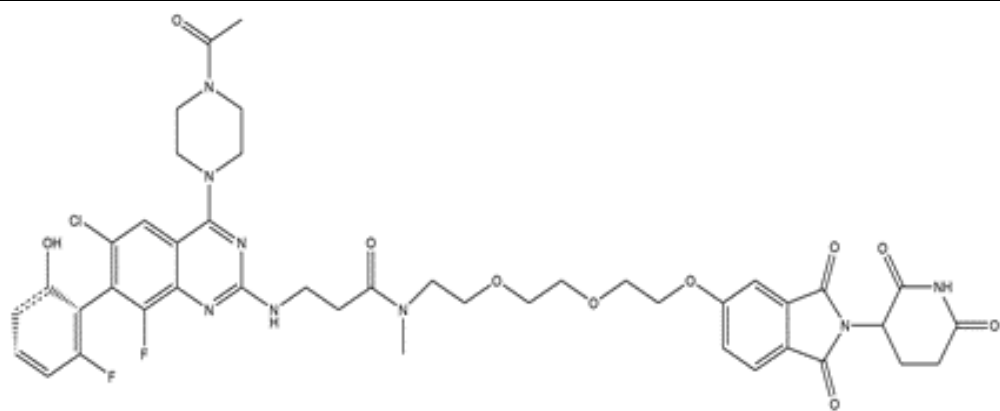


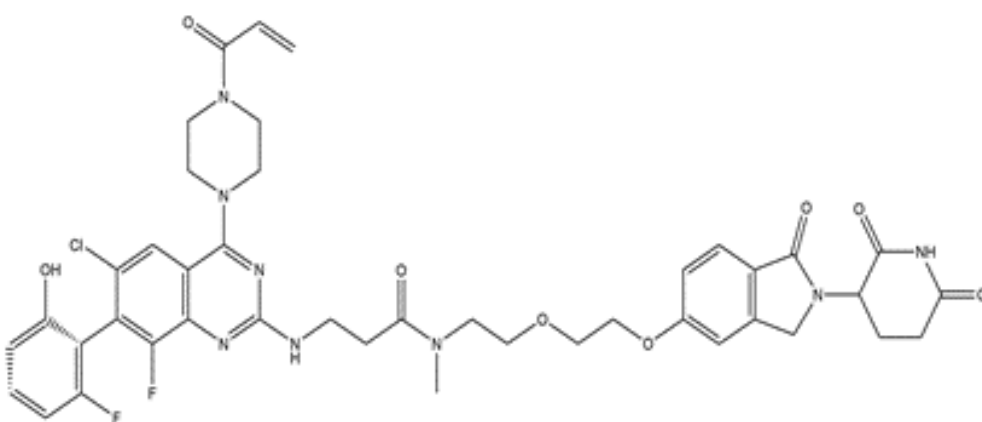
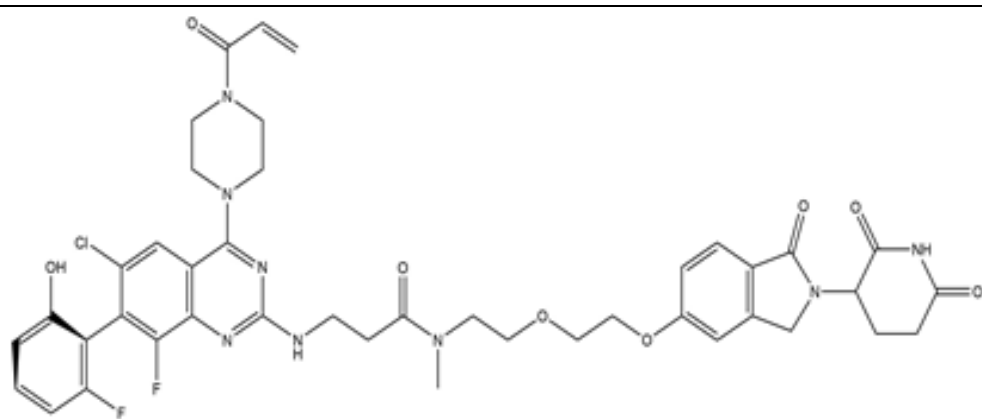
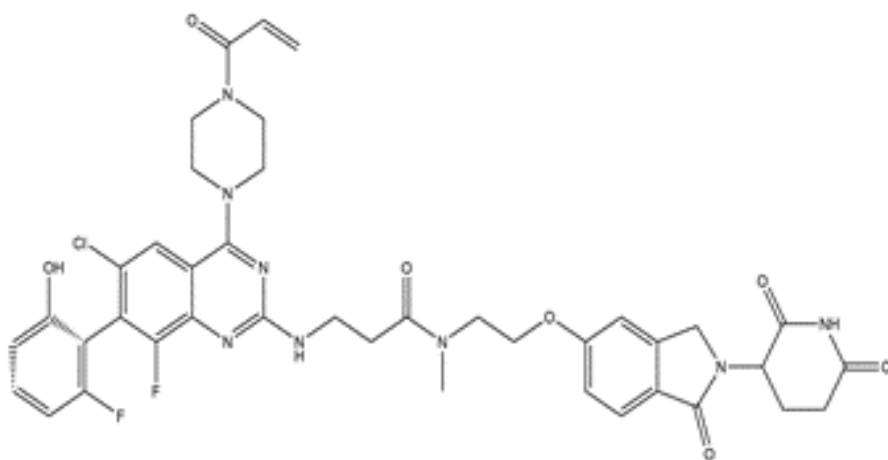
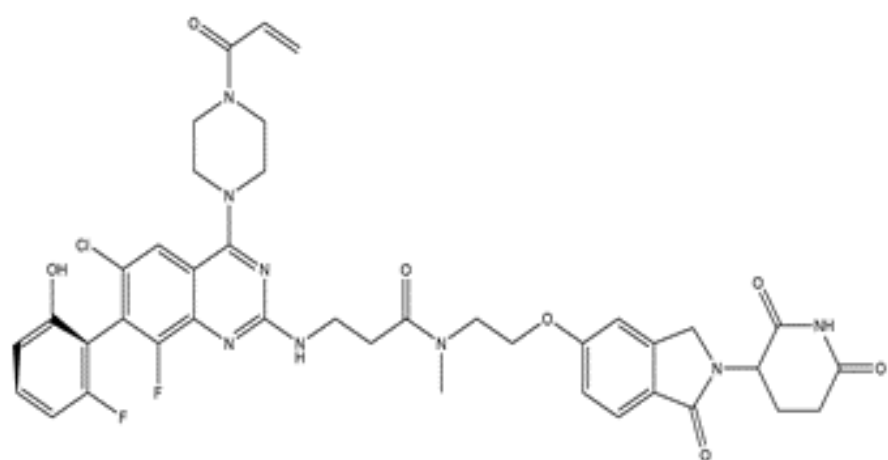


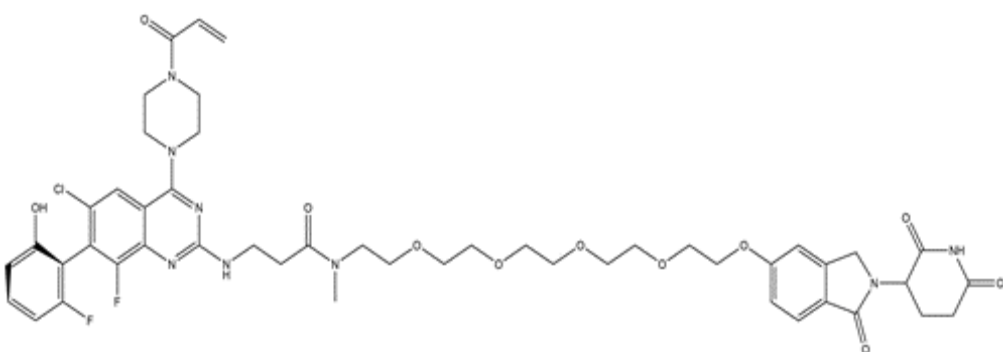
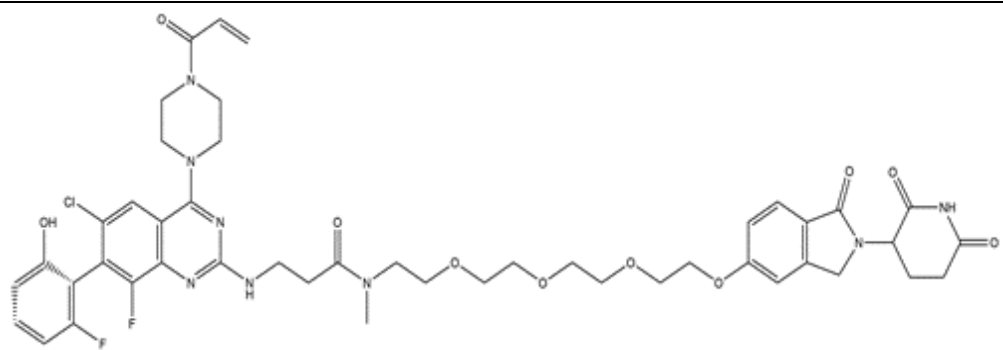
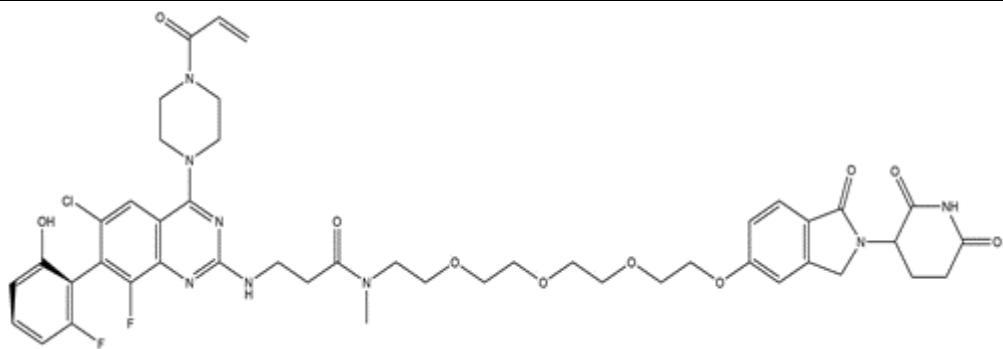
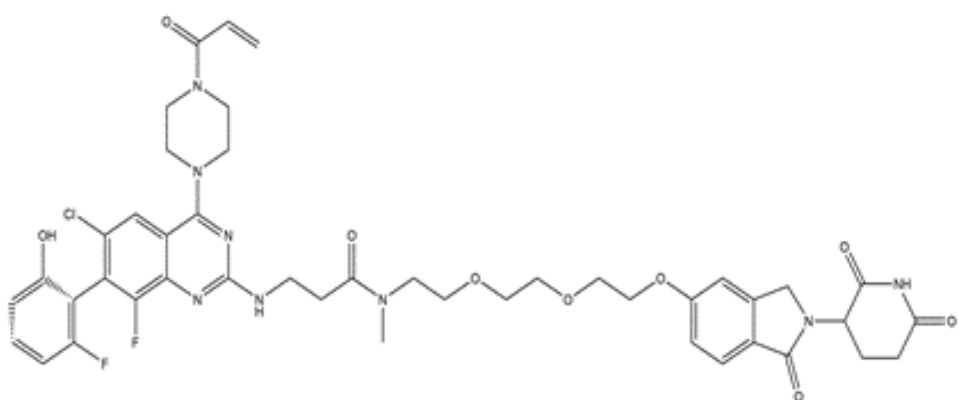
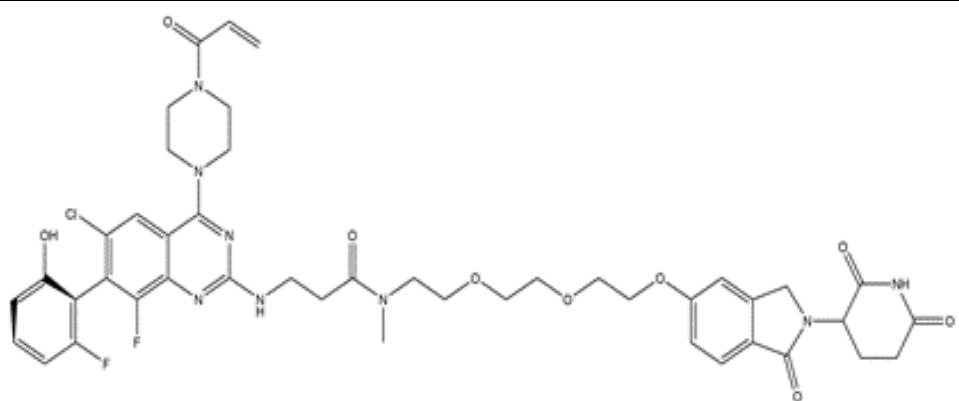


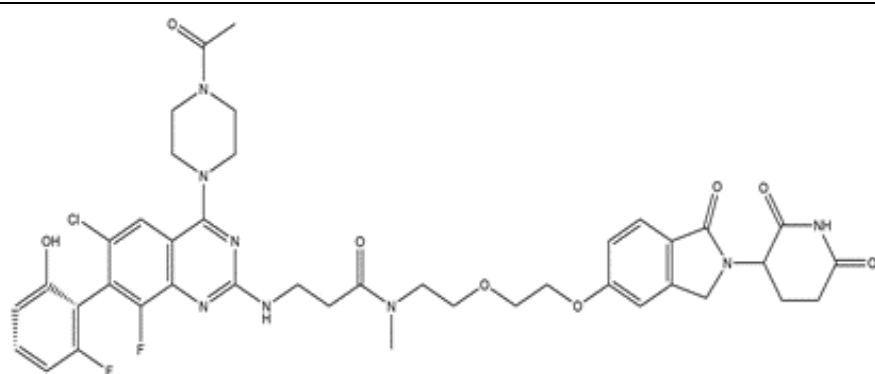
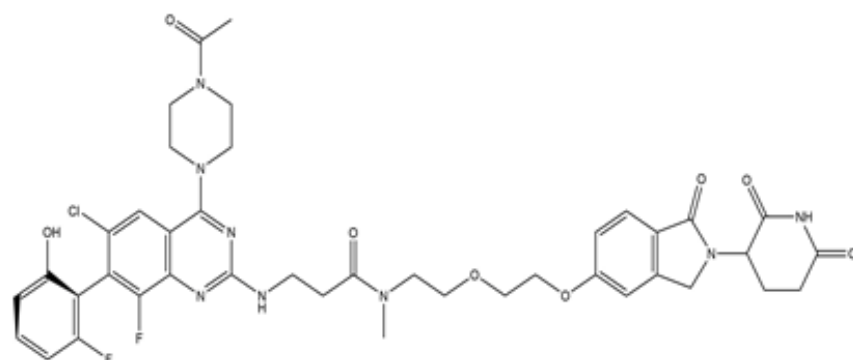
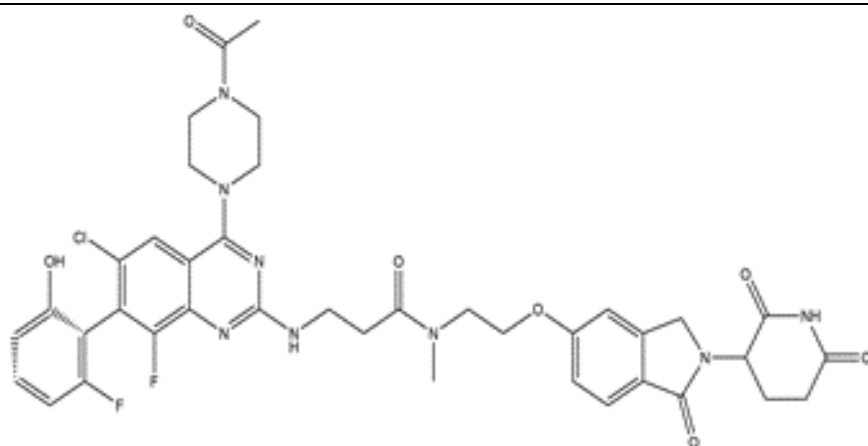
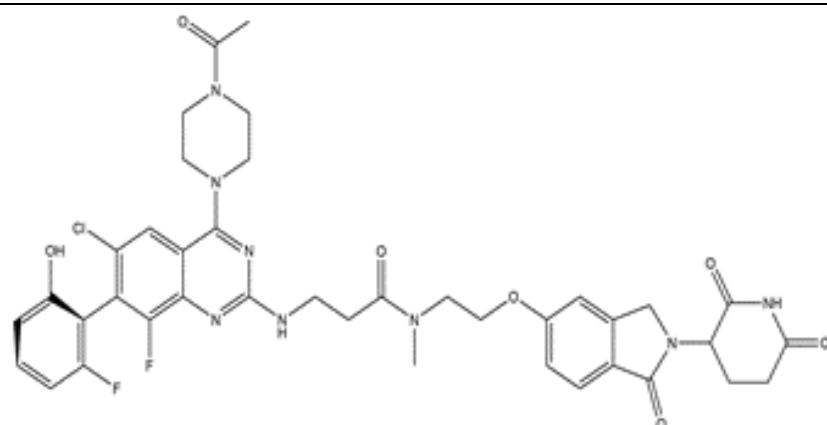
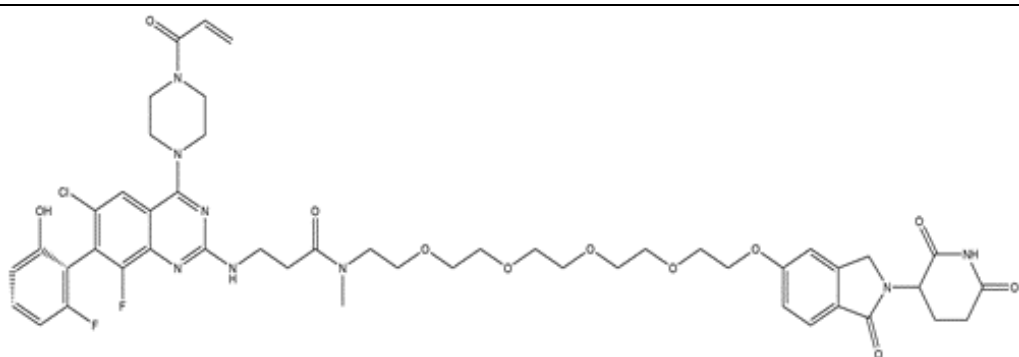


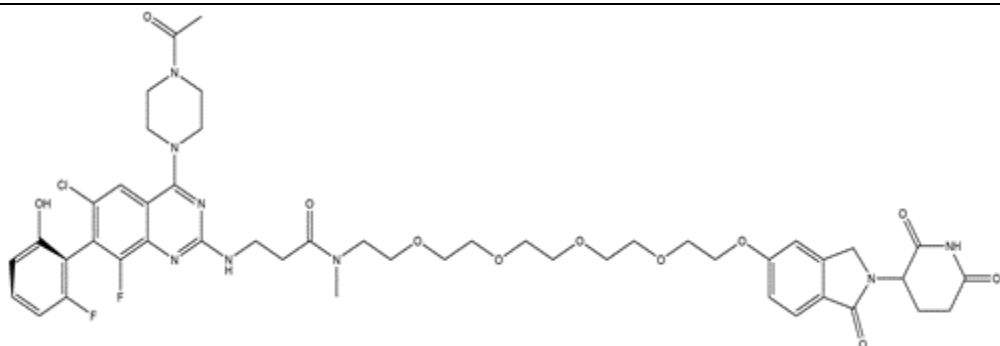
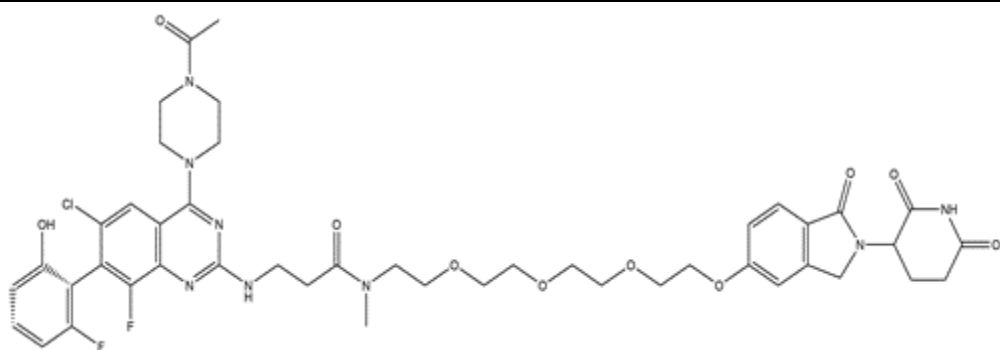
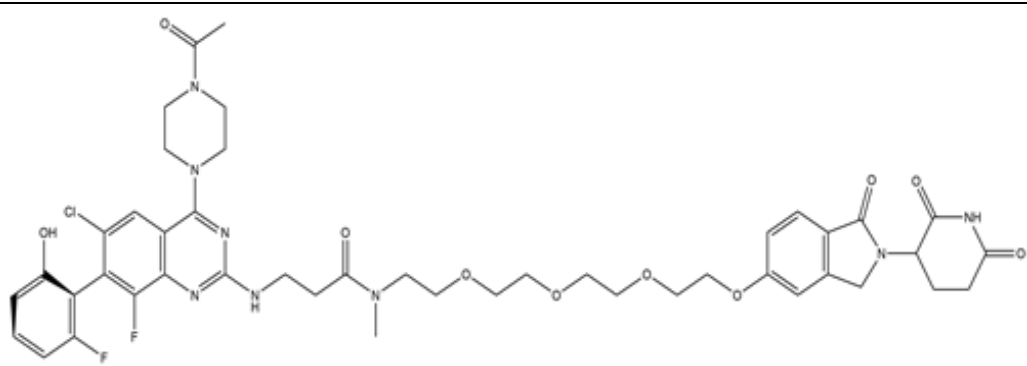
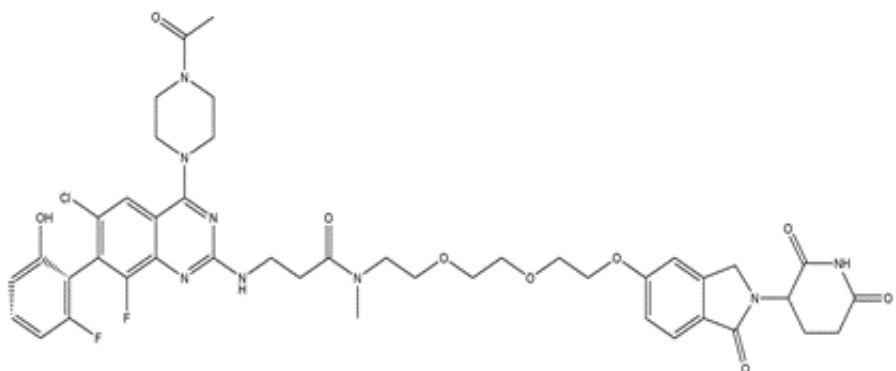
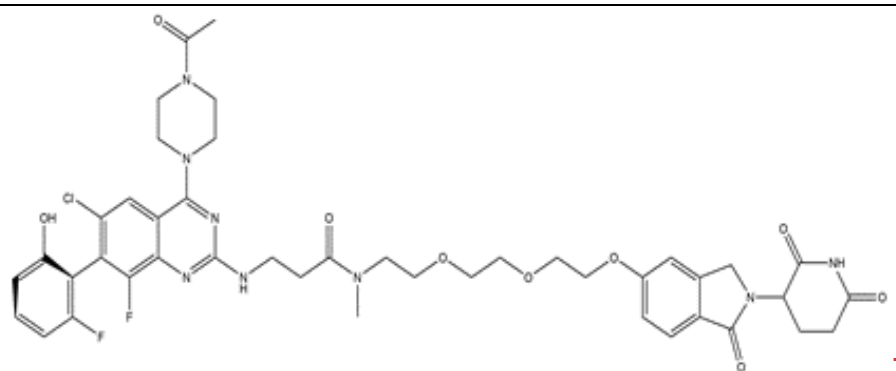


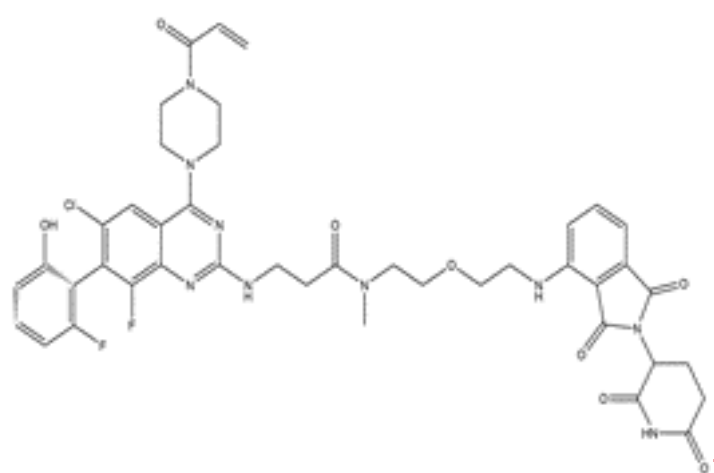
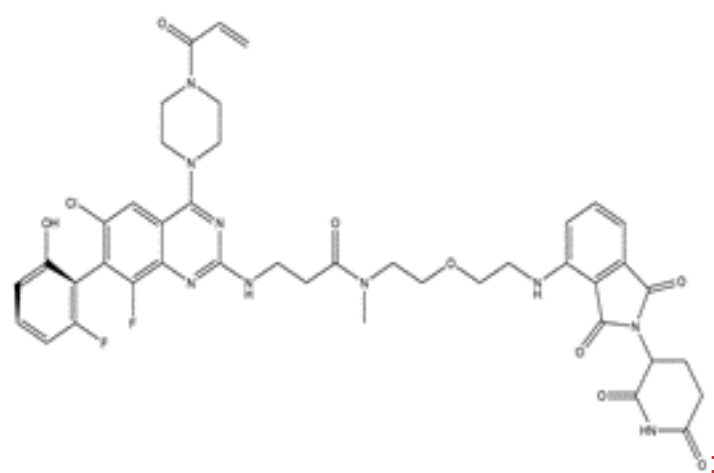
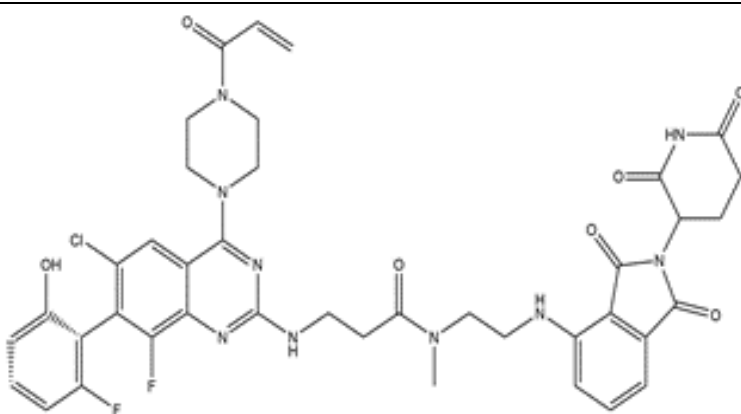
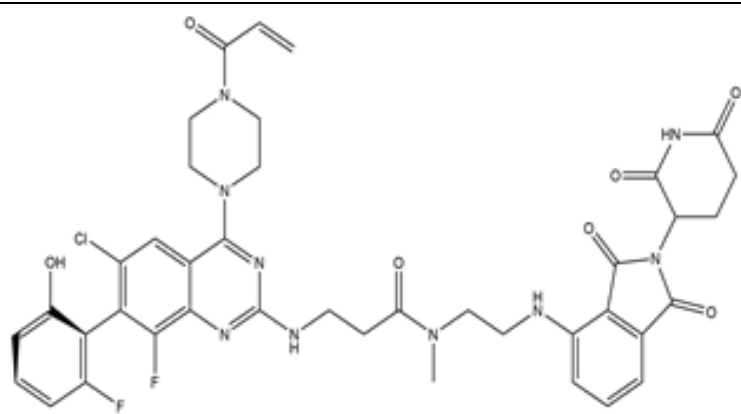
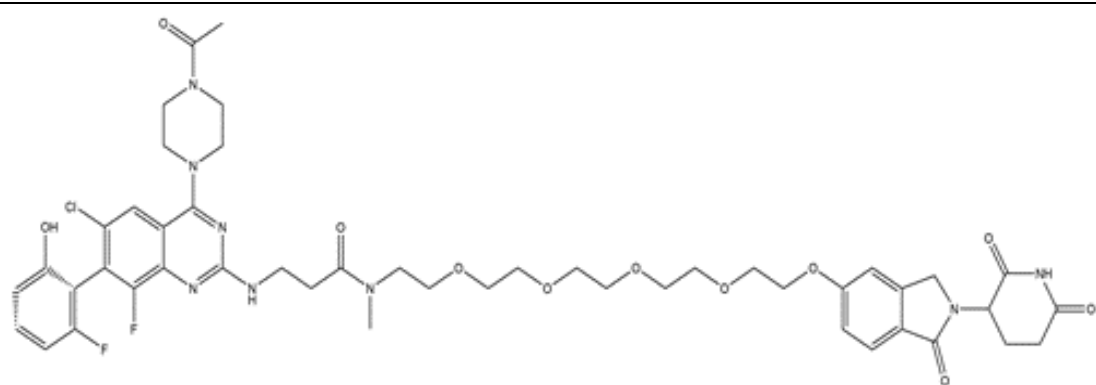


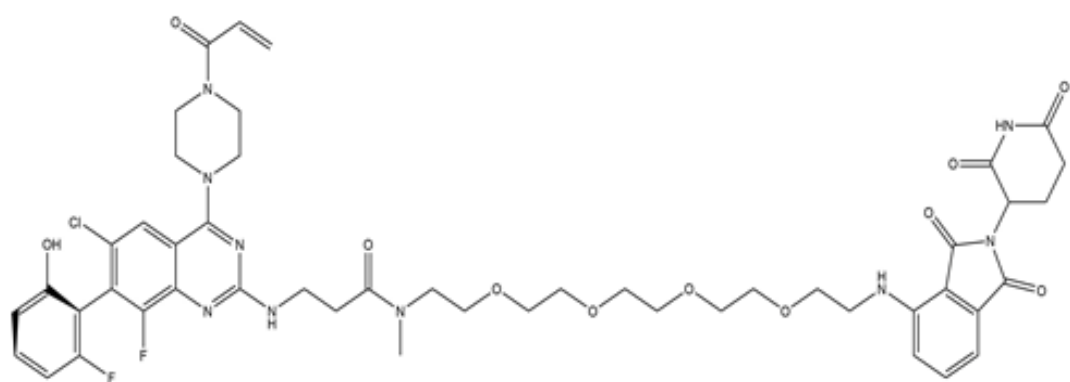
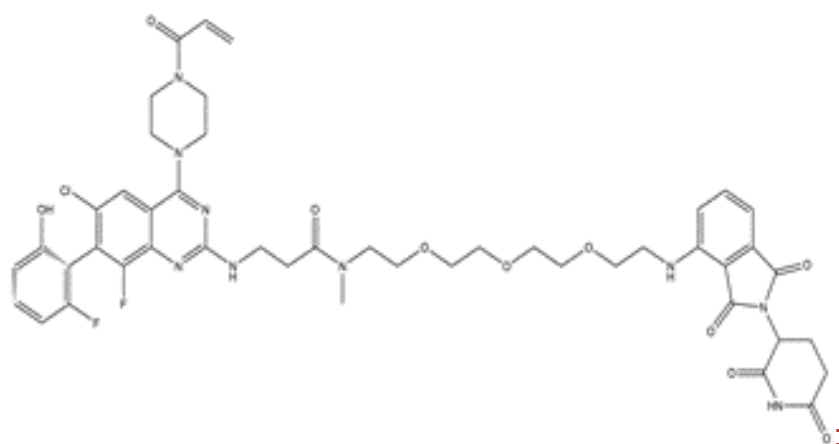
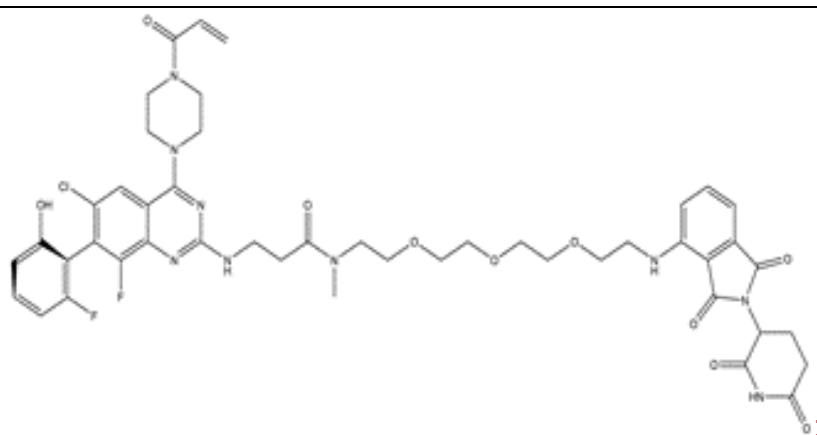
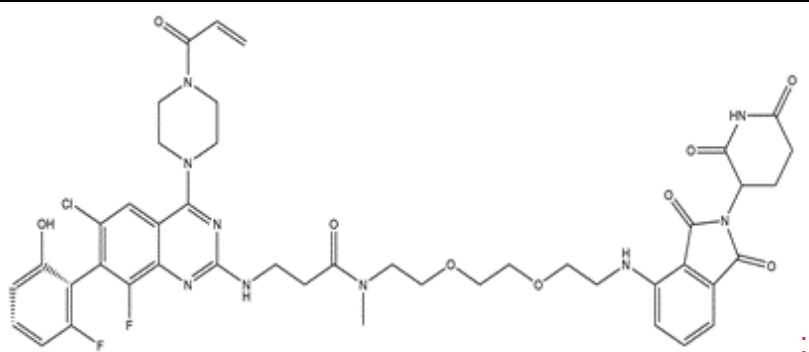
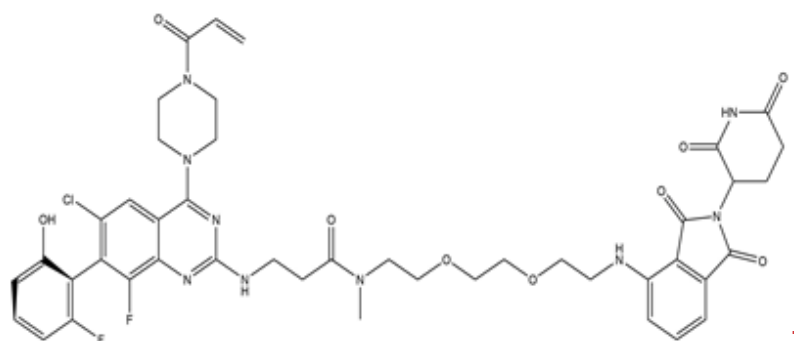


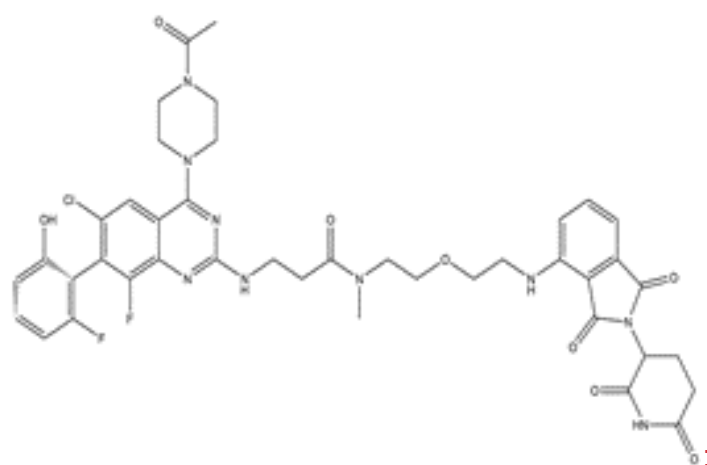
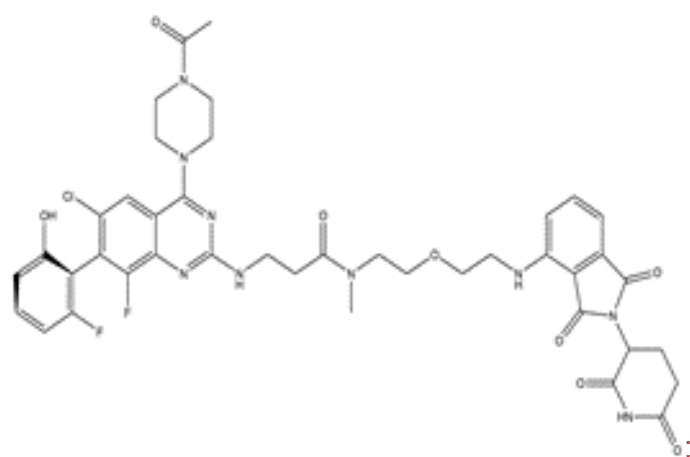
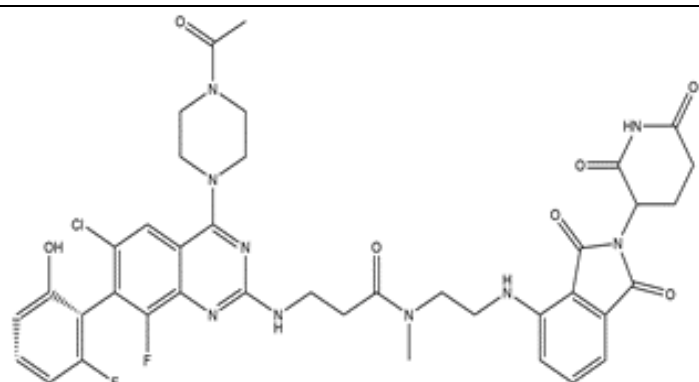
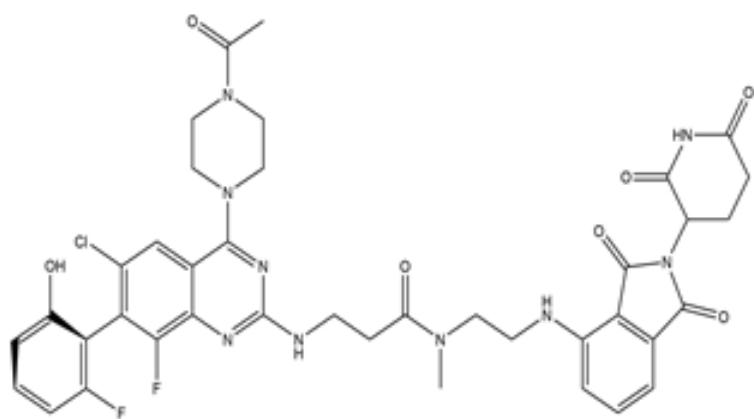
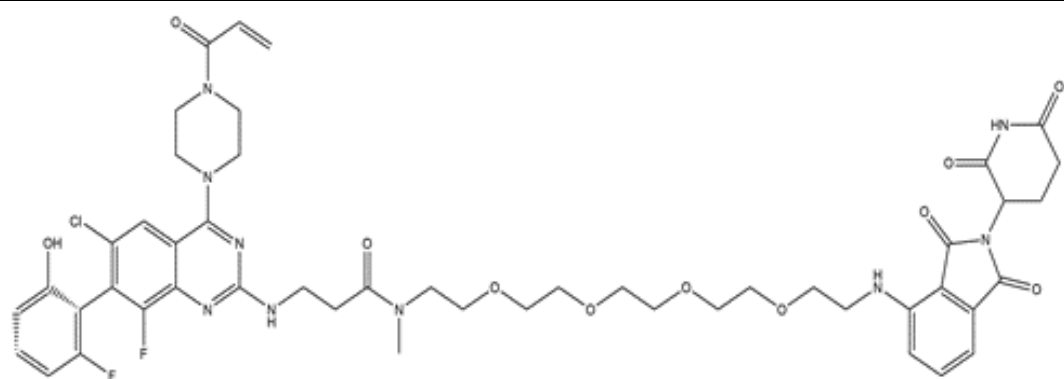


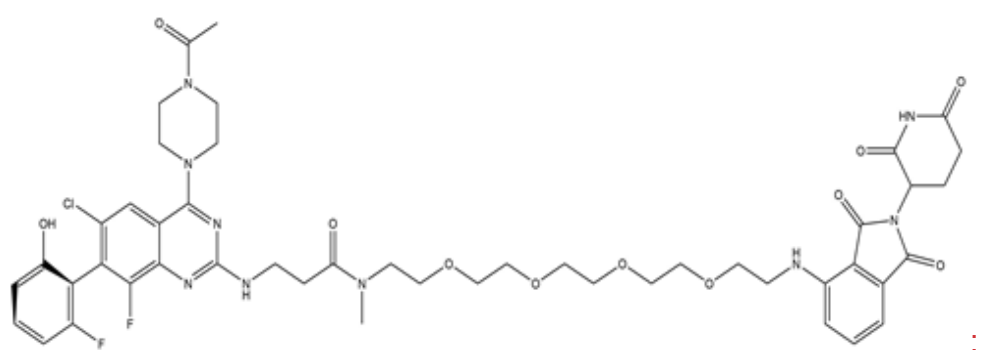
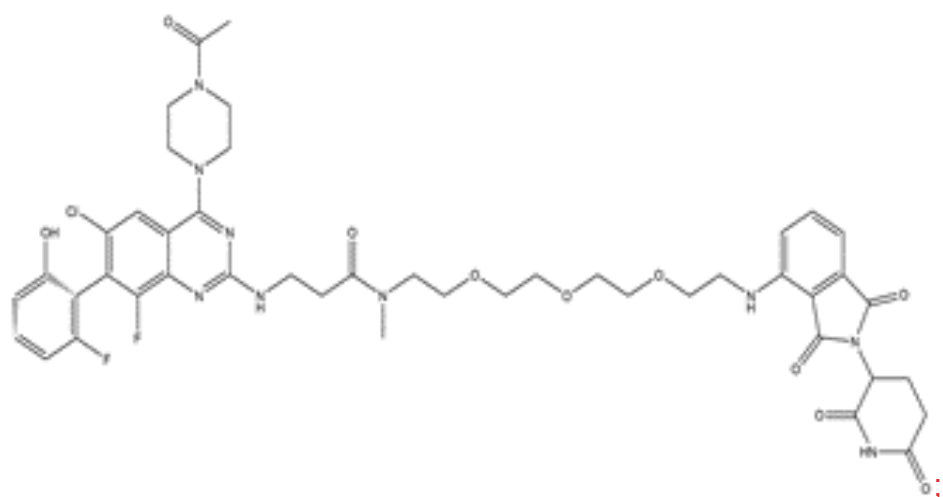
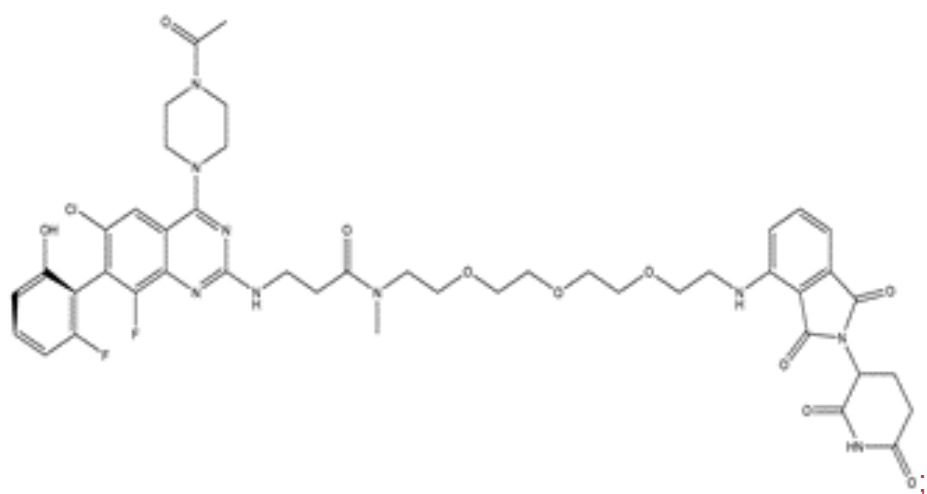
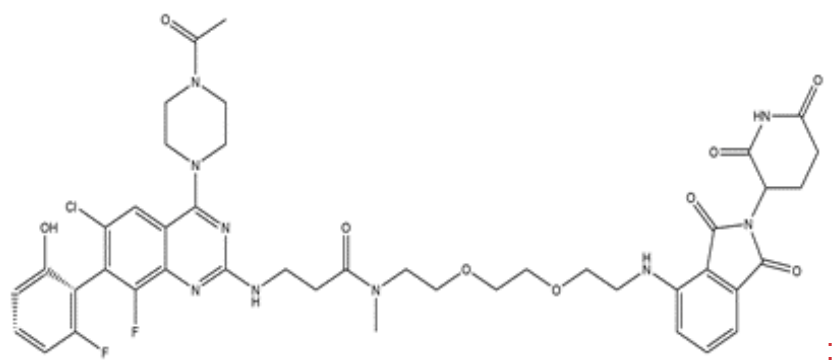
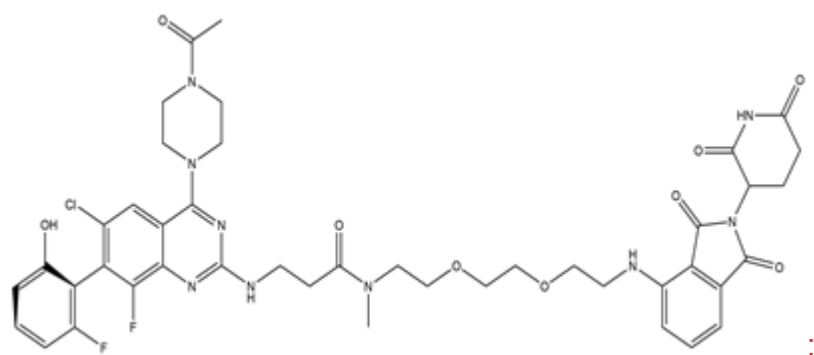


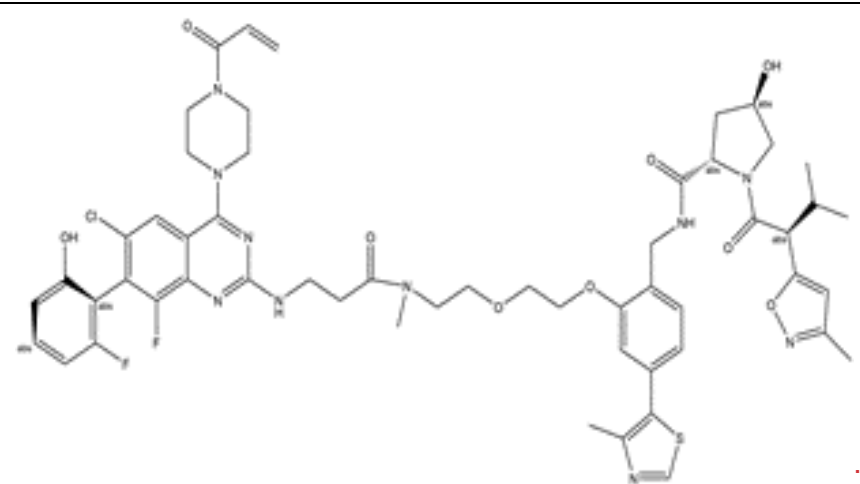
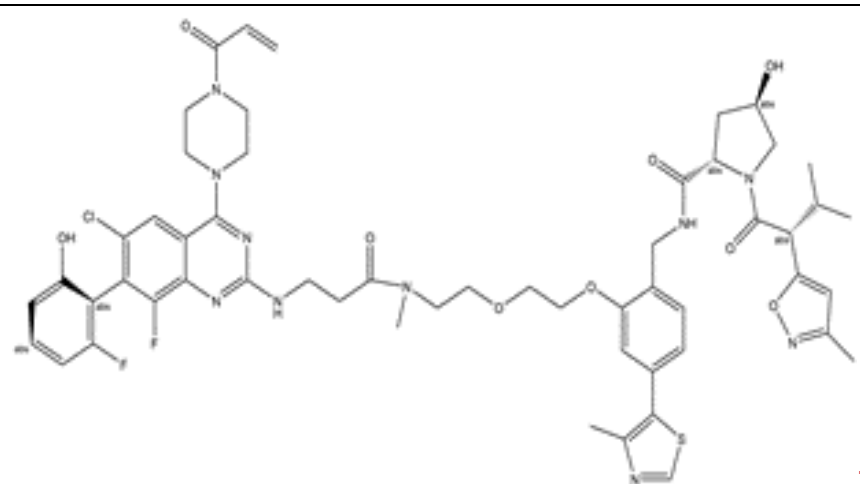
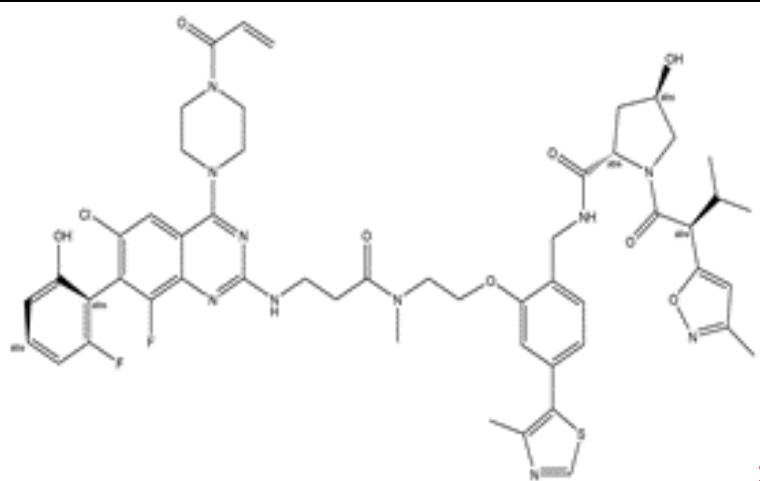
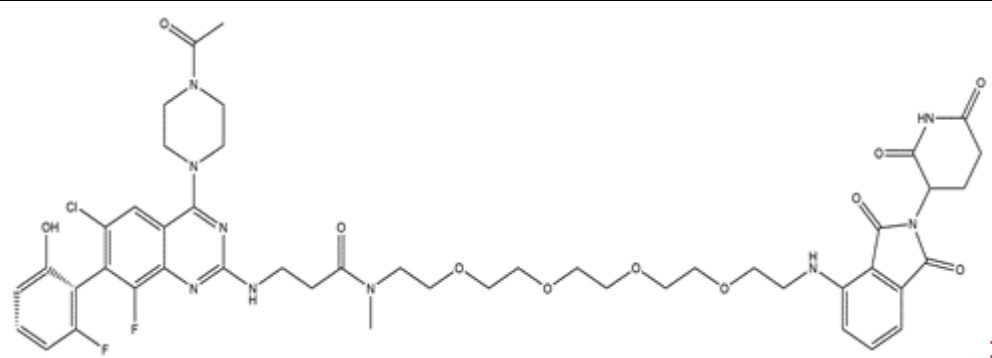


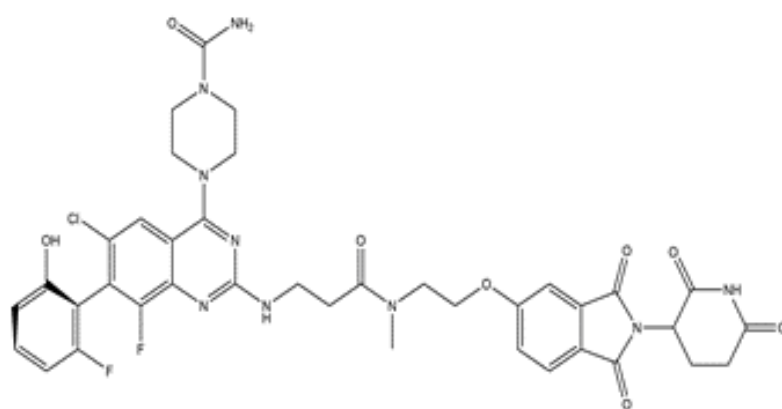
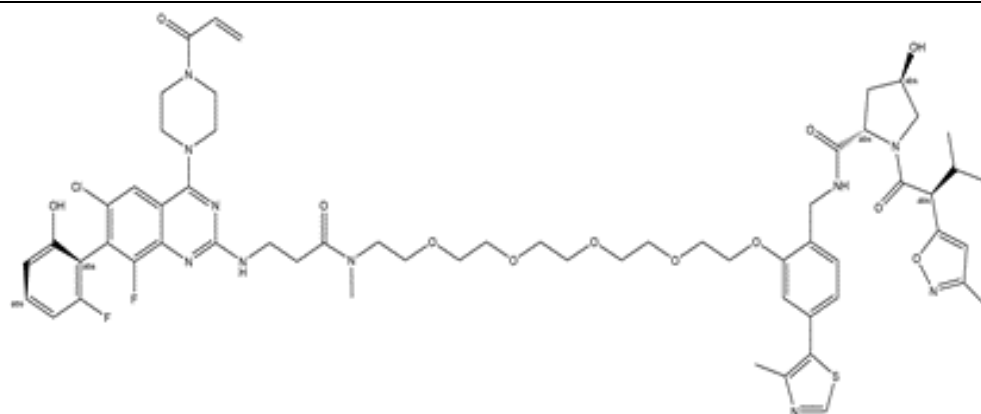
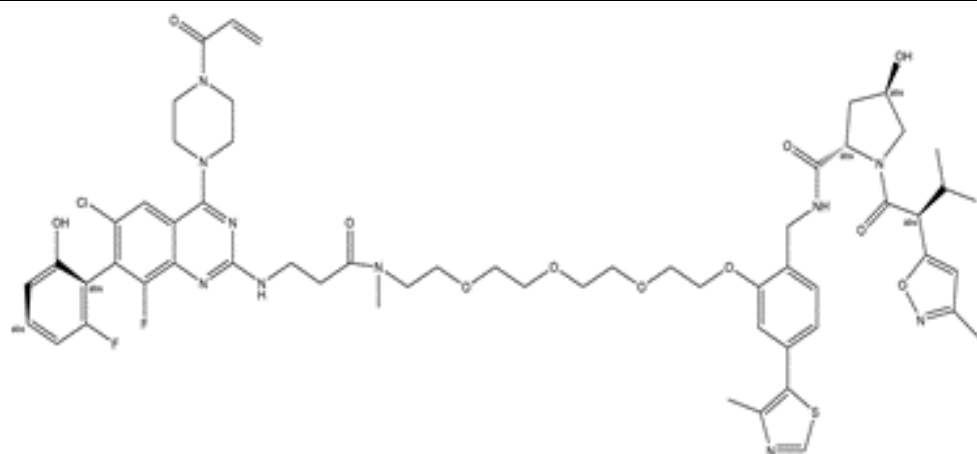
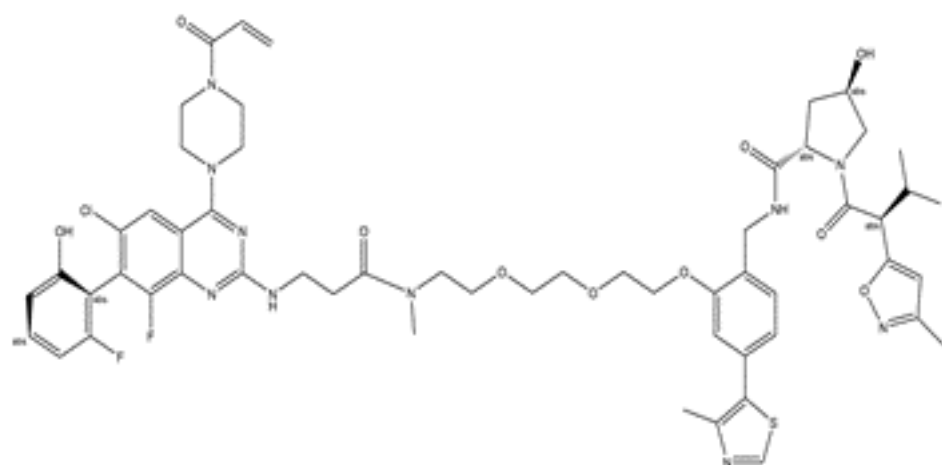


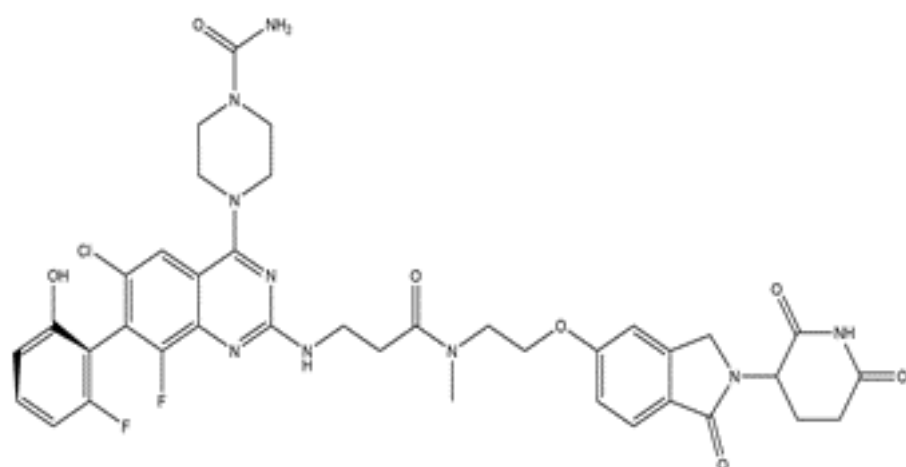
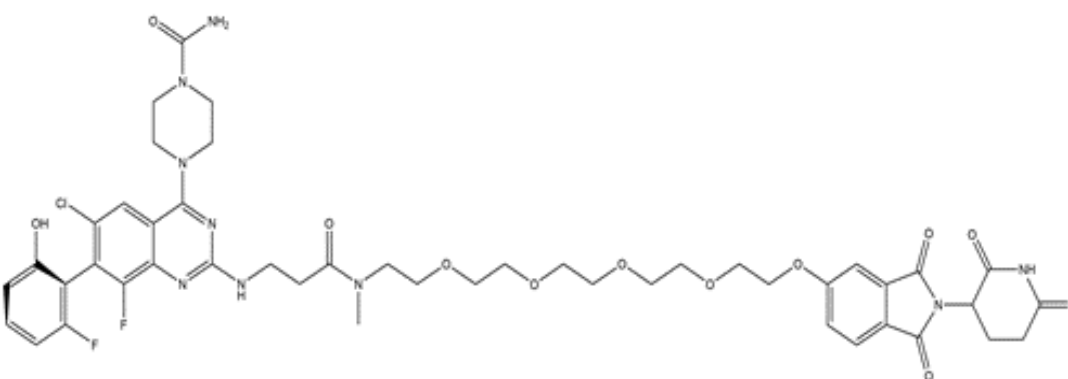
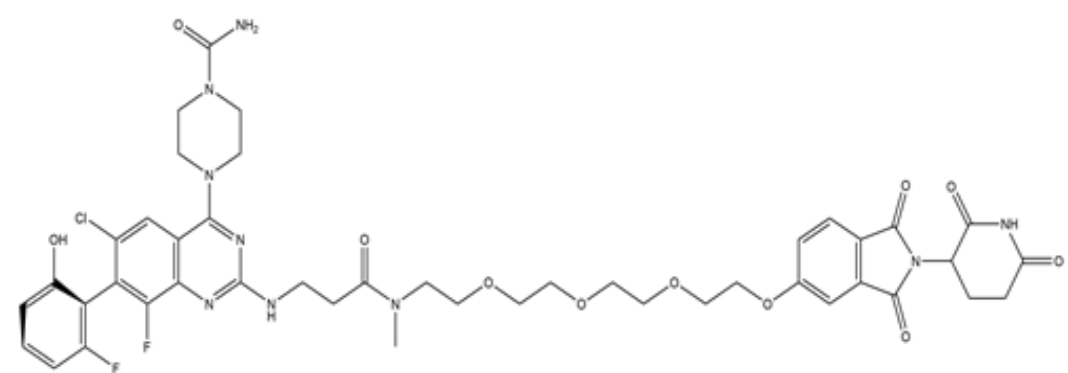
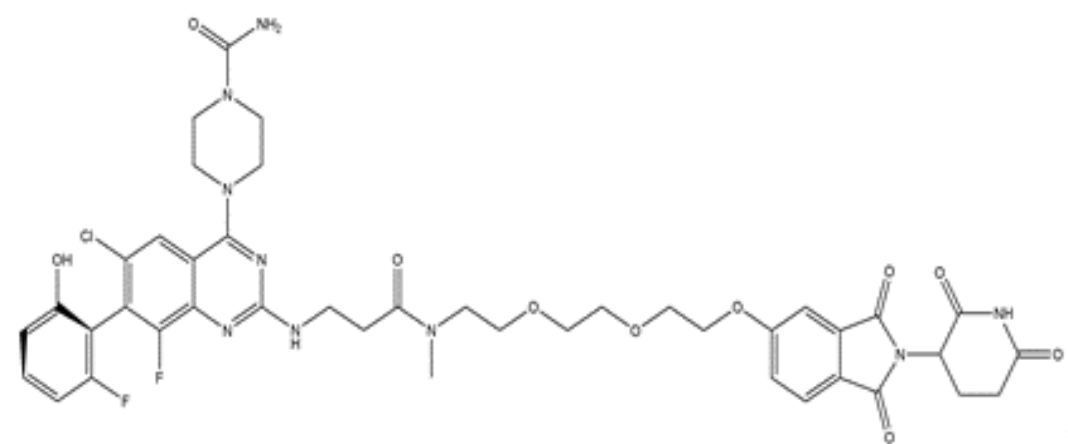
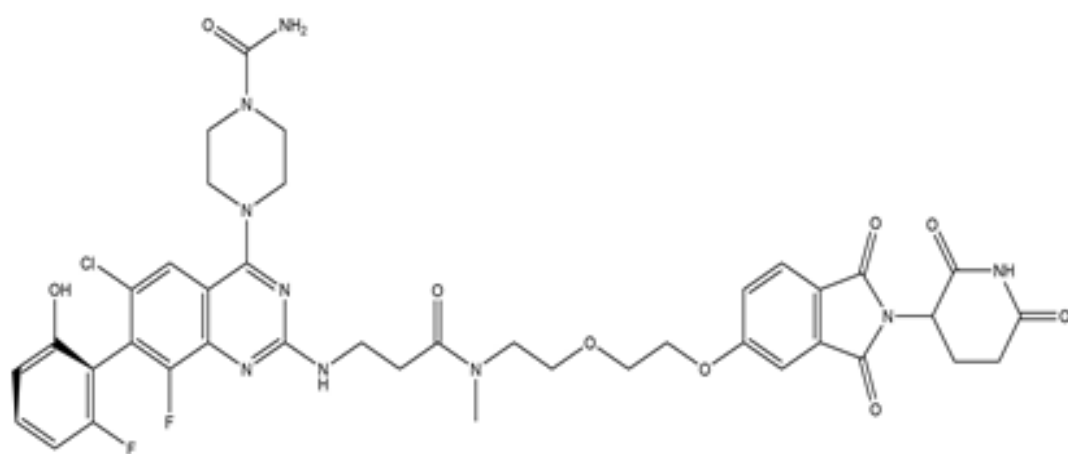


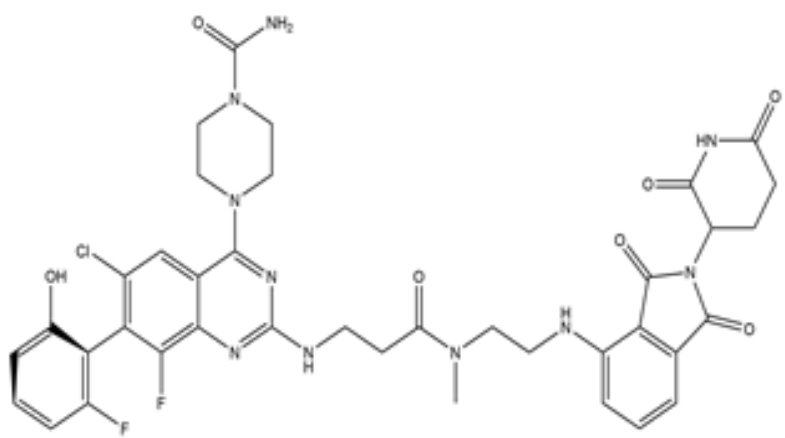
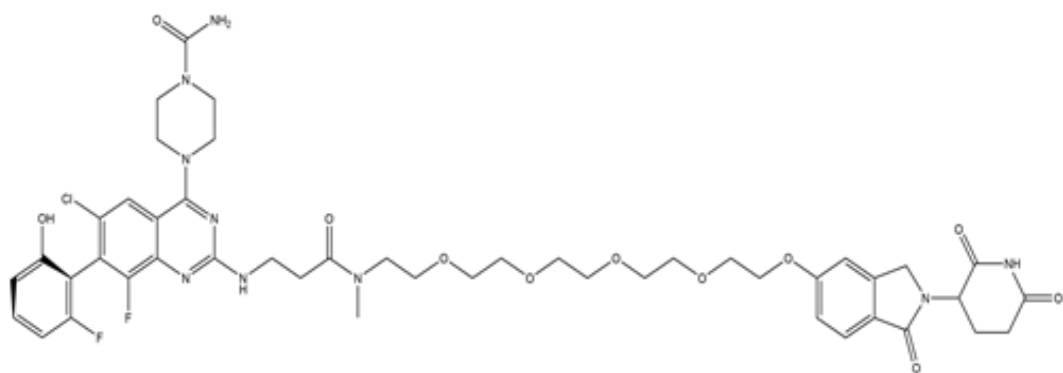
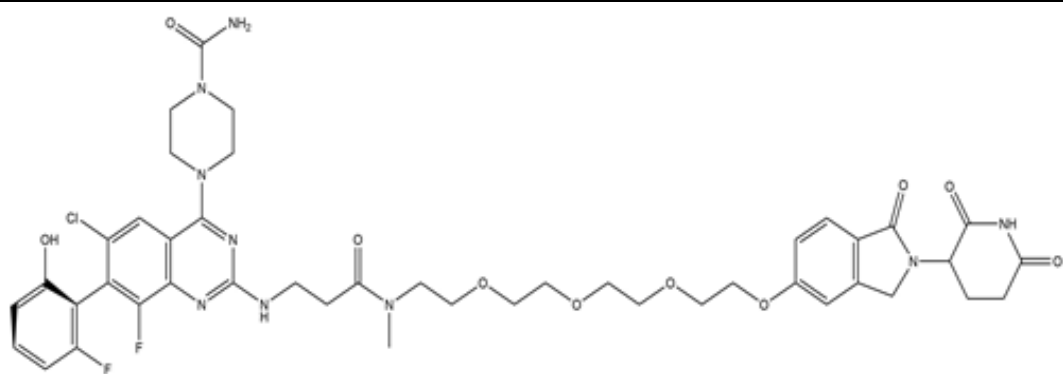
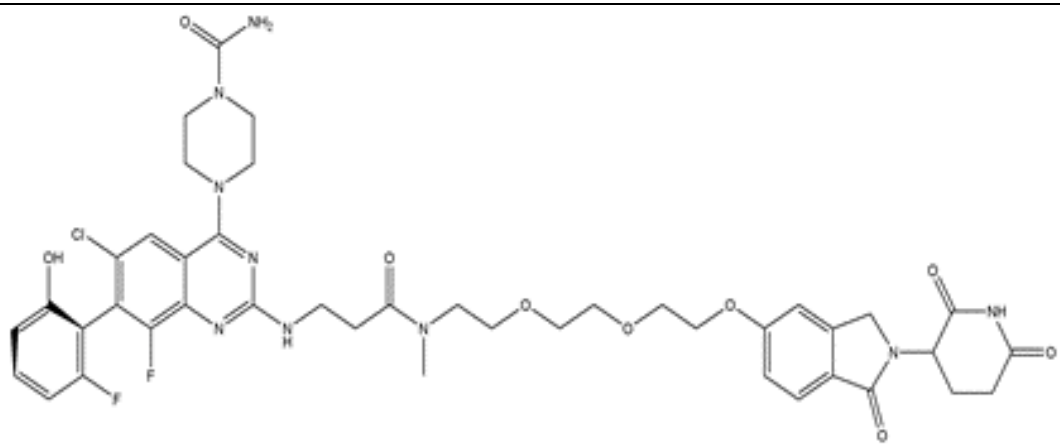
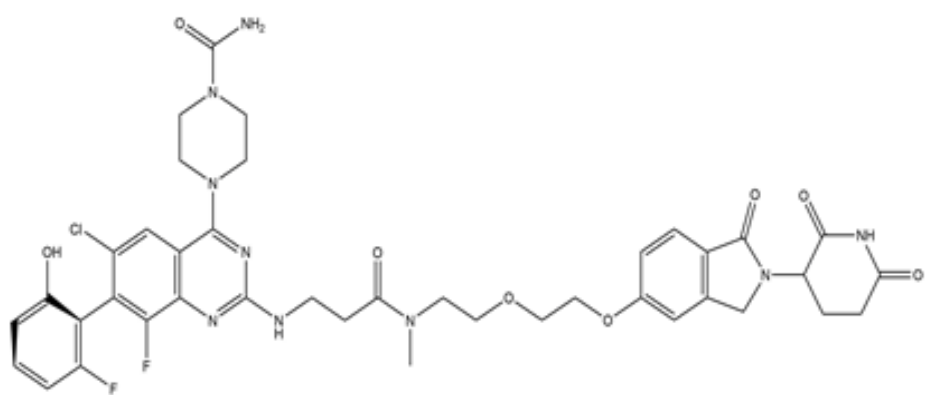


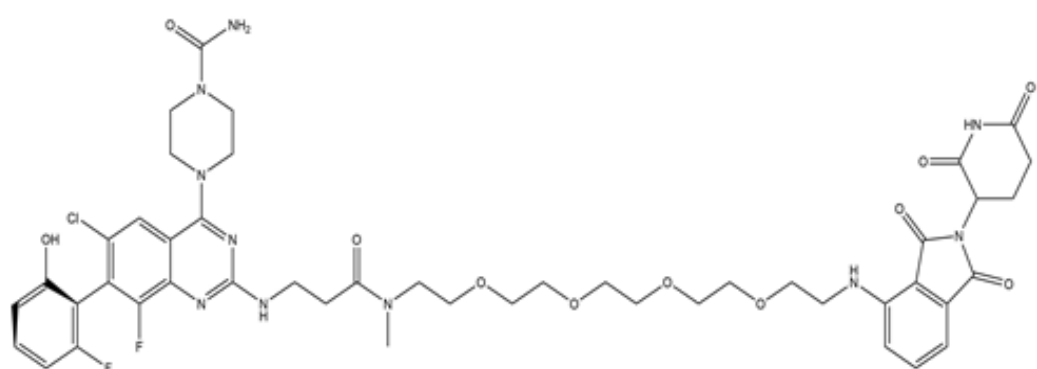
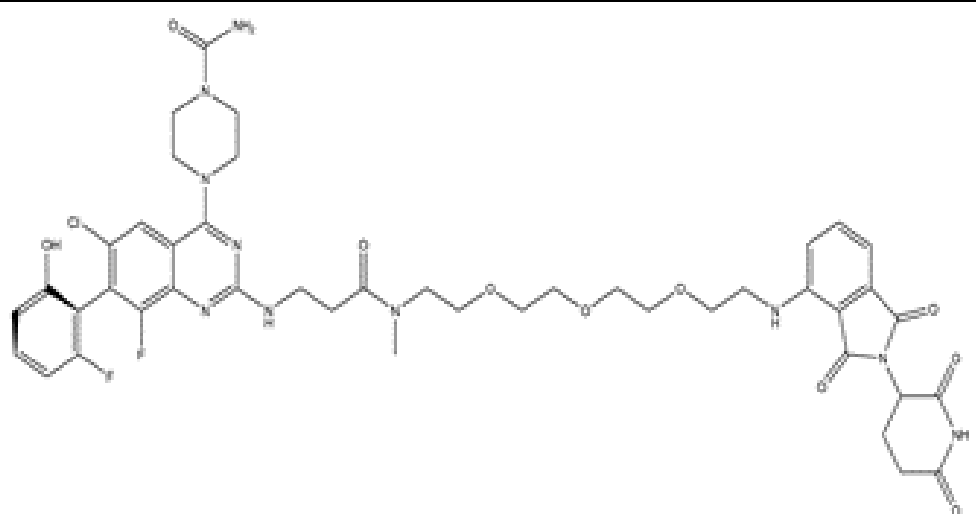
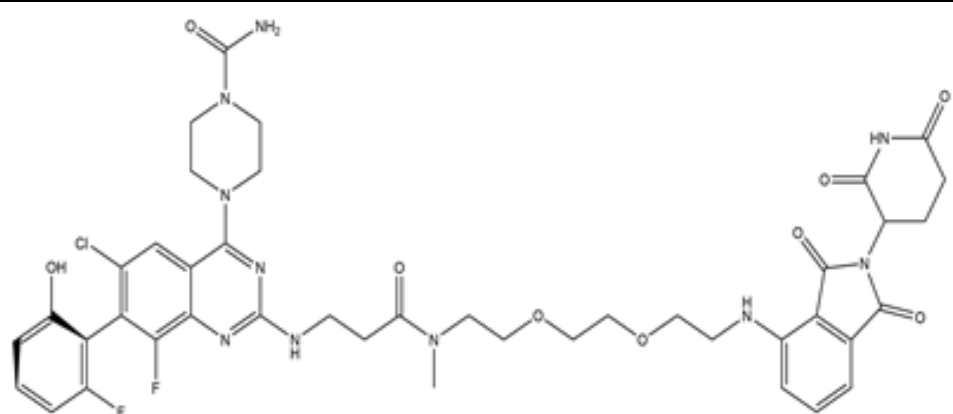
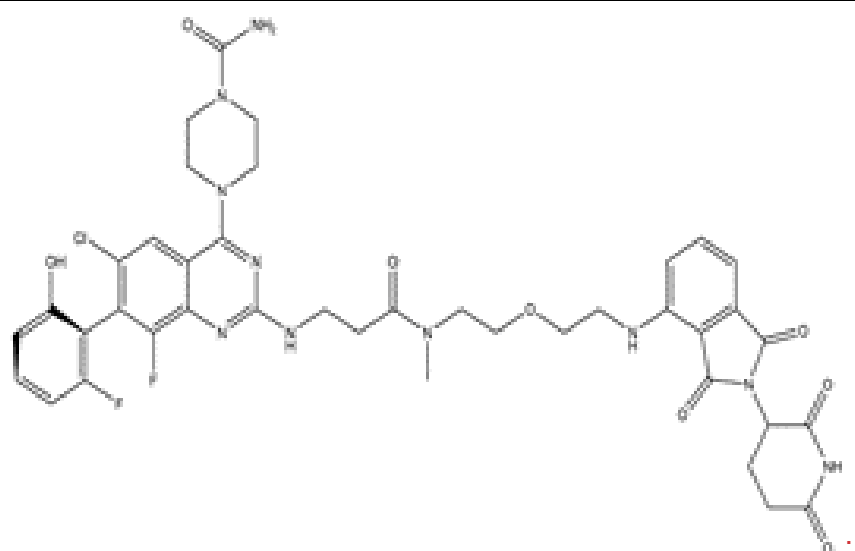


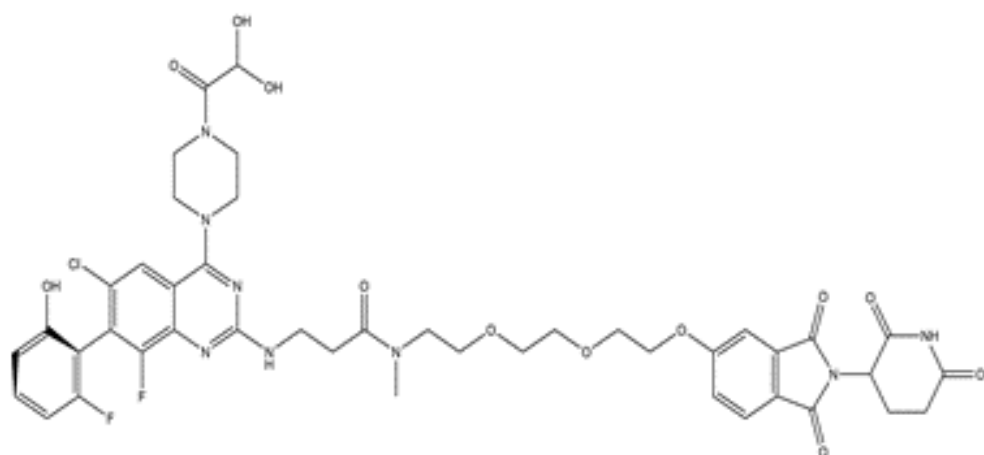
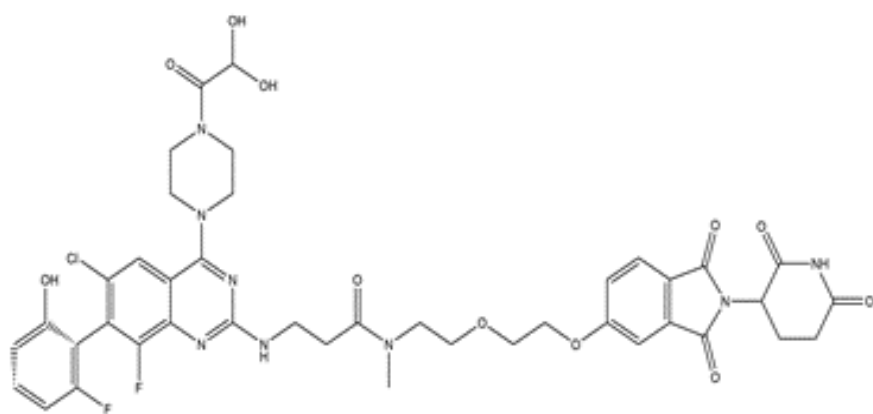
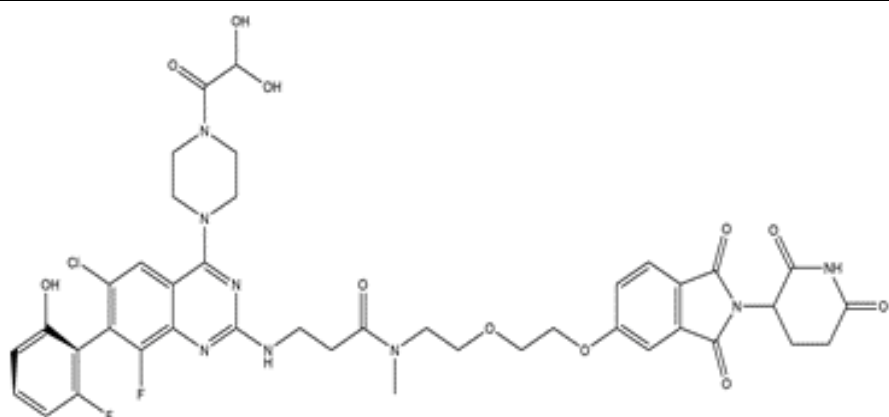
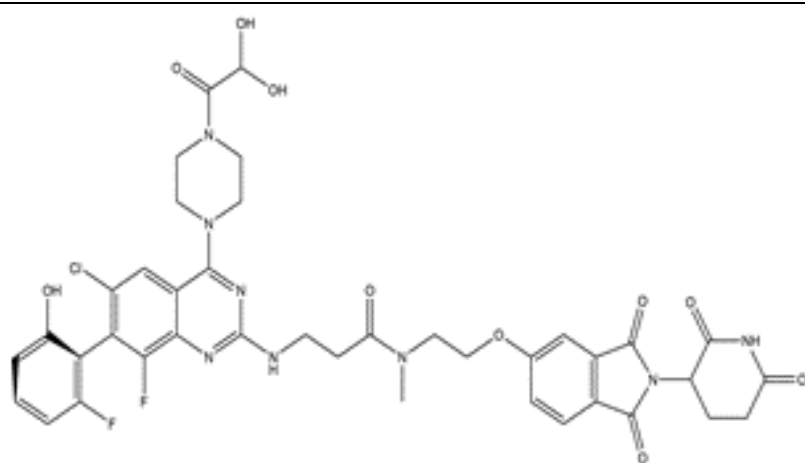


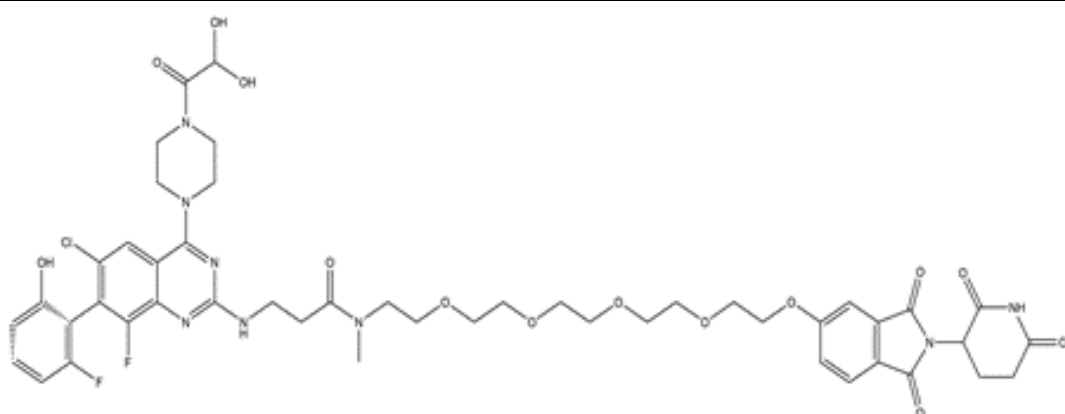
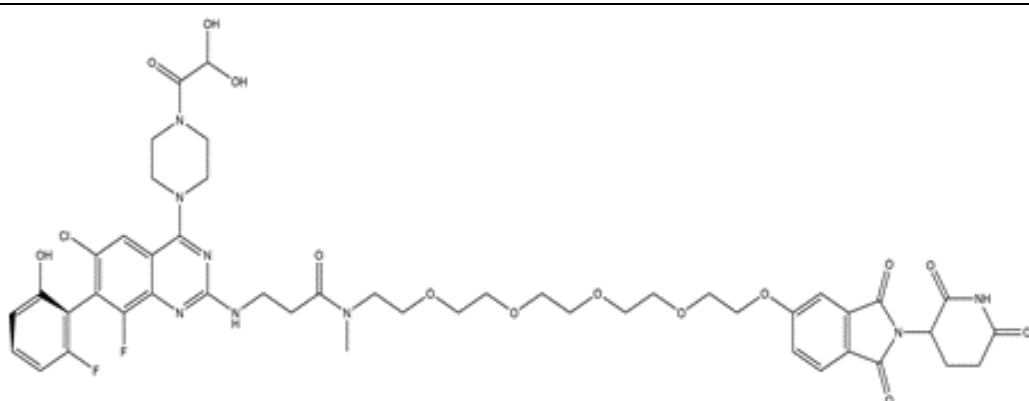
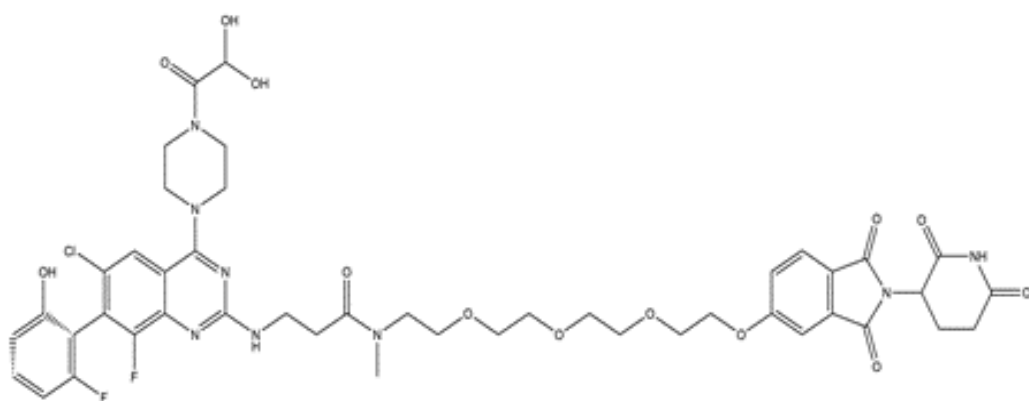
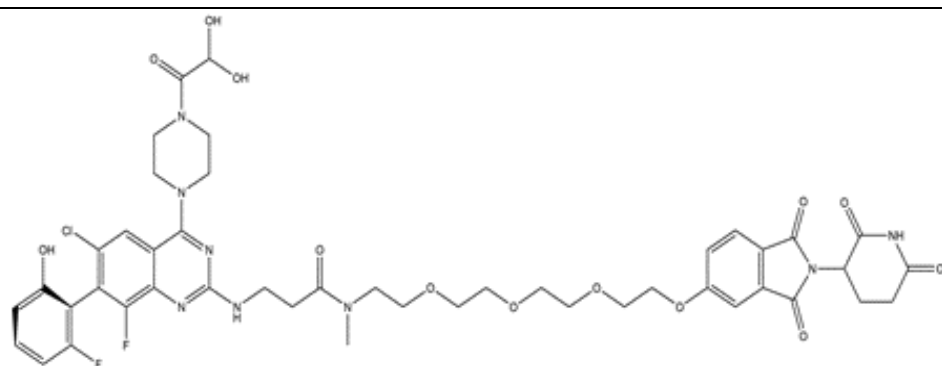
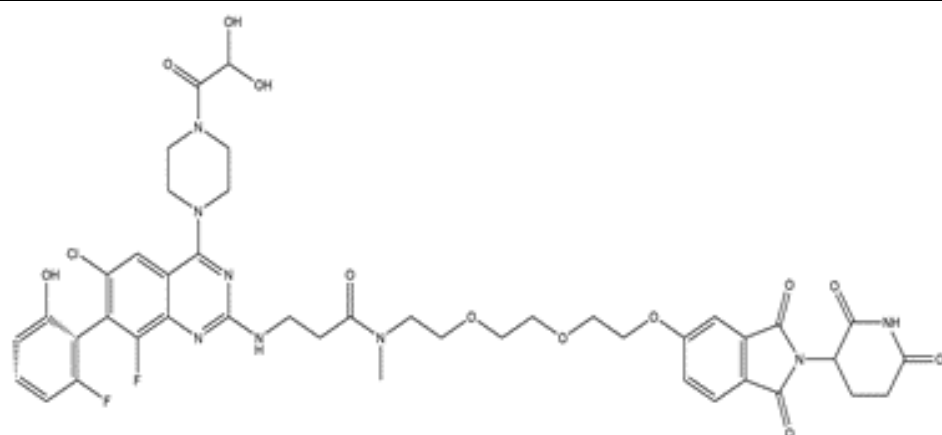


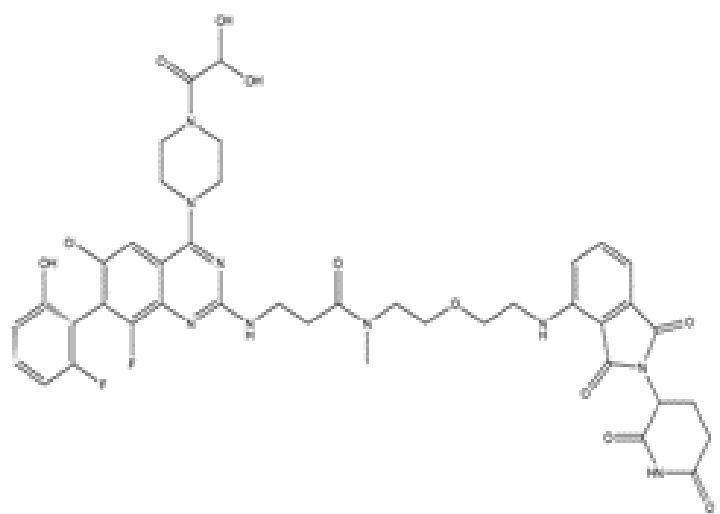
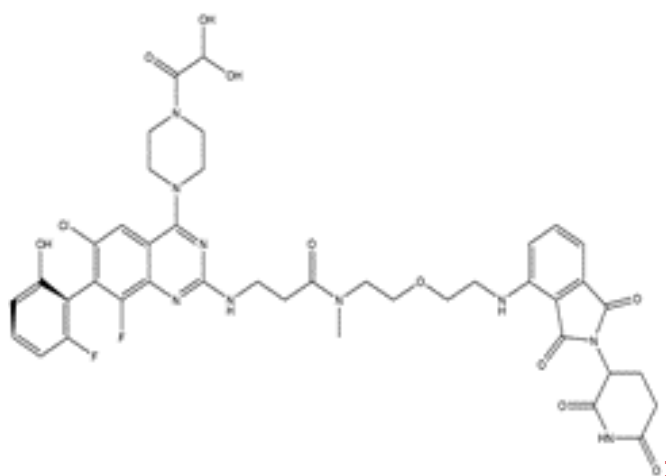
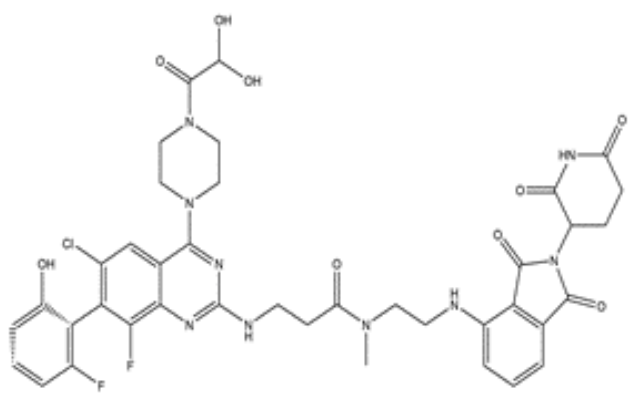
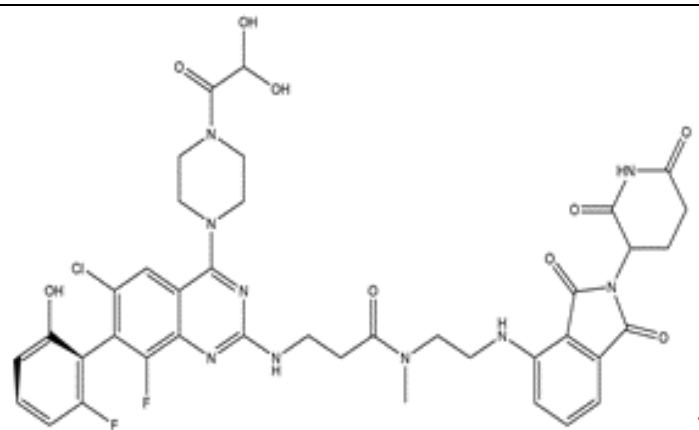


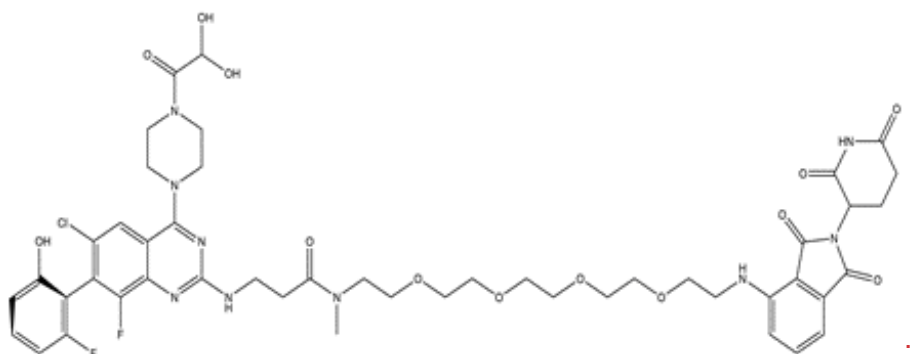
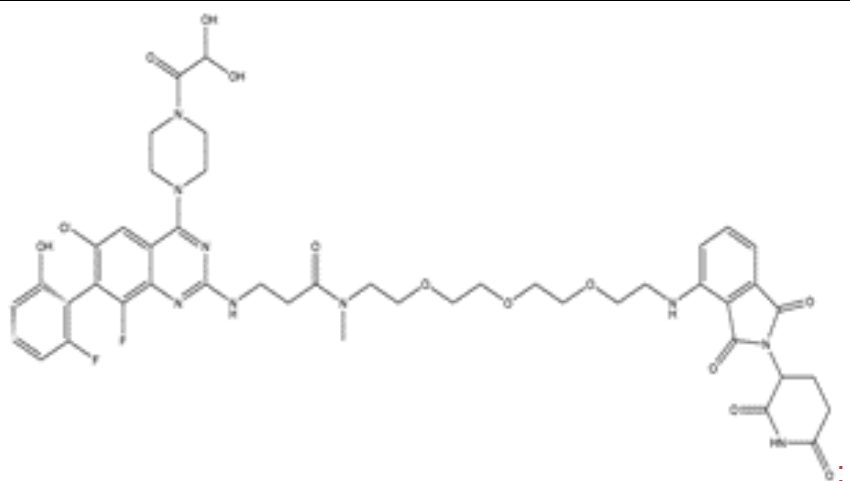
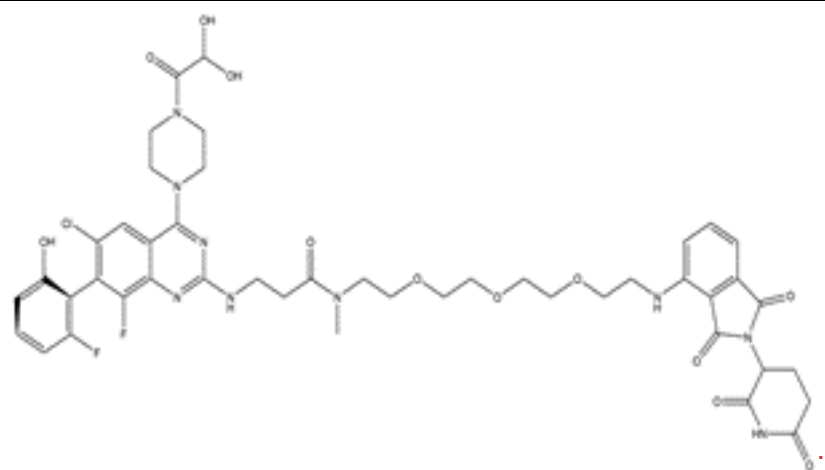
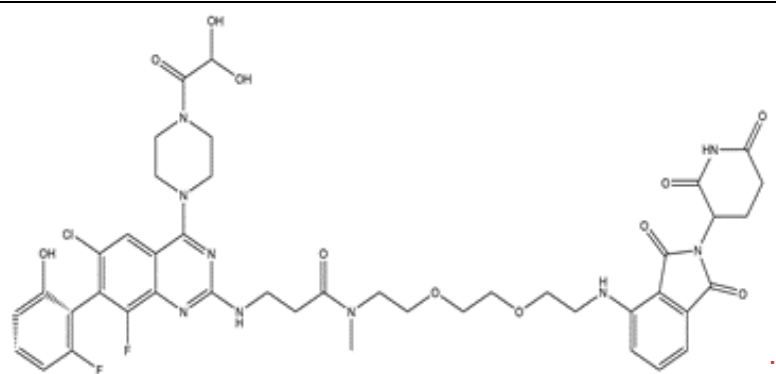
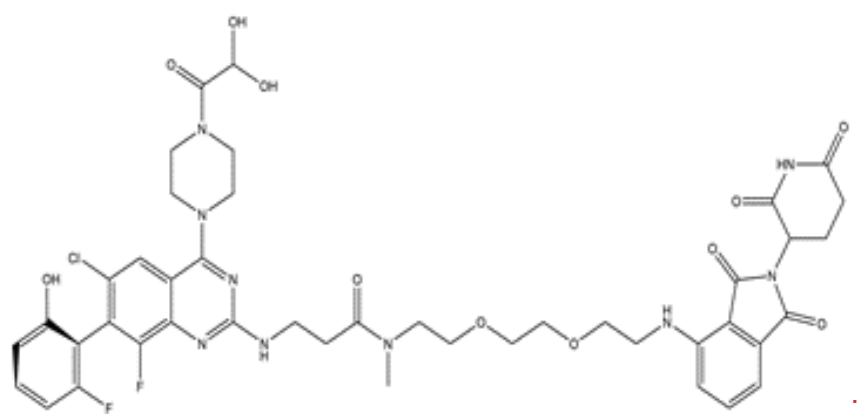


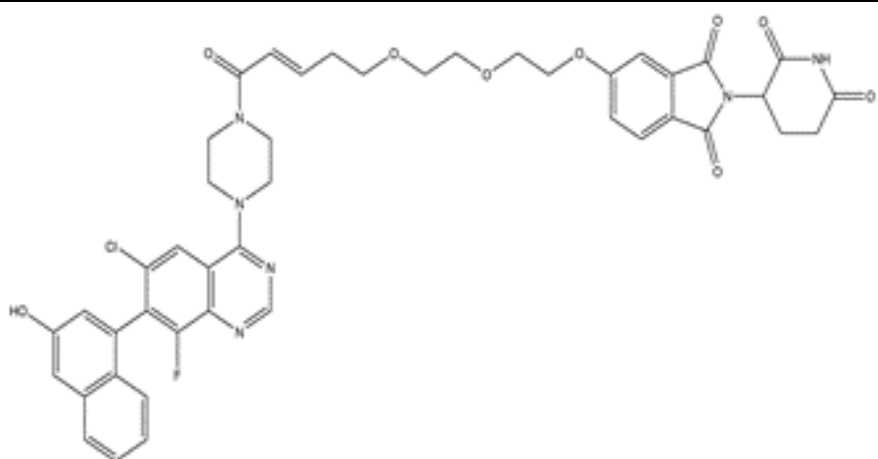
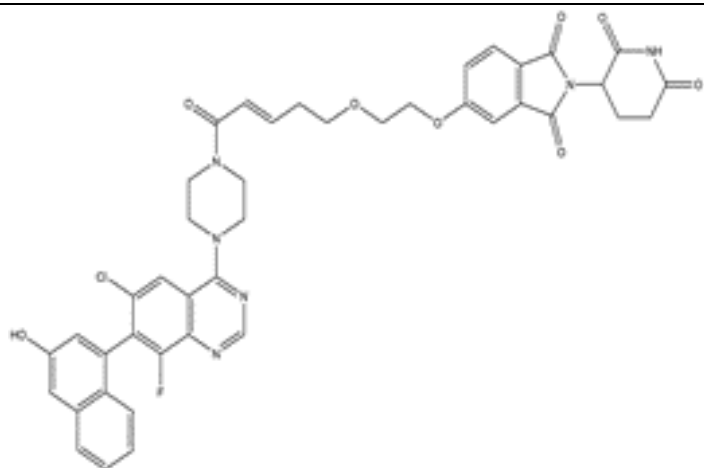
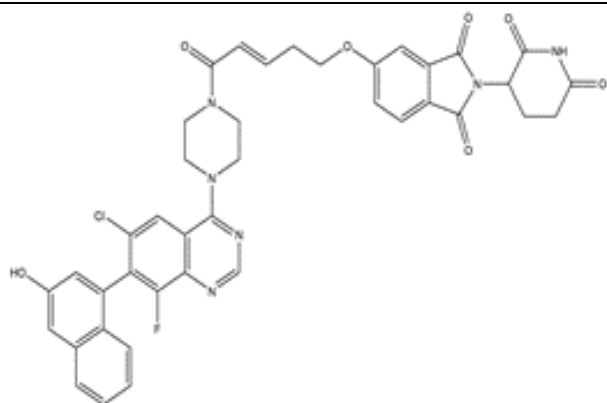
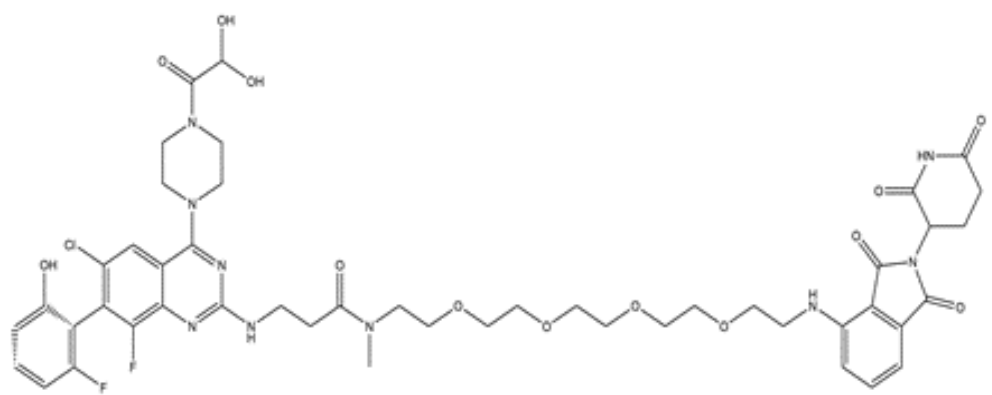


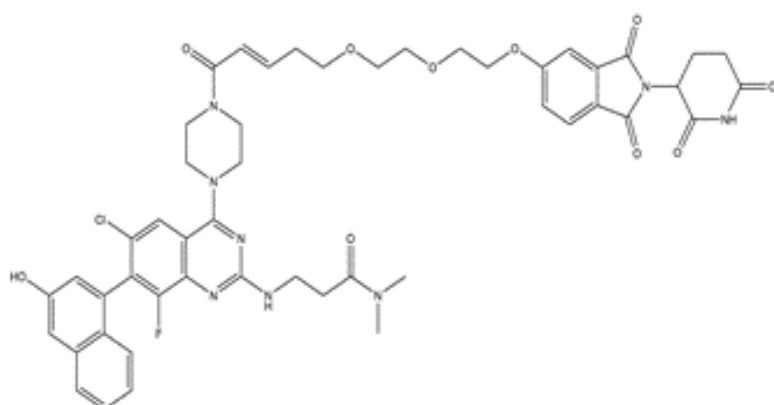
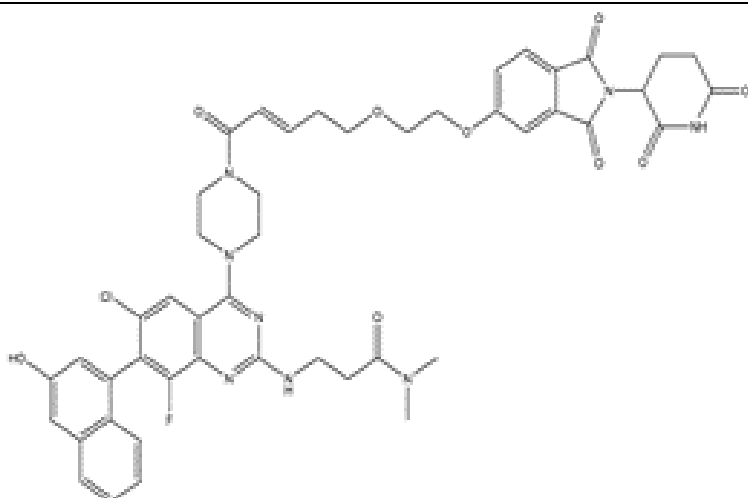
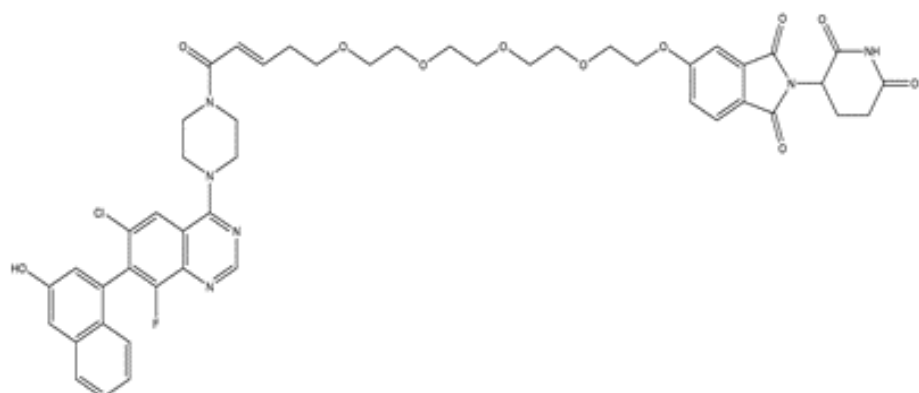
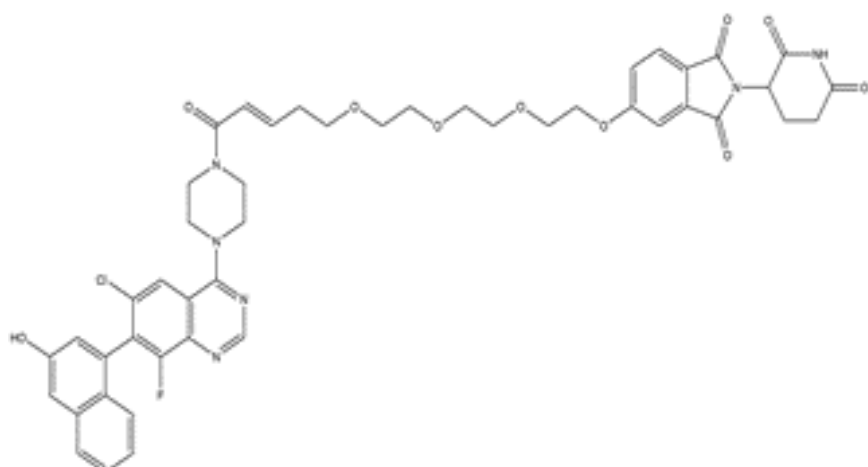


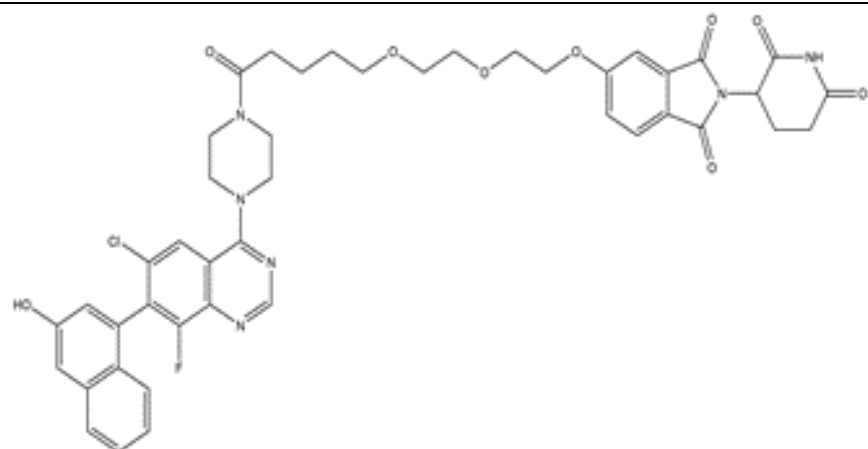
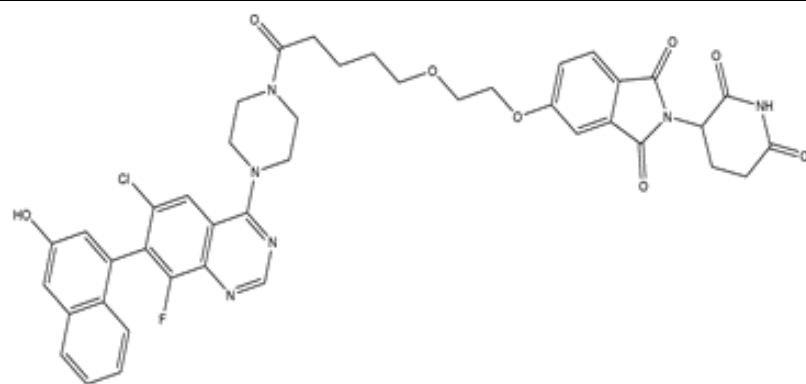
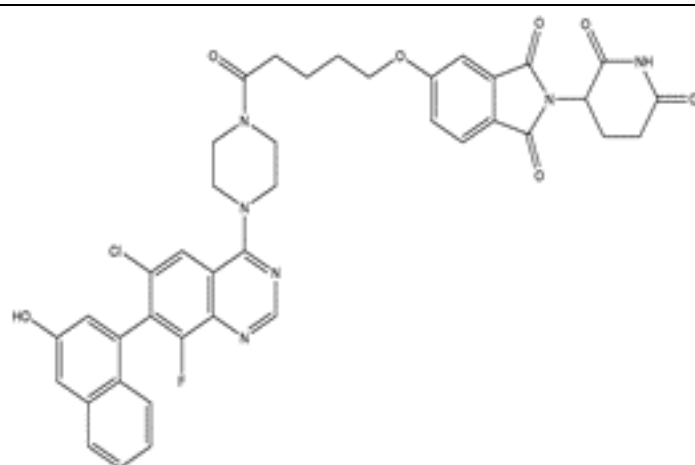
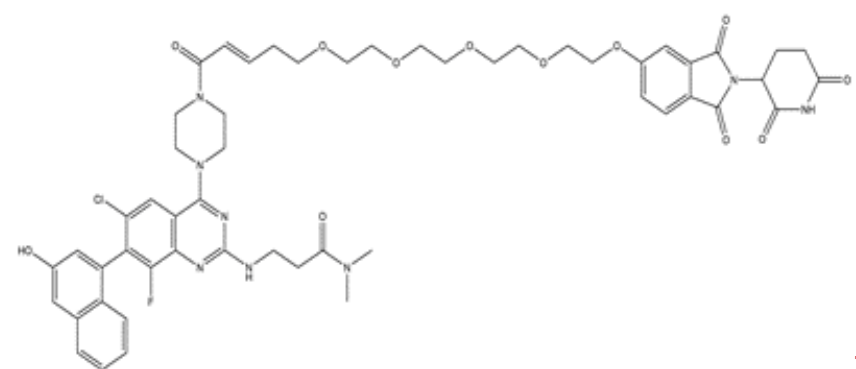
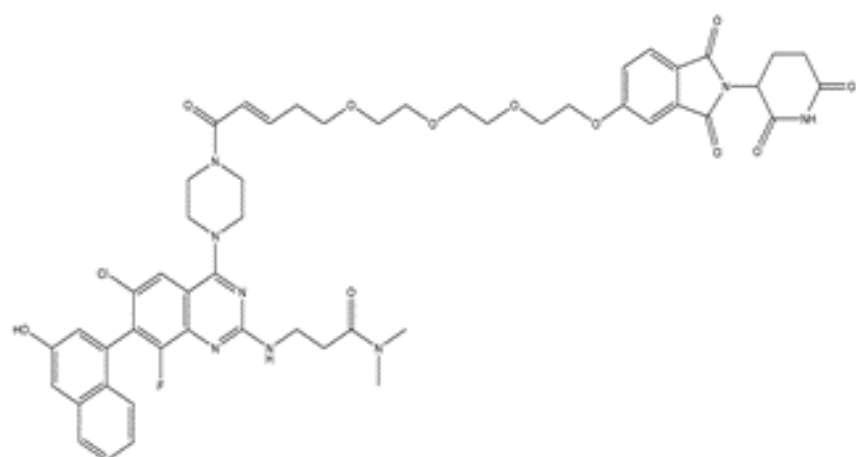


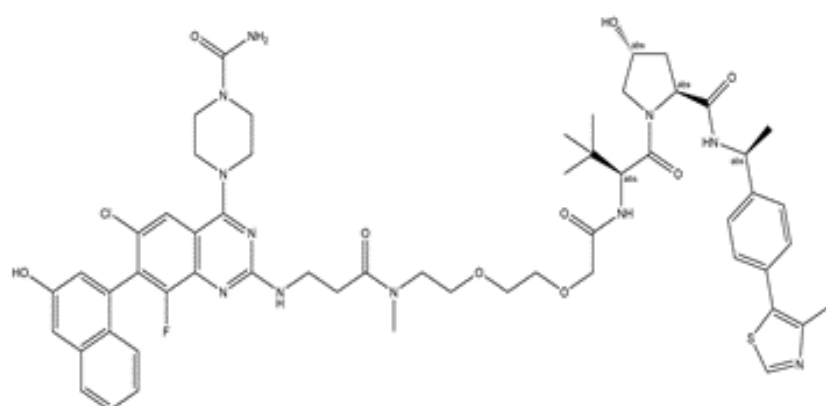
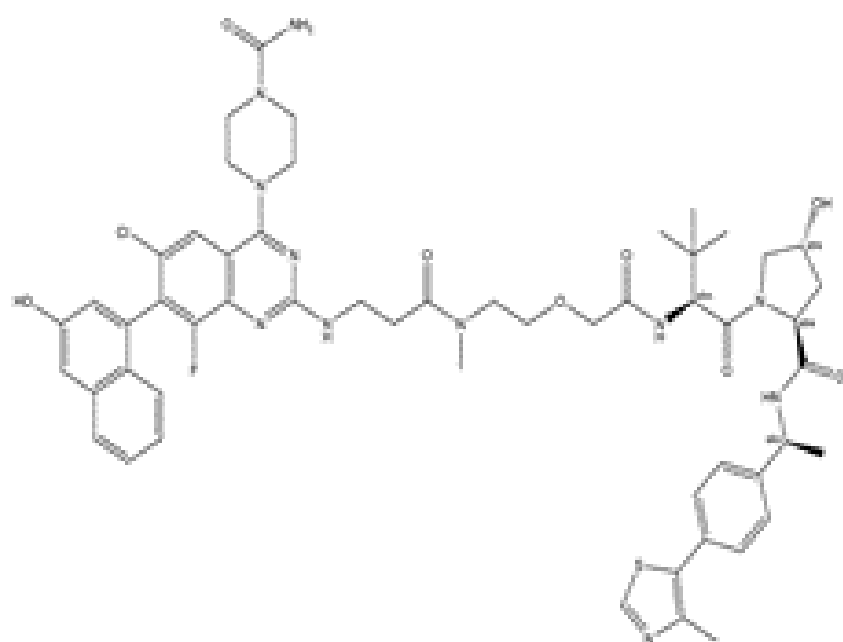
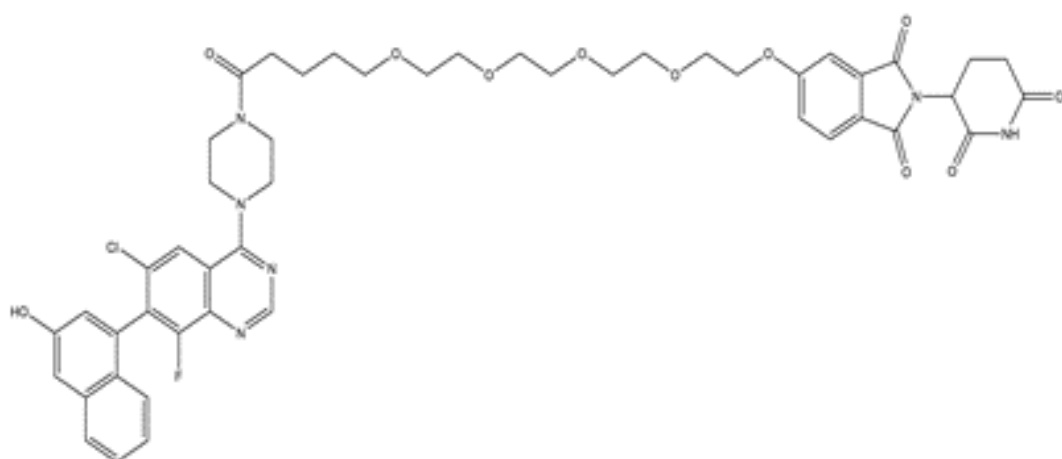
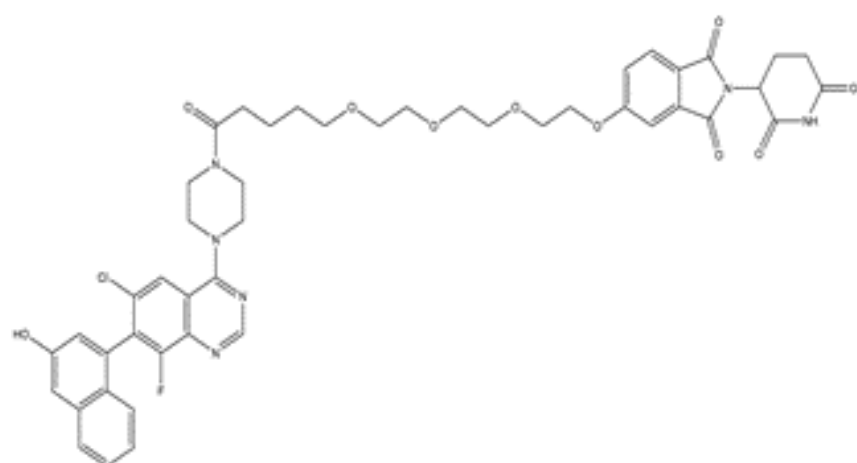


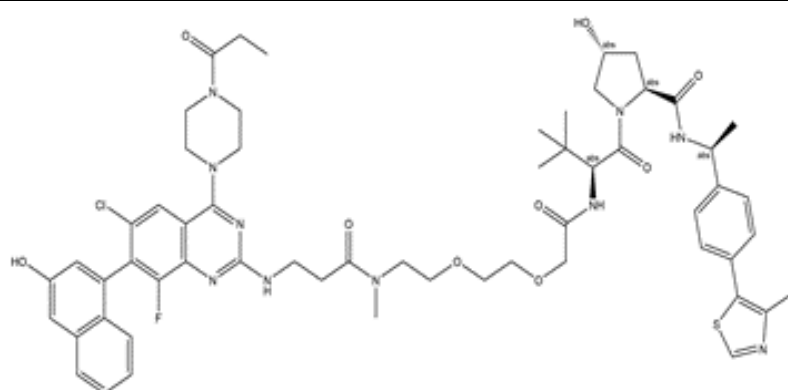
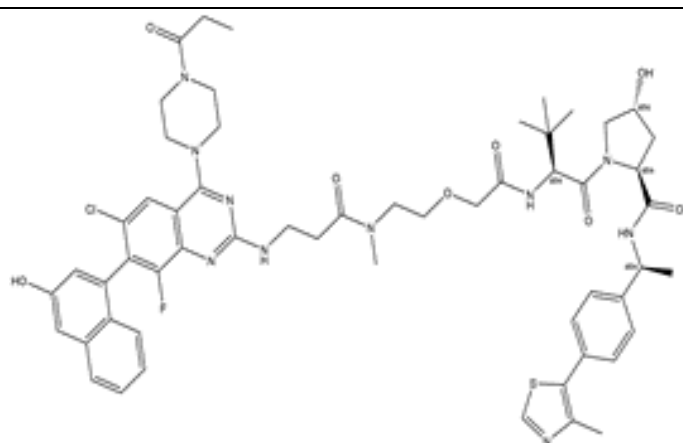
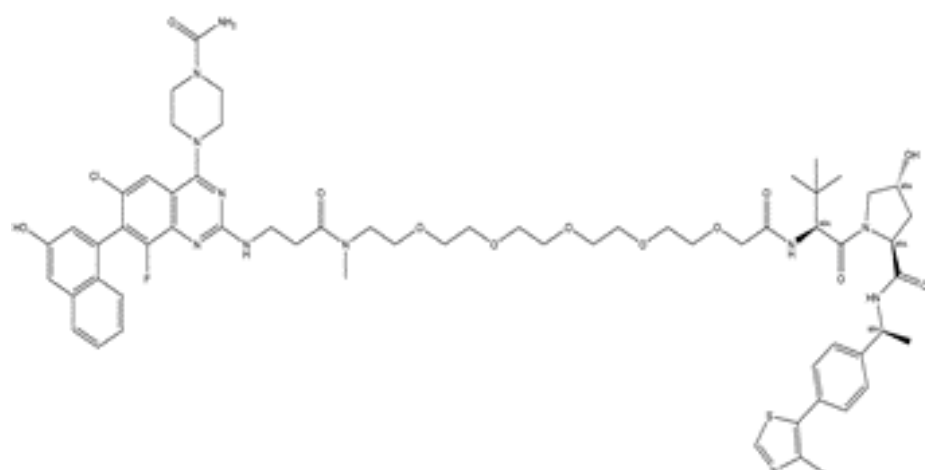
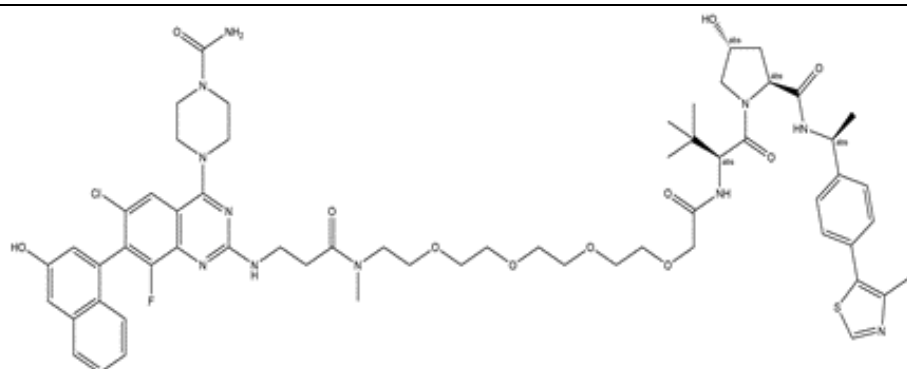
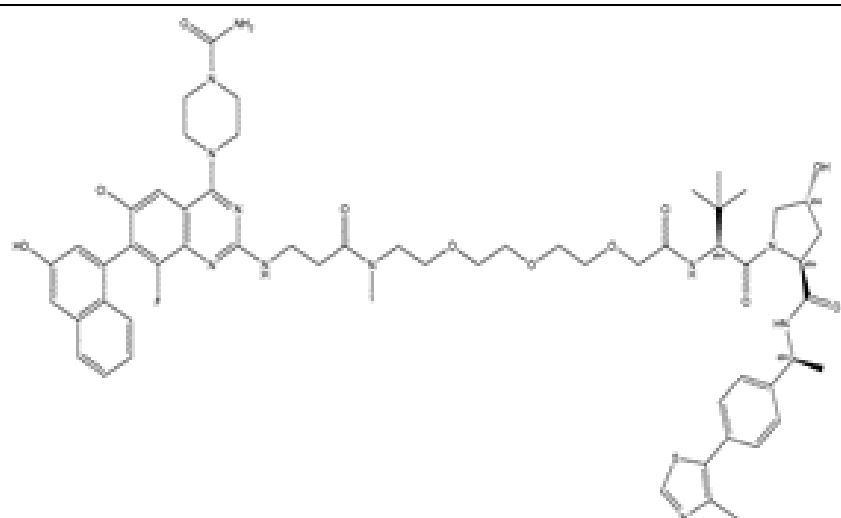


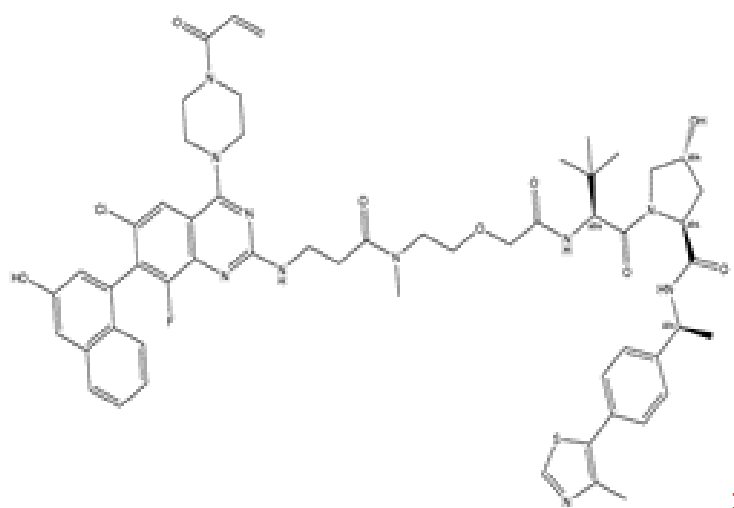
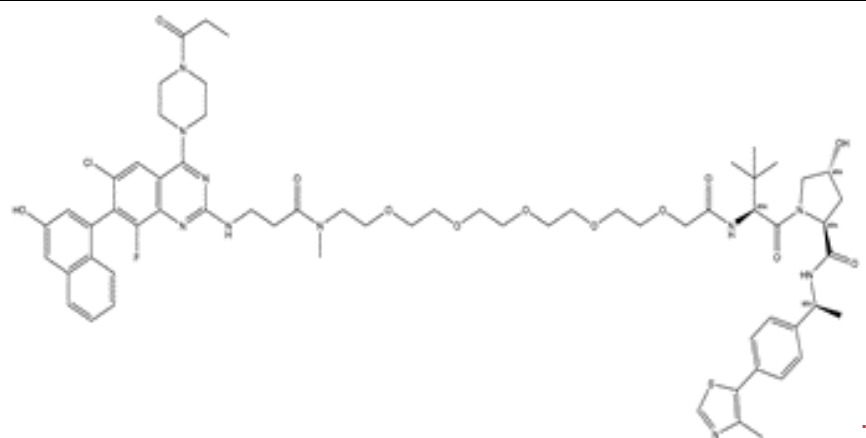
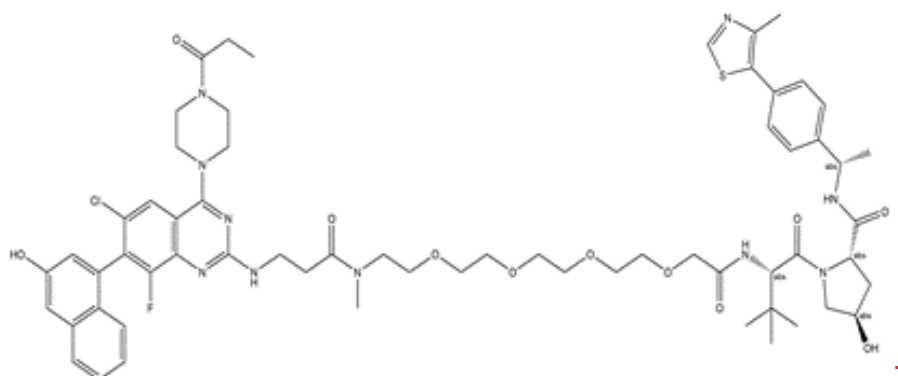
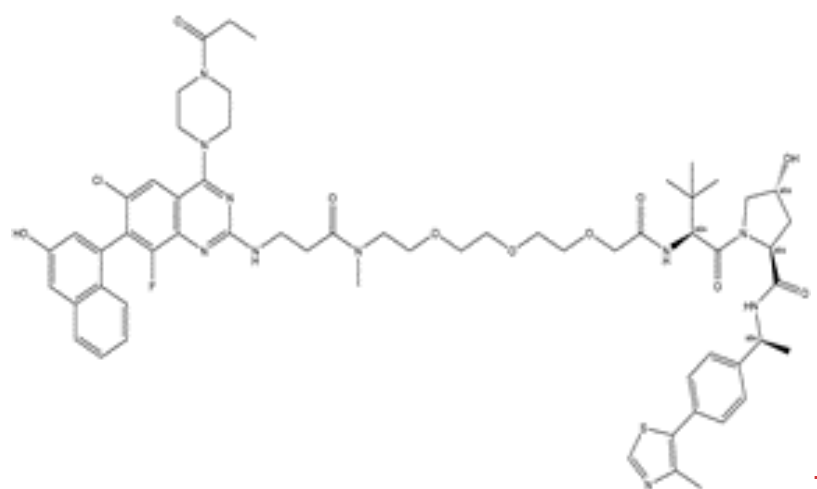


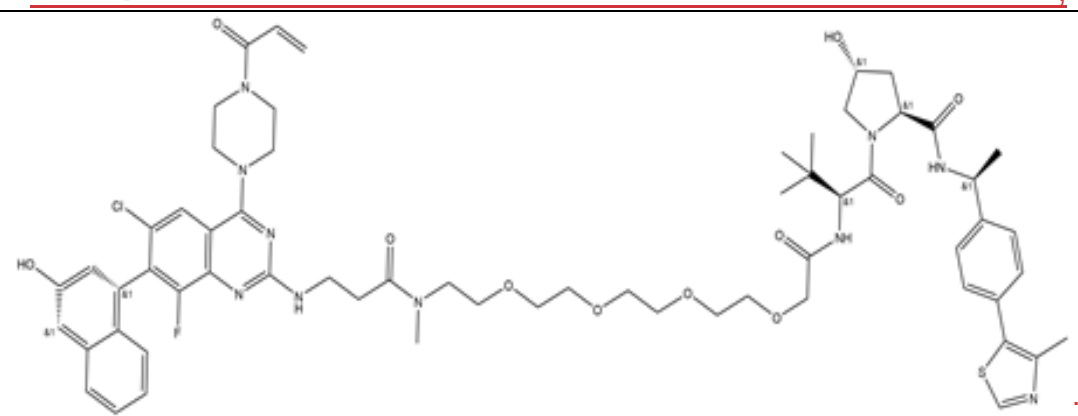
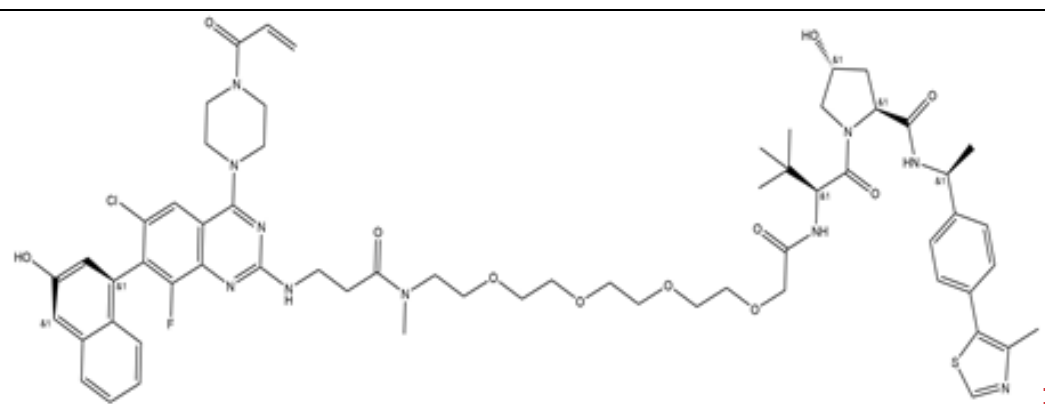
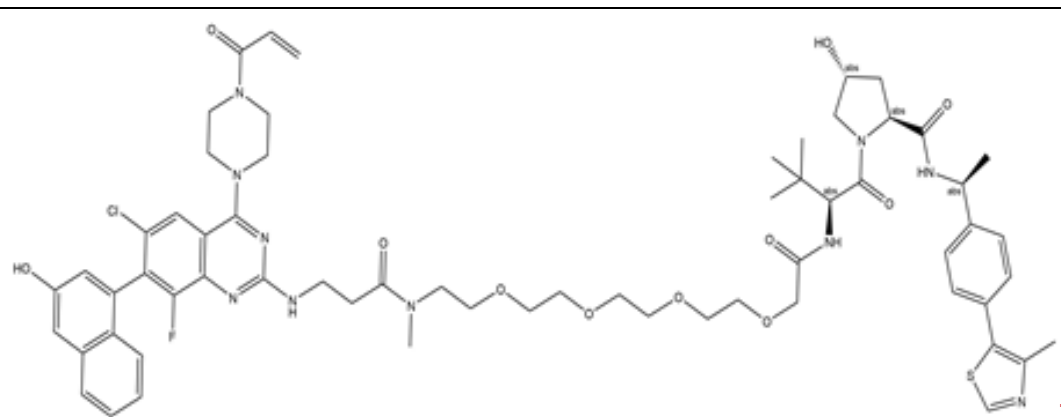
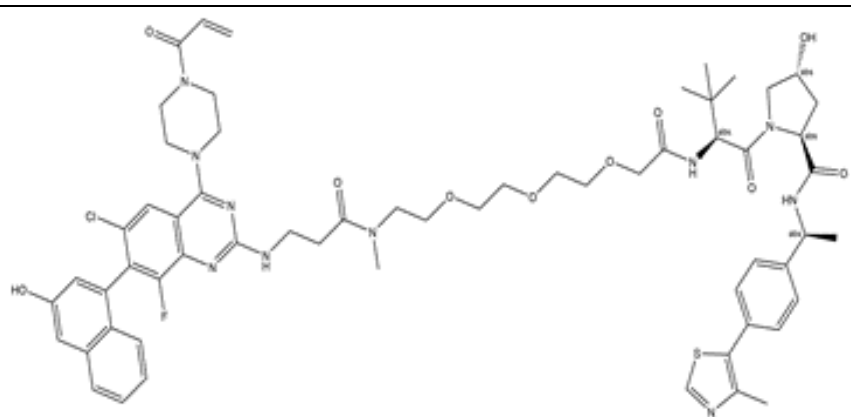
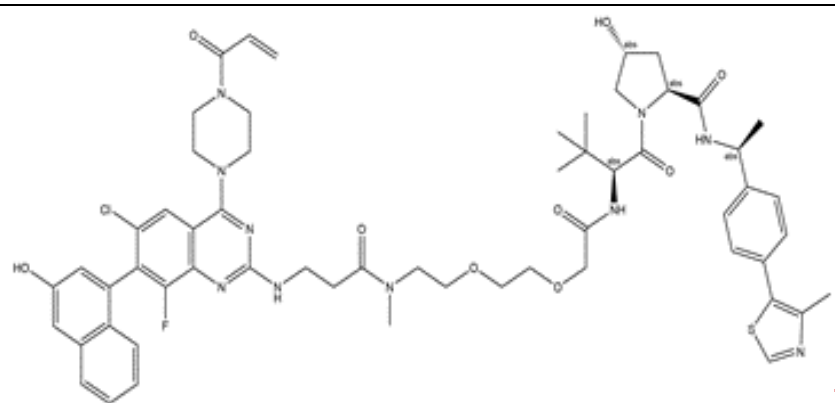


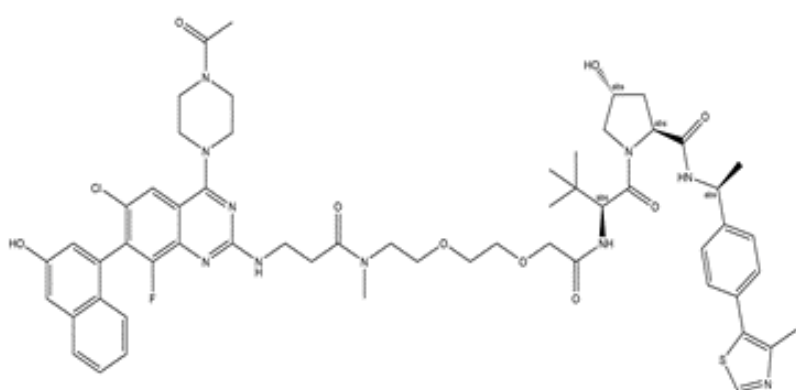
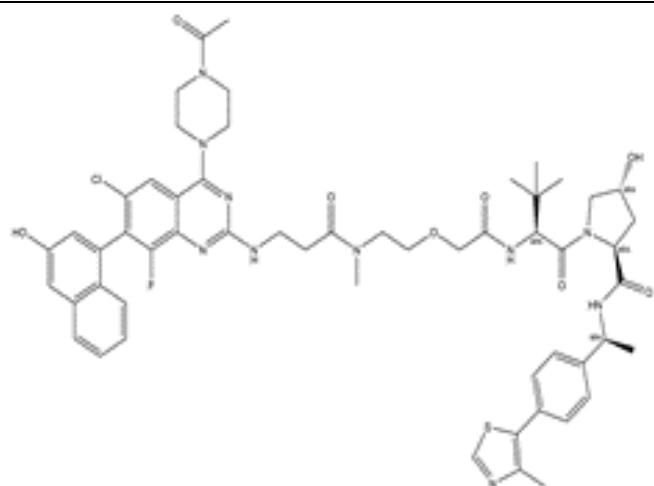
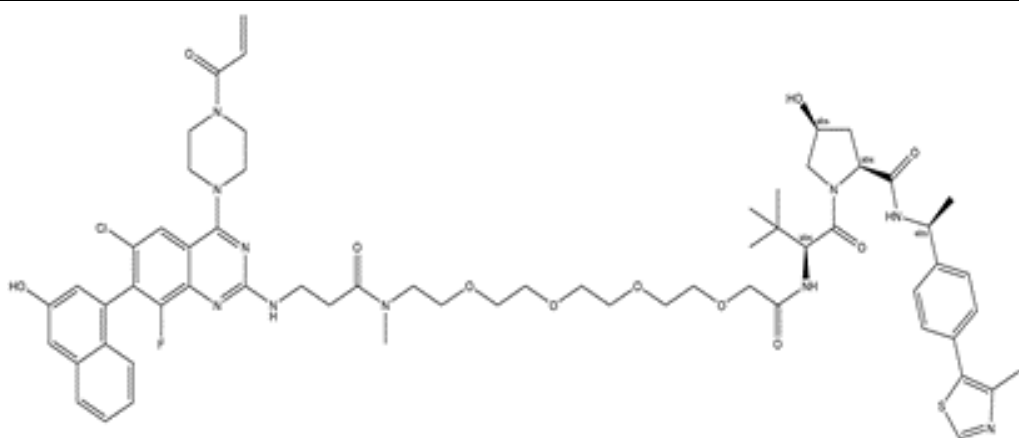
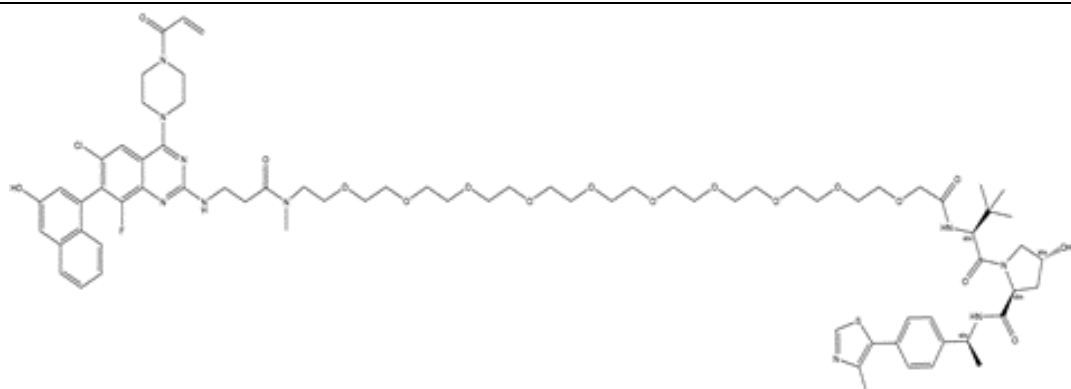
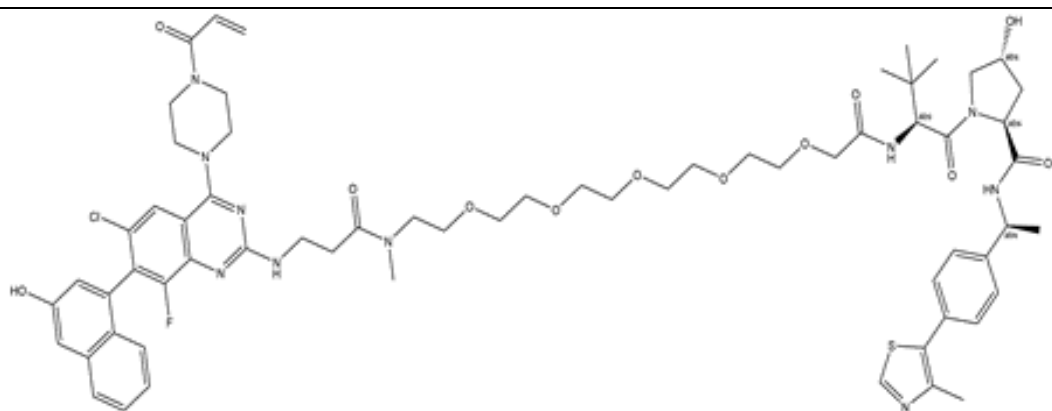


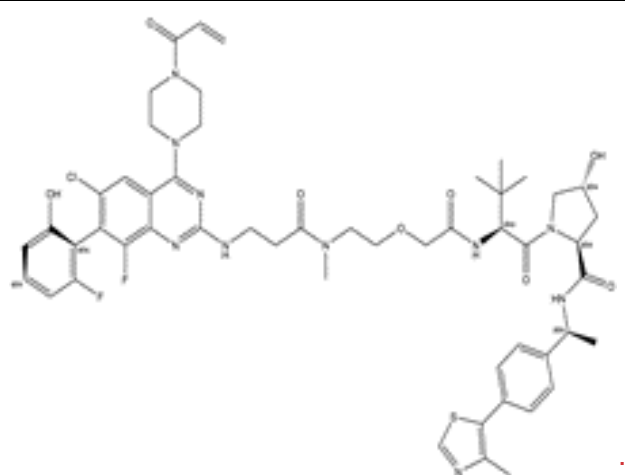
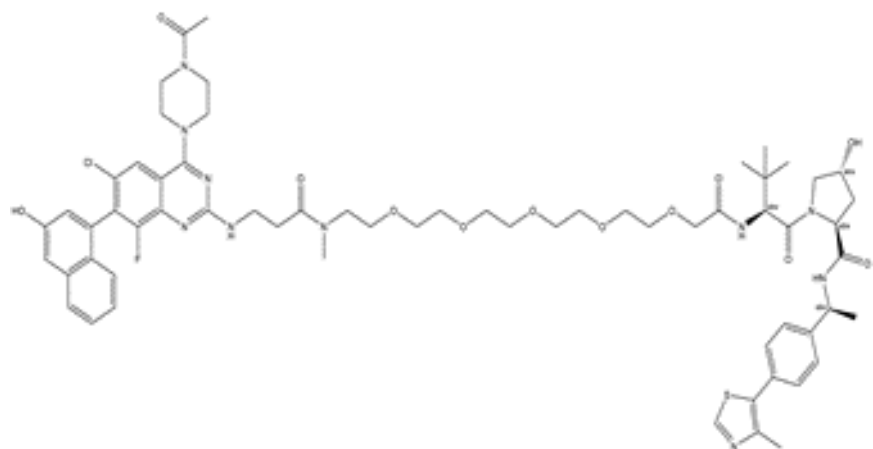
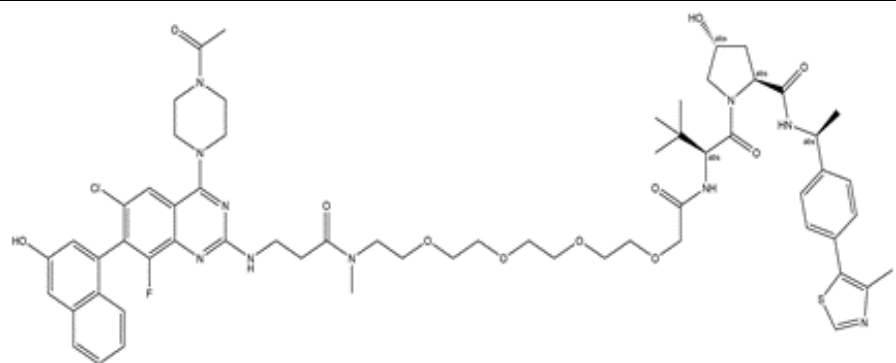
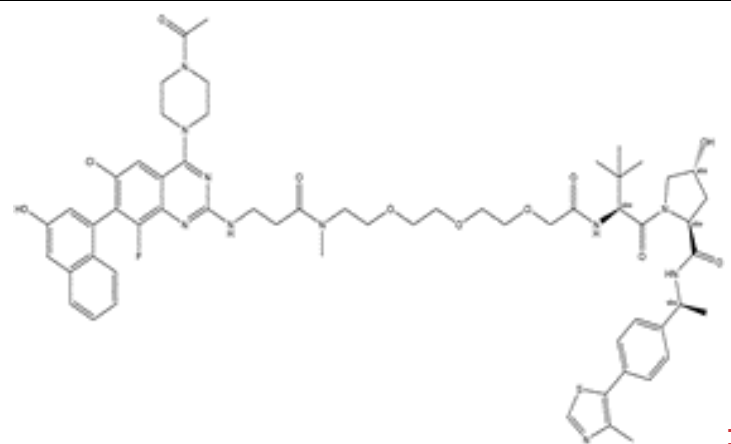


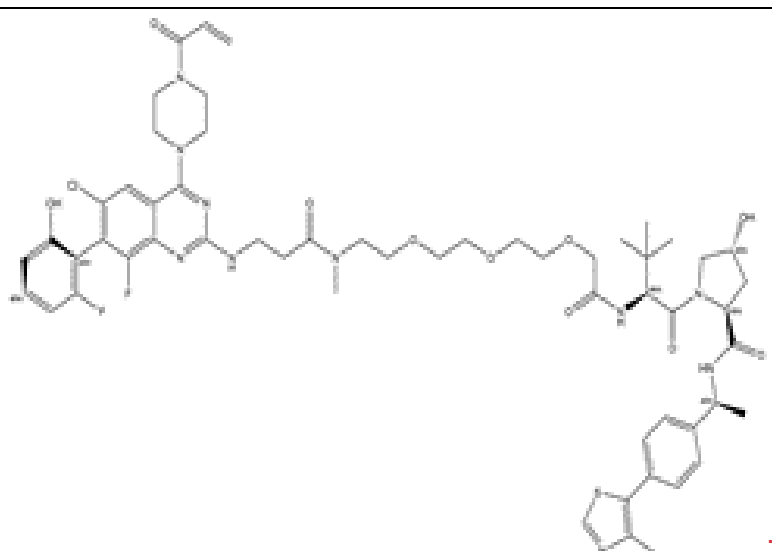
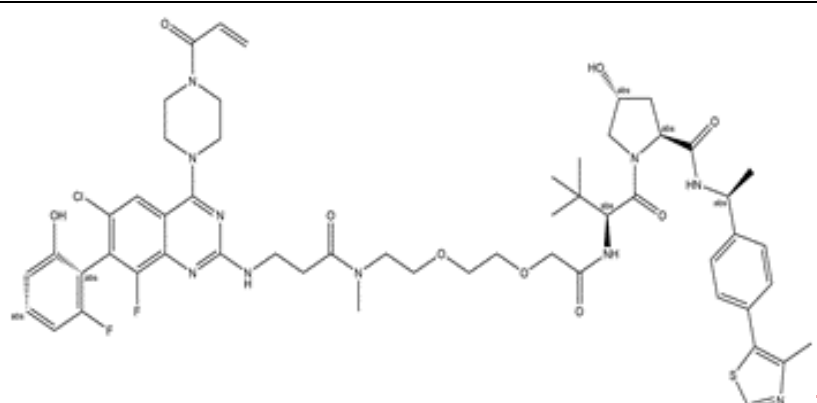
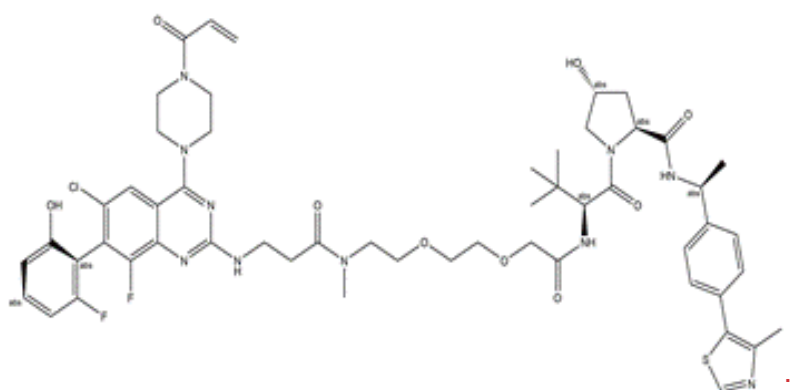
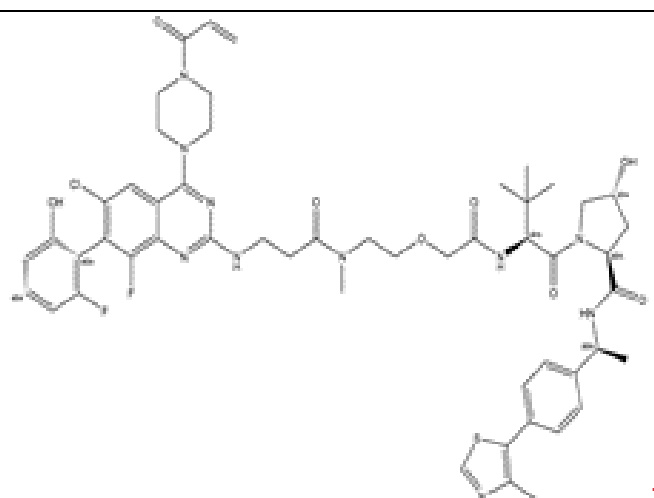




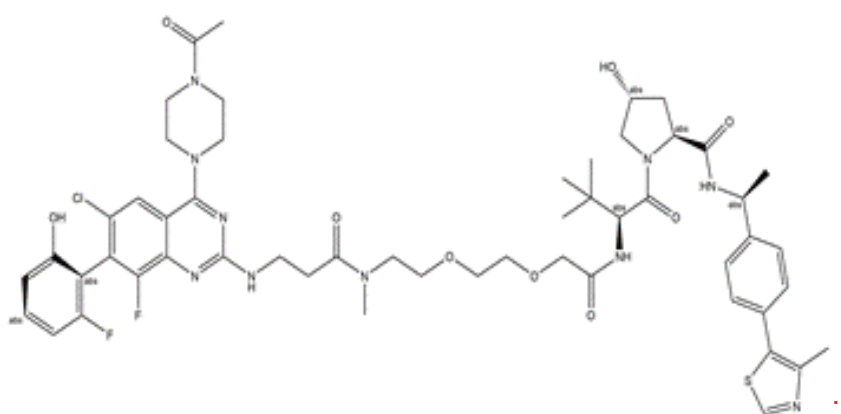
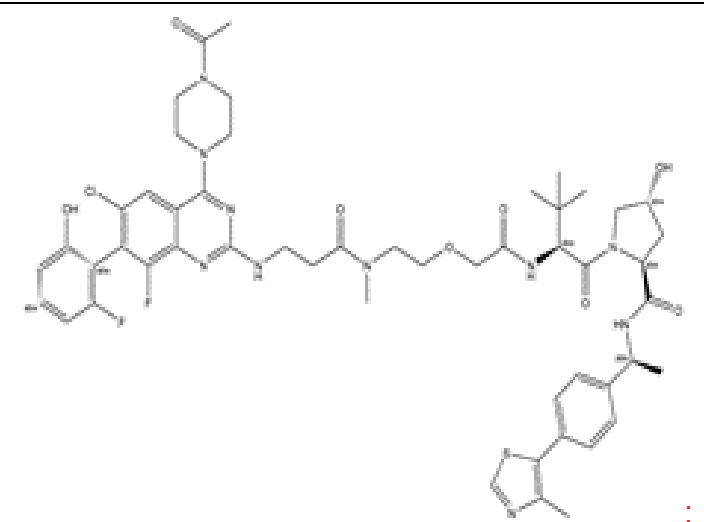
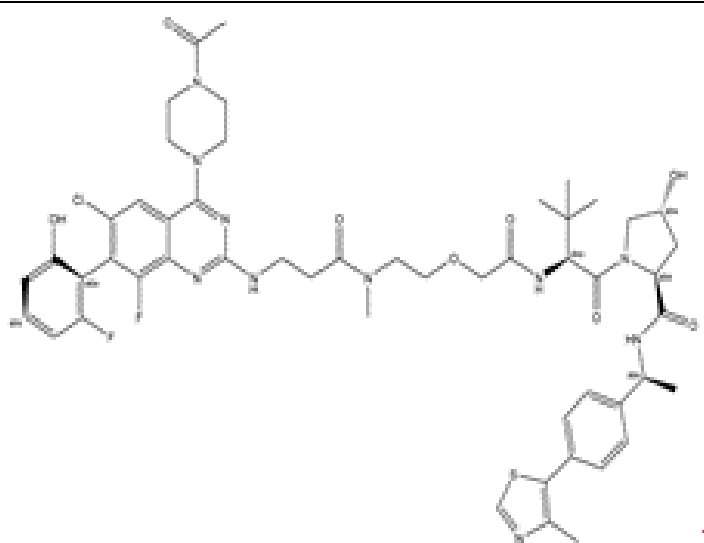
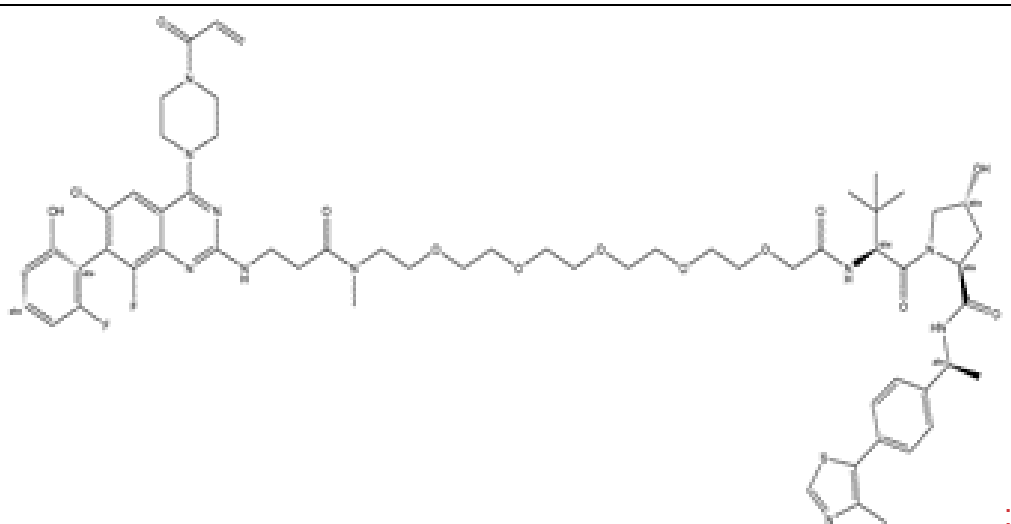


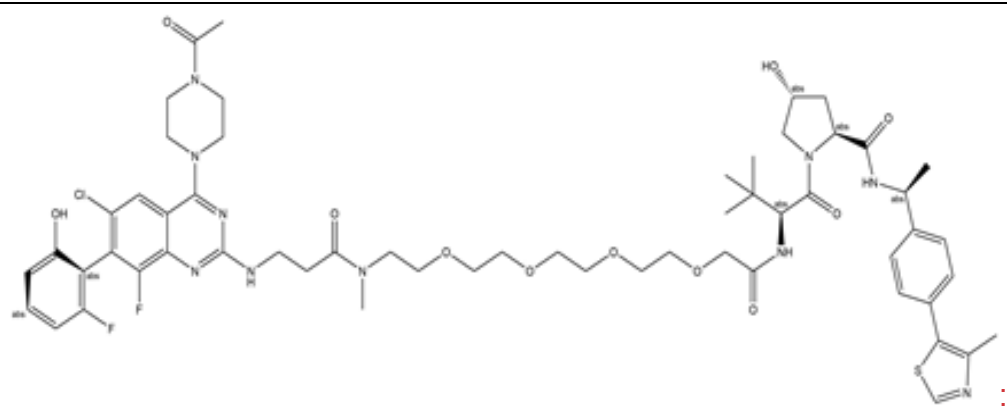
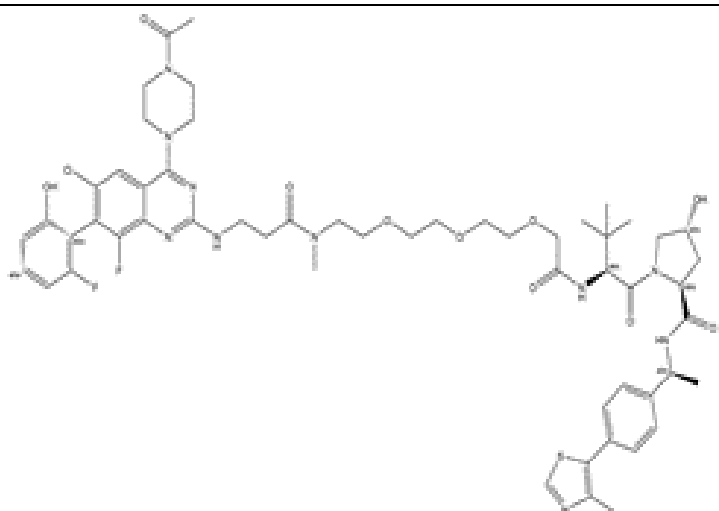
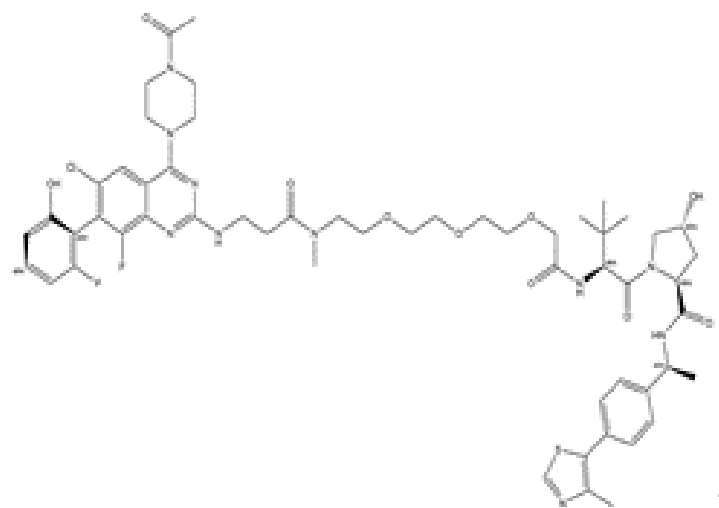
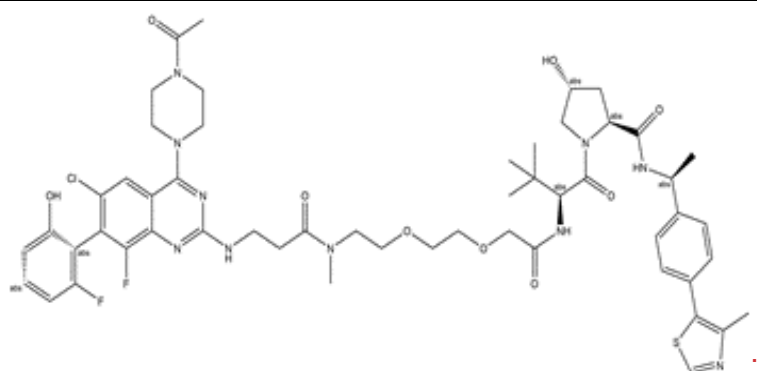


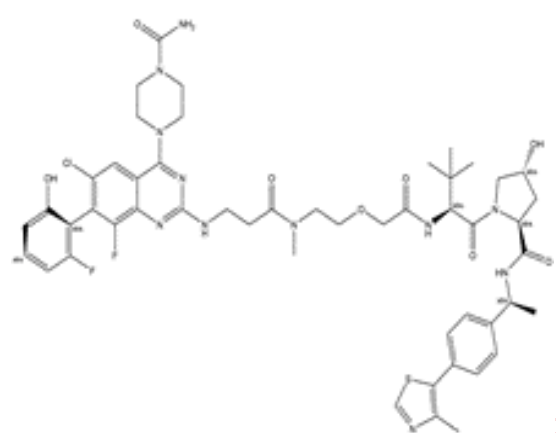
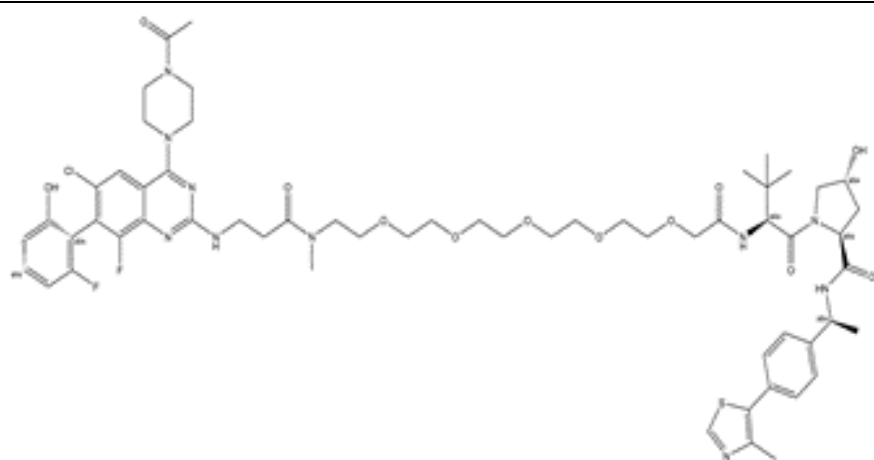
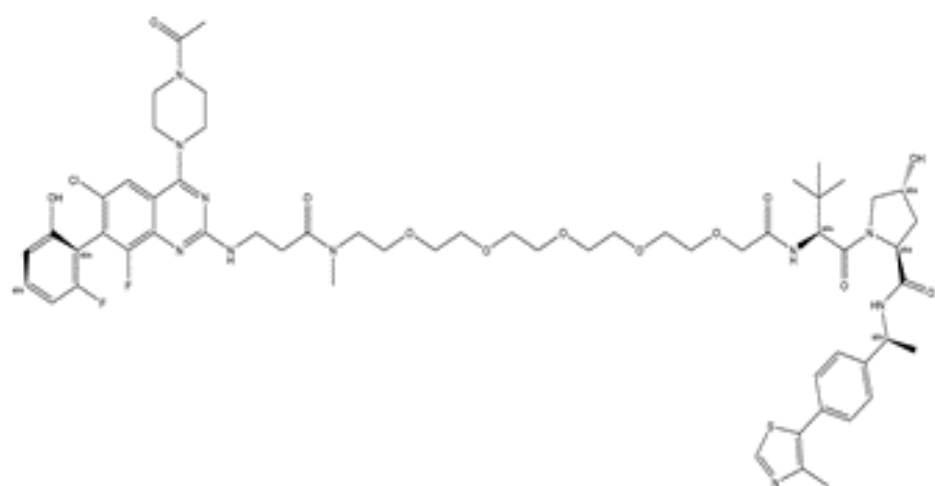
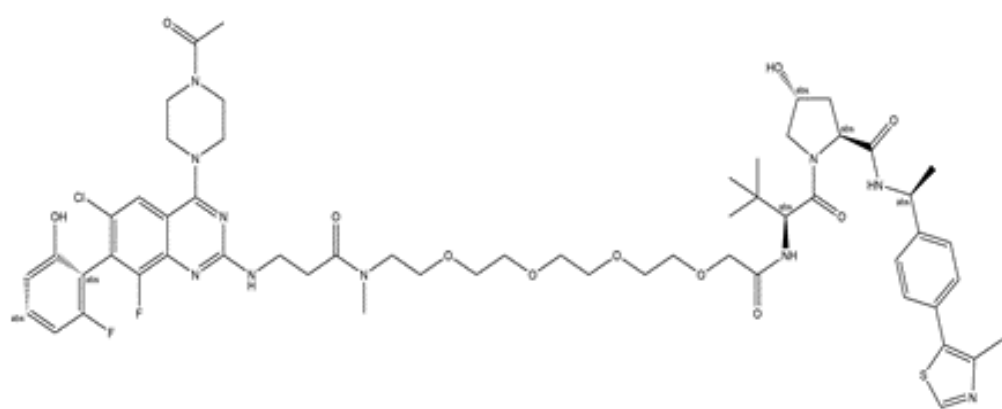


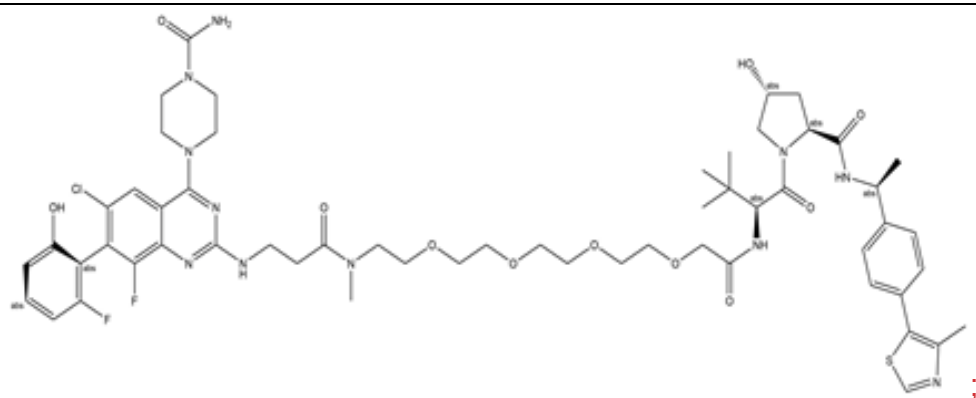
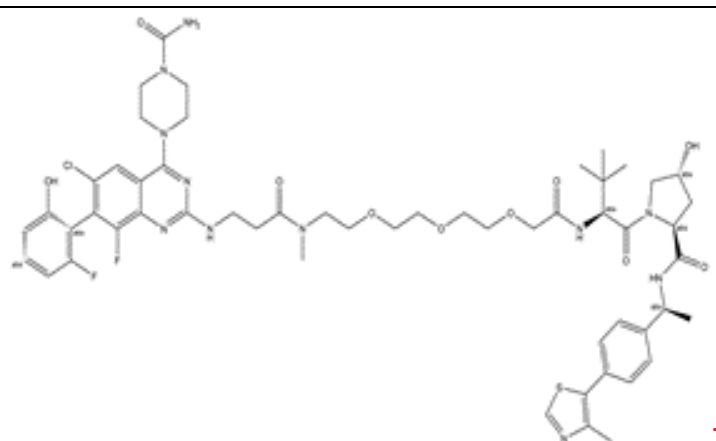
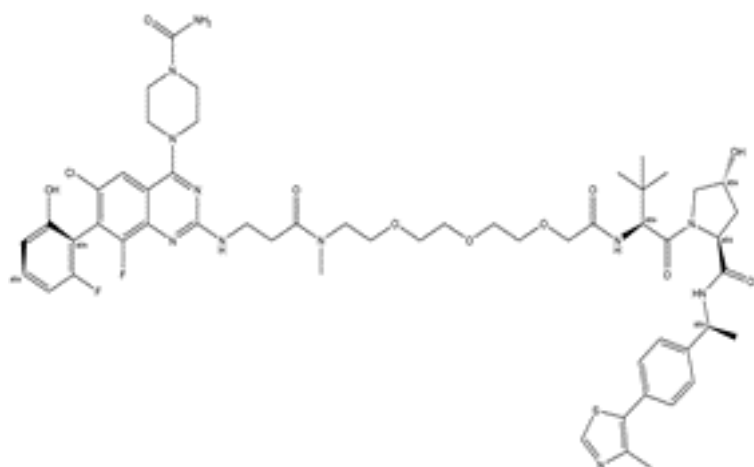
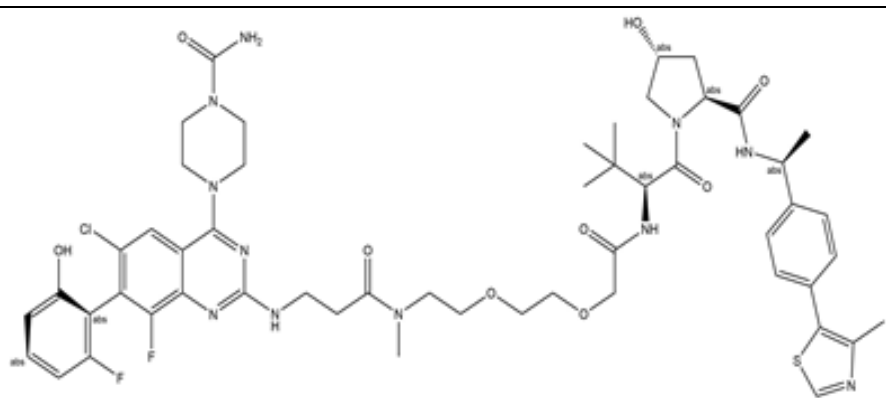
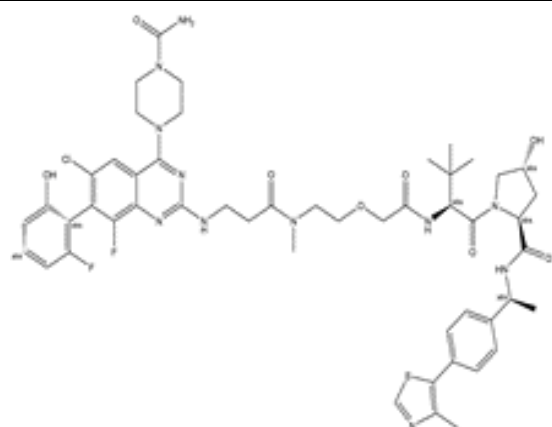


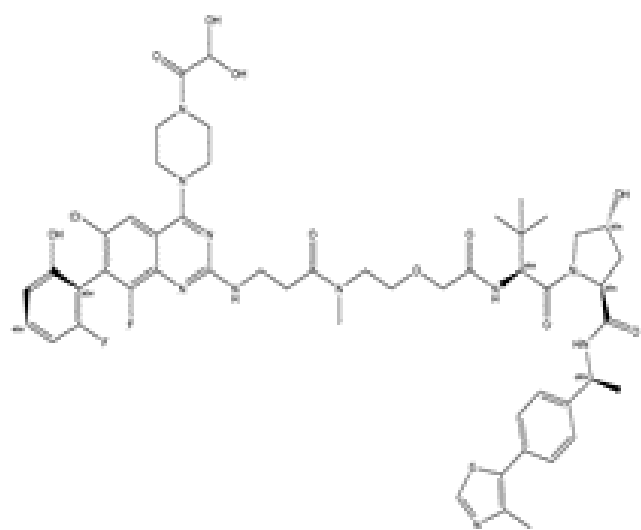
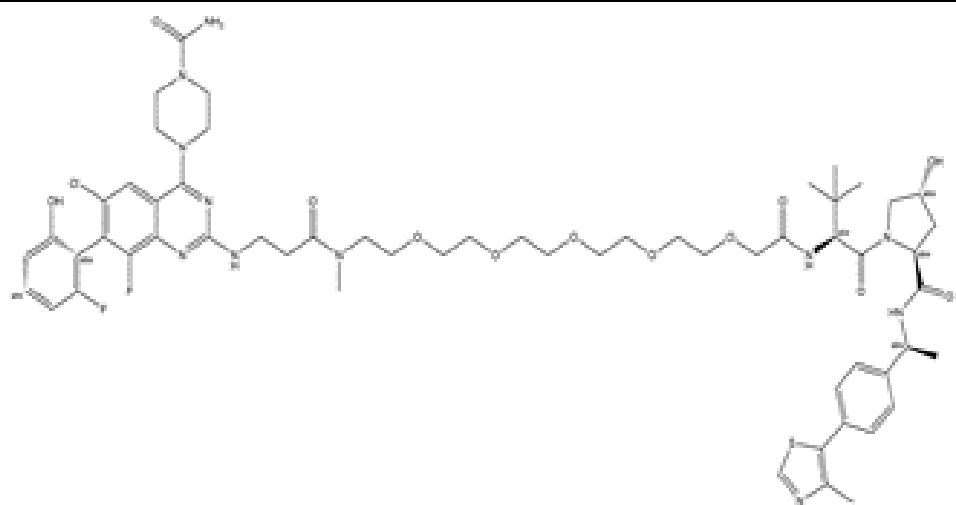
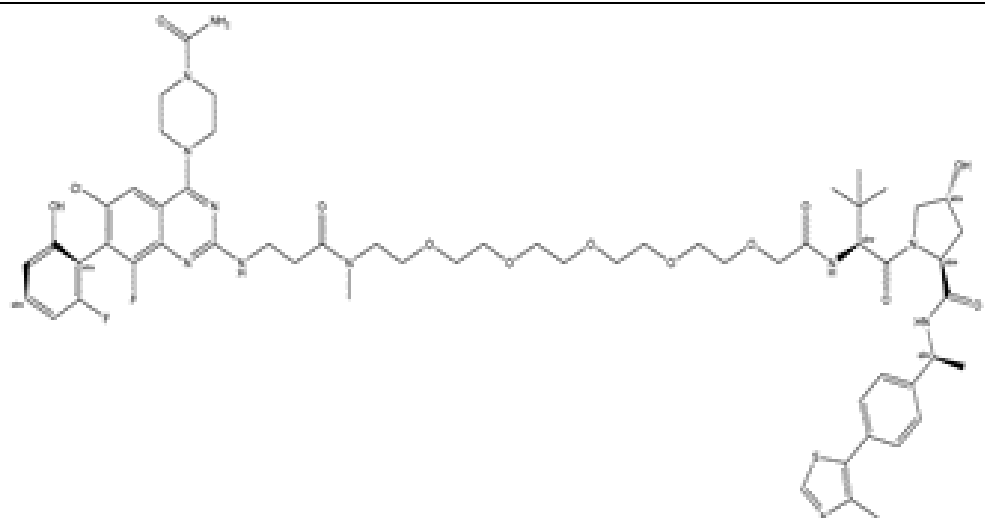
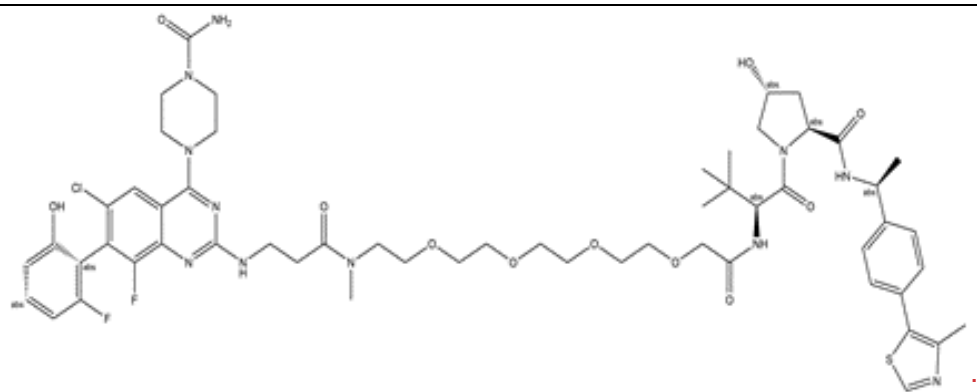


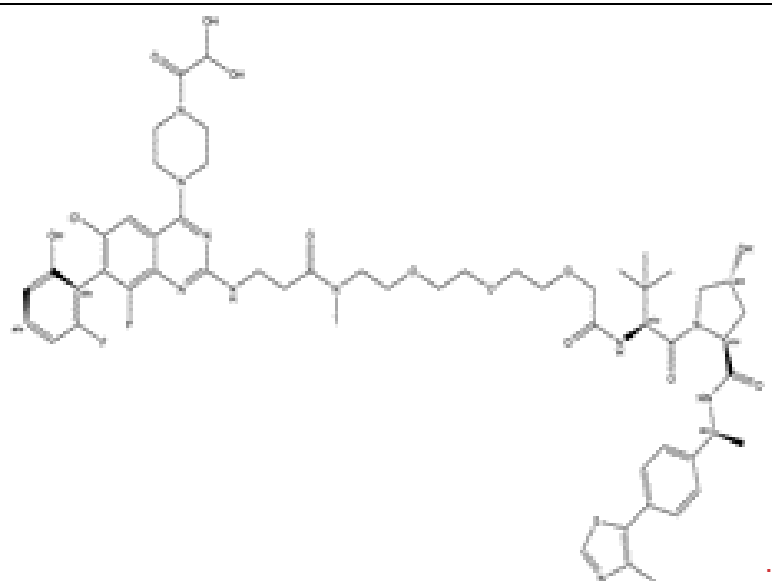
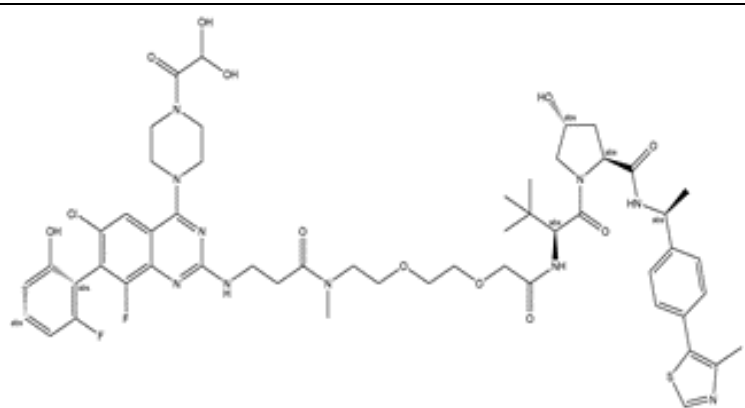
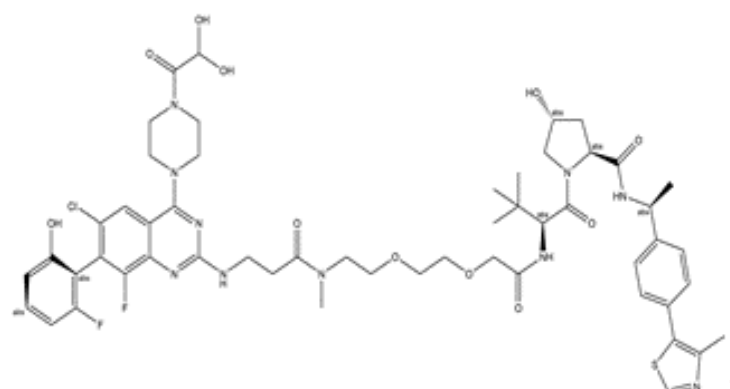
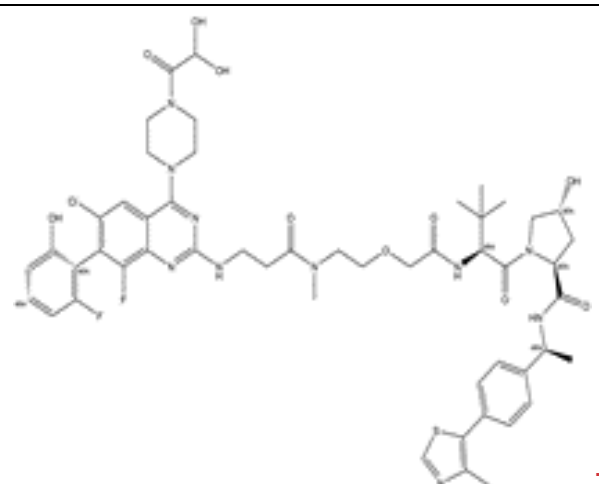


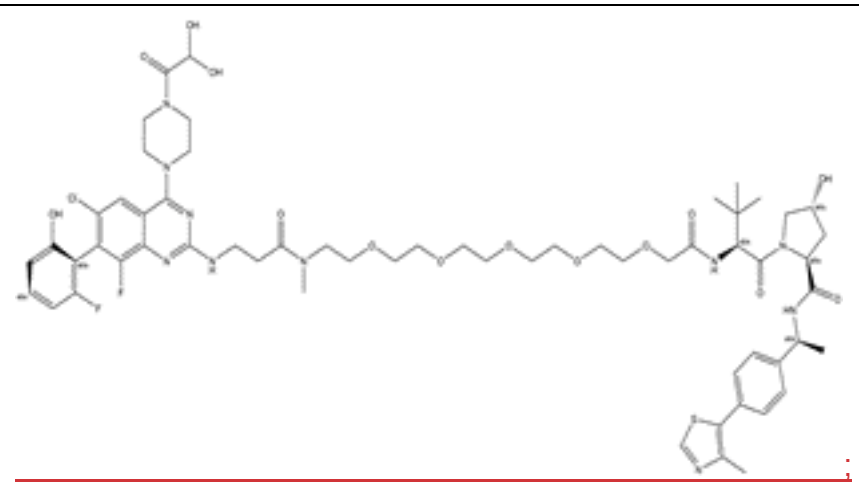
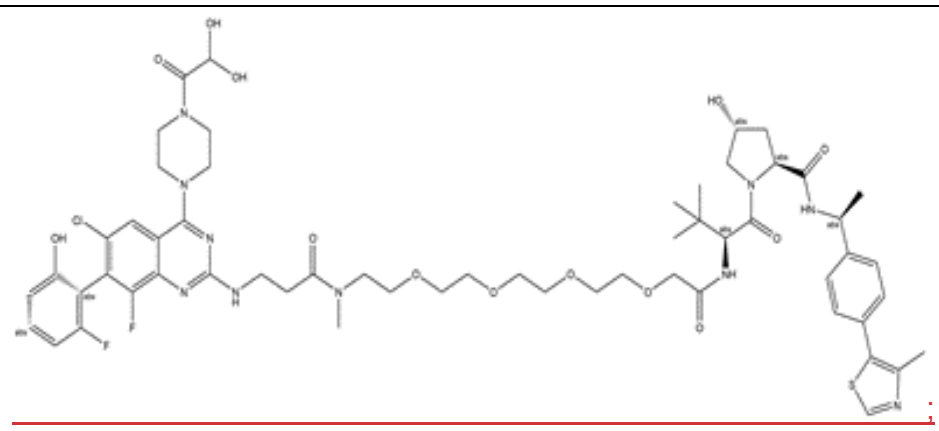
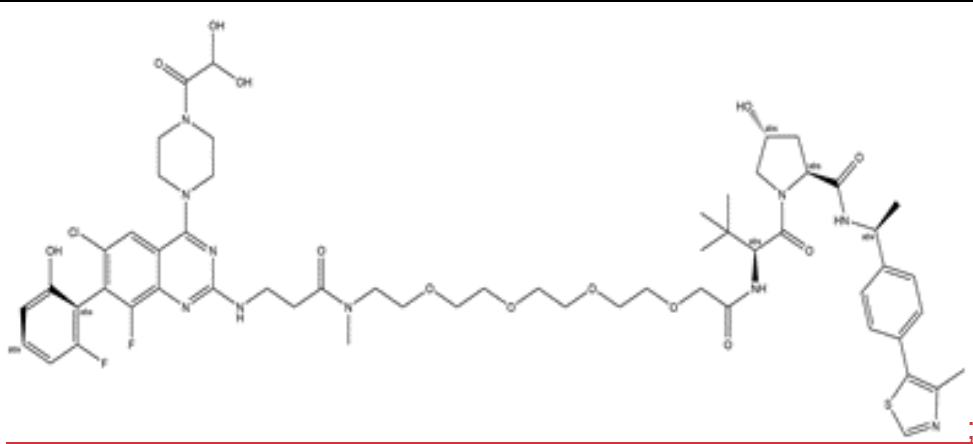
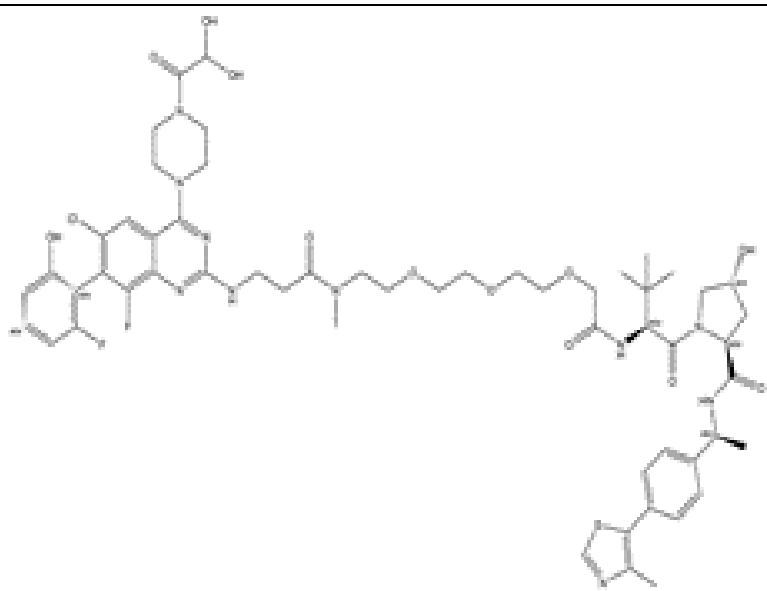


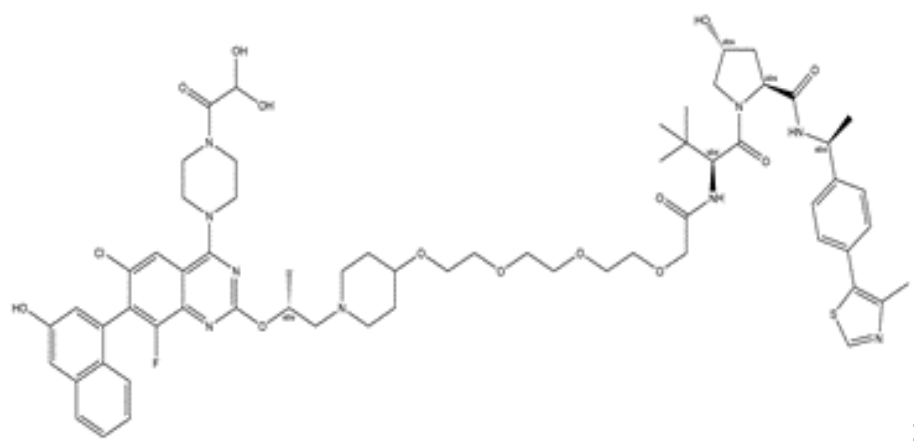
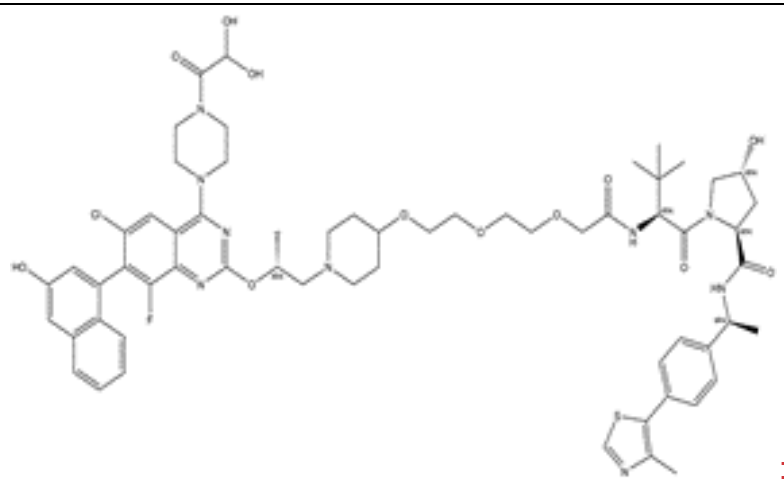
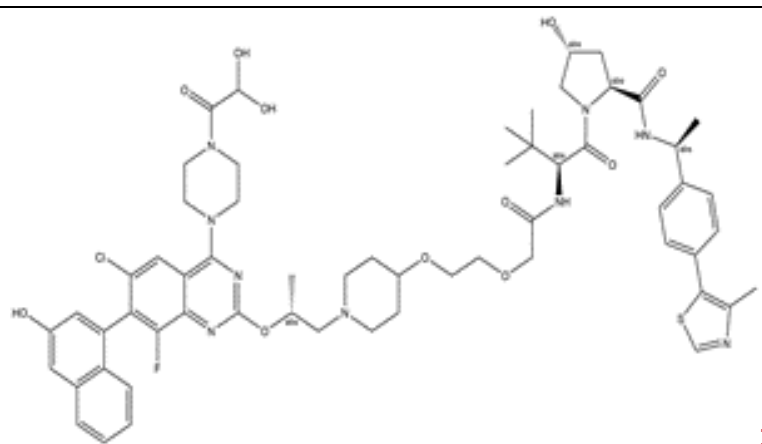
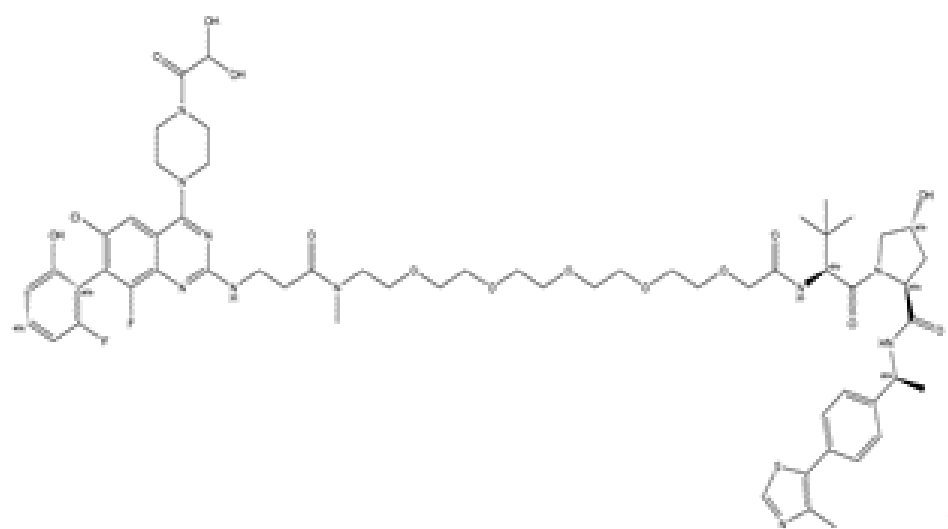


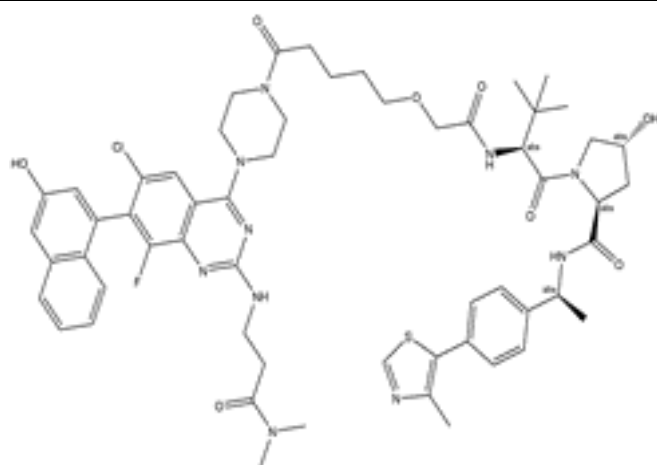
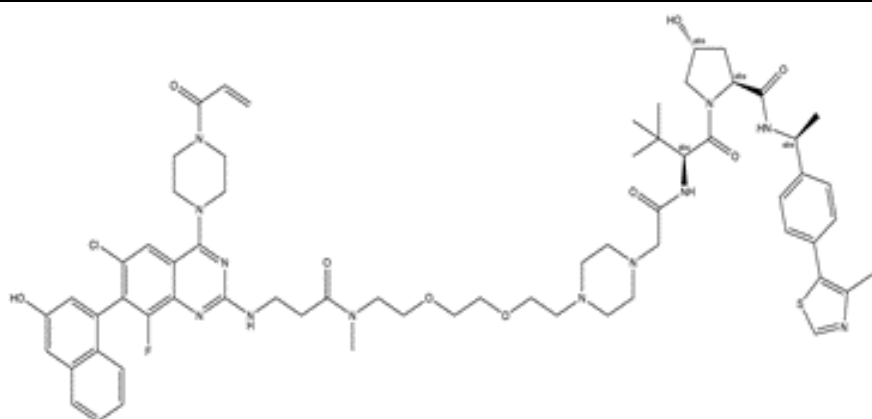
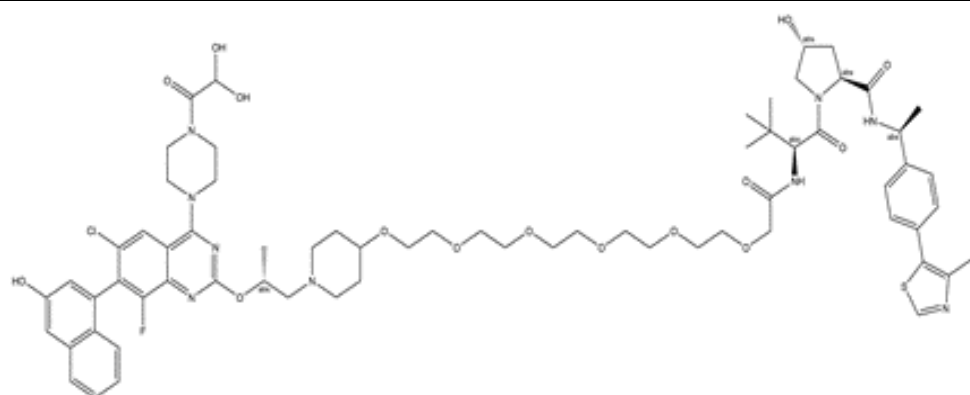
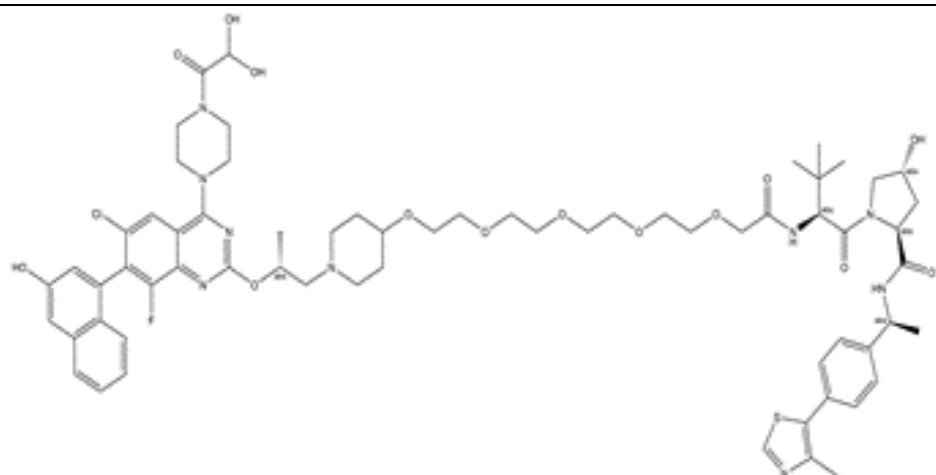


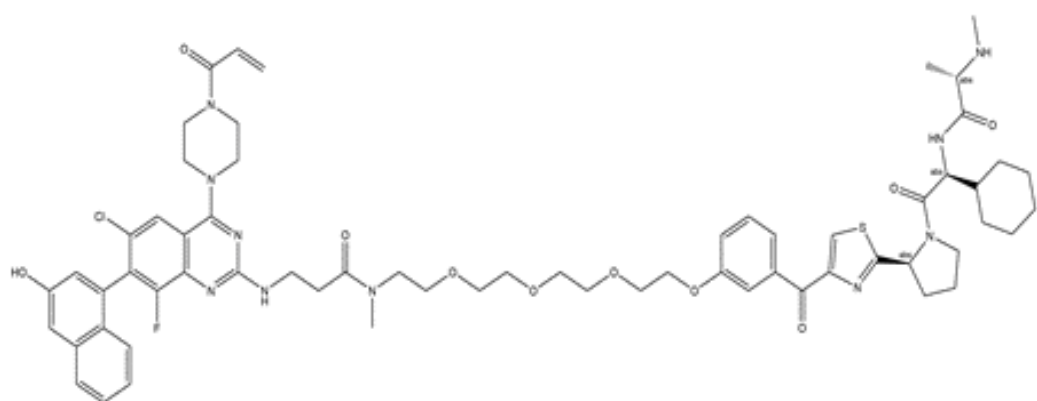
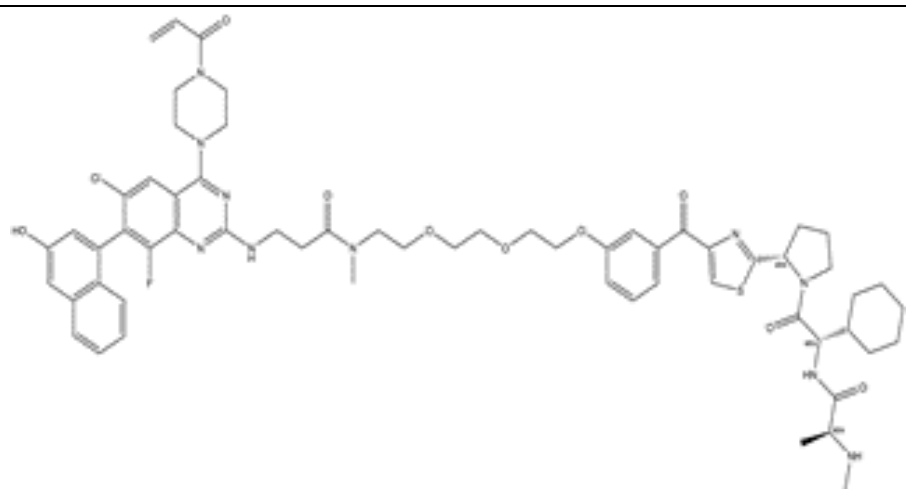
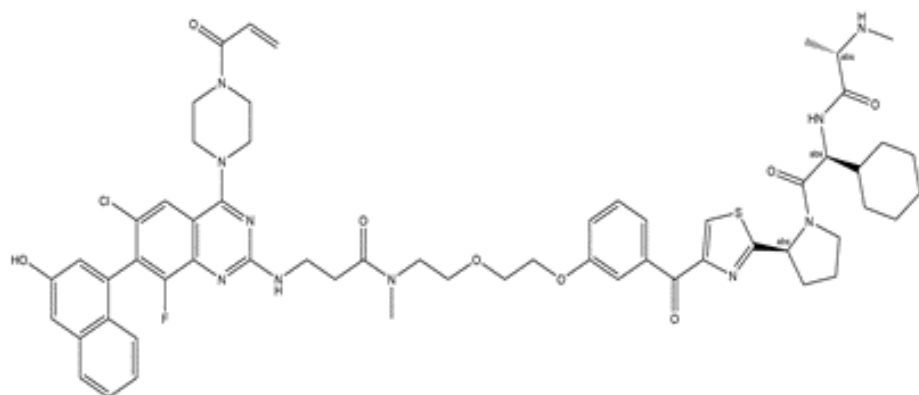
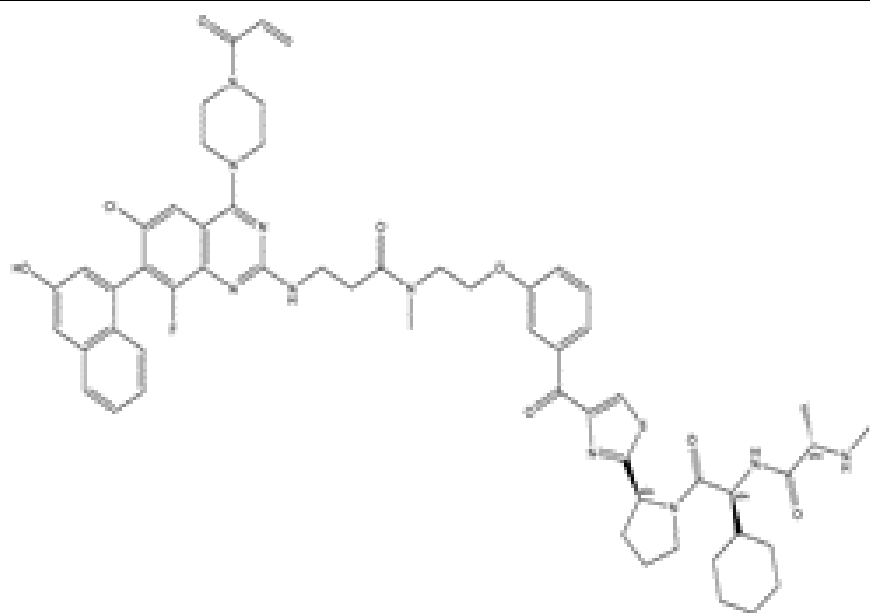


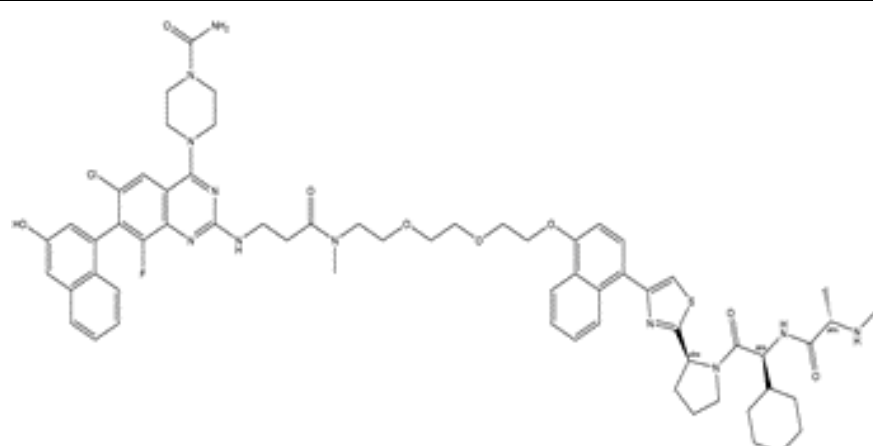
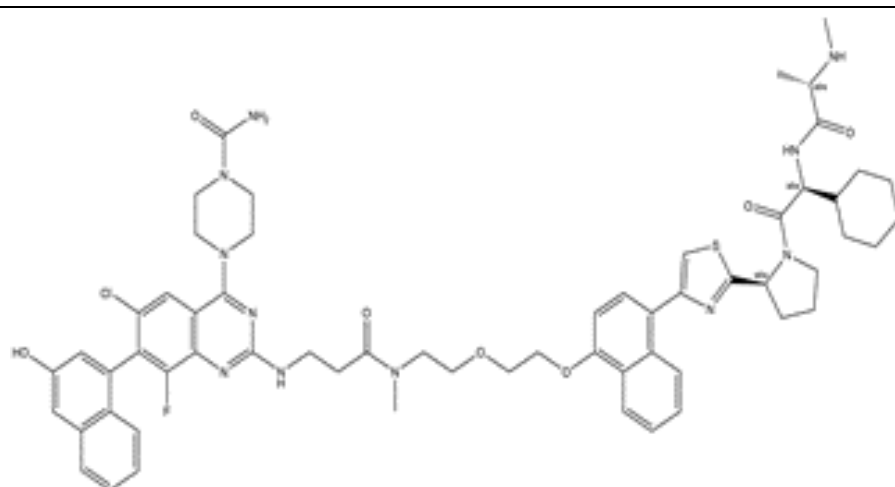
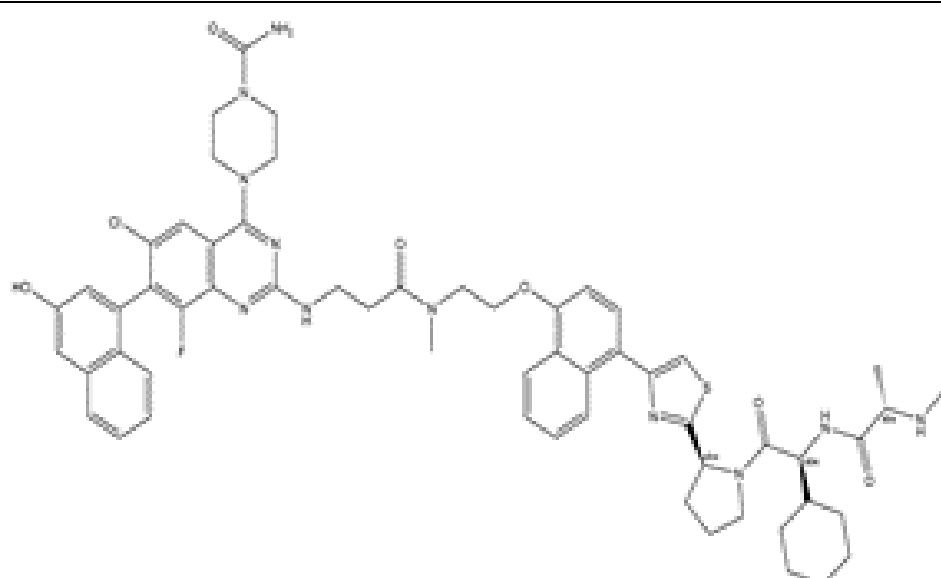
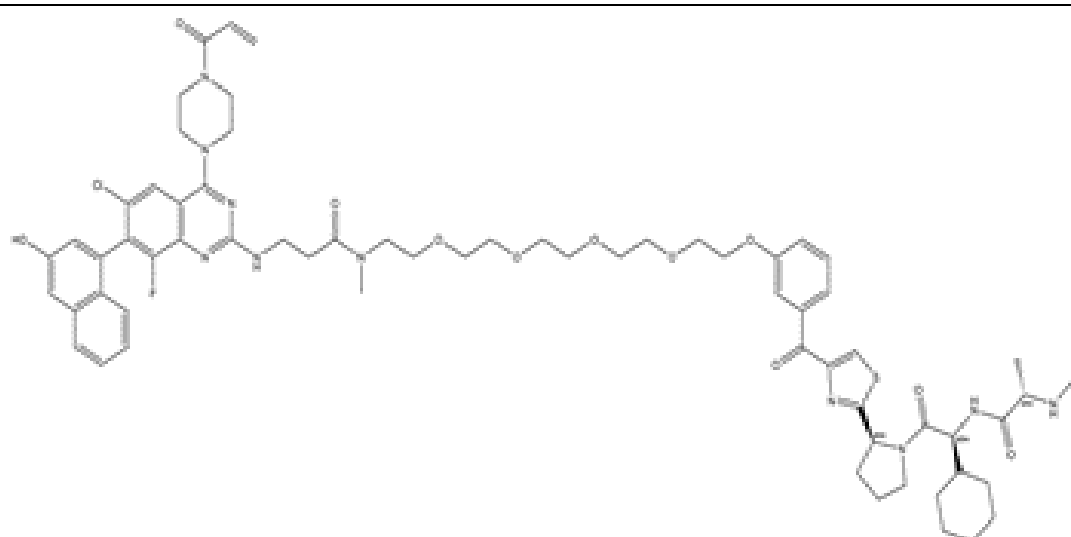




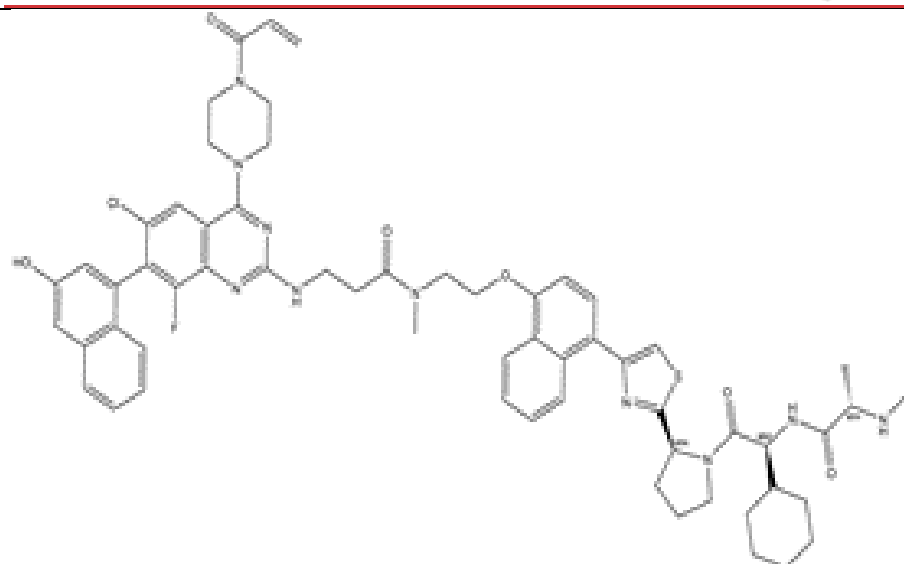
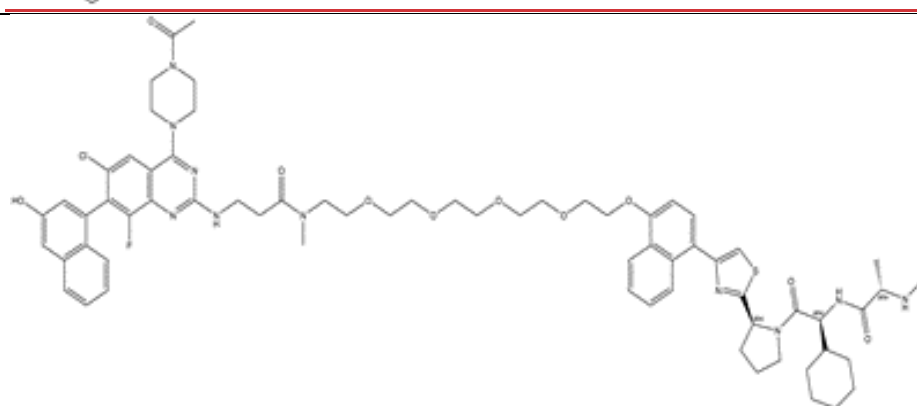
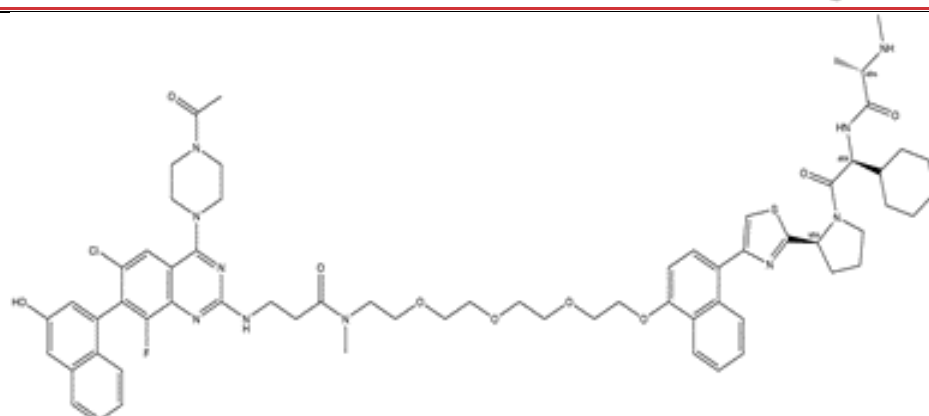
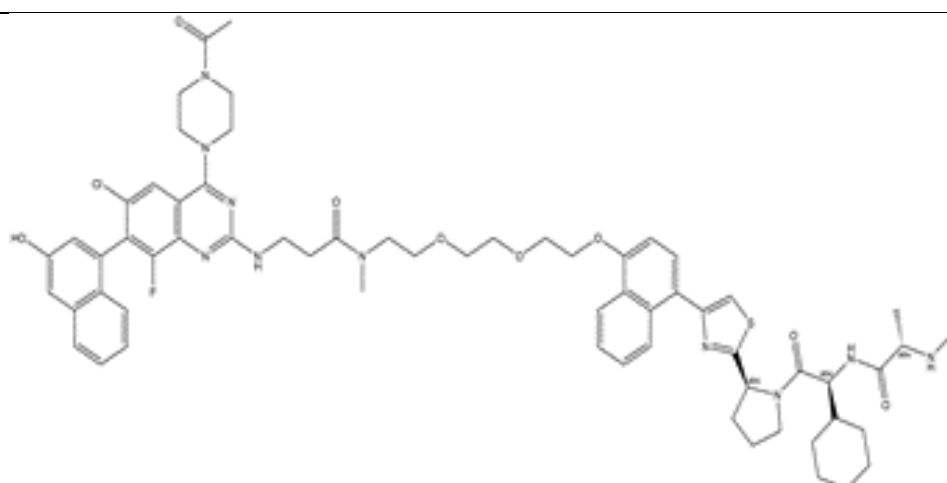




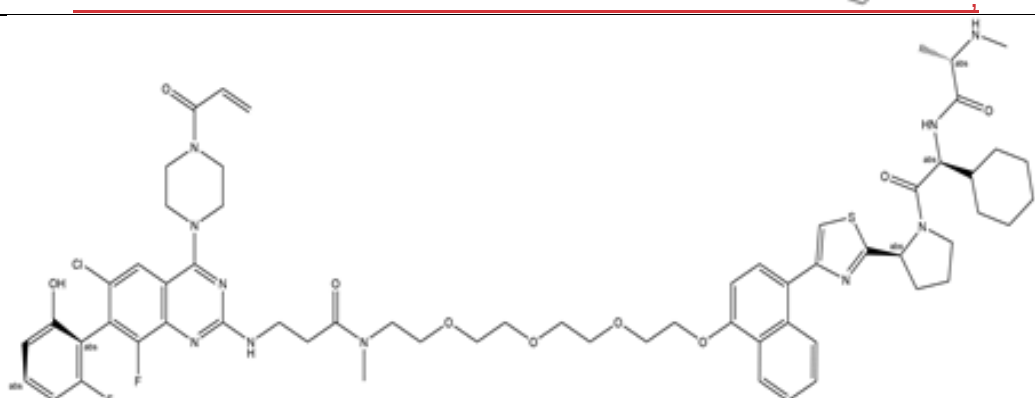
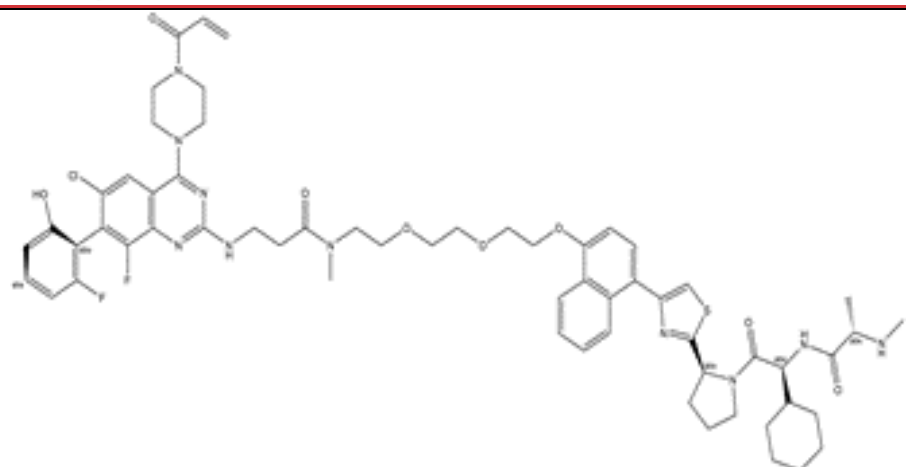
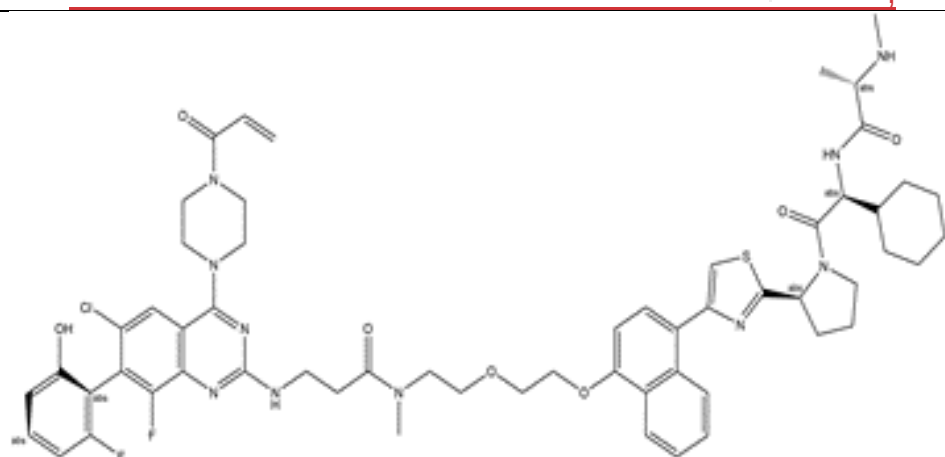
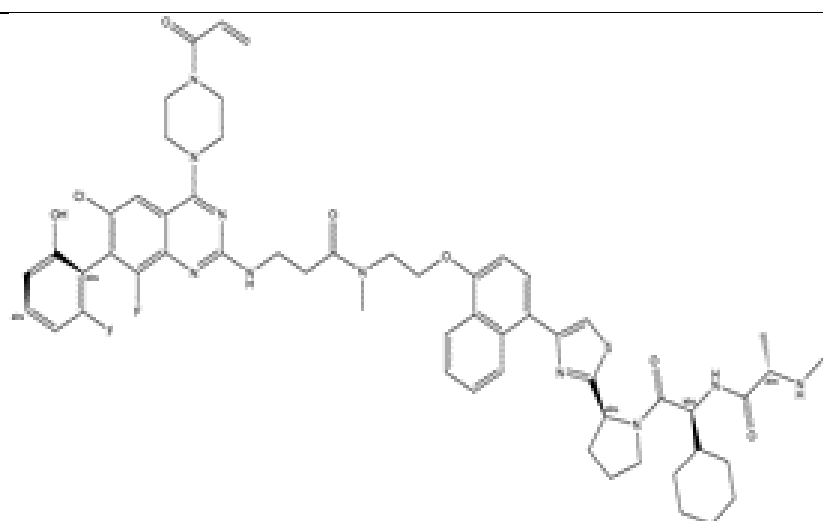


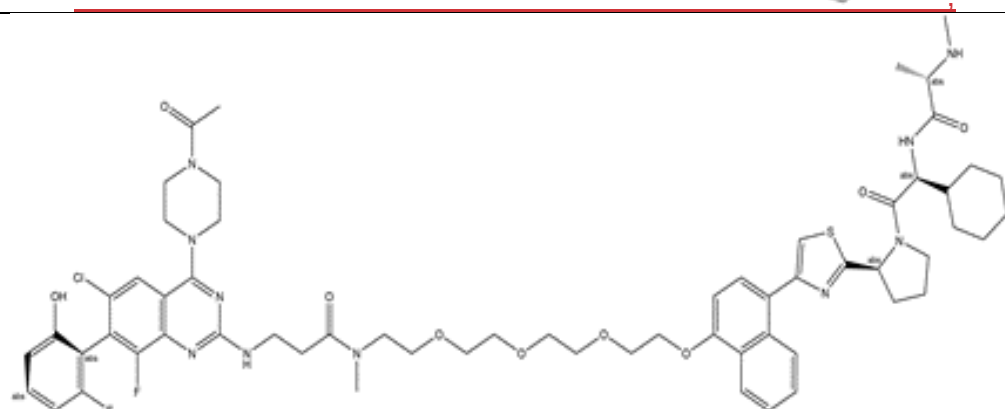
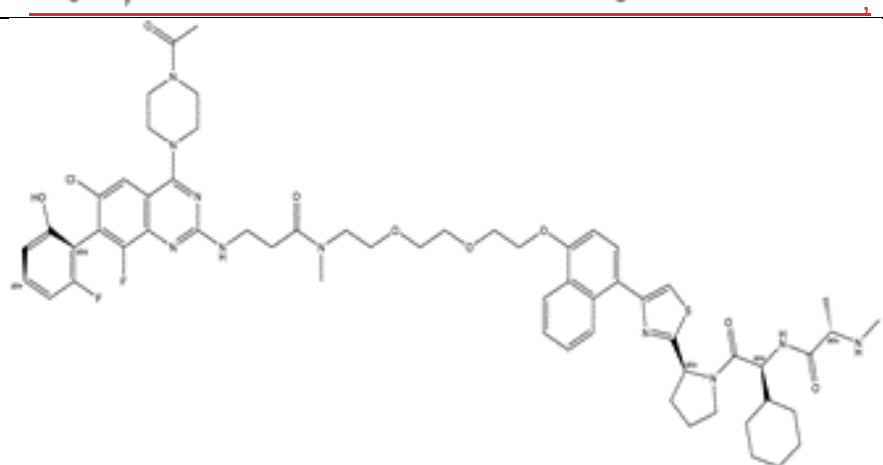
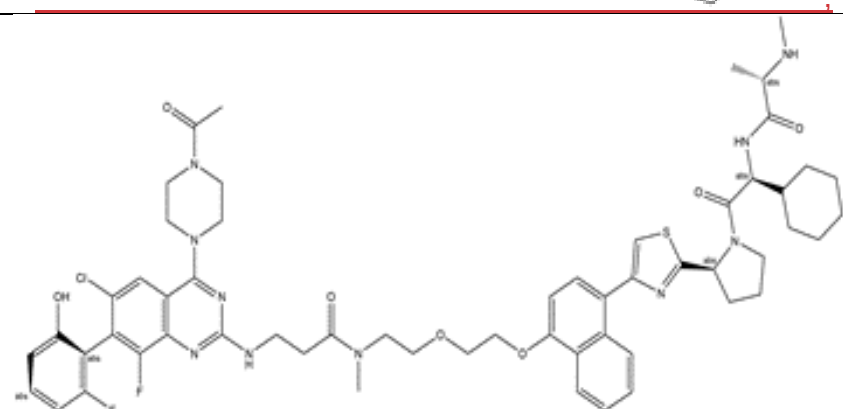
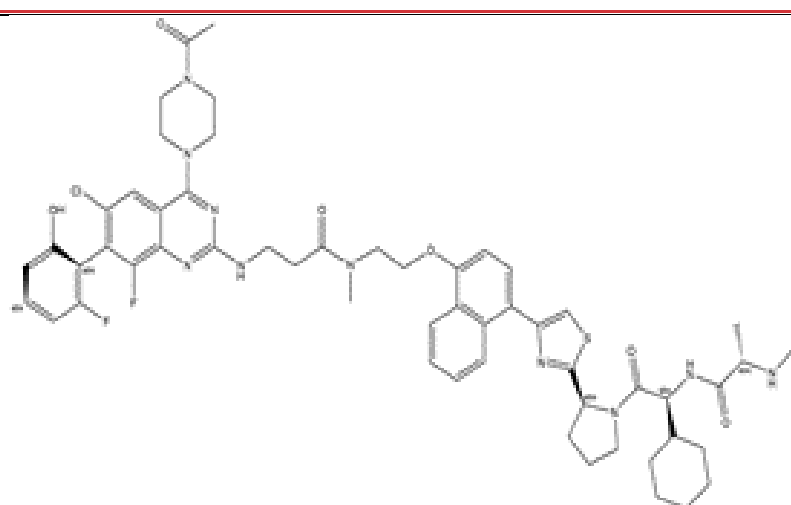
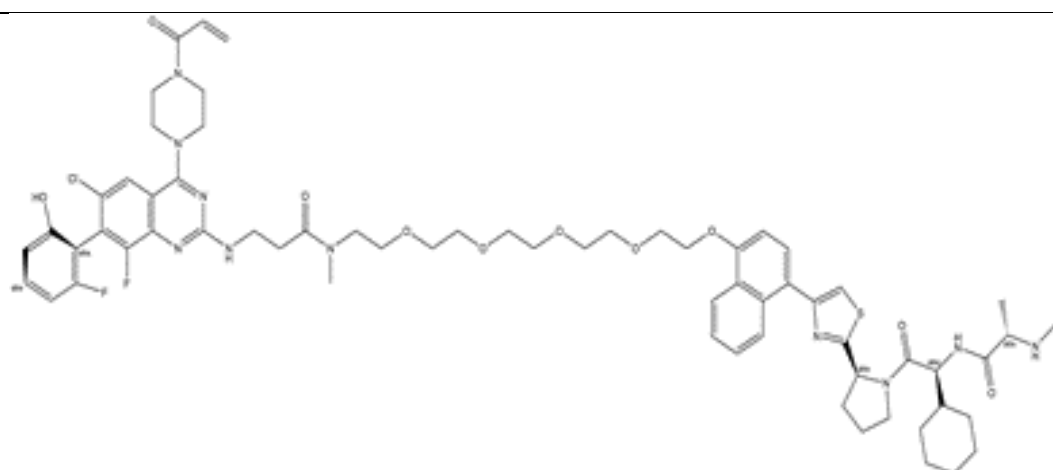


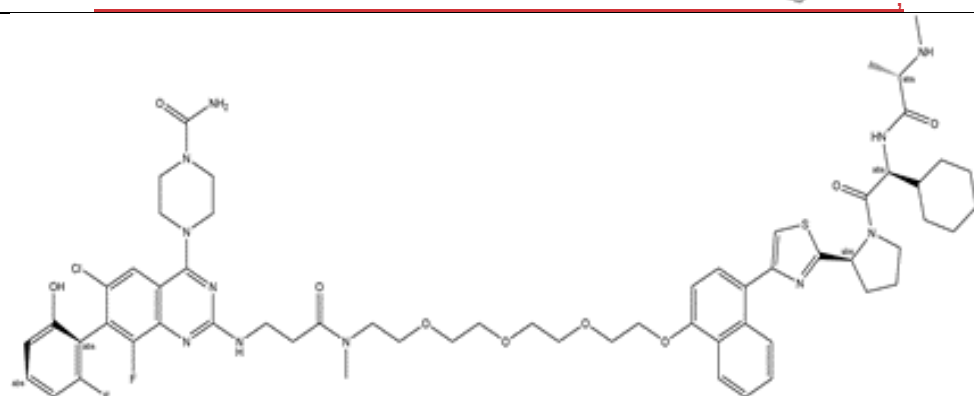
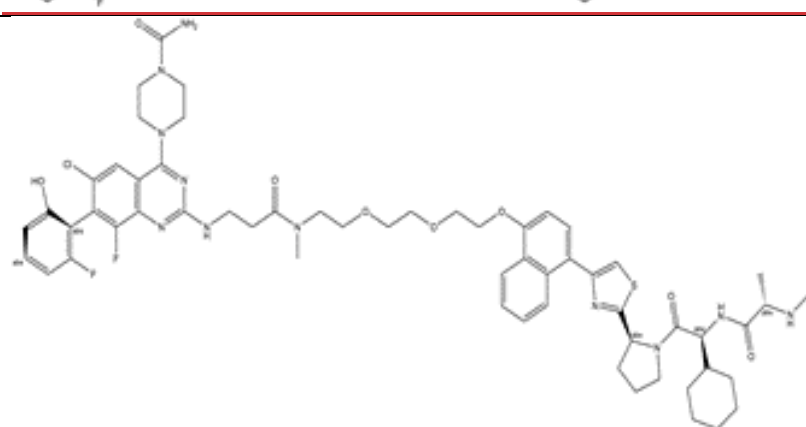
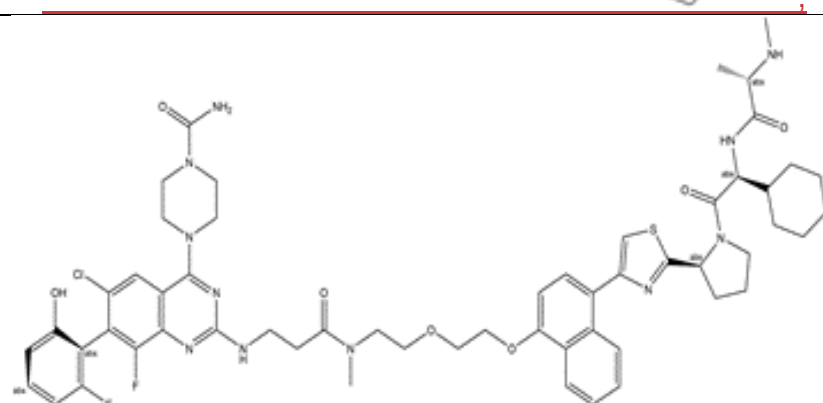
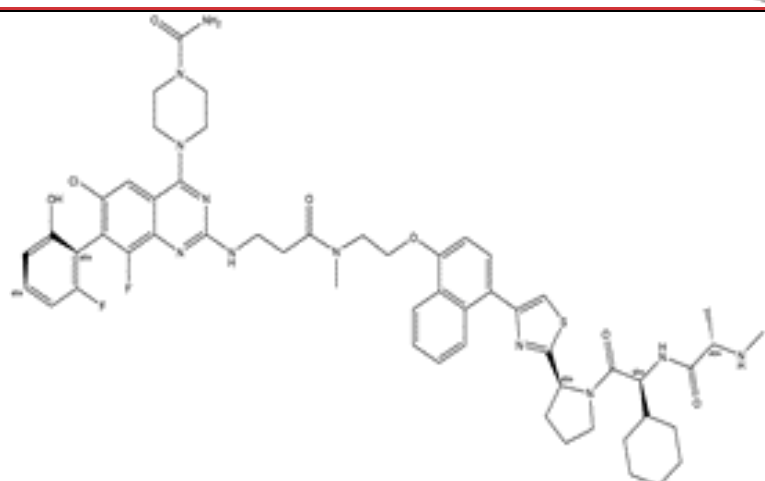
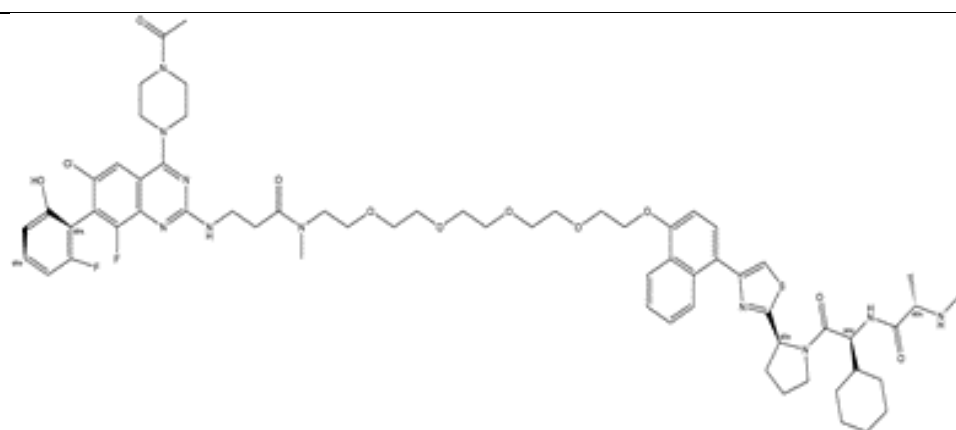


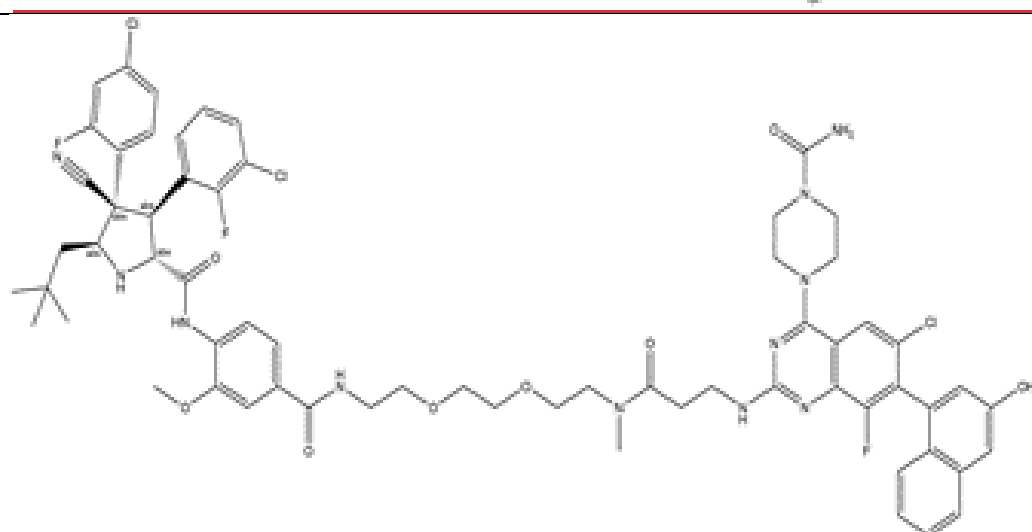
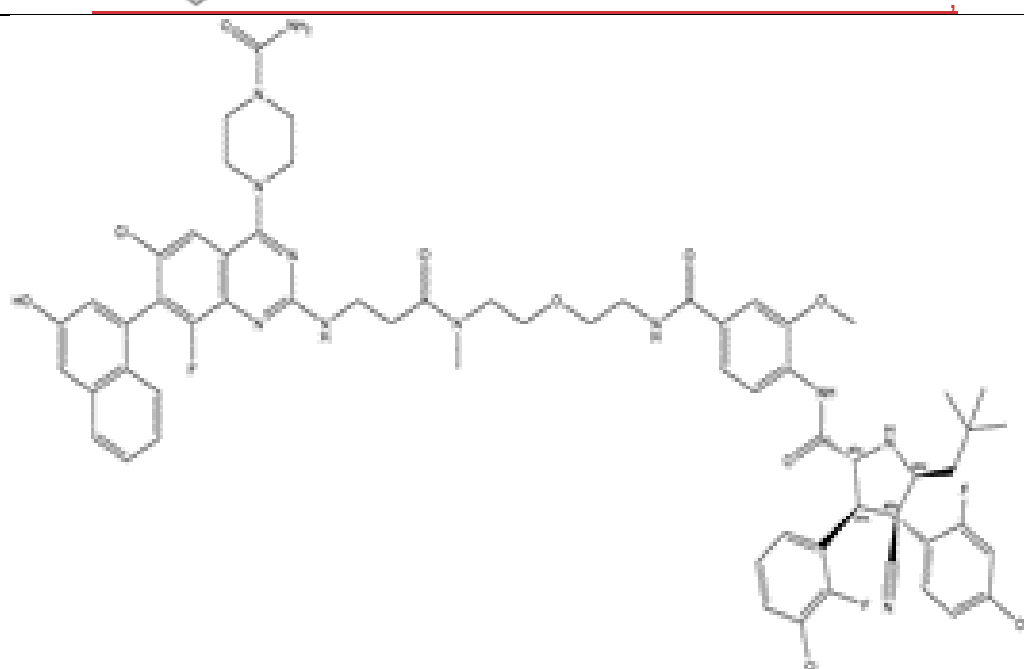
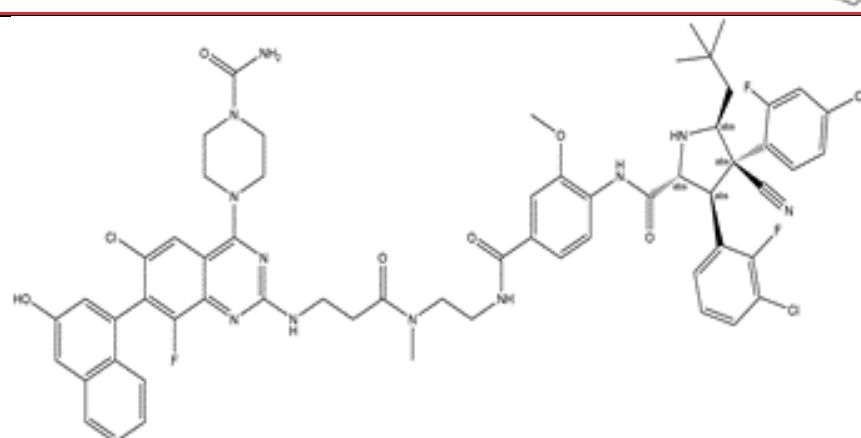
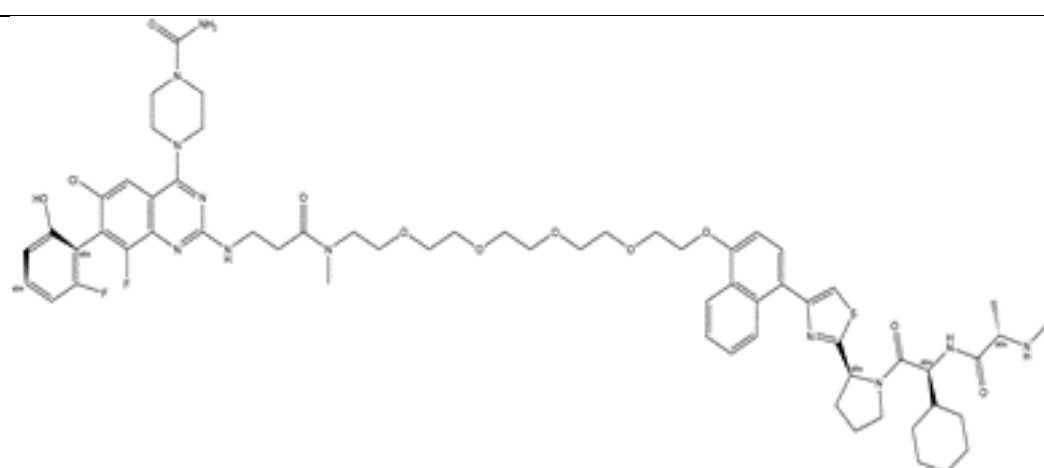


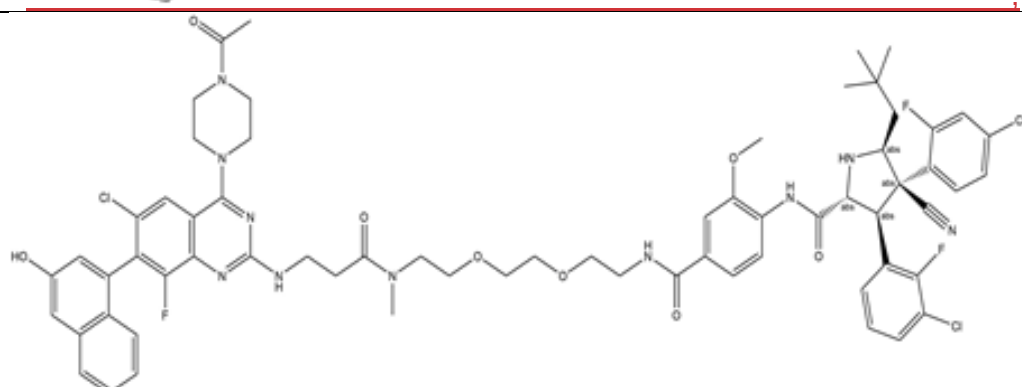
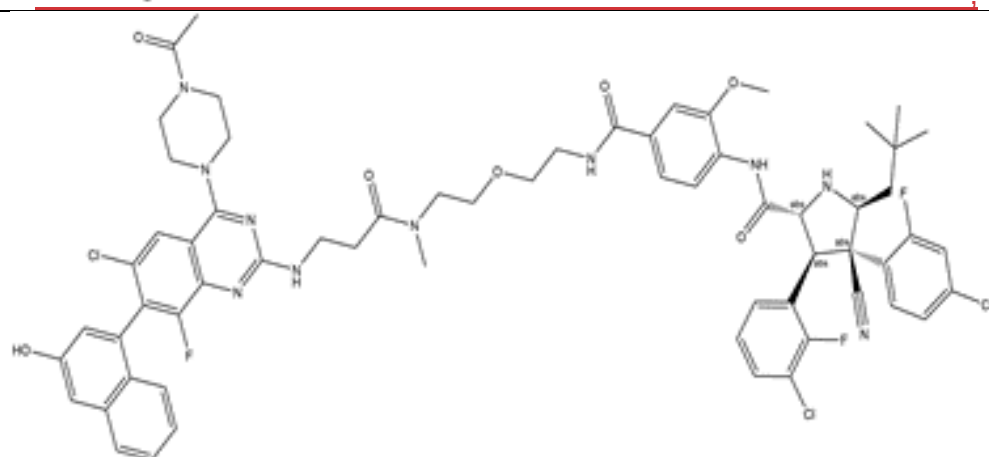
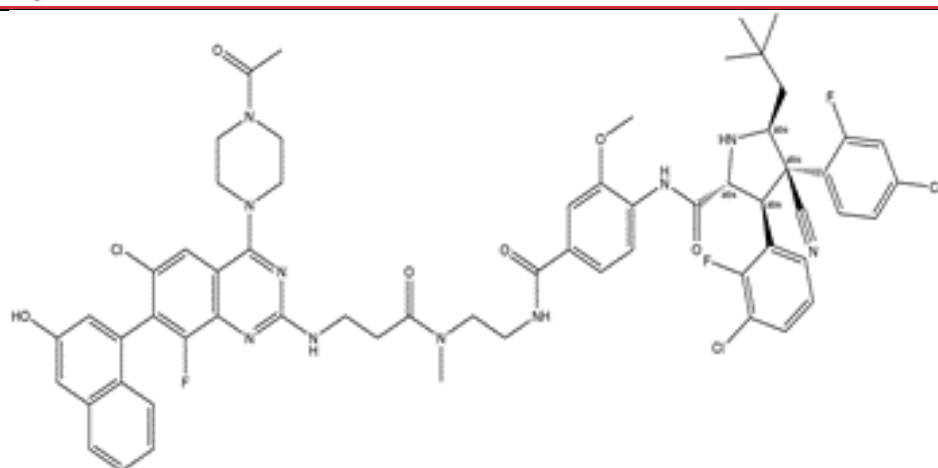
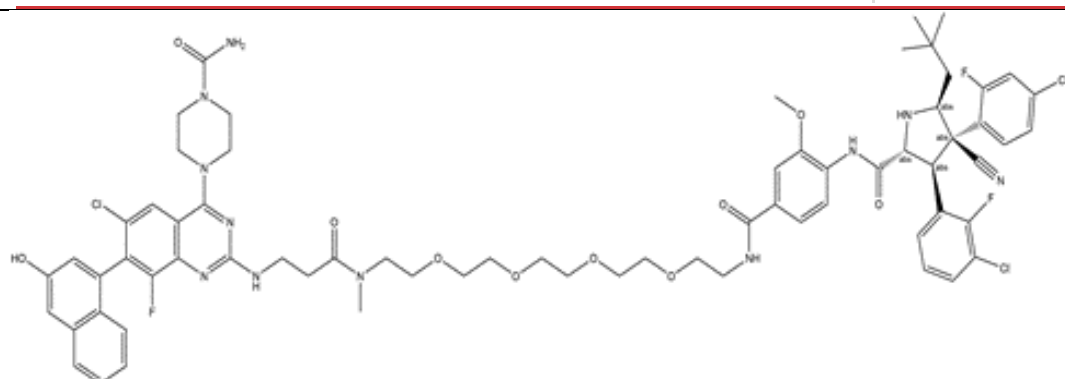
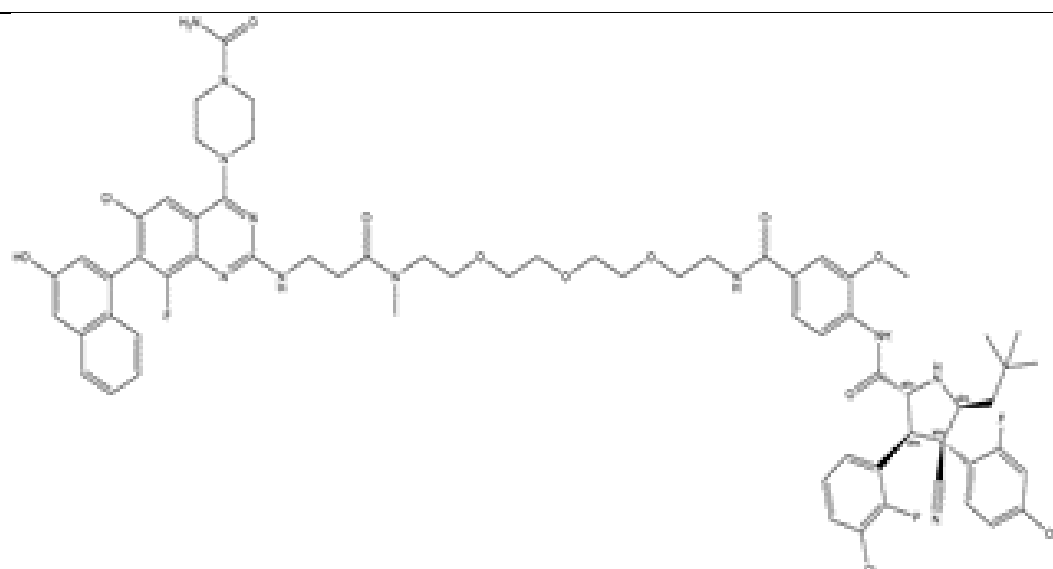


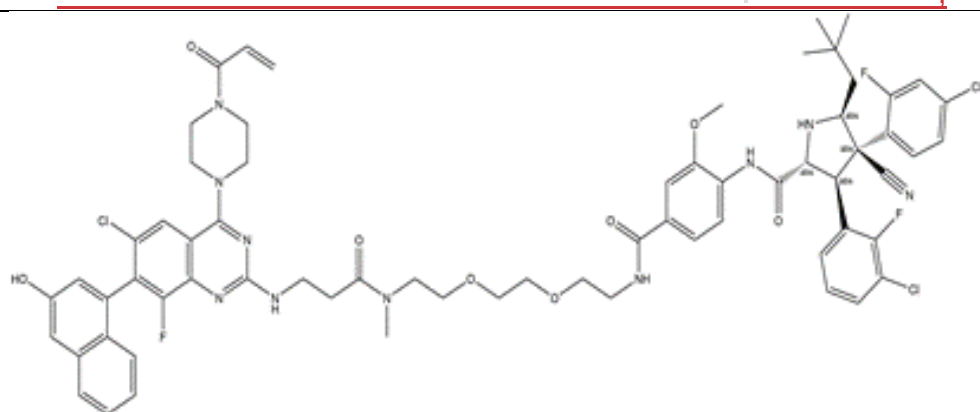
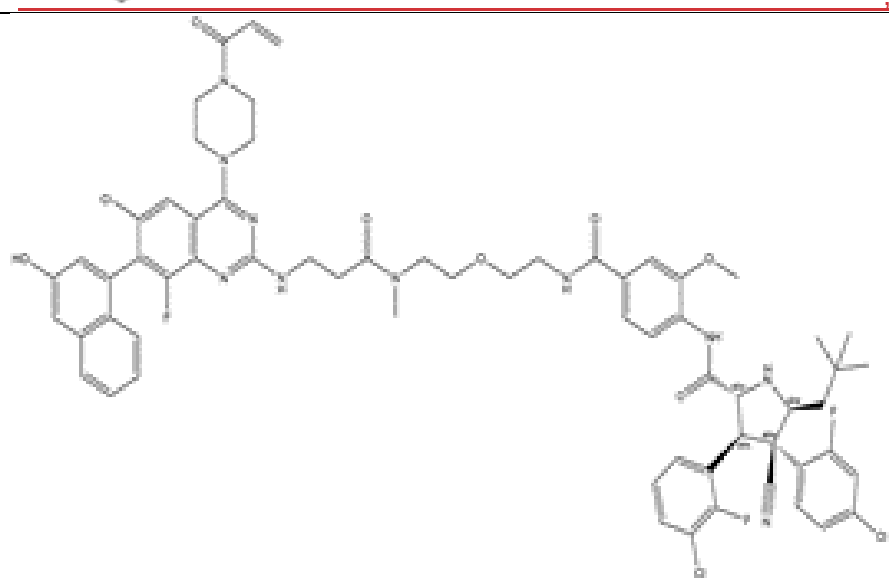
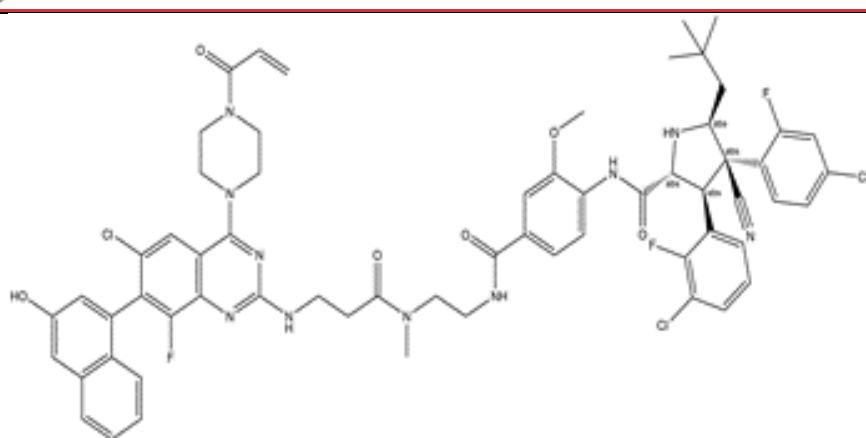
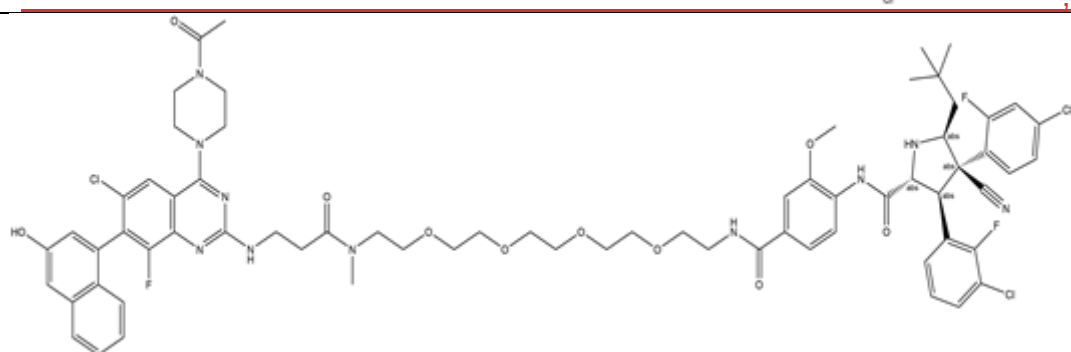
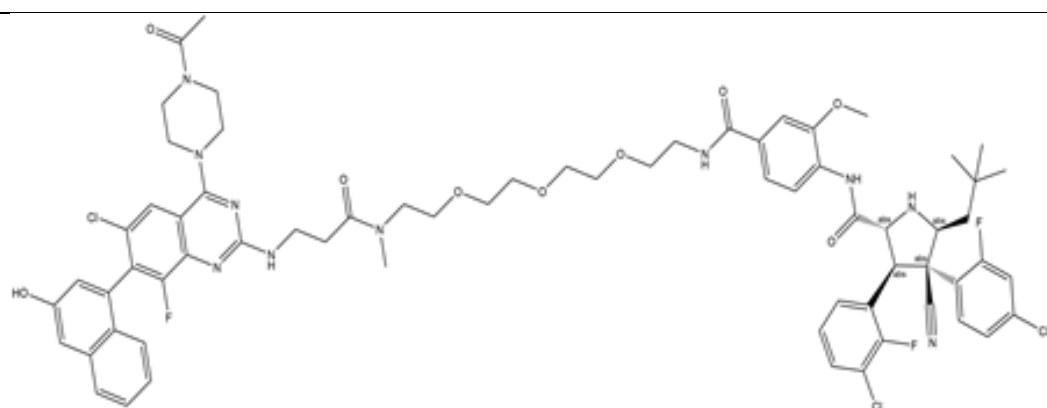


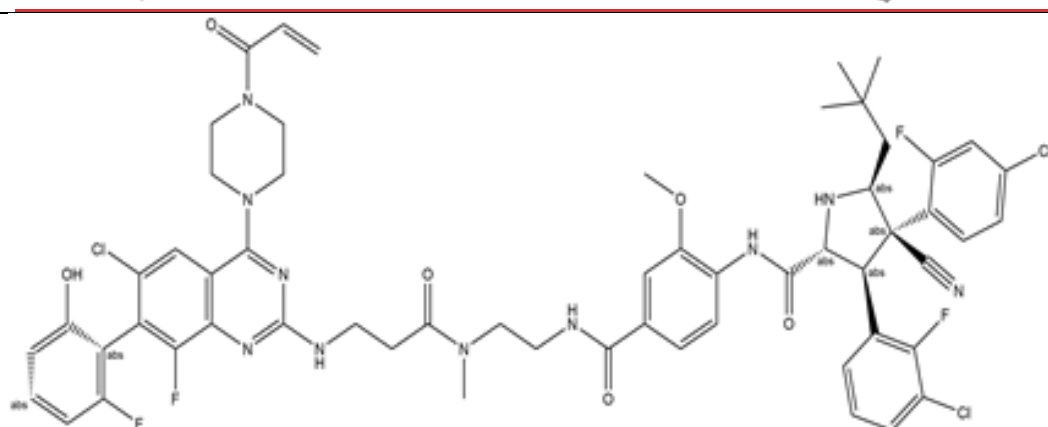
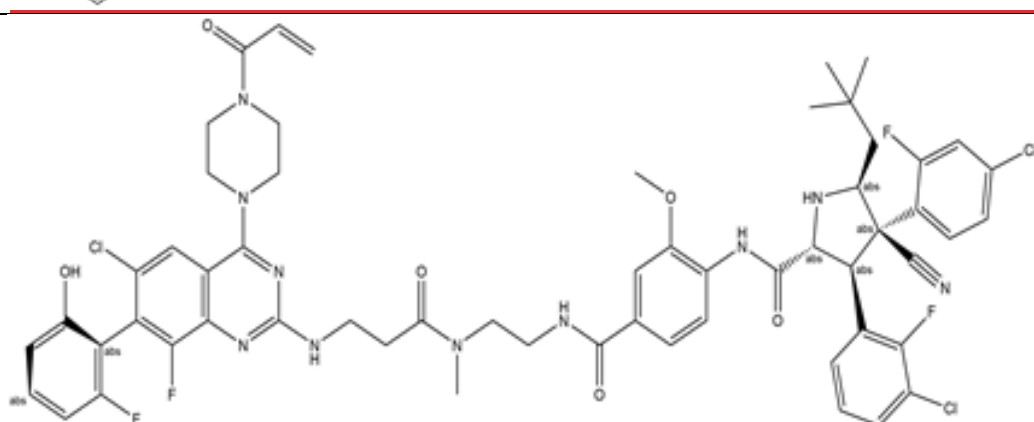
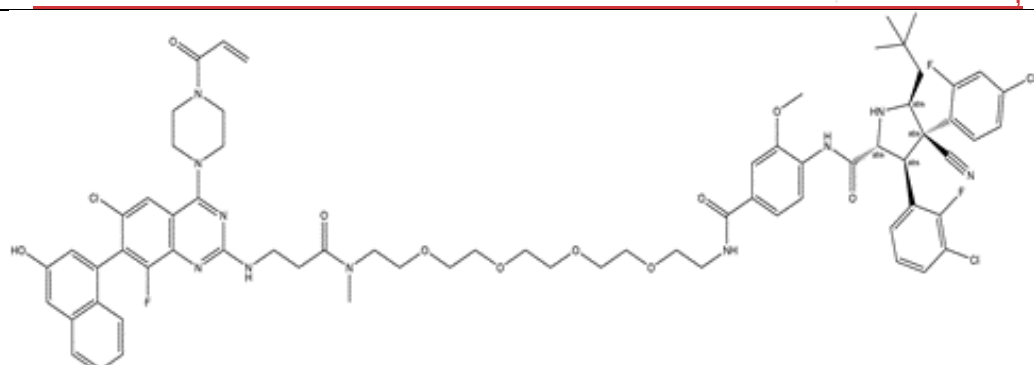
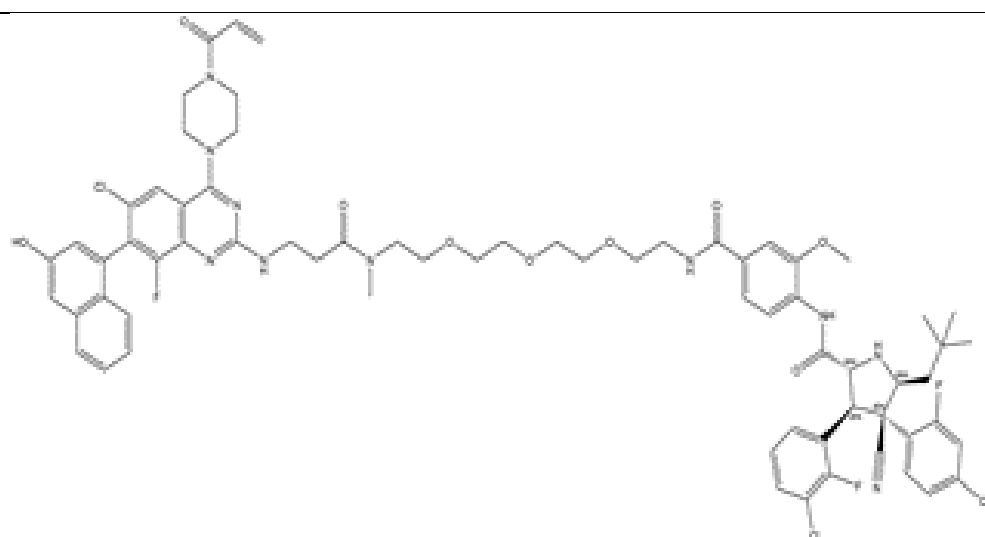


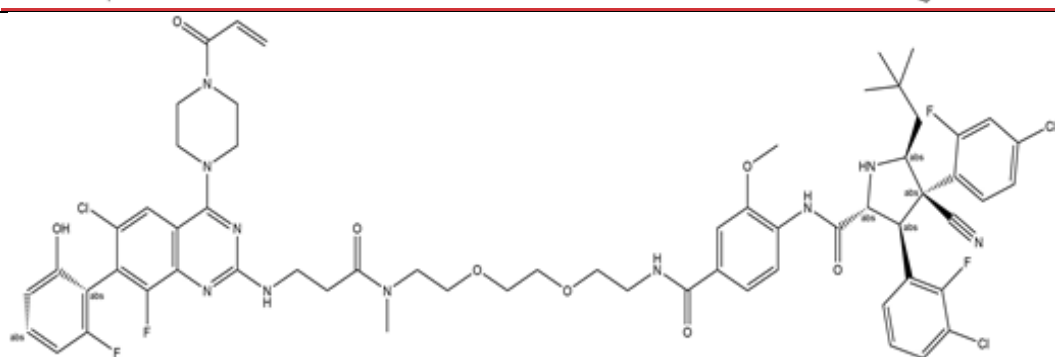
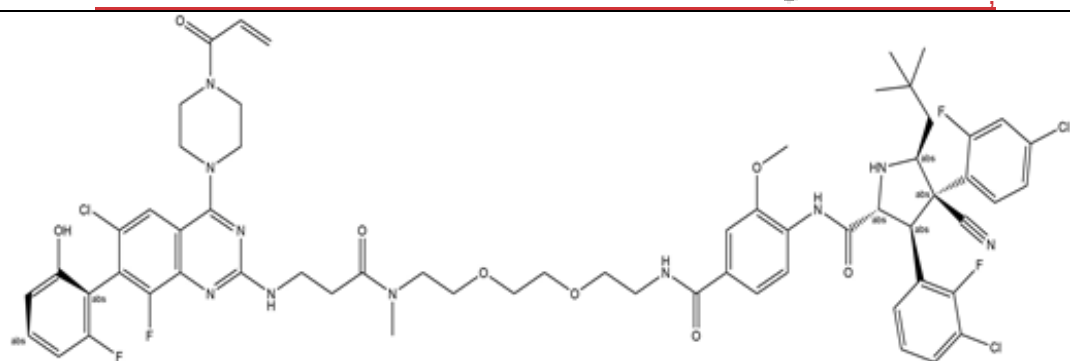
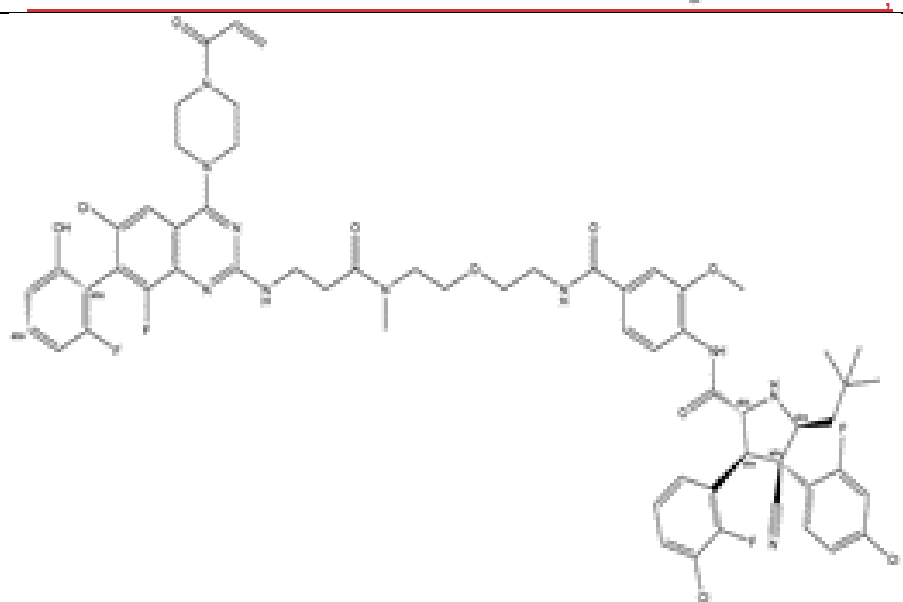
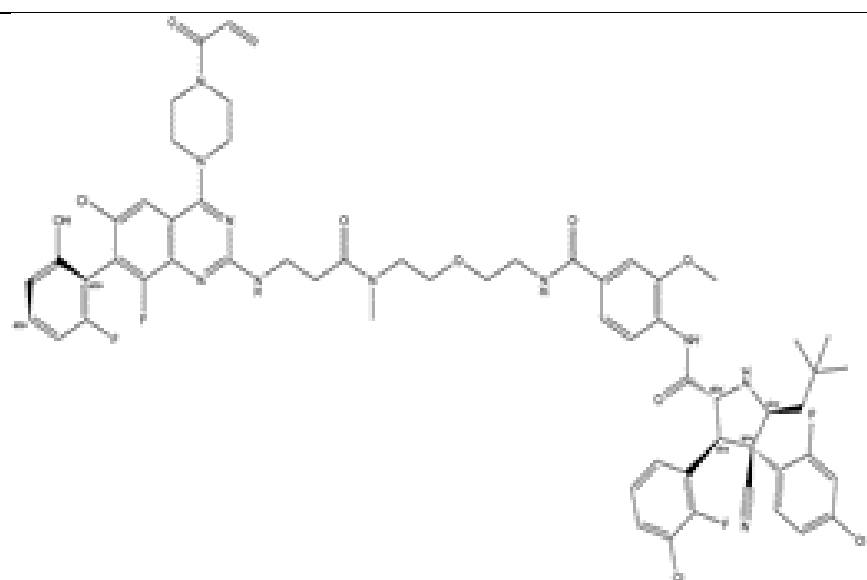


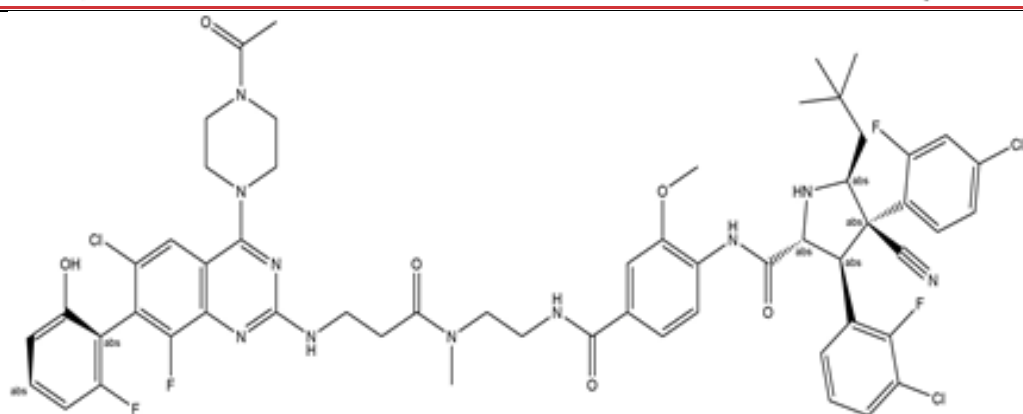
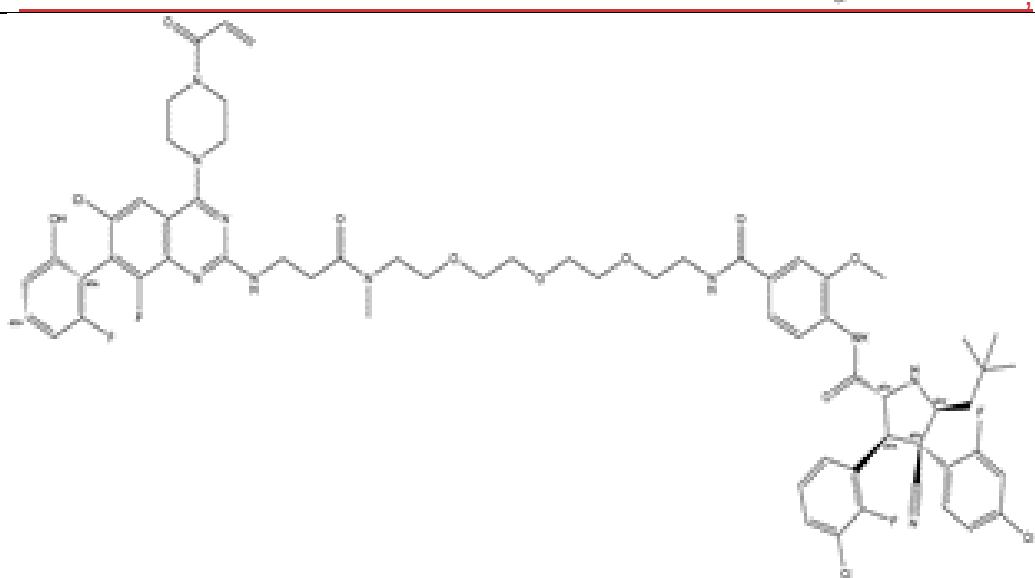
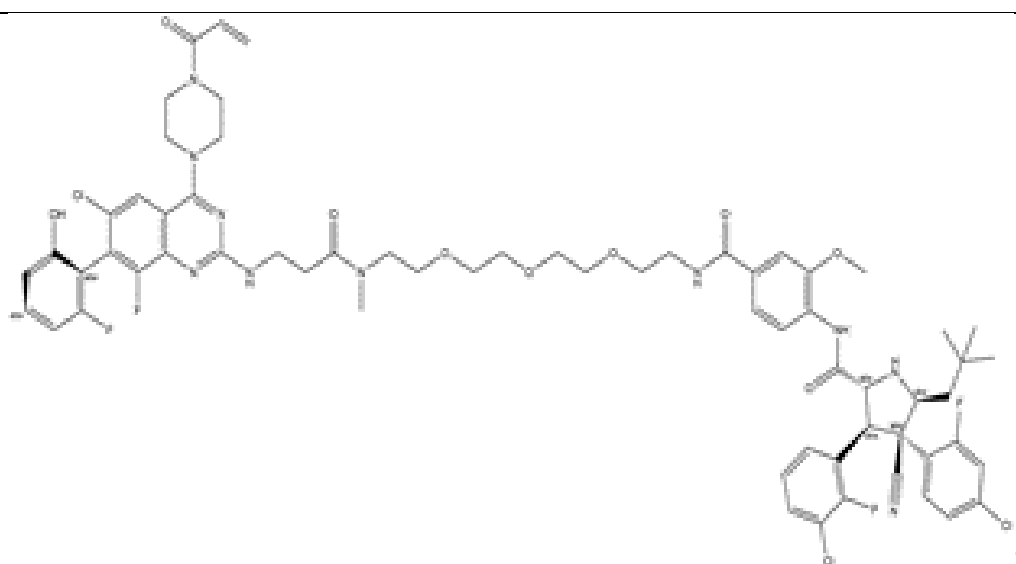


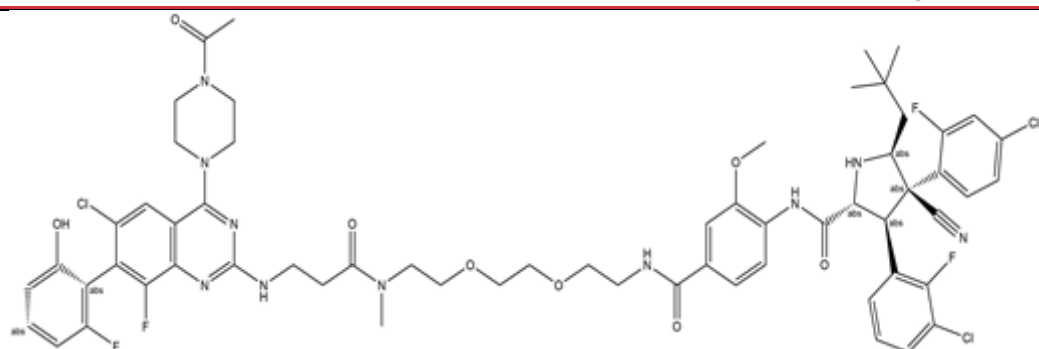
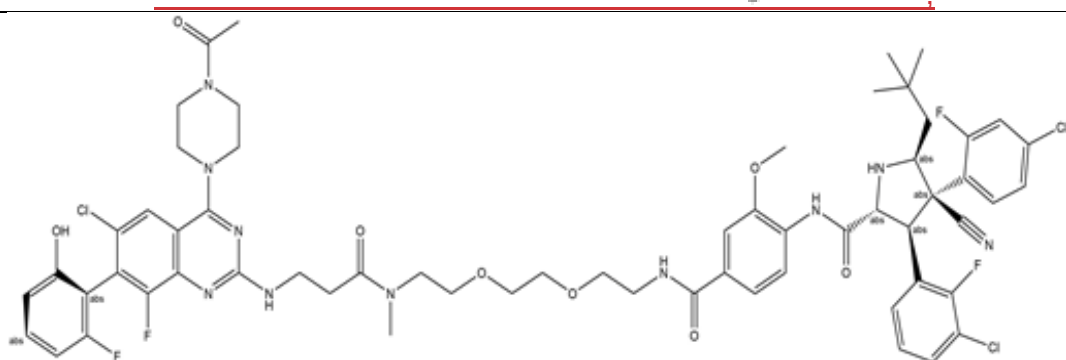
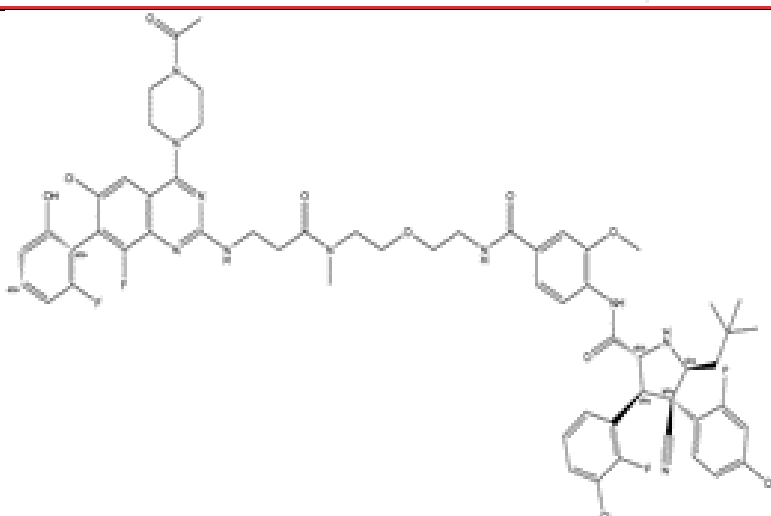
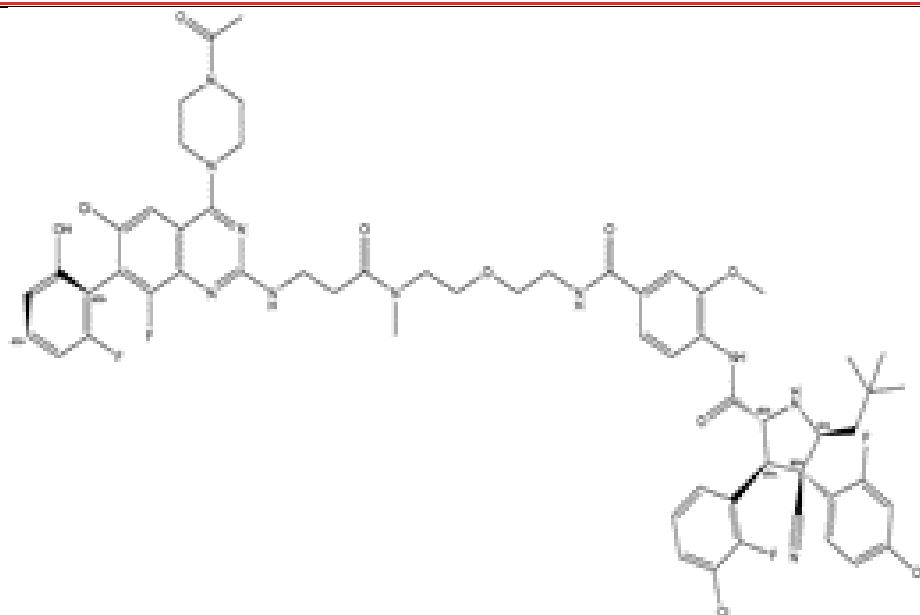
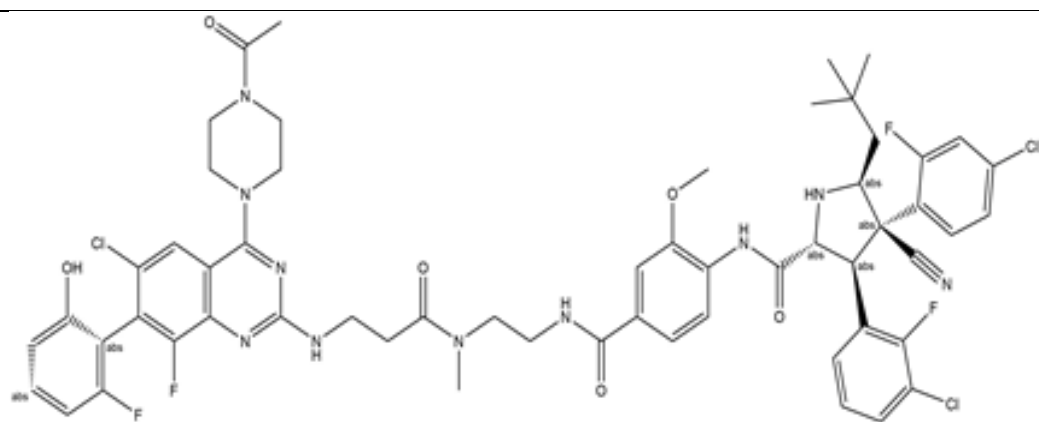


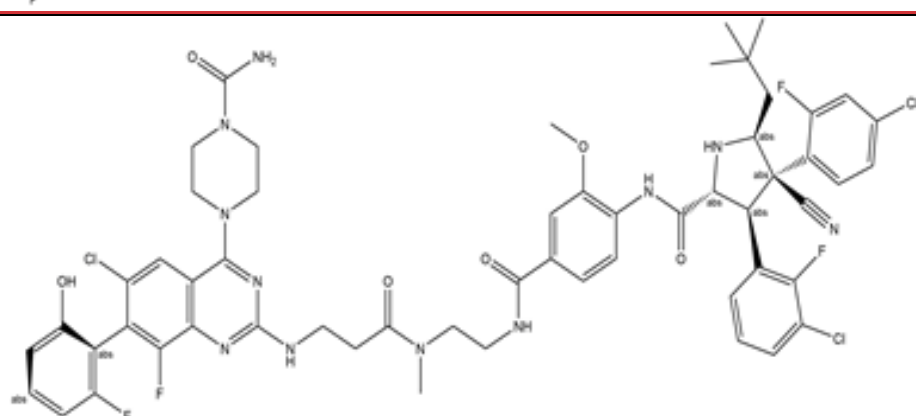
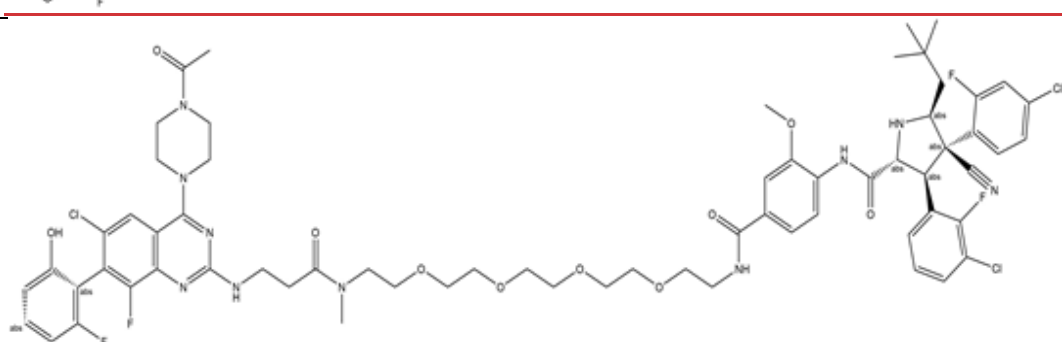
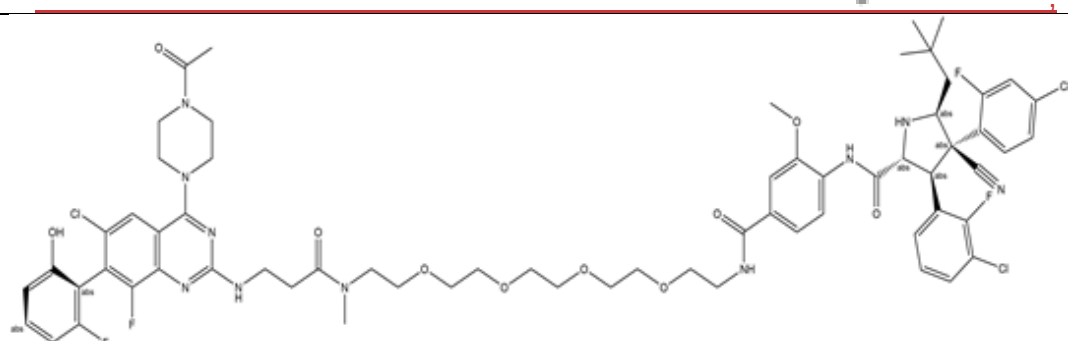
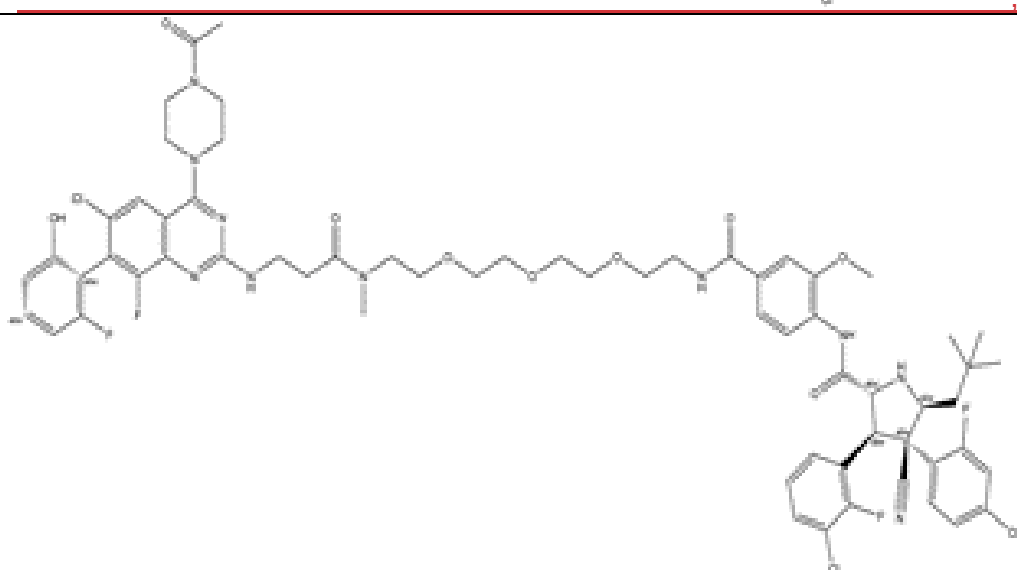
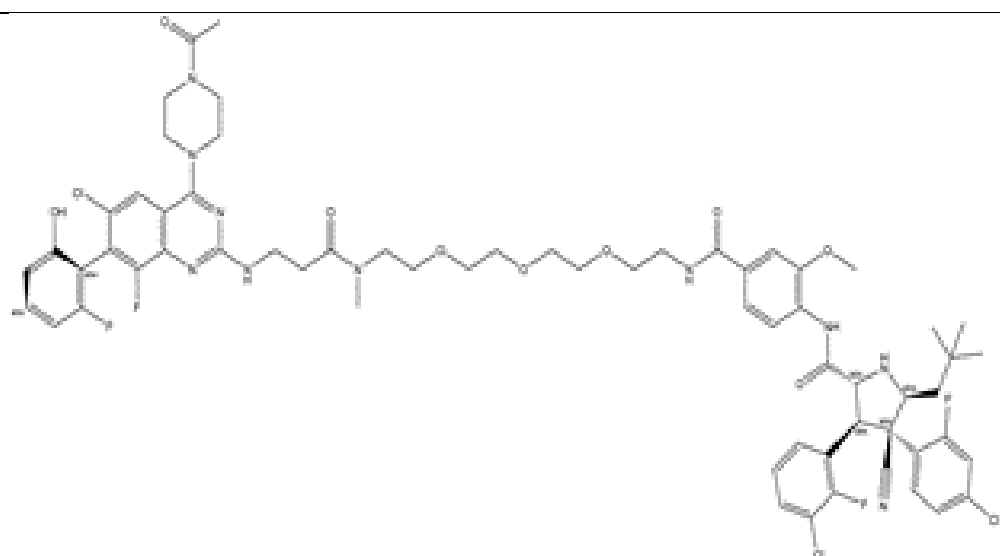


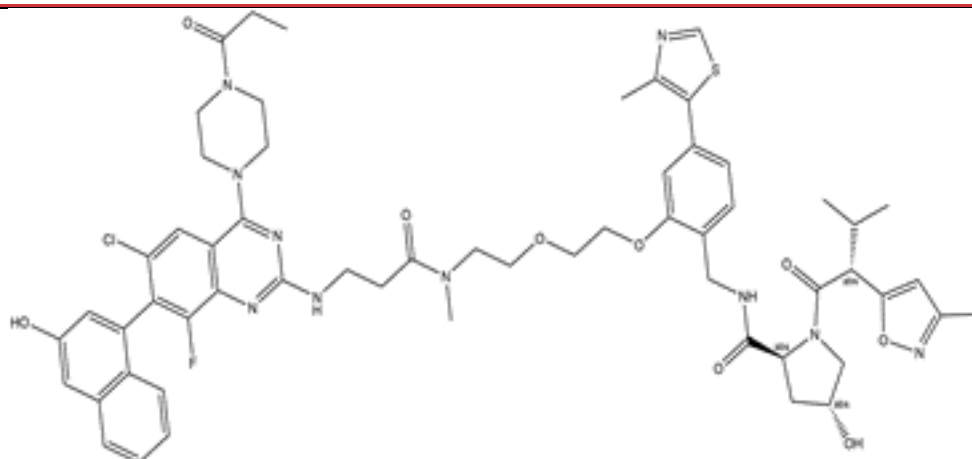
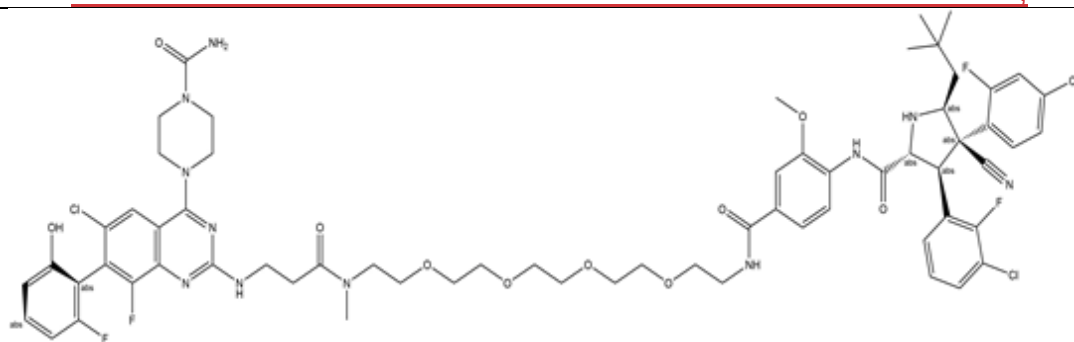
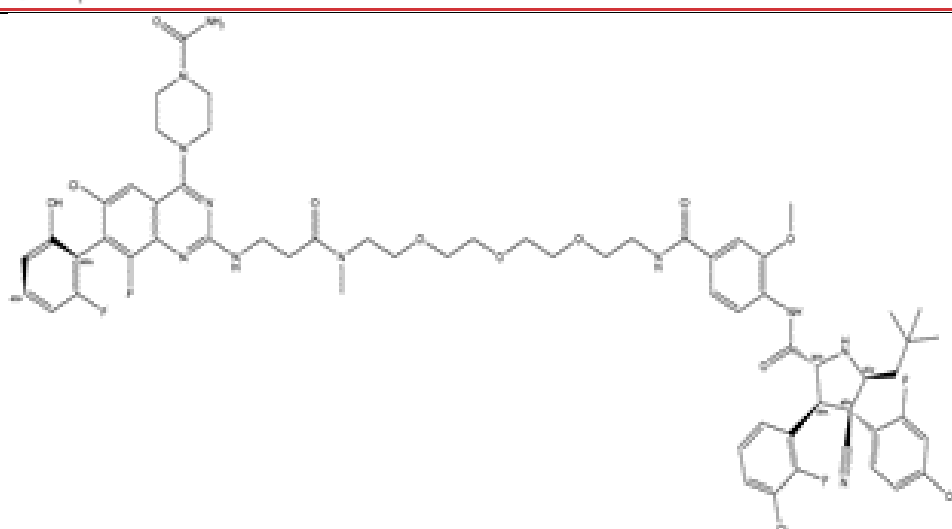
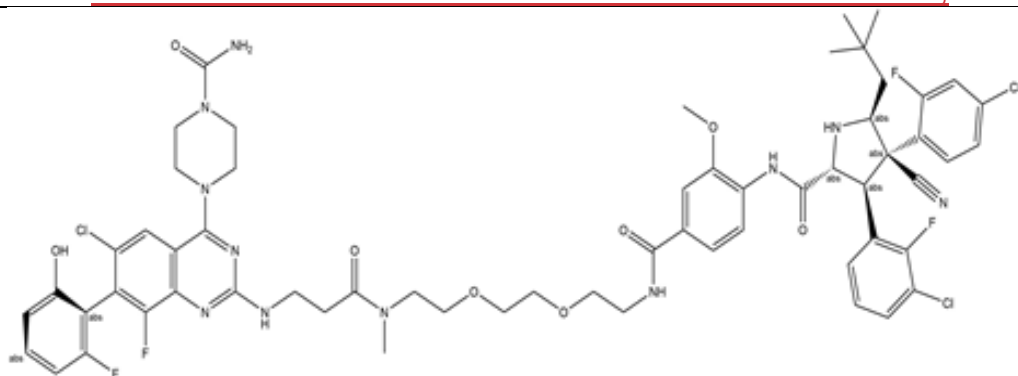
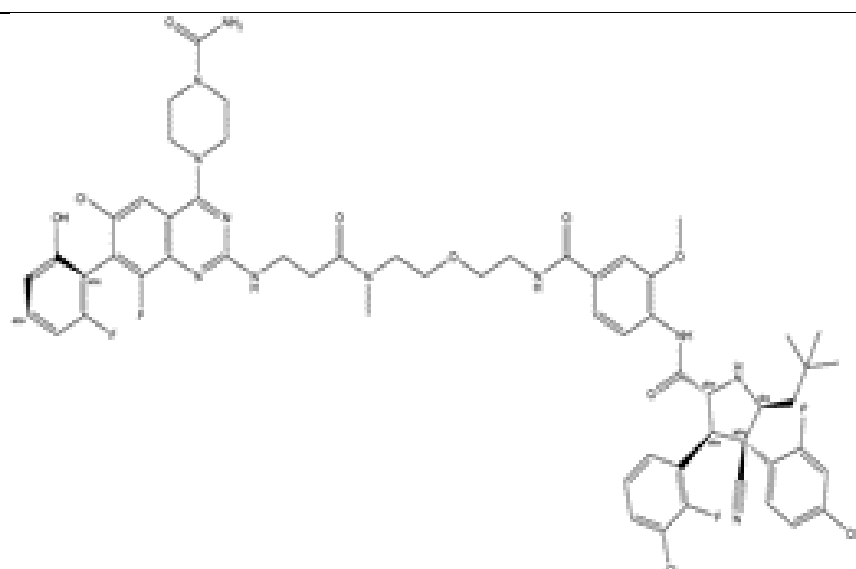


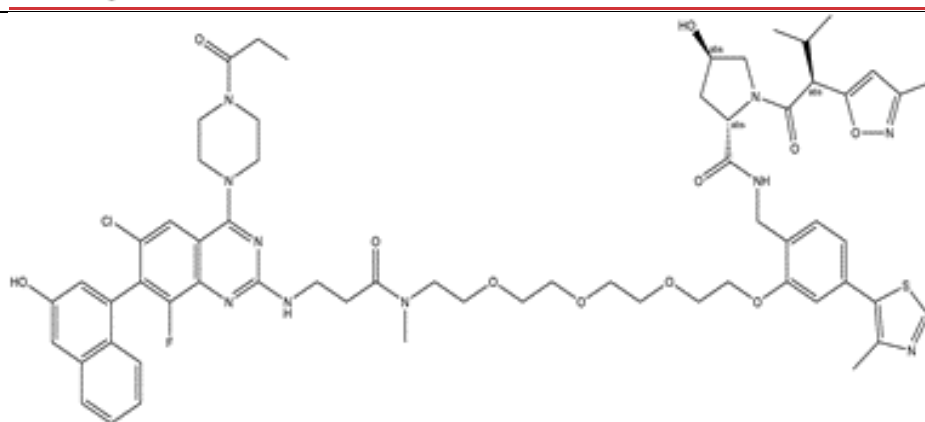
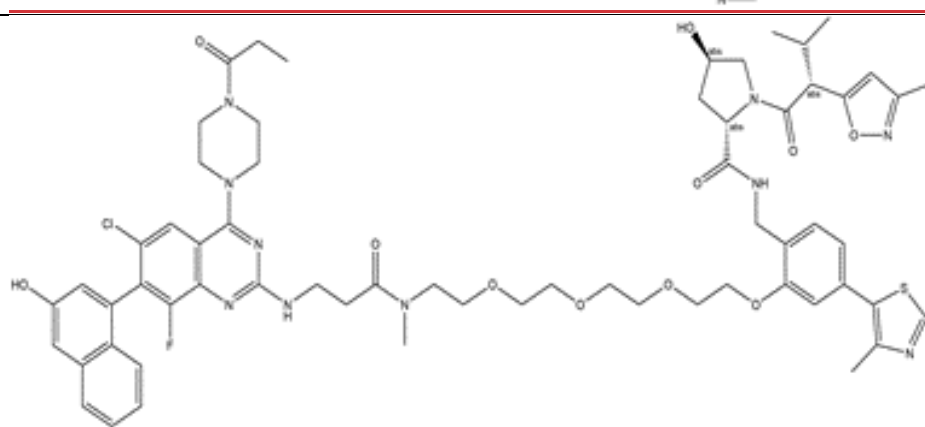
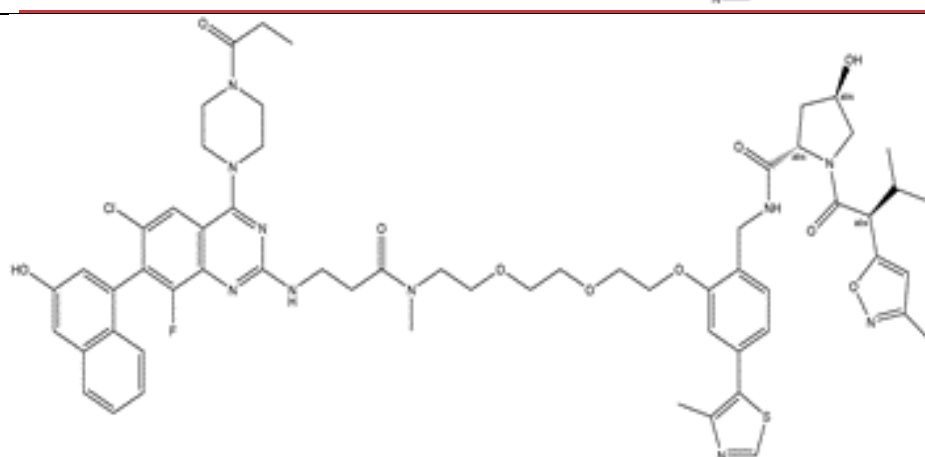
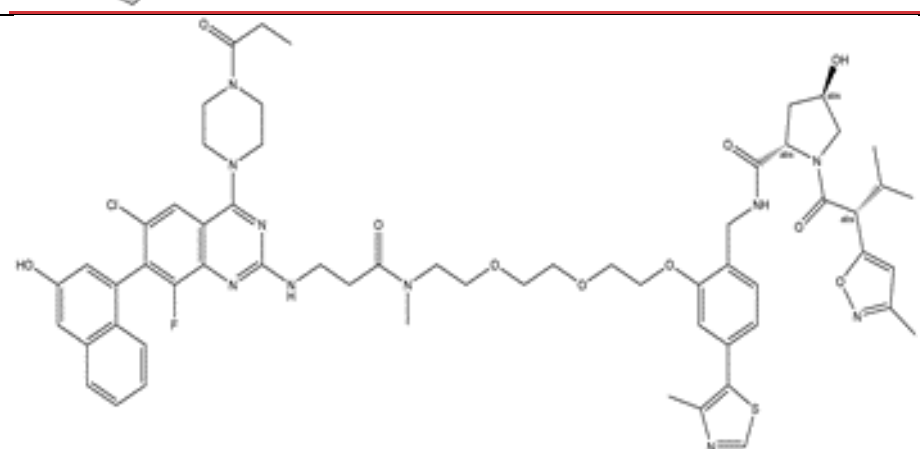
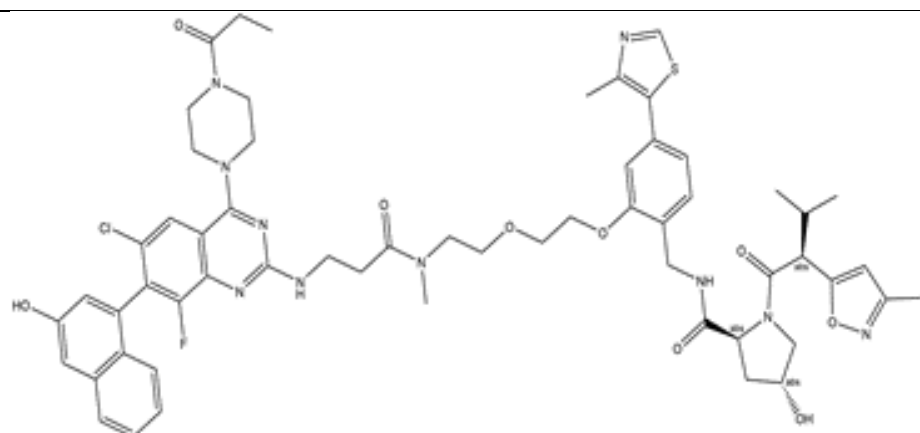


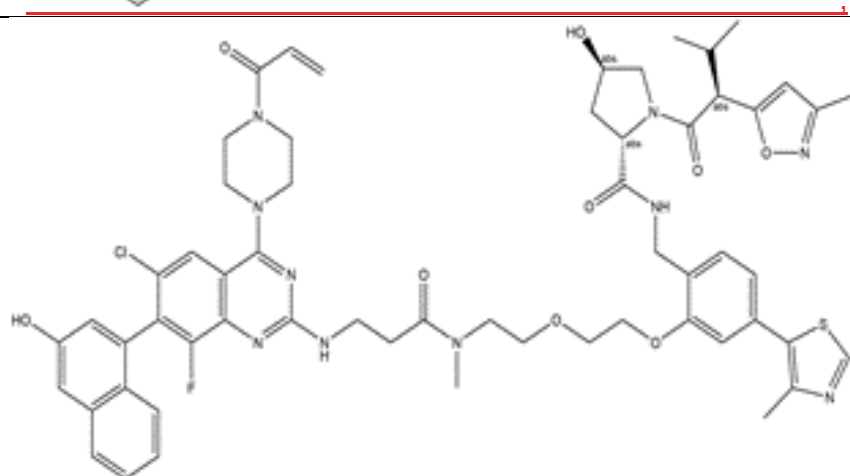
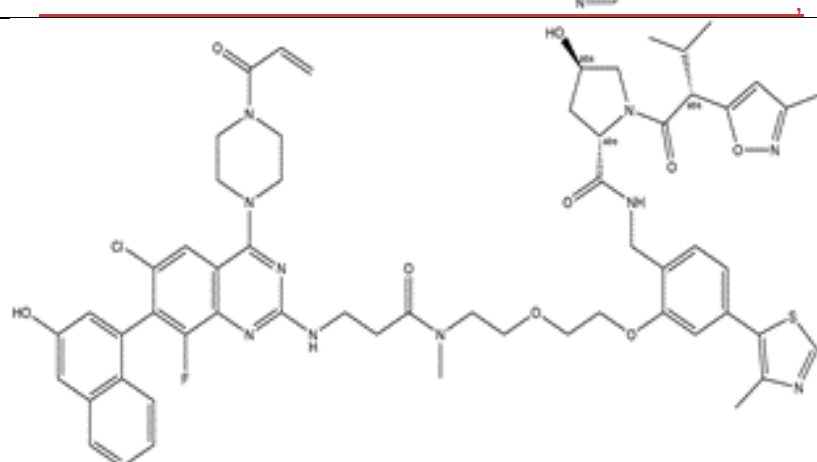
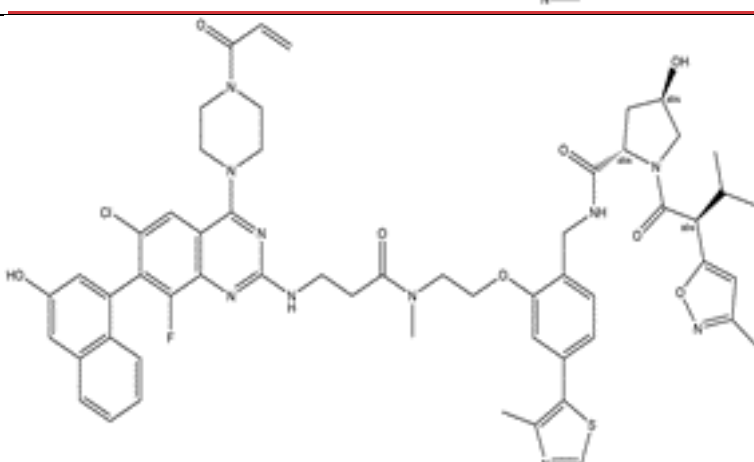
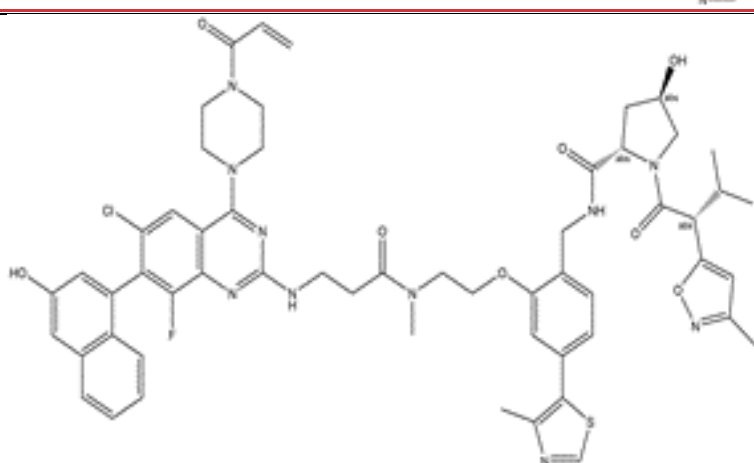
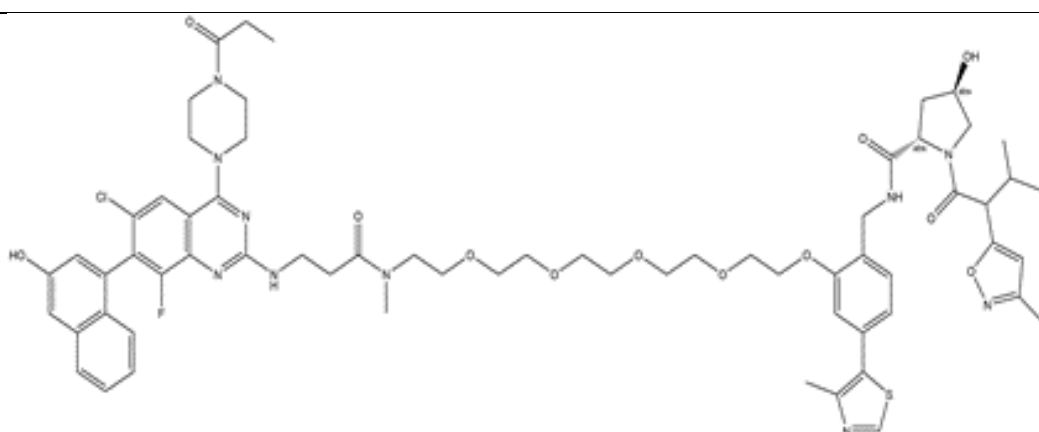


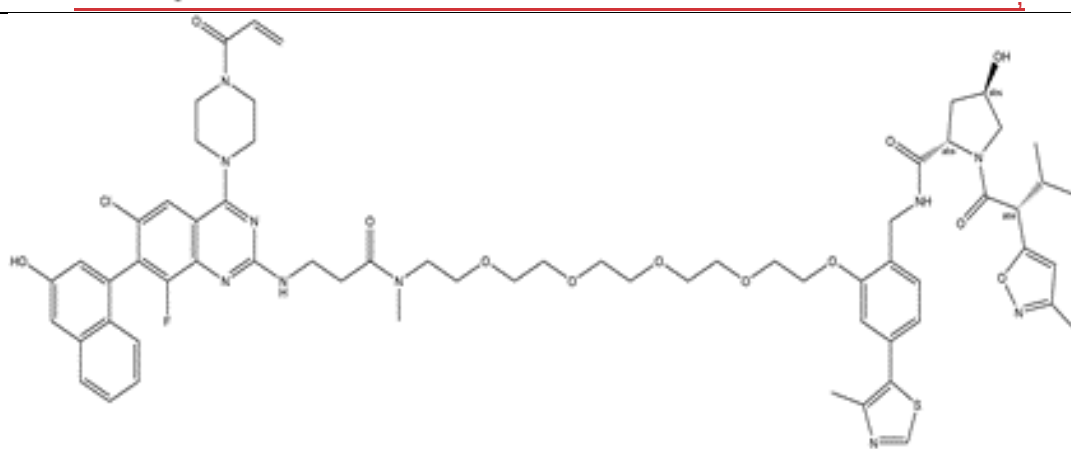
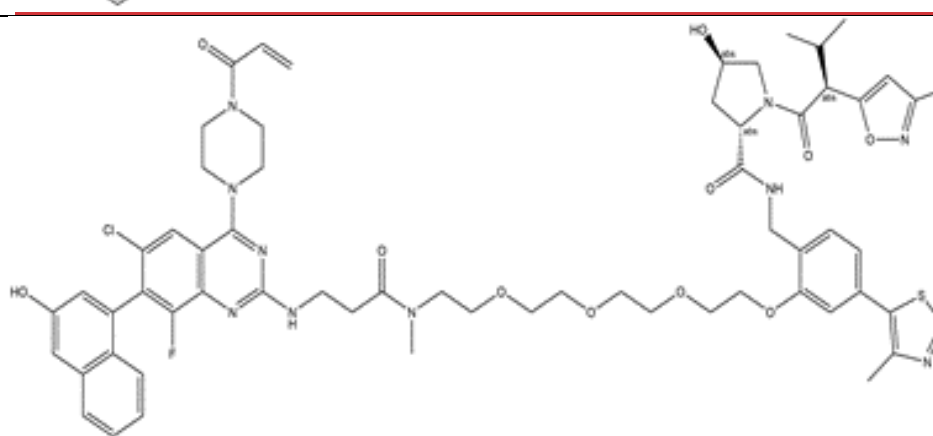
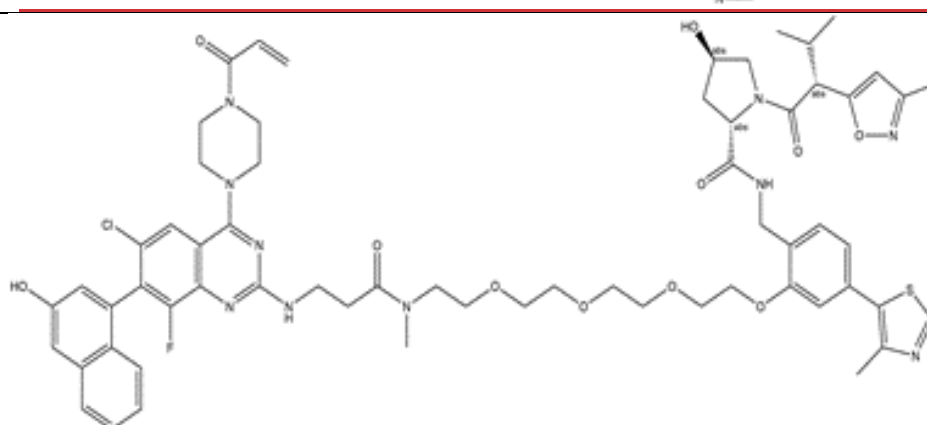
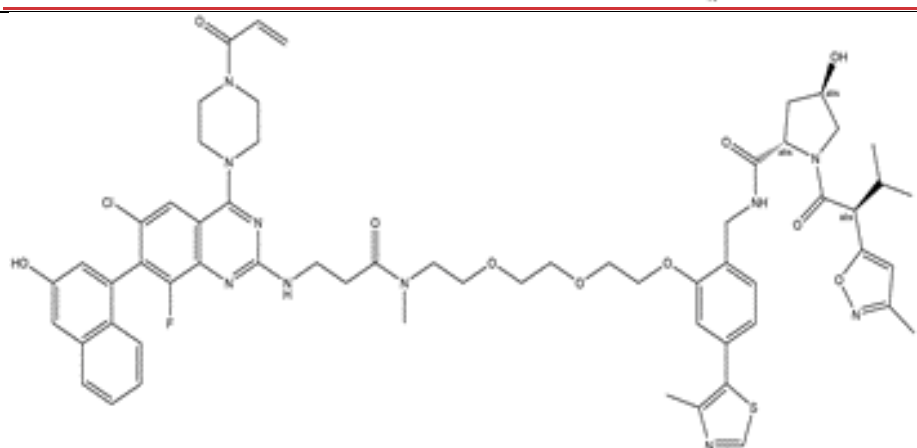
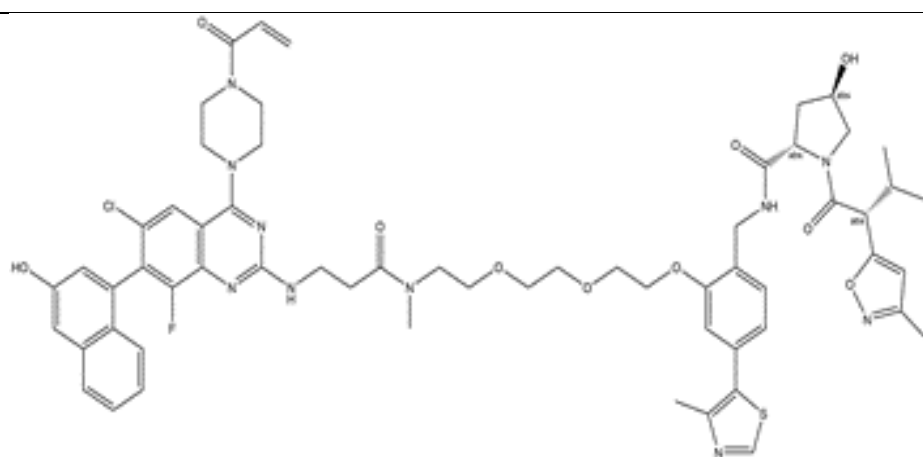


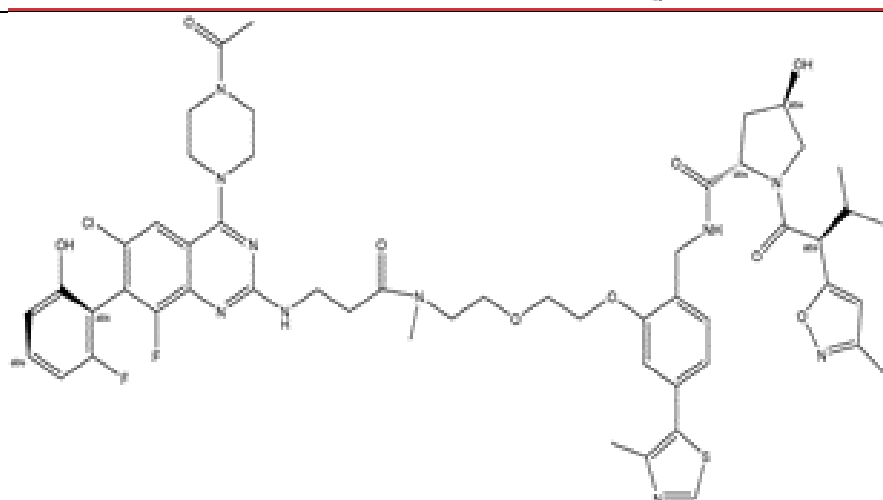
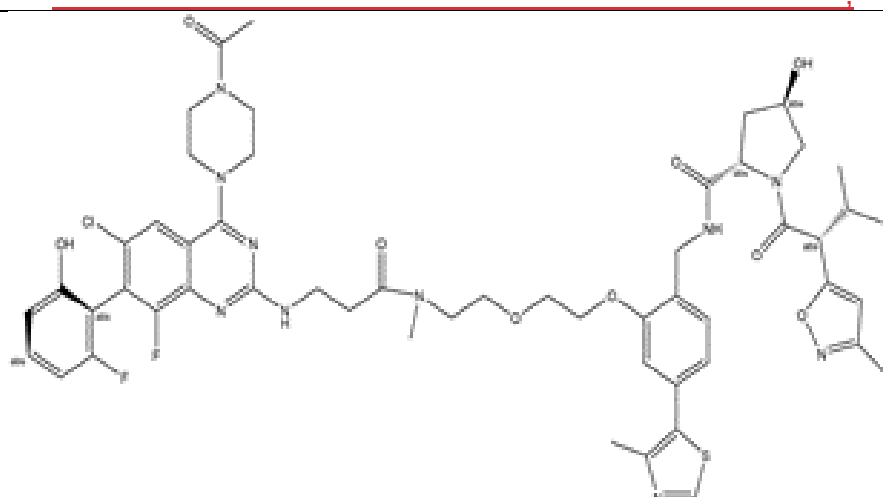
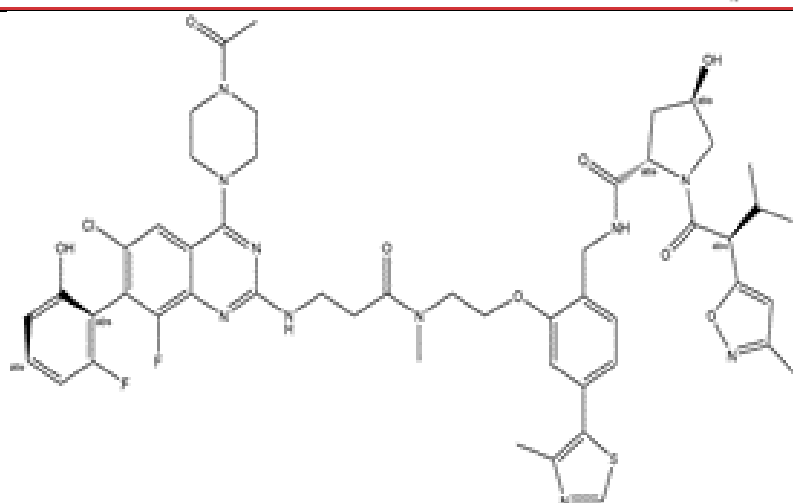
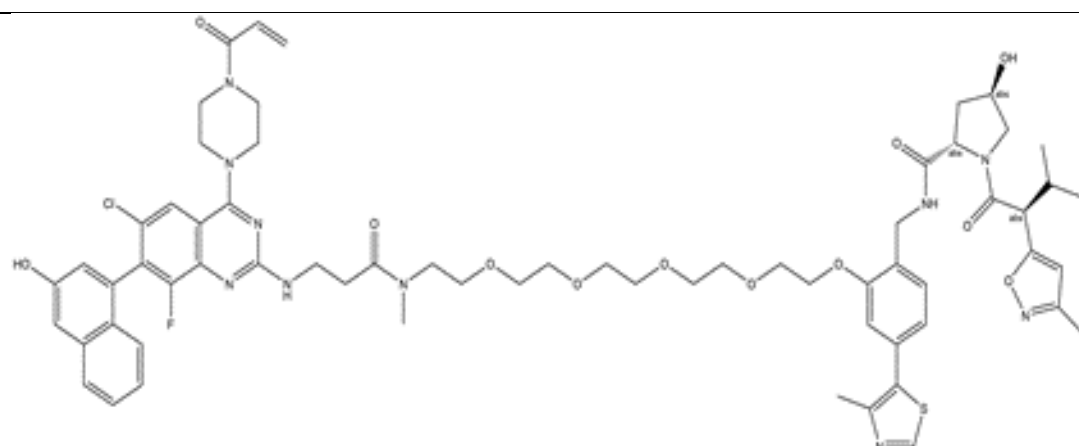


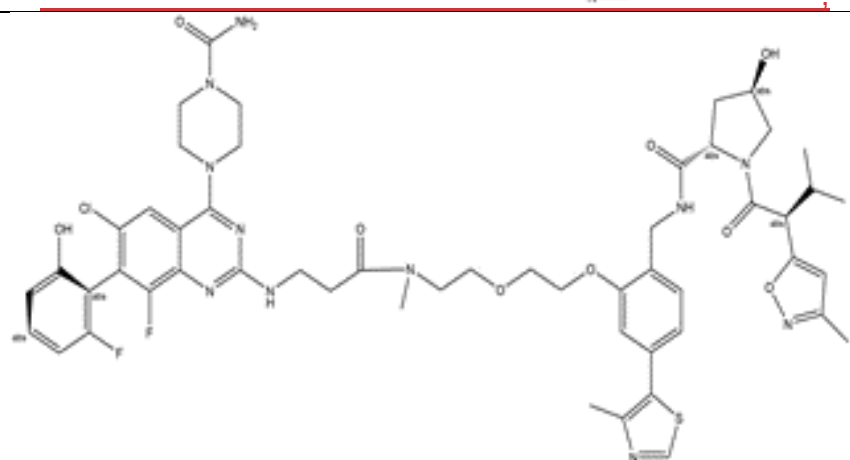
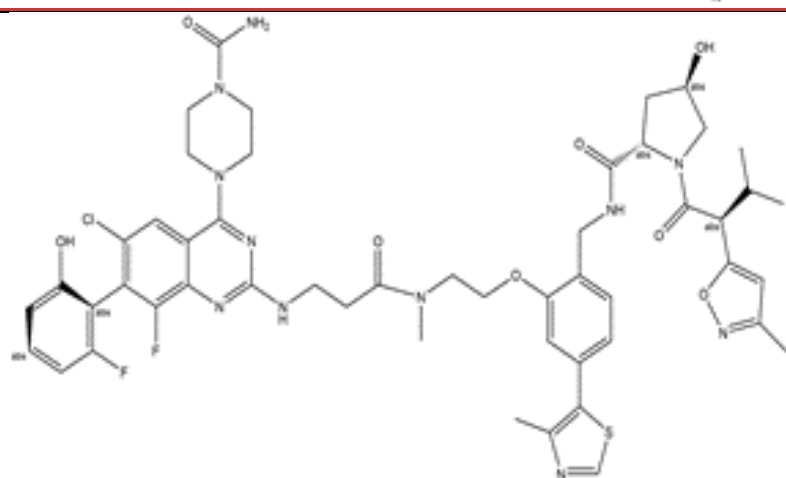
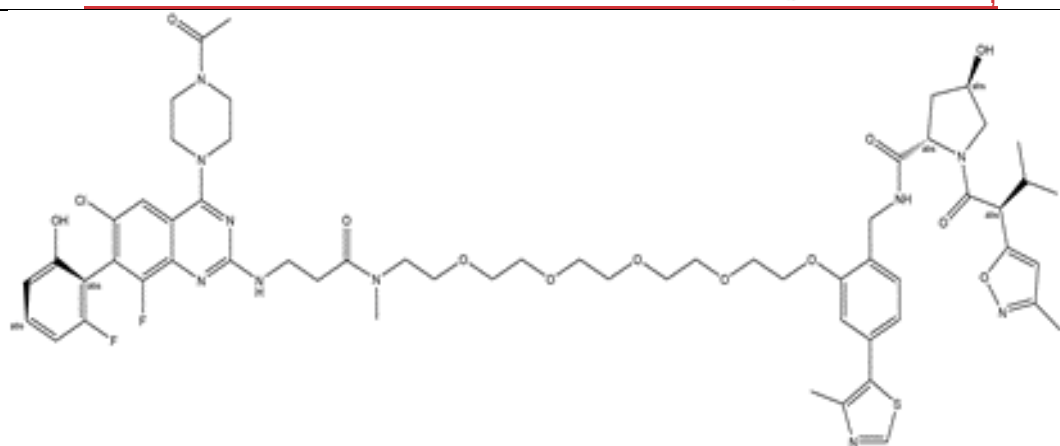
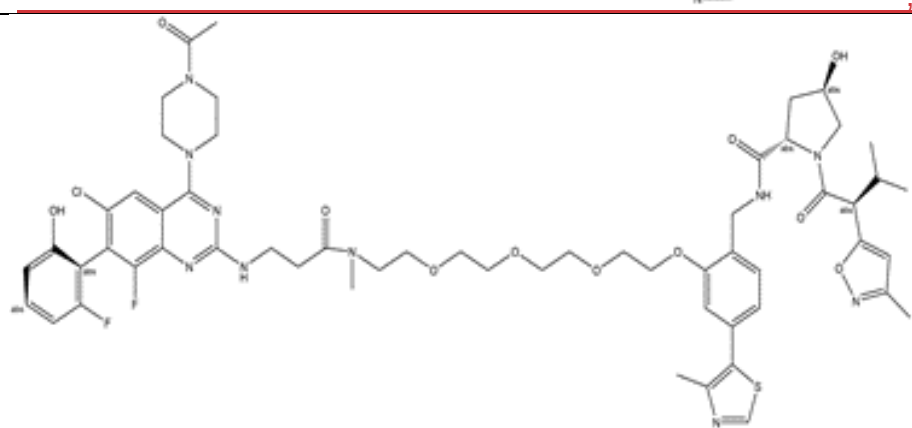
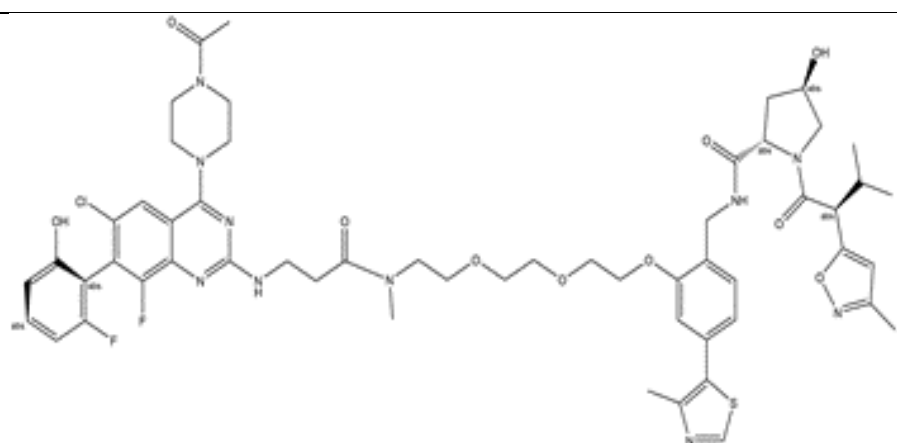


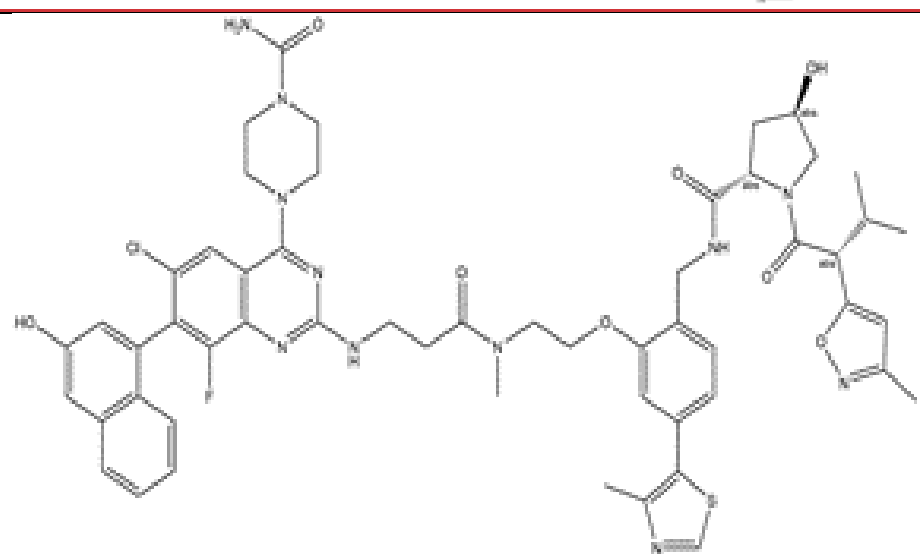
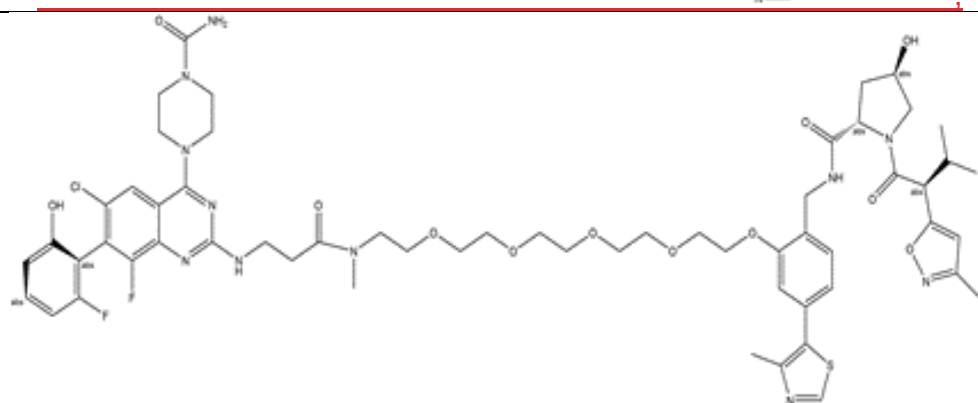
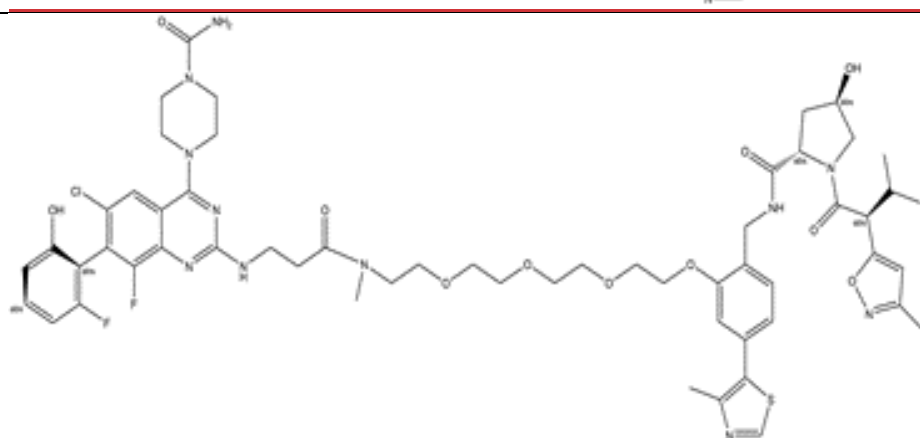
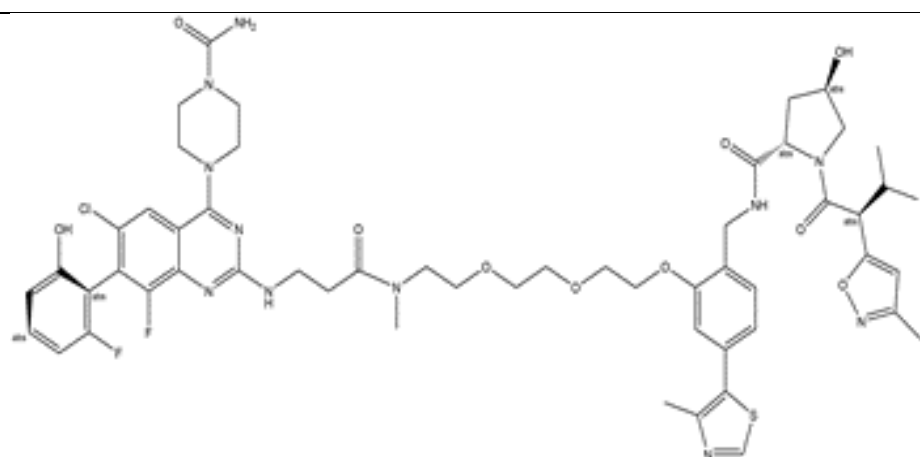


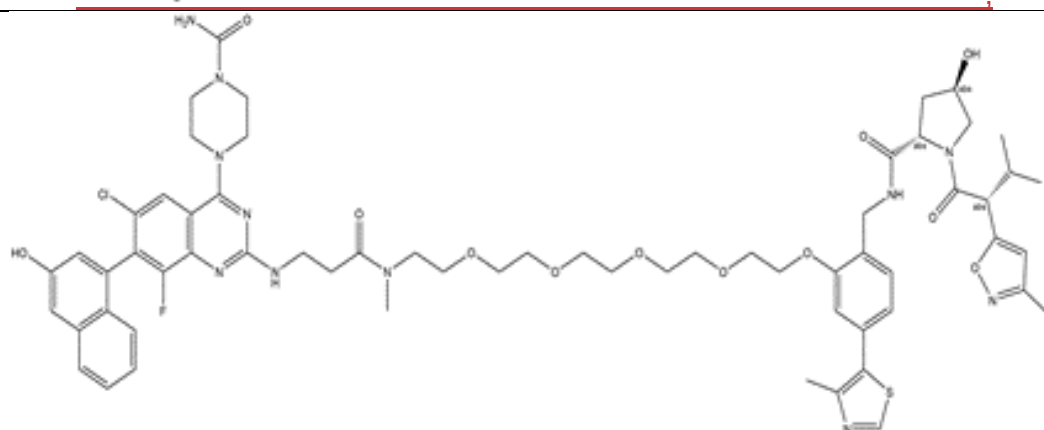
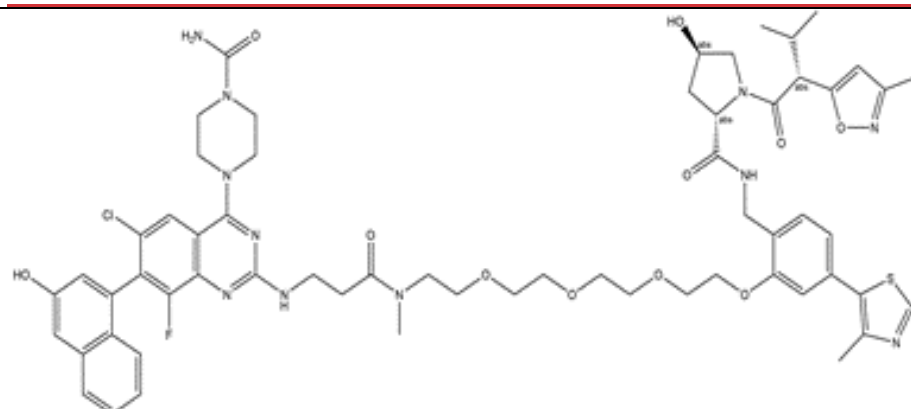
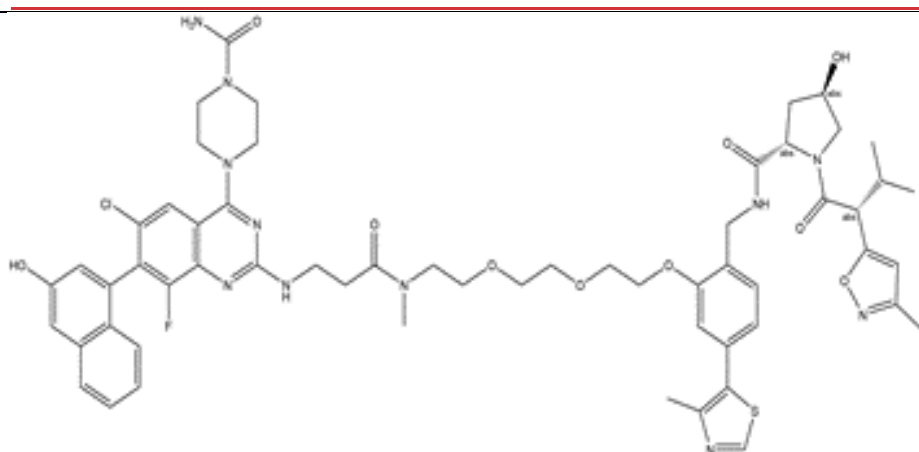
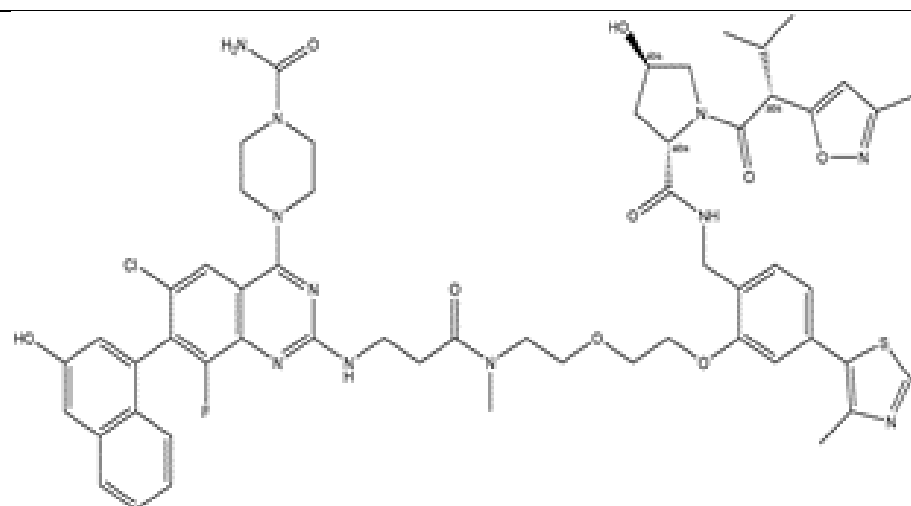


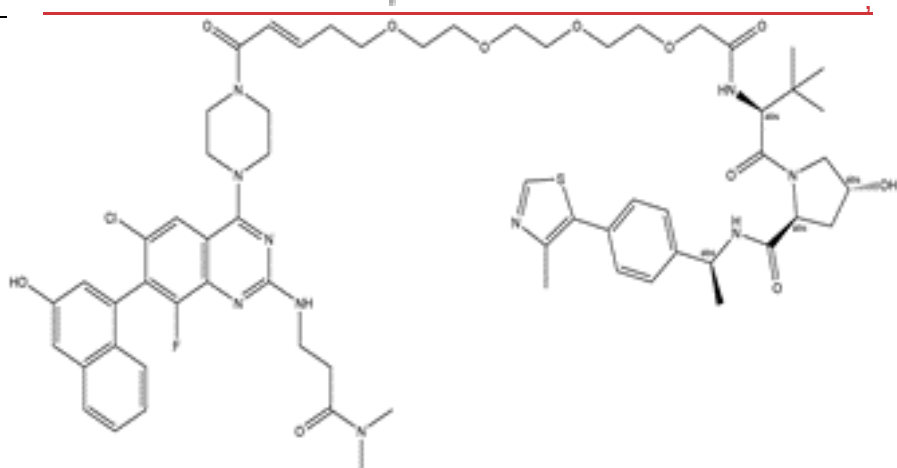
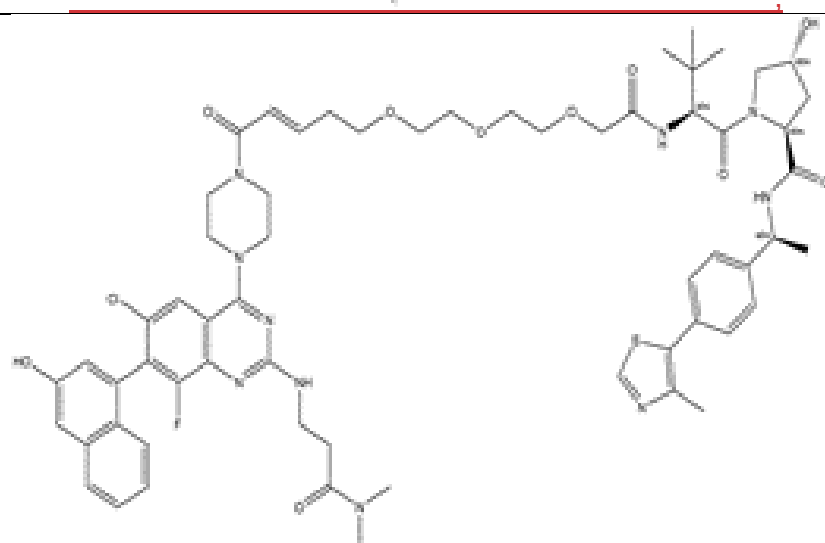
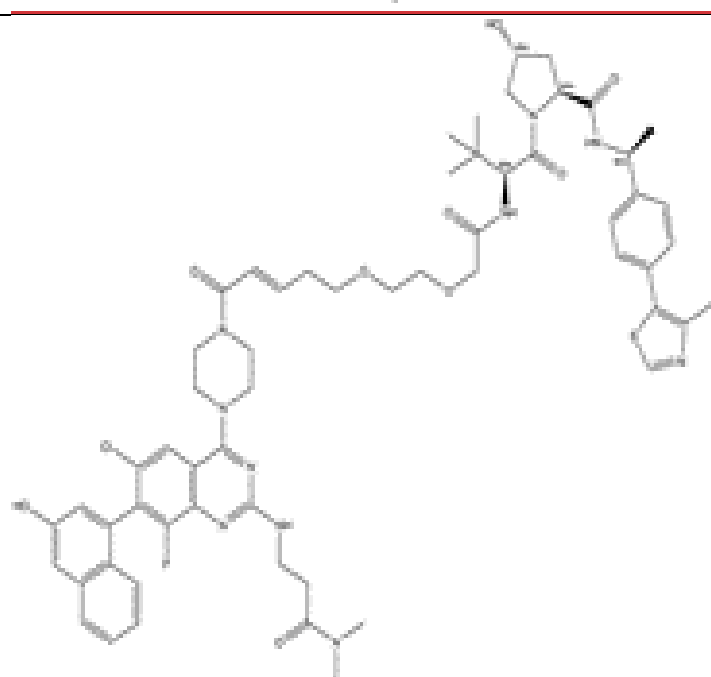
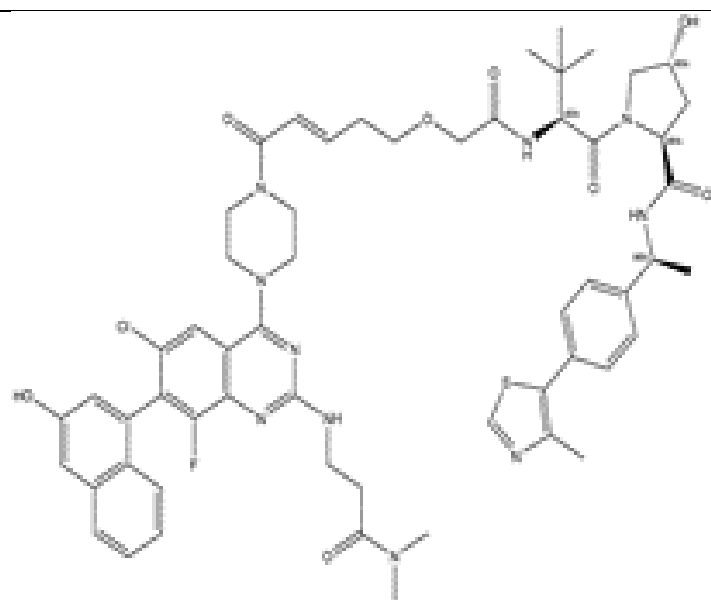


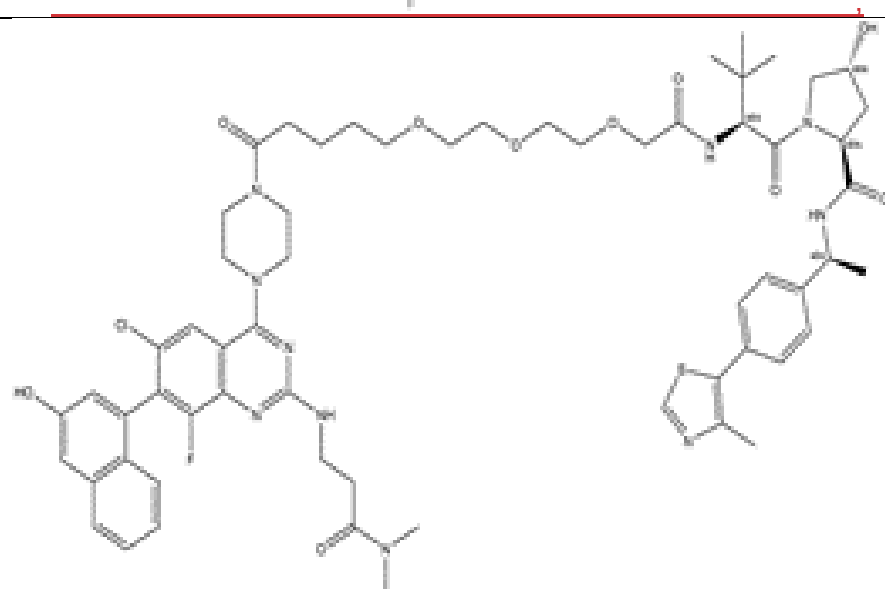
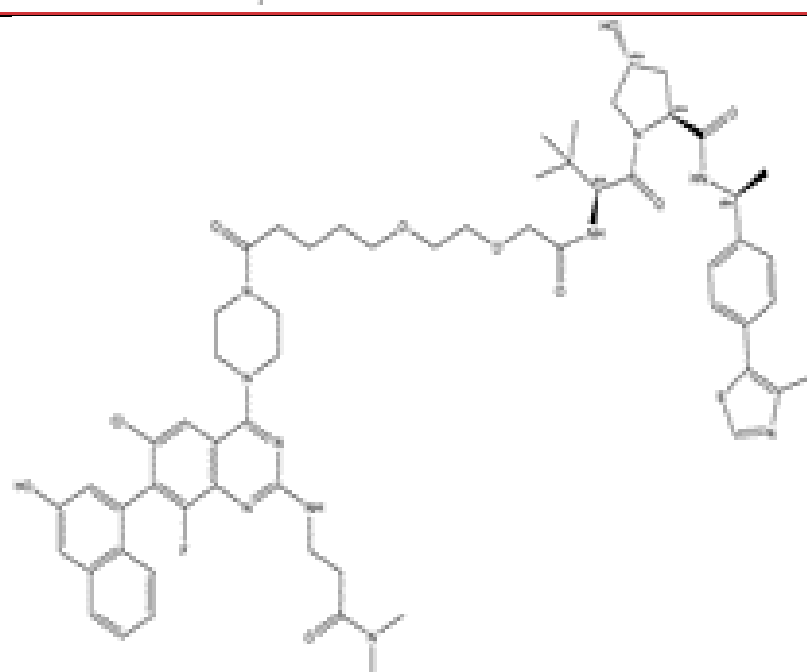
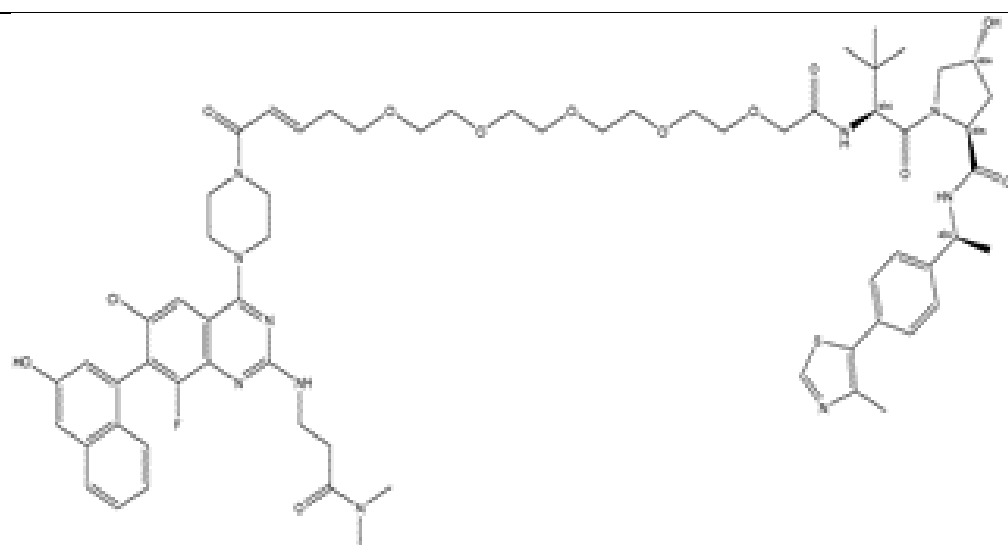


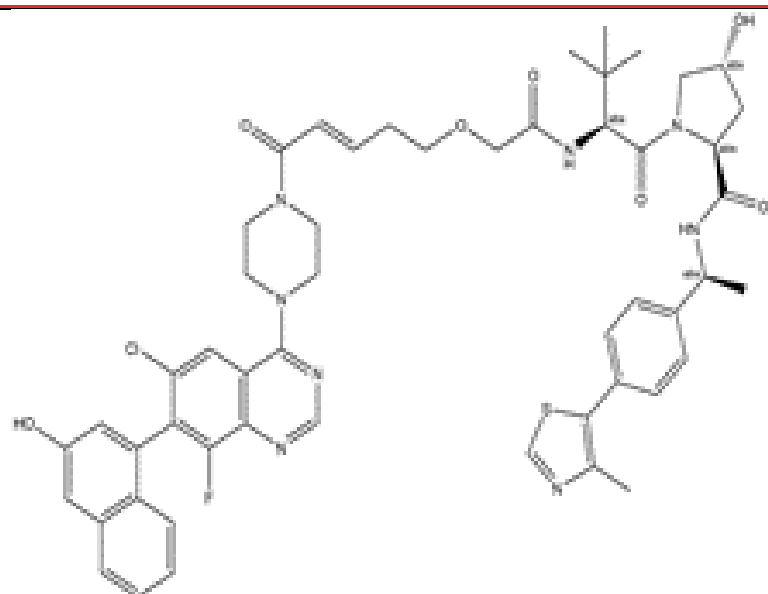
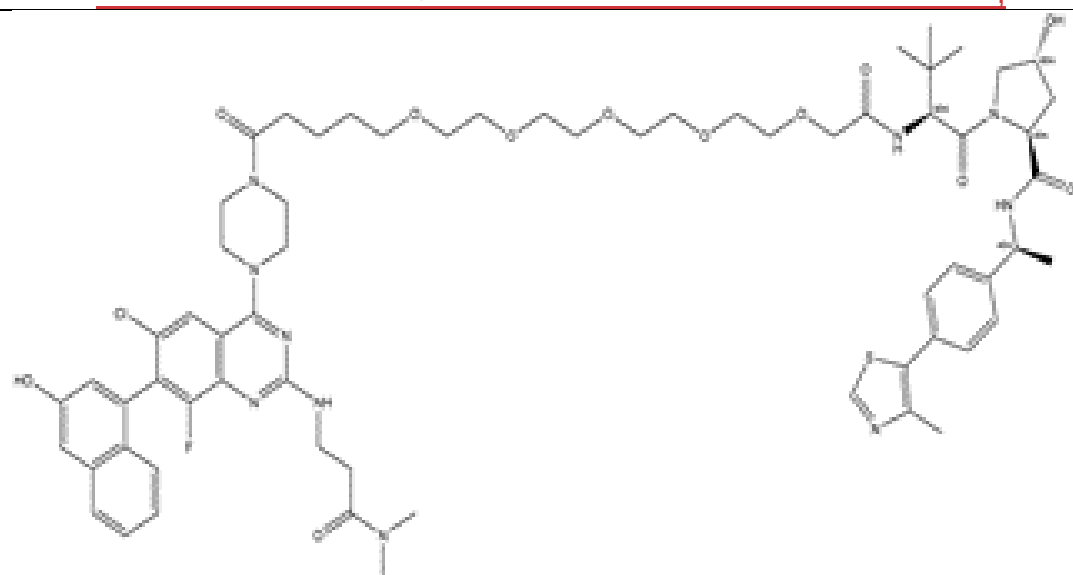
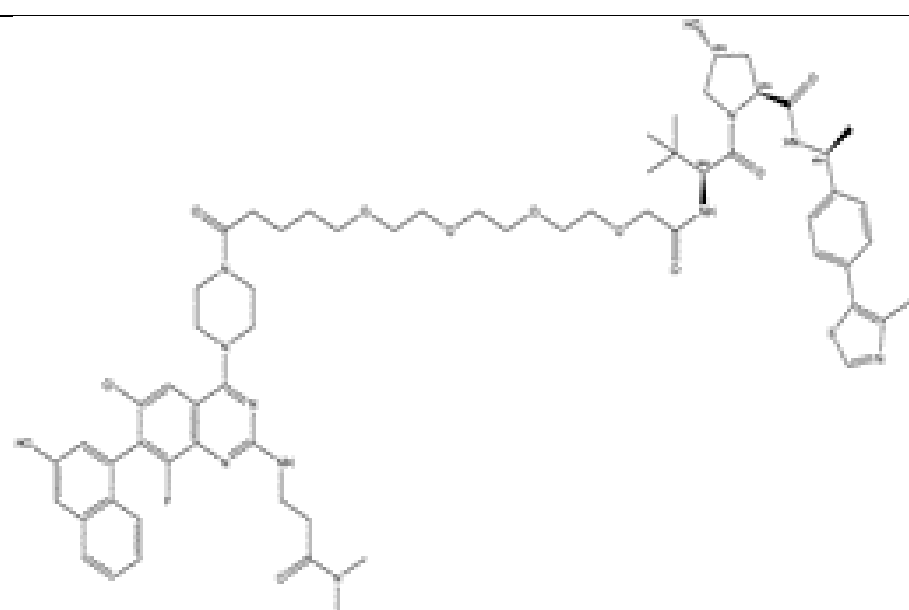


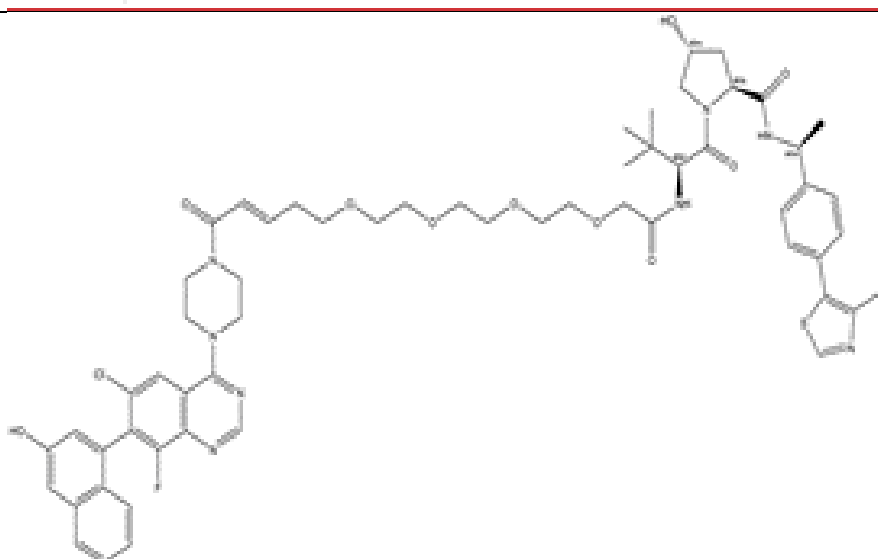
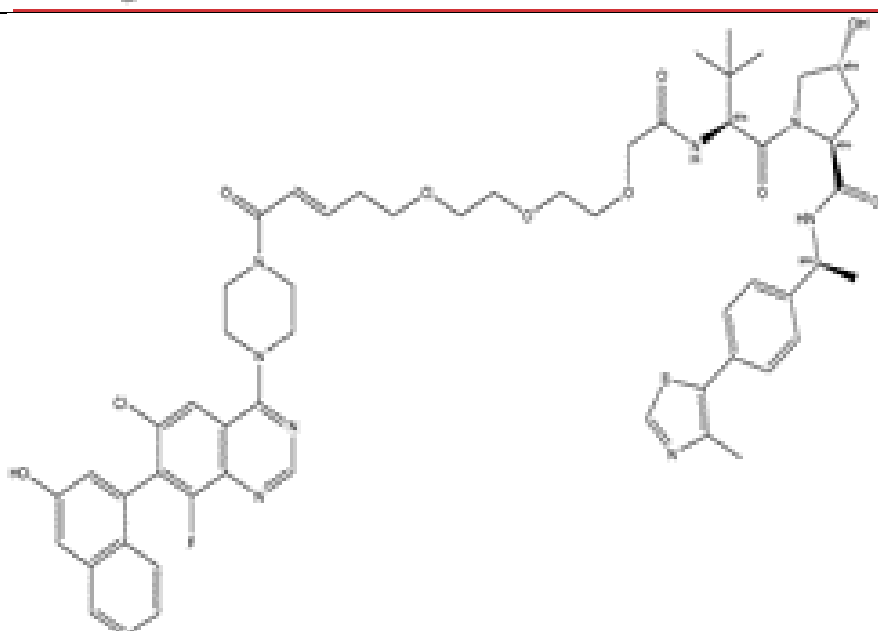
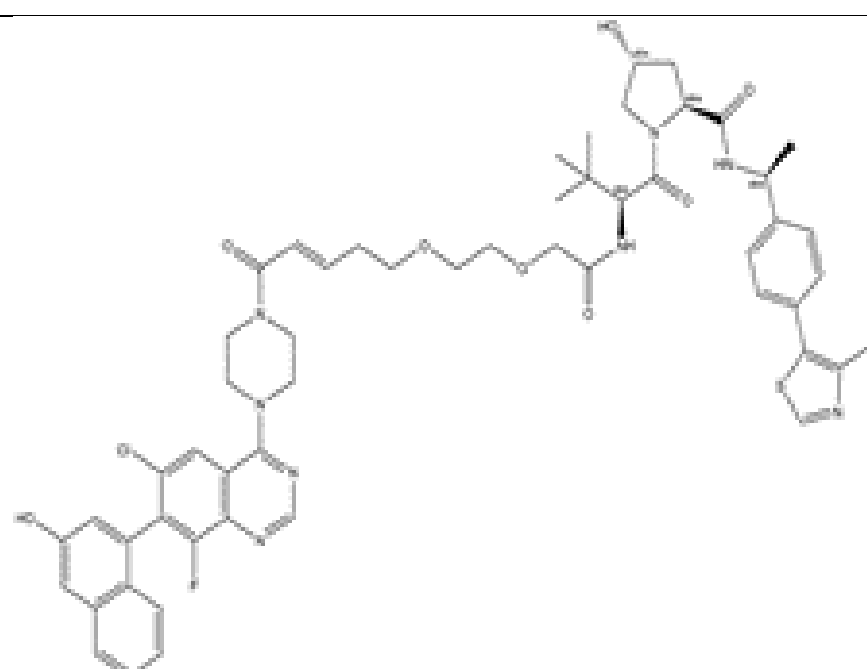


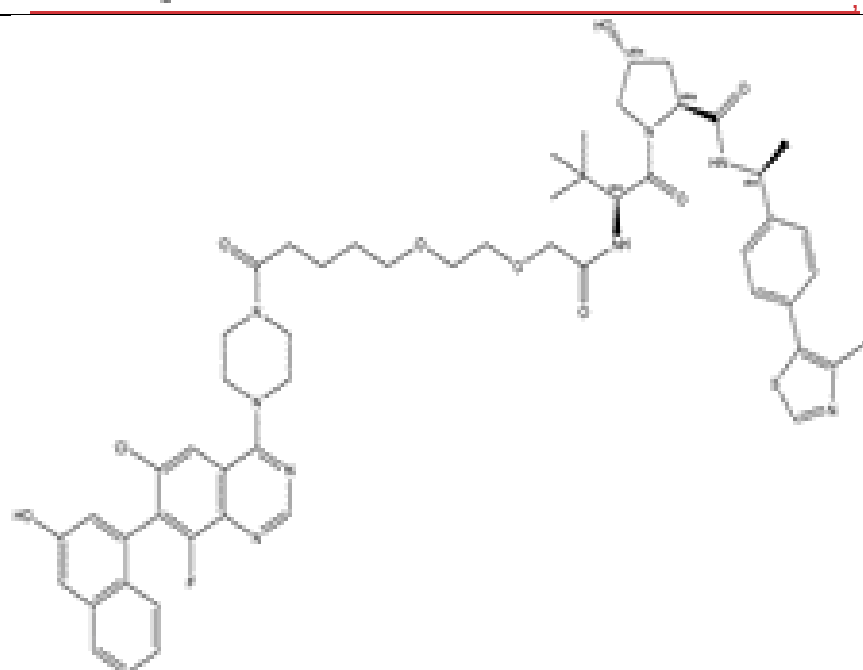
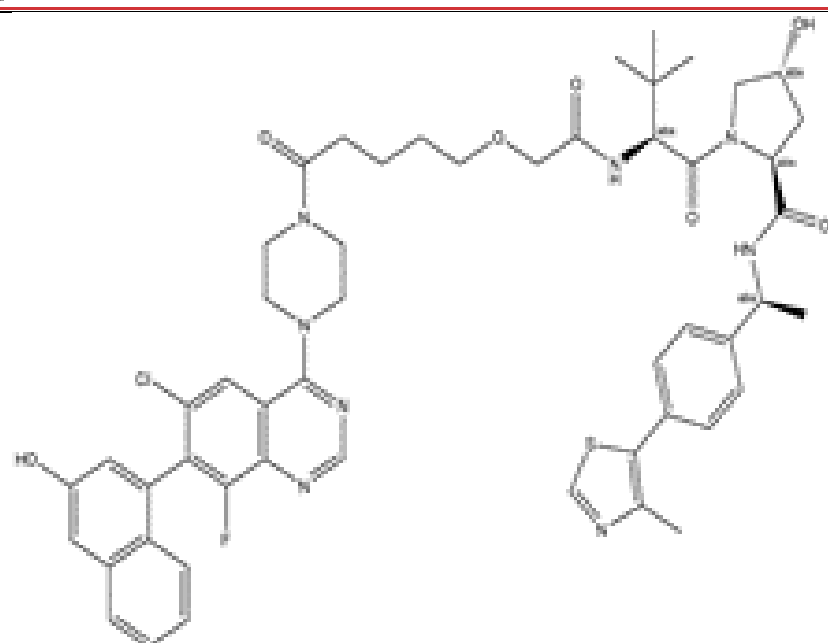
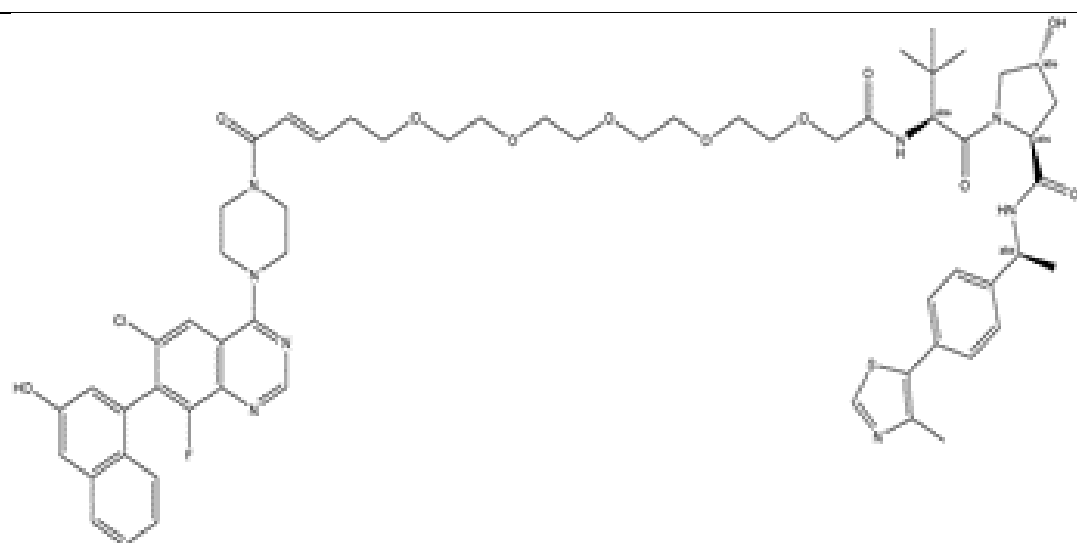


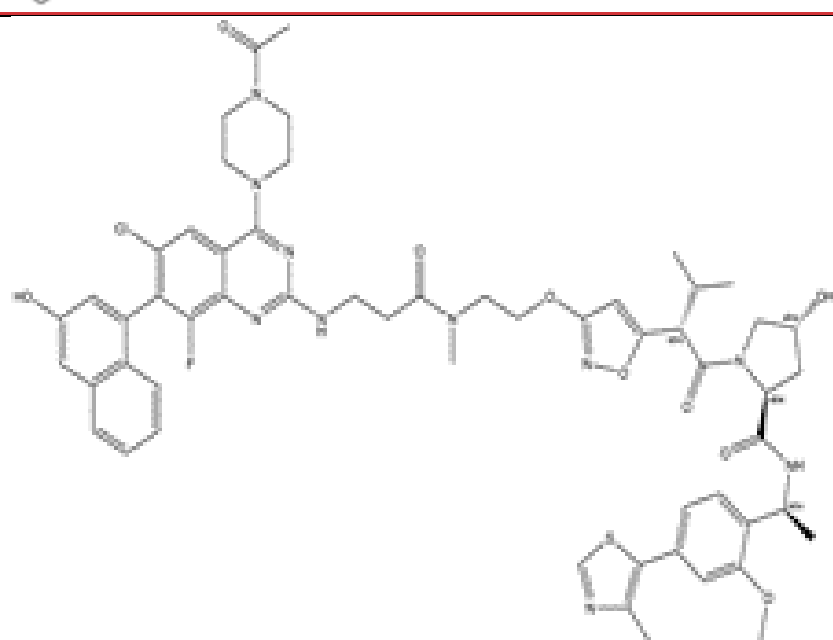
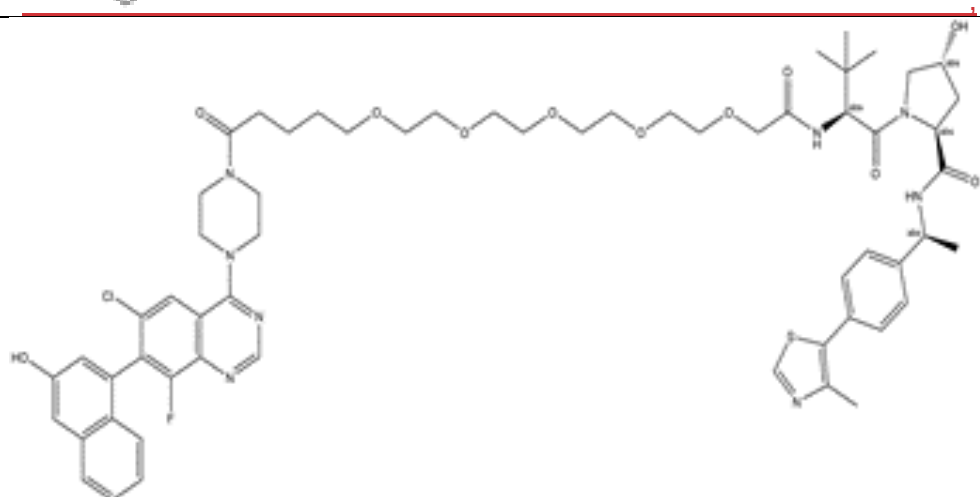
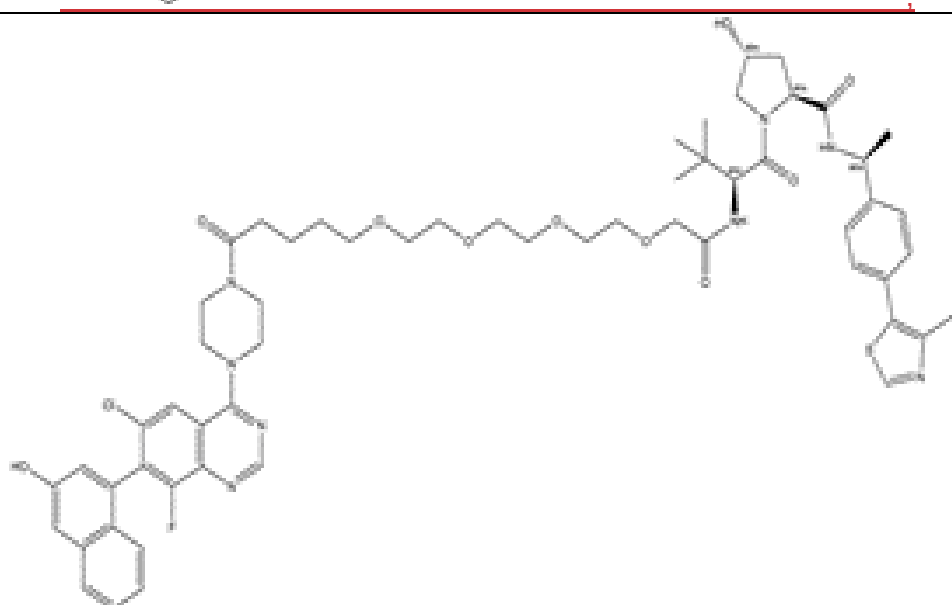
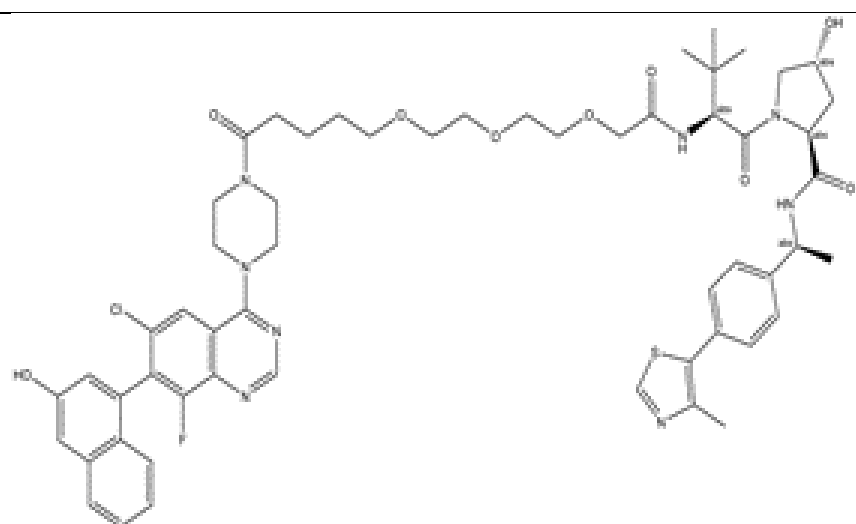


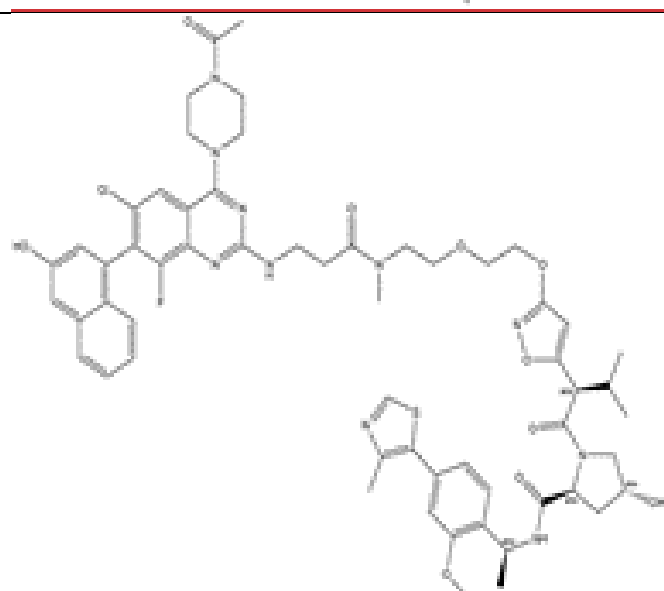
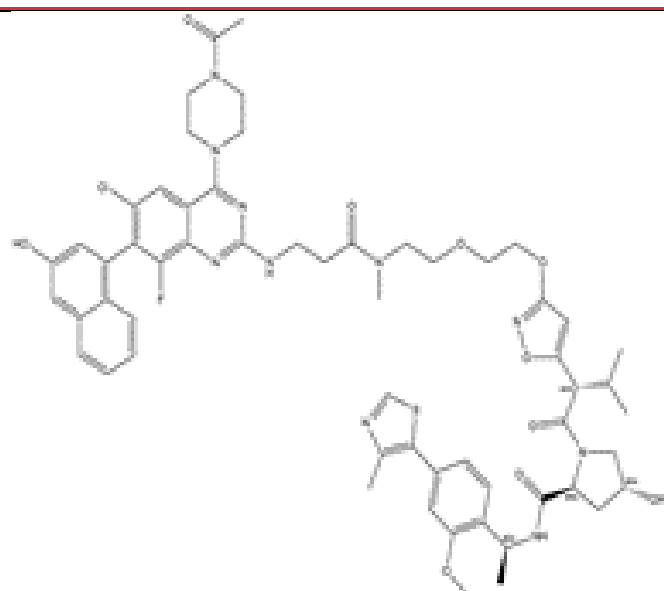
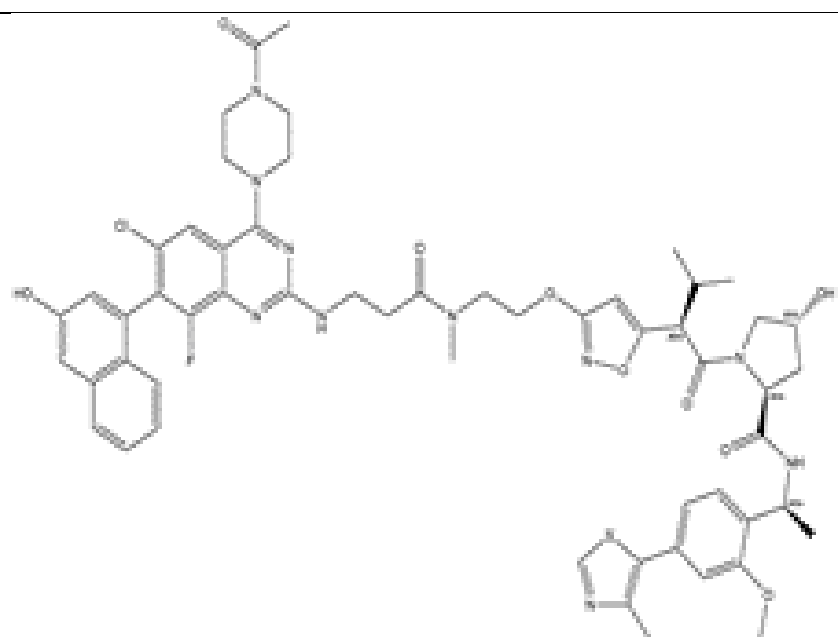


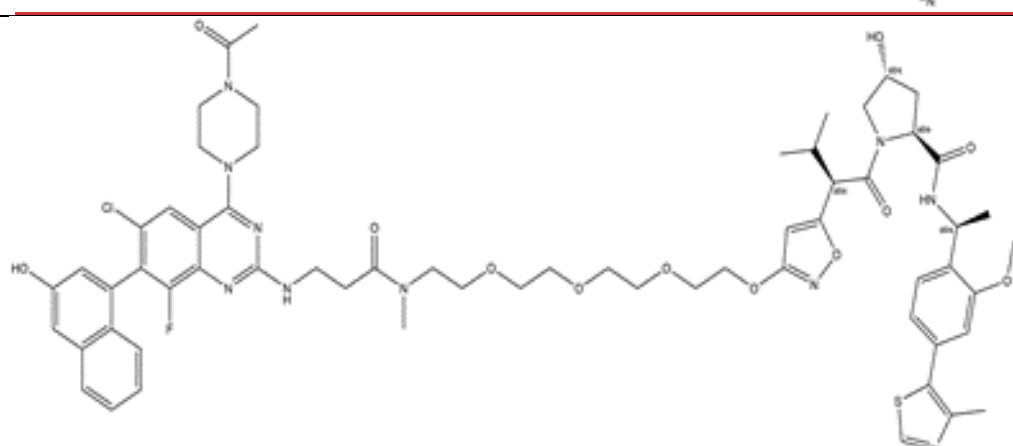
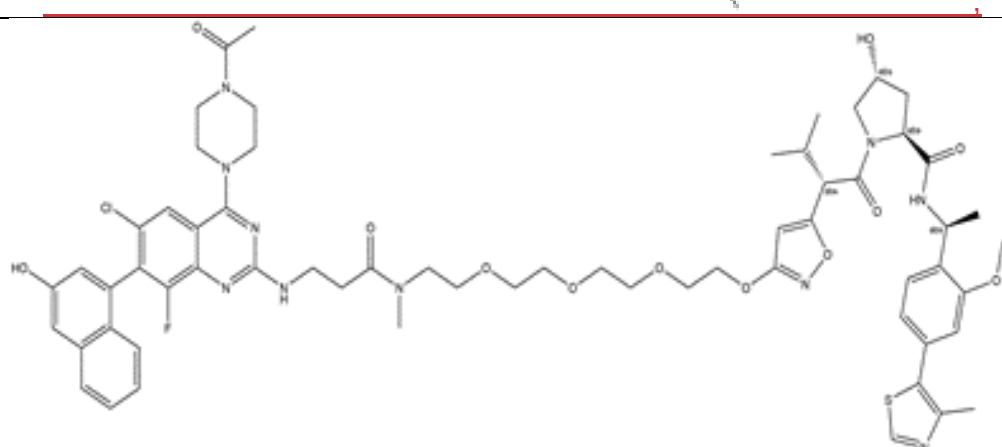
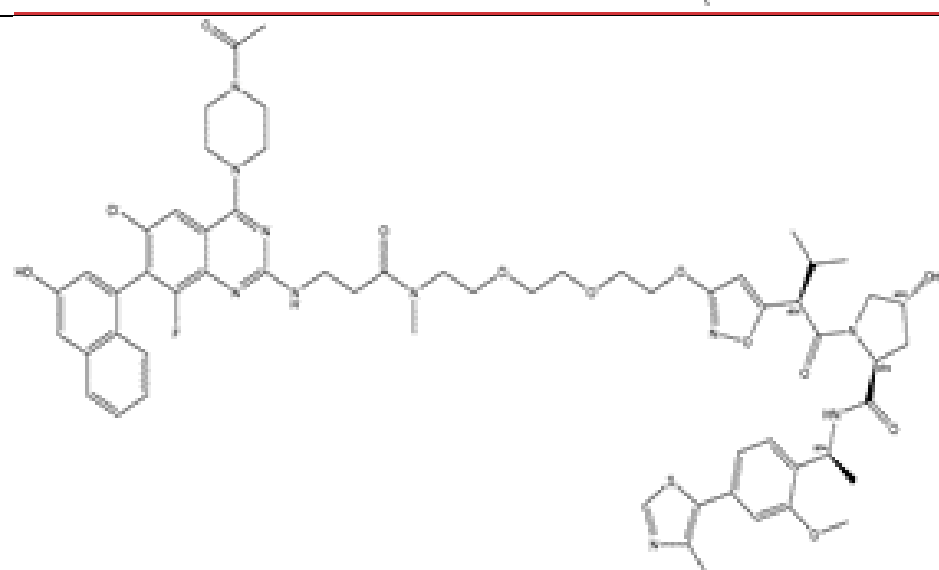
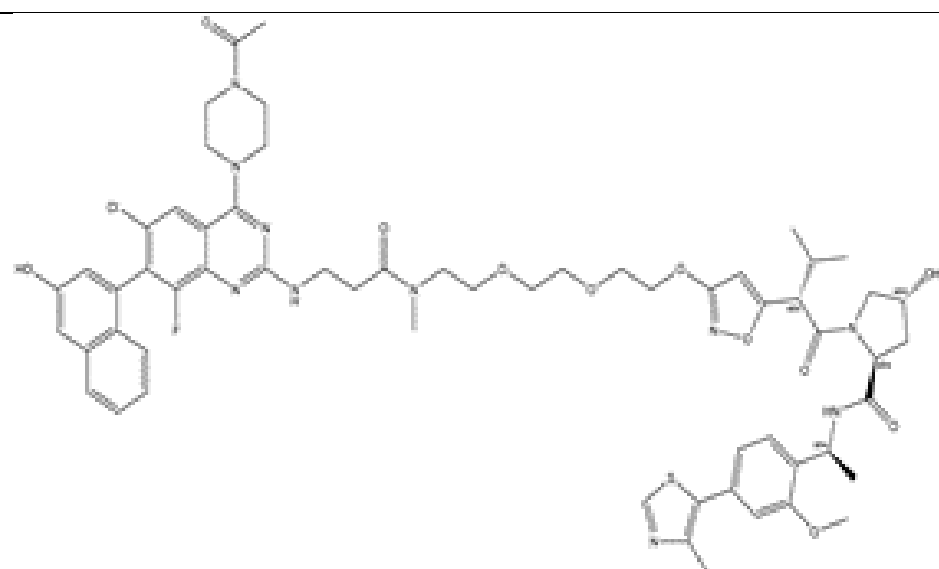


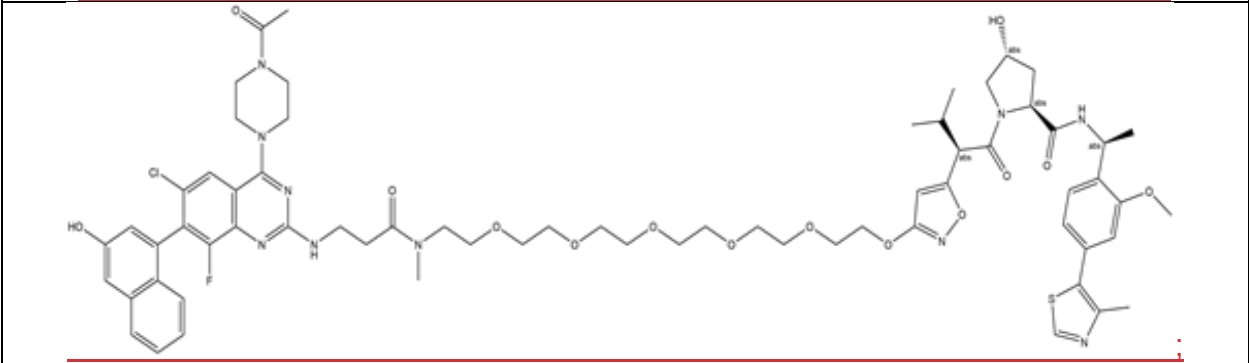
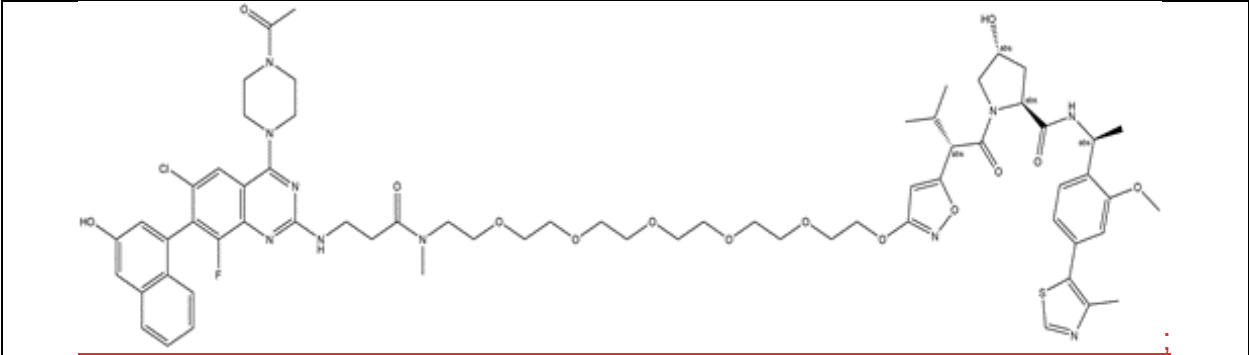
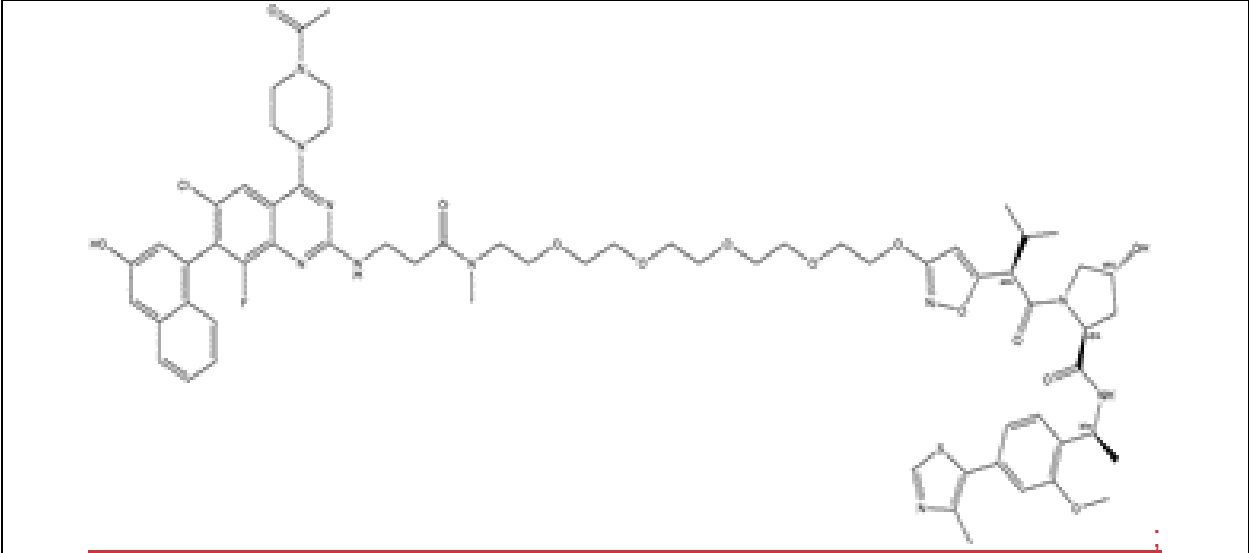
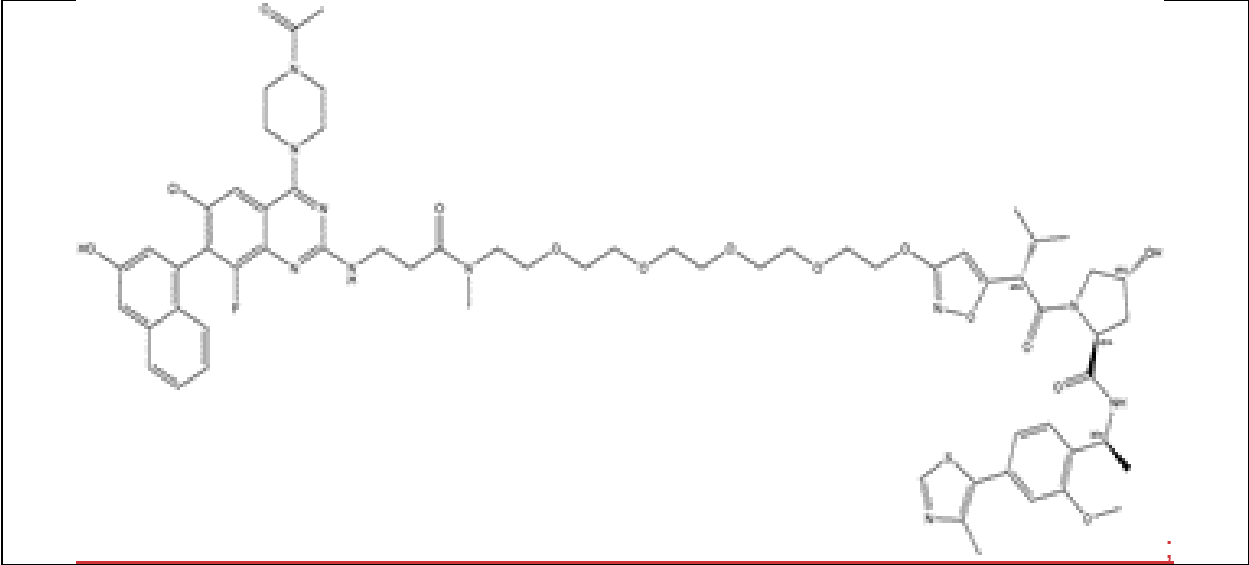


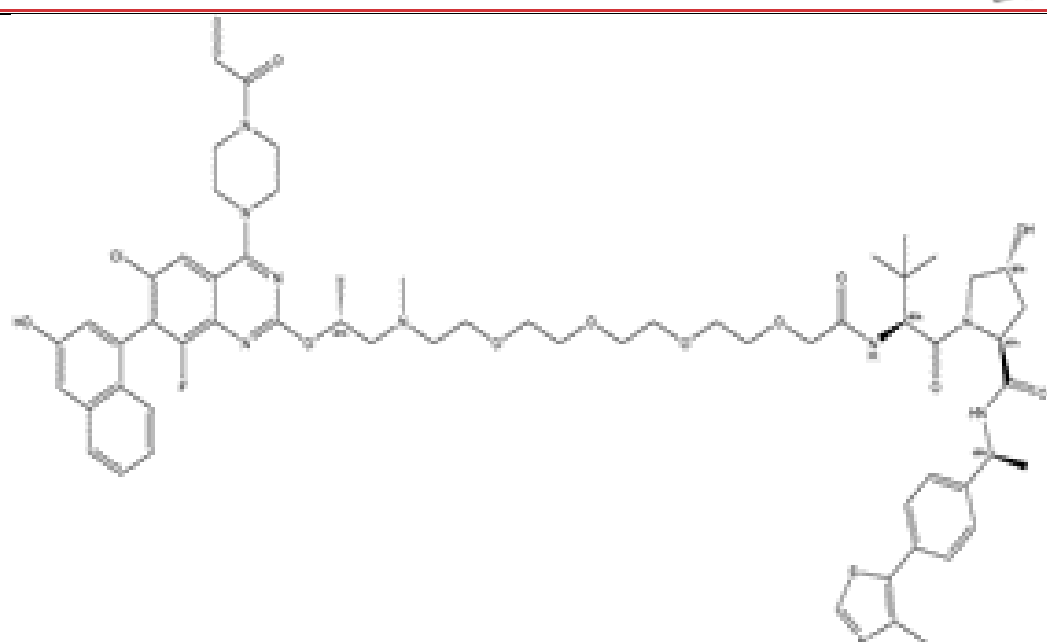
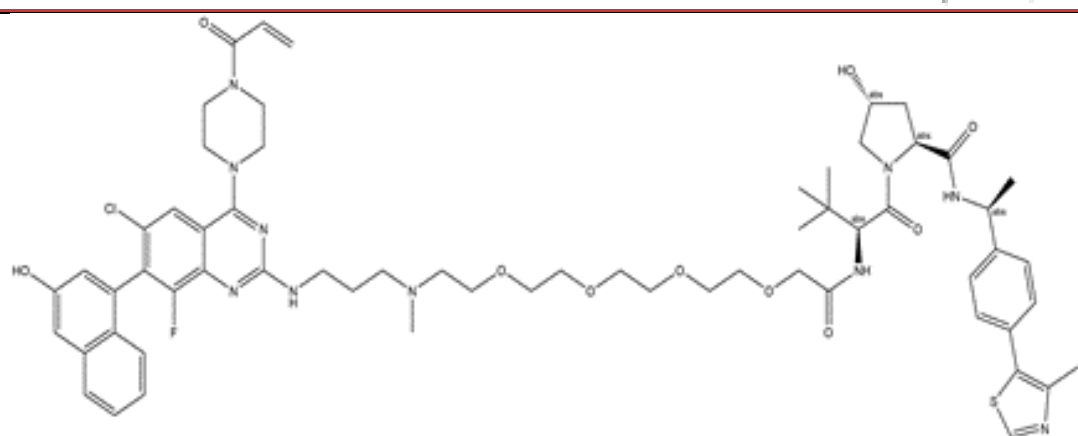
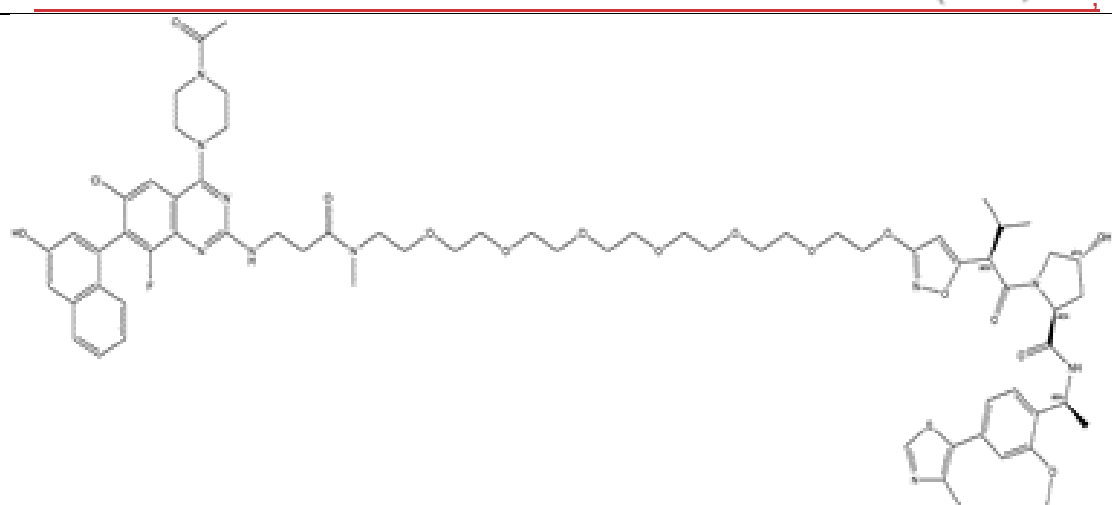
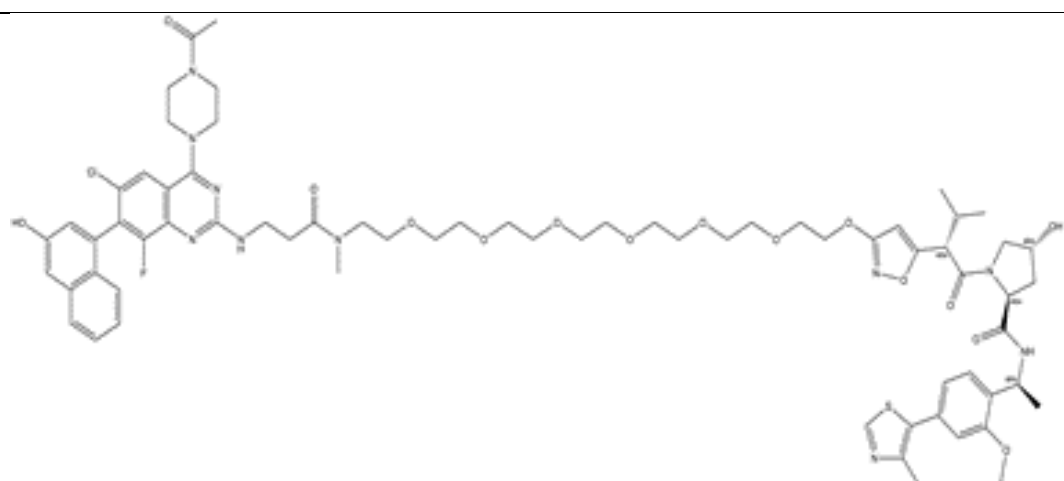


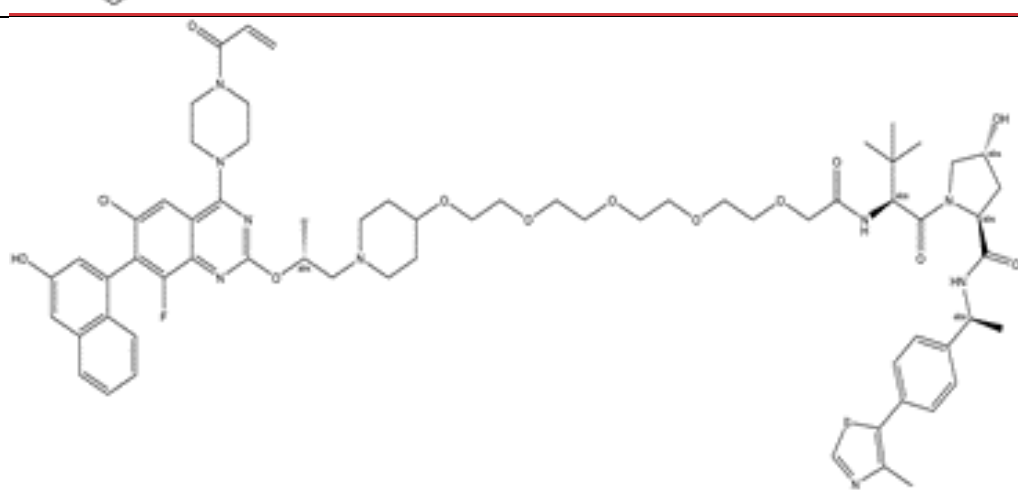
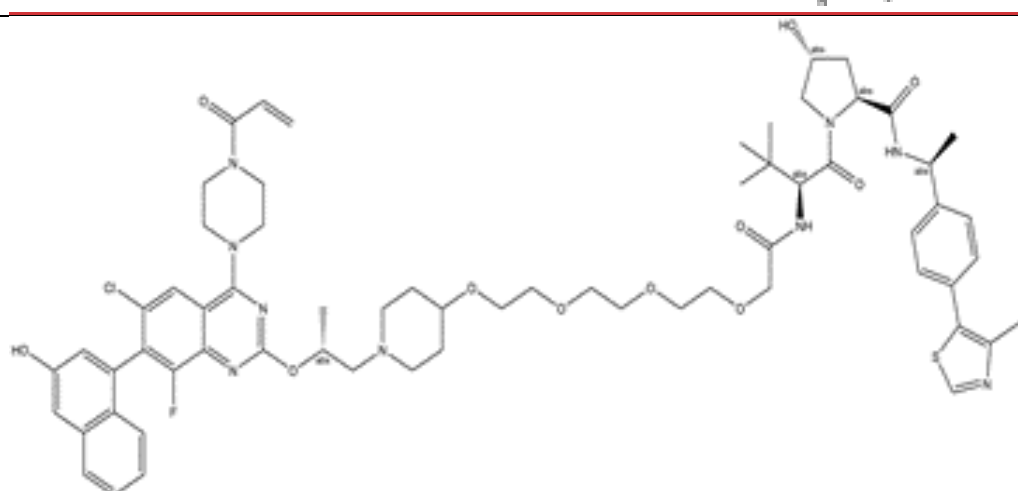
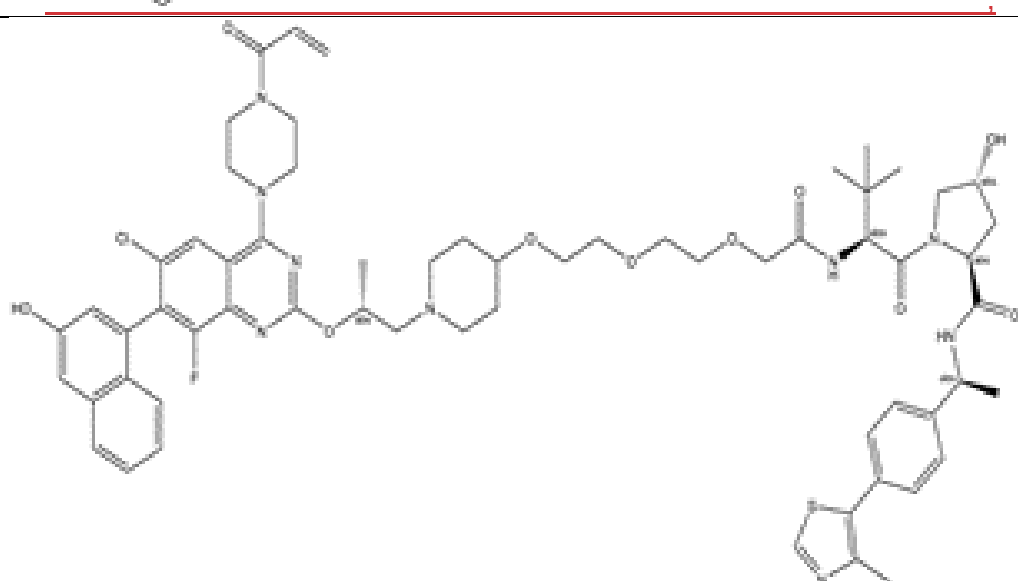
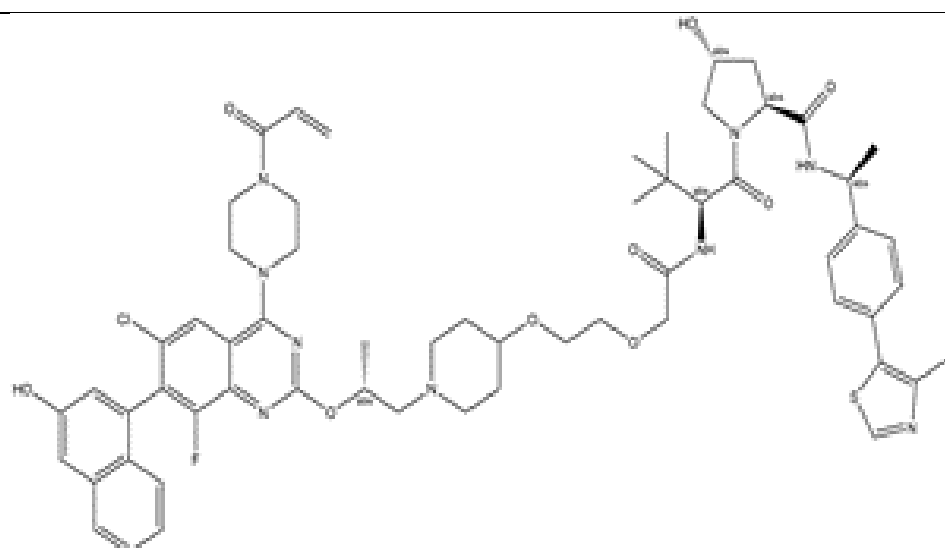


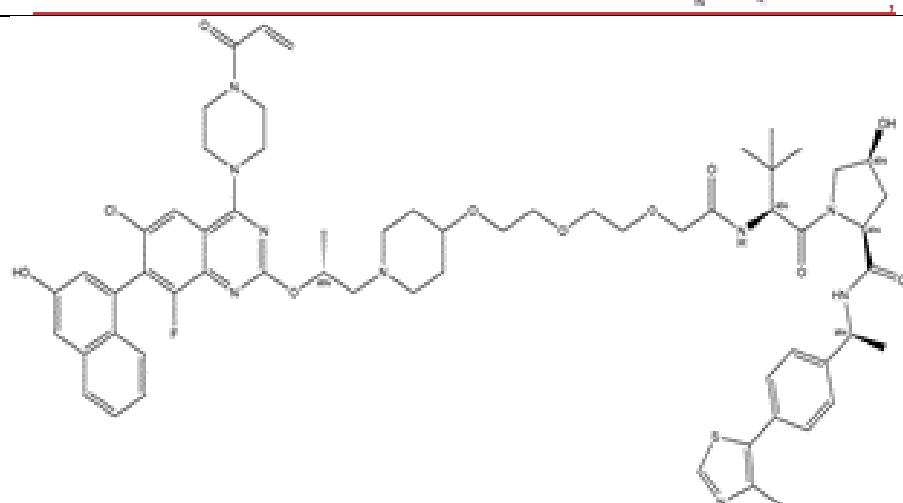
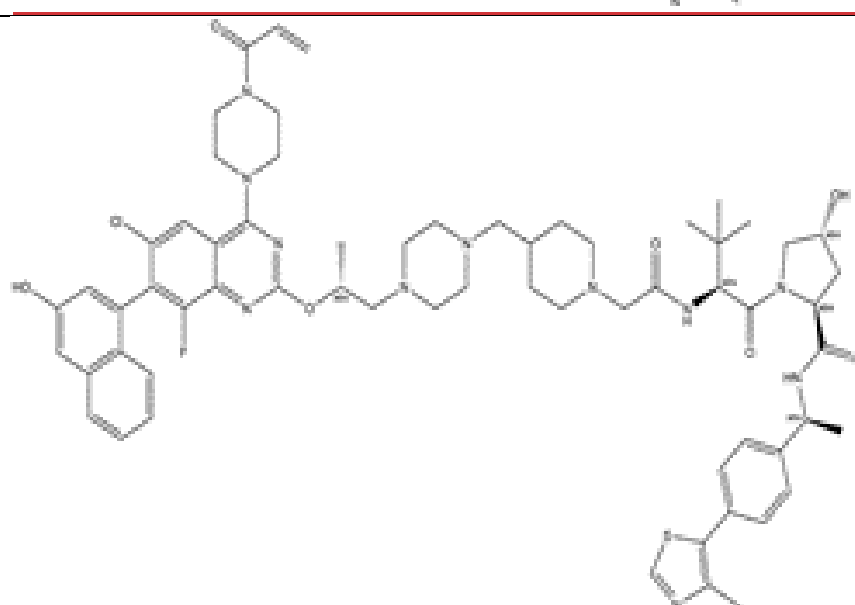
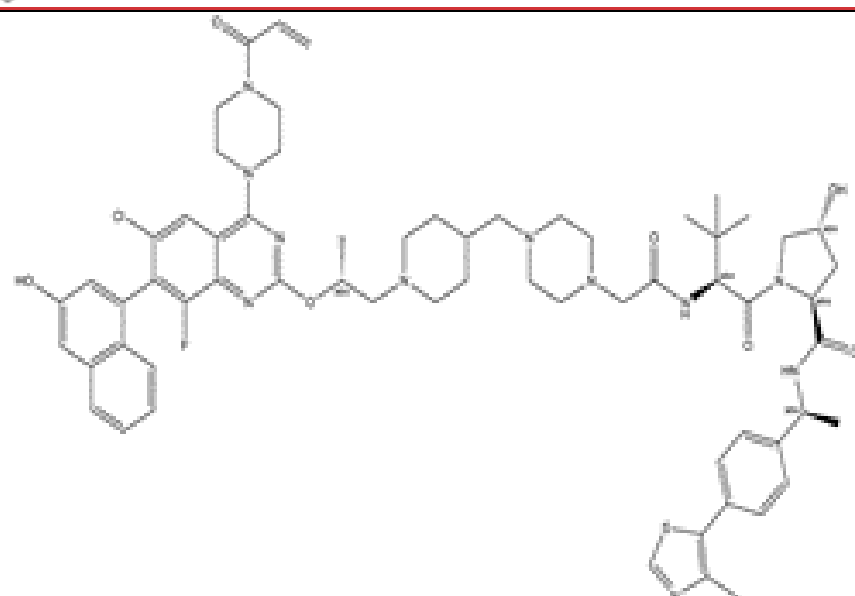
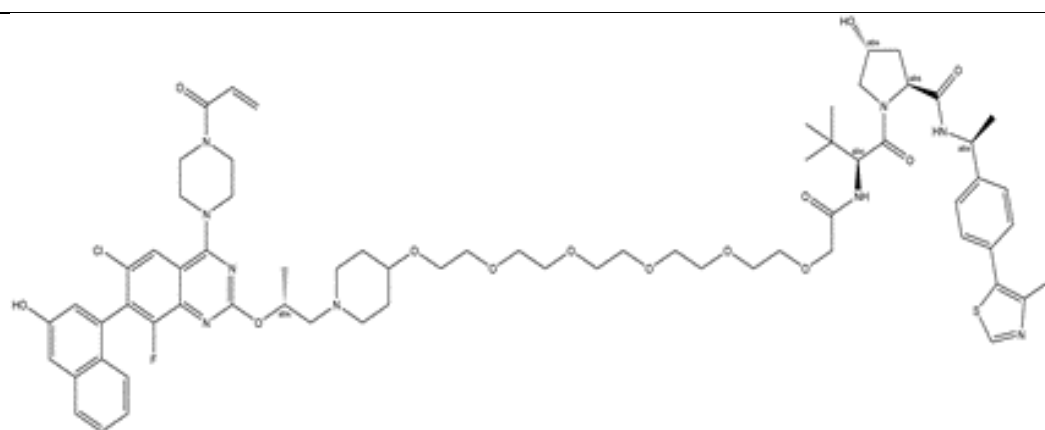


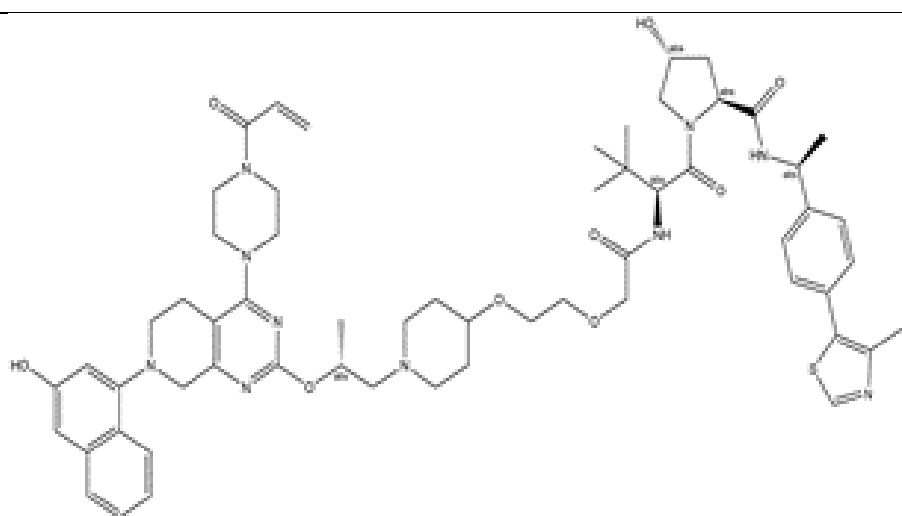


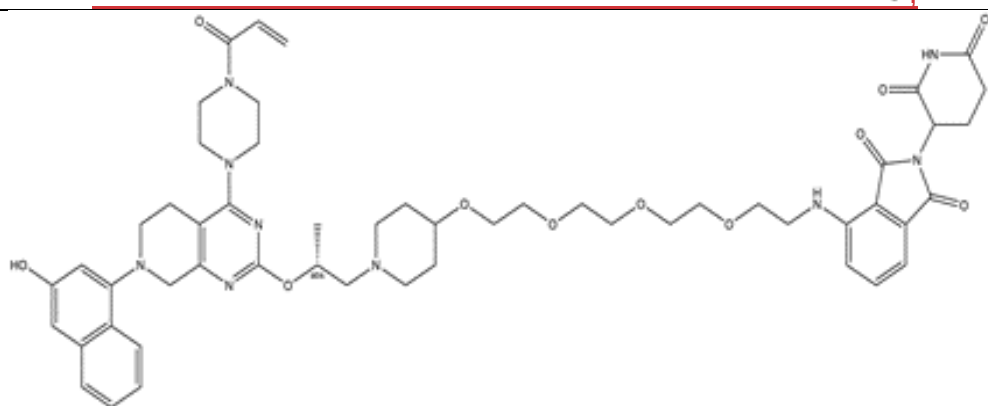
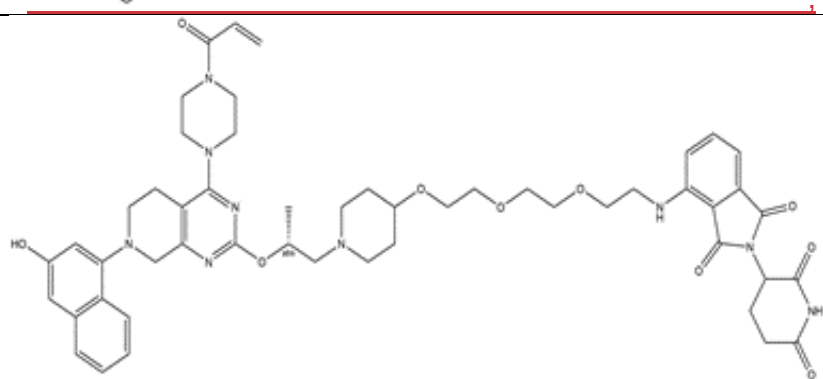
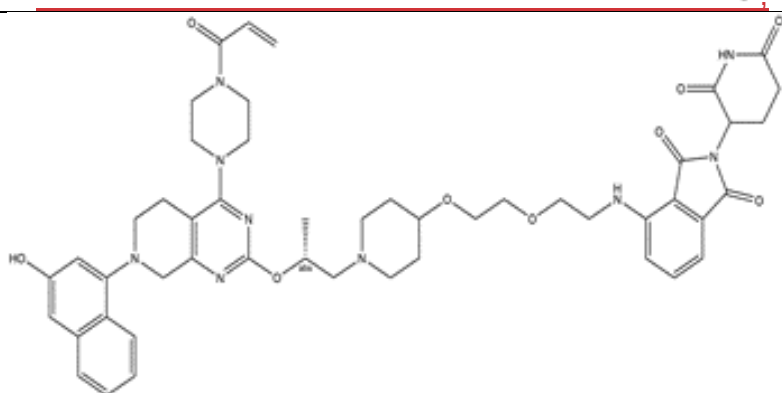
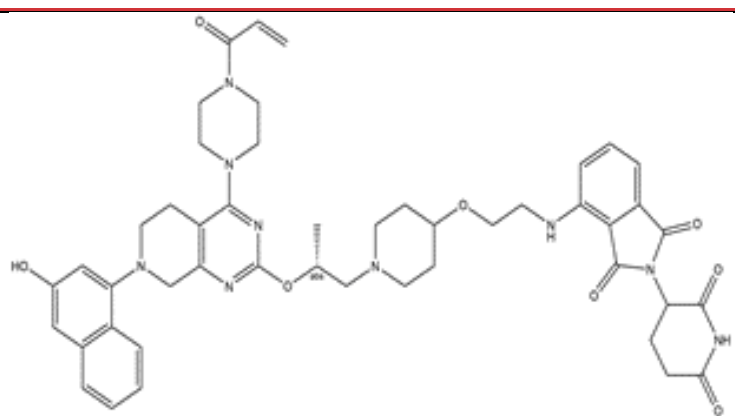
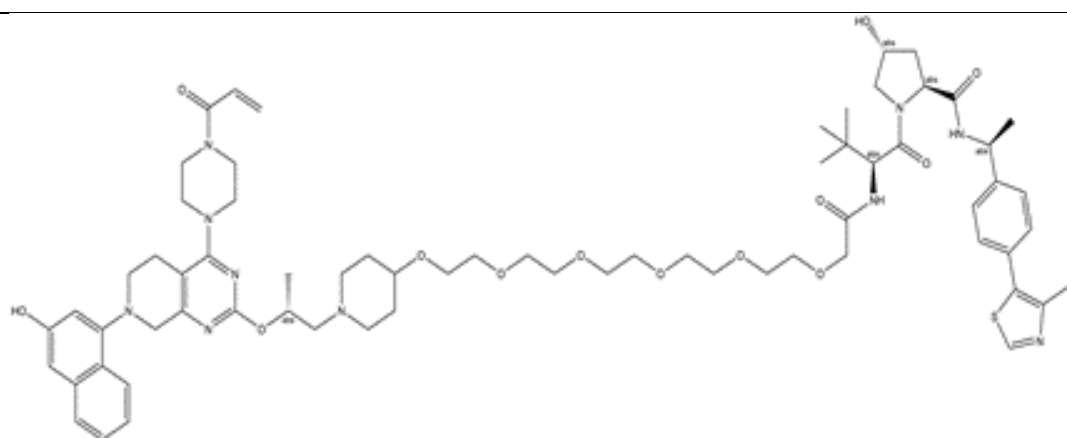


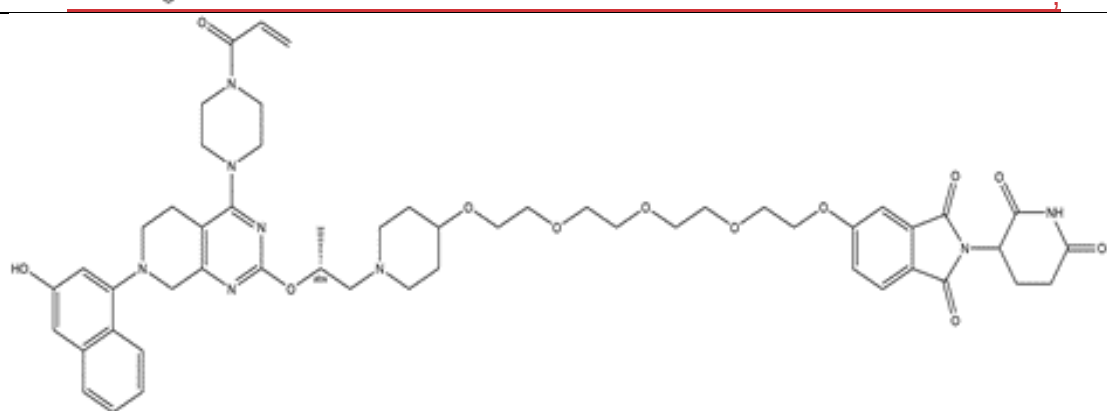
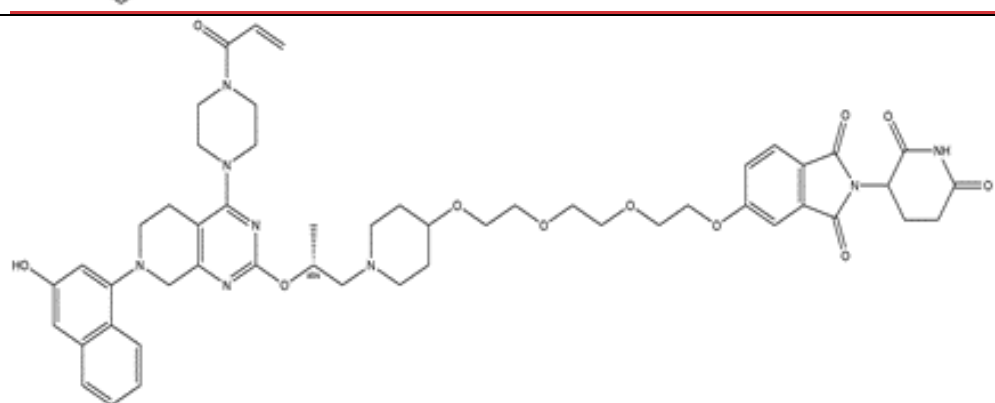
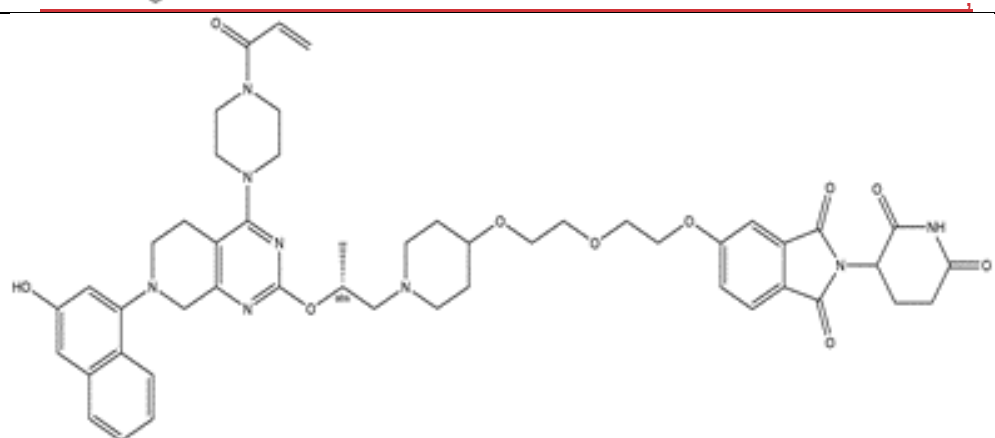
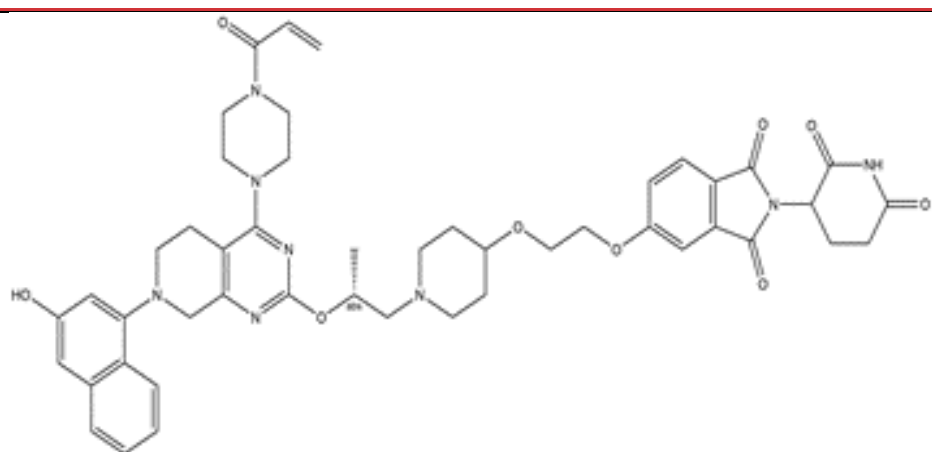
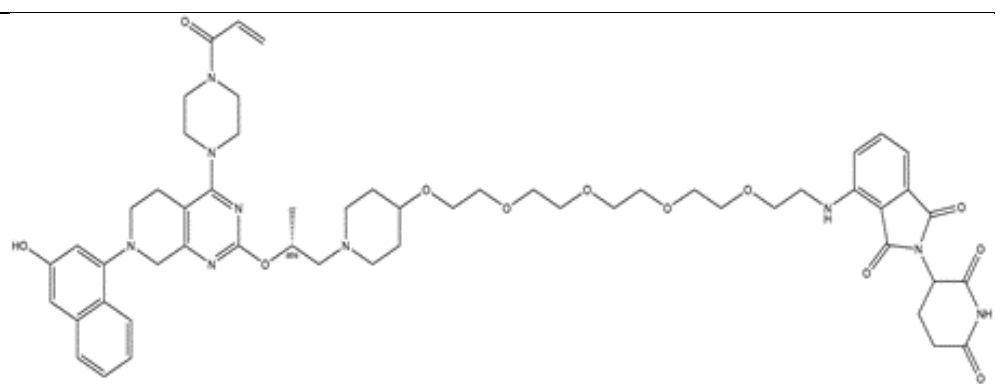


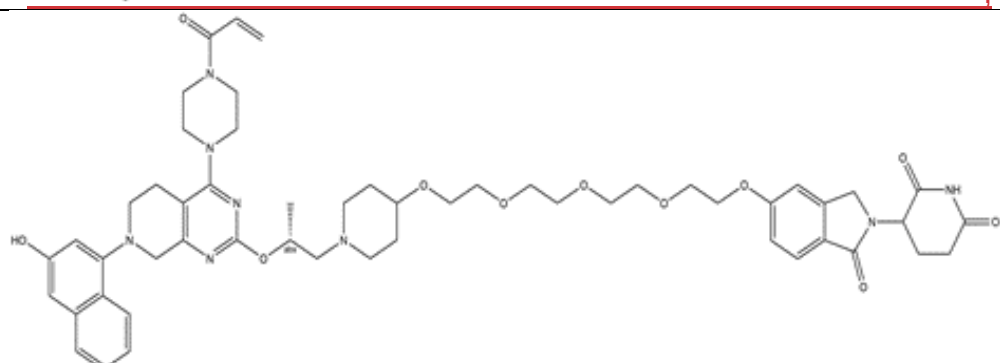
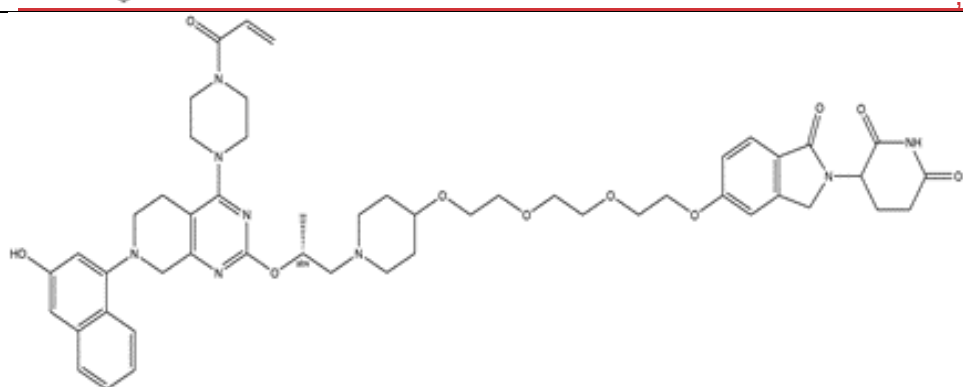
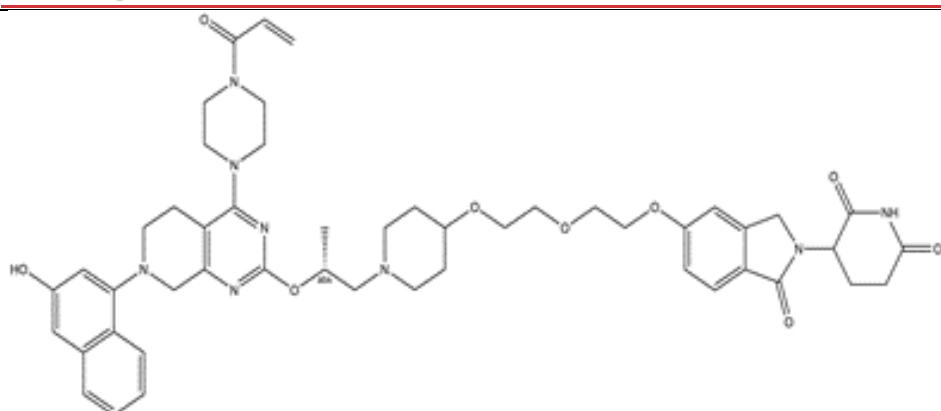
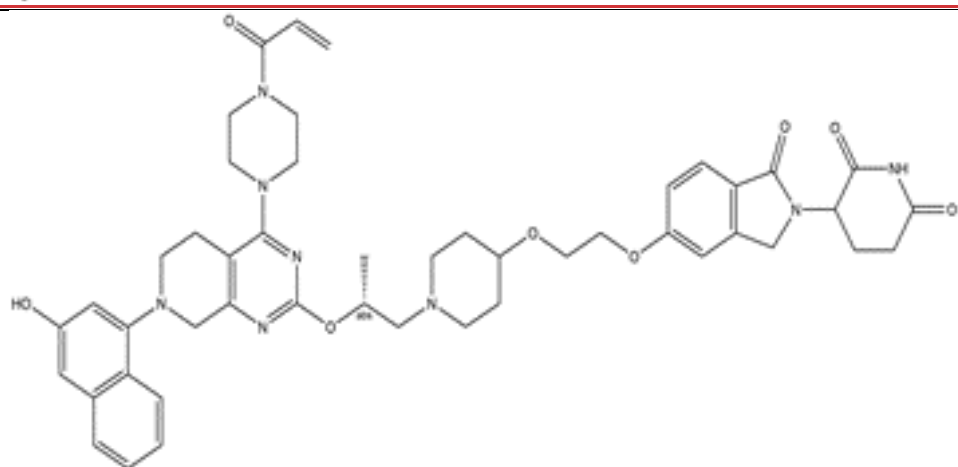
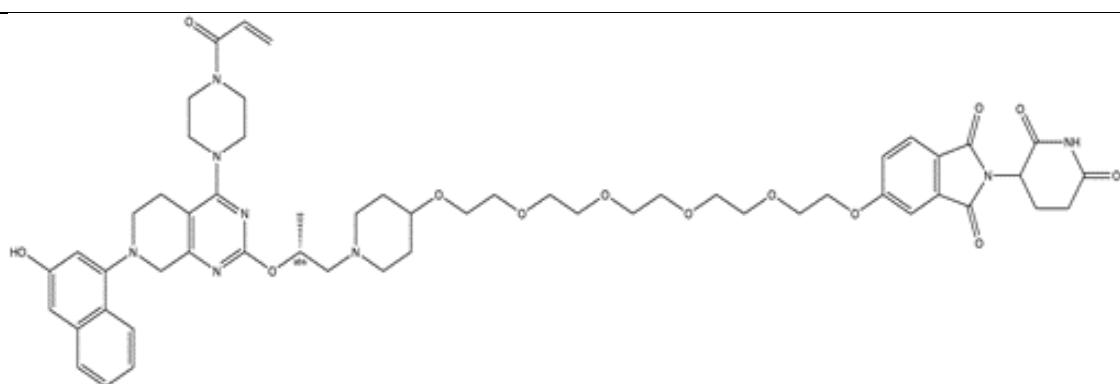


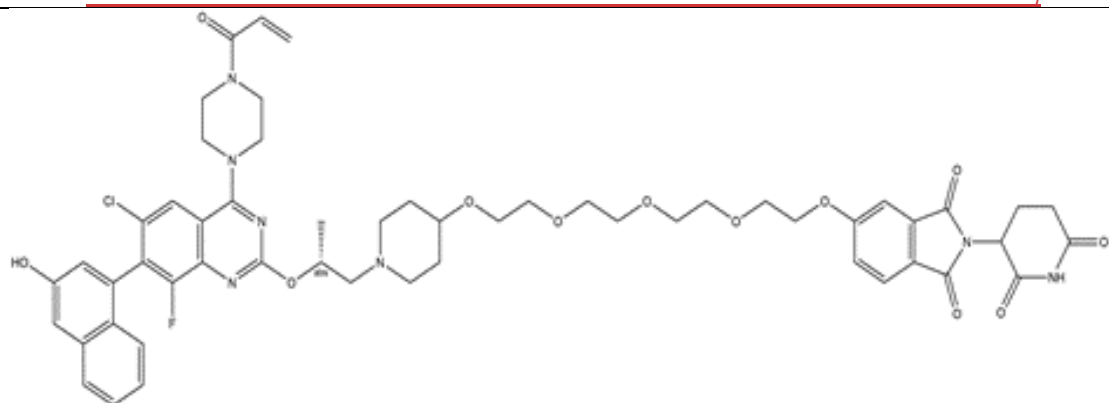
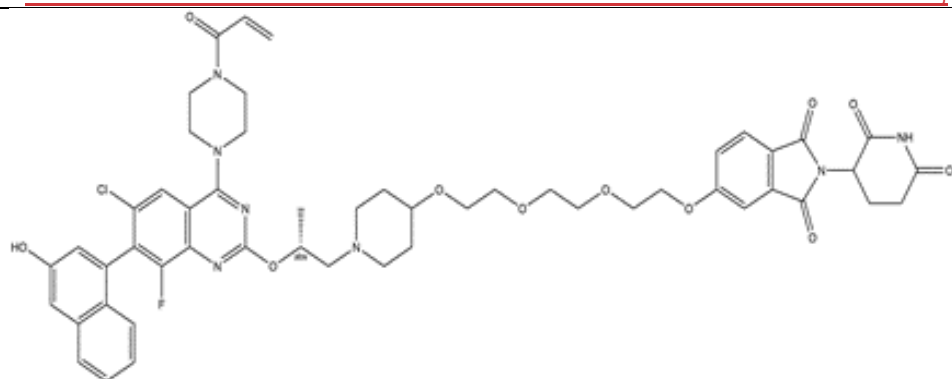
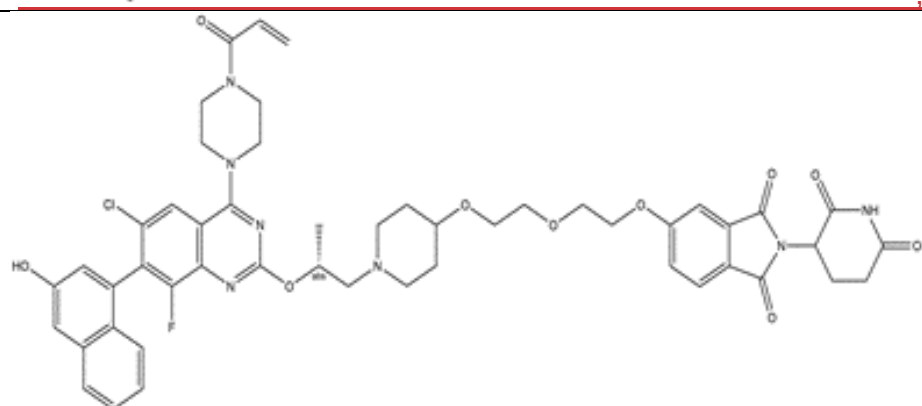
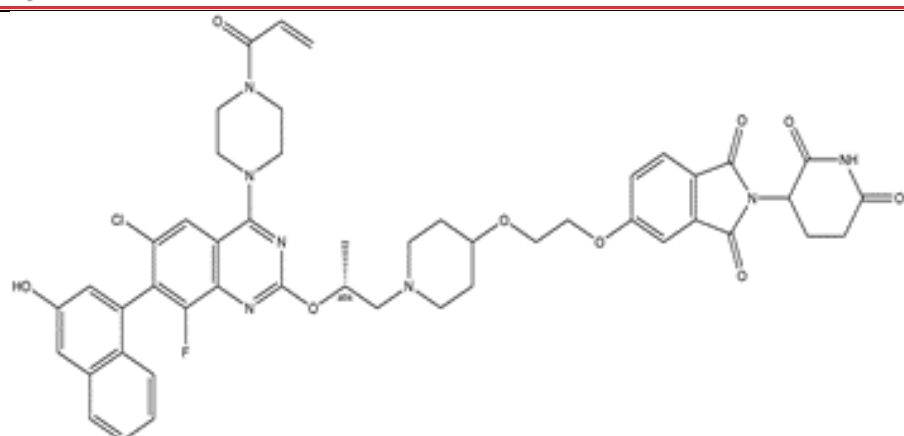
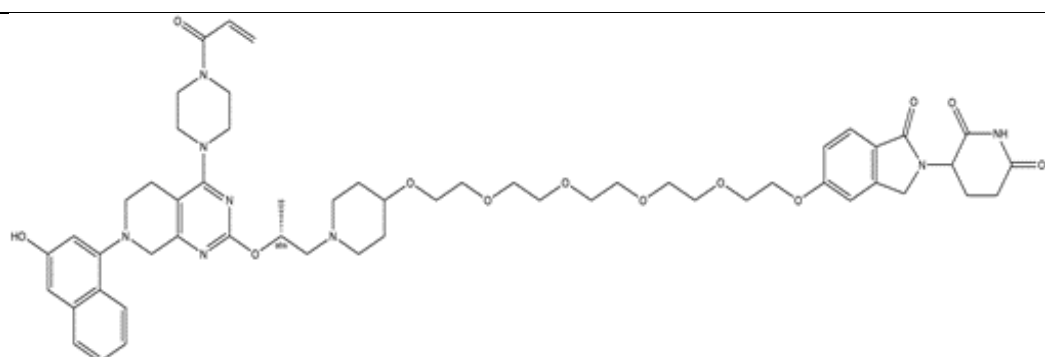


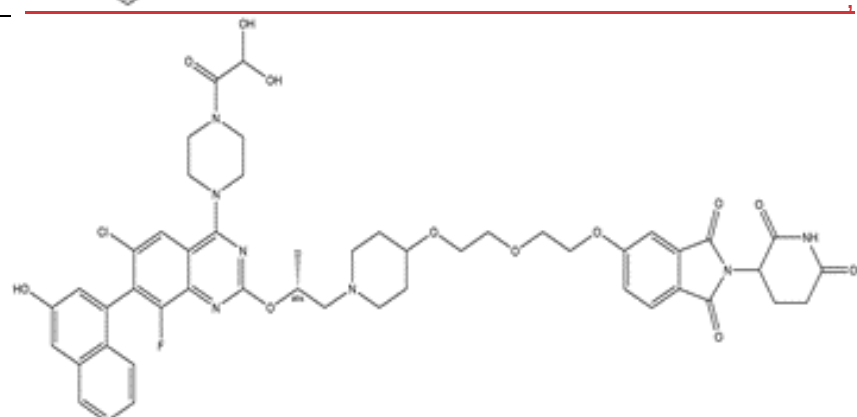
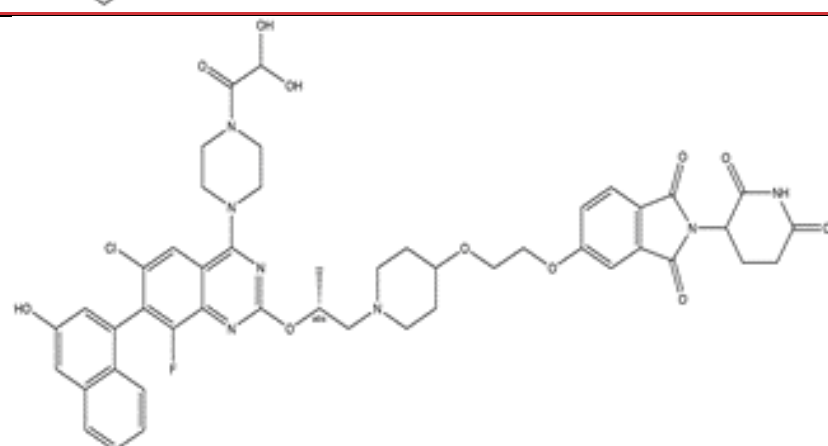
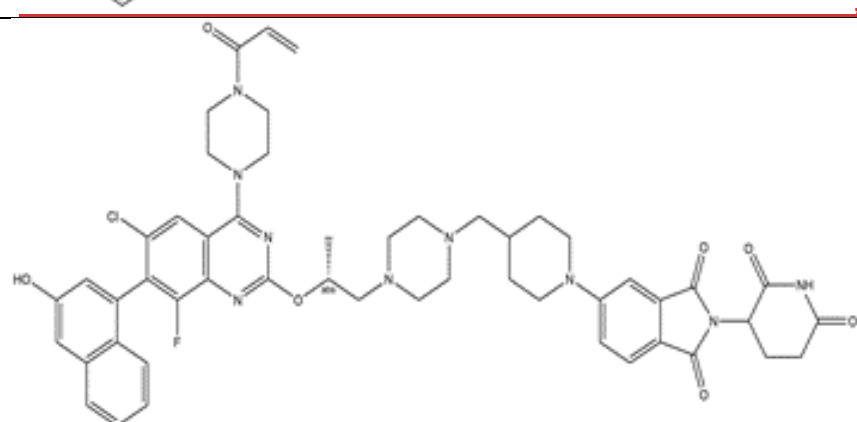
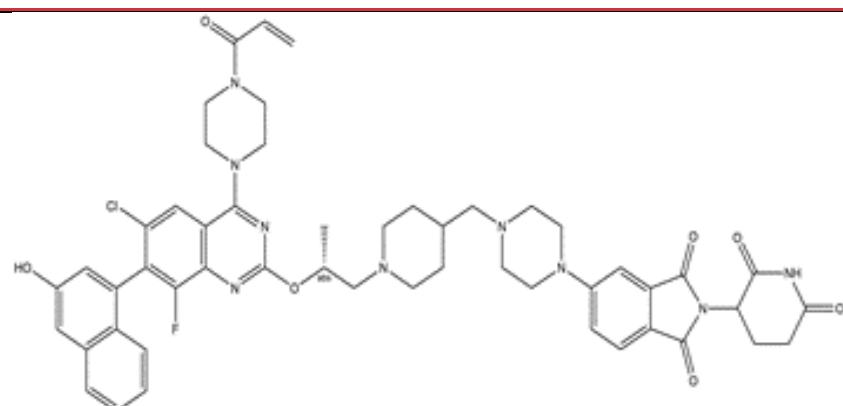
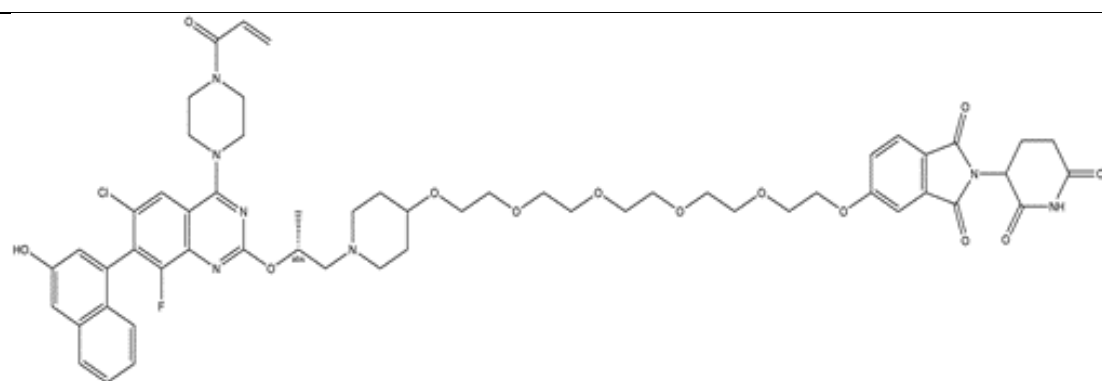


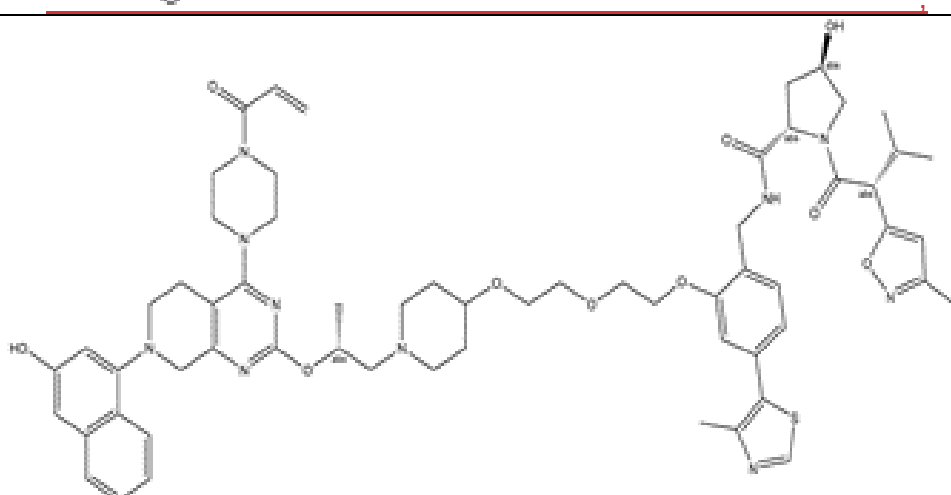
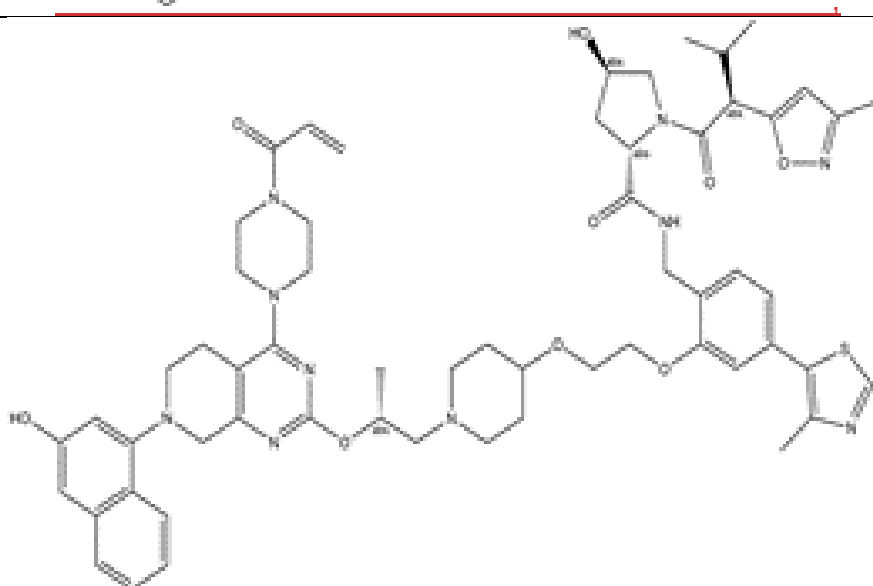
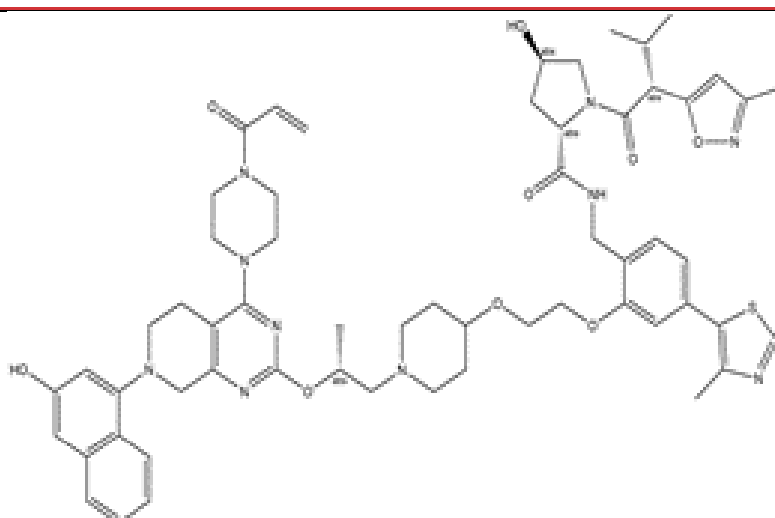
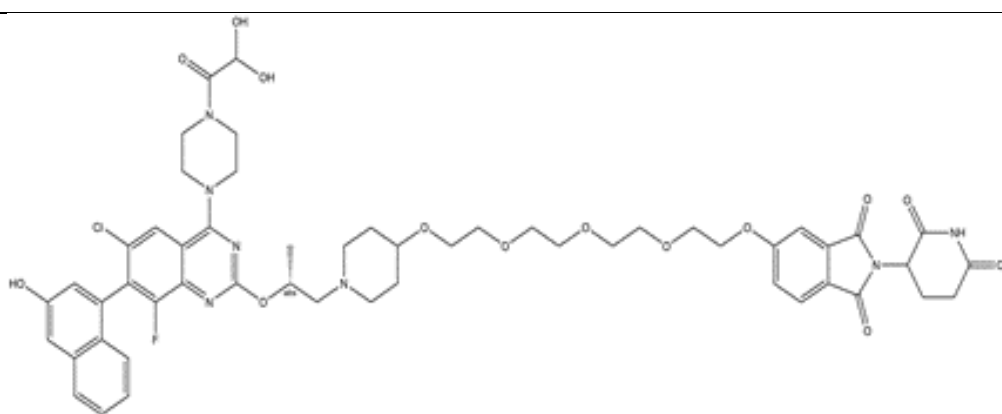


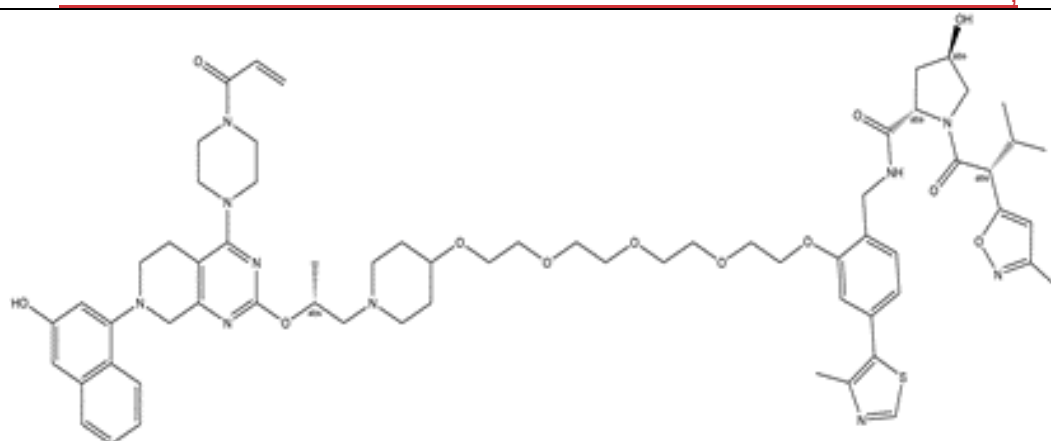
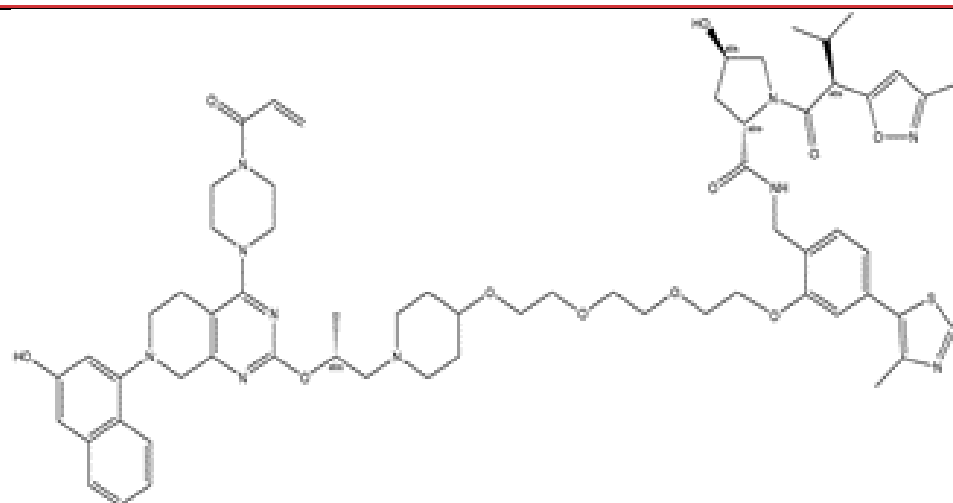
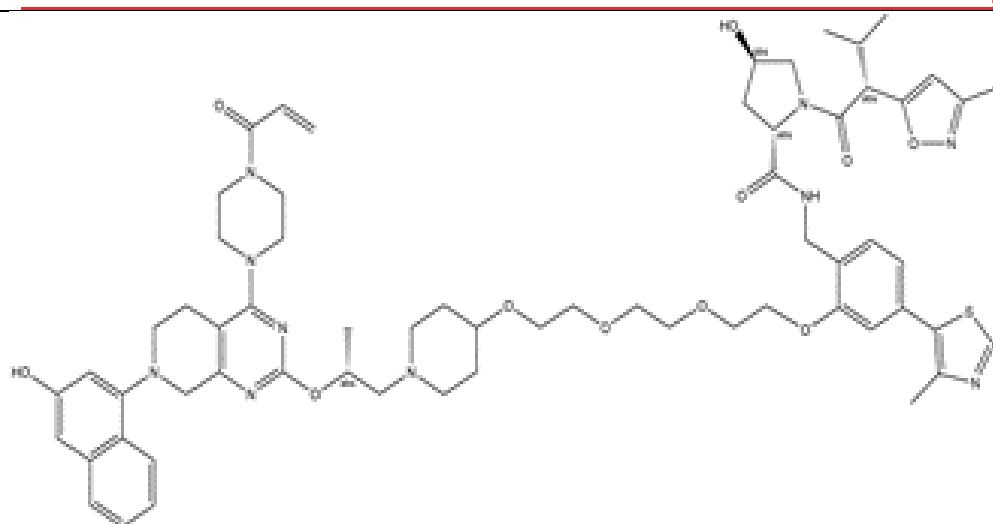
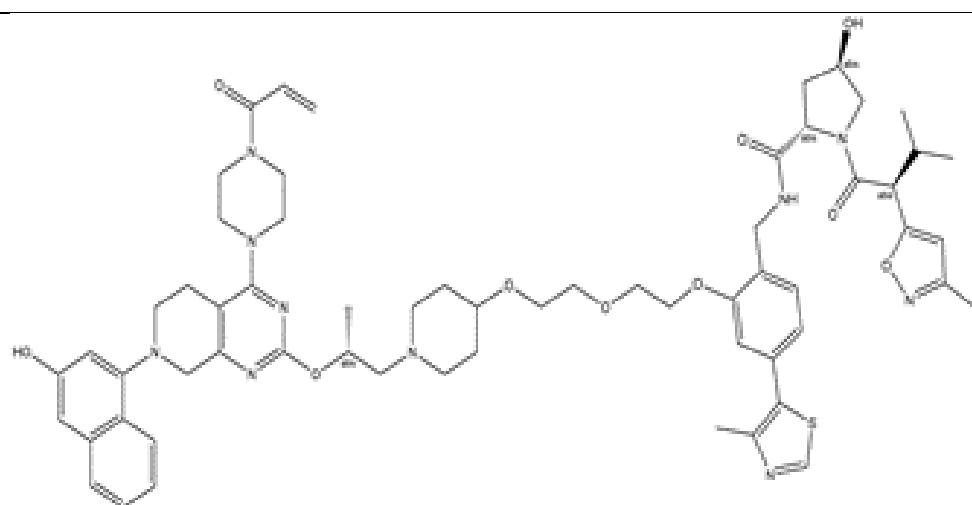


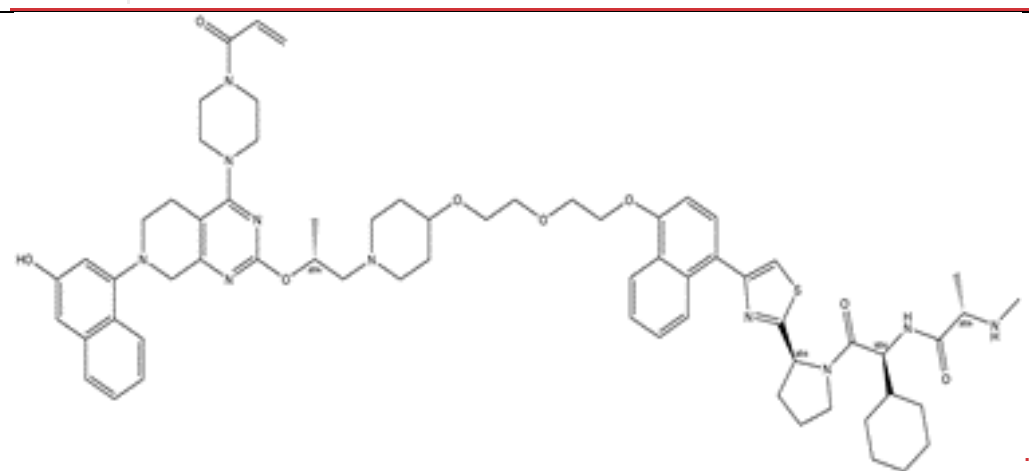
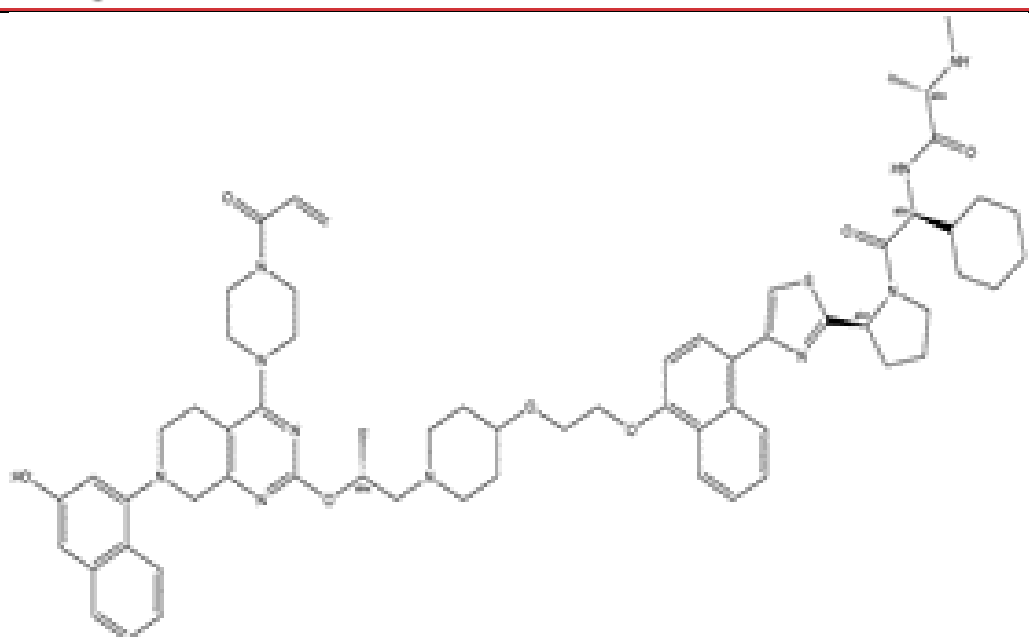
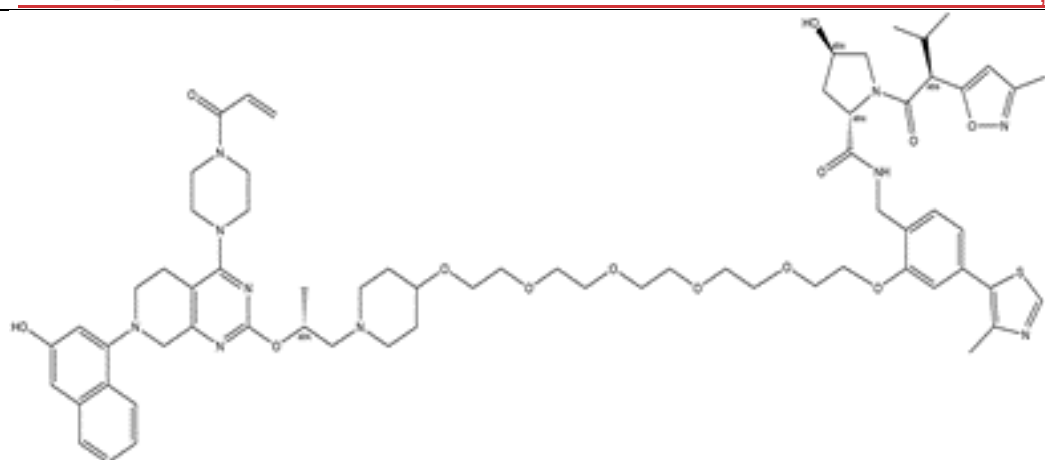
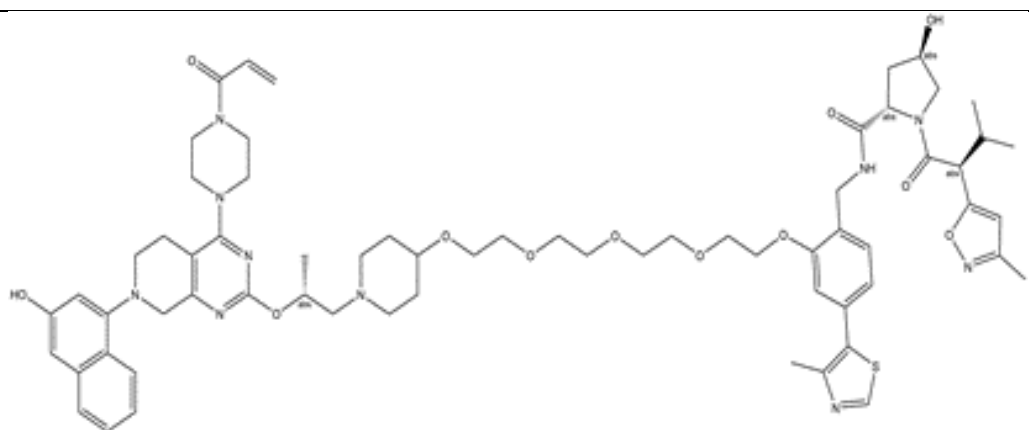


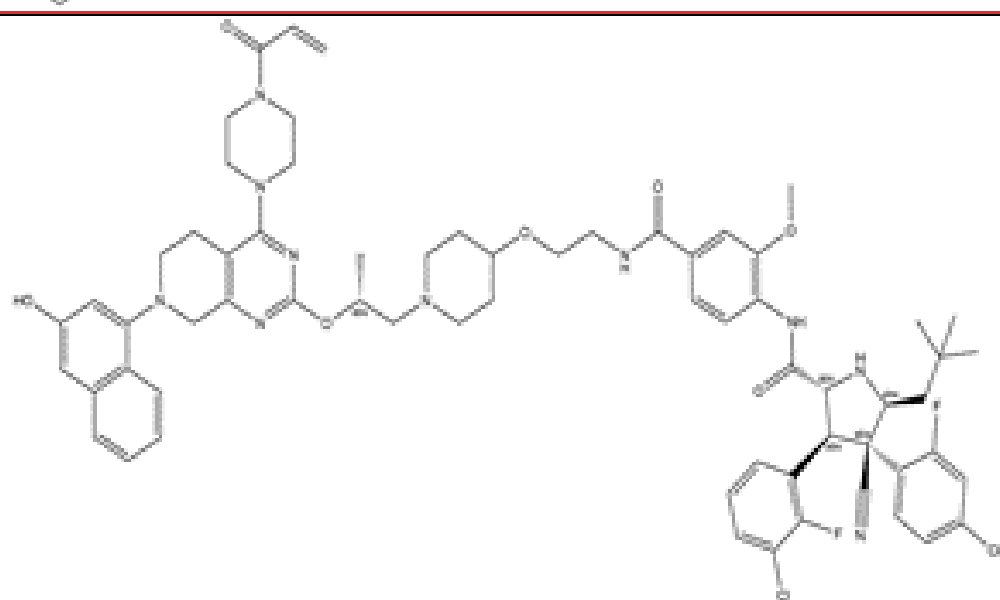
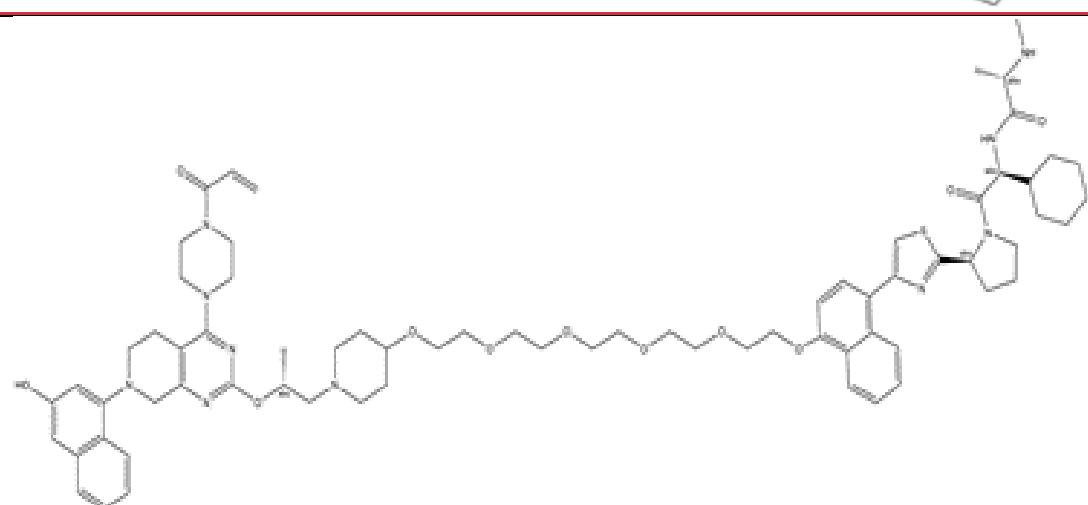
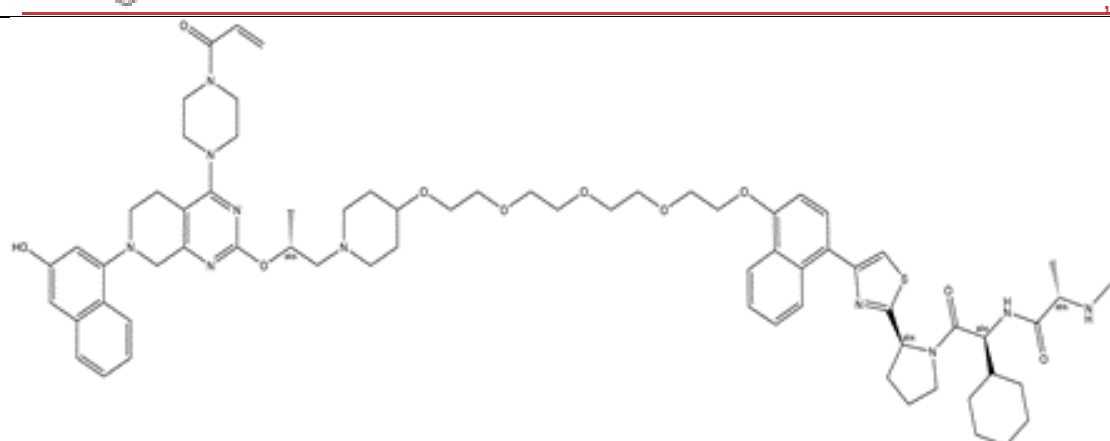
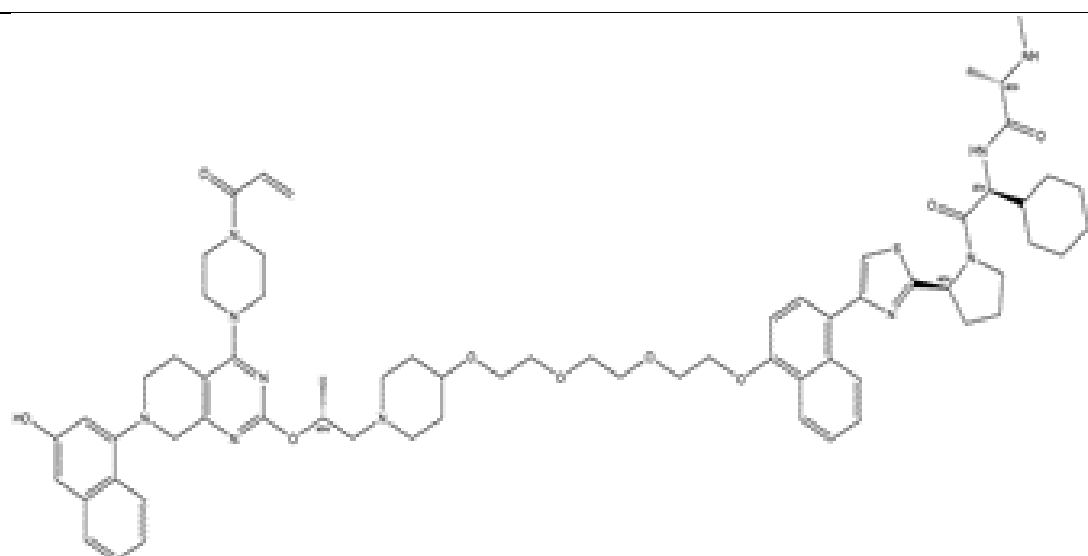


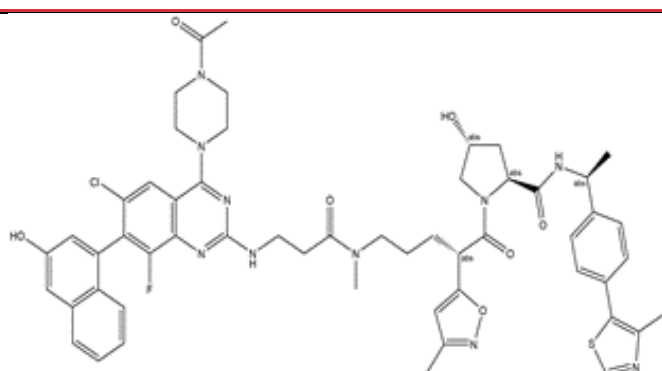
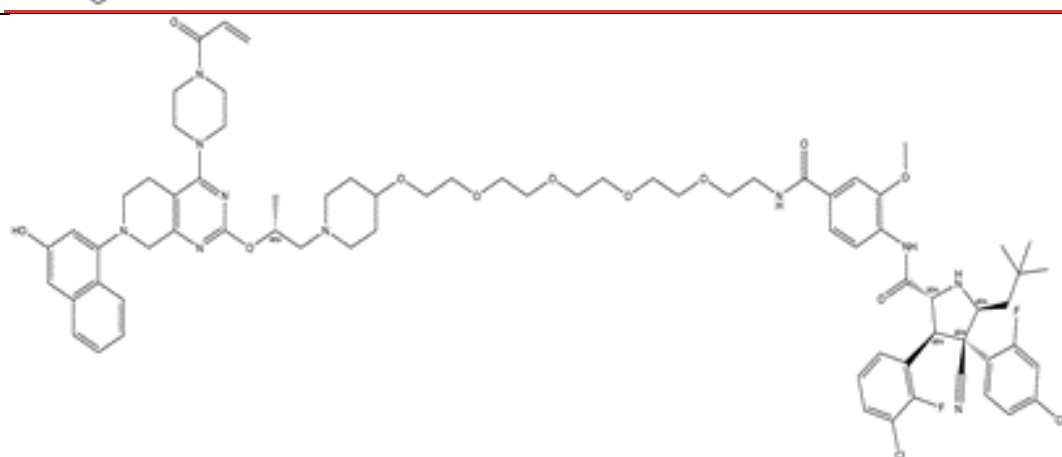
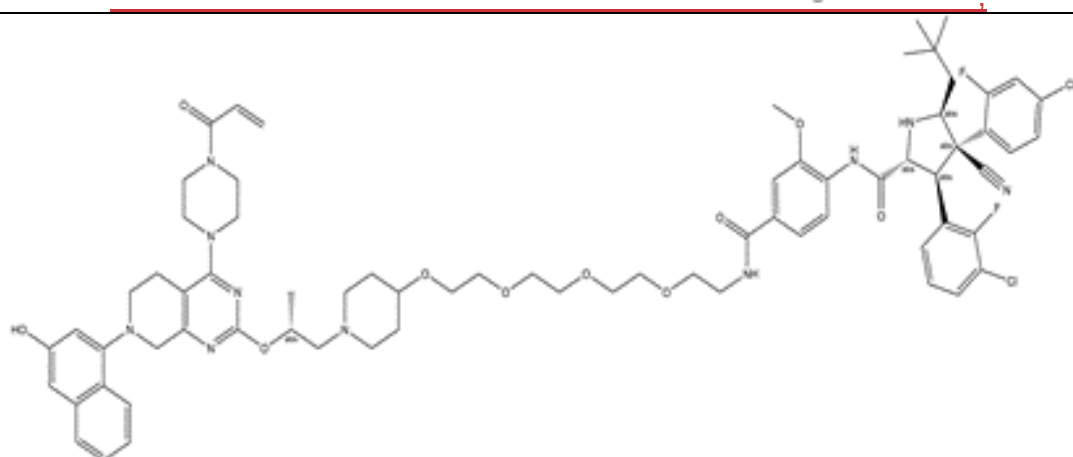
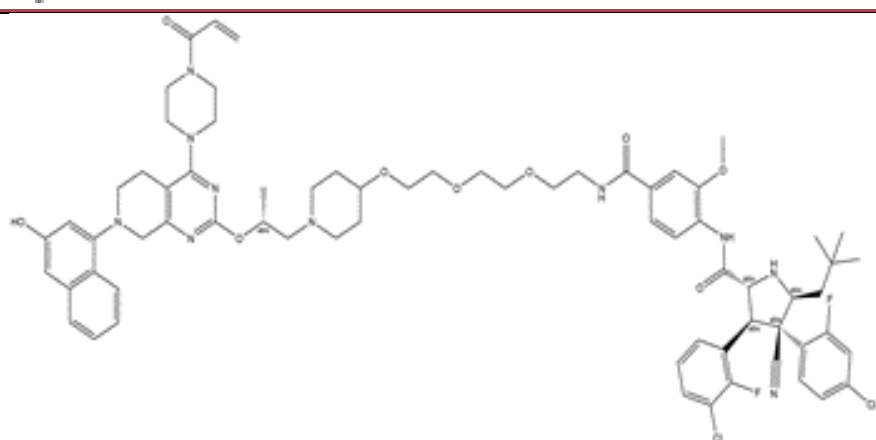
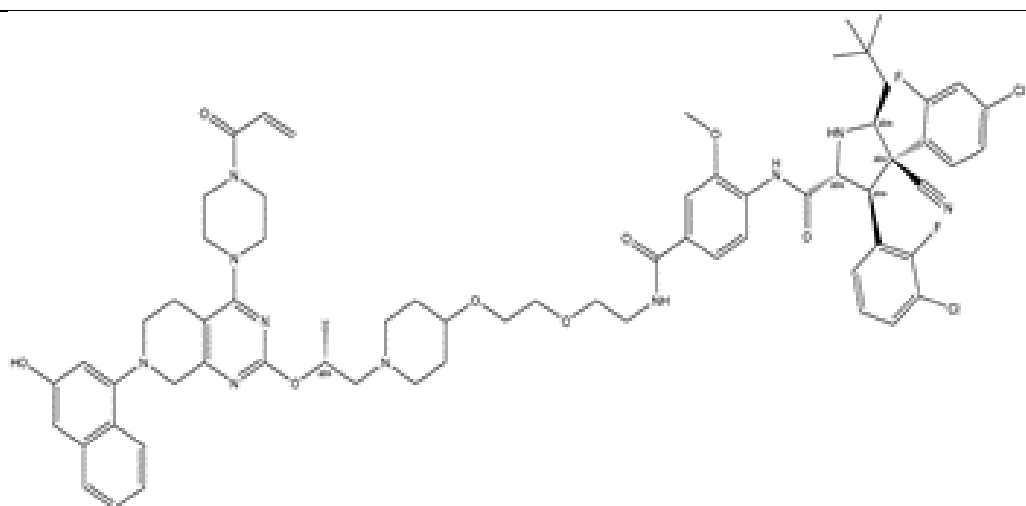


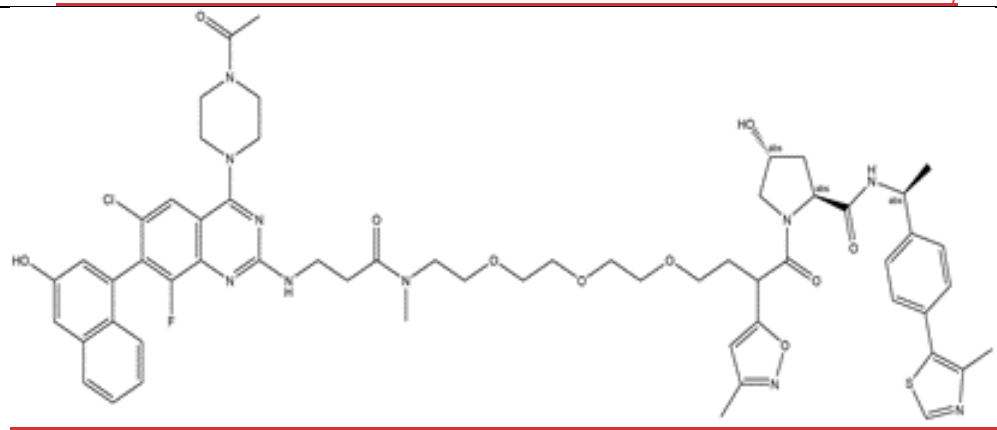
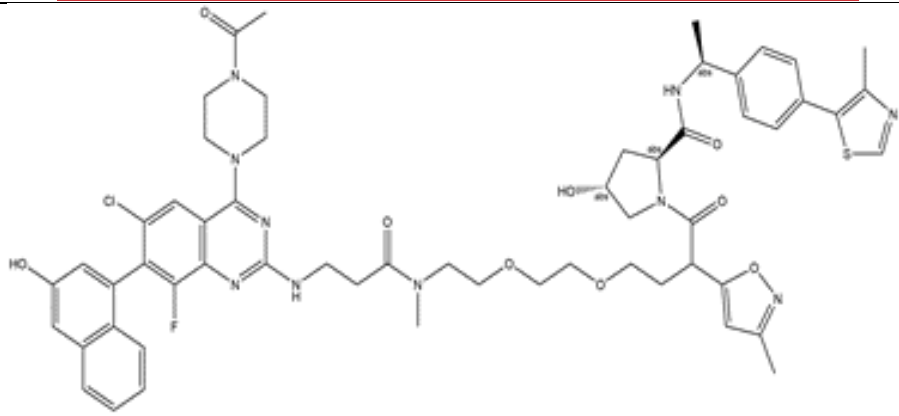
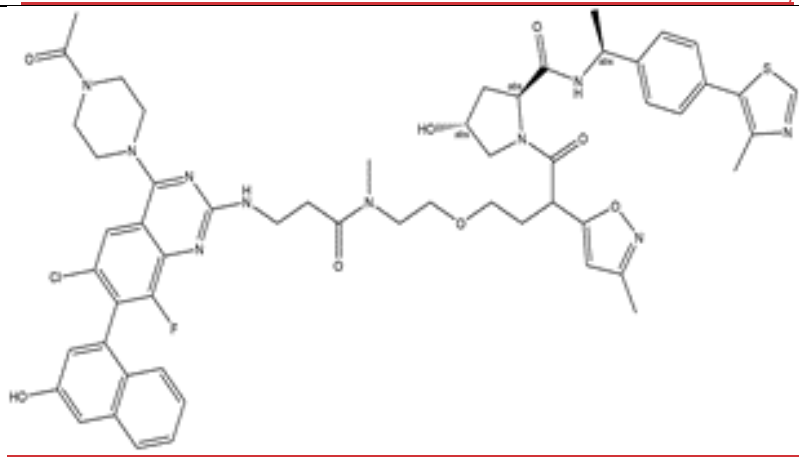
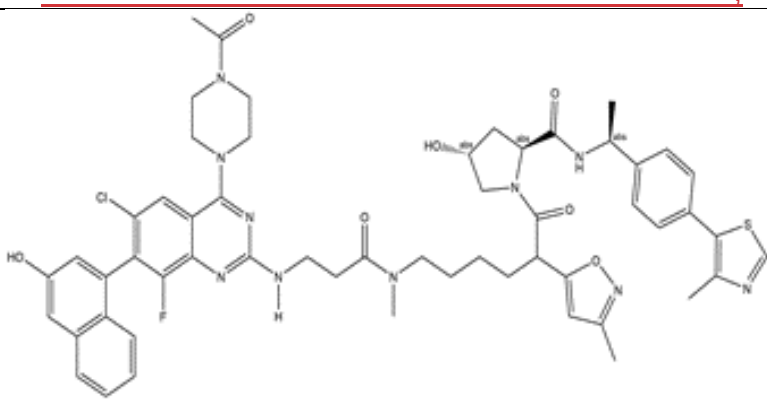
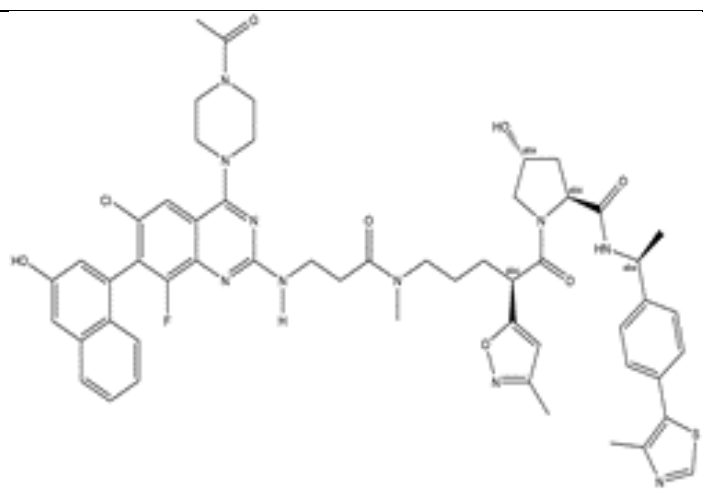


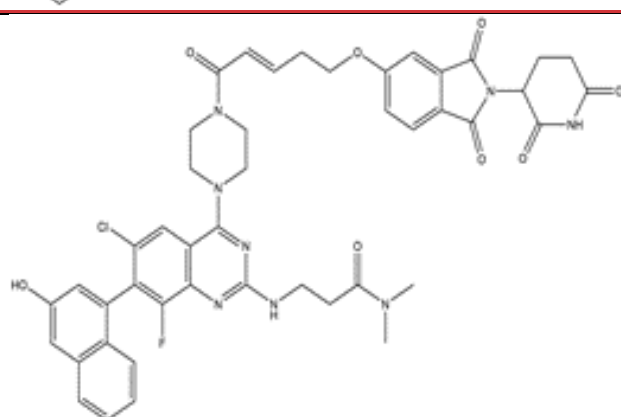
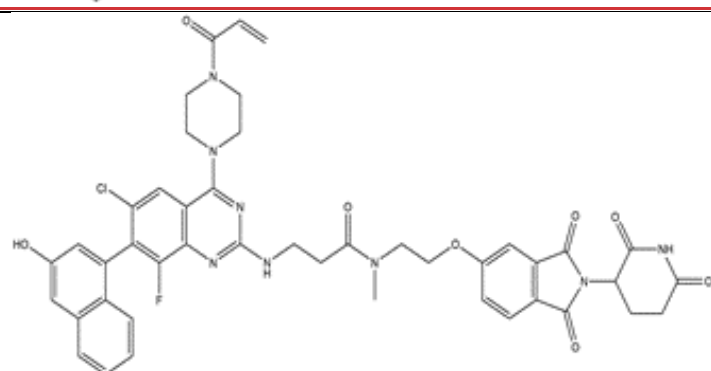
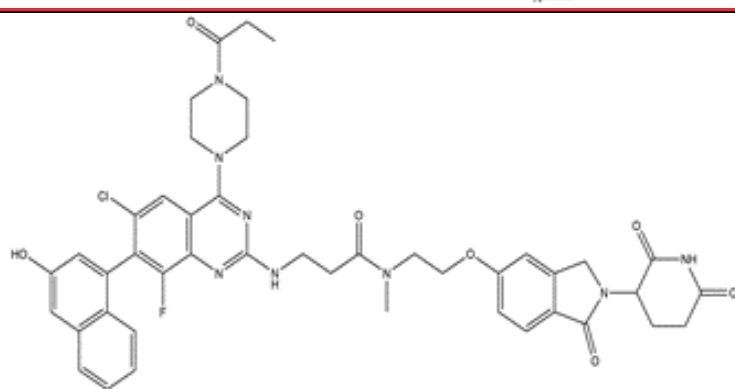
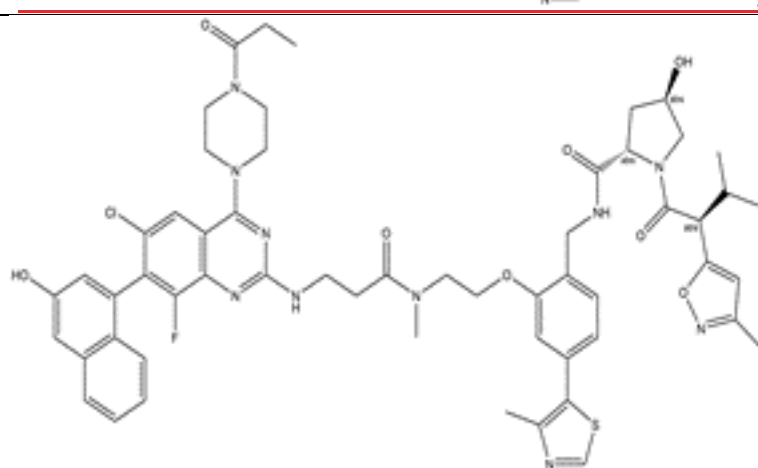
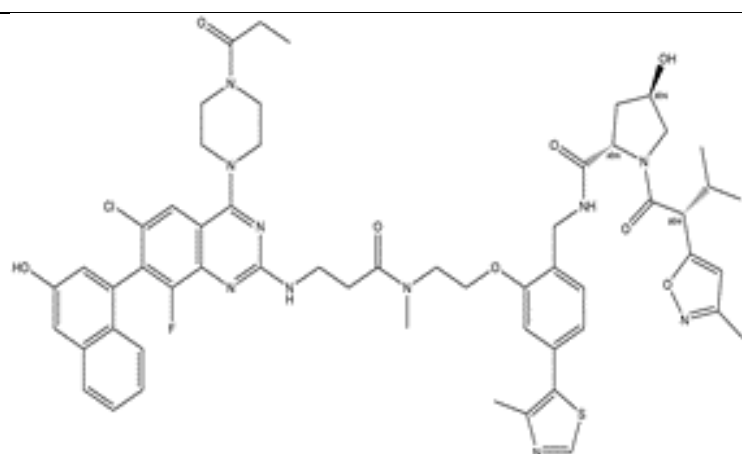


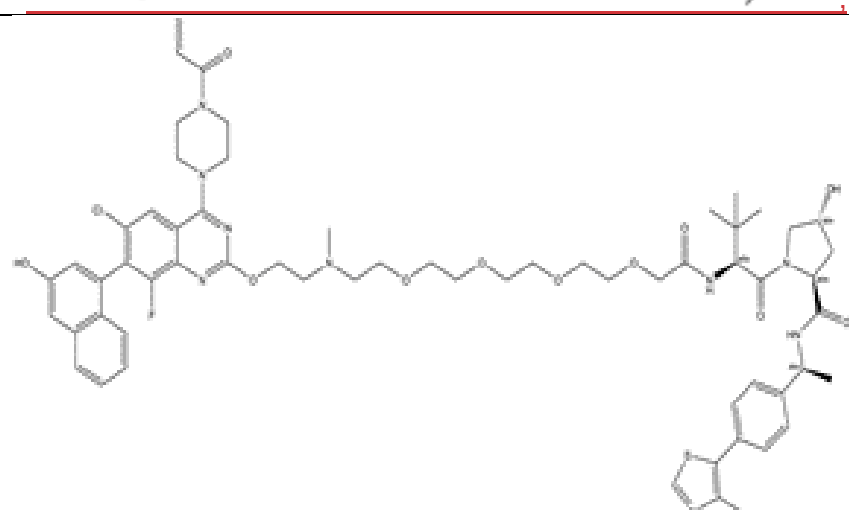
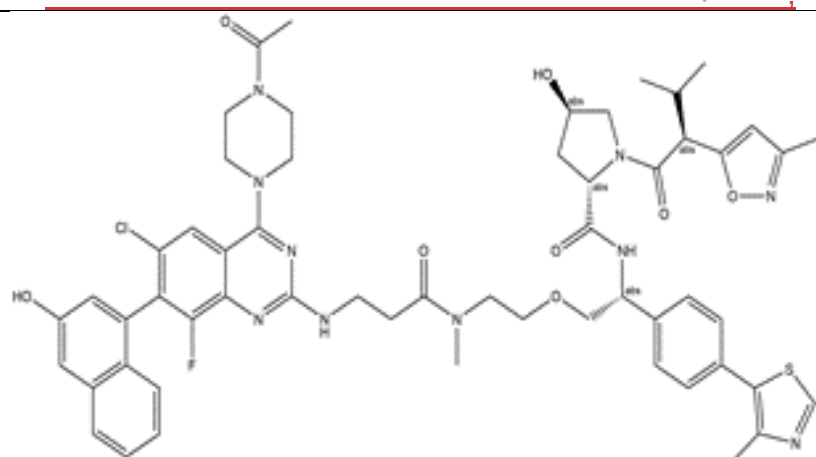
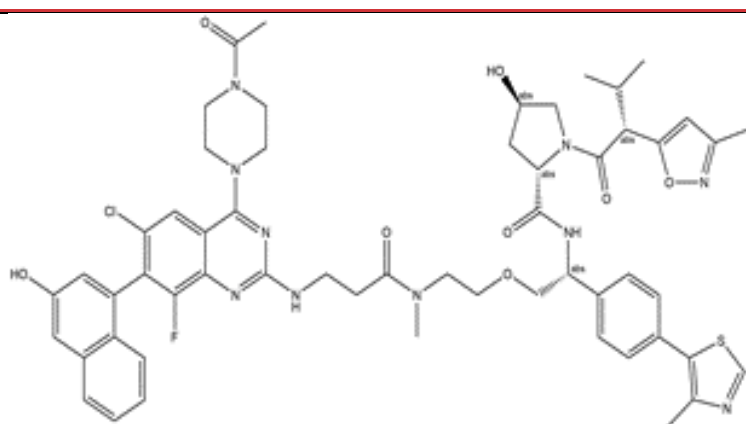
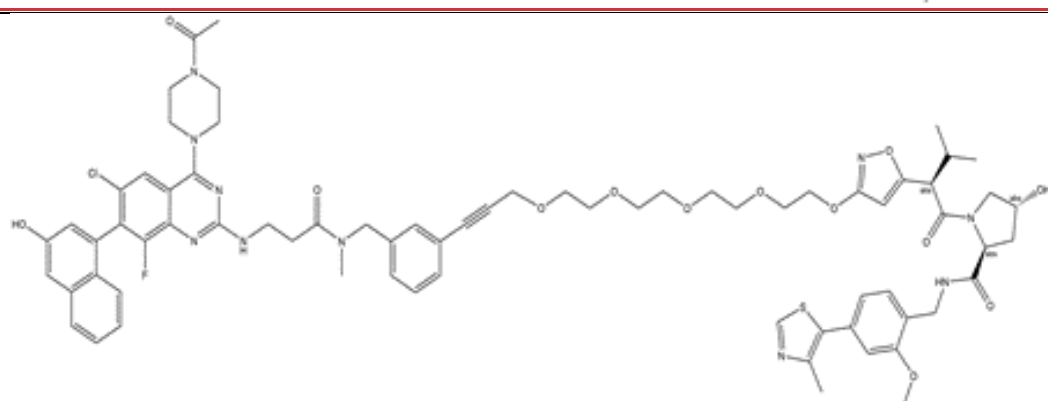
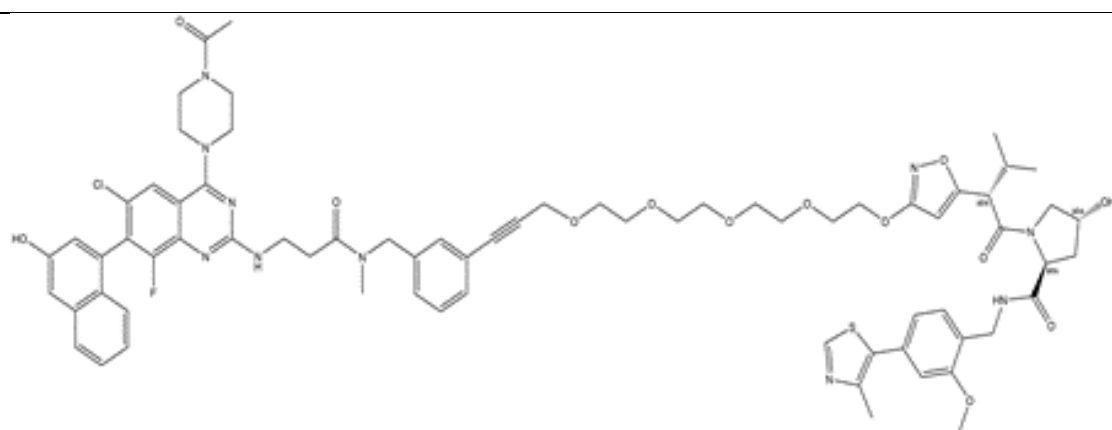


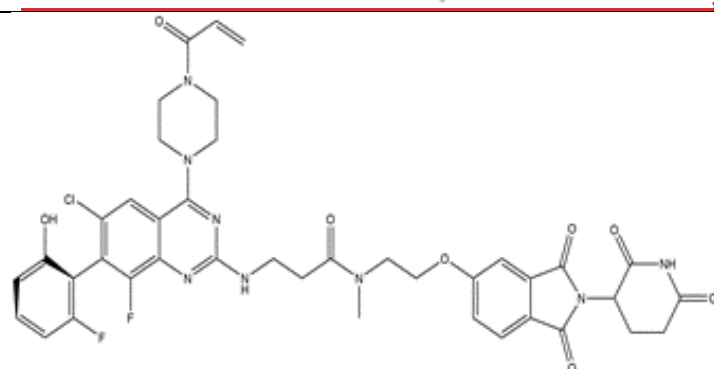
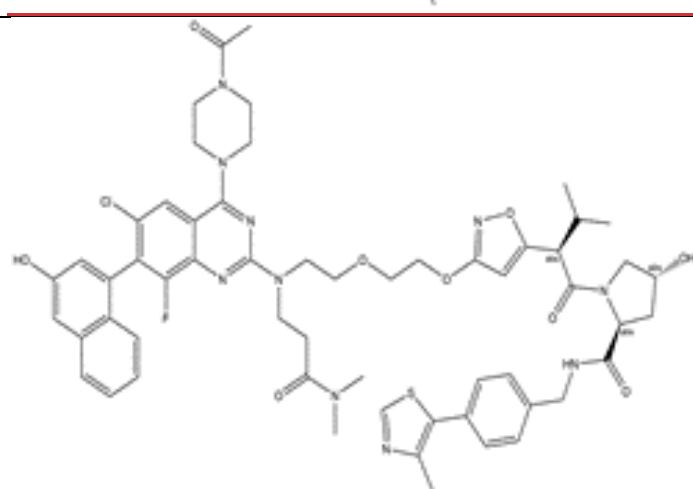
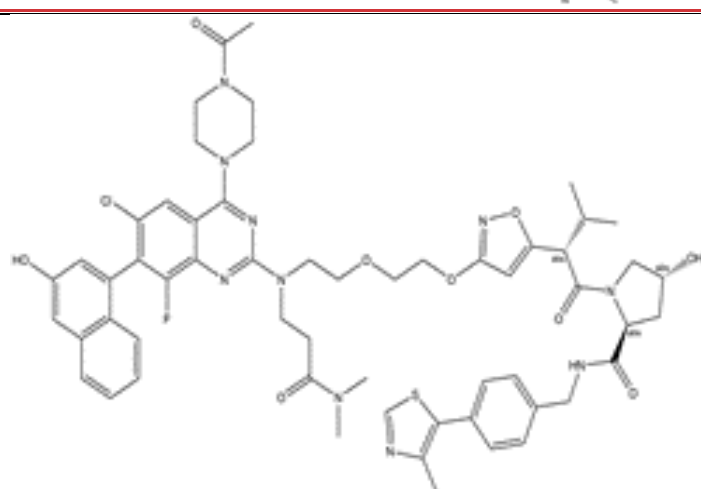
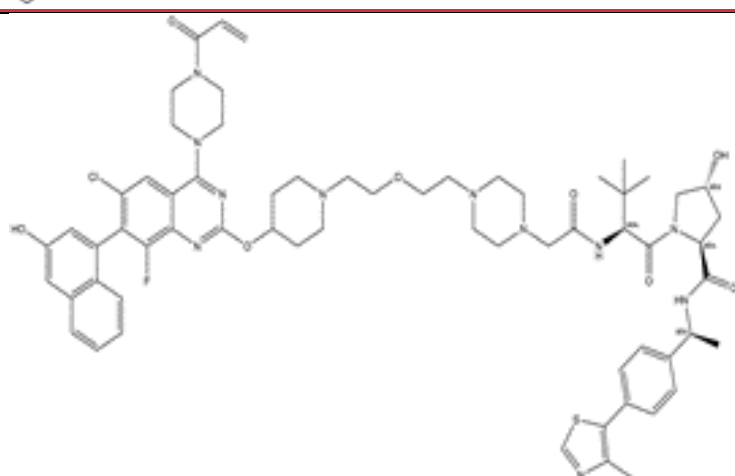
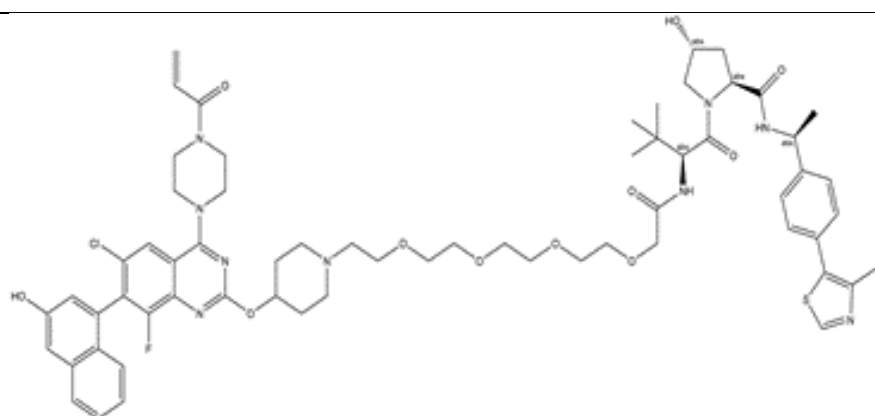


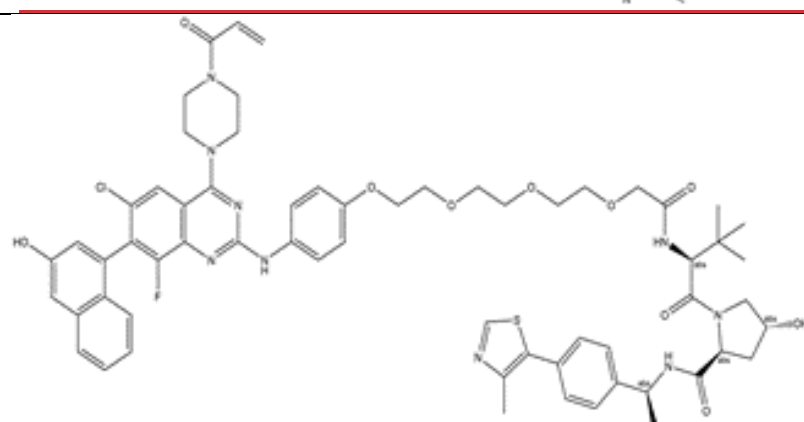
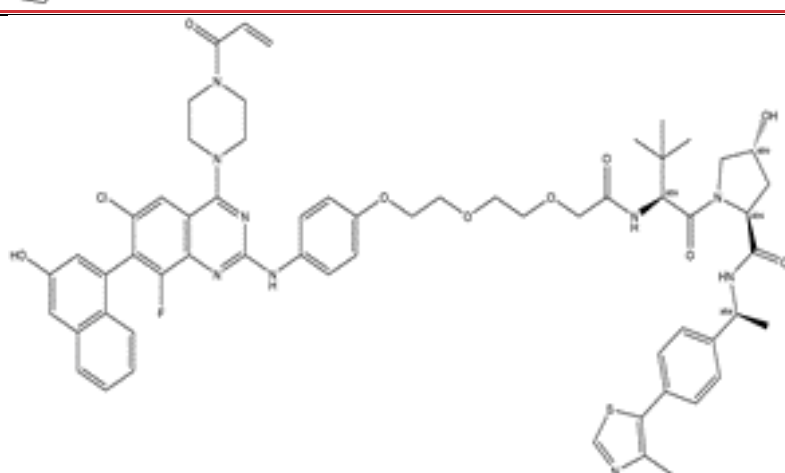
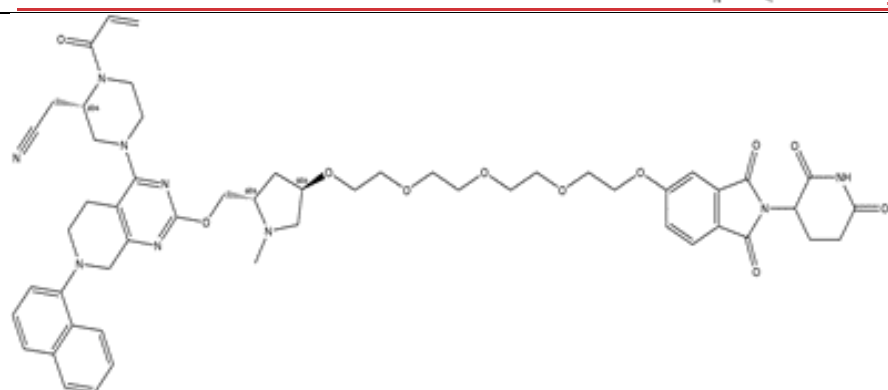
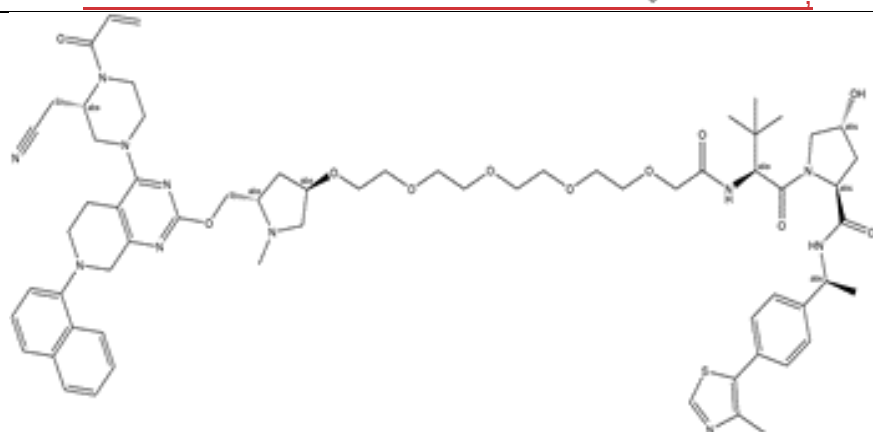
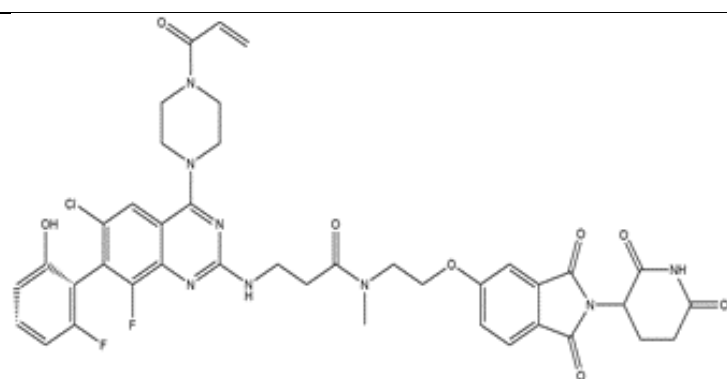


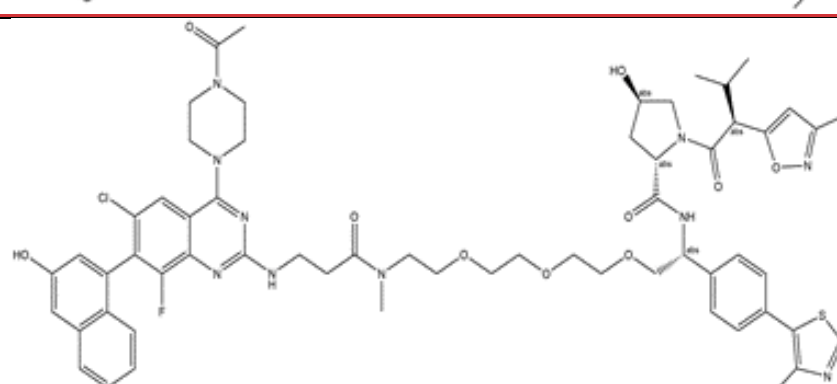
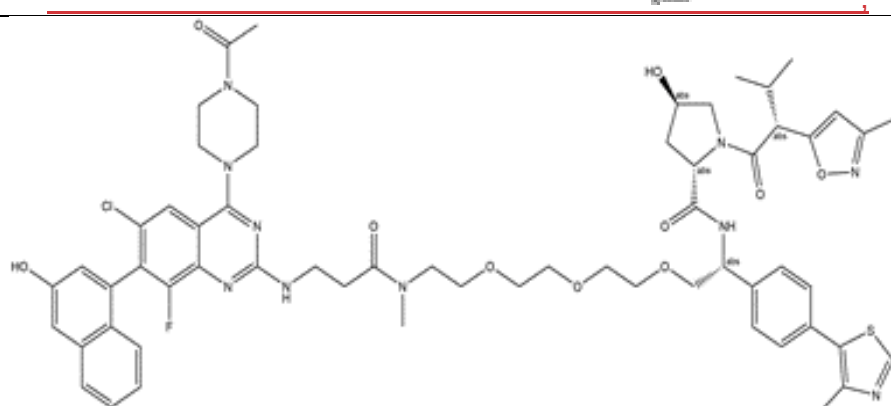
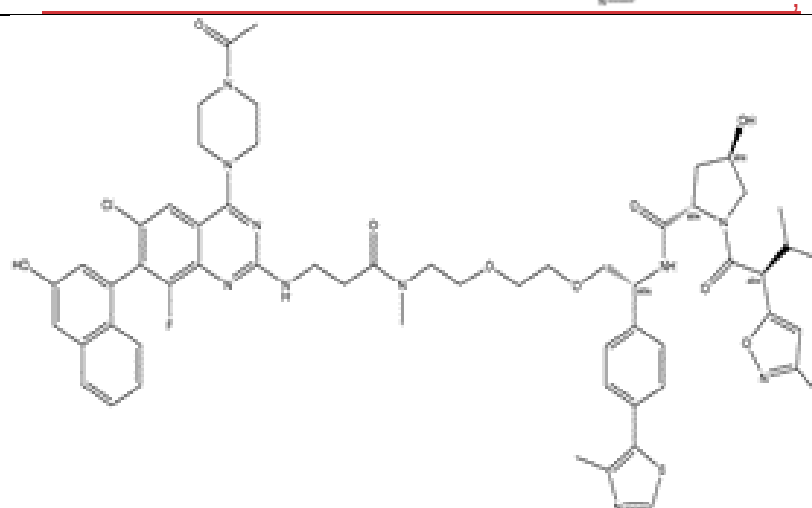
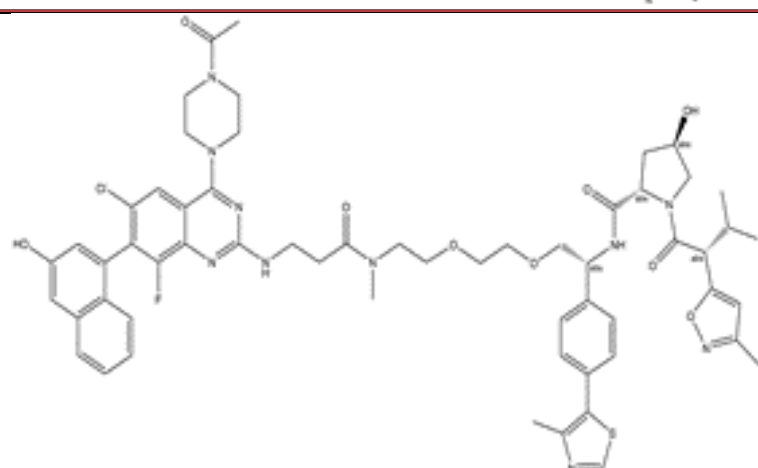
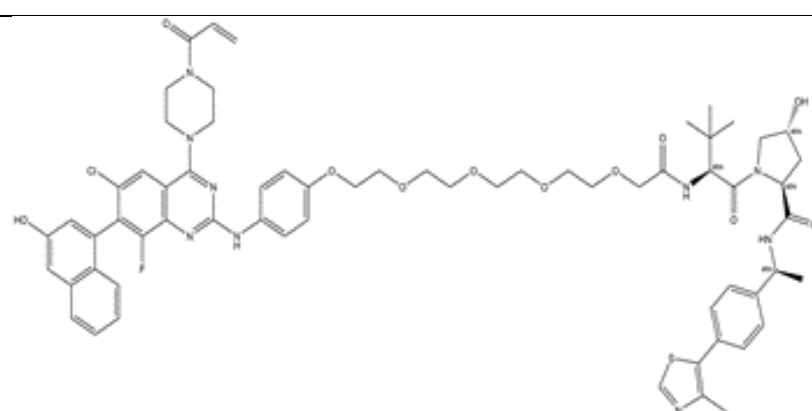


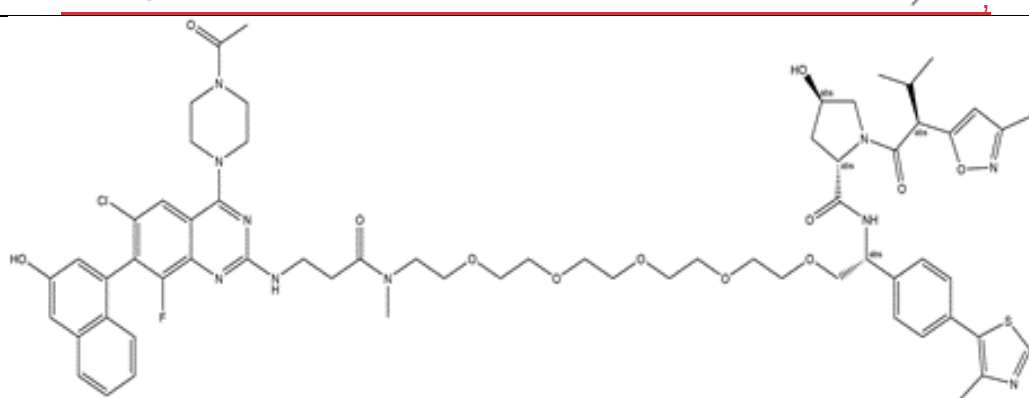
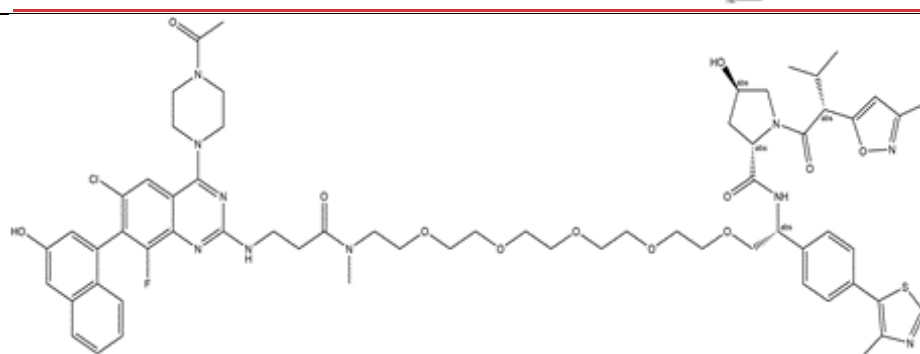
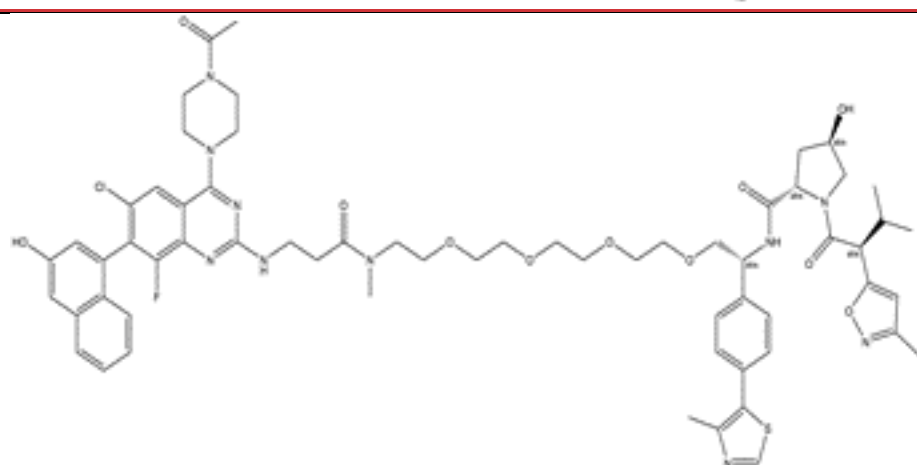
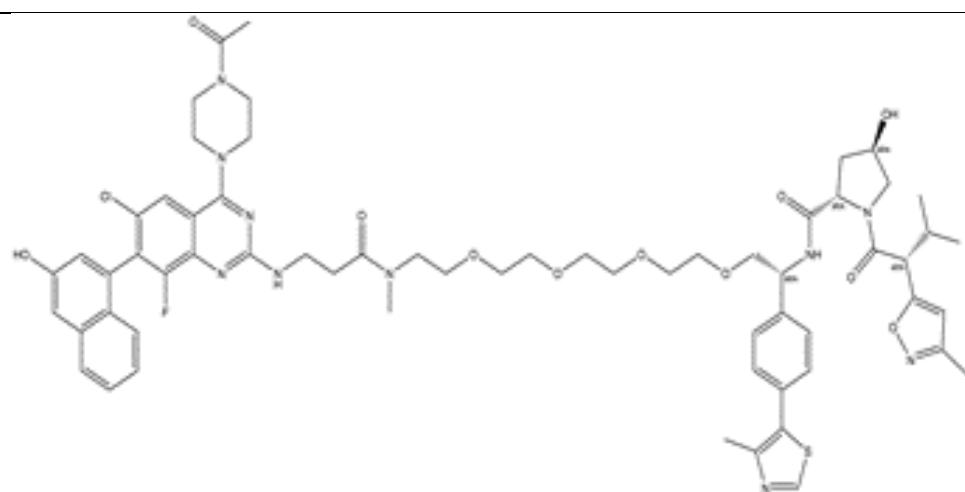


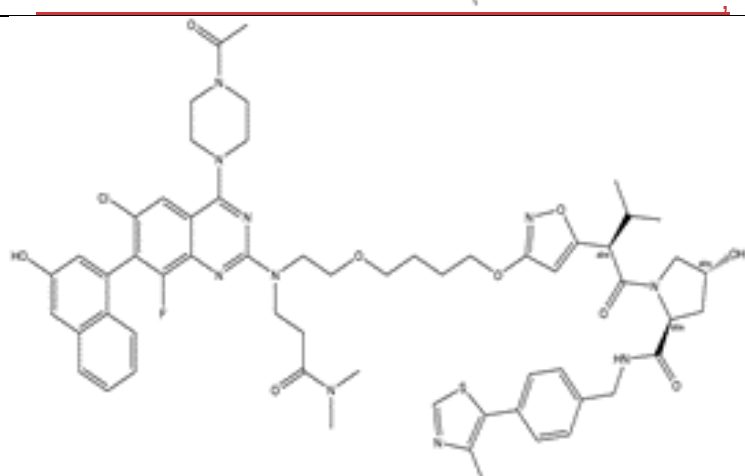
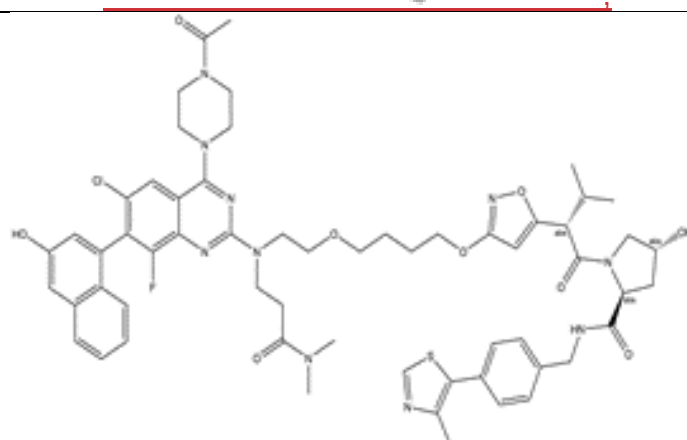
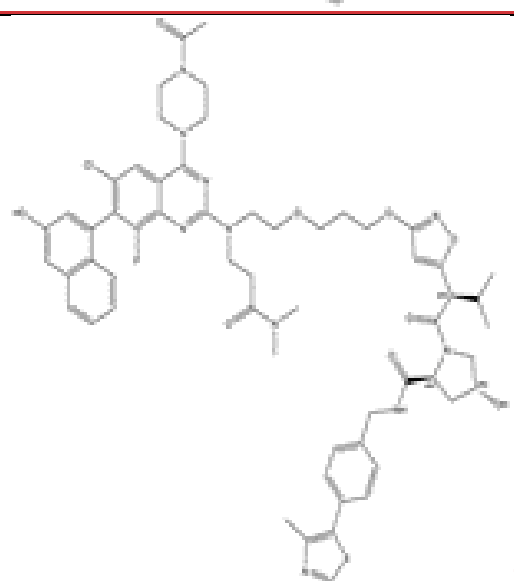
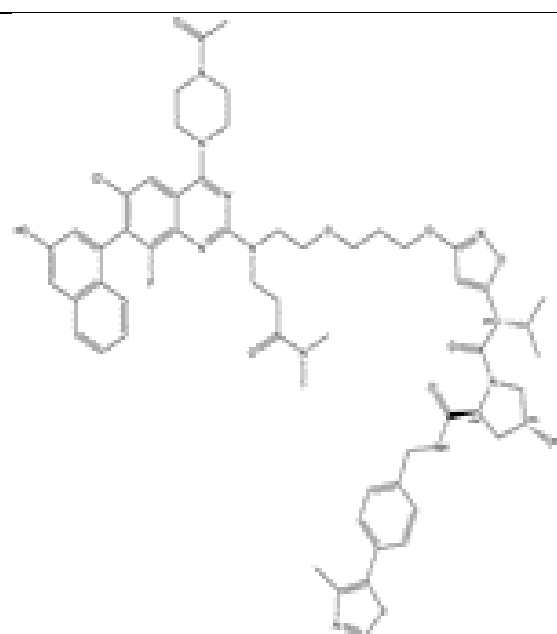


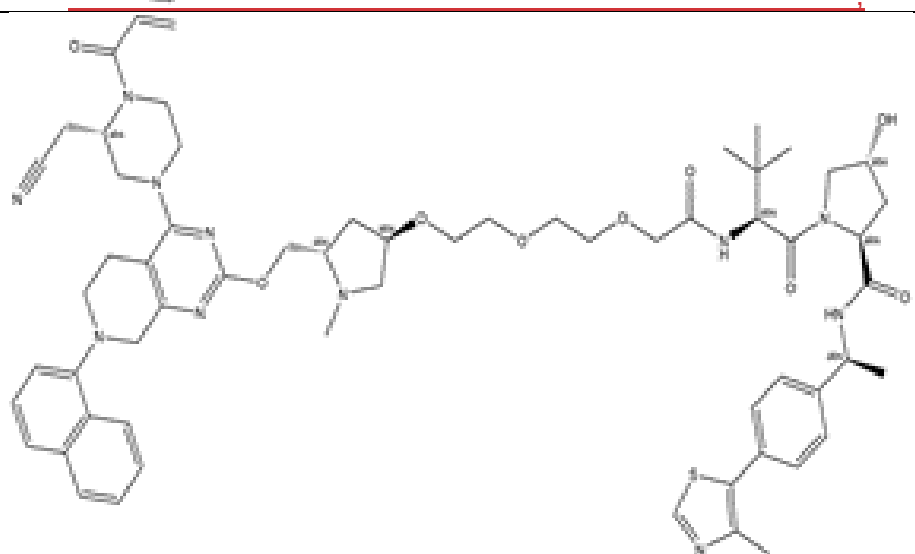
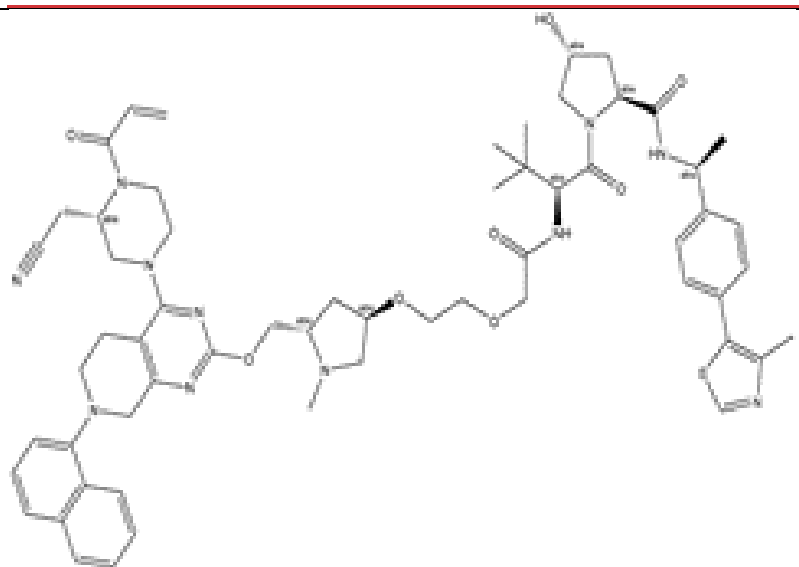
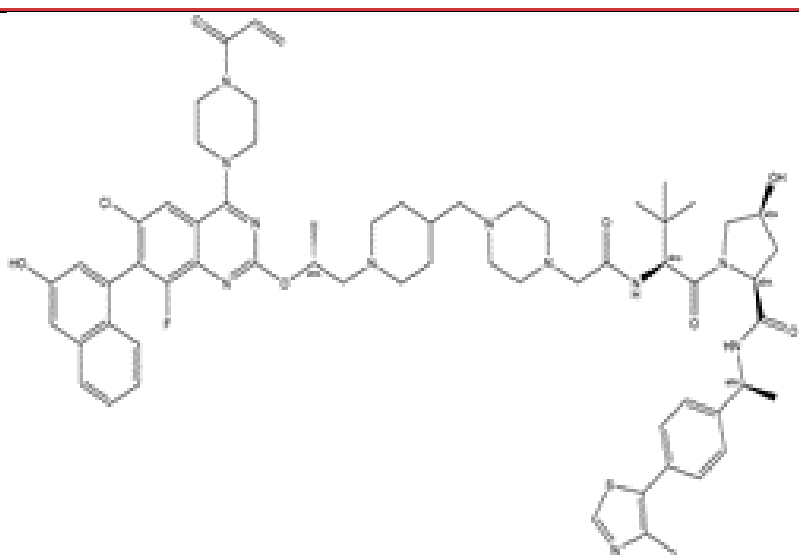
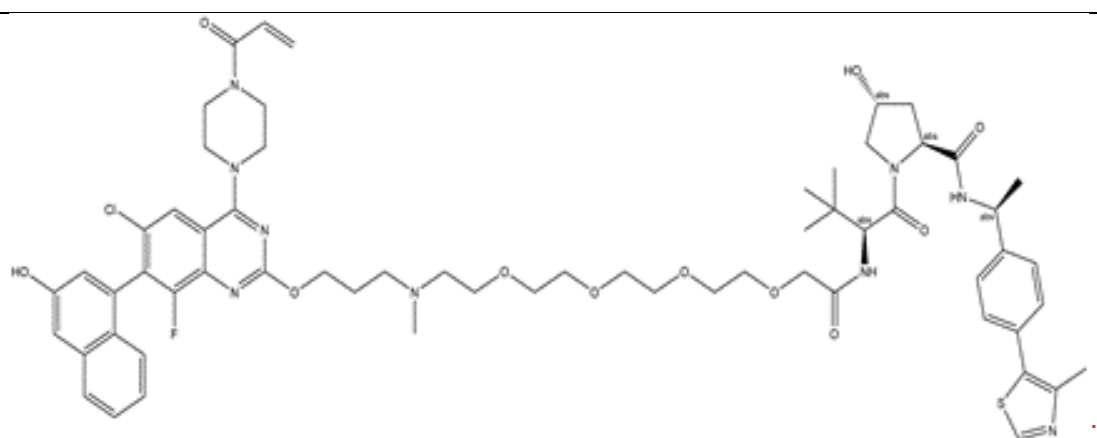


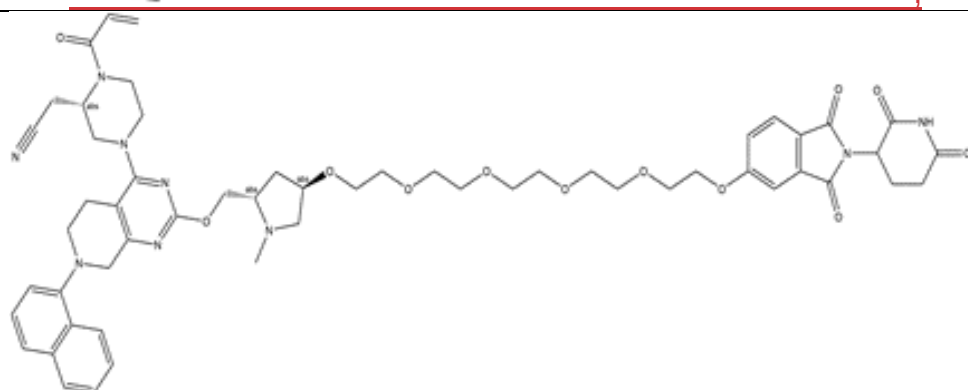
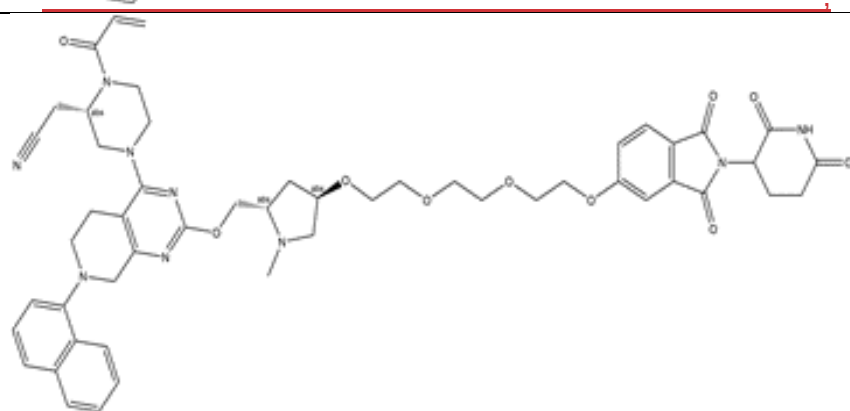
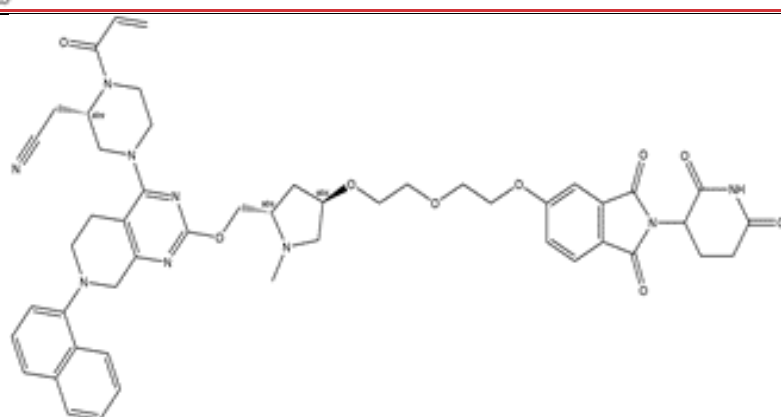
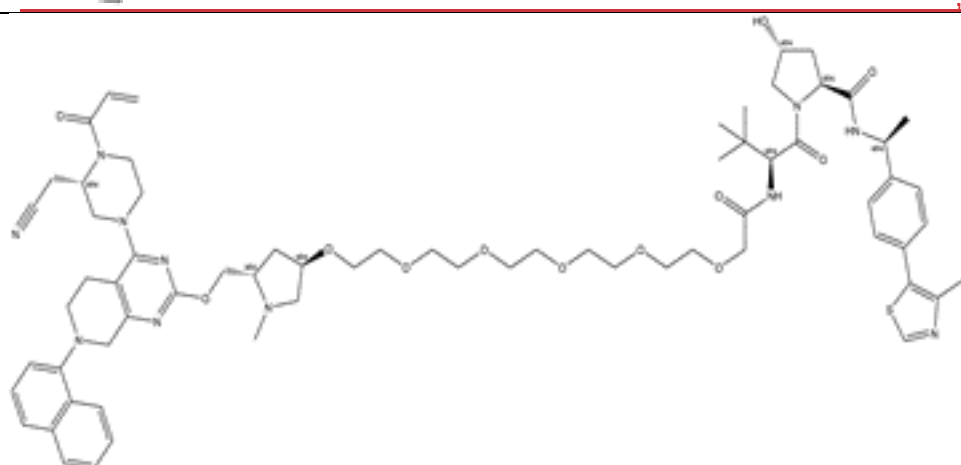
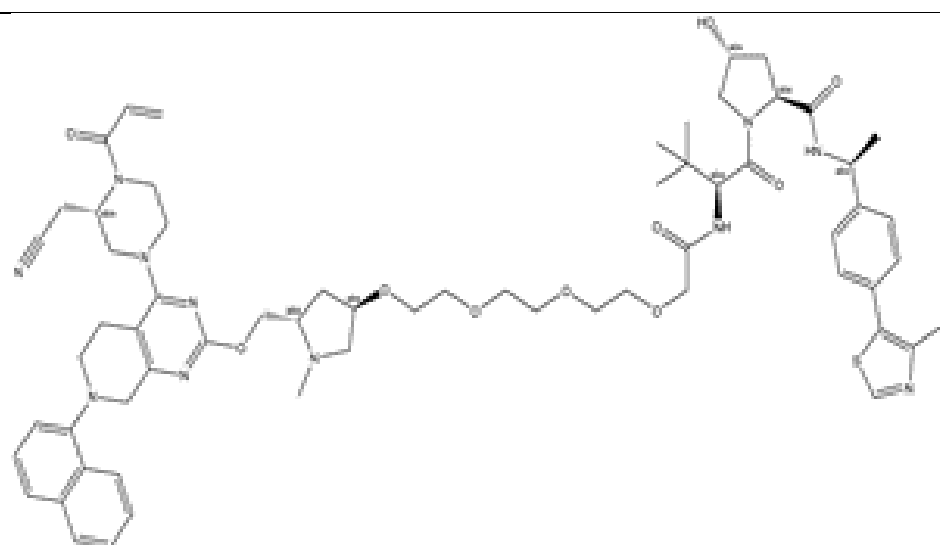


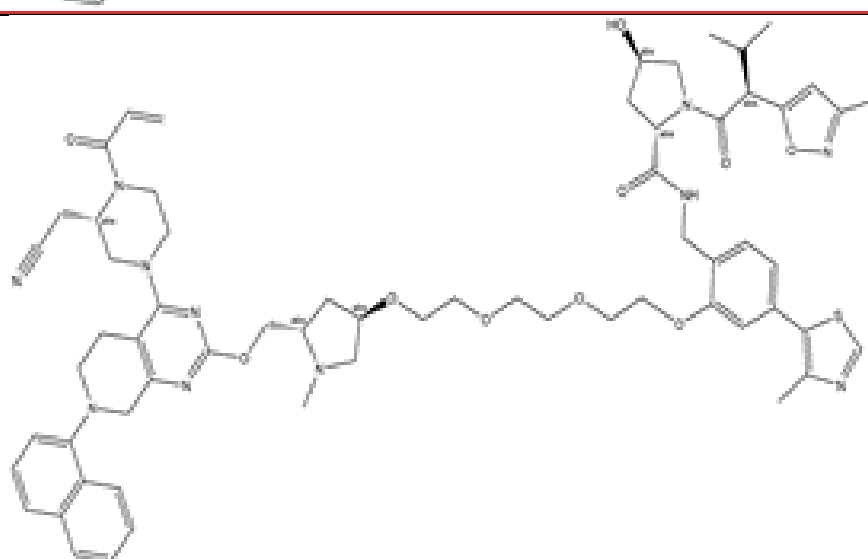
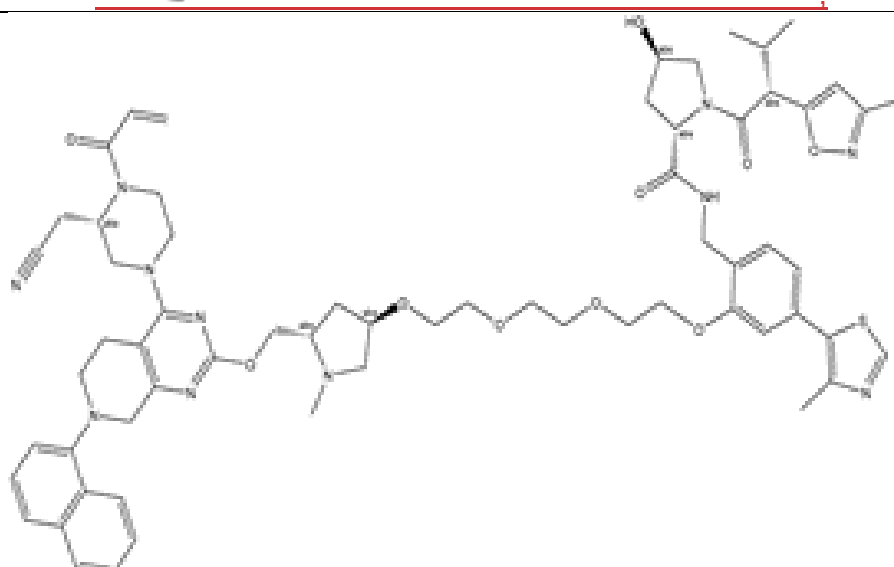
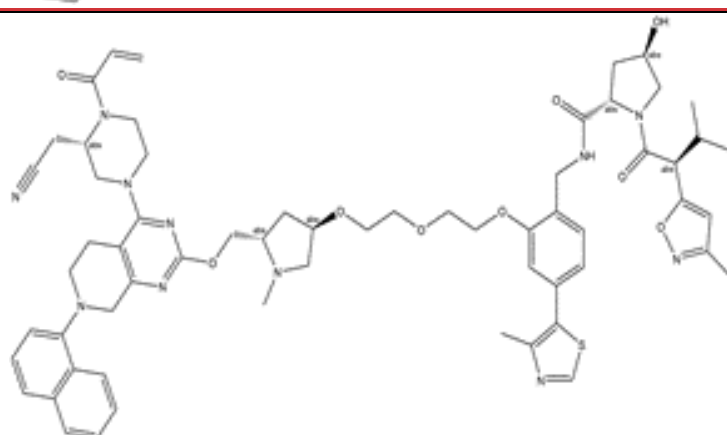
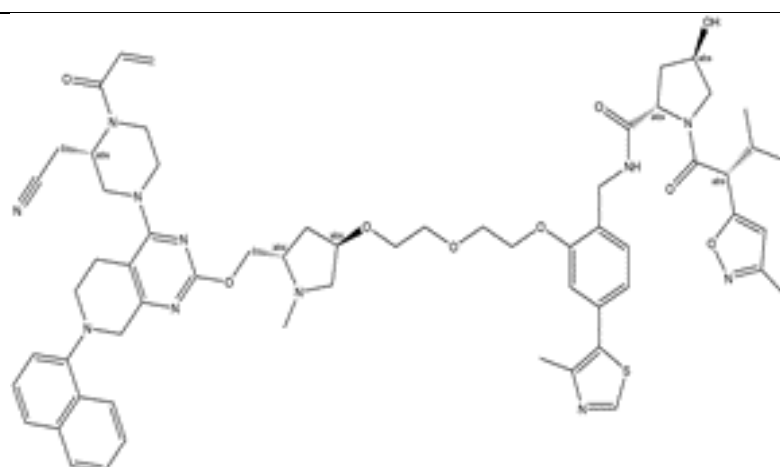


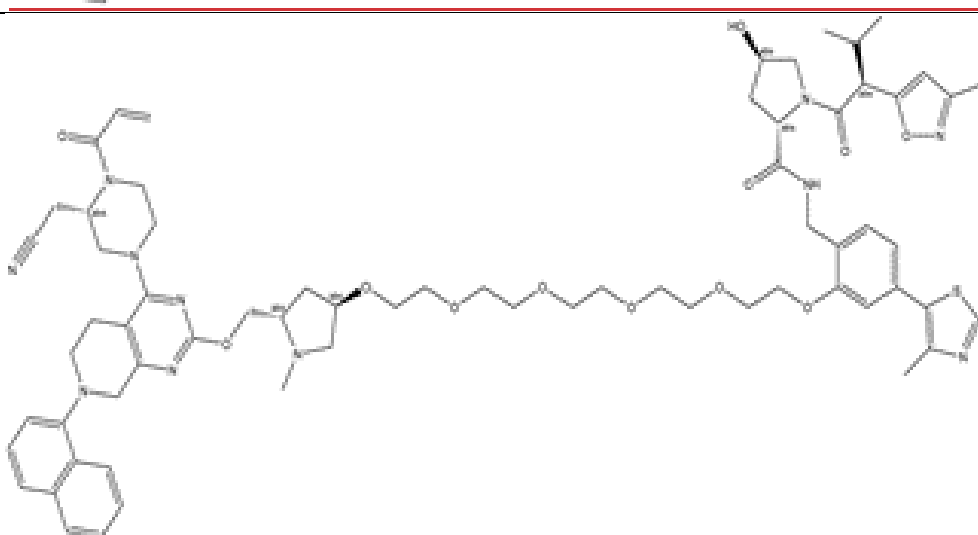
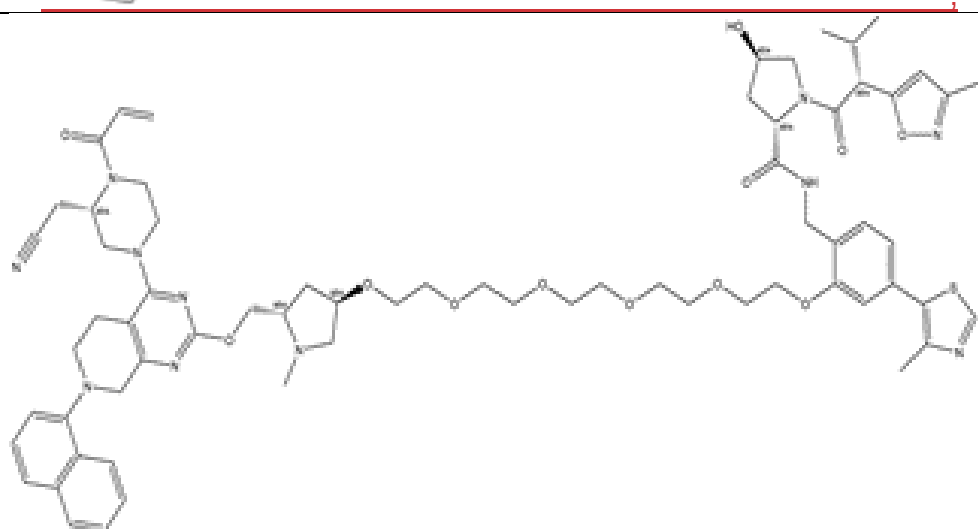
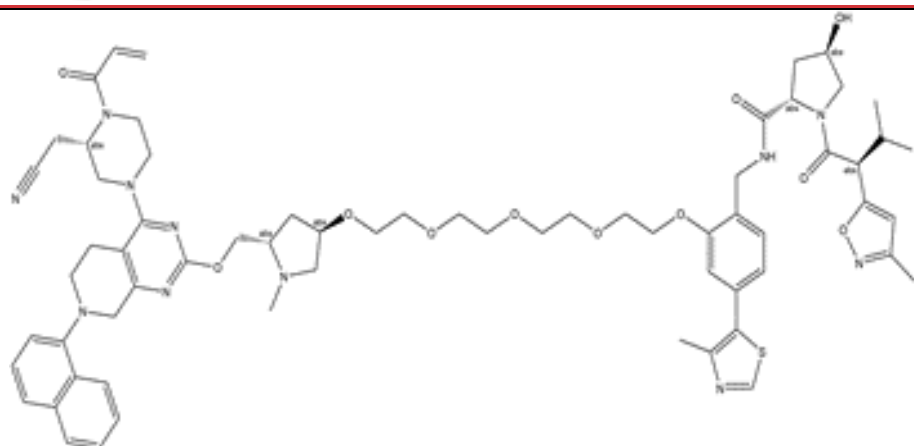
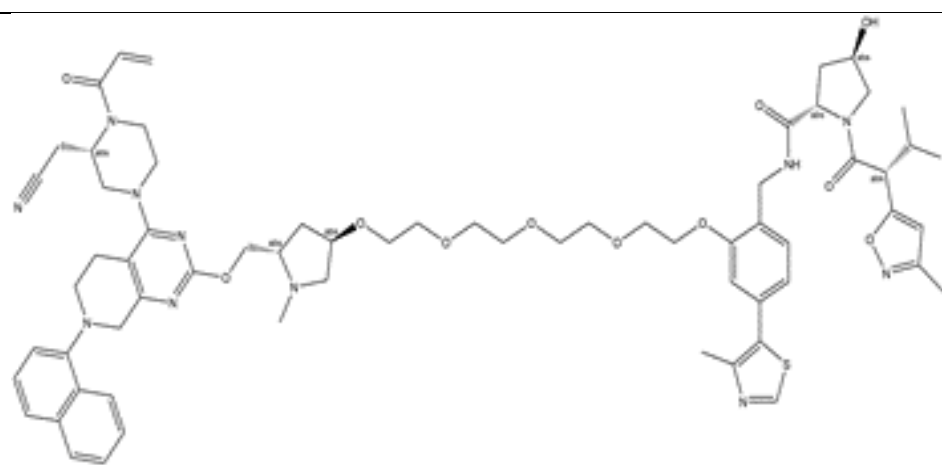


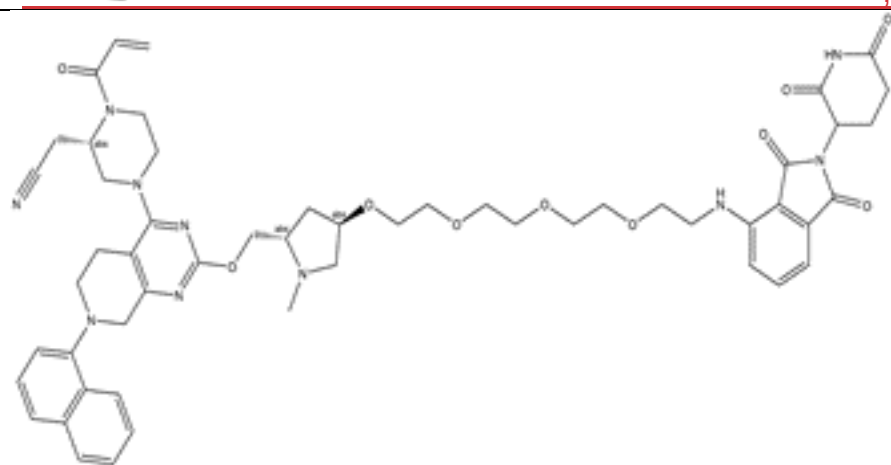
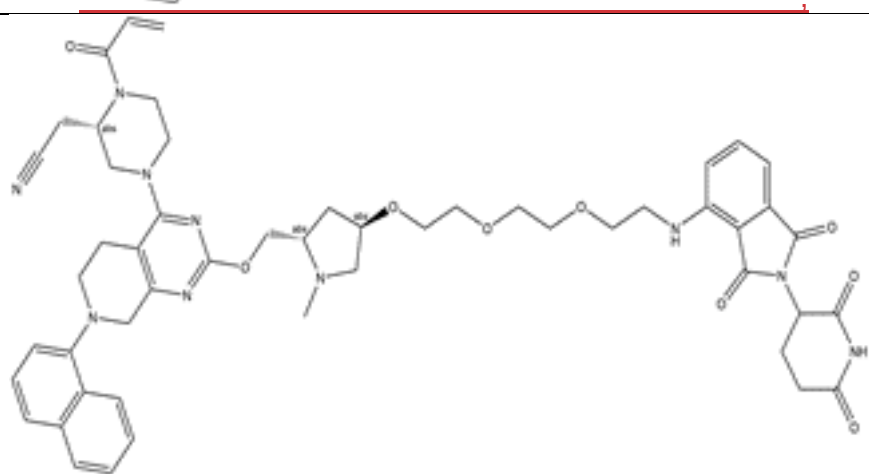
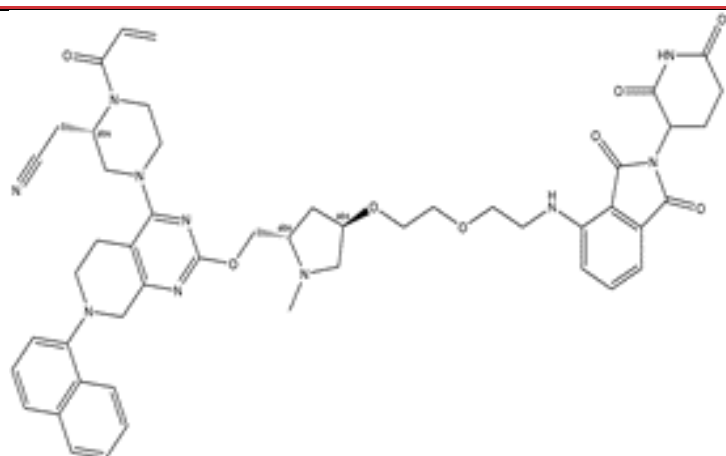
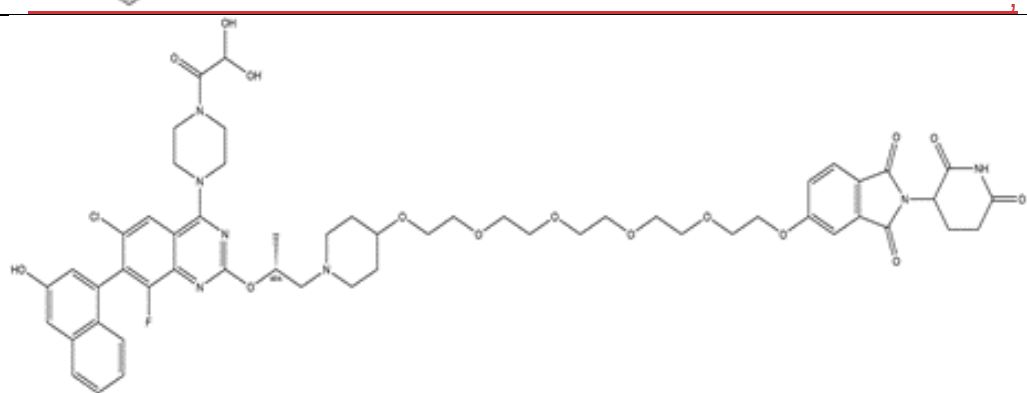
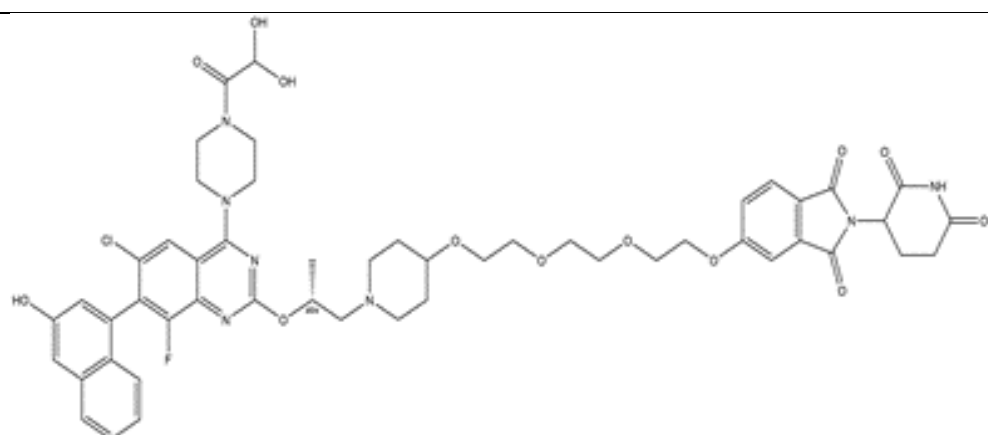


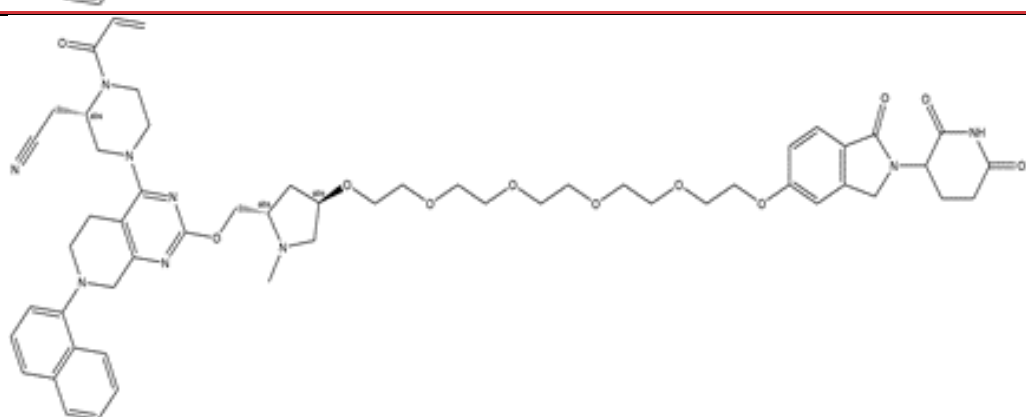
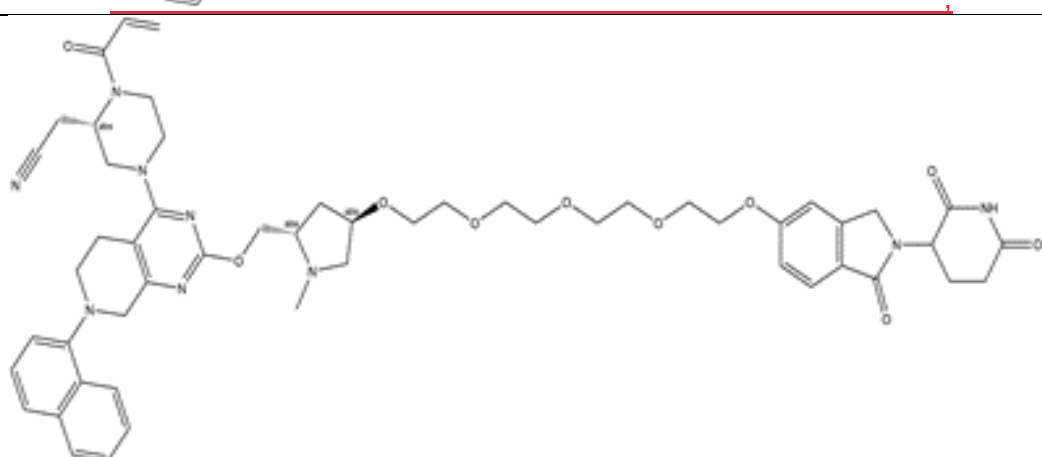
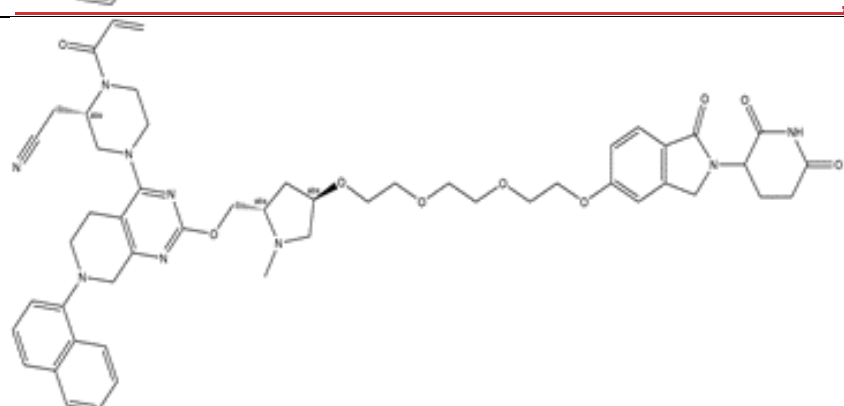
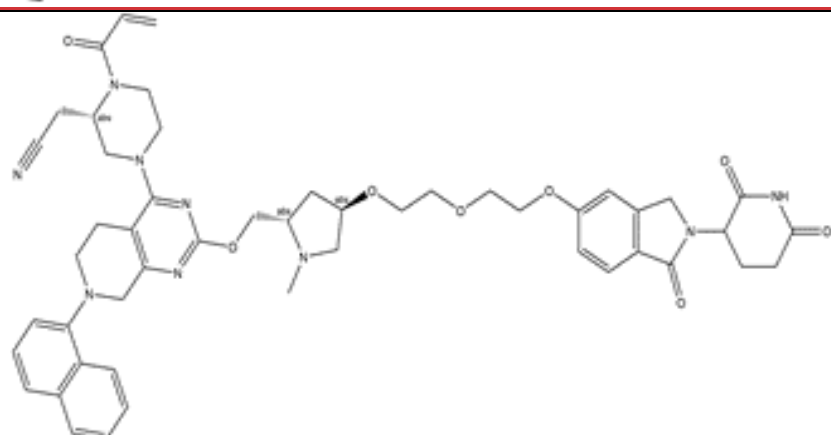
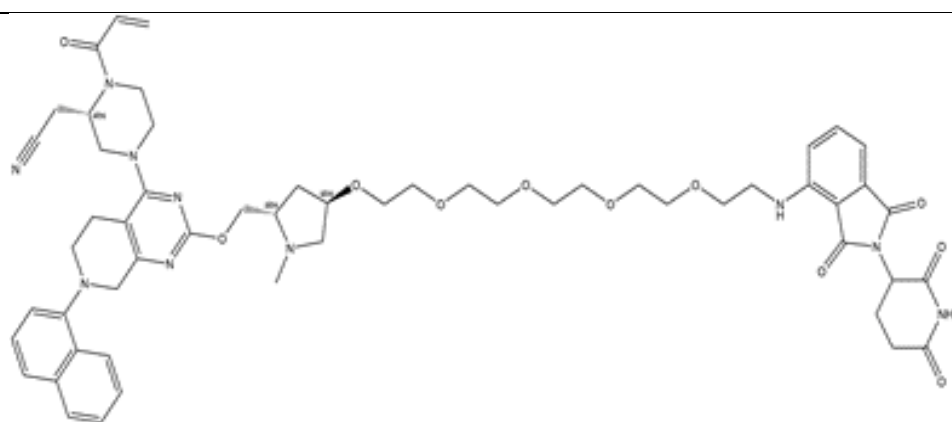


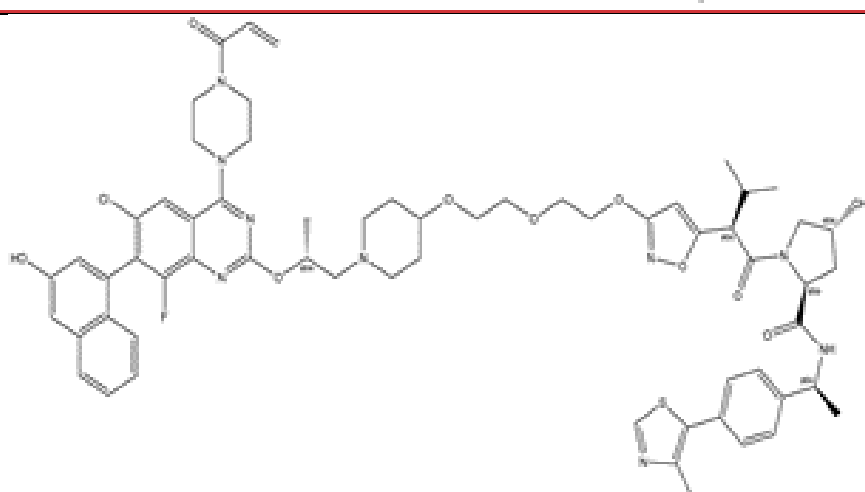
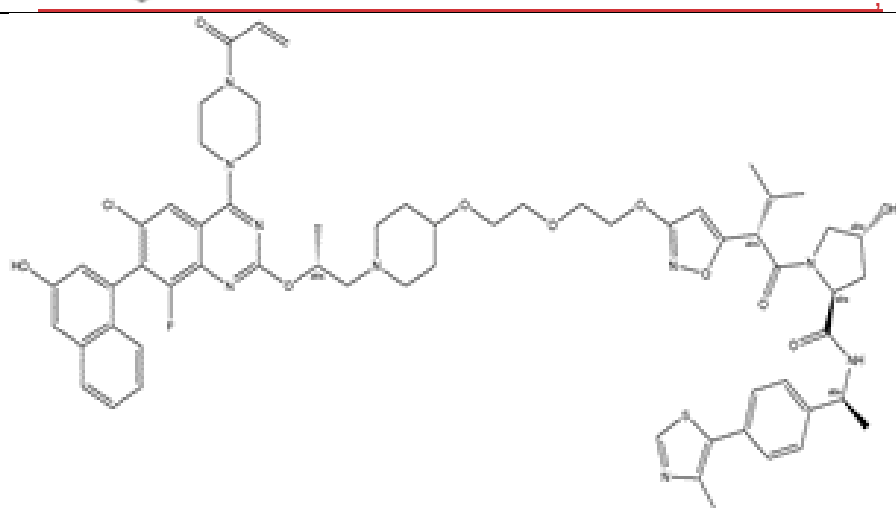
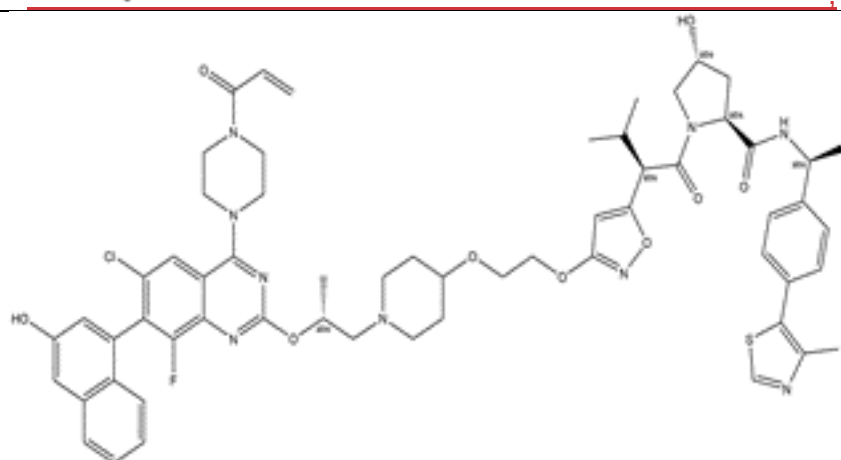
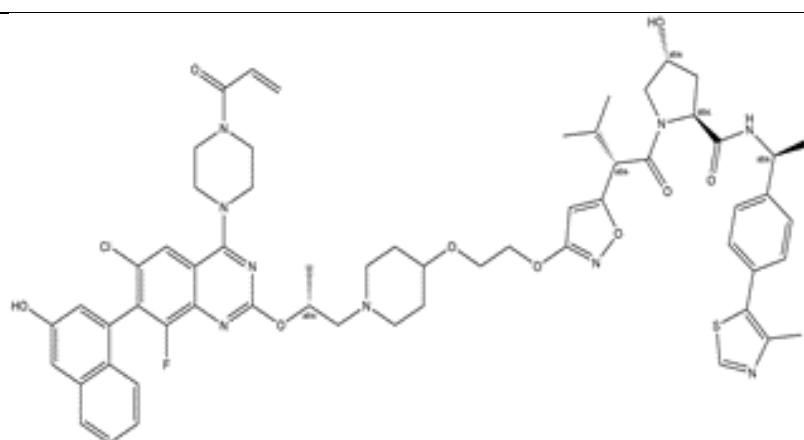


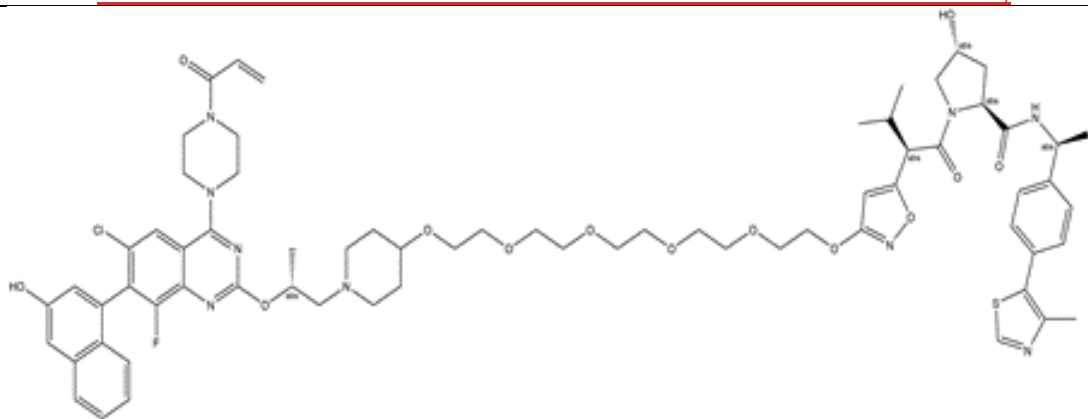
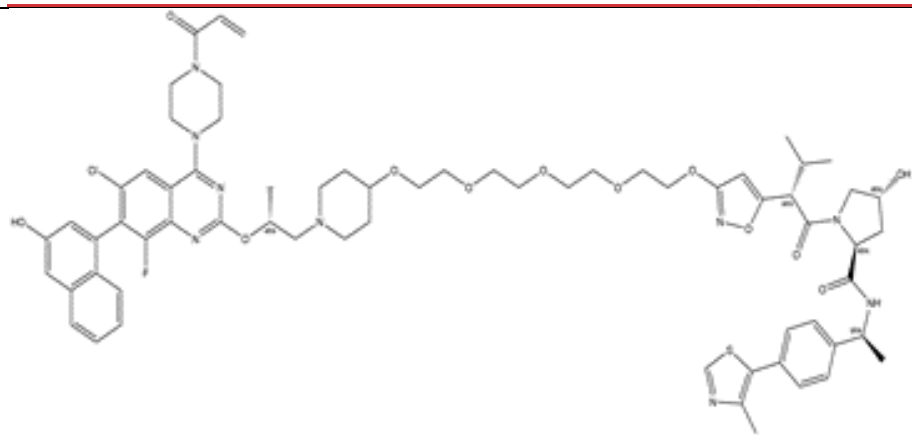
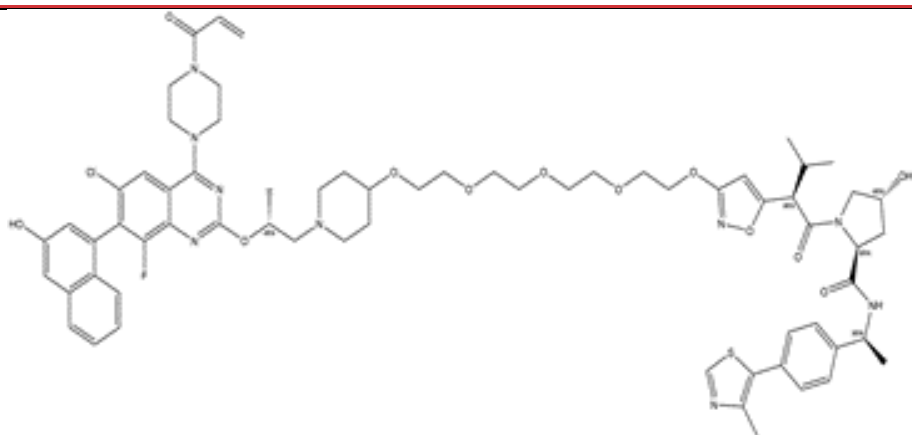
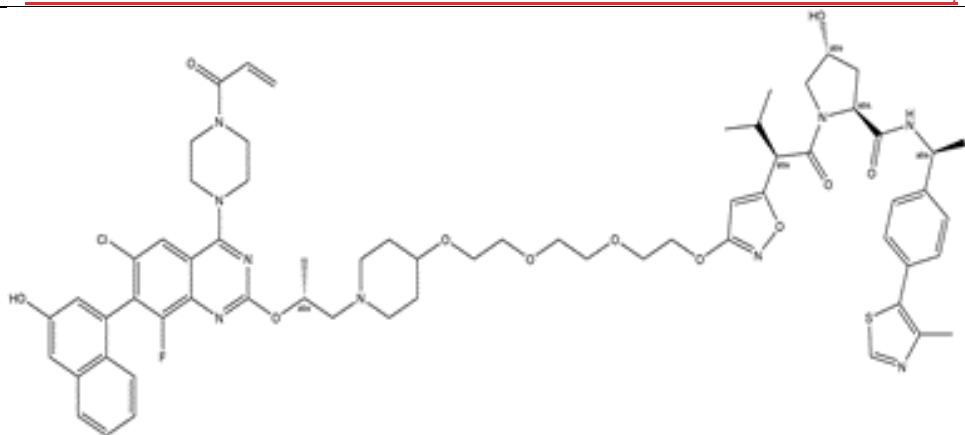
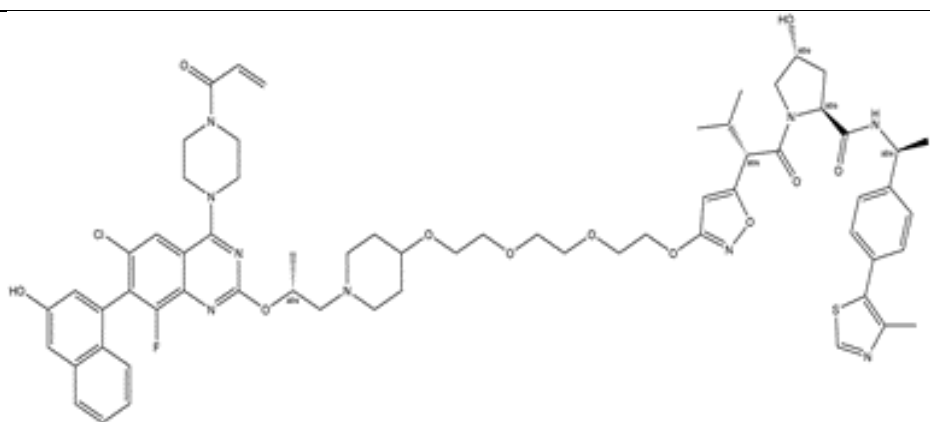


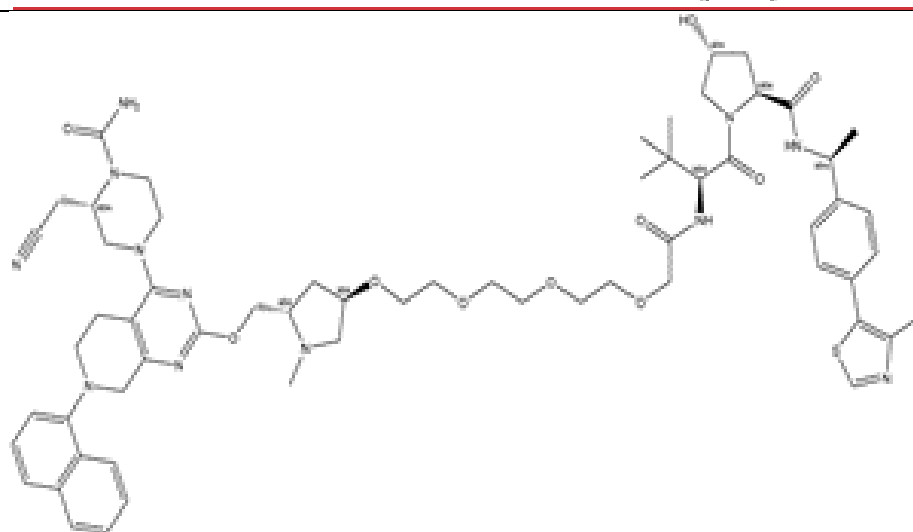
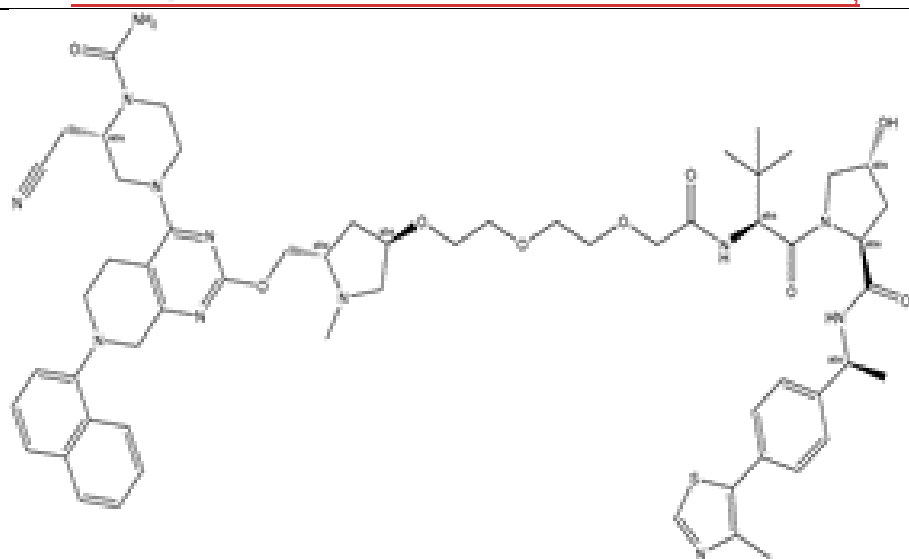
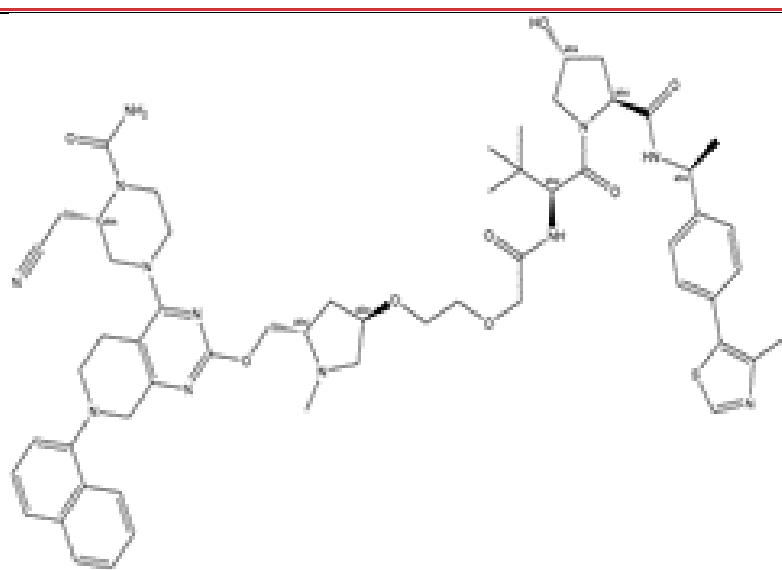
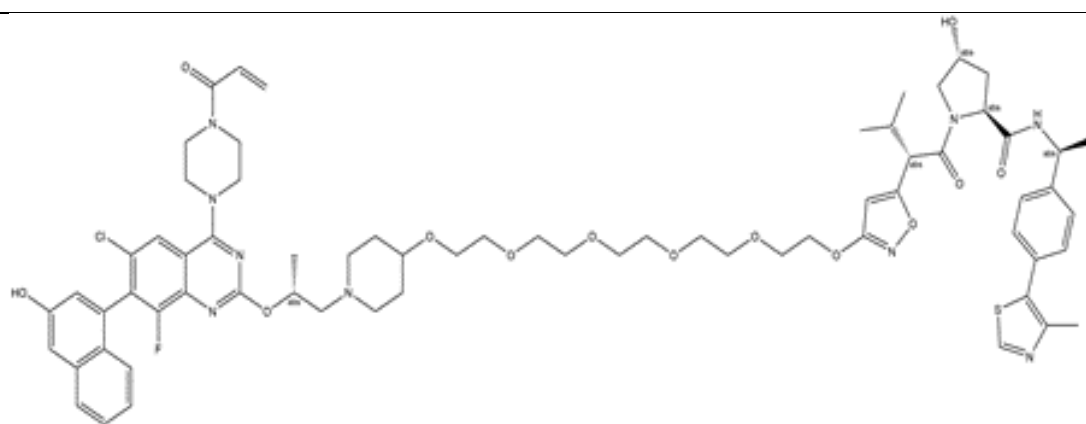


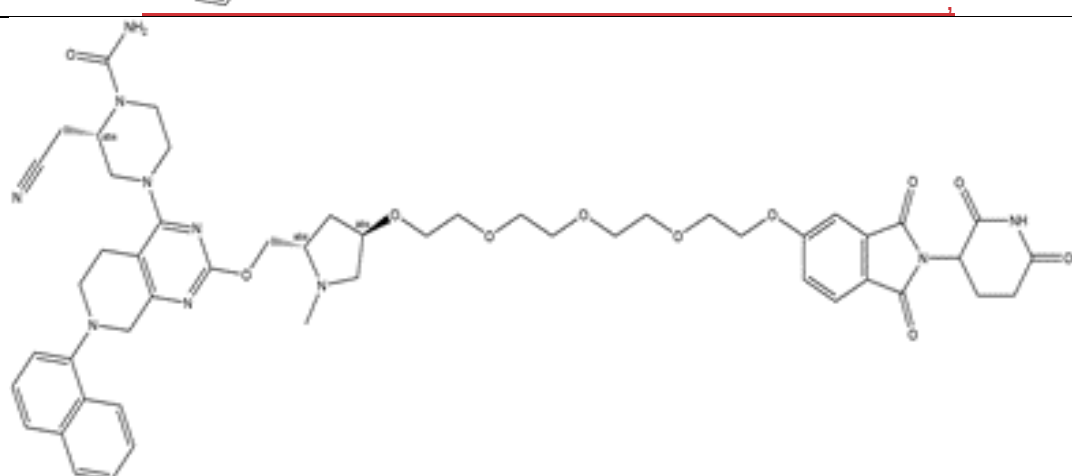
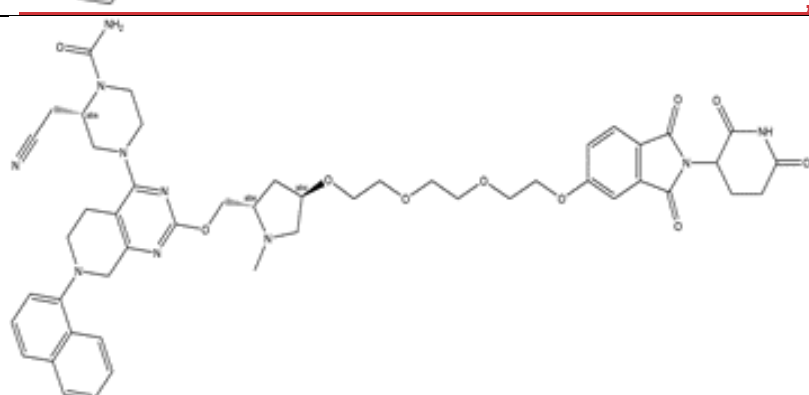
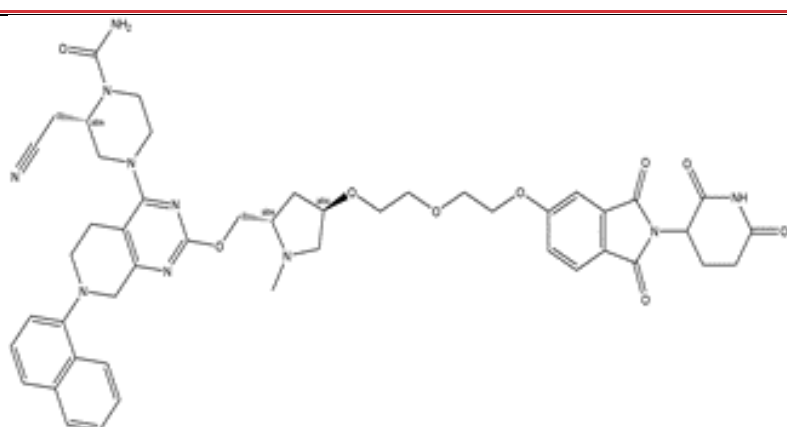
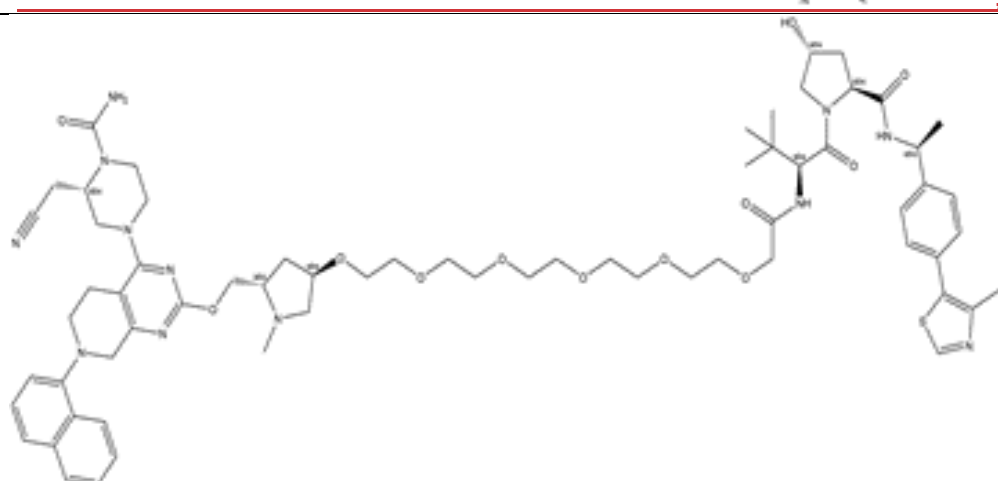
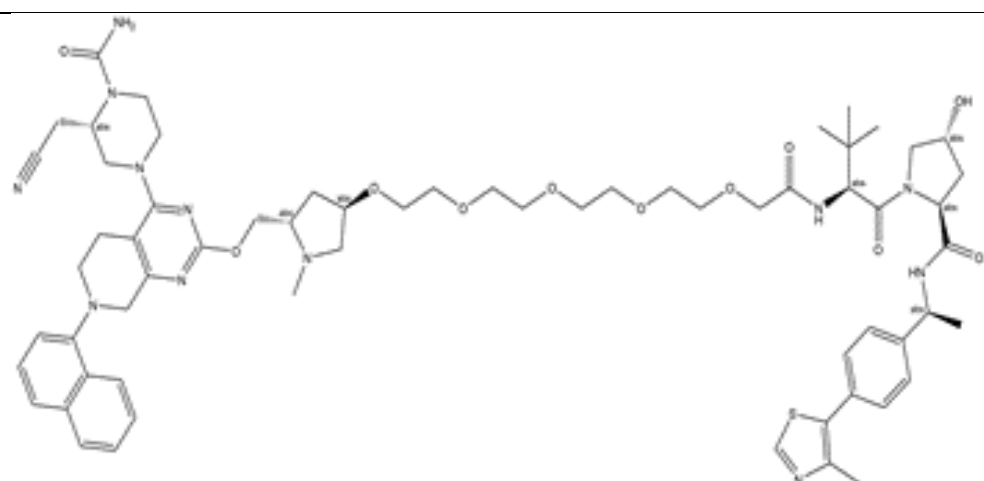


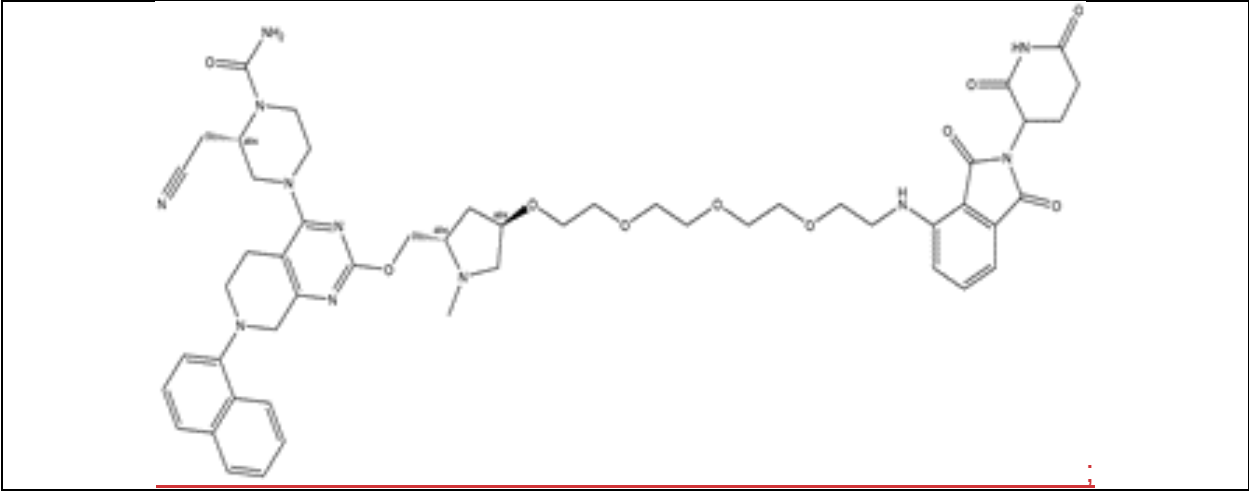
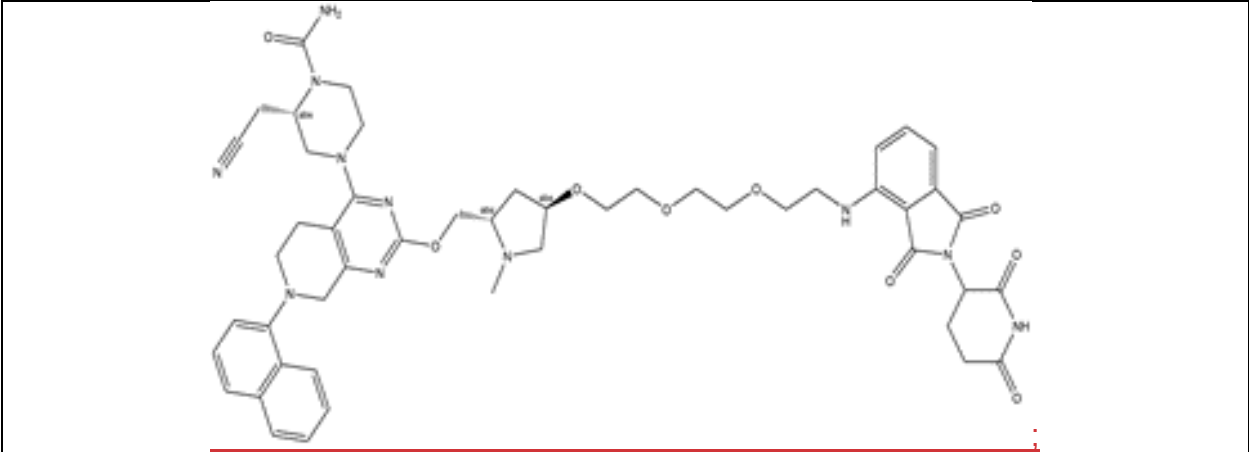
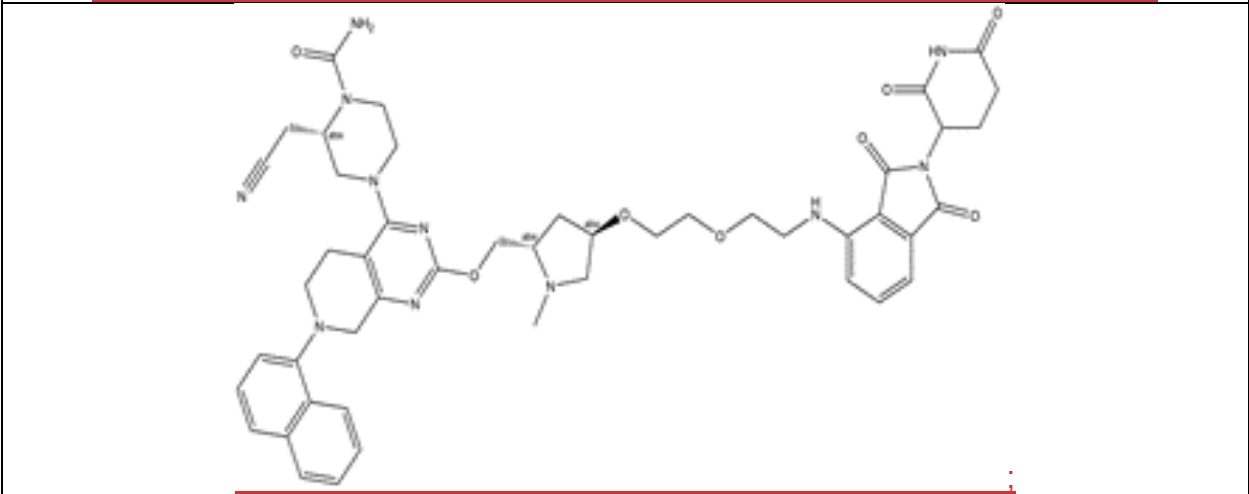
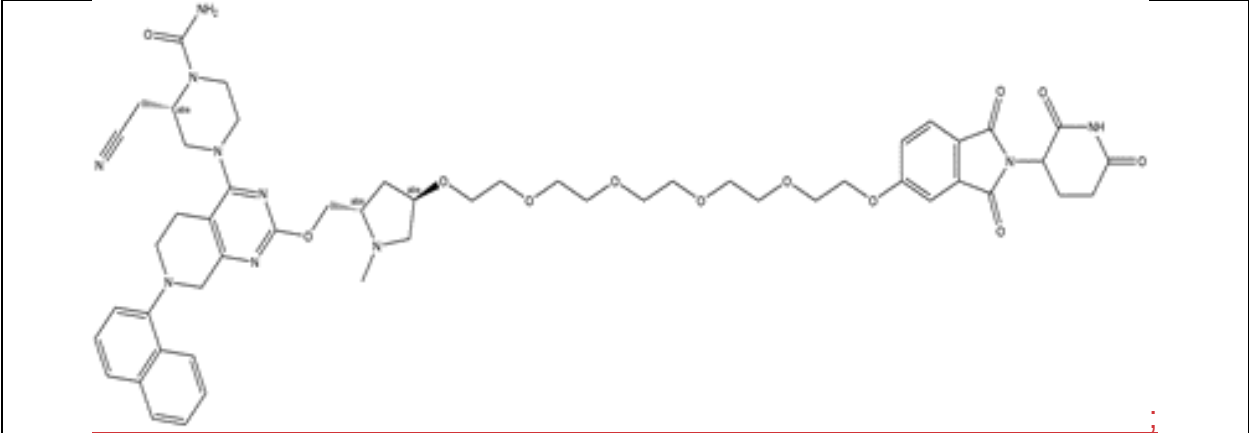


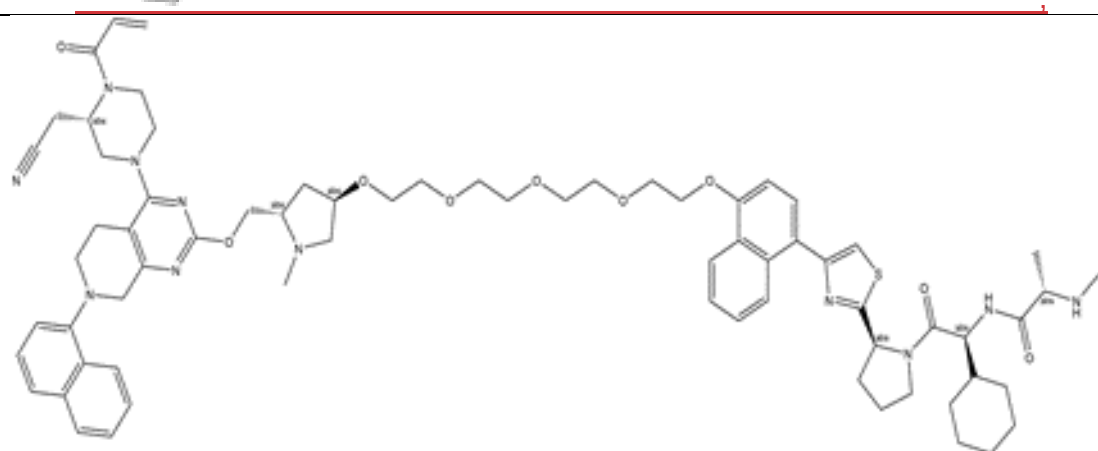
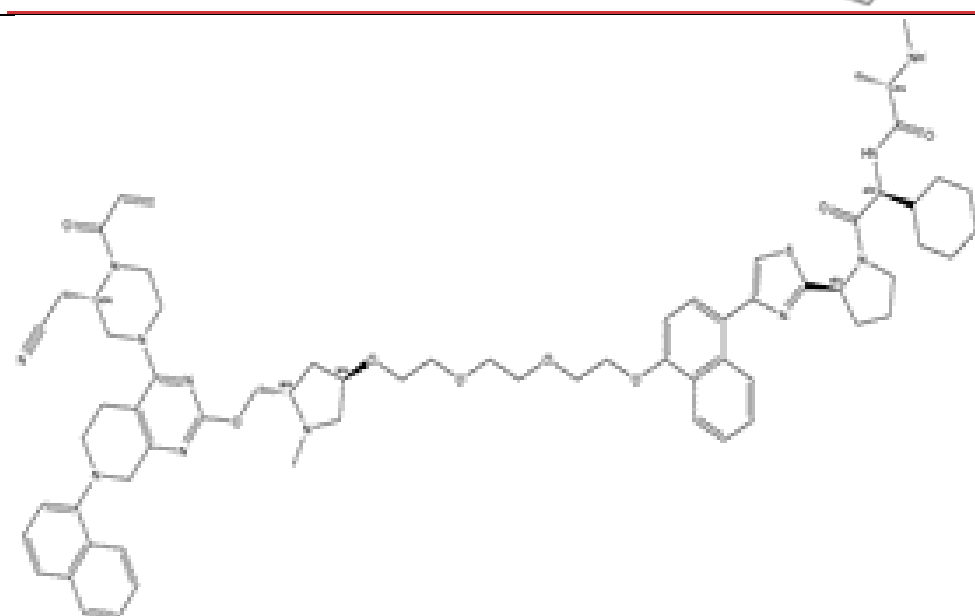
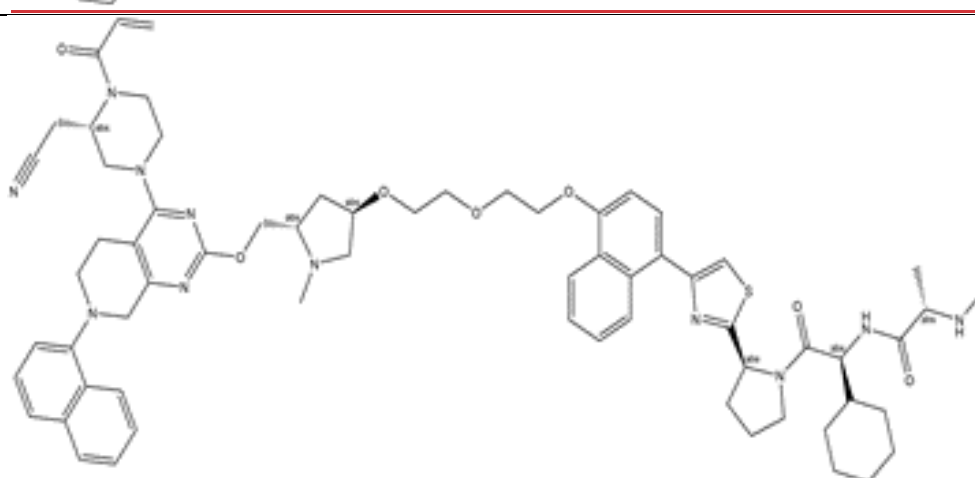
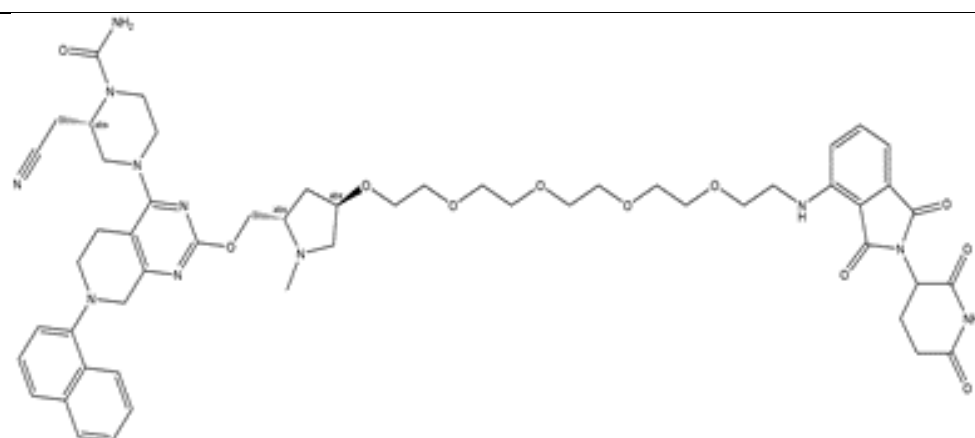


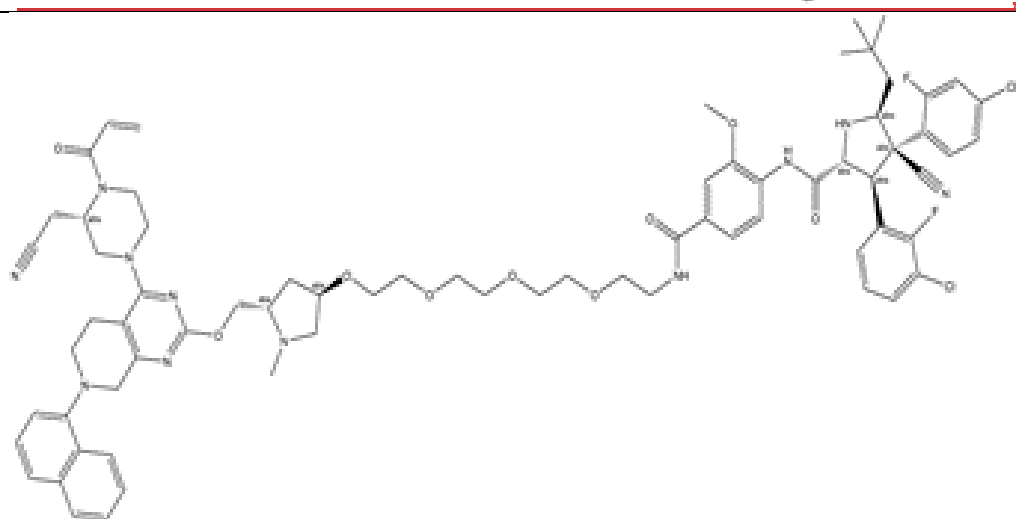
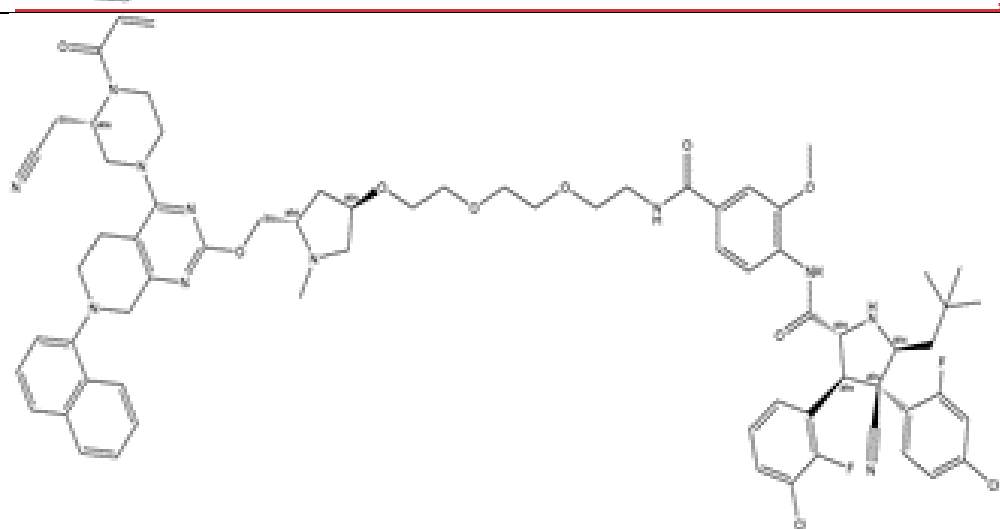
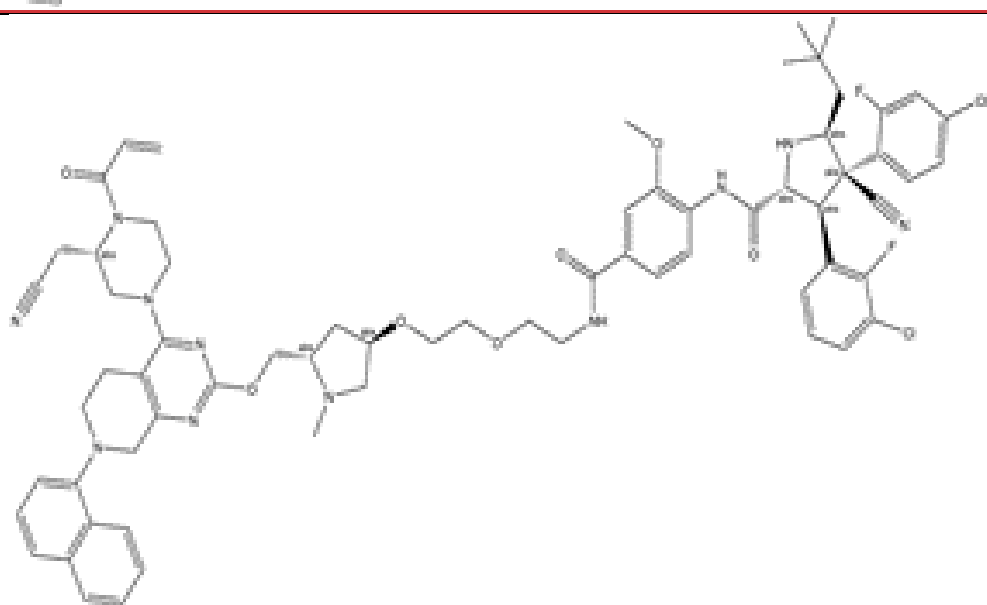
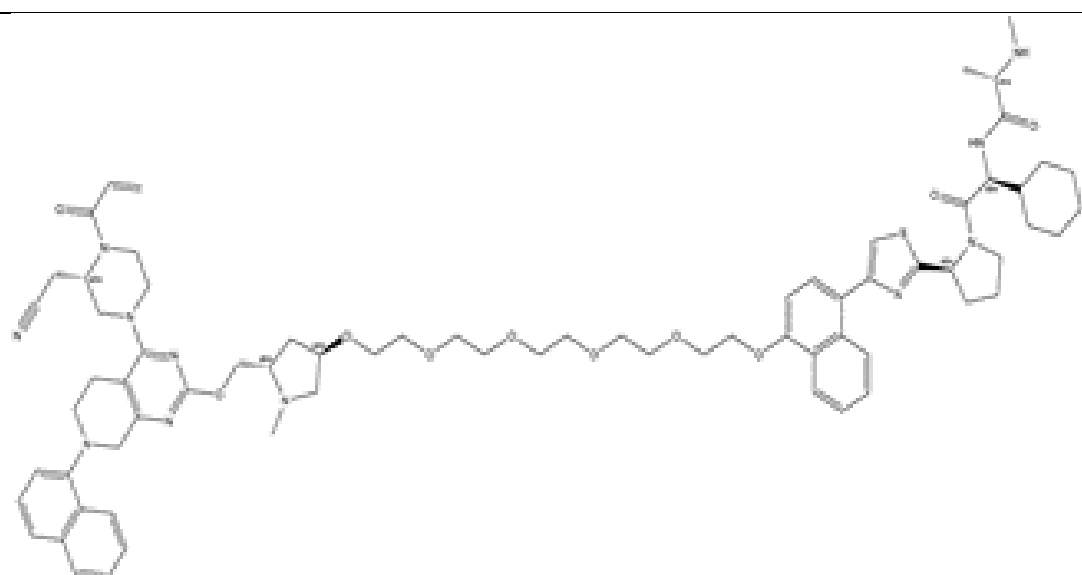


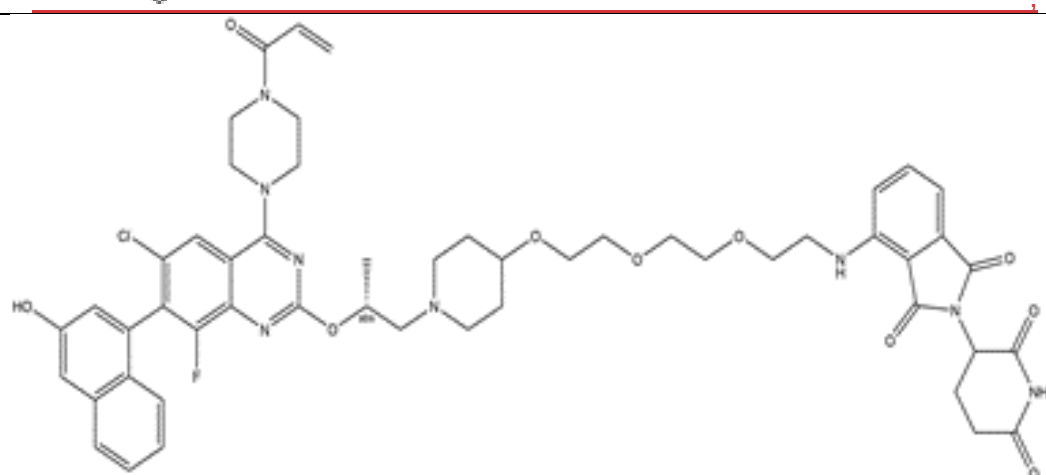
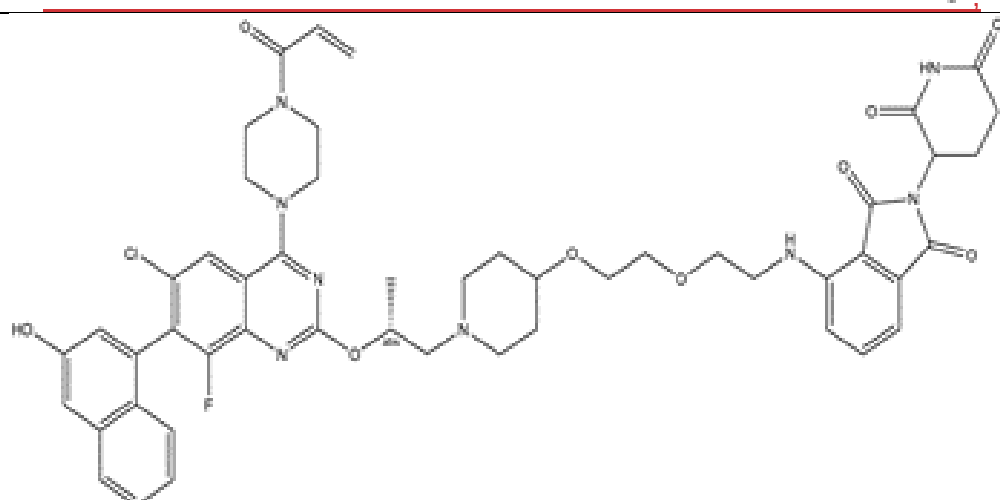
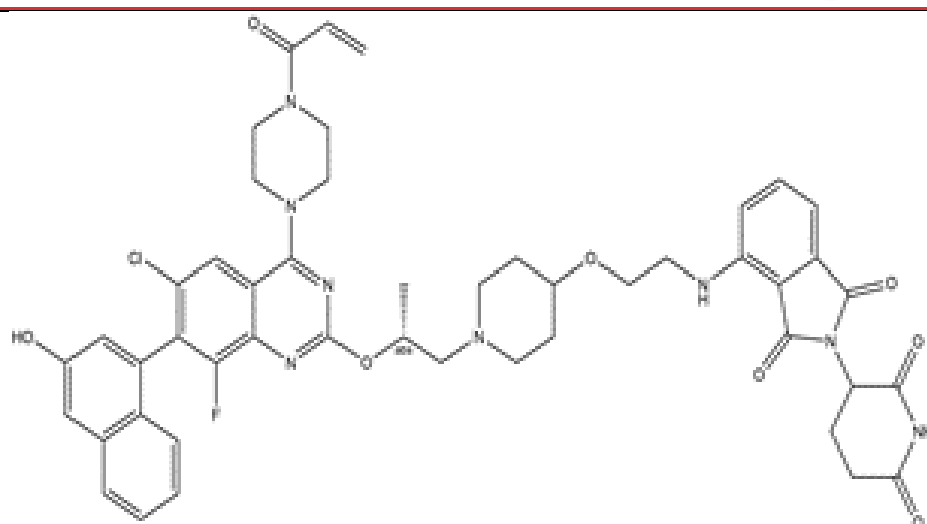
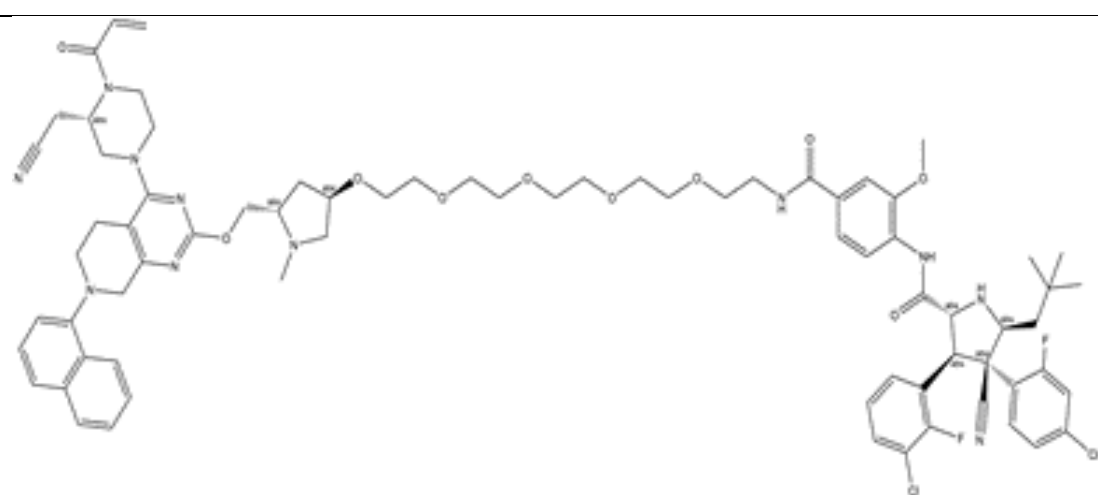


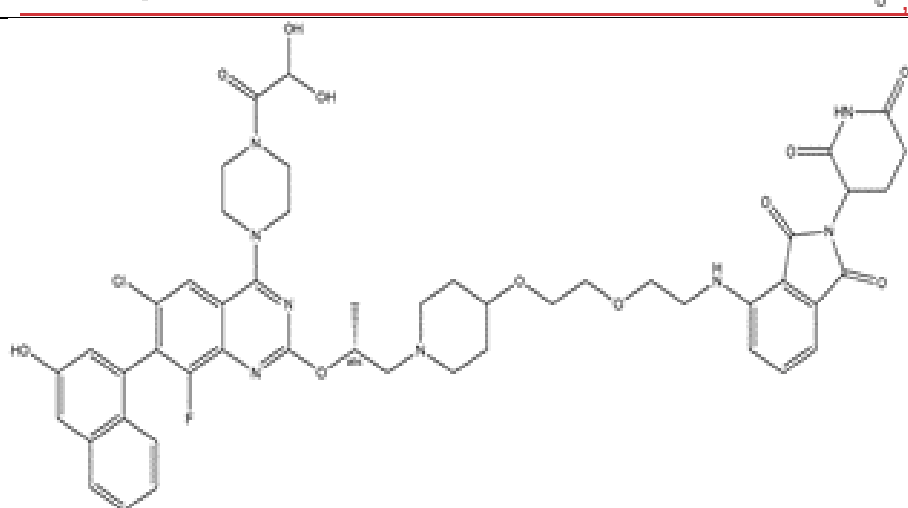
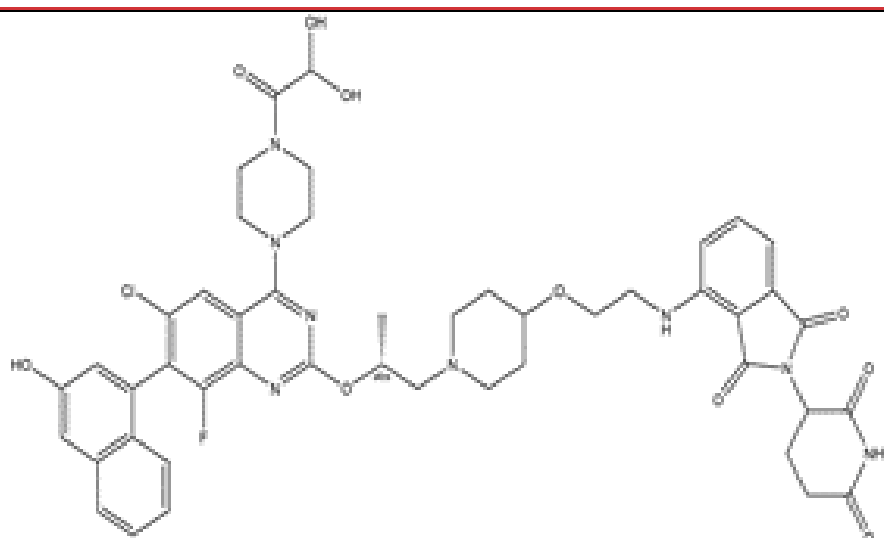
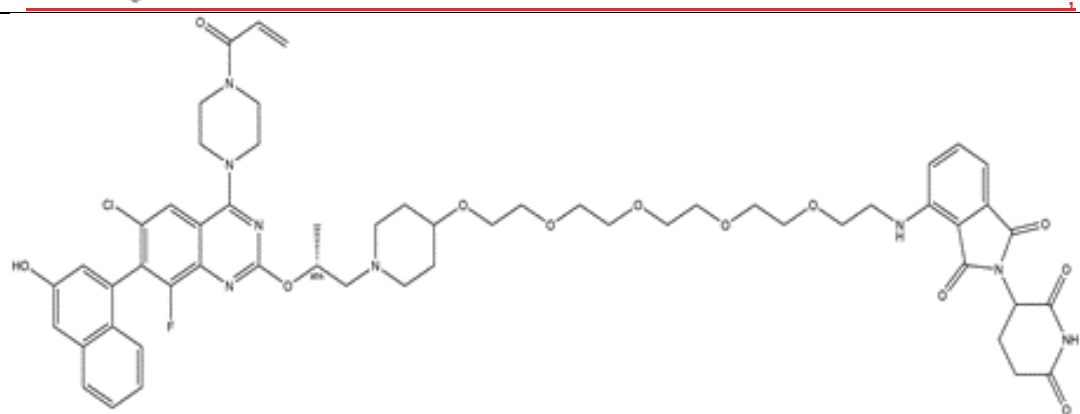
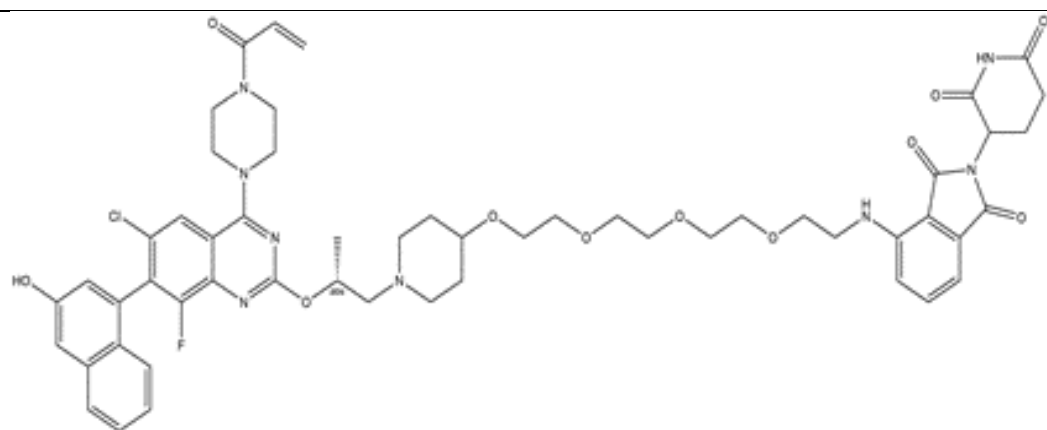


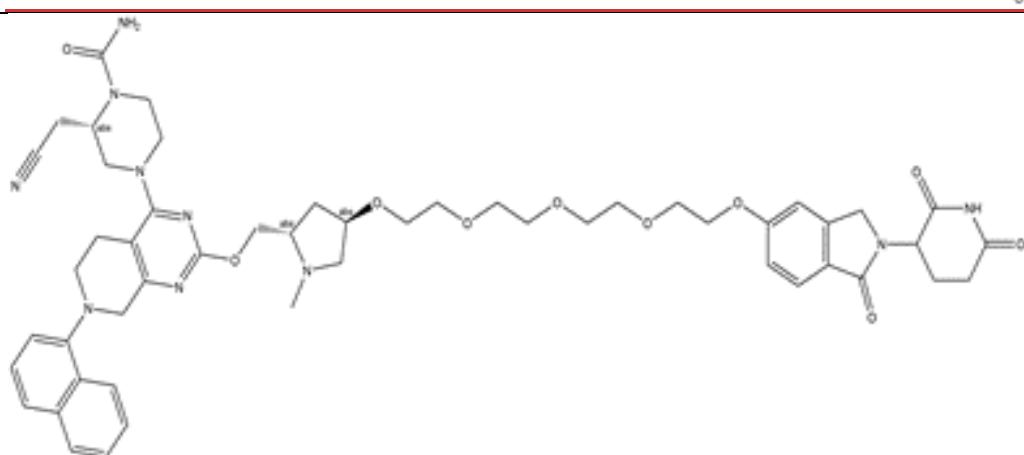
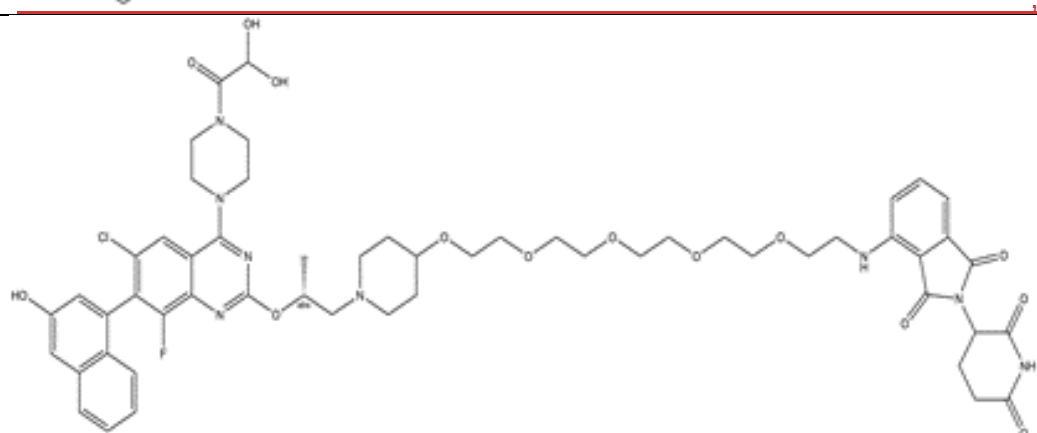
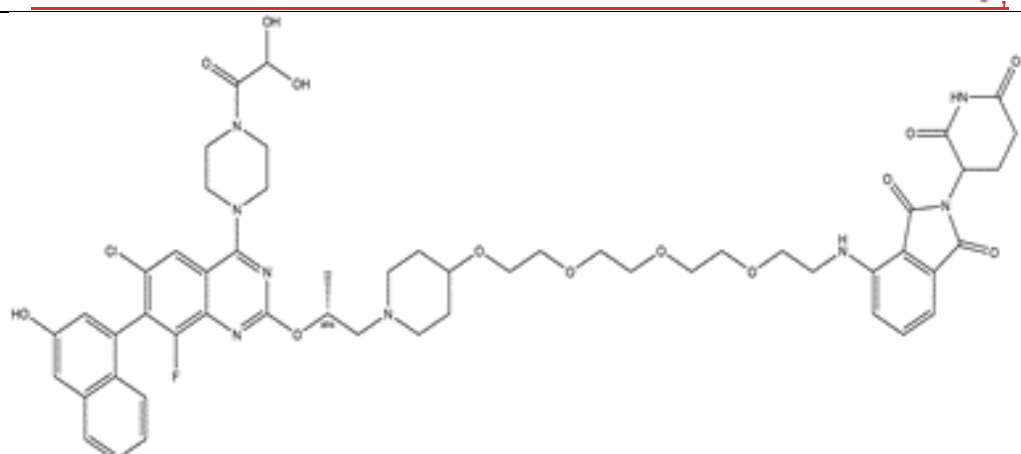
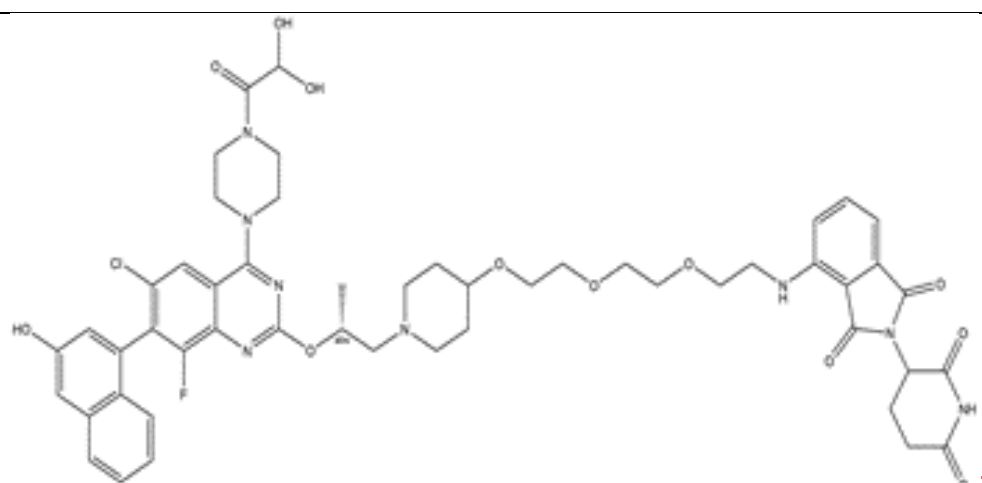


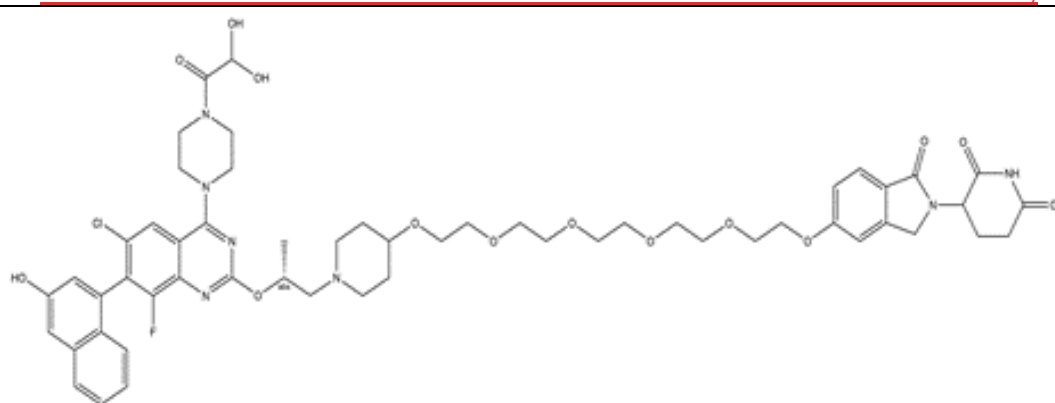
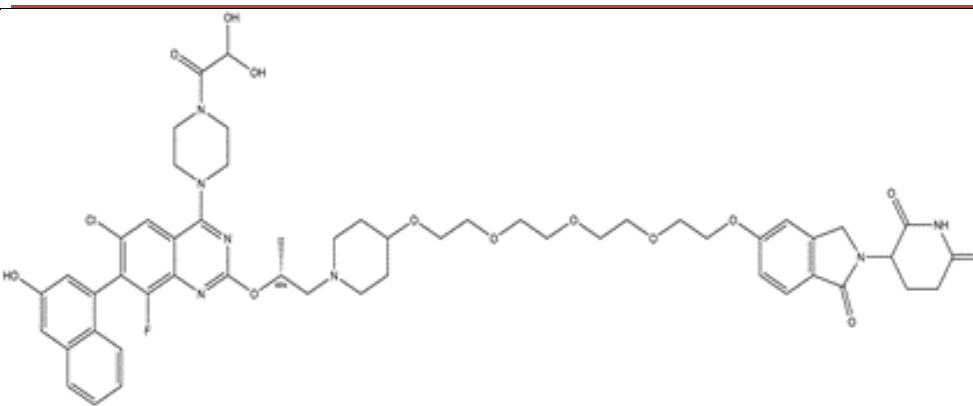
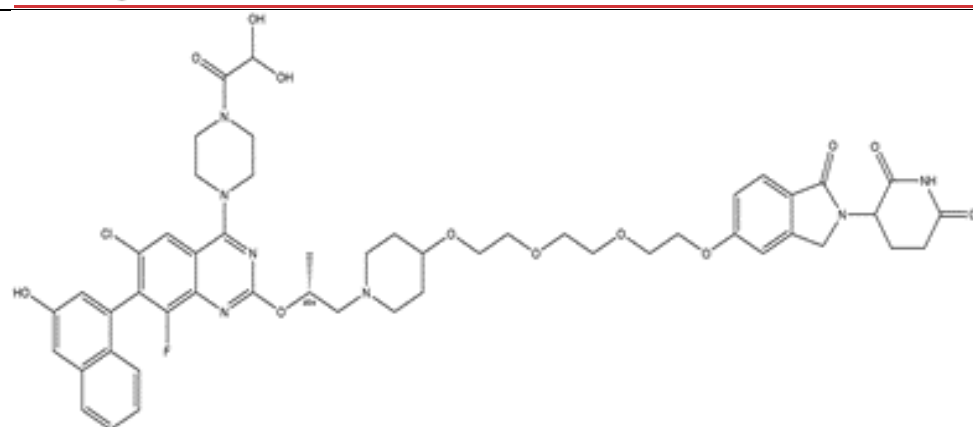
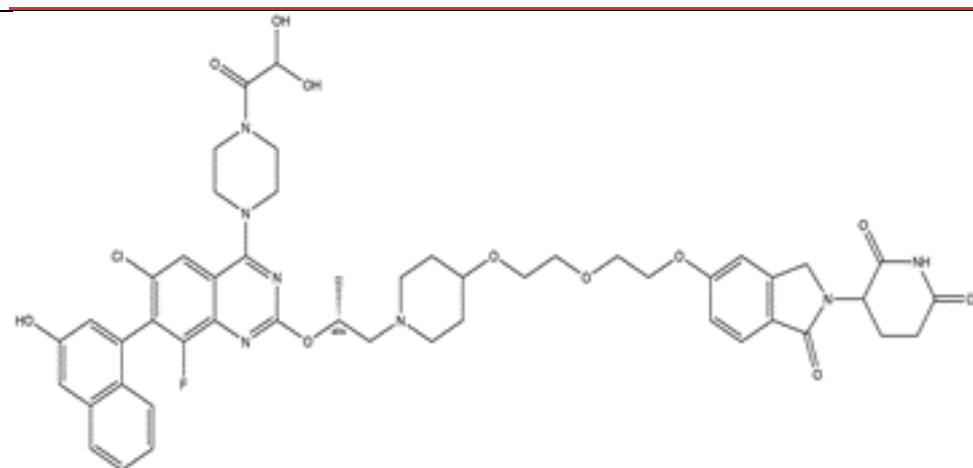
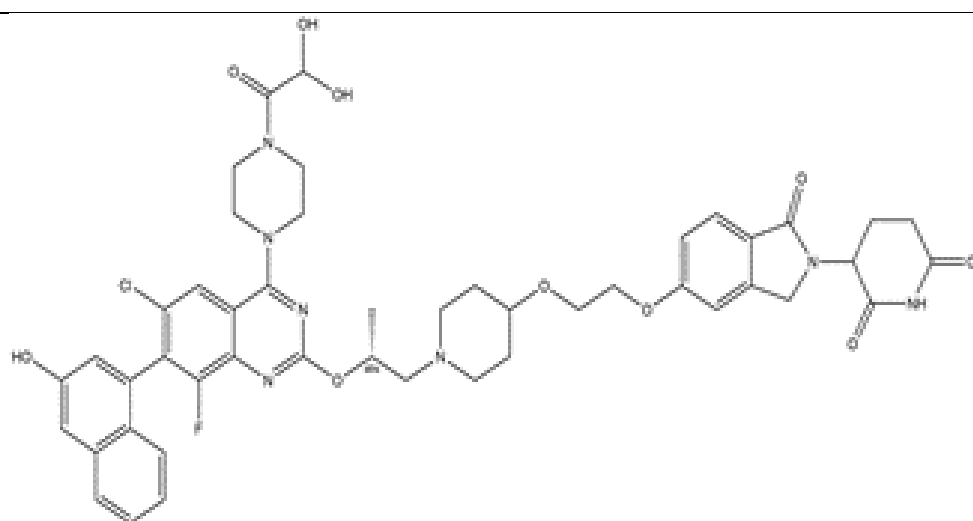


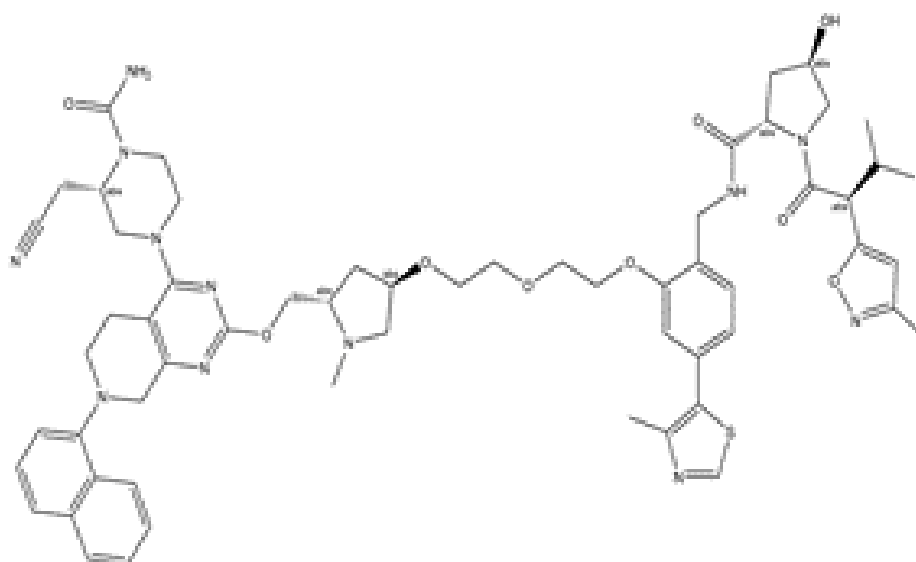




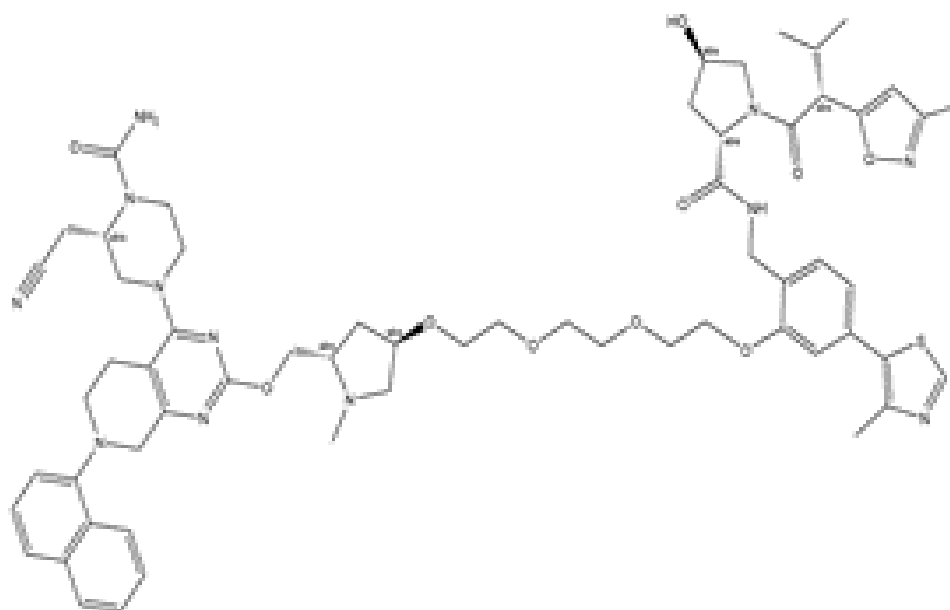




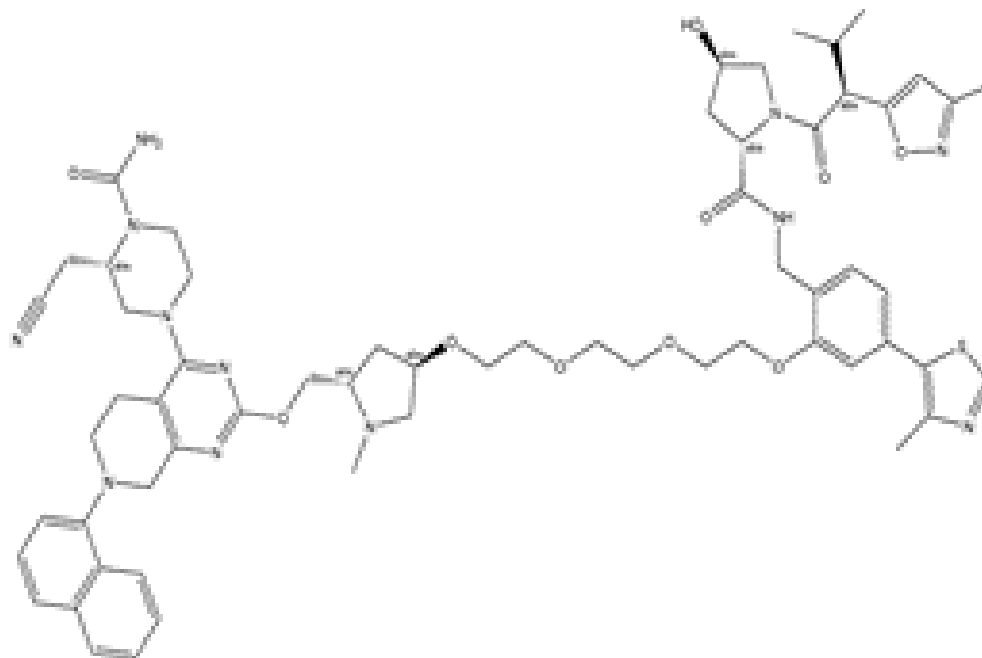




_____;



_____;



y _____,

o una sal farmacéuticamente aceptable de este.

30.13. Una composición farmacéutica que comprende ~~una cantidad eficaz de~~ un compuesto bifuncional de cualquiera de las reivindicaciones 1-~~29~~ a 3, y 5 a 12 y un portador farmacéuticamente aceptable.

31.14. La composición farmacéutica de la reivindicación ~~30~~13, donde la composición

comprende además ~~al menos uno de~~ un agente bioactivo adicional ~~u otro compuesto bifuncional de cualquiera de las reivindicaciones 1-29.~~

32.15. La composición farmacéutica de la reivindicación ~~31~~14, en donde el agente bioactivo adicional es un agente contra el cáncer ~~(p. ej., un inhibidor de receptores del factor de crecimiento epidérmico).~~

~~33. — Una composición que comprende un portador farmacéuticamente aceptable y una cantidad eficaz de al menos un compuesto de cualquiera de las reivindicaciones 1-29 para tratar una enfermedad o un trastorno en un sujeto, donde el método comprende administrar la composición a un sujeto que lo necesite, donde el compuesto es eficaz en el tratamiento o la mejora de al menos un síntoma de la enfermedad o del trastorno.~~

~~34. — La composición de la reivindicación 33, donde la enfermedad o el trastorno se asocia al menos a una acumulación, agregación, sobreactivación, o combinaciones de estas, de KRas.~~

~~35. — La composición de la reivindicación 33 o 34, donde la enfermedad o el trastorno es un cáncer asociado a la acumulación, agregación y/o sobreactivación de KRas.~~

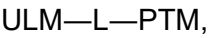
~~36. — La composición de la reivindicación 34 o 35, donde la enfermedad o el trastorno es cáncer pancreático, cáncer de colon, cáncer colorrectal, cáncer pulmonar, cáncer pulmonar no microcítico, neoplasias malignas de las vías biliares, cáncer de endometrio, cáncer de cuello uterino, cáncer de vejiga, cáncer de hígado, leucemia mieloide y cáncer de mama.~~

~~37. — La composición de cualquiera de las reivindicaciones 34-36, donde la enfermedad o el trastorno es cáncer pancreático, cáncer de colon, cáncer pulmonar, cáncer pulmonar no microcítico.~~

16. — La composición farmacéutica de la reivindicación 15, en donde el agente contra el cáncer es un inhibidor de receptores del factor de crecimiento epidérmico.

REIVINDICACIONES

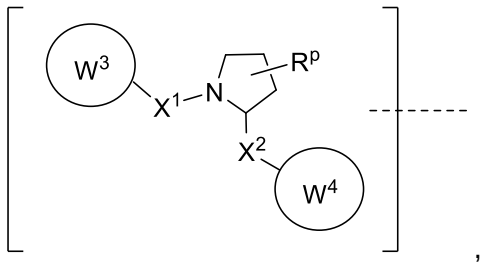
1. Un compuesto bifuncional que tiene la estructura química:



o una sal farmacéuticamente aceptable de este,

donde:

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;

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

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

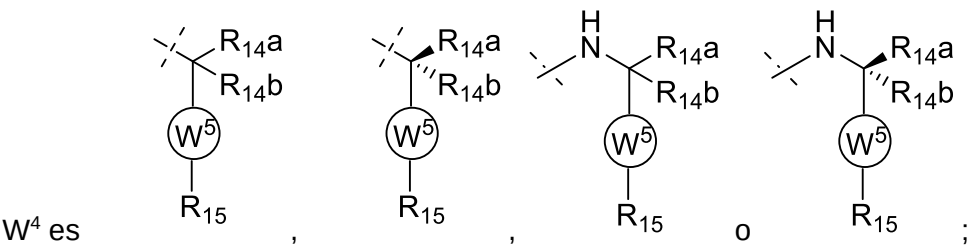
R₁₁ se selecciona de entre heterociclilo de 3-11 miembros, alcoxi C₁₋₆, heteroarilo

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;



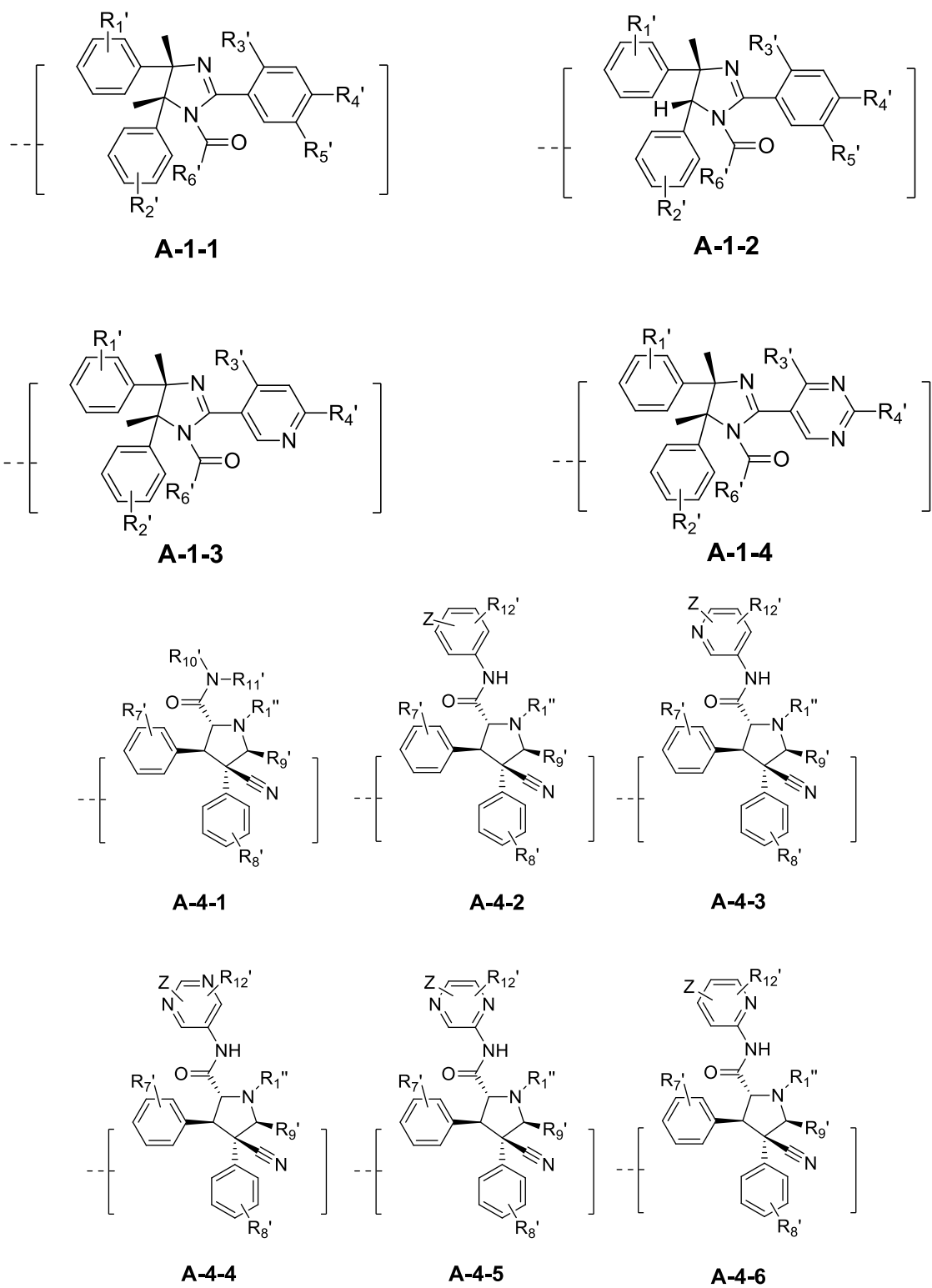
R_{14a} y R_{14b} se seleccionan cada uno de manera independiente de H, haloalquilo C₁₋₆ o alquilo C₁₋₆ opcionalmente sustituido;

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 cicloheteroalquilo de 3-11 miembros opcionalmente sustituido;

o ULM es



donde:

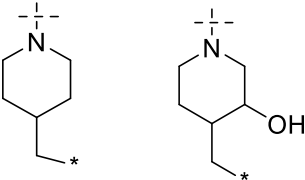
R₁' y R₂' de las Fórmulas A-1-1 a A-1-4 se seleccionan de manera independiente de F, Cl, Br, I, acetileno, CN, CF₃ y NO₂;

R₃' se selecciona de entre -OCH₃, -OCH₂CH₃, -OCH₂CH₂F, -OCH₂CH₂OCH₃ y -OCH(CH₃)₂;

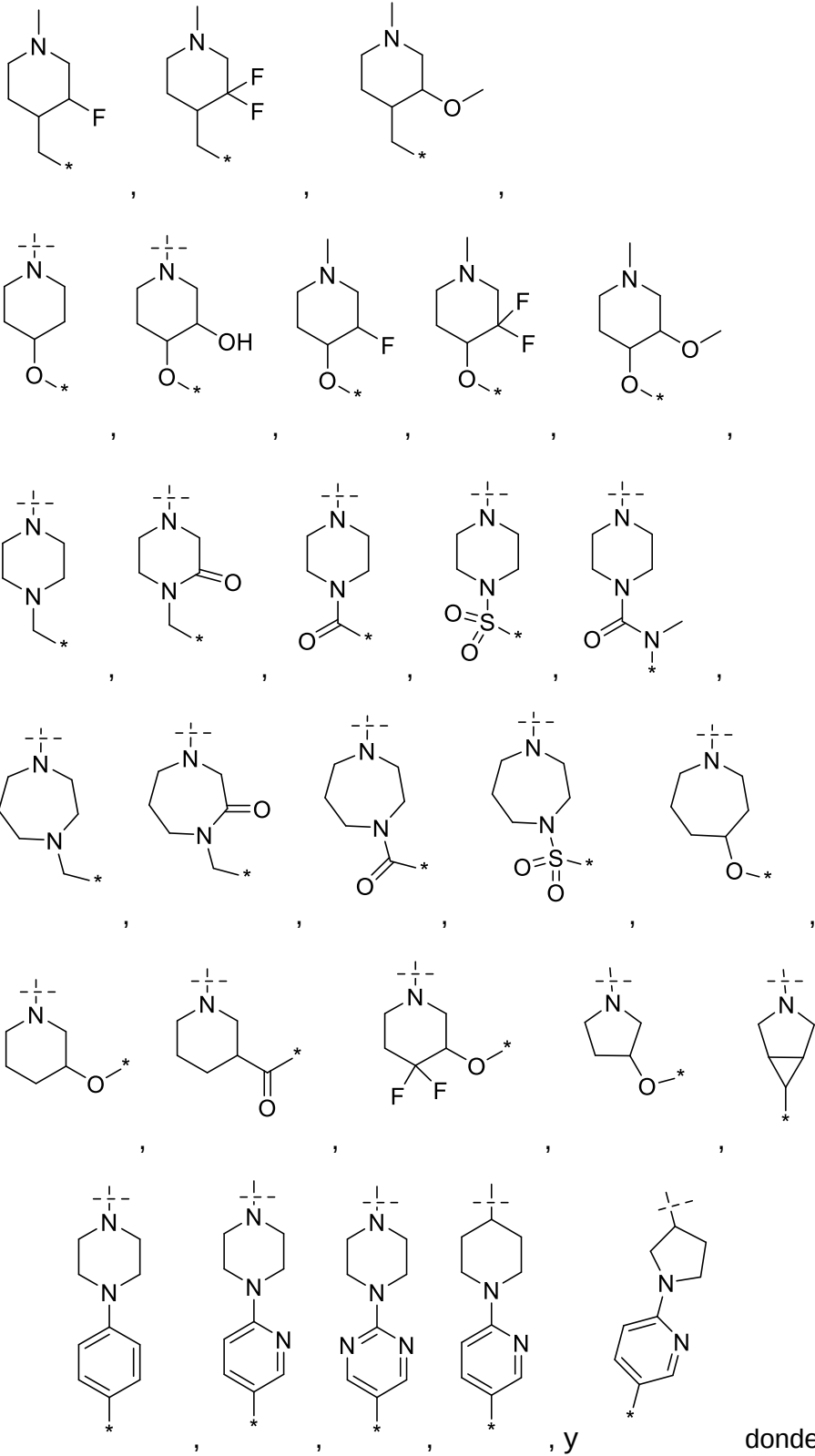
R₄' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre H, halógeno, -CH₃, -CF₃,

-OCH₃, -C(CH₃)₃, -CH(CH₃)₂, -ciclopropilo, -CN, -C(CH₃)₂OH, -C(CH₃)₂OCH₂CH₃, -C(CH₃)₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₃, -C(CH₃)₂CH₂OCH₂CH₂OH, -C(CH₃)₂CH₂OCH₂CH₂CH₃, -C(CH₃)₂CN, -C(CH₃)₂C(O)CH₃, -C(CH₃)₂C(O)NHCH₃, -C(CH₃)₂C(O)N(CH₃)₂, -SCH₃, -SCH₂CH₃, -S(O)₂CH₃, -S(O)₂CH₂CH₃, -NHC(CH₃)₃, -N(CH₃)₂, pirrolidinilo y 4-morfolinilo;

R5' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre halógeno, -ciclopropilo, -S(O)₂CH₃, -S(O)₂CH₂CH₃, 1-pirrolidinilo, -NH₂, -N(CH₃)₂ y -NHC(CH₃)₃; y



R6' de las Fórmulas A-1-1 a A-1-4 se selecciona de entre H,



donde L se une al «*» de

R6' o al átomo del extremo de R4';

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, heteroarilo, 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;

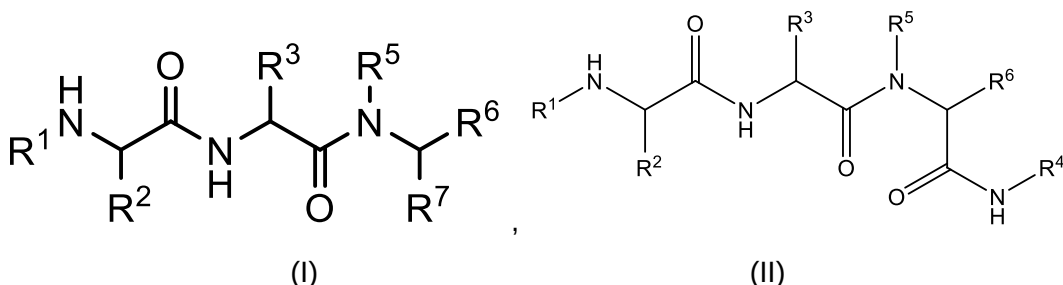
m, n y p son de manera independiente de 0 a 6;

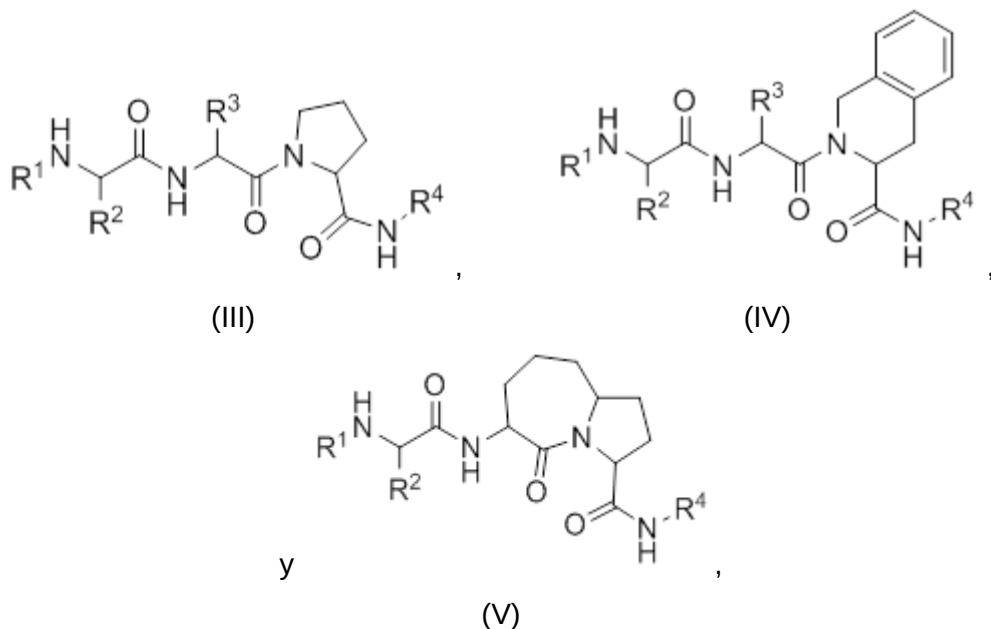
R12' de la Fórmula A-4-1 a A-4-6 se selecciona de entre -O-(alquilo), -O-(alquilo)-acoxi, -C(O)-(alquilo), -C(OH)-alquilo-alcoxi, -C(O)-NH-(alquilo), -C(O)-N-(alquilo)₂, -S(O)-(alquilo), S(O)₂-(alquilo), -C(O)-(amino cíclico) y -O-arilo-(alquilo), -O-arilo-(alcoxi);

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 aloxi, cicloalquilo, cicloalquilo sustituido con ari, y cicloalquilo sustituido con alcoxi; y

----- indica conexión con L;

o ULM se selecciona de entre:





en donde:

R^1 para las Fórmulas (I), (II), (III), (IV) y (V) es H o alquilo;

R^2 para las Fórmulas (I), (II), (III), (IV) y (V) es H o alquilo;

R^3 para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre H, alquilo, cicloalquilo y heterocicloalquilo;

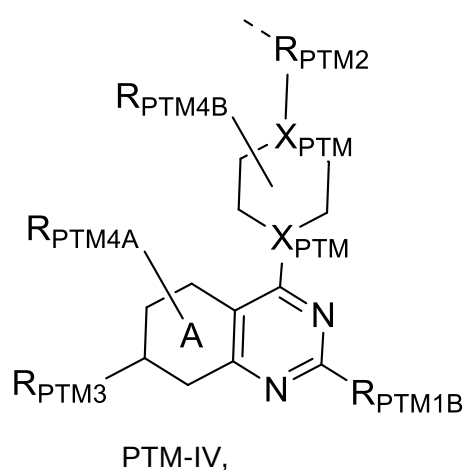
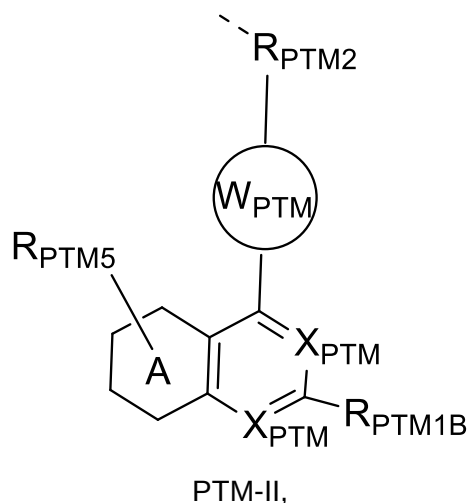
R^5 y R^6 para las Fórmulas (I), (II), (III), (IV) y (V) se seleccionan de manera independiente de entre H, alquilo, cicloalquilo, heterocicloalquilo, o R^5 y R^6 tomados juntos para las Fórmulas (I), (II), (III), (IV) y (V) forman un anillo pirrolidina o piperidina opcionalmente fusionado de manera 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;

R^3 y R^5 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;

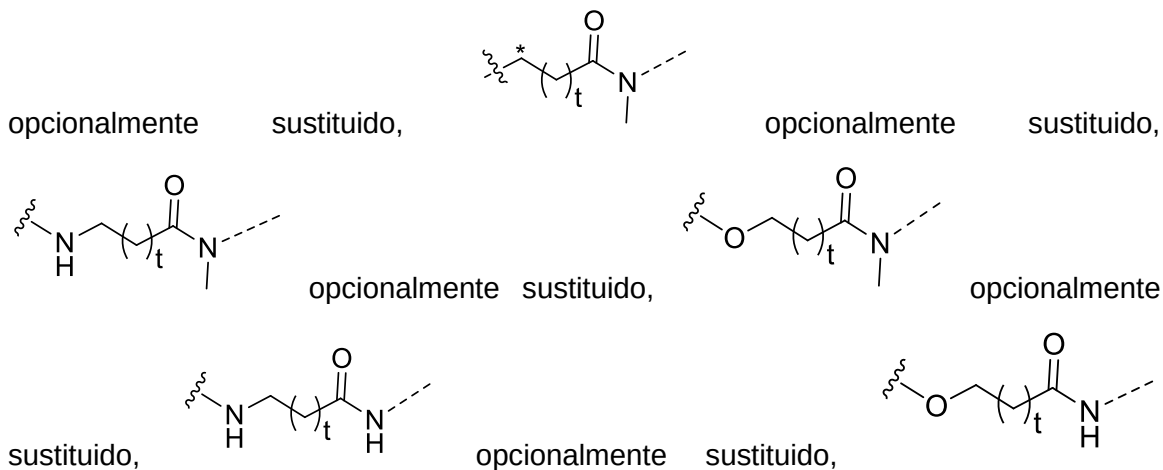
R^7 para las Fórmulas (I), (II), (III), (IV) y (V) se selecciona de entre cicloalquilo, cicloalquilalquilo, heterocicloalquilo, heterocicloalquilalquilo, arilo, arilo-C(O)- R^4 , arilalquilo, heteroarilo, heteroarilo-C(O)- R^4 , heteroarilo- R^4 , heteroarilo-naftaleno, heteroarilalquilo o -C(O)NH- R^4 , 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- R^4 o C(O)- R^4 ; y

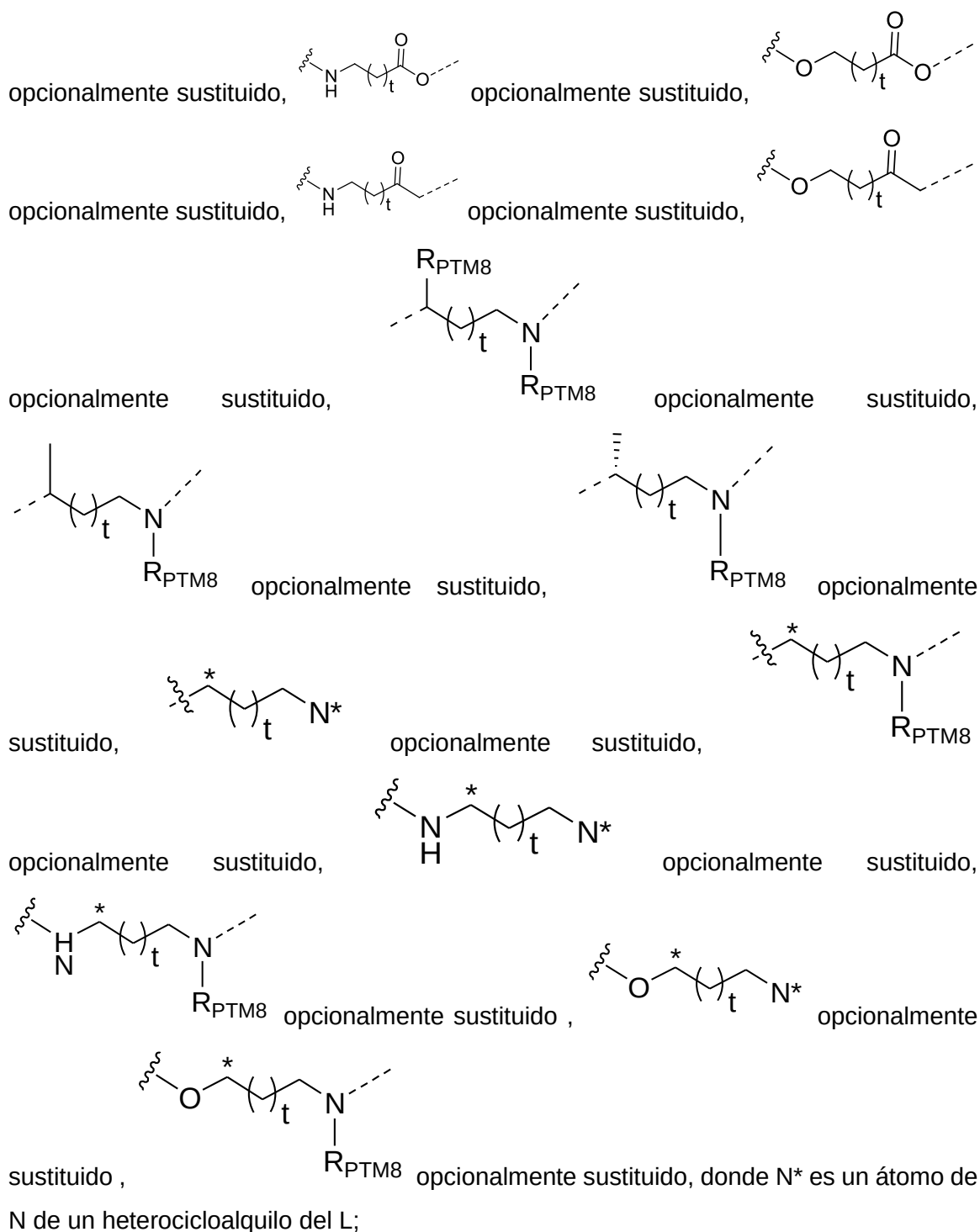
R^4 se selecciona de entre alquilo, cicloalquilo, heterocicloalquilo, cicloalquilalquilo, heterocicloalquilalquilo, arilo o arilo bicíclico, arilalquilo, heteroarilo o heteroarilo bicíclico, heteroarilalquilo, opcionalmente sustituido de manera adicional;

PTM se selecciona de entre:

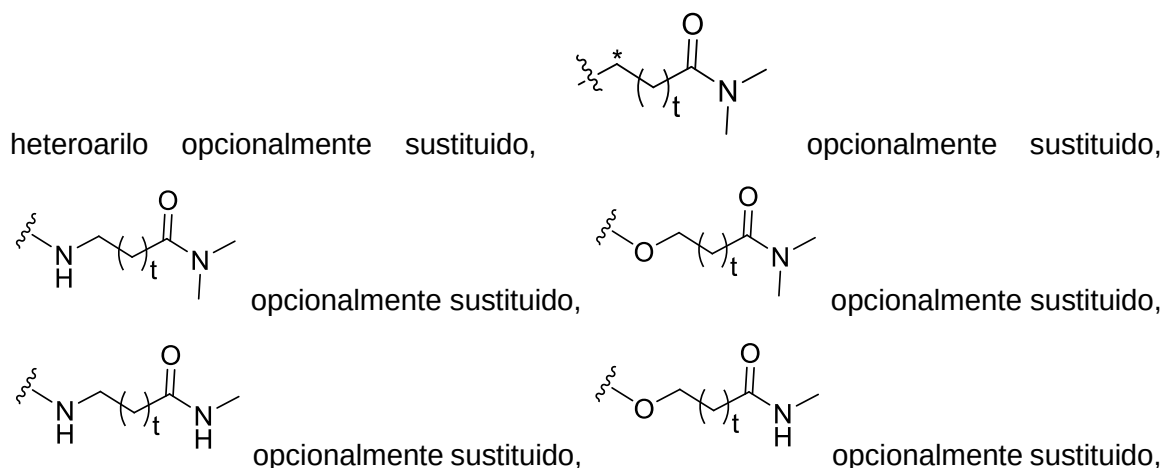

$$X_{PTM} \text{ es } C \text{ o } N;$$

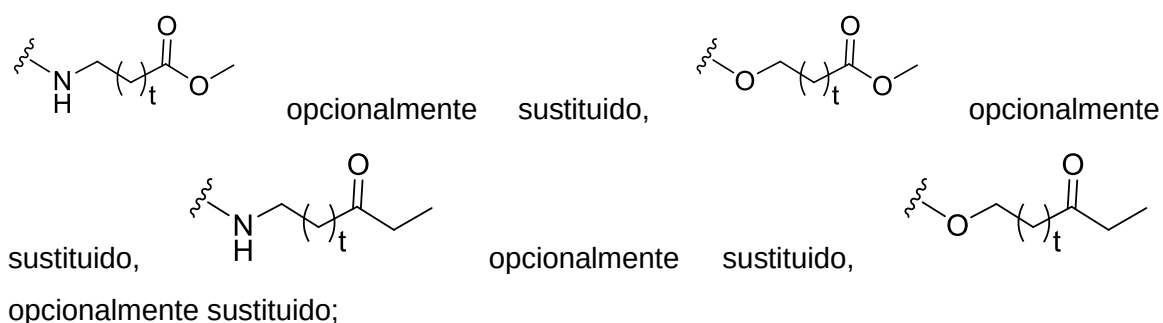
R_{PTM1A} es NR_{PTM9}R_{PTM10}, OR_{PTM9}R_{PTM10}, H, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, cicloalquilo C₃₋₆ opcionalmente sustituido, O-(cicloalquilo C₃₋₆) opcionalmente sustituido, -O-alquilo C₁₋₄ -cicloalquilo C₃₋₆ opcionalmente sustituido, heteroalquilo C₃₋₆ opcionalmente 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-heteroarilo





R_{PTM1B} es $NR_{PTM9}R_{PTM10}$, $OR_{PTM9}R_{PTM10}$, 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-





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

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

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

R_{PTM3} es alquilo, alcoxi, fenilo o naftaleno, cada uno sustituido de manera independiente con OH, H, o halógeno;

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

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

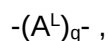
R_{PTM5} se selecciona de arilo opcionalmente sustituido, biarilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, biheteroarilo opcionalmente sustituido, cicloalquilo C_{3-6} opcionalmente sustituido, cicloheteroalquilo de 3-6 miembros opcionalmente sustituido, halógeno, H, alquilo opcionalmente sustituido, OH y alcoxi;

R_{PTM8} es un H o alquilo;

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

— indica el sitio de unión de L; y

L es:



donde:

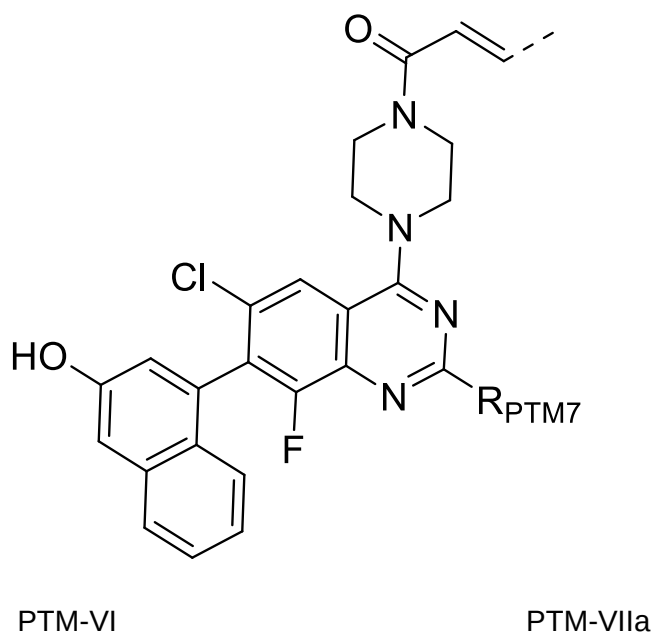
$(A^L)_q$ es un grupo que se conecta con al menos uno de un ULM, PTM, o ambos;

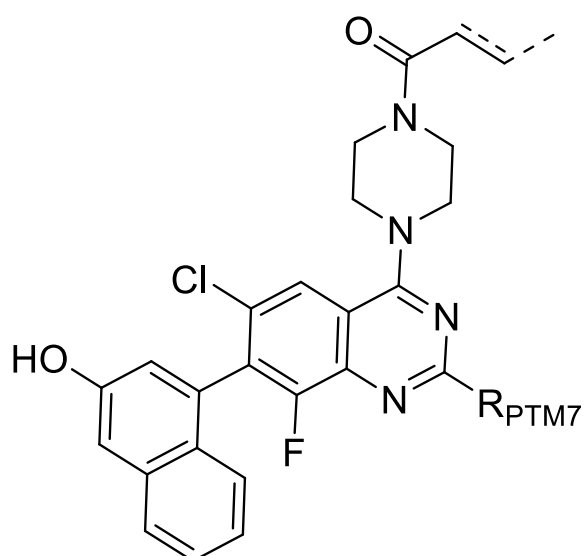
q es un número entero mayor o igual que 1;

cada A^L se selecciona de manera independiente de entre un enlace, $CR^{L1}R^{L2}$, O, S, SO, 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 grupos R^{L1} y/o R^{L2} , heterociclilo C_{3-11} 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} , 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, opcionalmente sustituido con 0-4 grupos R^{L5} ; y

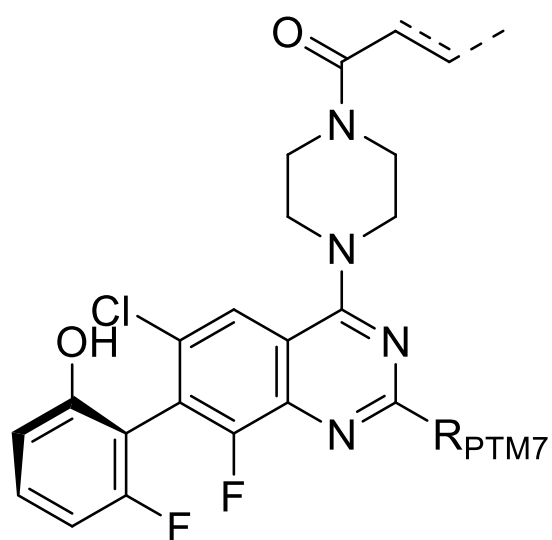
R^{L1} , R^{L2} , R^{L3} , R^{L4} y R^{L5} son, cada uno de manera independiente, H, halo, alquilo C_{1-8} , Oalquilo C_{1-8} , Salquilo C_{1-8} , NHalquilo C_{1-8} , N(alquilo C_{1-8})₂, cicloalquilo C_{3-11} , arilo, heteroarilo, heterociclilo C_{3-11} , Ocicloalquilo C_{1-8} , Scicloalquilo C_{1-8} , 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 ,

2. El compuesto bifuncional de acuerdo con la reivindicación 1, donde el PTM es representado por:

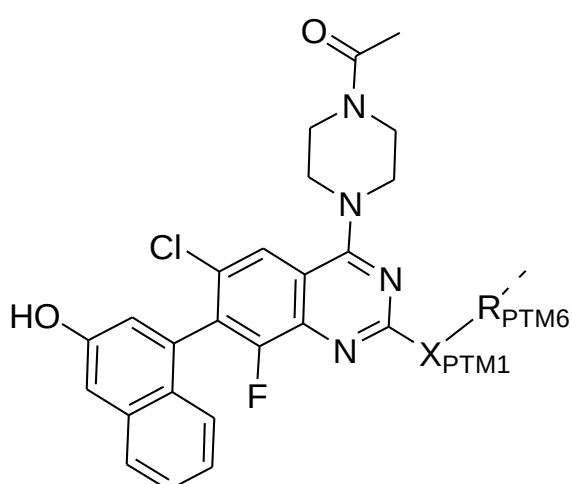




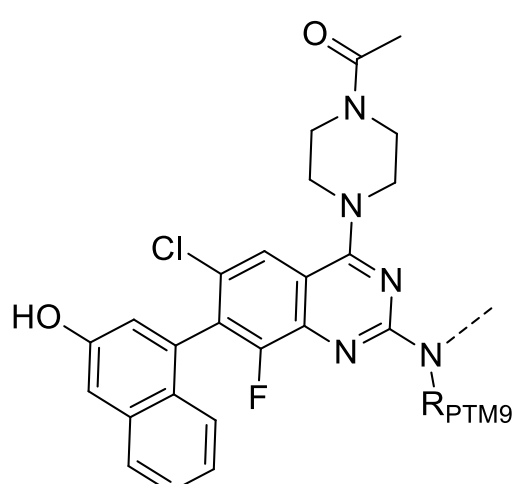
PTM-VIIb



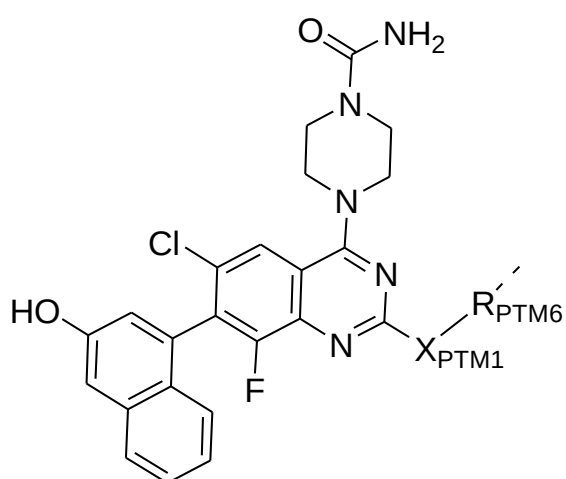
PTM-VIII



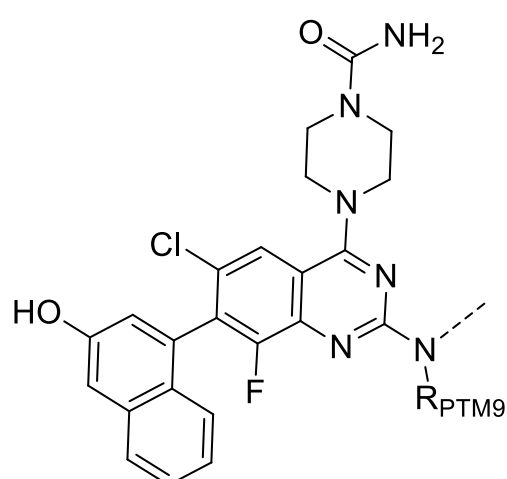
PTM-IXa



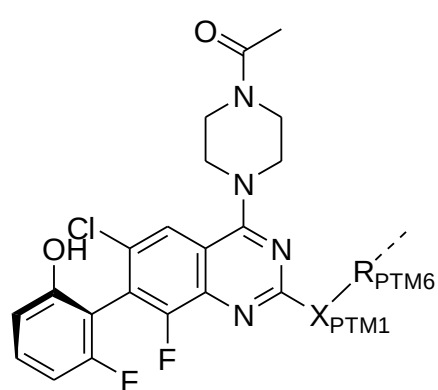
PTM-I-Xb



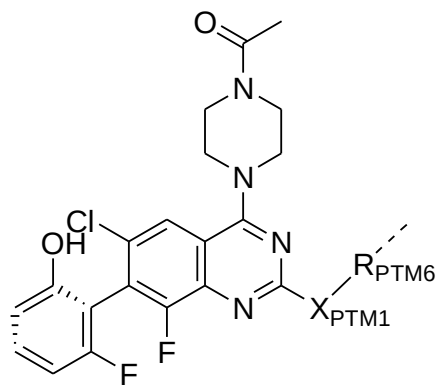
PTM-Xa



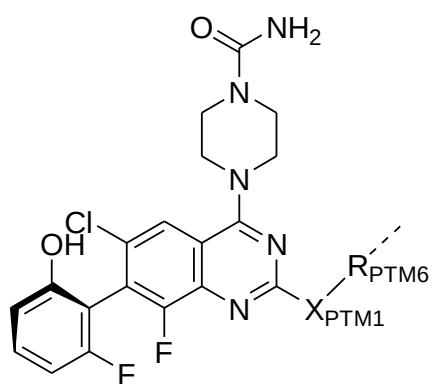
PTM-Xb



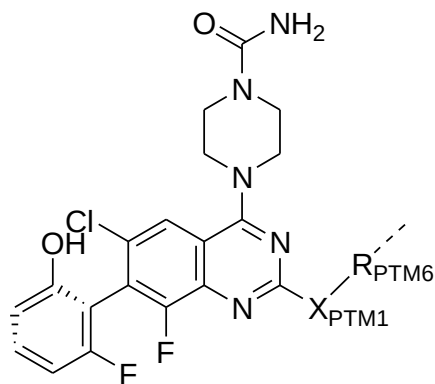
PTM-XI



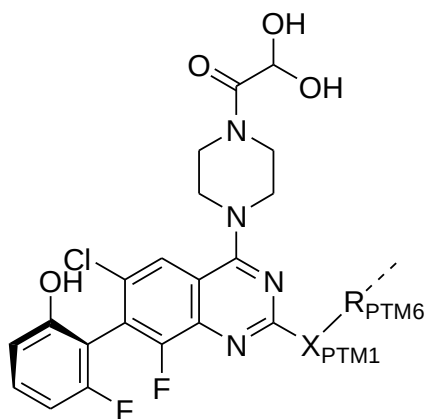
PTM-XII



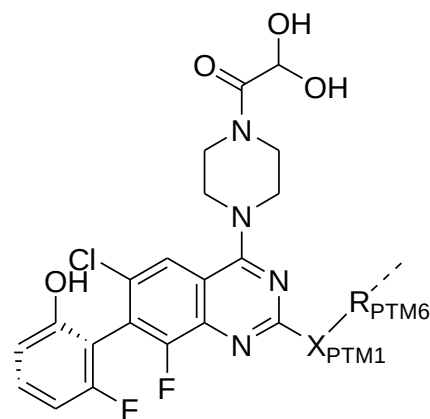
PTM-XIII



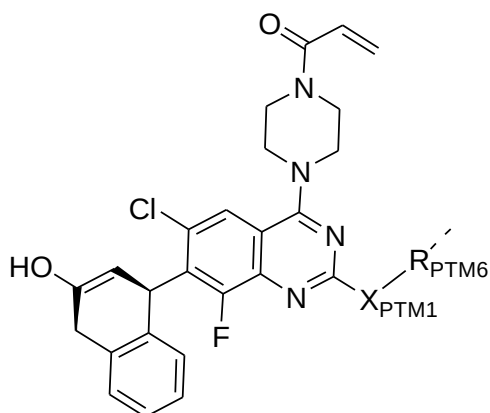
PTM-XIV



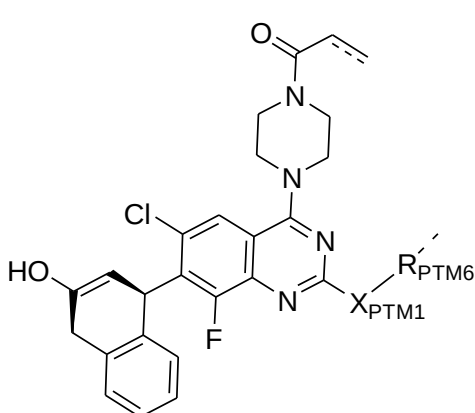
PTM-XV



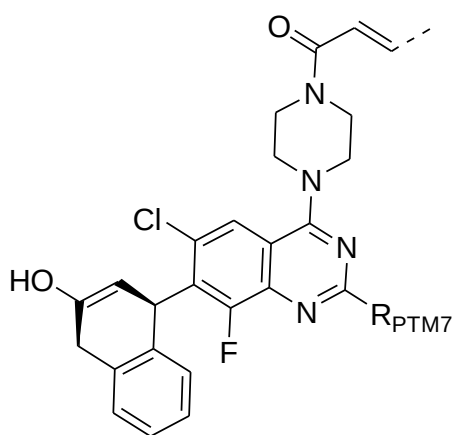
PTM-XVI



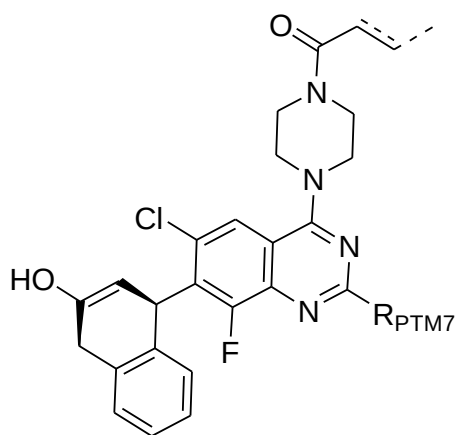
PTM-XVIIa



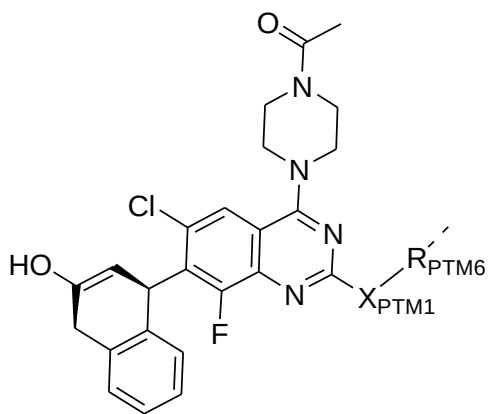
PTM-XVIIb



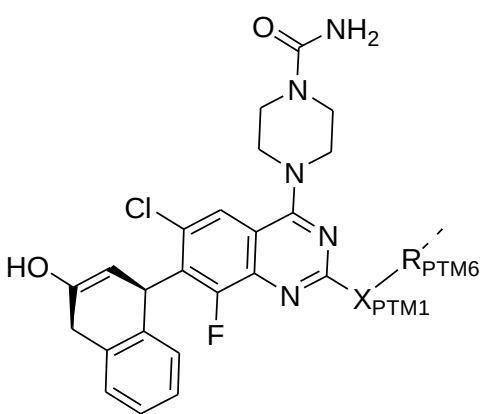
PTM-XVIII



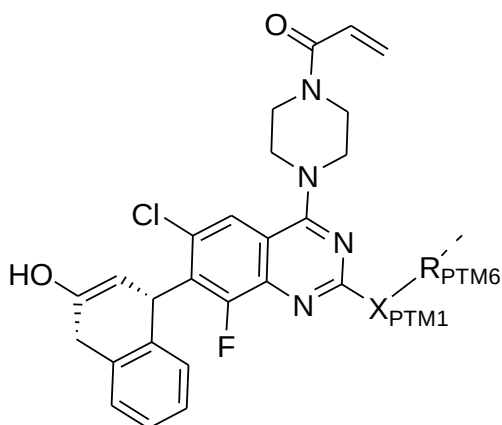
PTM-XIV



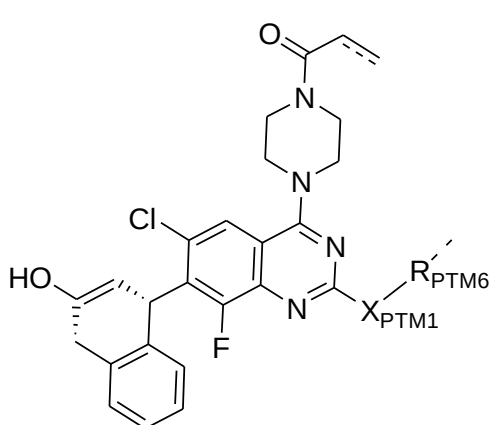
PTM-XV



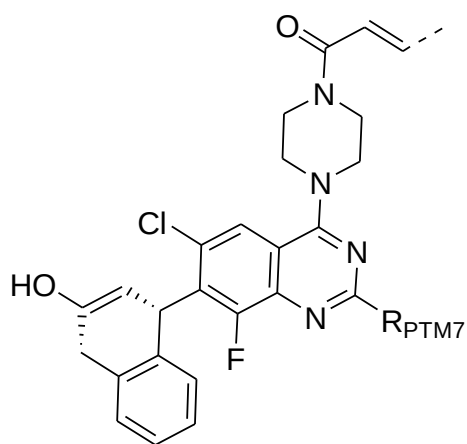
PTM-XVI



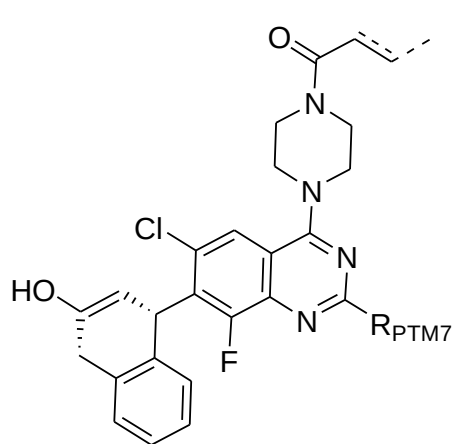
PTM-XVIIa



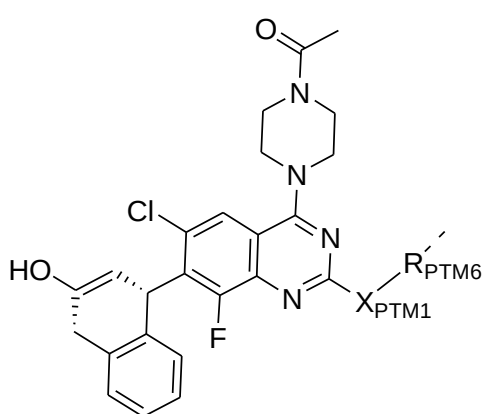
PTMXVIIb



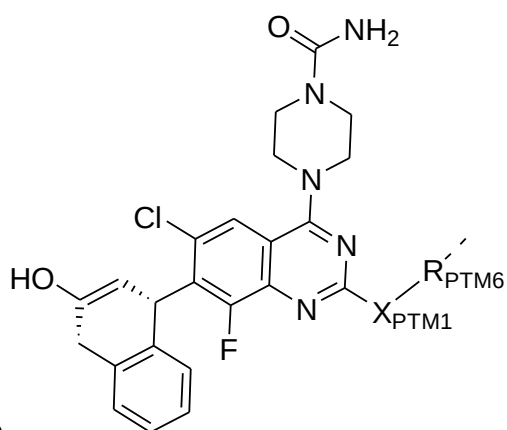
PTM-XVIII



PTM-XIX



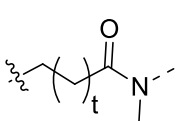
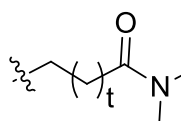
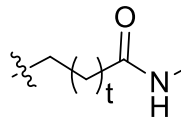
PTM-XX

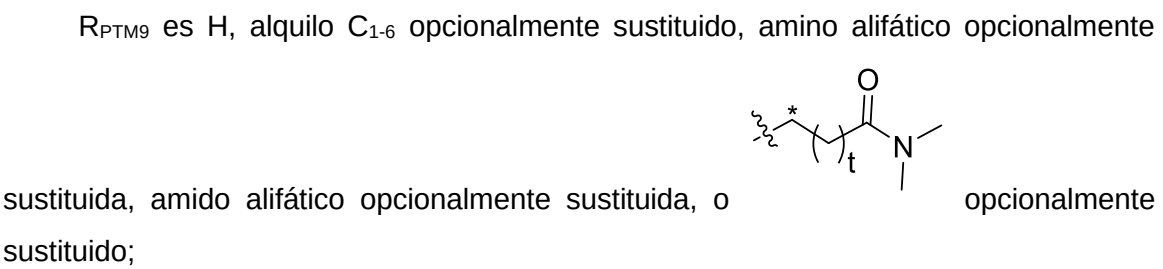
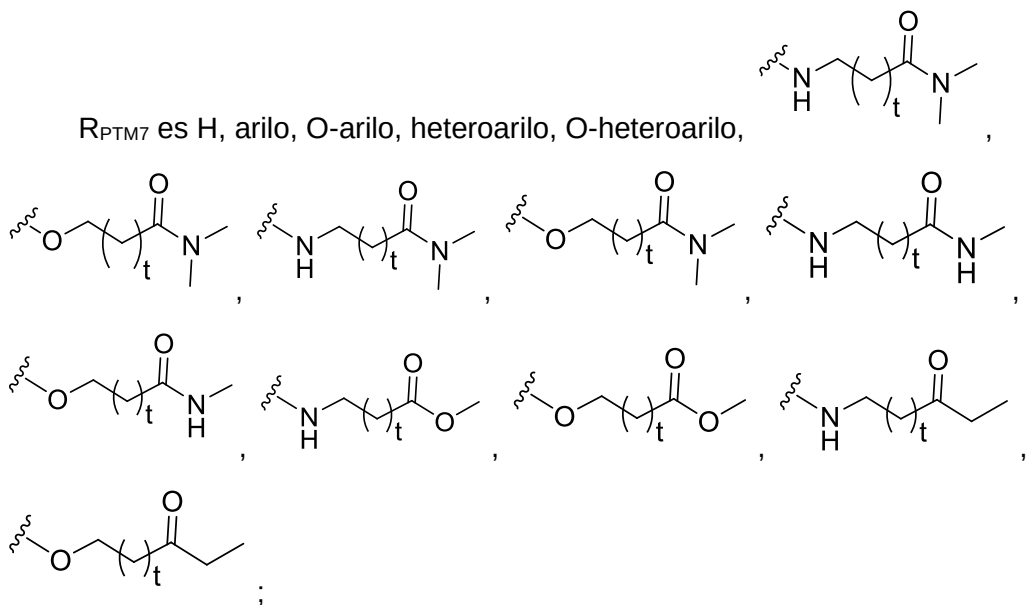
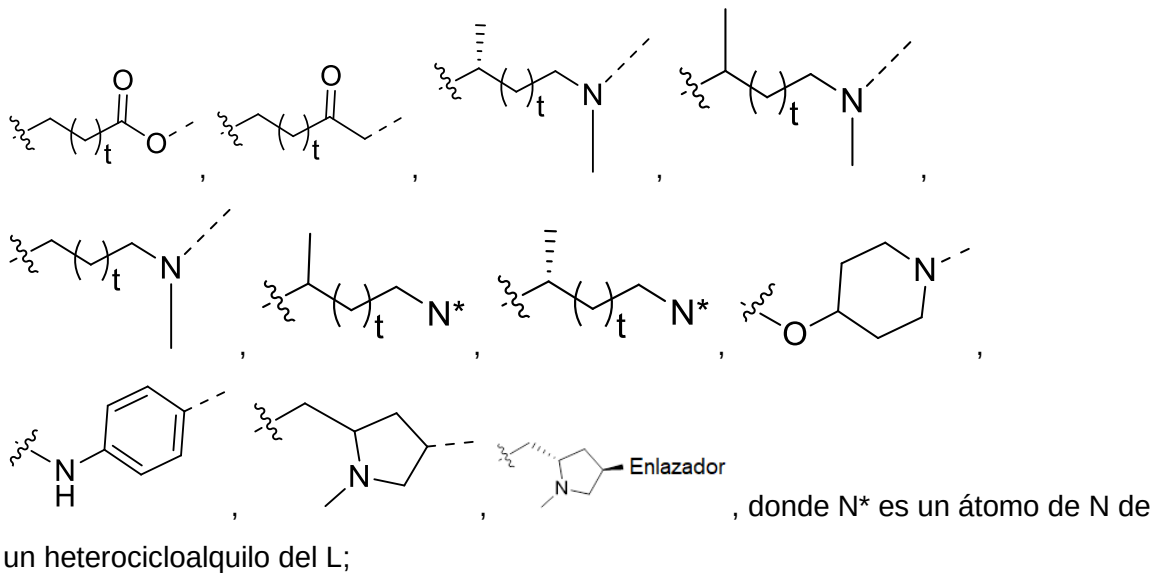


PTM-XXI

donde:

X_{PTM1} es NH u O;

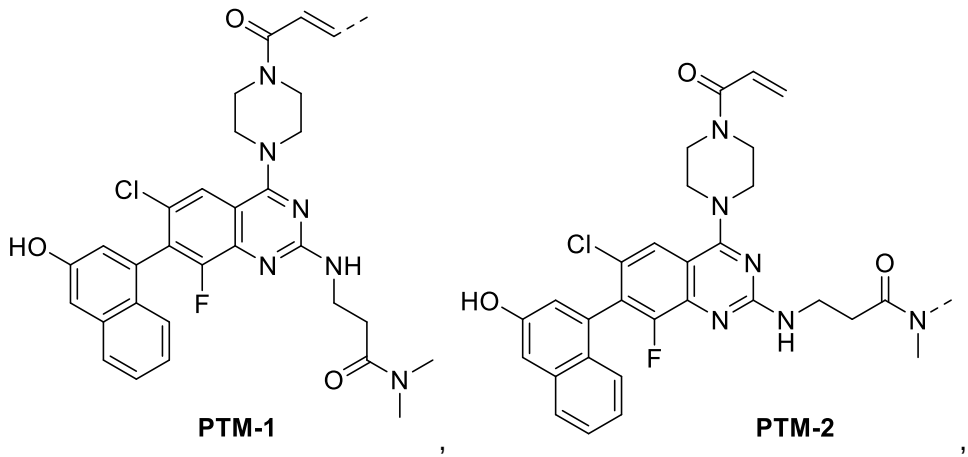
R_{PTM6} es arilo, heteroarilo, , , ,

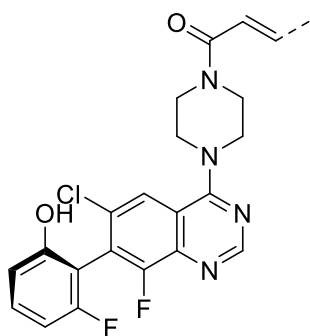


puede ser un enlace simple o un enlace doble; y

indica el sitio de unión del L.

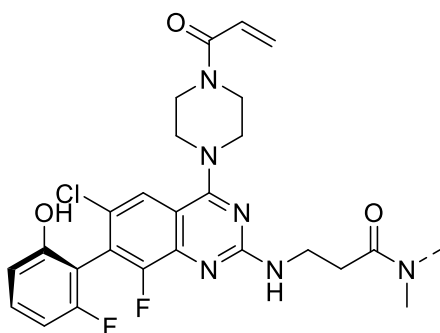
3. El compuesto bifuncional de acuerdo con cualquiera de la reivindicación 1 o reivindicación 2, donde el PTM es representado por la estructura química:





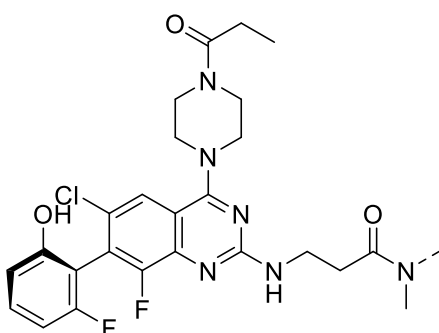
PTM-3

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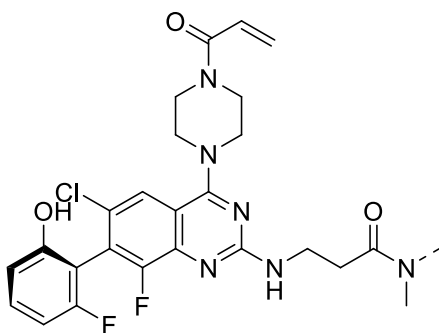
PTM-4

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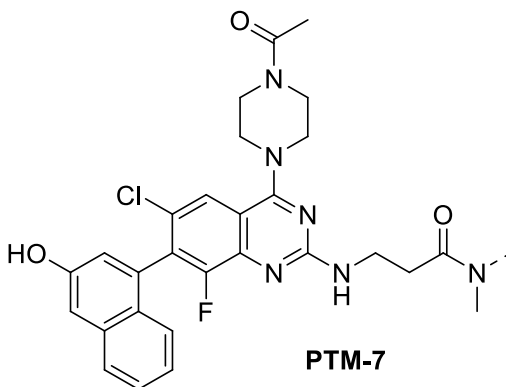
PTM-5

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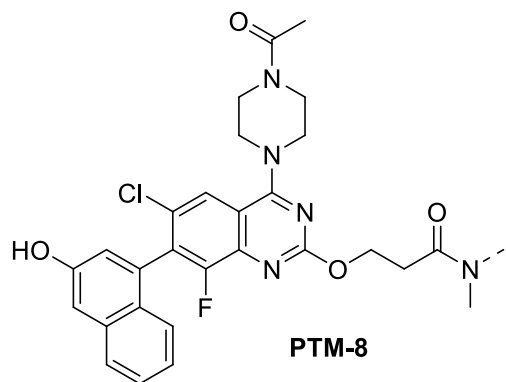
PTM-6

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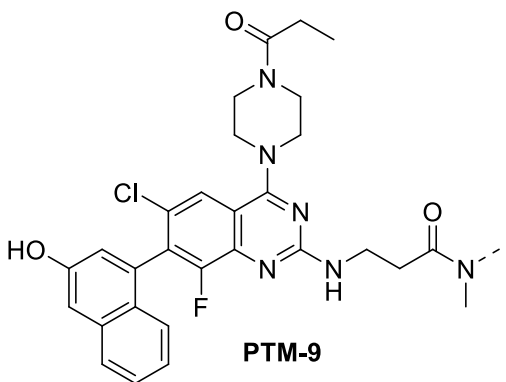
PTM-7

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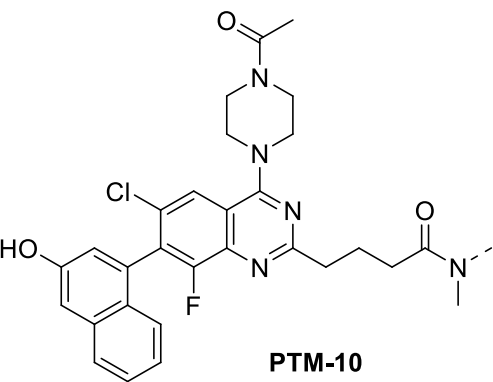
PTM-8

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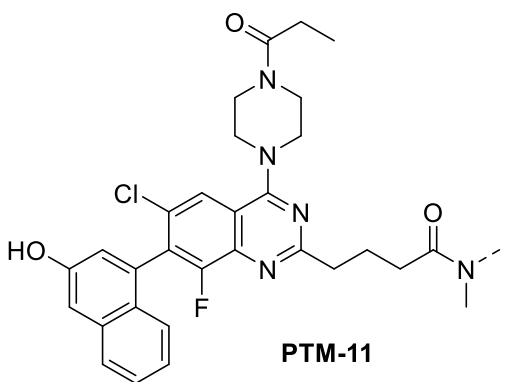
PTM-9

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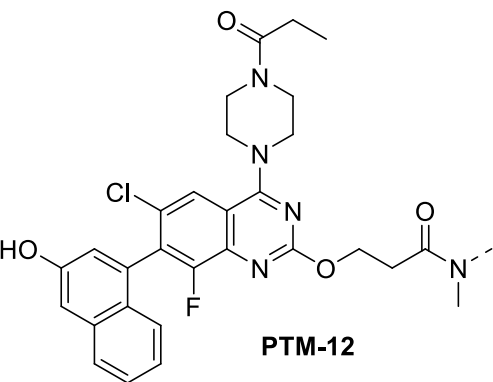
PTM-10

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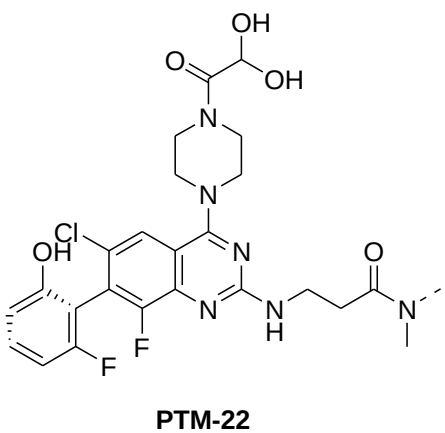
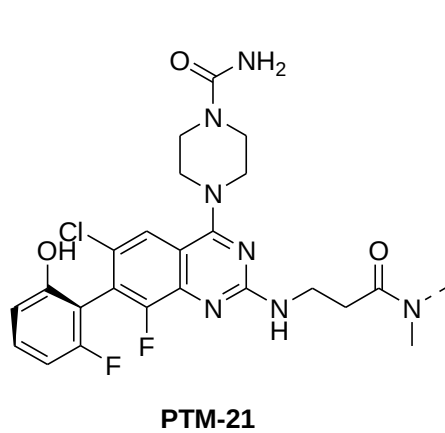
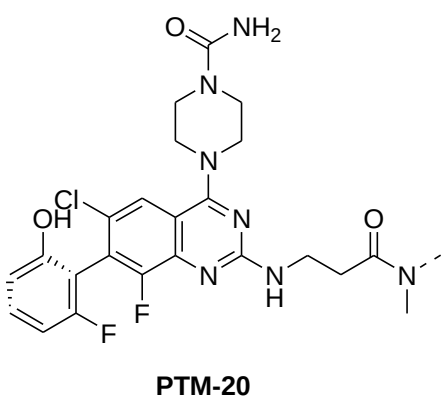
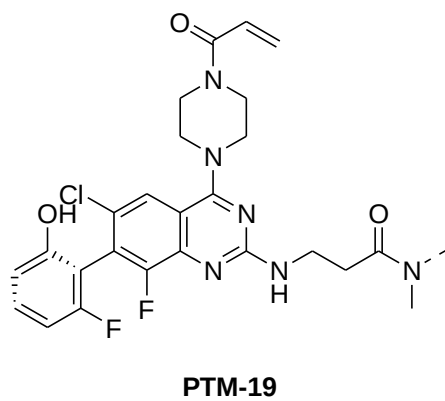
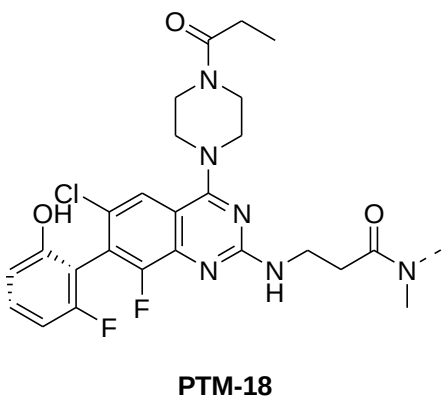
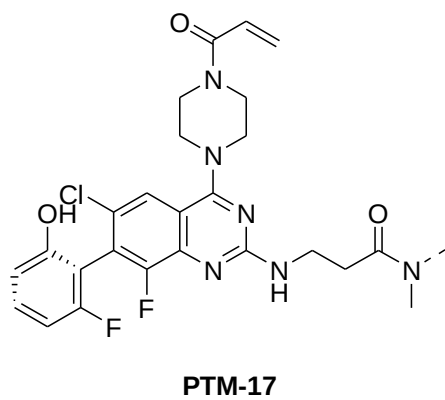
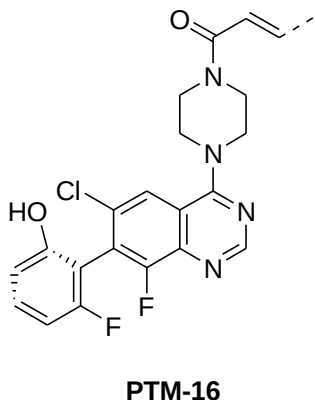
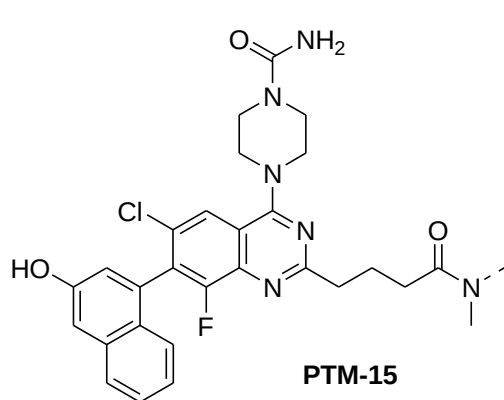
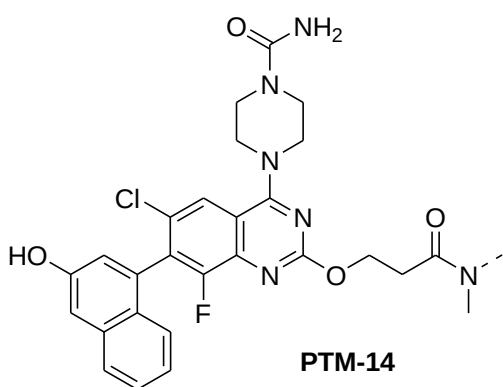
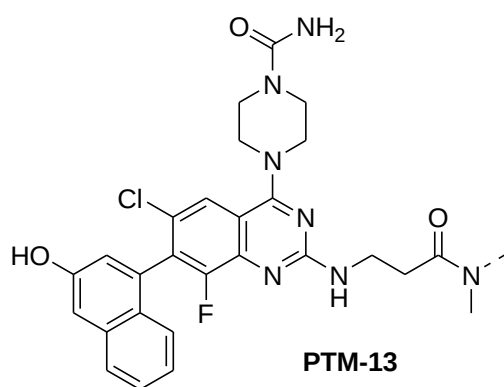
PTM-11

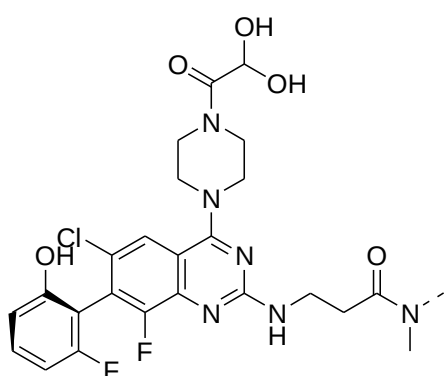
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PTM-12

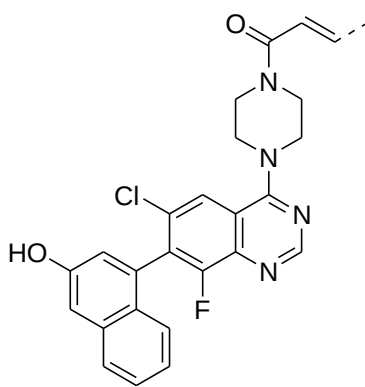
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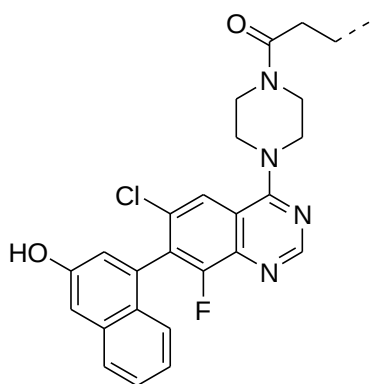
PTM-23

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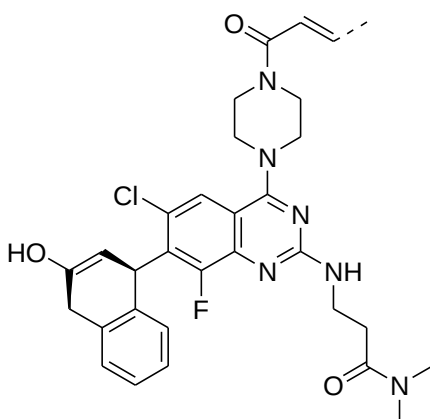
PTM-23

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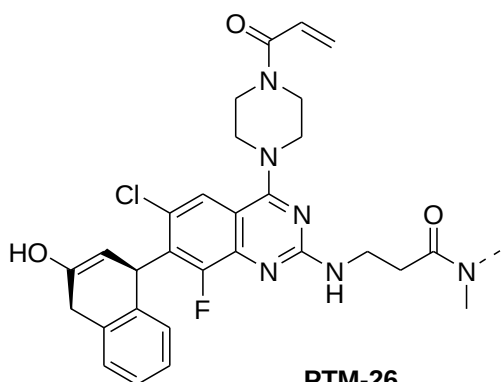
PTM-24

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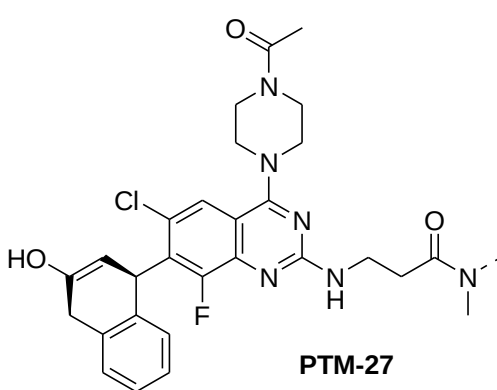
PTM-25

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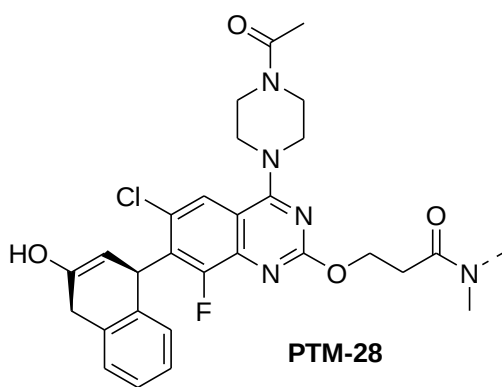
PTM-26

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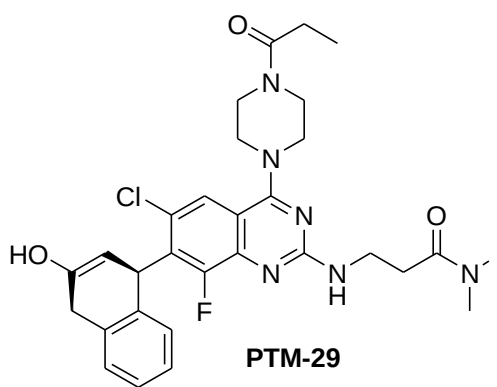
PTM-27

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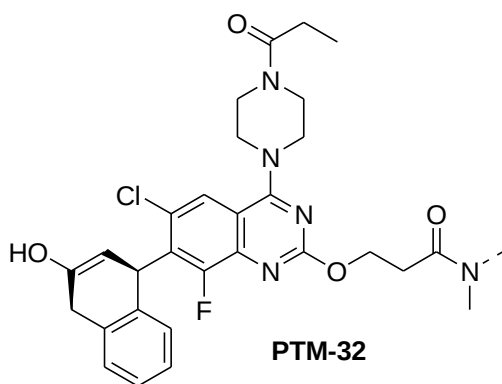
PTM-28

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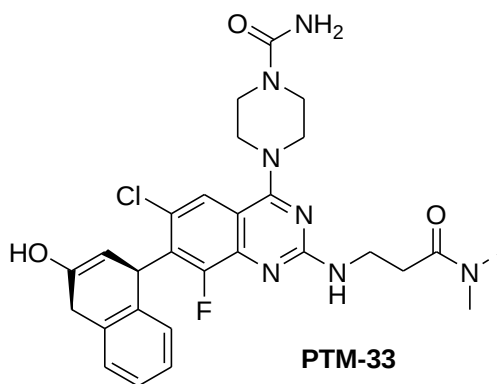
PTM-29

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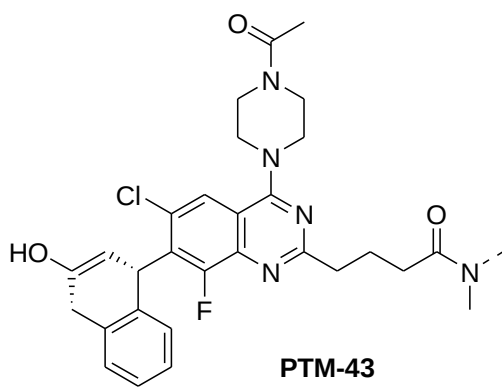
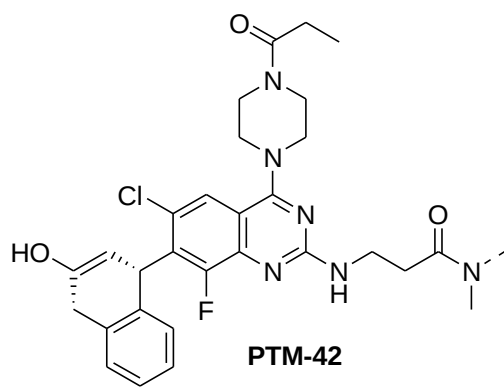
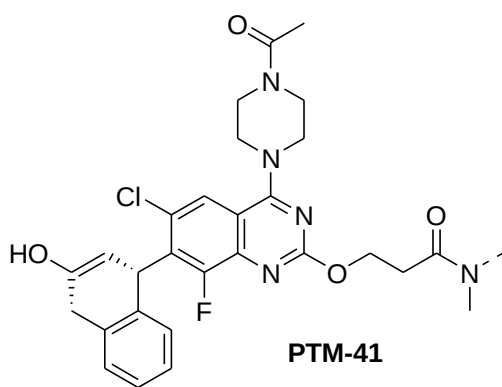
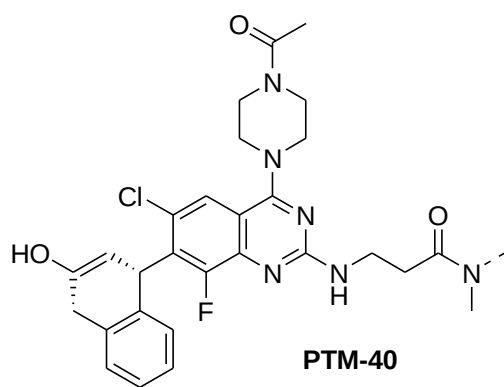
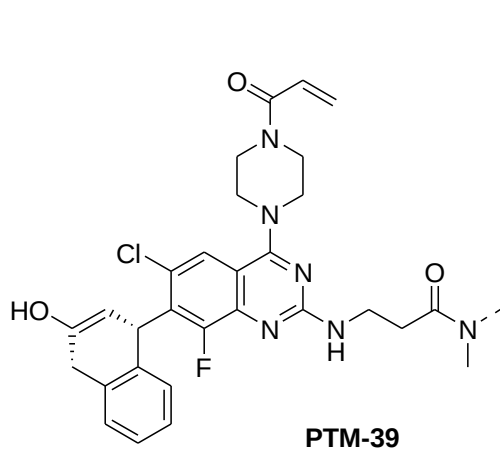
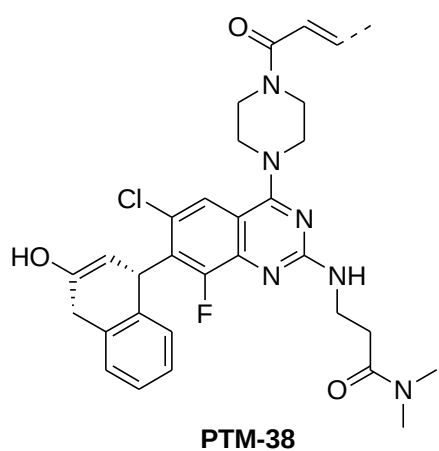
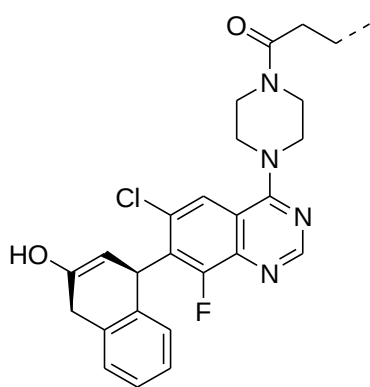
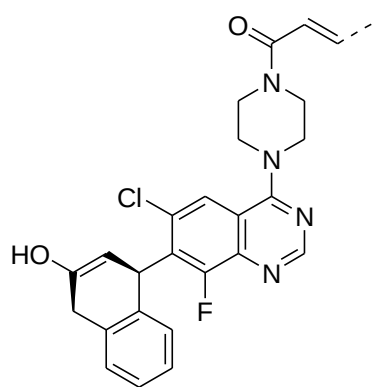
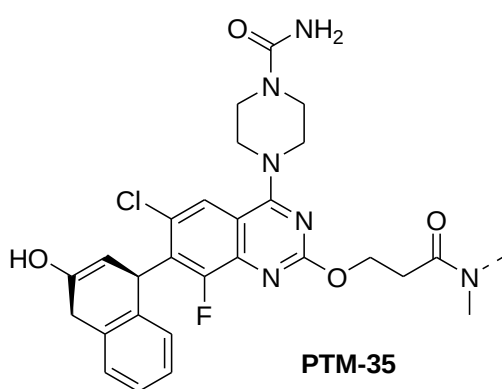
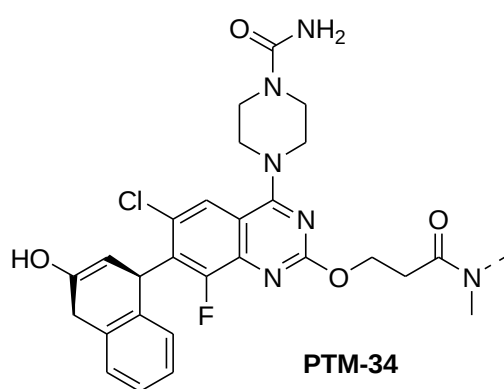
PTM-32

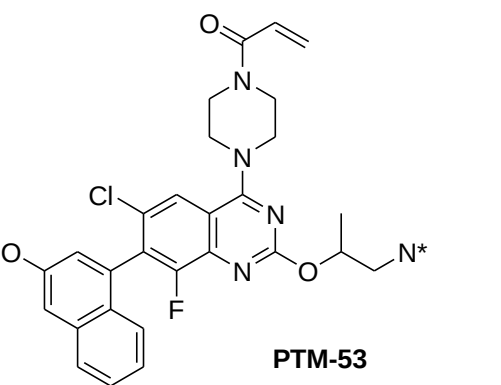
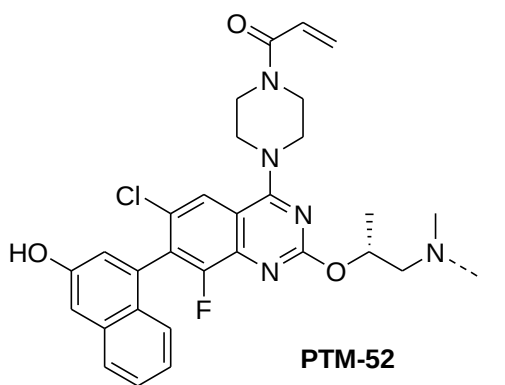
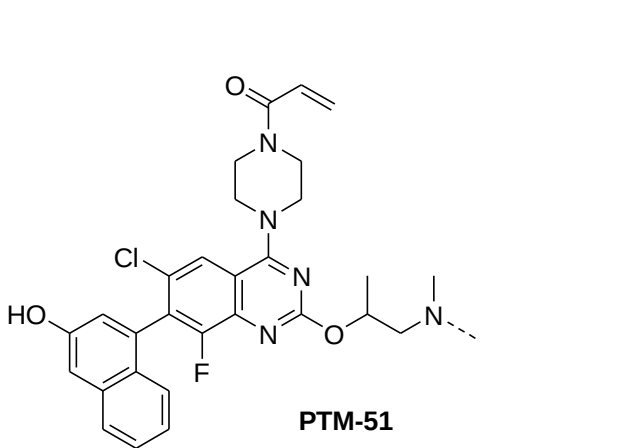
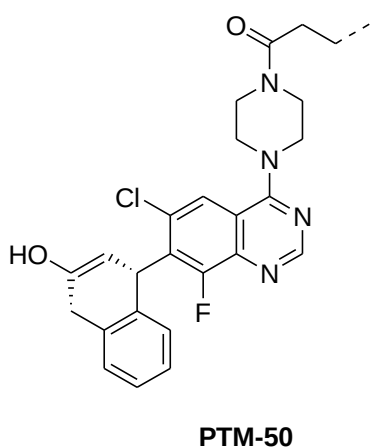
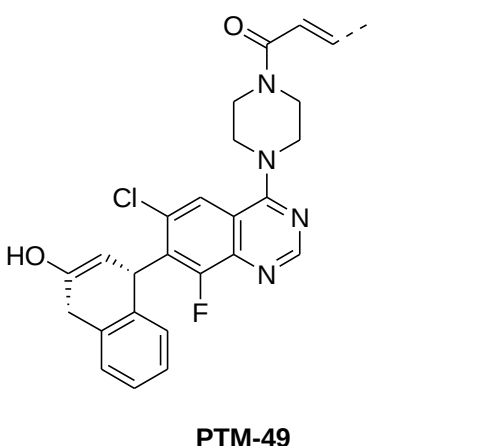
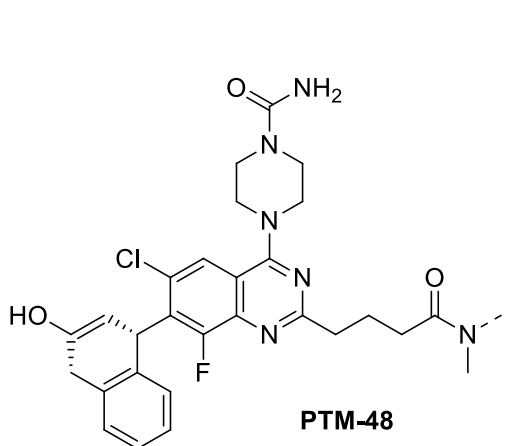
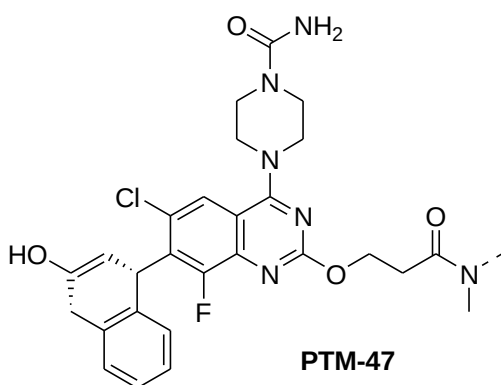
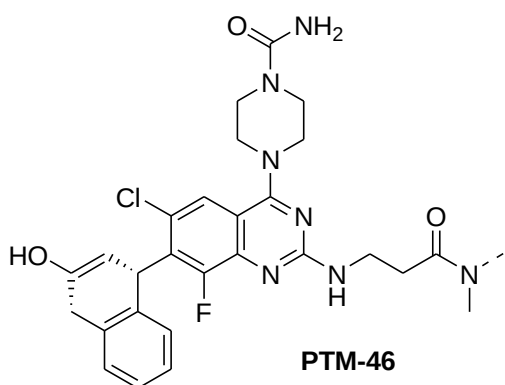
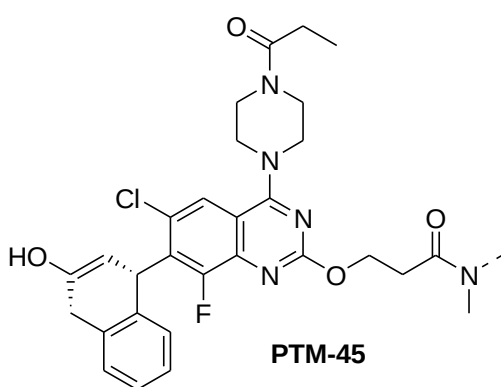
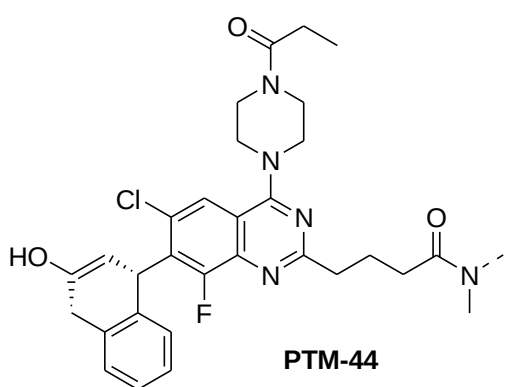
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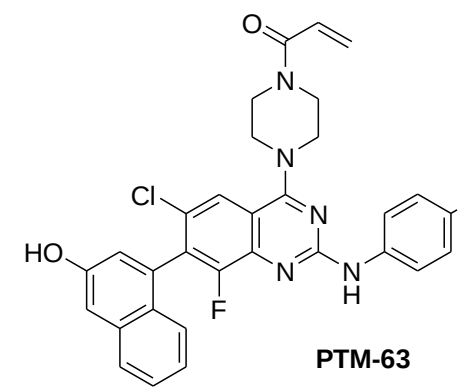
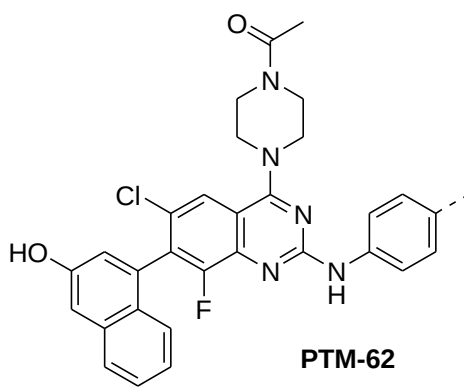
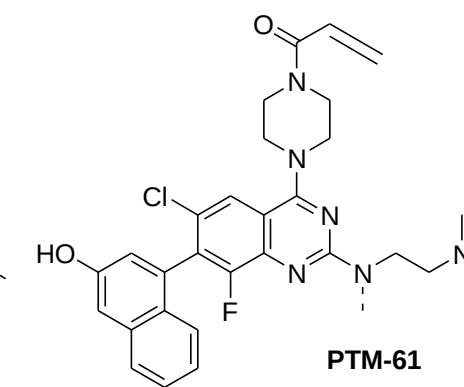
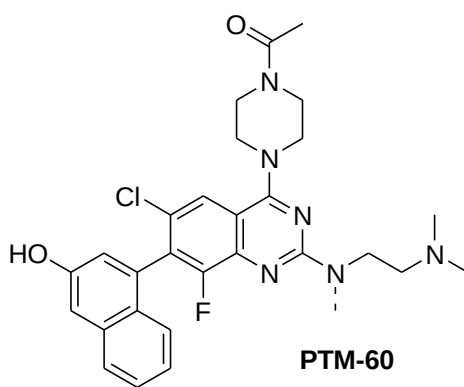
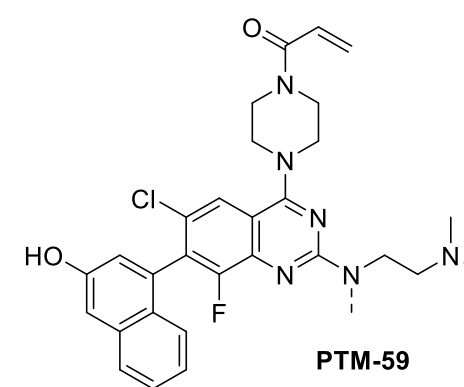
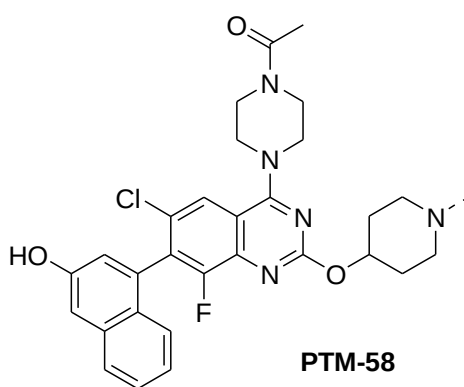
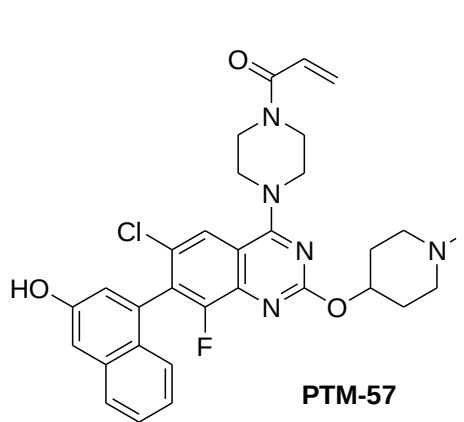
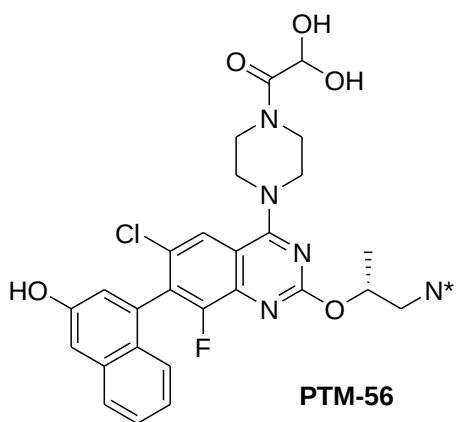
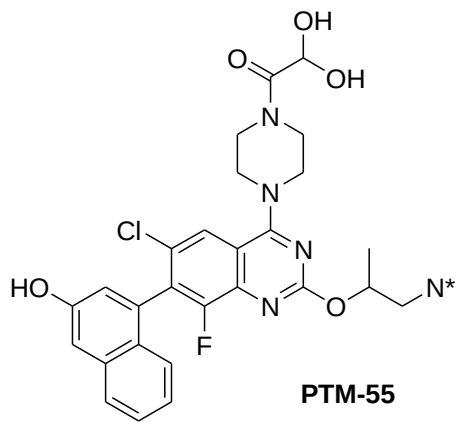
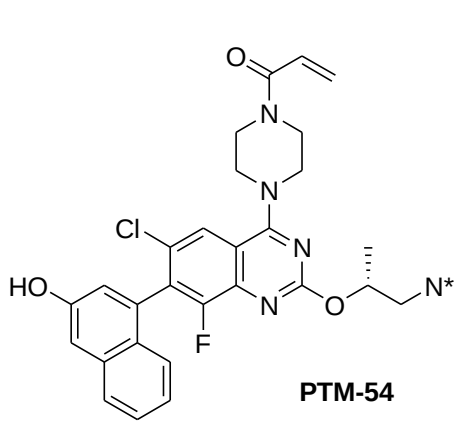


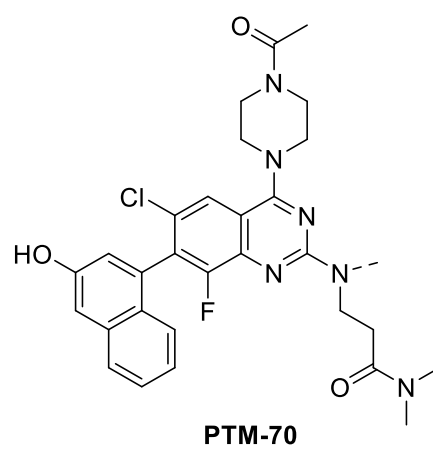
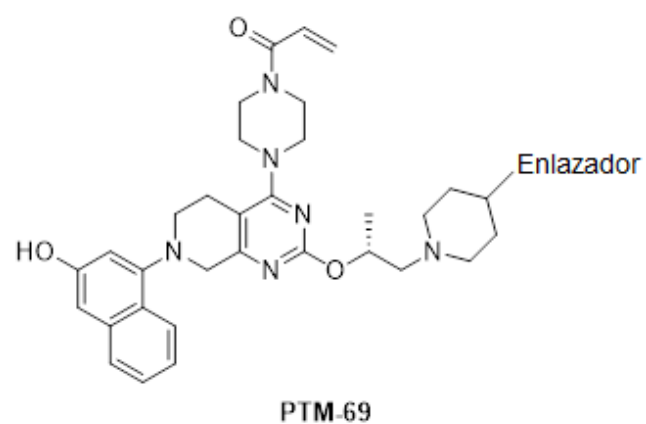
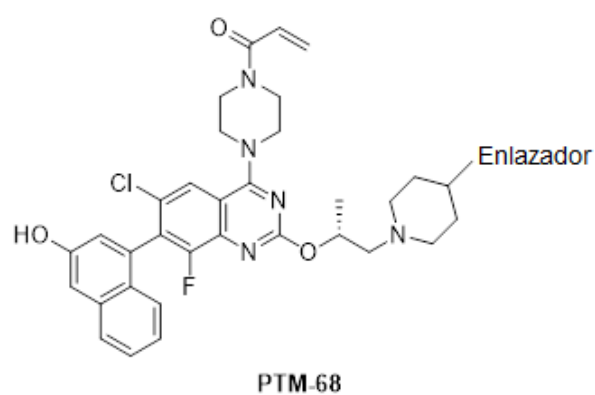
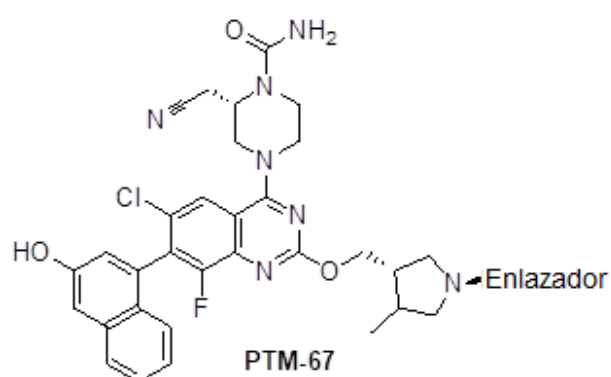
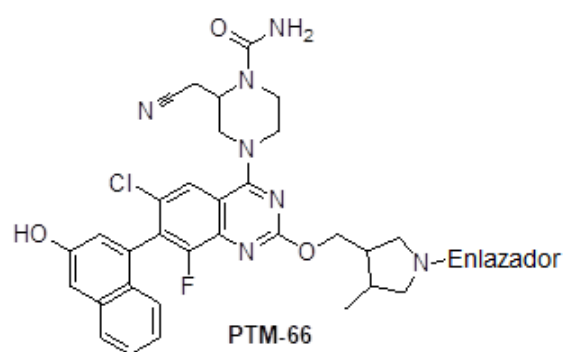
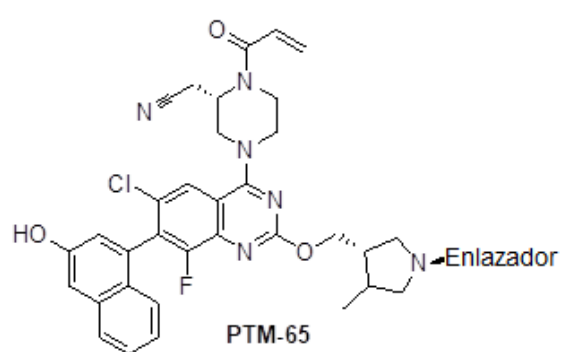
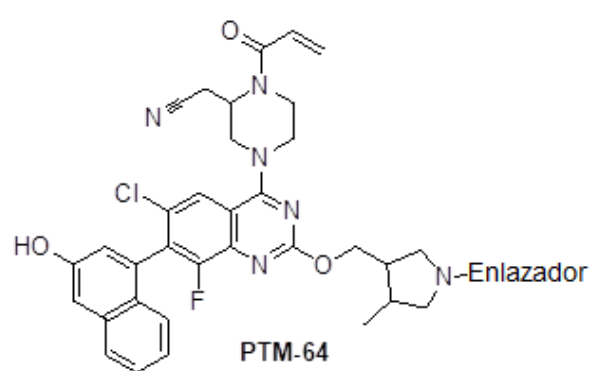
PTM-33

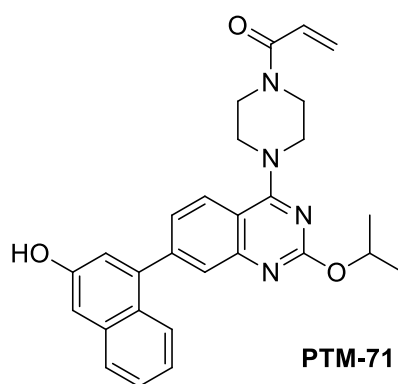
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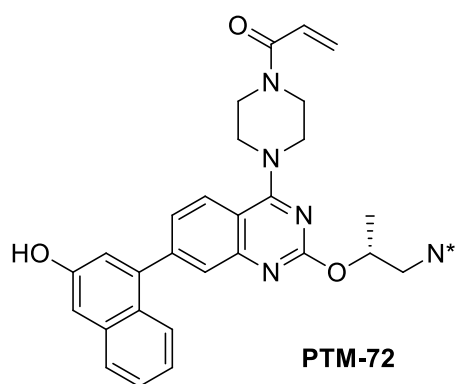




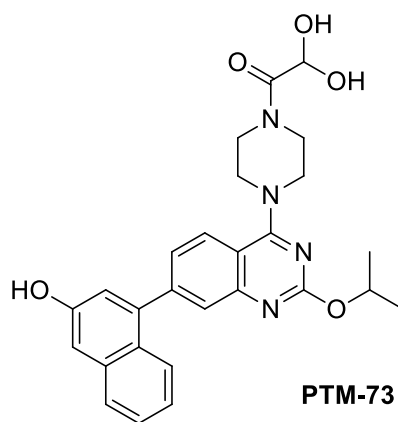




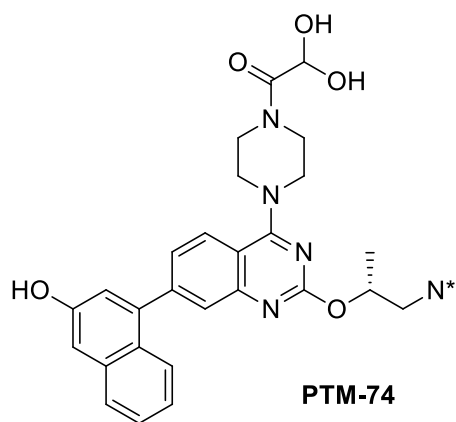
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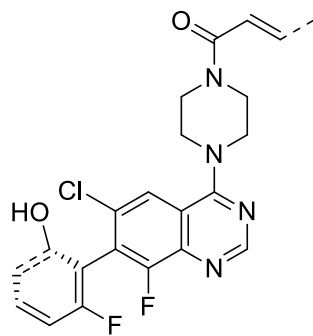
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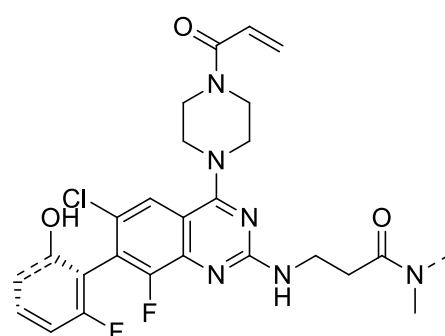
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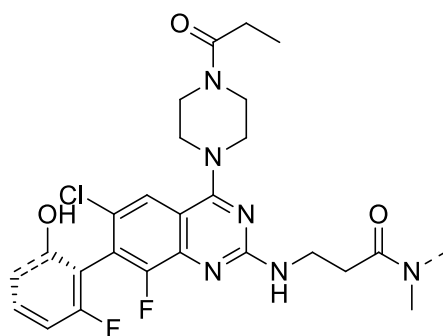
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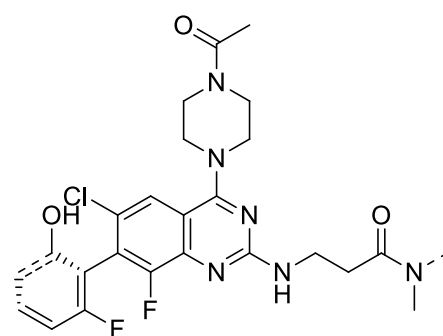
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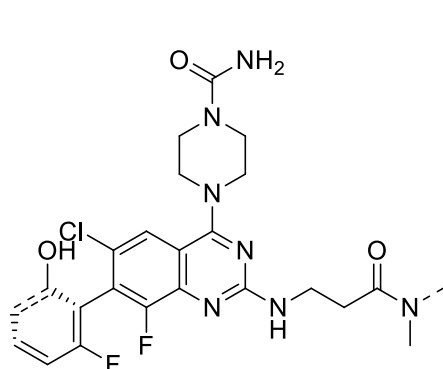
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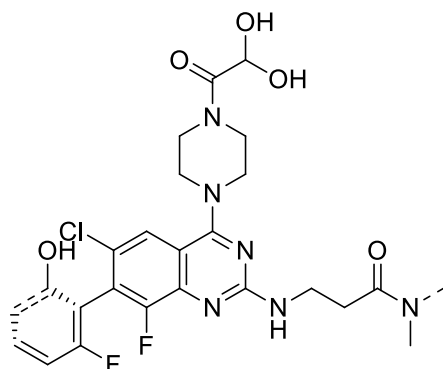
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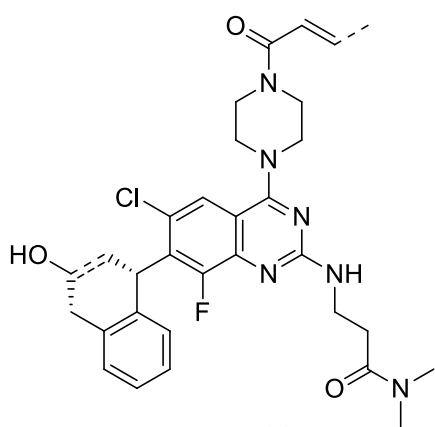
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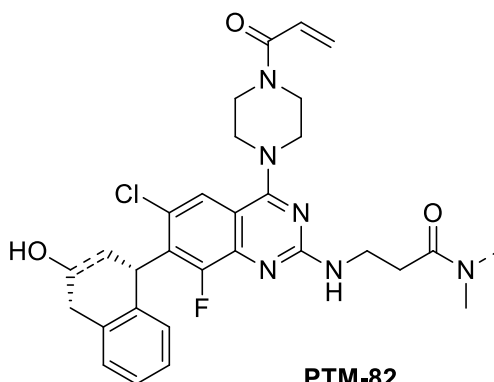
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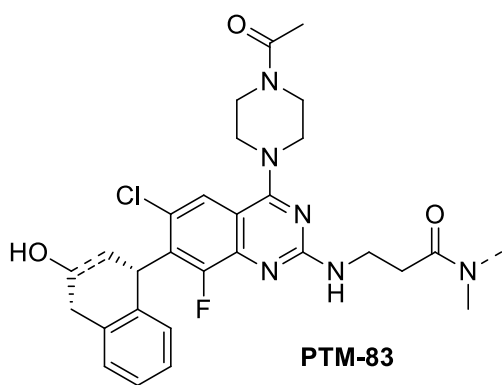
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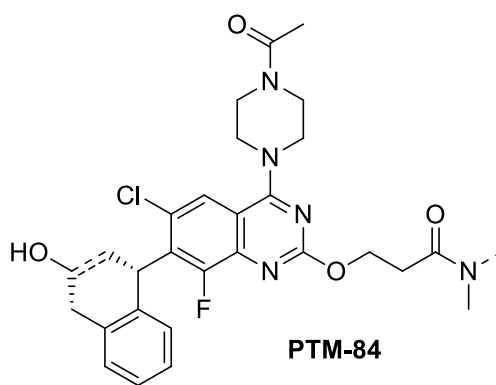
PTM-81



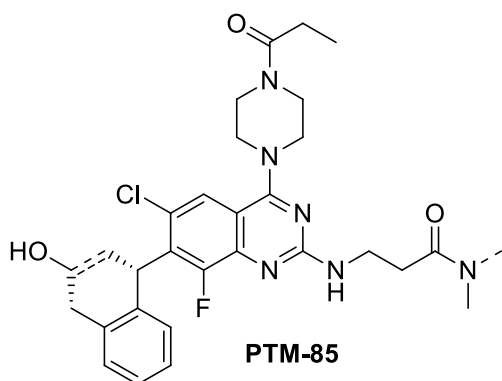
PTM-82



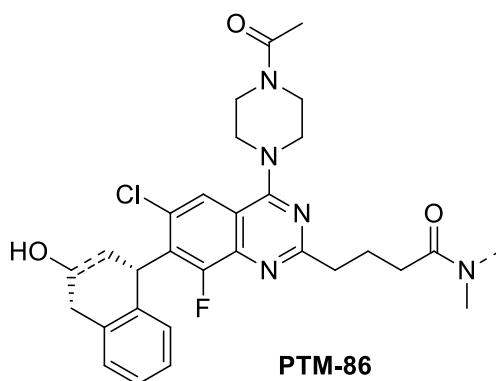
PTM-83



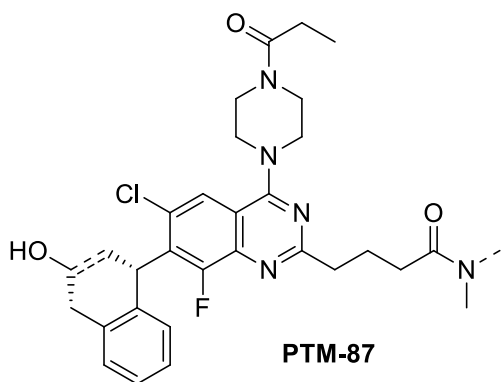
PTM-84



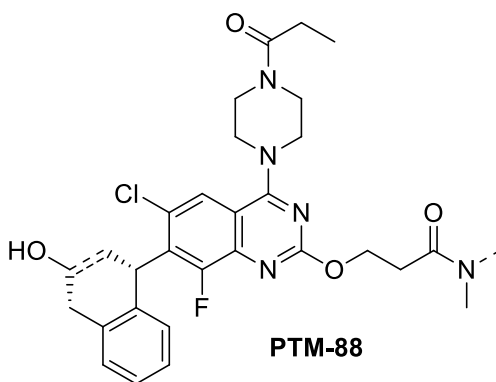
PTM-85



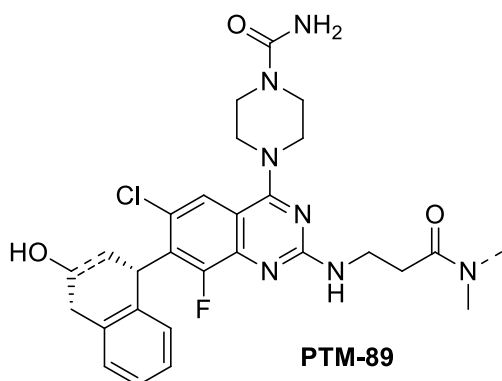
PTM-86



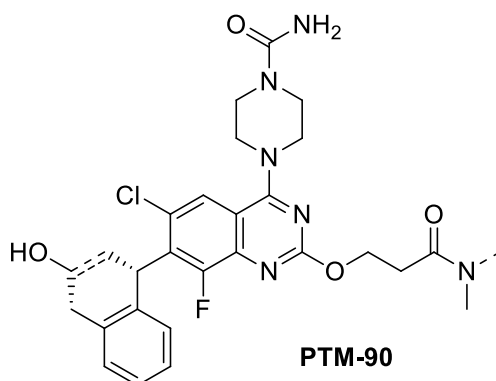
PTM-87



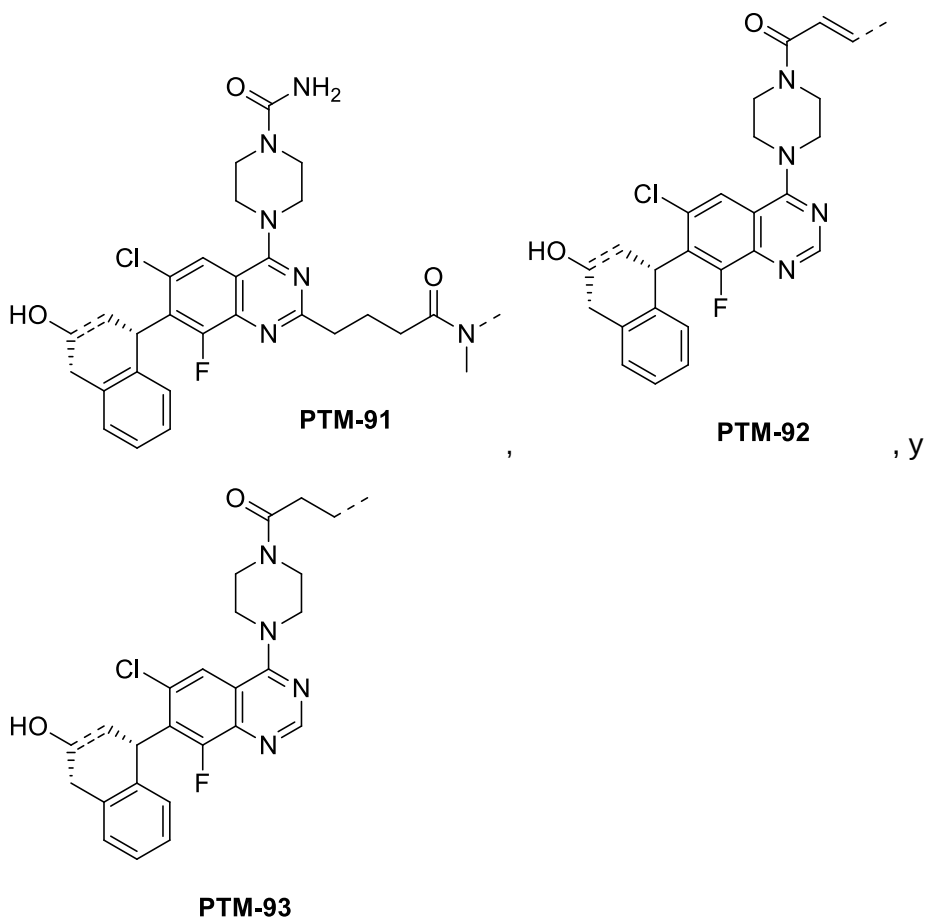
PTM-88



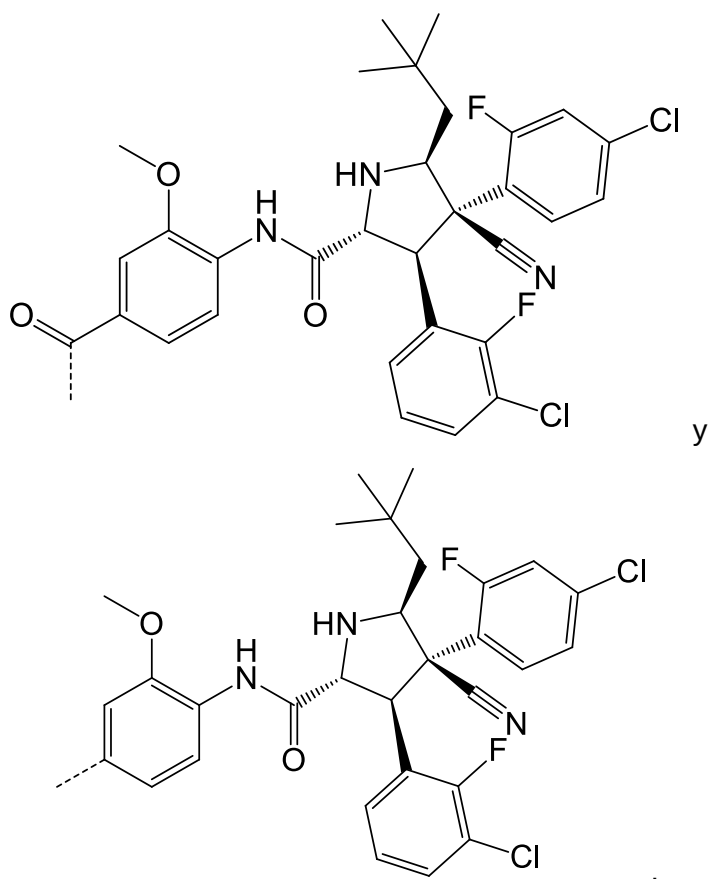
PTM-89



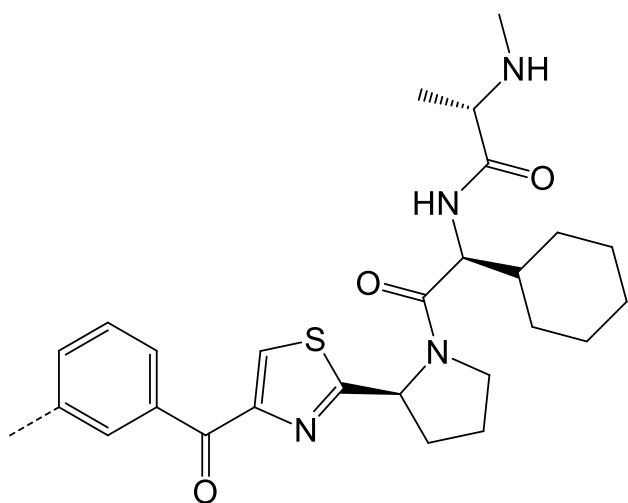
PTM-90



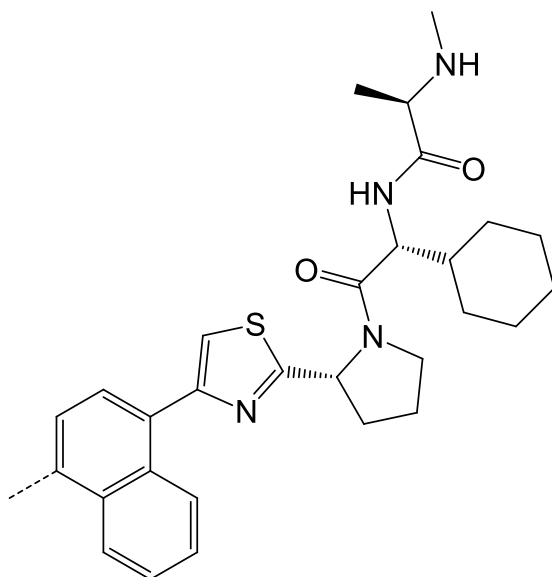
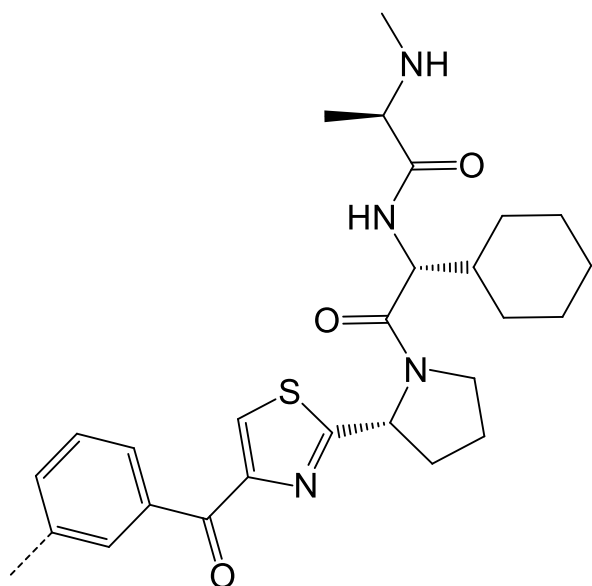
4. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el MLM se selecciona de entre:



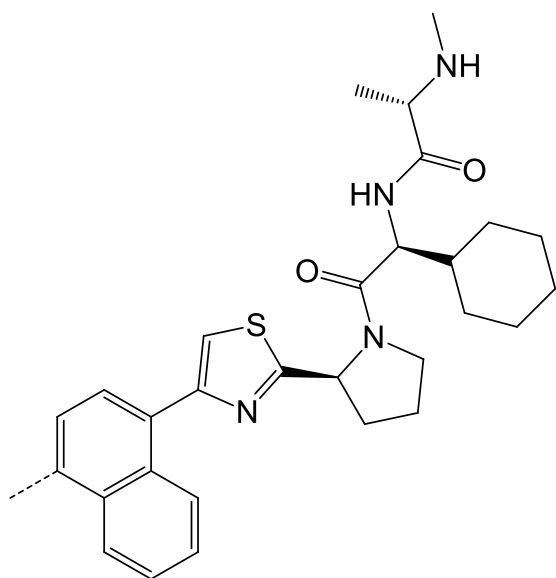
5. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 3, donde el ILM se selecciona de entre:



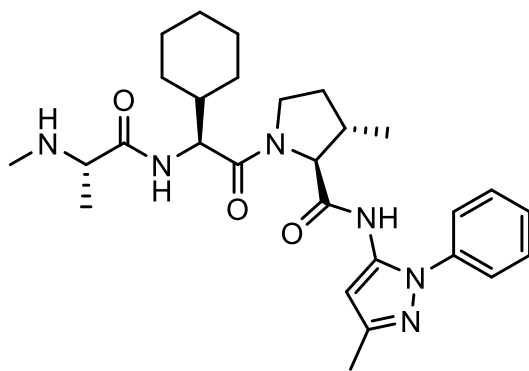
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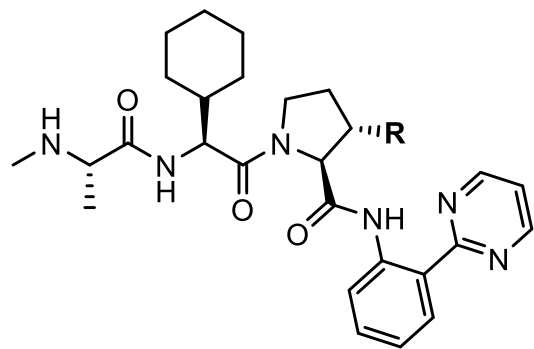
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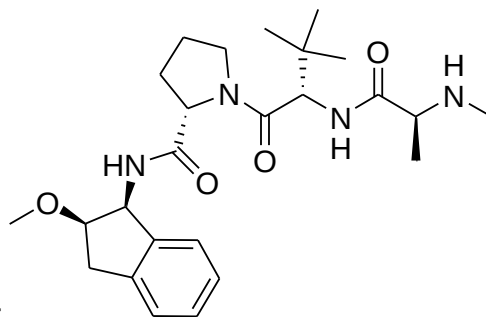
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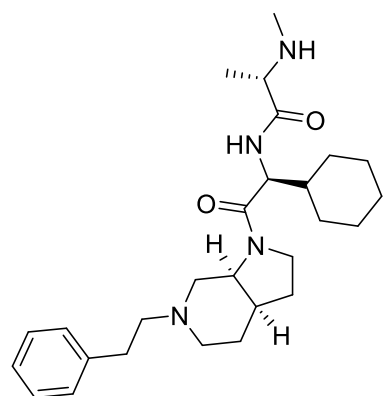
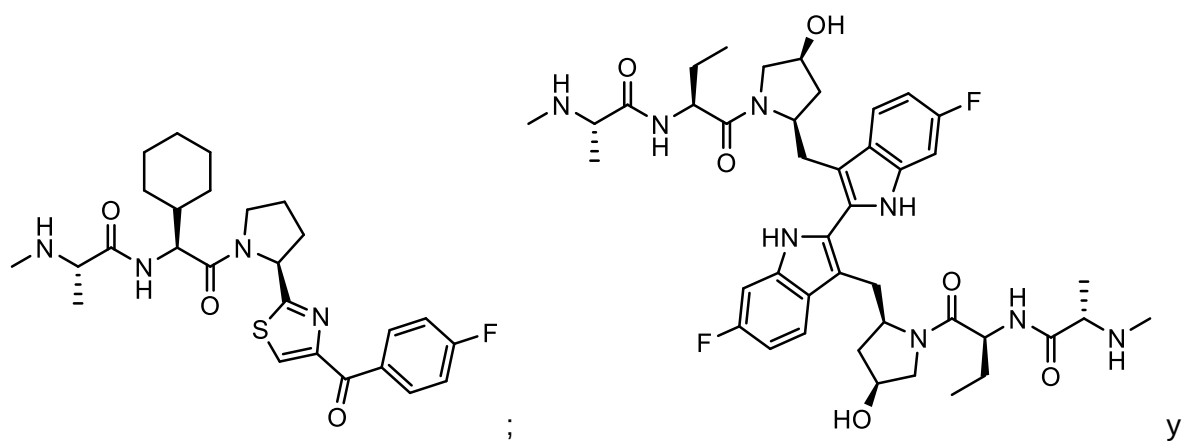
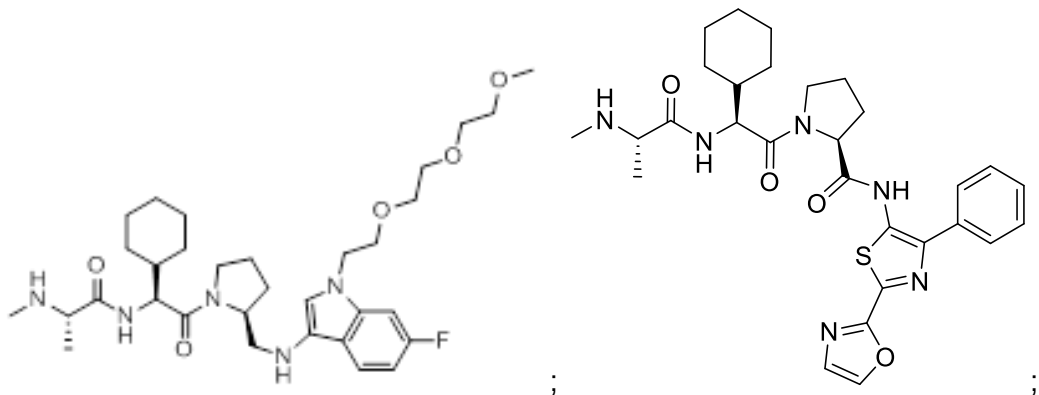
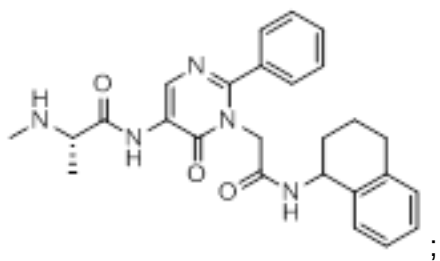
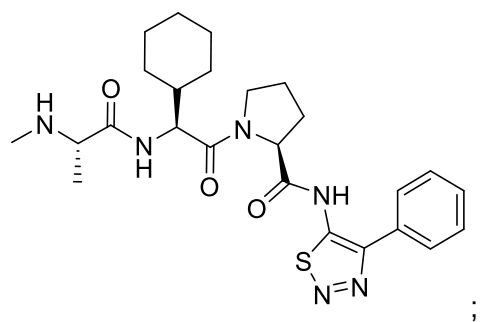
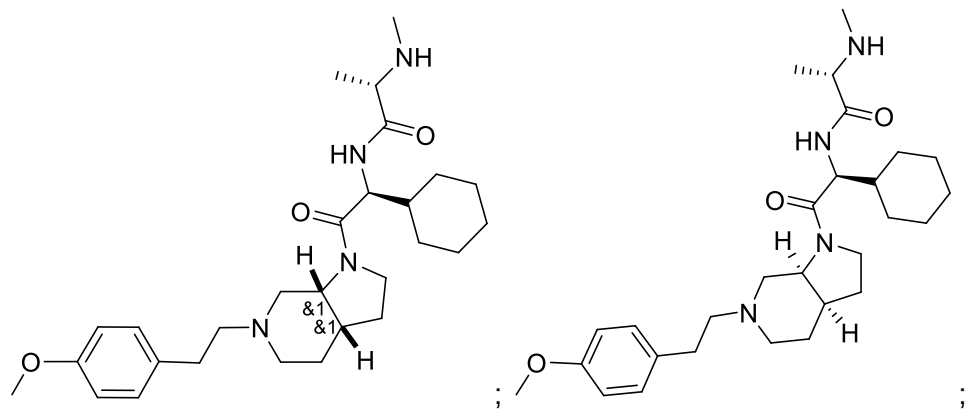
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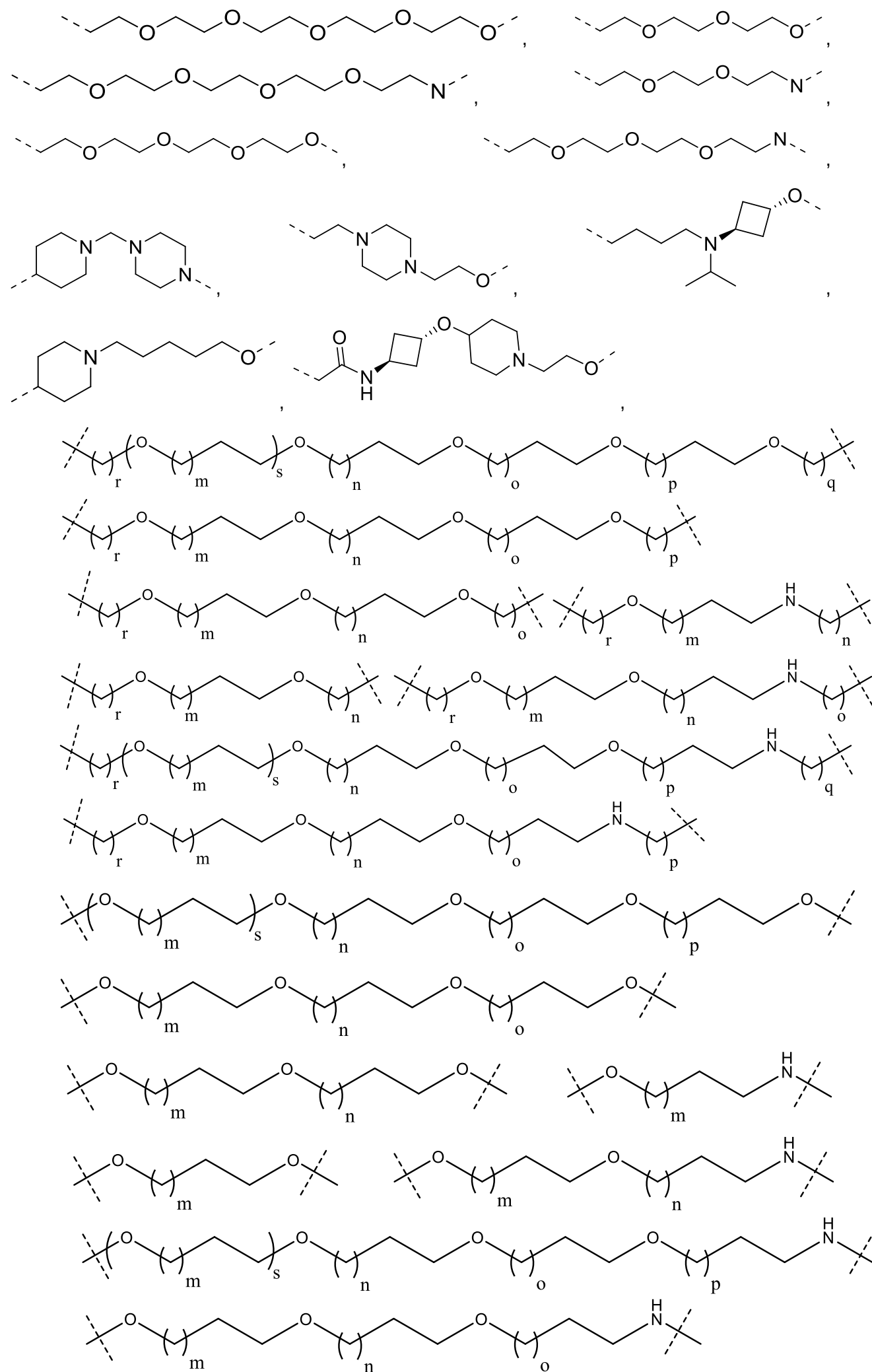
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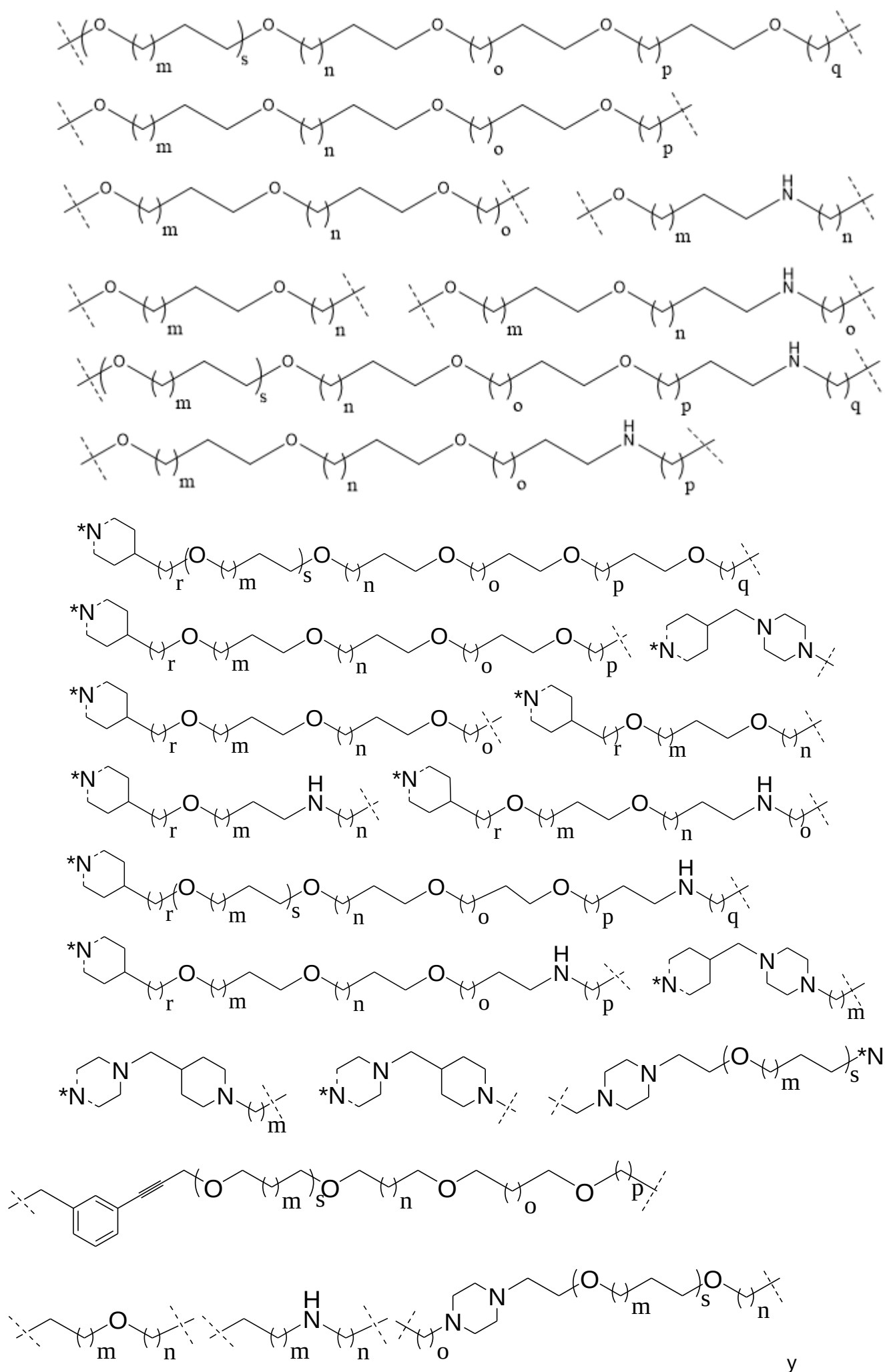


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6. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde L se selecciona de entre:





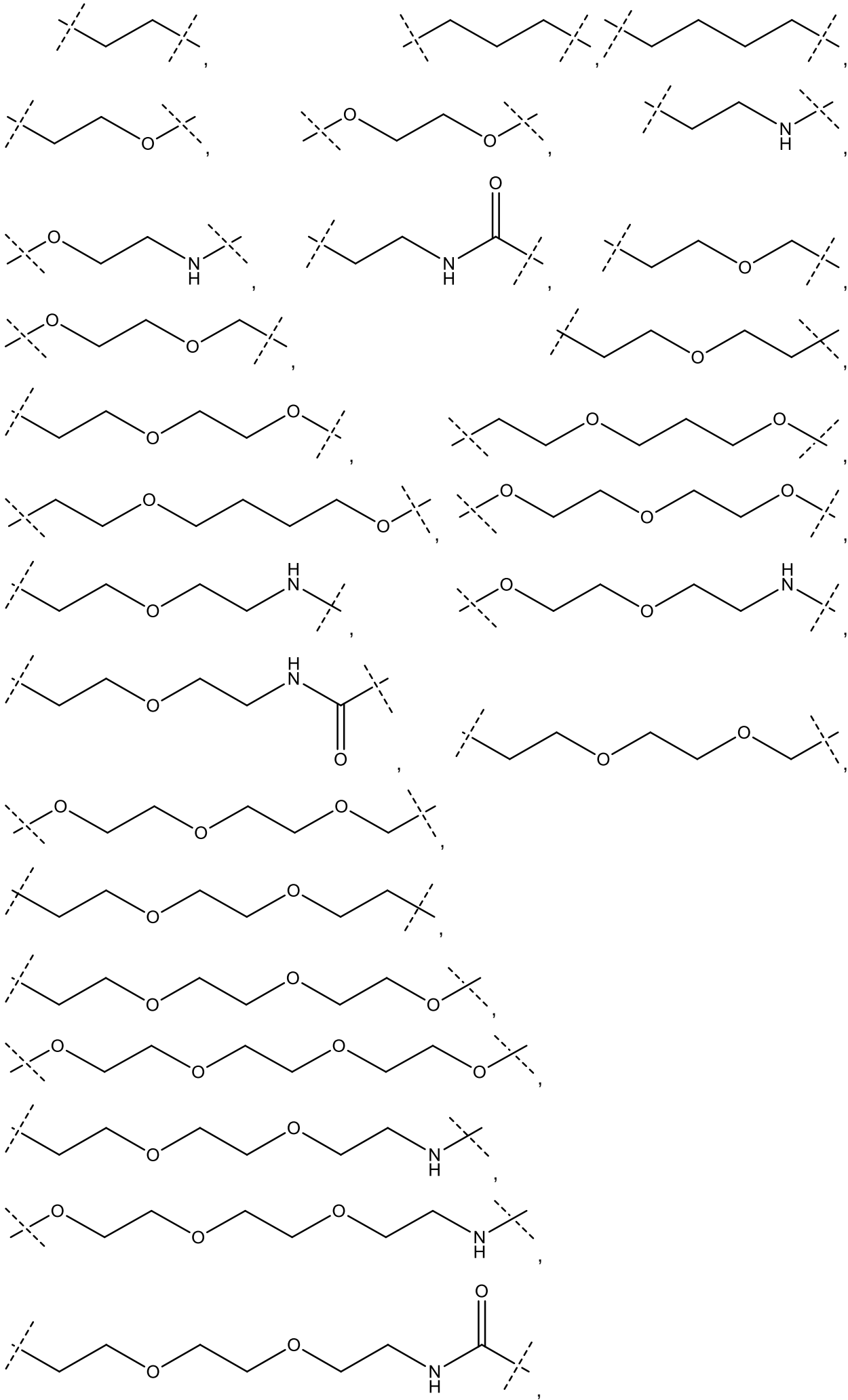
alquilo C₁₋₆; o

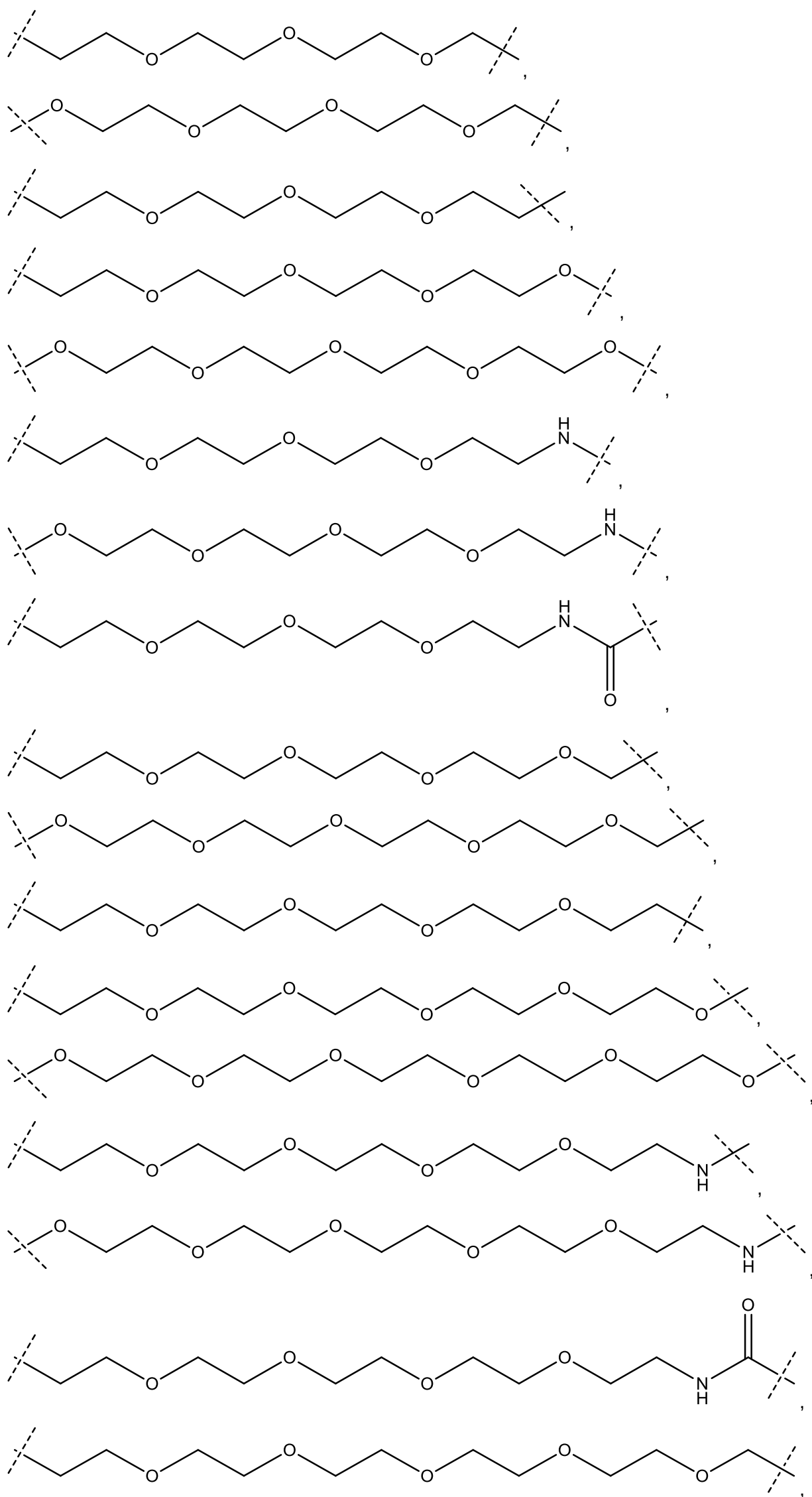
donde:

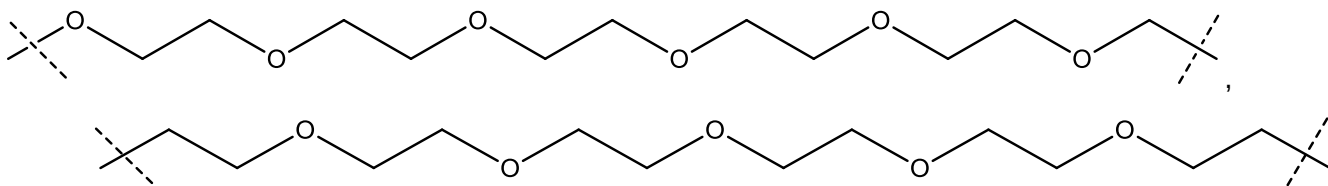
*N del heterocicloalquilo es compartido con el PTM; y

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. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde L se selecciona de entre:







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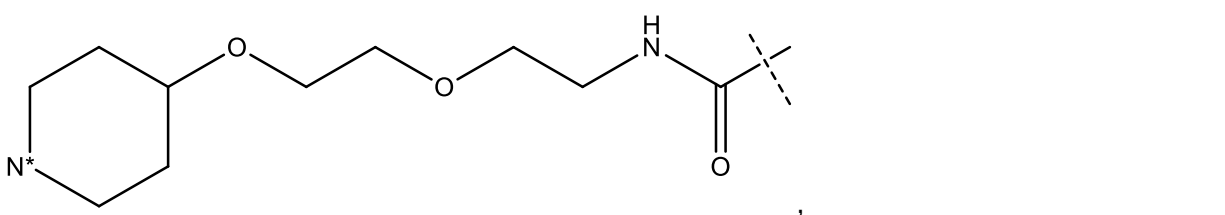
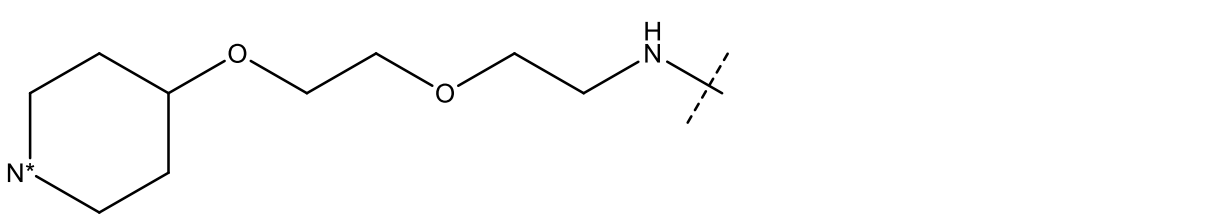
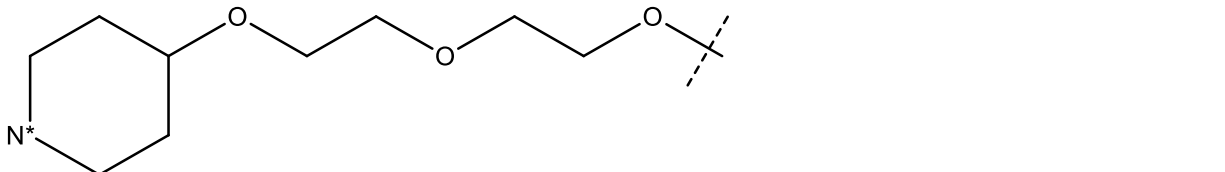
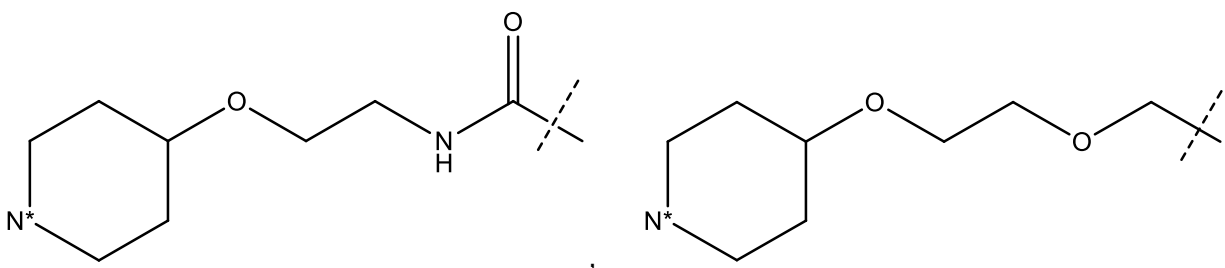
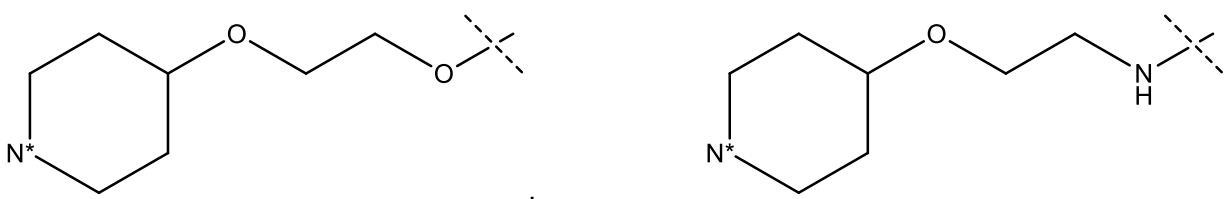
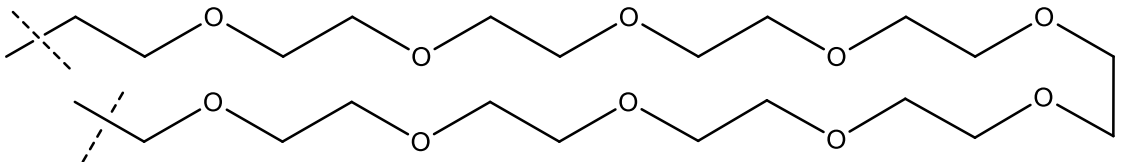
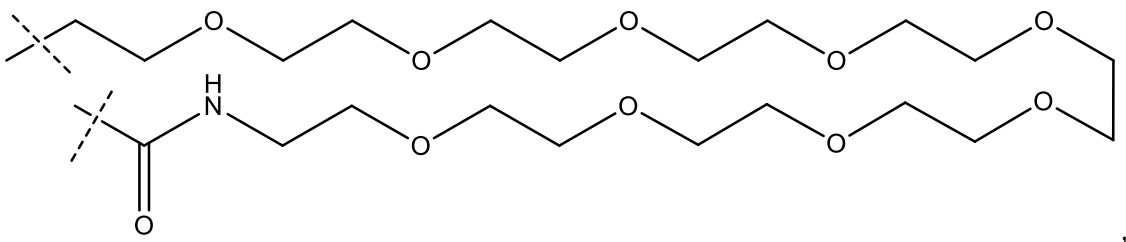
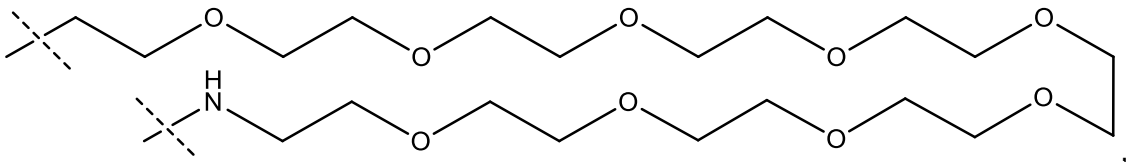
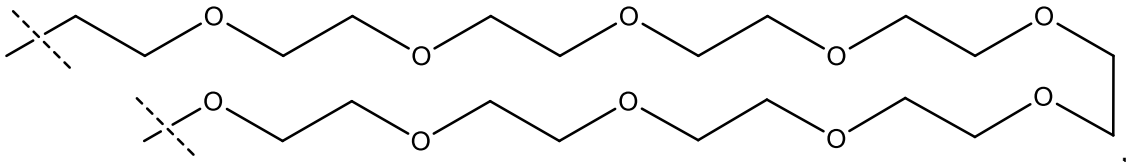
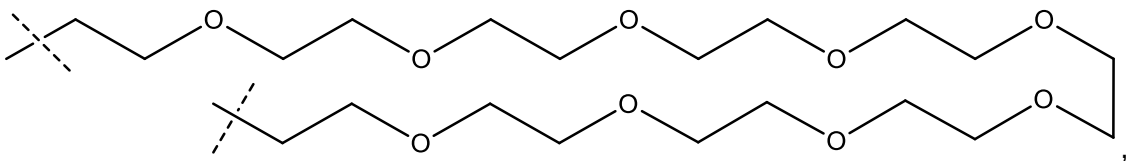
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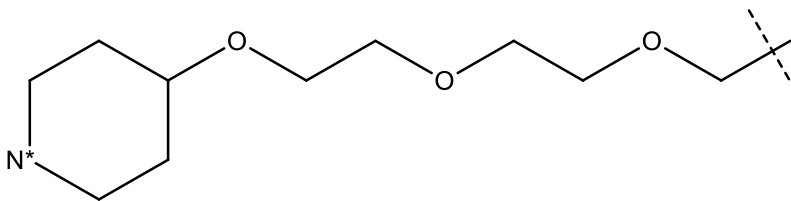
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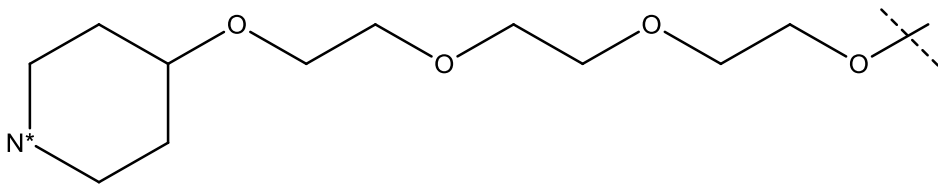
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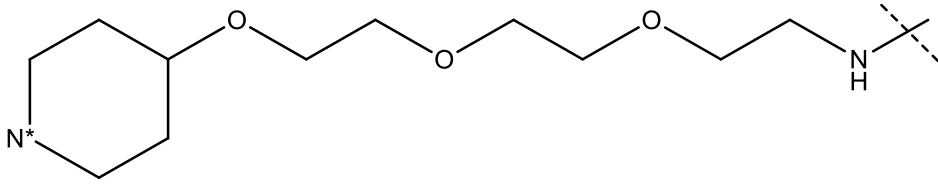




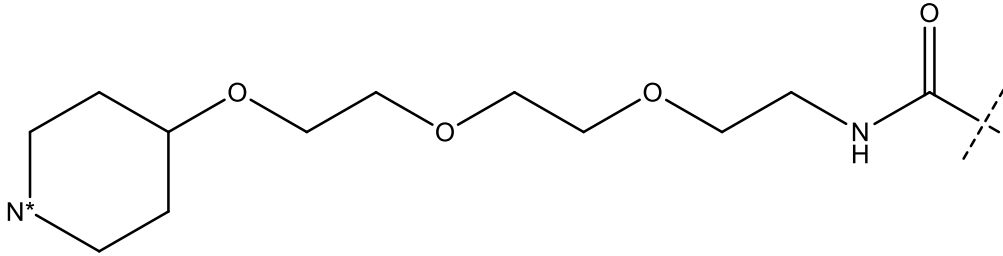
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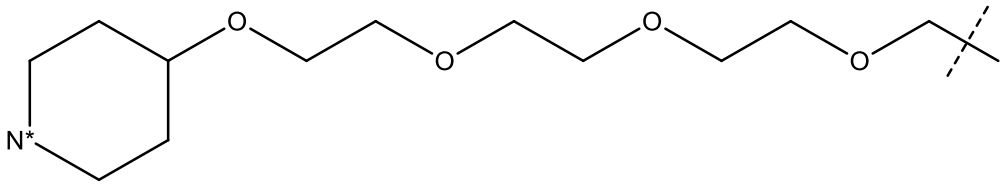
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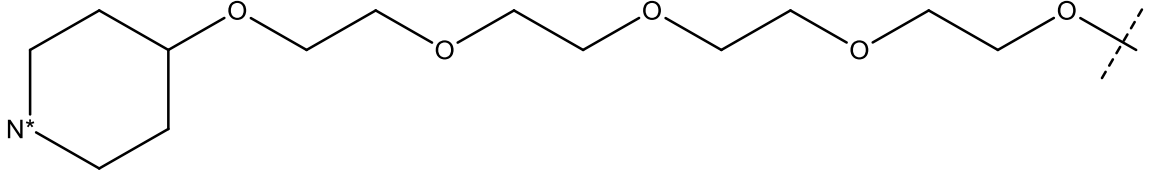
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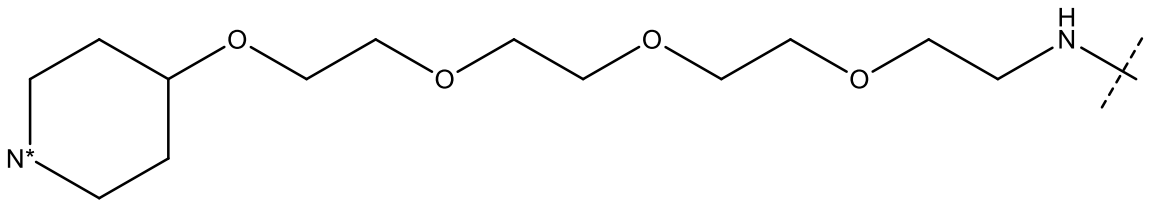
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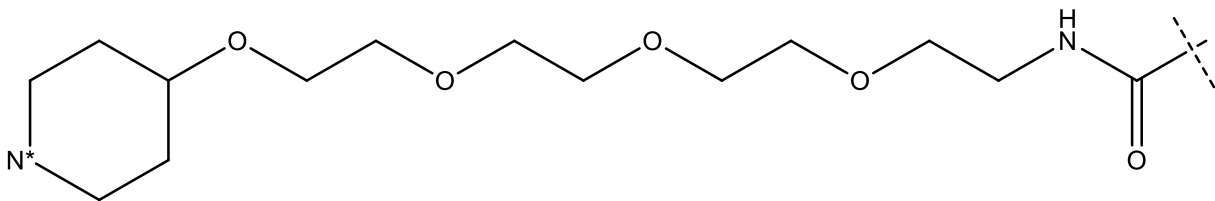
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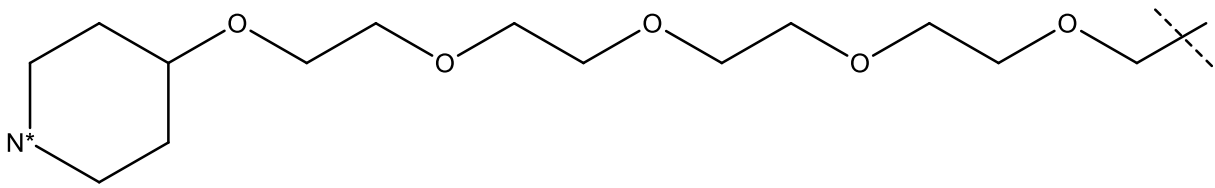
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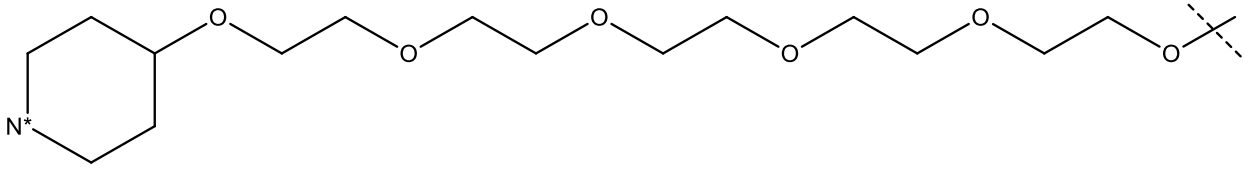
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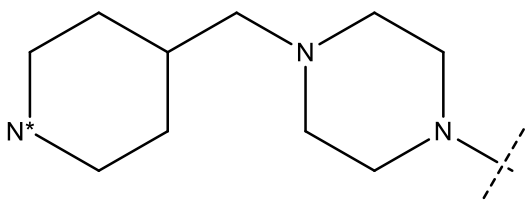
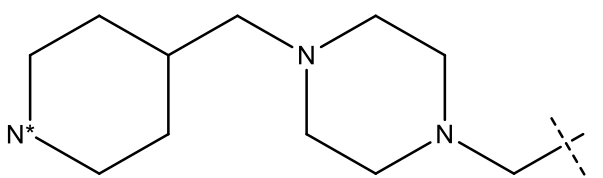
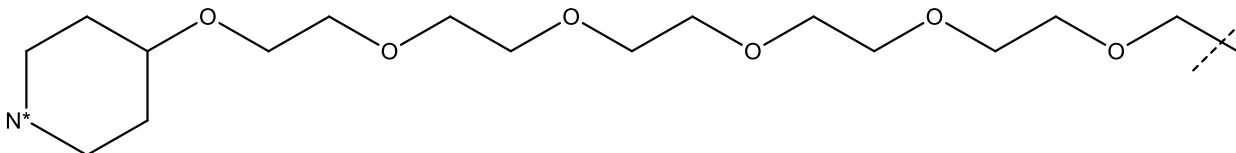
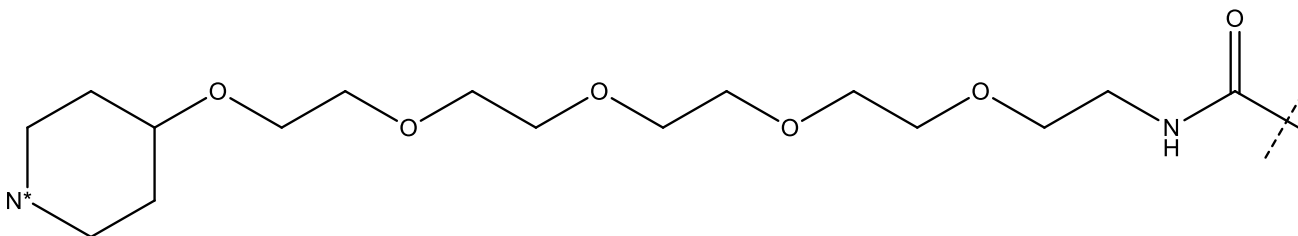
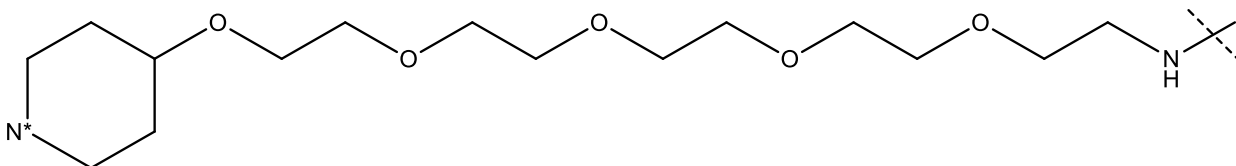
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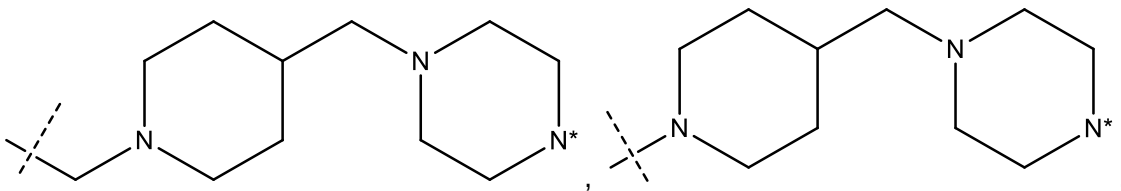
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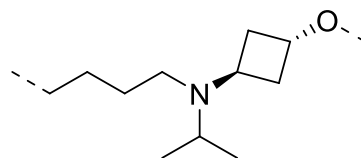
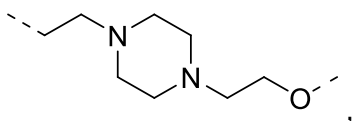
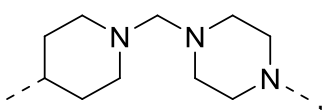
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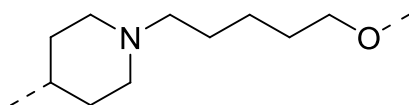
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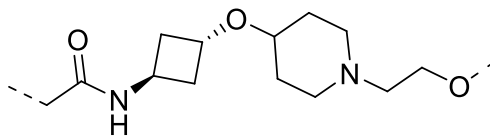
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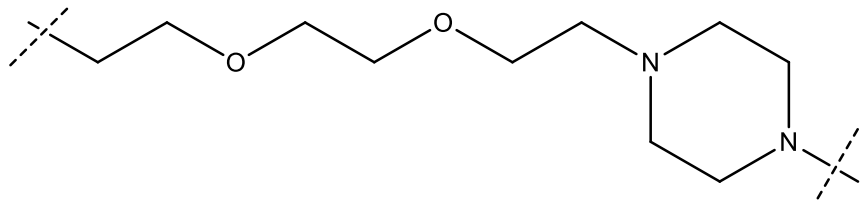
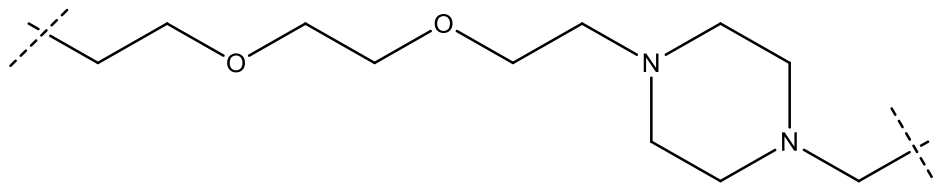
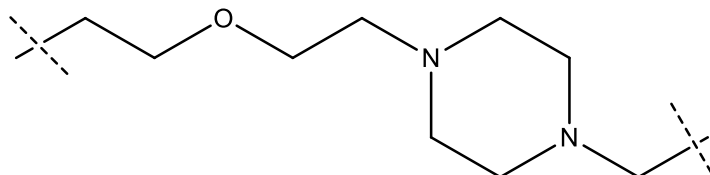
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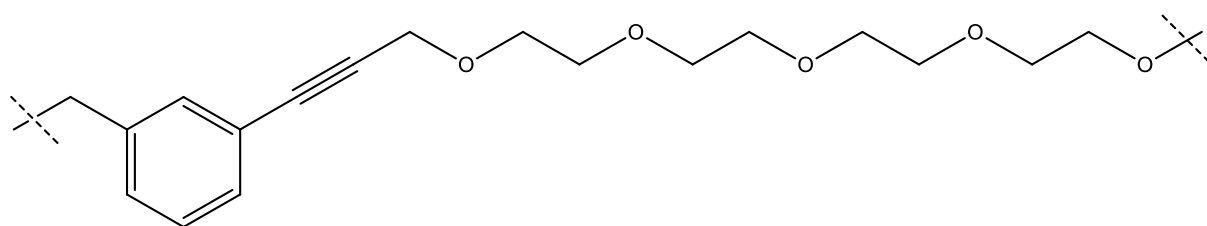


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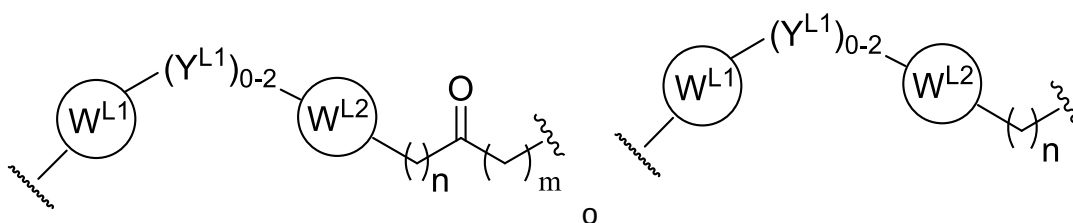


donde N* del heterocicloalquilo es compartido con el PTM.

8. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde L es un grupo polietileneoxi con 1 a 10 unidades de etilenglicol opcionalmente sustituido con arilo.

9. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde L es un alquilo C_{1-50} , 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. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde L es:



donde:

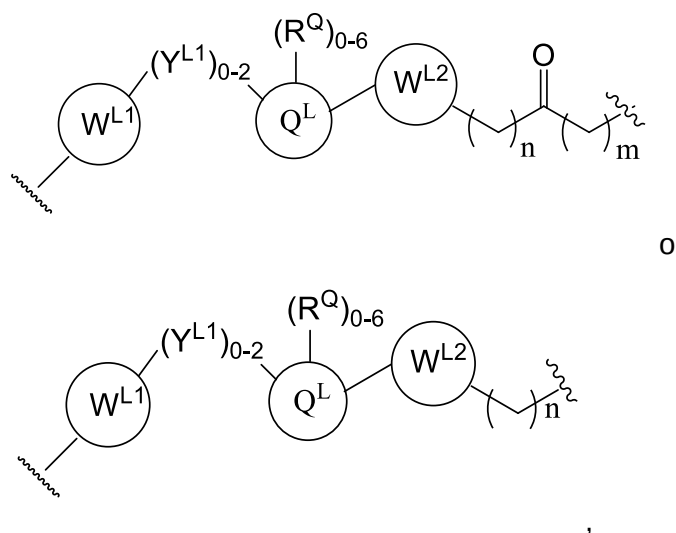
cada uno de W^{L1} y W^{L2} de manera independiente está ausente, o es un anillo de 4-8 miembros con 0-4 heteroátomos, opcionalmente sustituido con RQ, cada RQ es de manera independiente un H, halo, OH, CN, CF_3 , alquilo C_{1-6} opcionalmente sustituido, alcoxi C_{1-6} opcionalmente sustituido, o 2 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;

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

n es 0-10; y

 indica el punto de unión a PTM o ULM.

11. El compuesto bifuncional de acuerdo con cualquiera de las reivindicaciones 1 a 5, donde 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 uno o más átomos de C se remplazan con O o N, alqueno C_{1-6} y opcionalmente uno o más átomos de C se remplazan con O, alquino C_{1-6} y opcionalmente uno o más átomos de C se remplazan con O, bicíclico, biarilo, biheteroarilo o biheterocíclico, cada uno opcionalmente sustituido con R^Q , 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 , $NR^{Y1}R^{Y2}$, 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^{YL1} , O, S, NR^{YL2} , $CR^{YL1}R^{YL2}$, C=O, C=S, SO, SO_2 , alquilo C_{1-6} opcionalmente sustituido y opcionalmente uno o más átomos de C se remplazan 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 , 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;

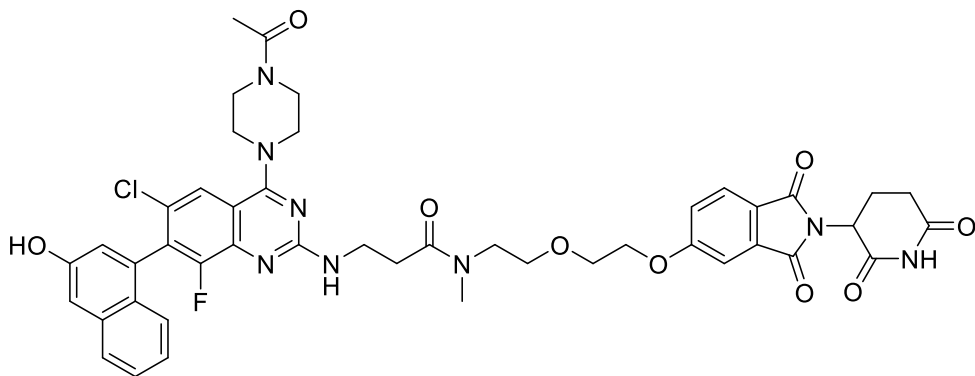
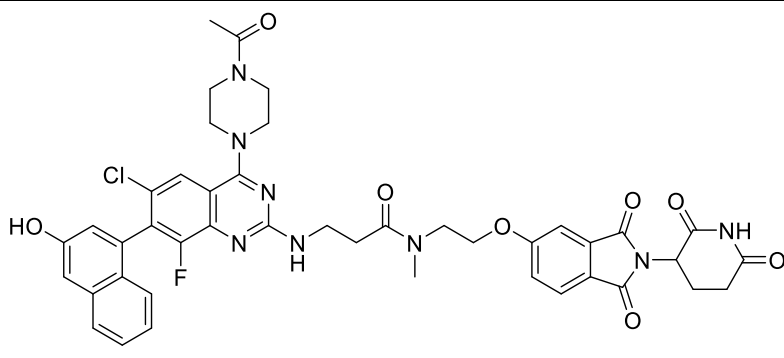
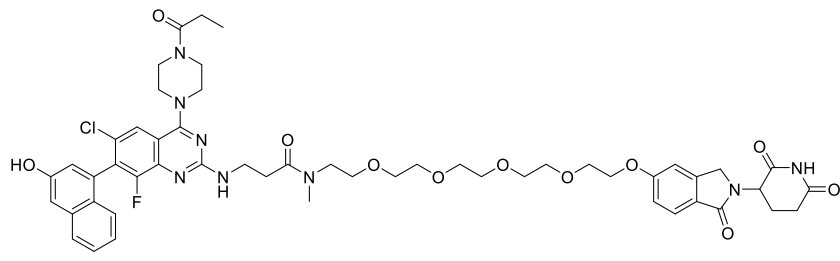
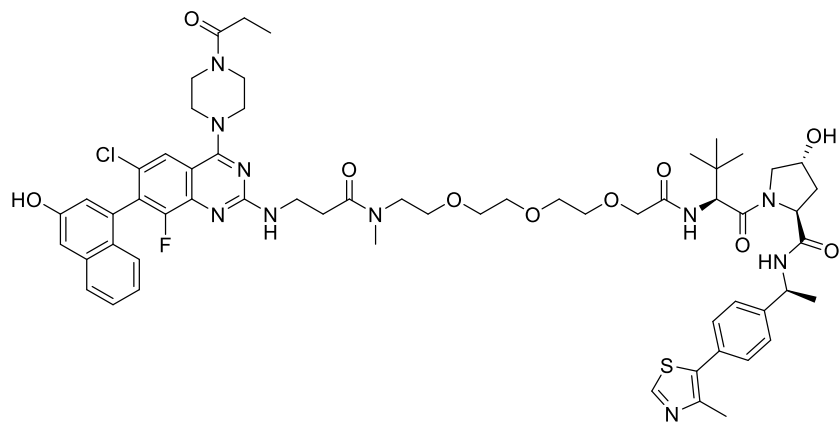
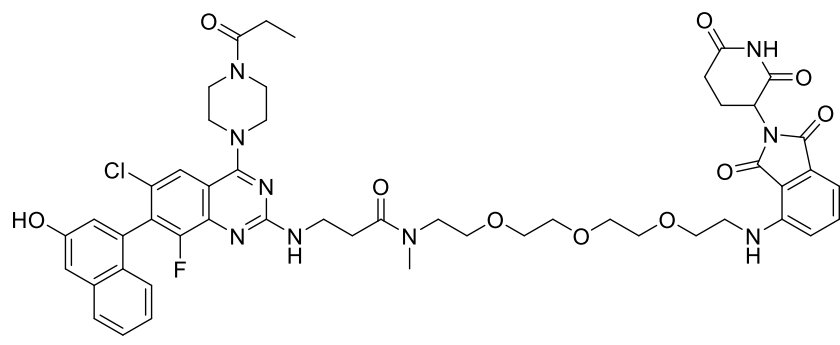
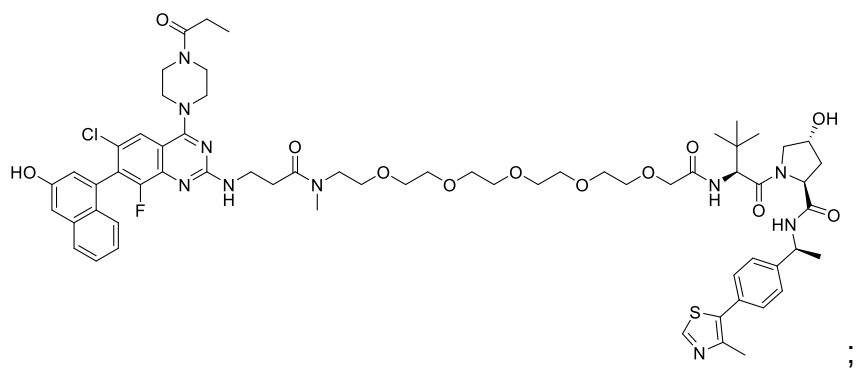
R^{YL1} y R^{YL2} son cada uno de manera independiente H, OH, alquilo C_{1-6} opcionalmente sustituido por 1 o más halo o alcóxilo C_{1-6} , o R^1 , tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos;

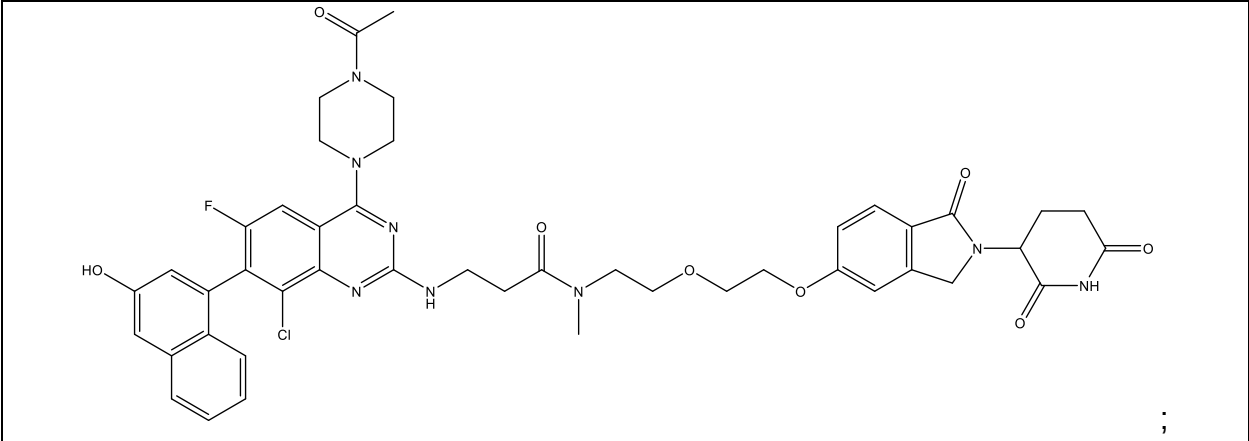
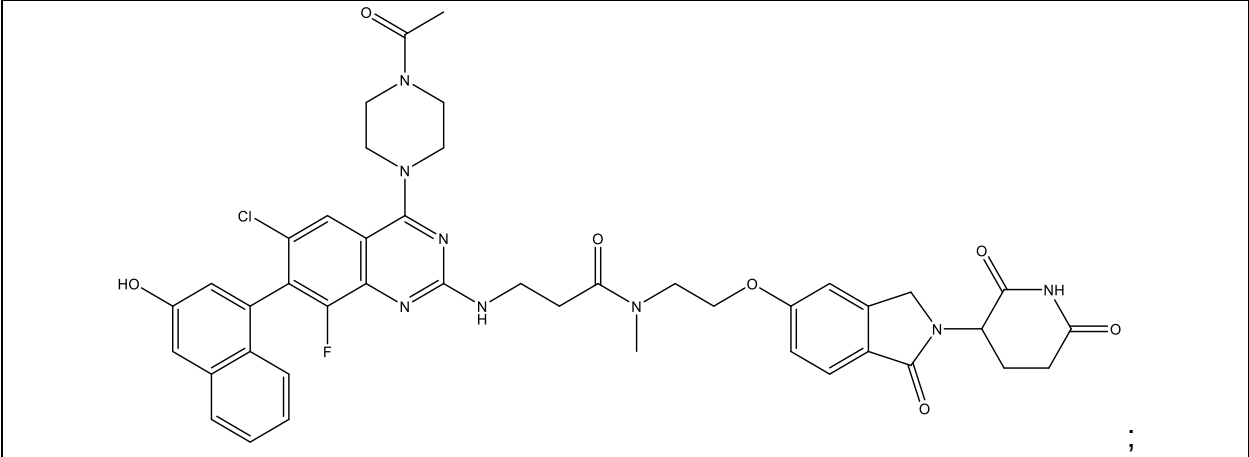
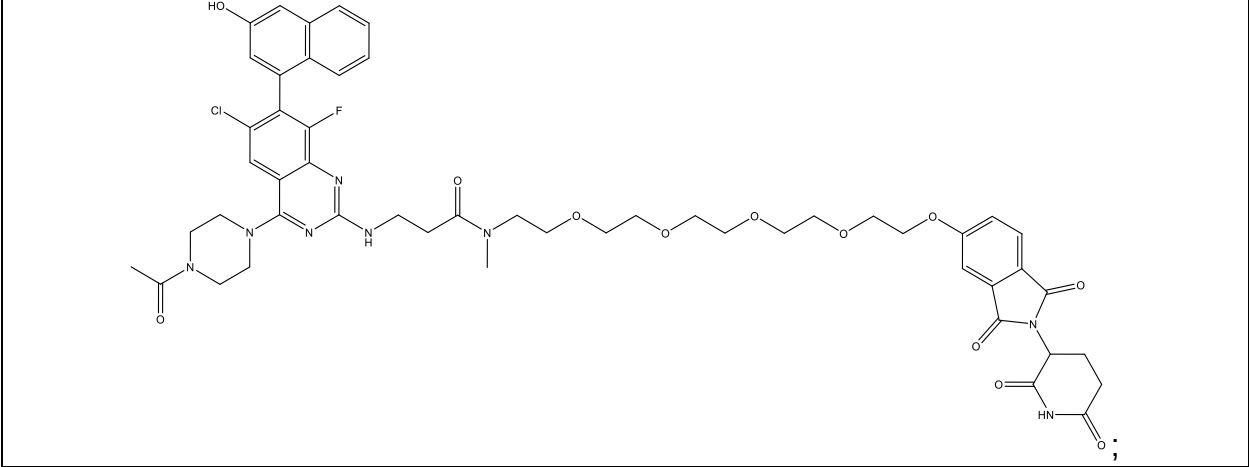
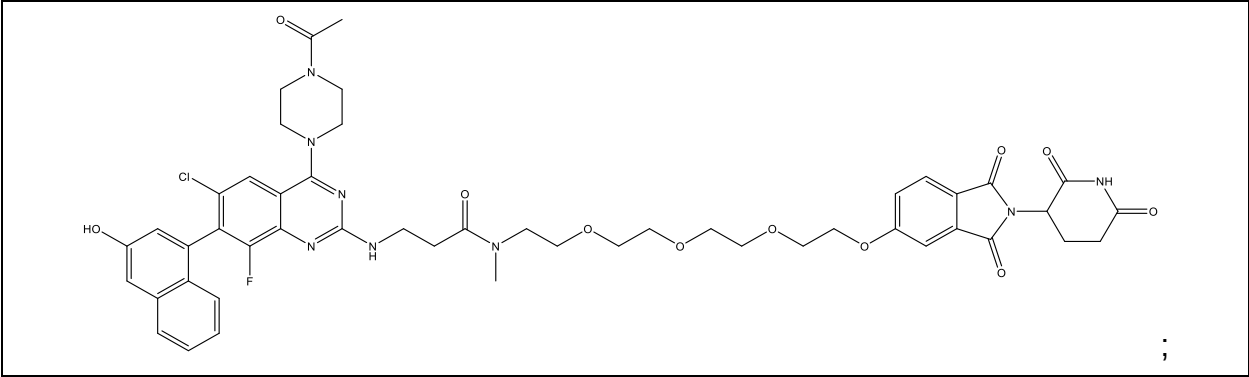
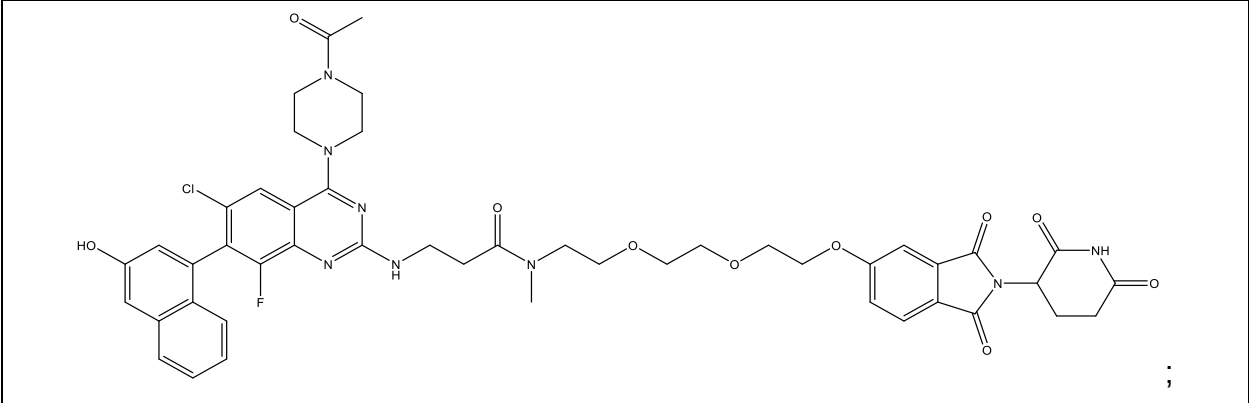
n es 0, 2, 3, 4, 5, 6, 7, 8, 9, o 10; y

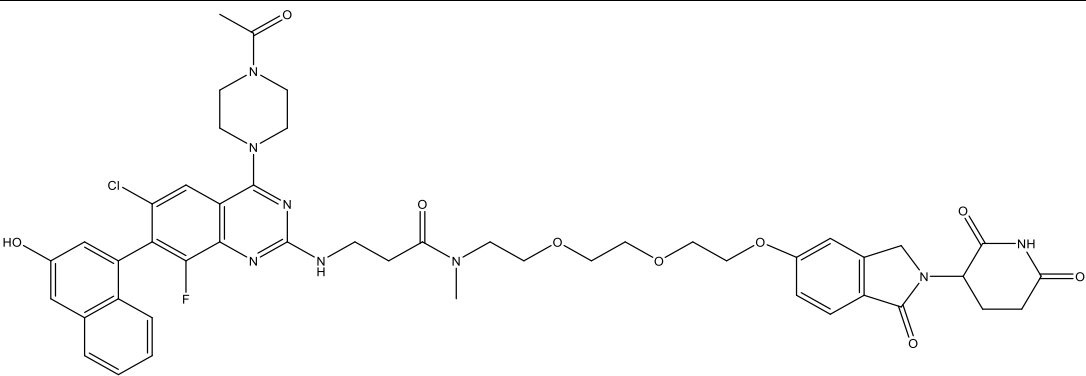
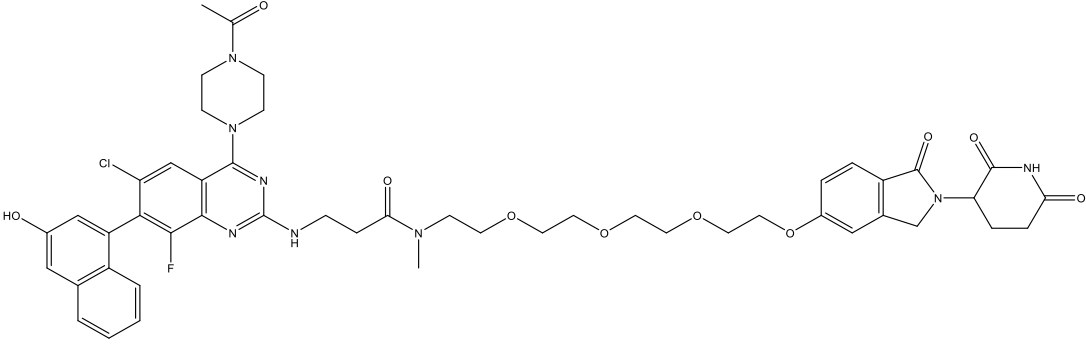
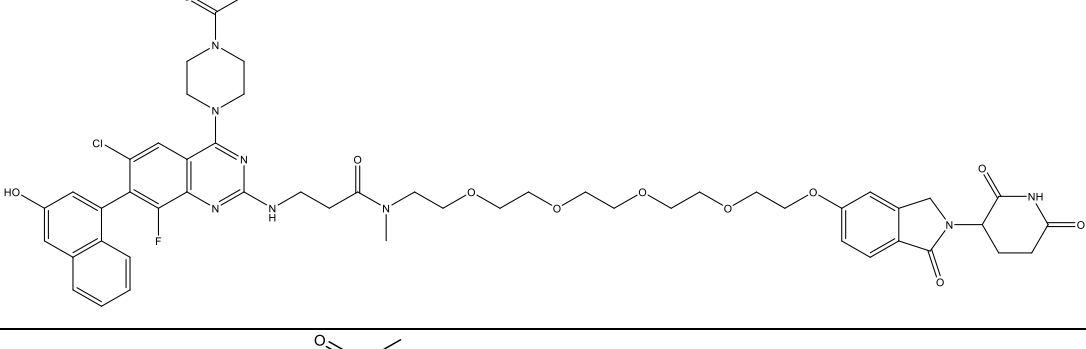
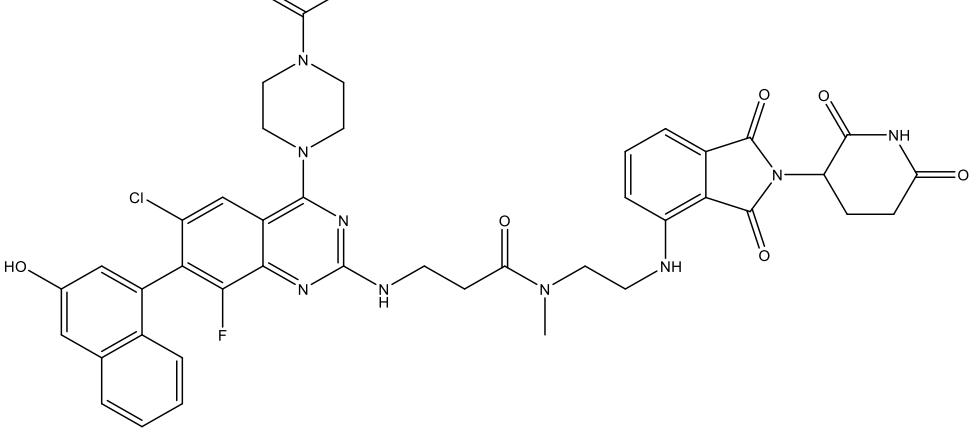
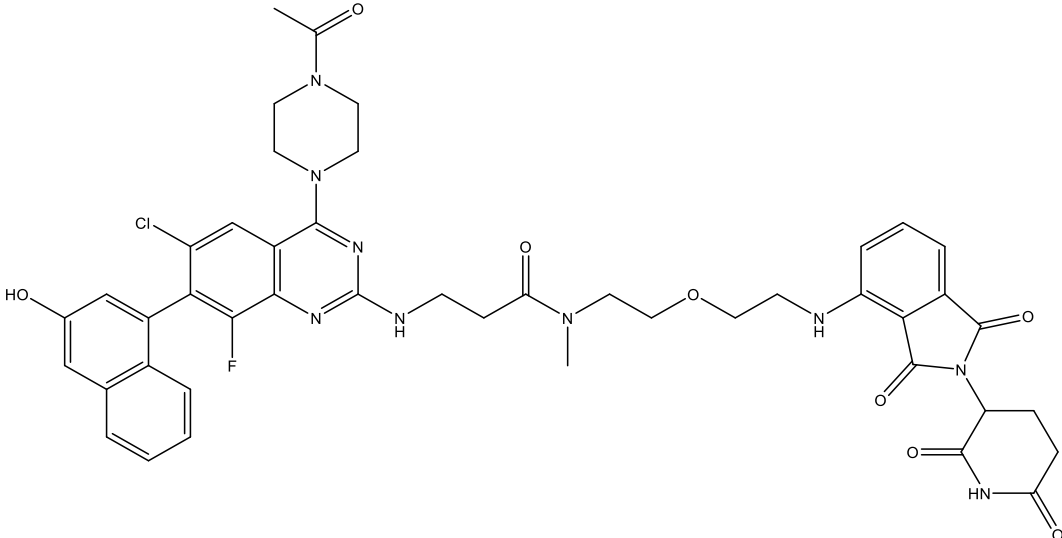
 indica el punto de unión a los restos PTM o ULM.

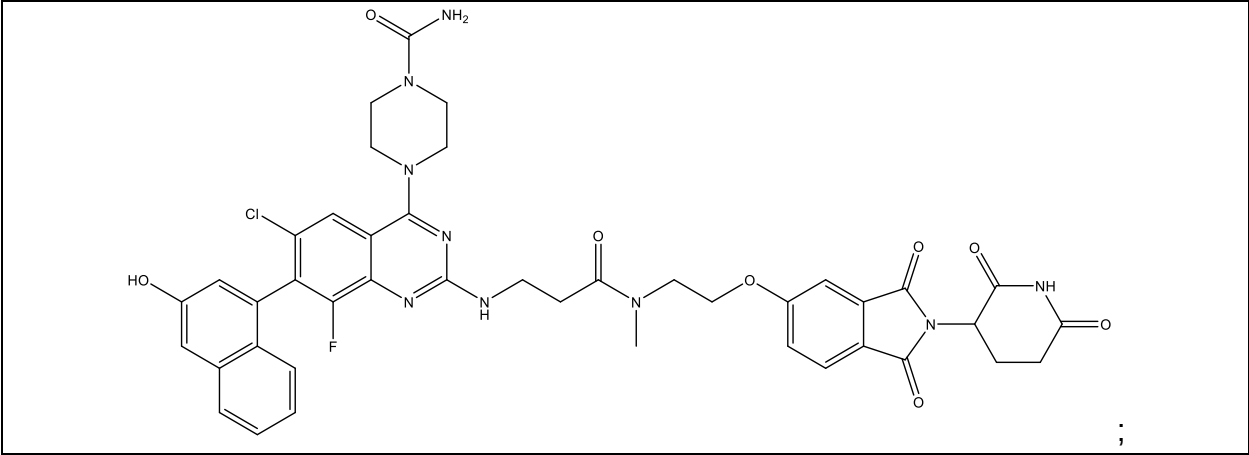
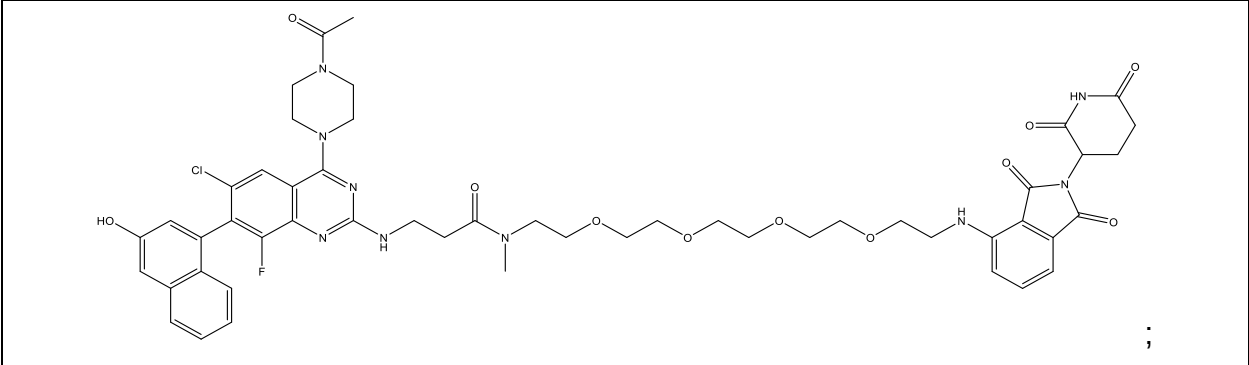
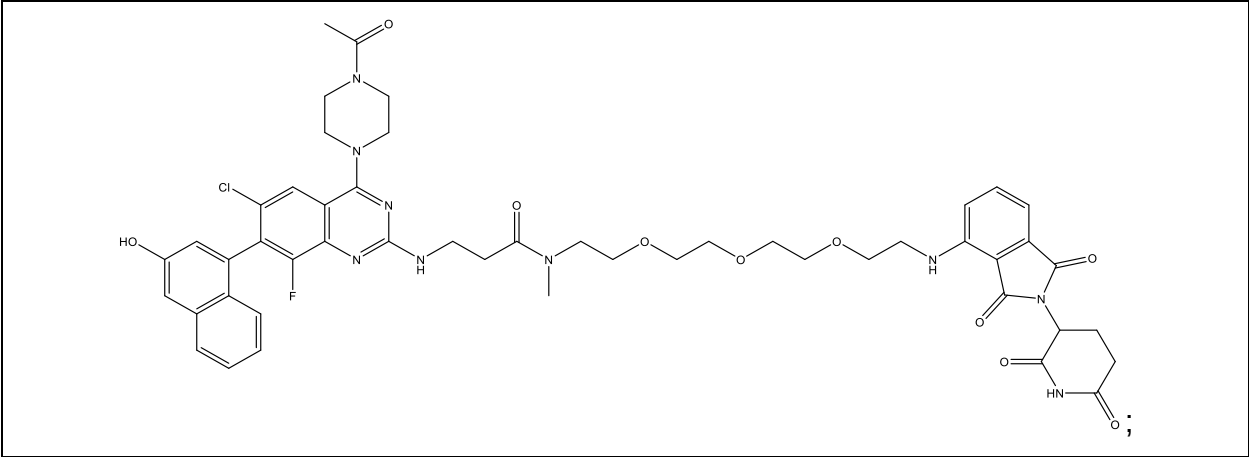
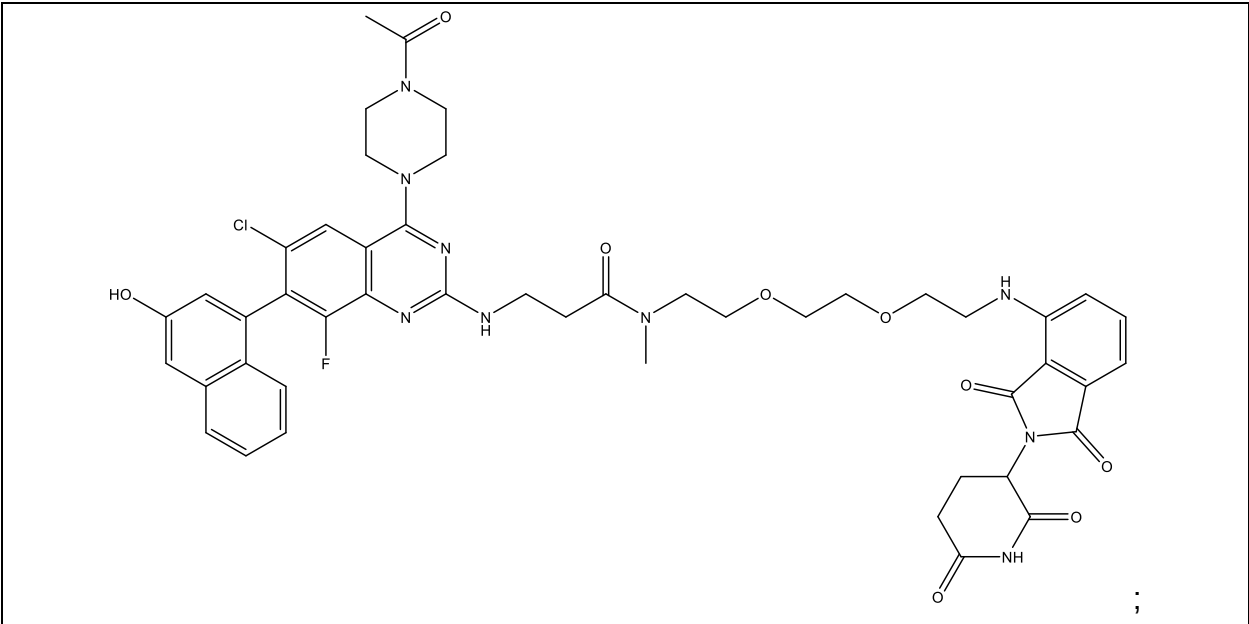
12. Un compuesto bifuncional seleccionado de entre:

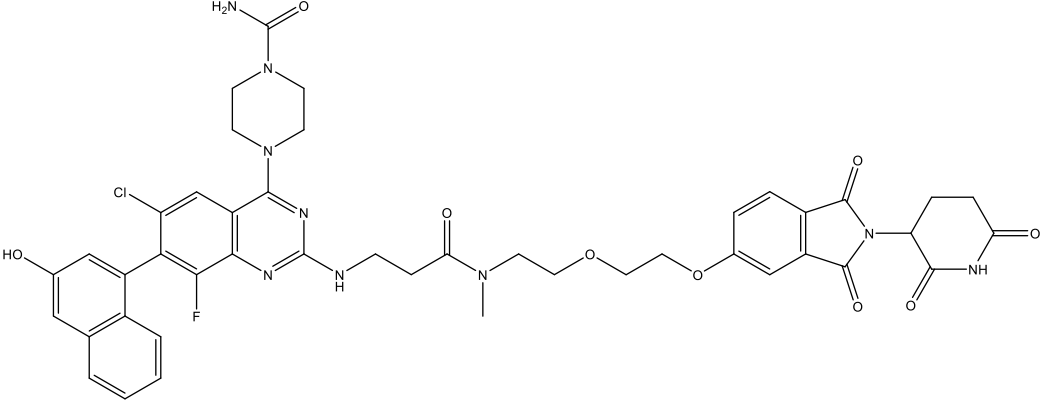
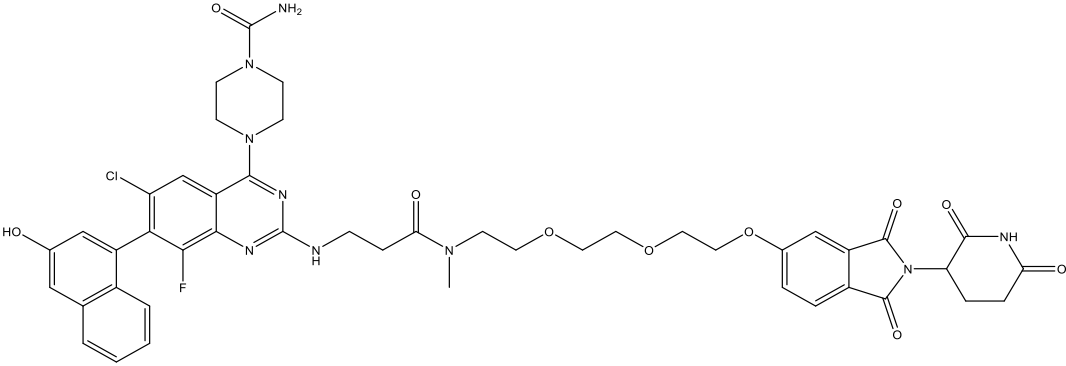
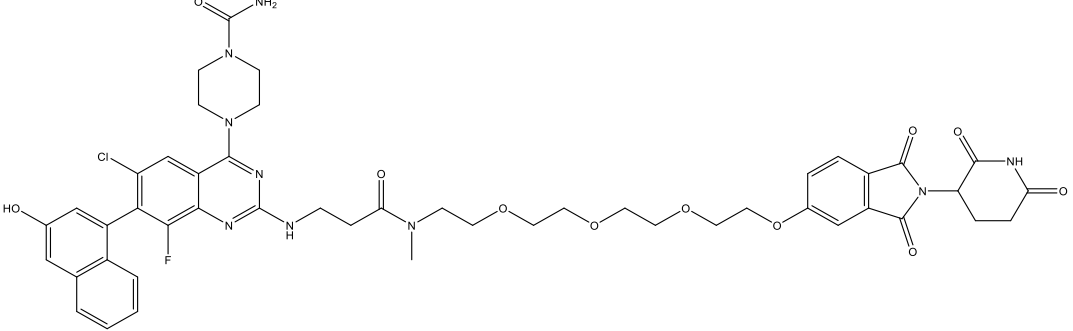
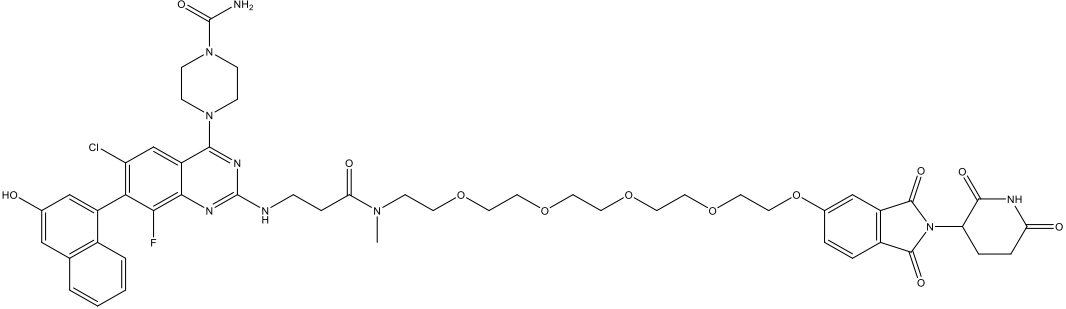
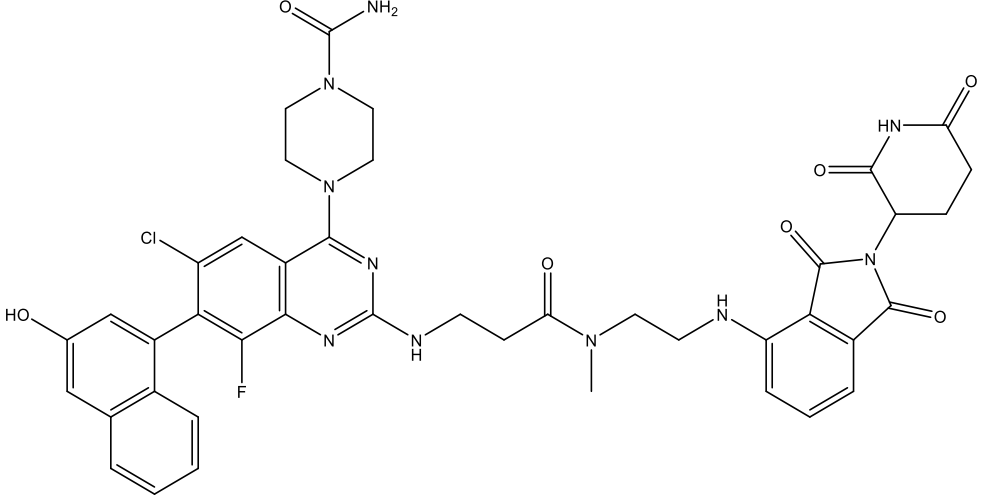
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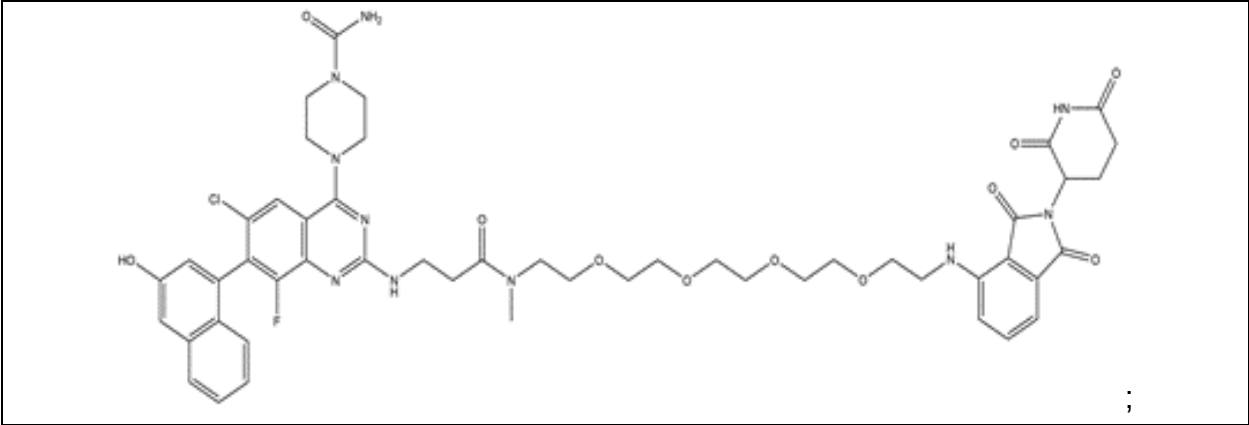
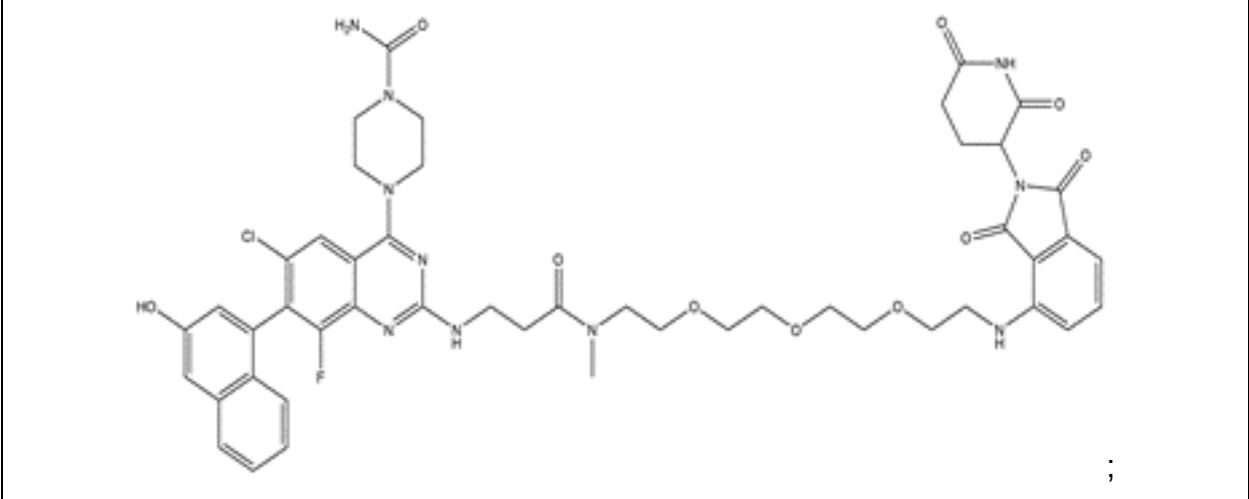
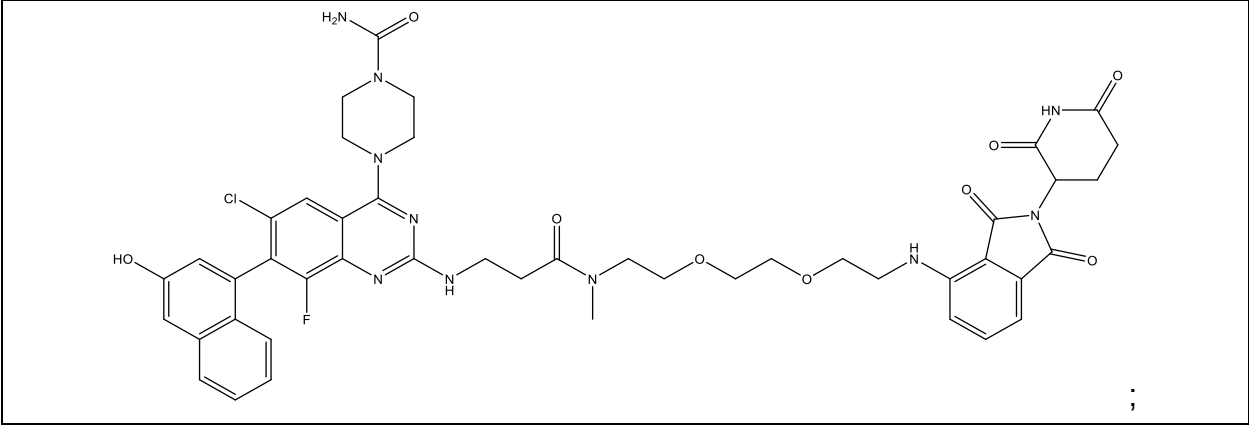
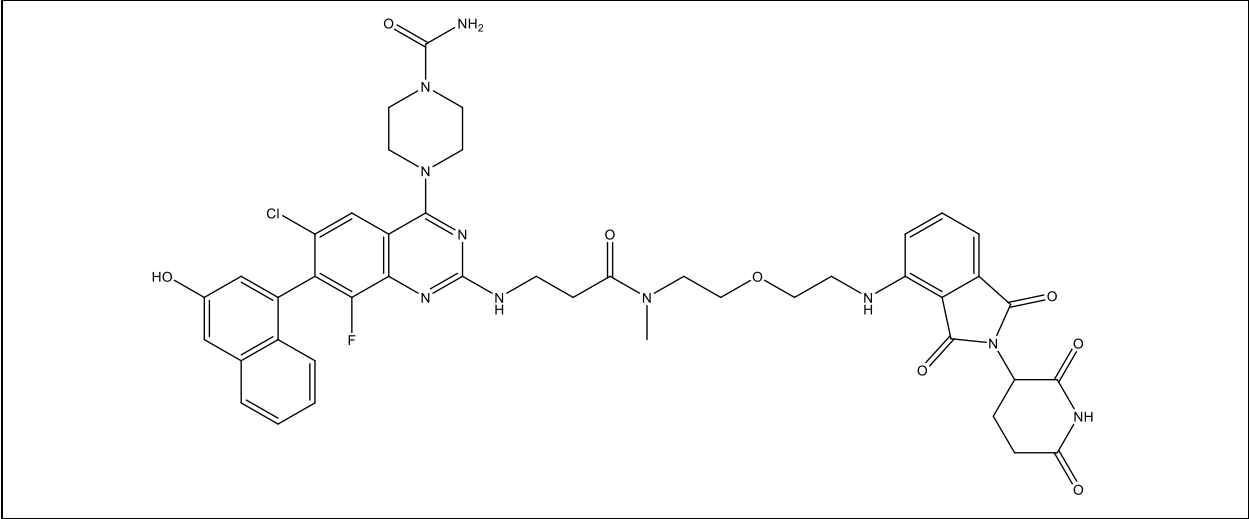


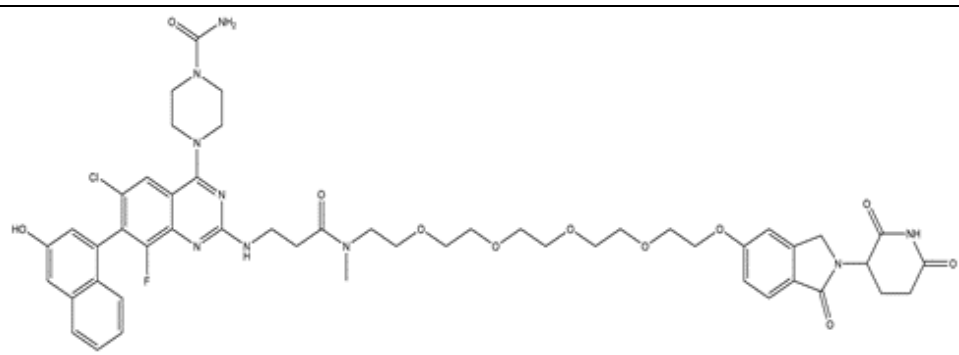
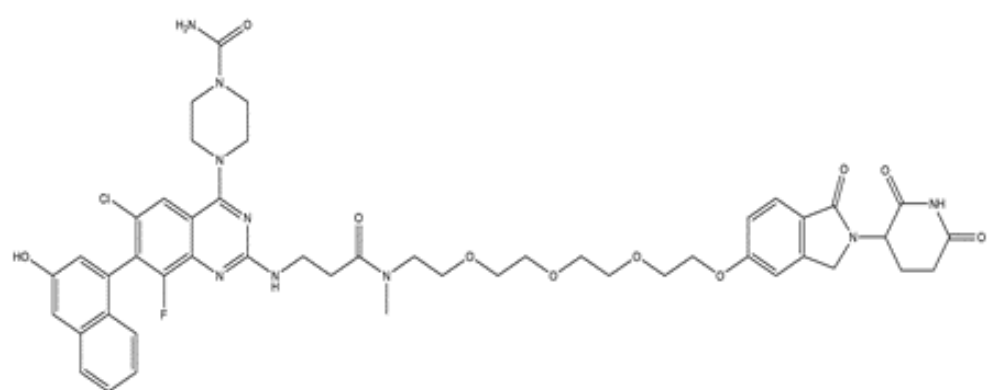
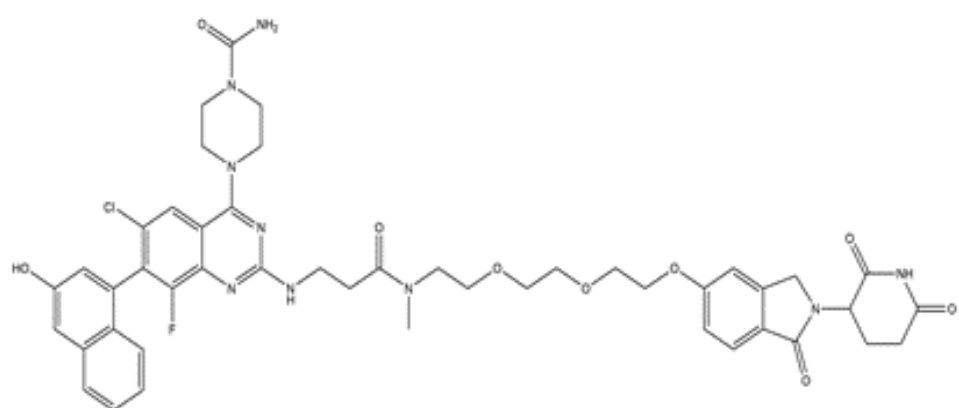
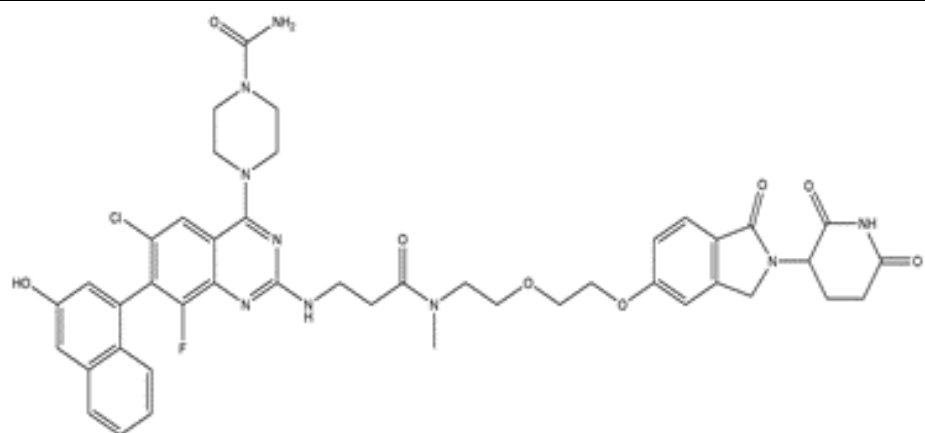
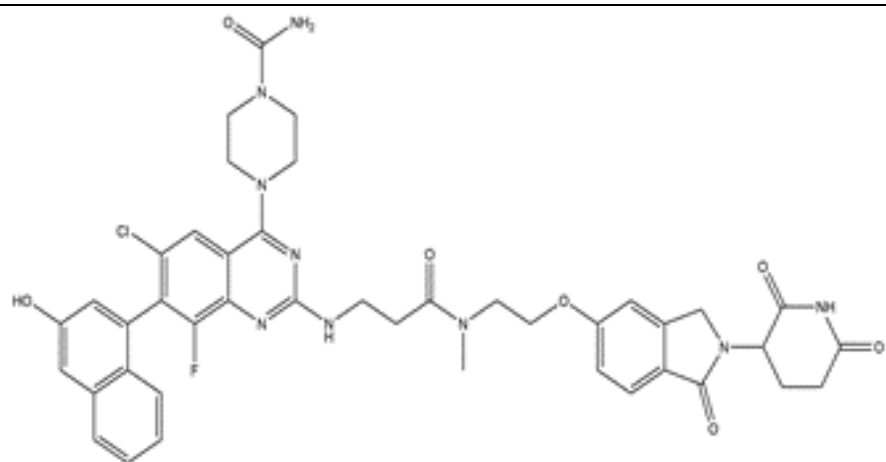


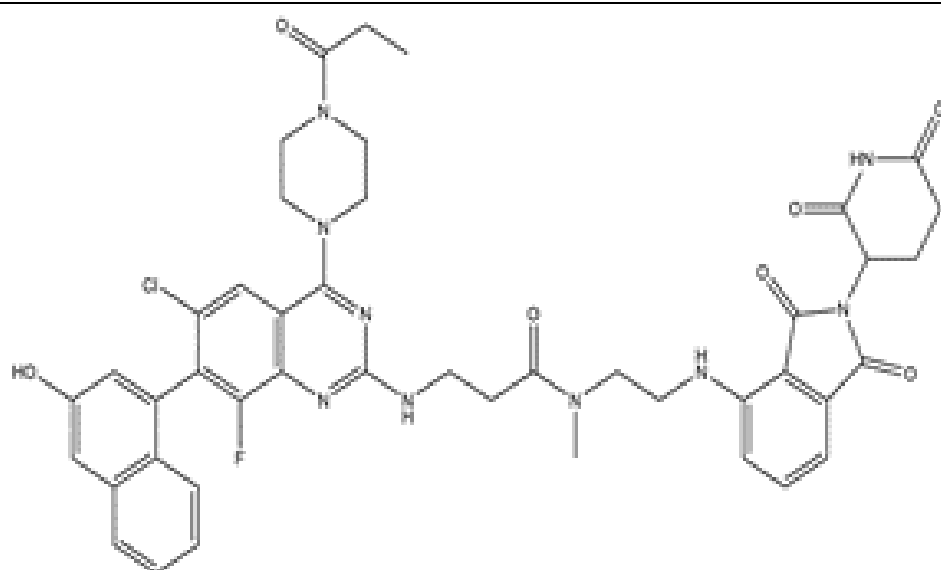
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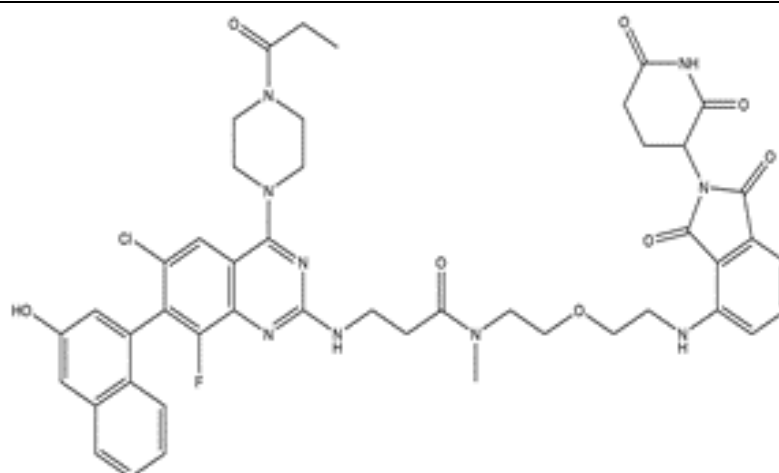
 Chemical structure 1: A complex molecule featuring a naphthalen-1-ol-4-yl group, a 2-chloro-6-fluoroquinazolin-4-yl group, a 4-aminobenzamide group, a 3-(dimethylamino)propan-1-yl group, a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl) group, and a 1-(2,6-dioxo-3,4-dihydro-1H-pyrimidin-5-yl) group.	1
 Chemical structure 2: Similar to structure 1, but with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group instead of a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl) group.	2
 Chemical structure 3: Similar to structure 1, but with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group instead of a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl) group.	3
 Chemical structure 4: Similar to structure 1, but with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group instead of a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl) group.	4
 Chemical structure 5: Similar to structure 1, but with a 2,2,6,6-tetramethyl-1,3-dioxane-5-yl group instead of a 2-(2,2,6,6-tetramethyl-1,3-dioxane-5-yl) group.	5



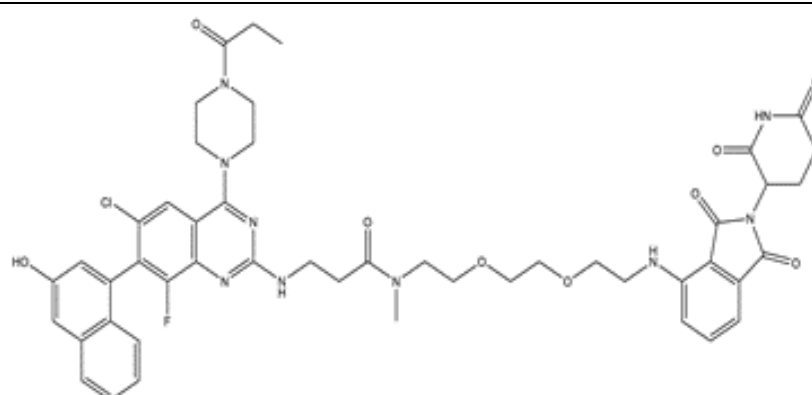




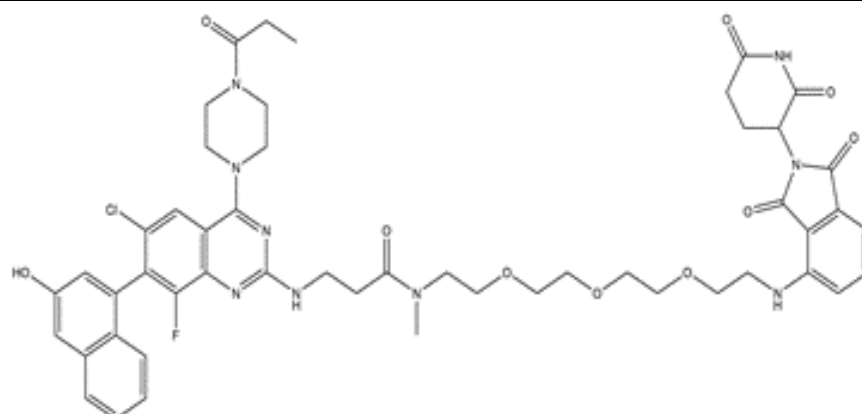
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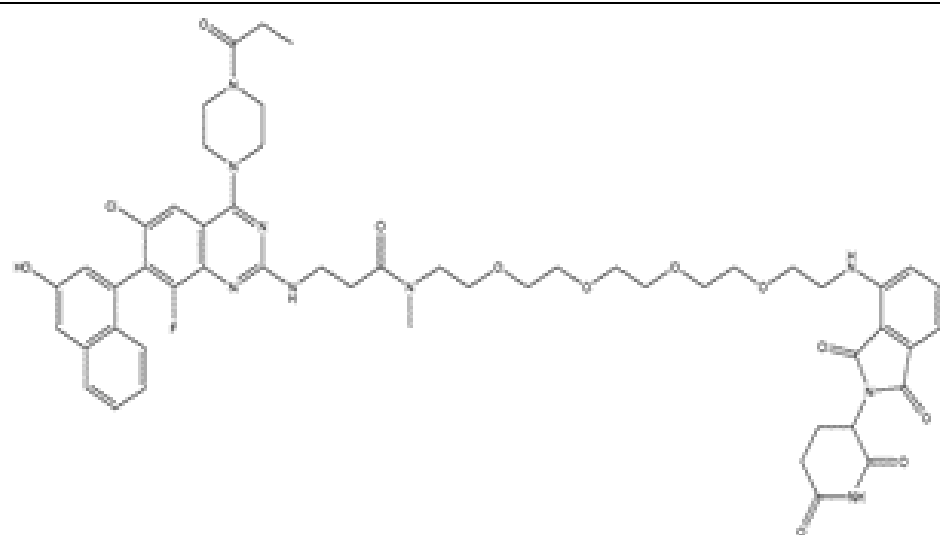
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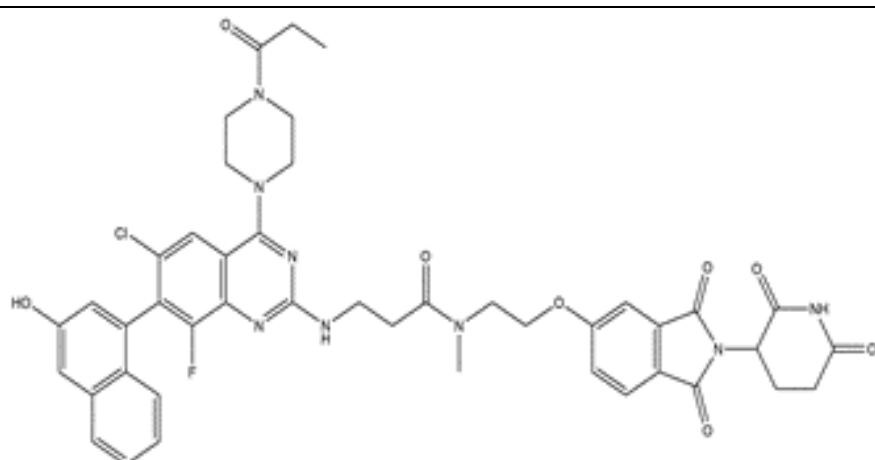
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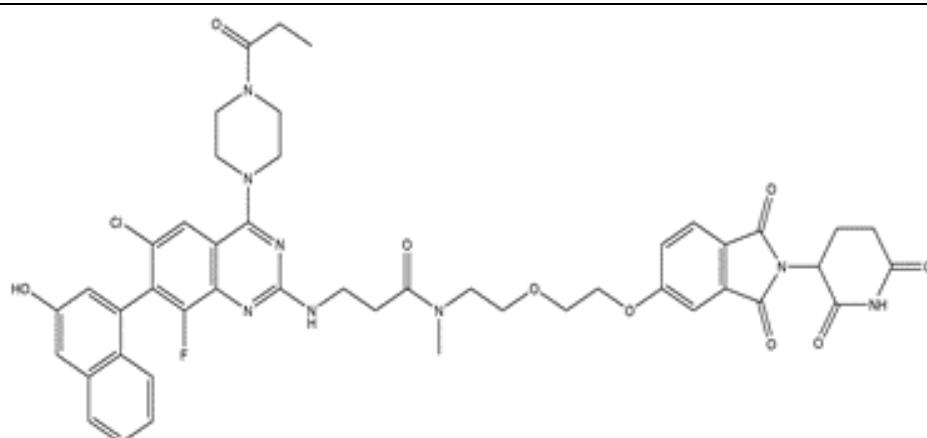
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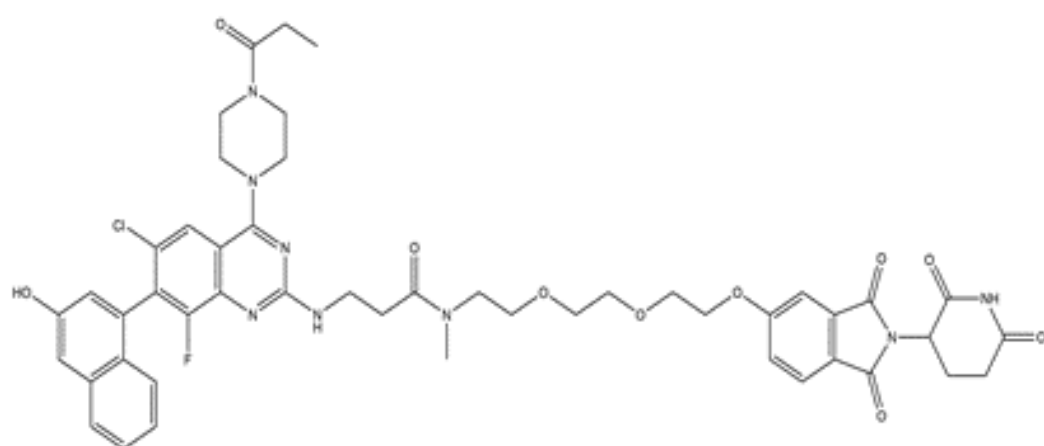
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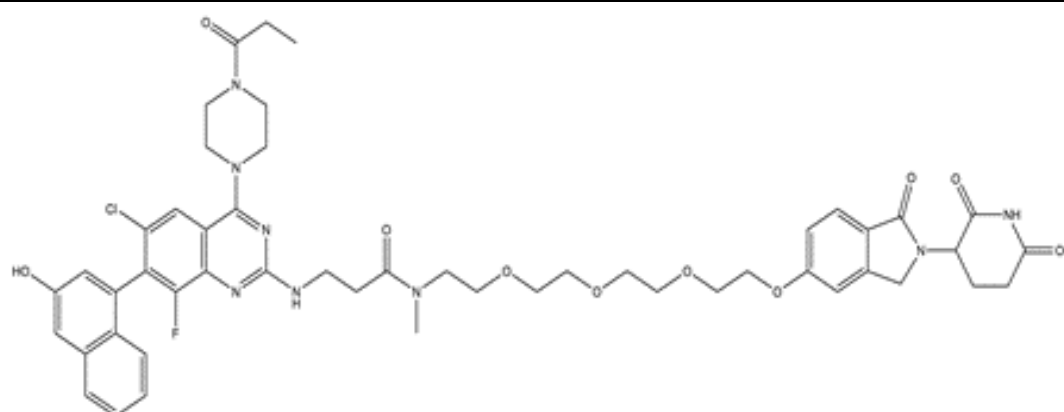
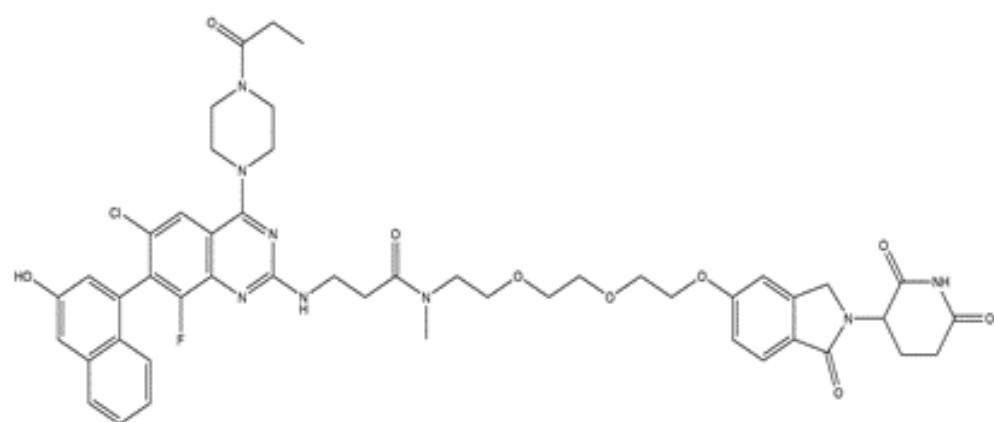
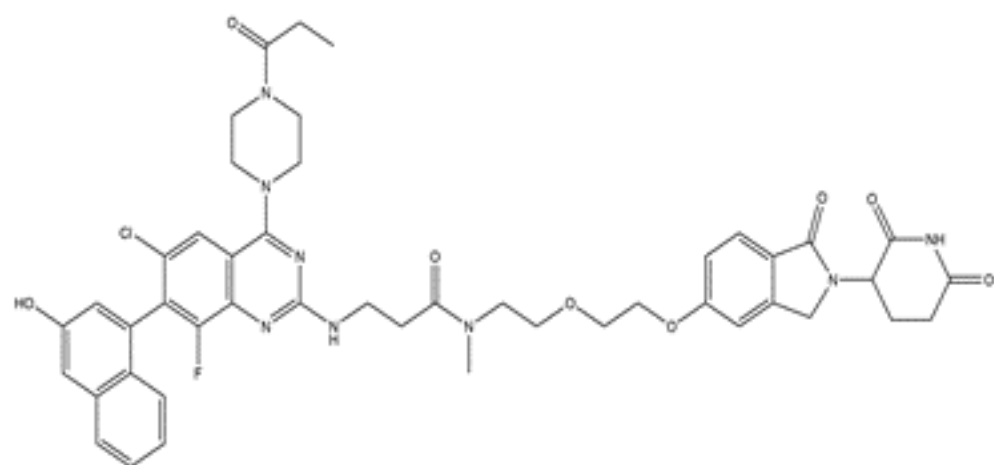
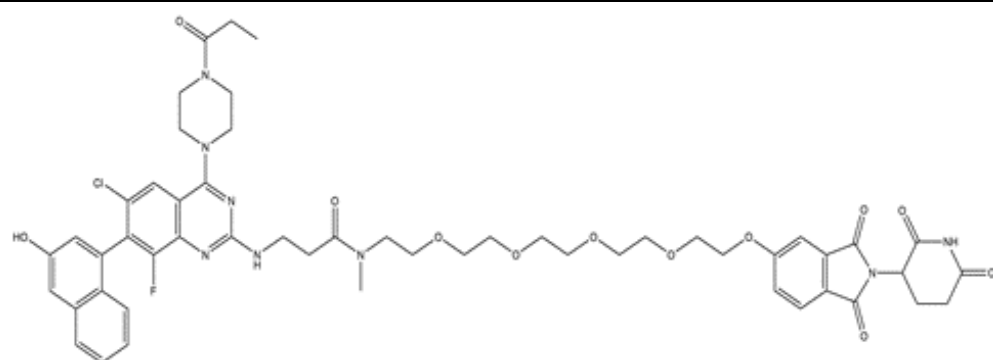
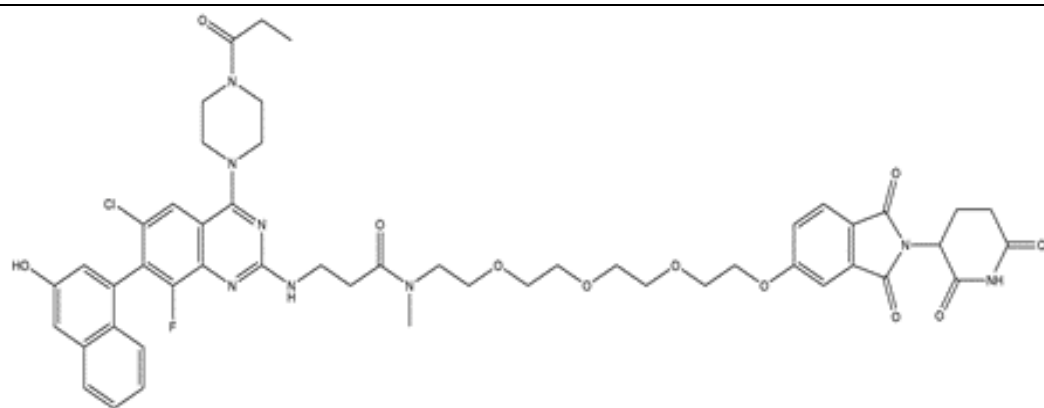
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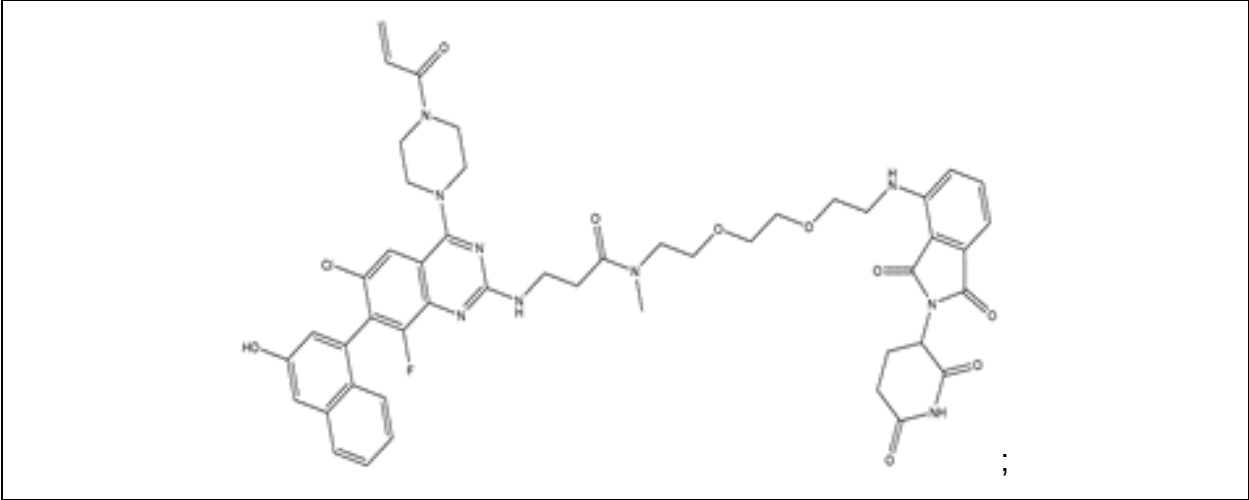
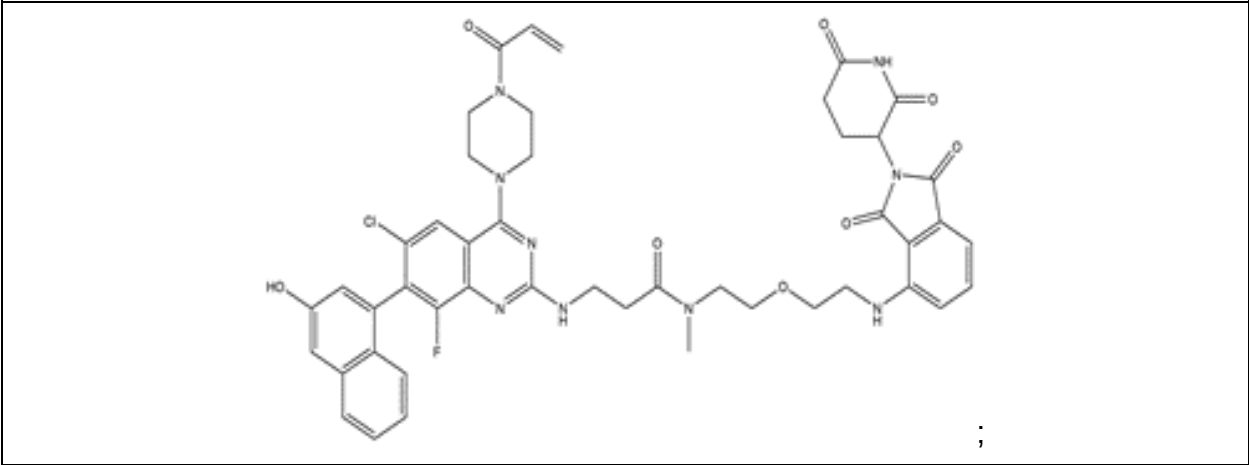
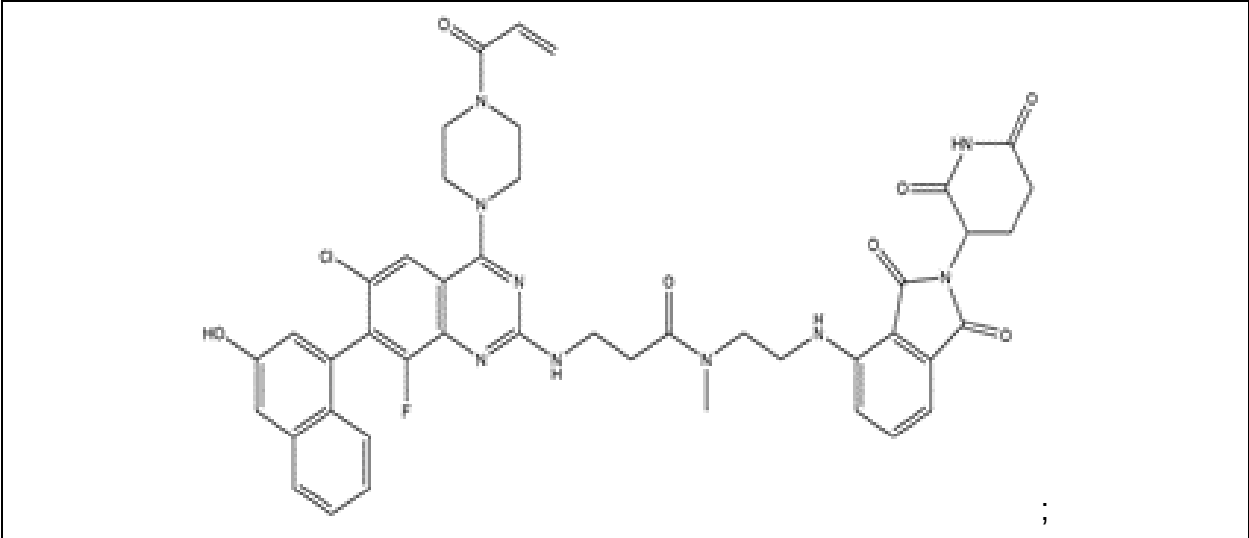
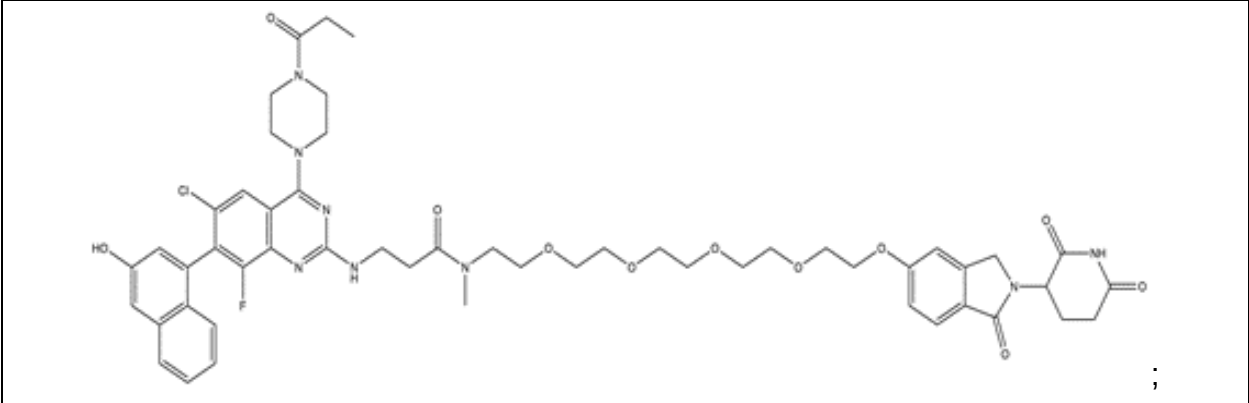


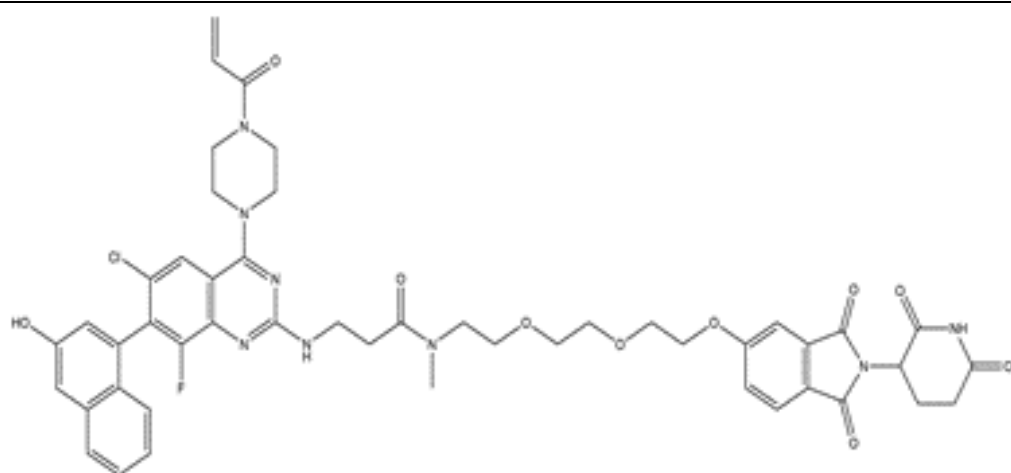
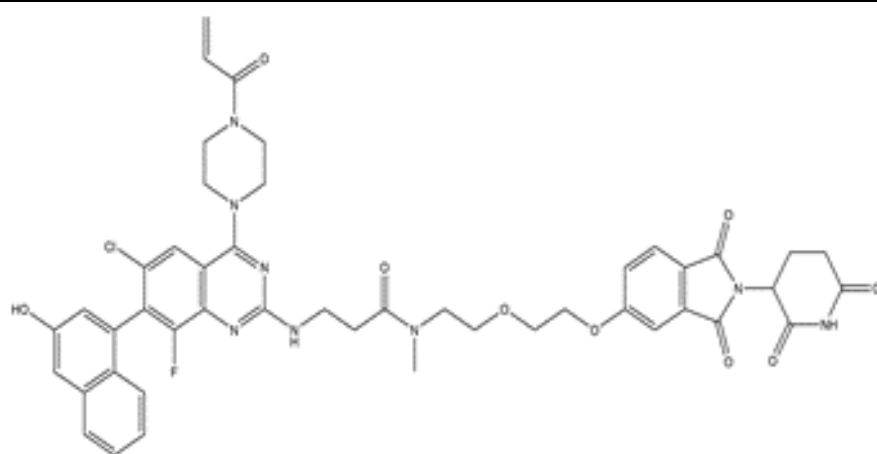
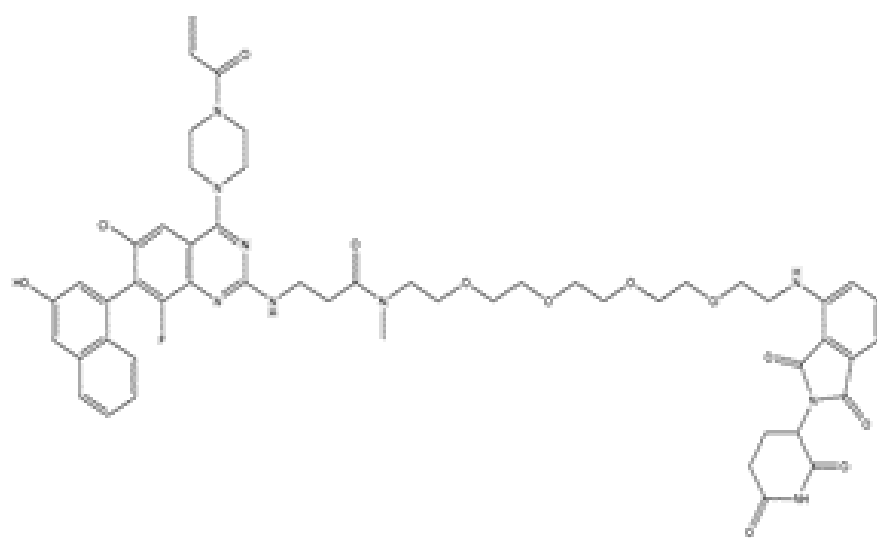
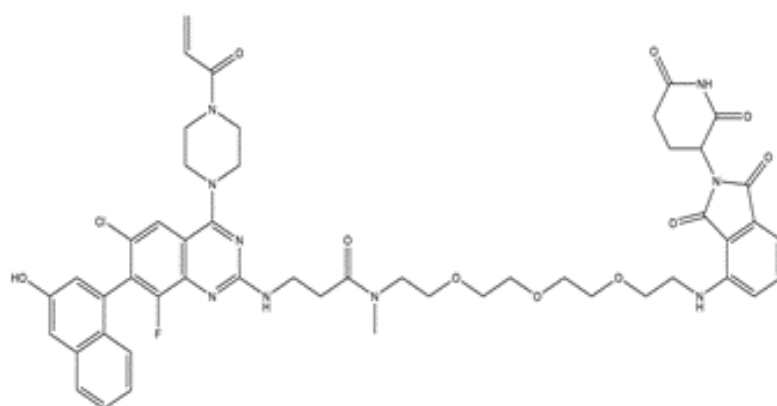
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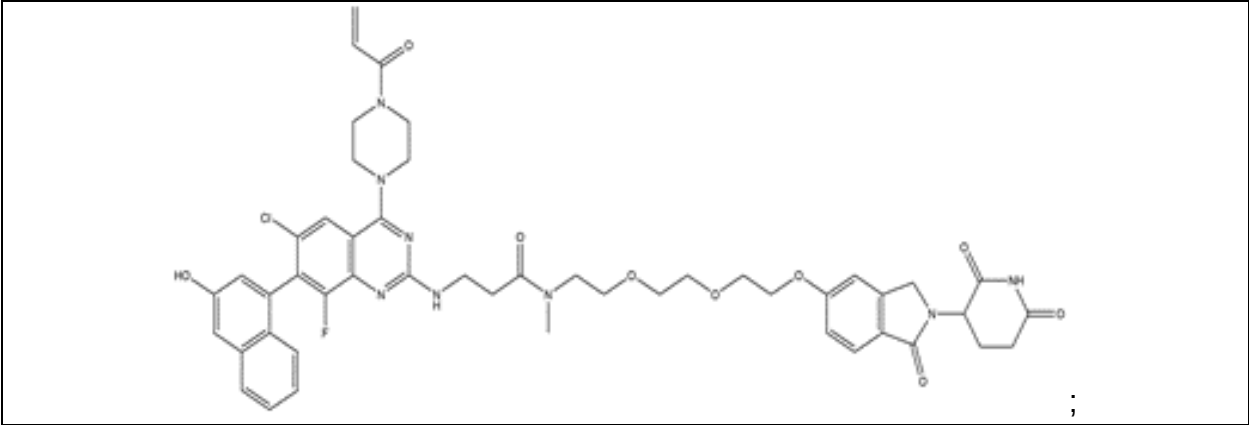
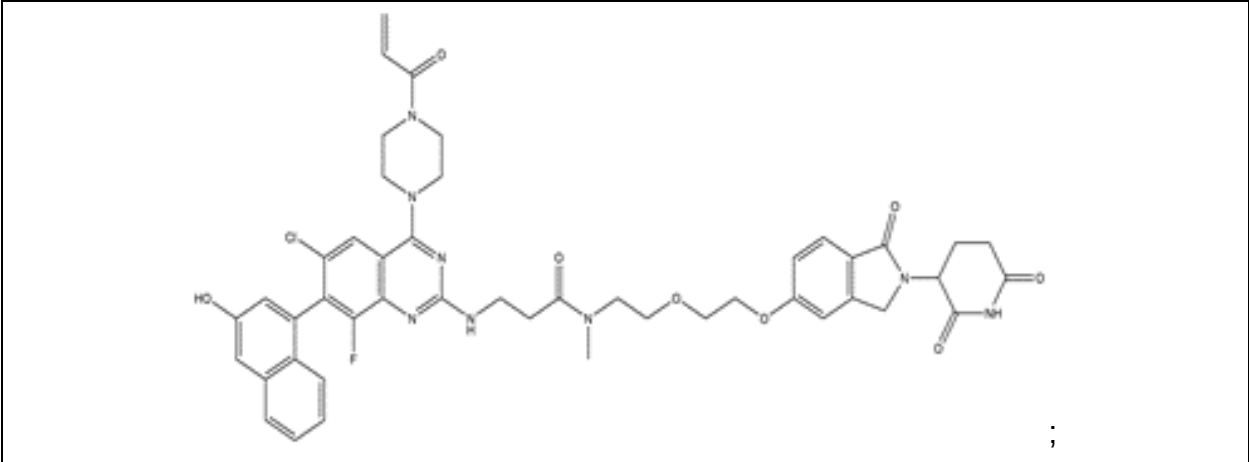
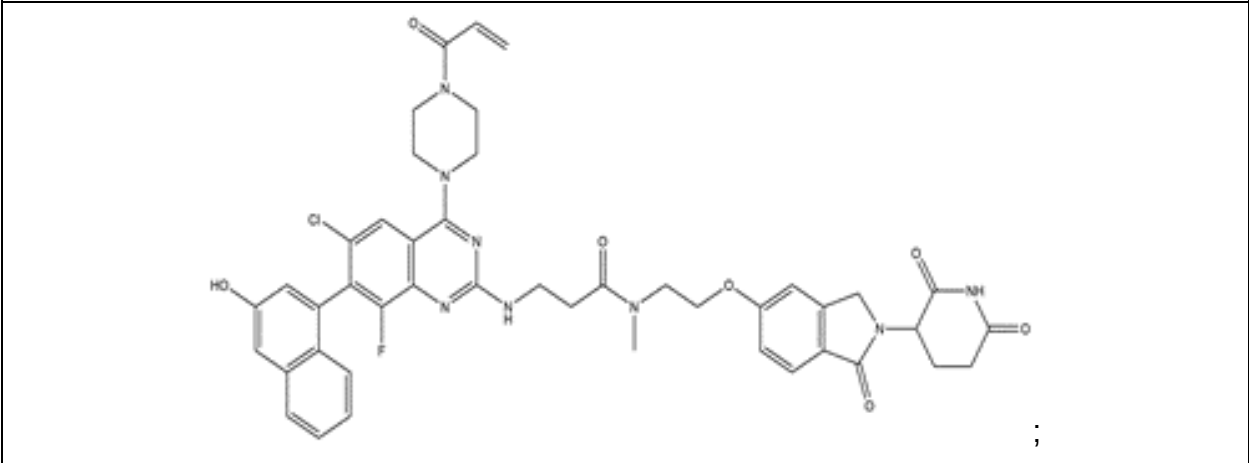
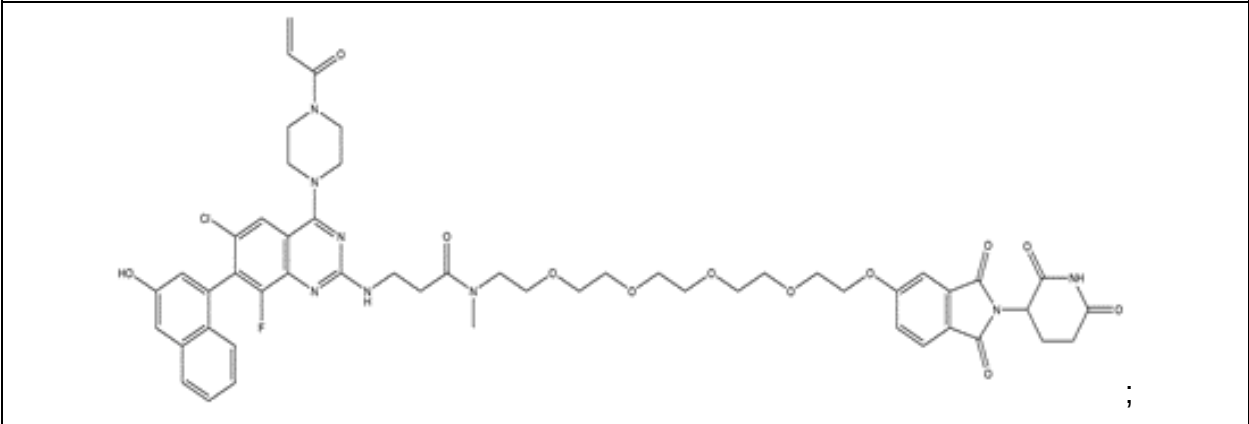
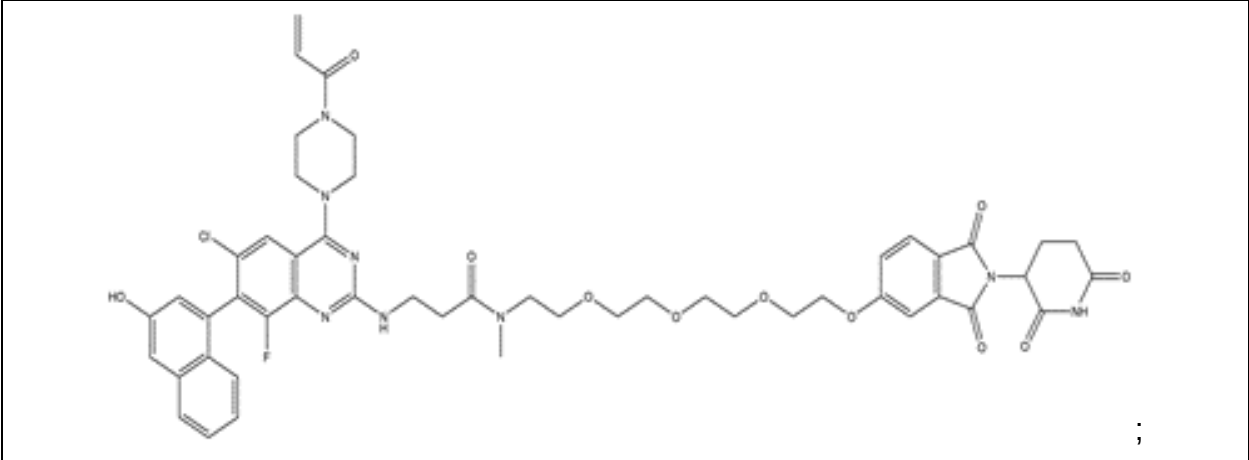


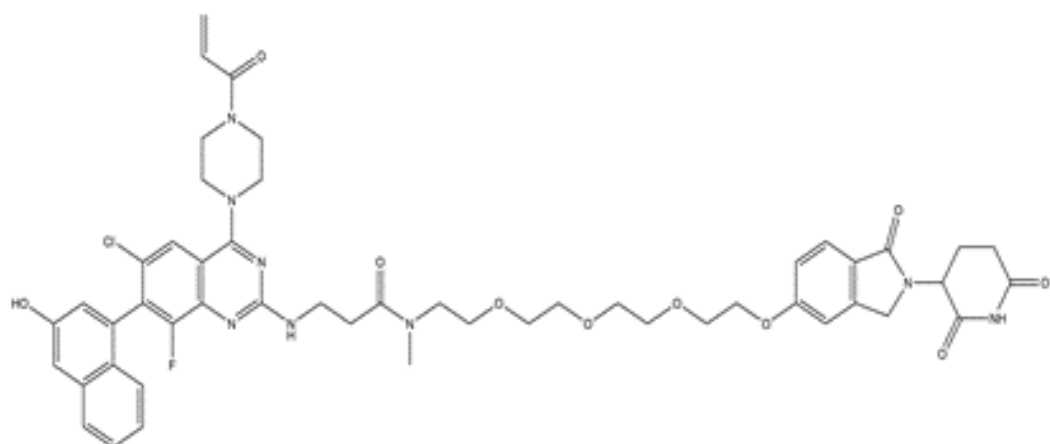
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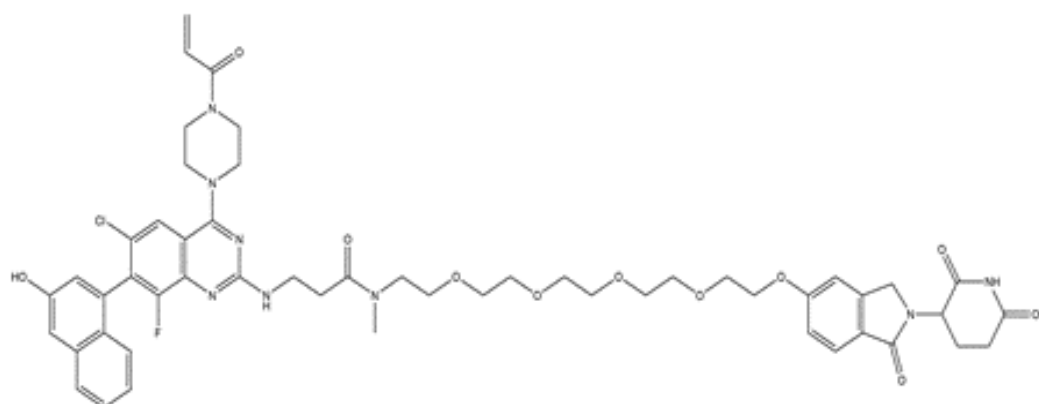




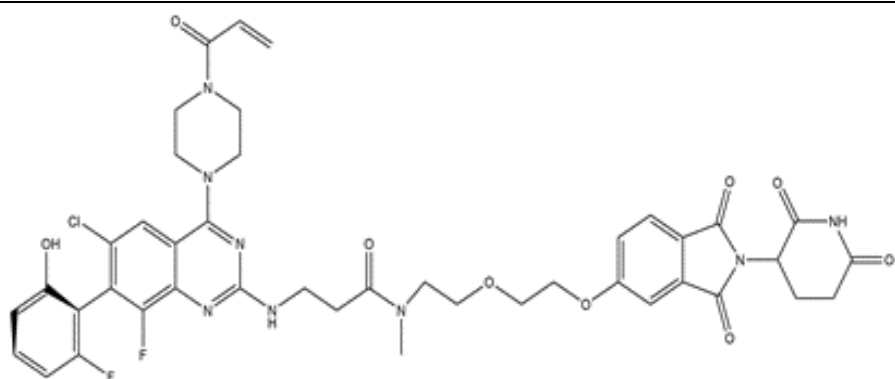




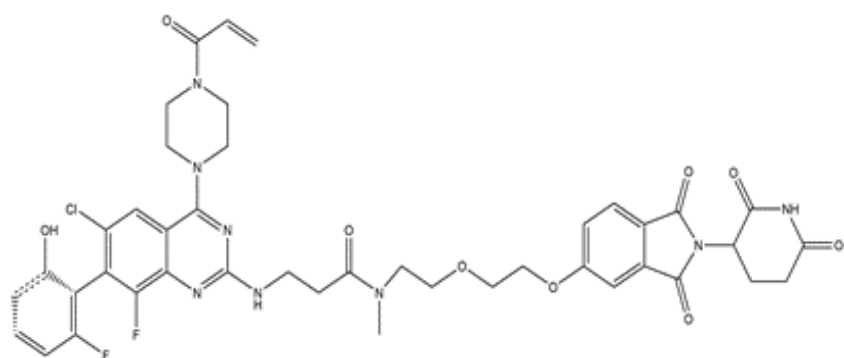
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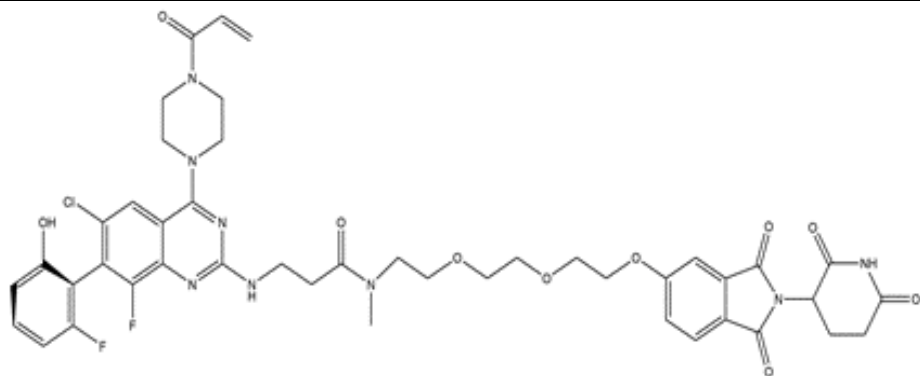
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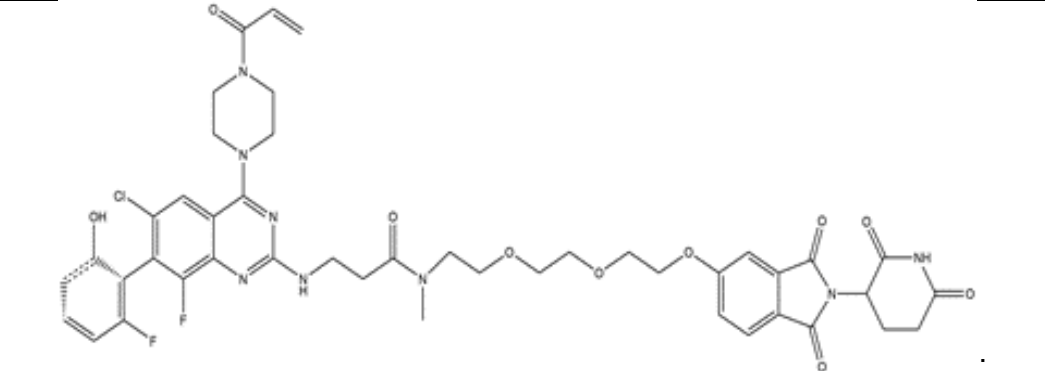
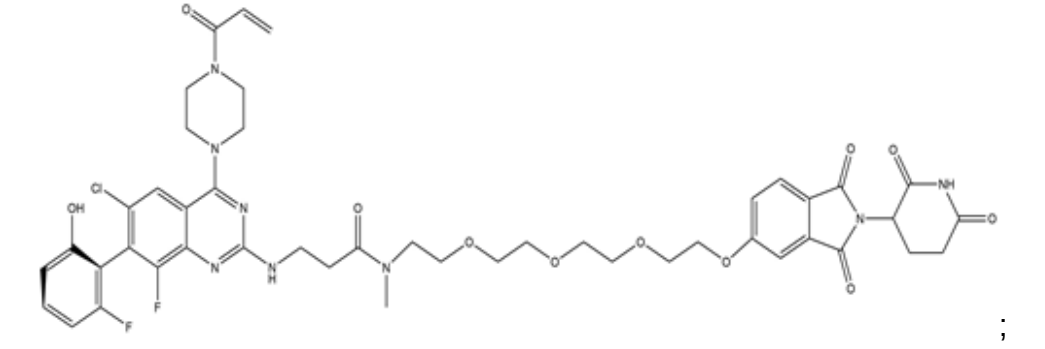
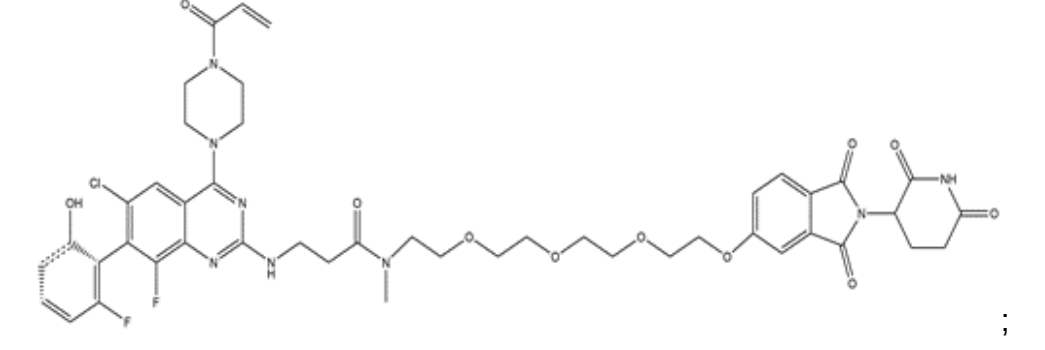
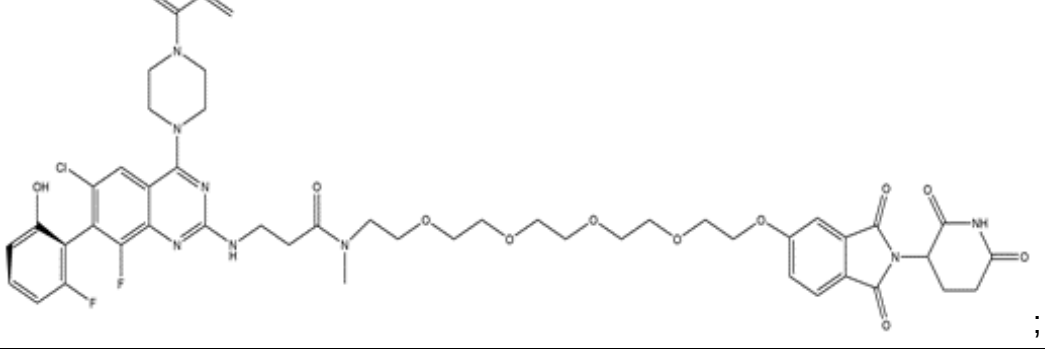
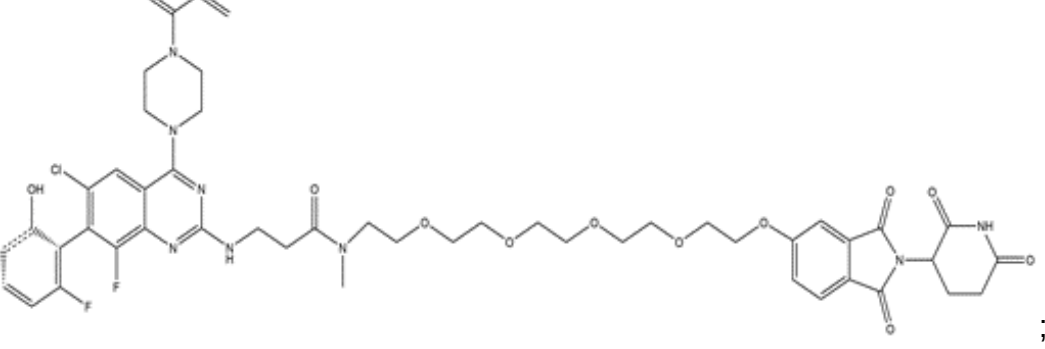
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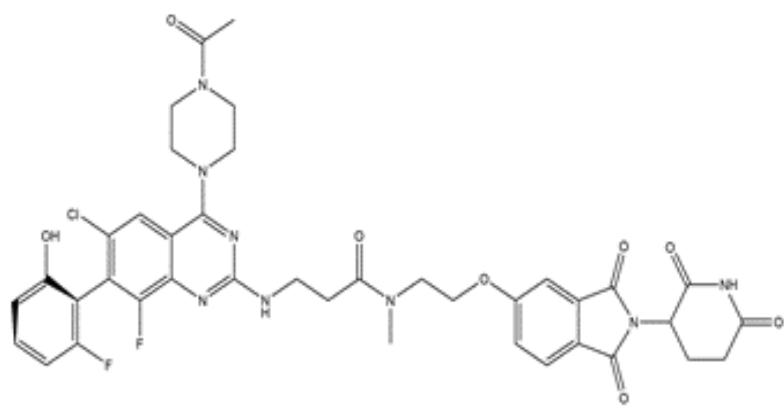


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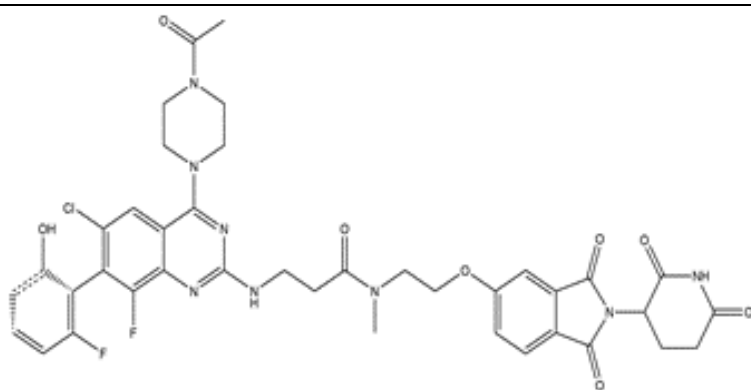


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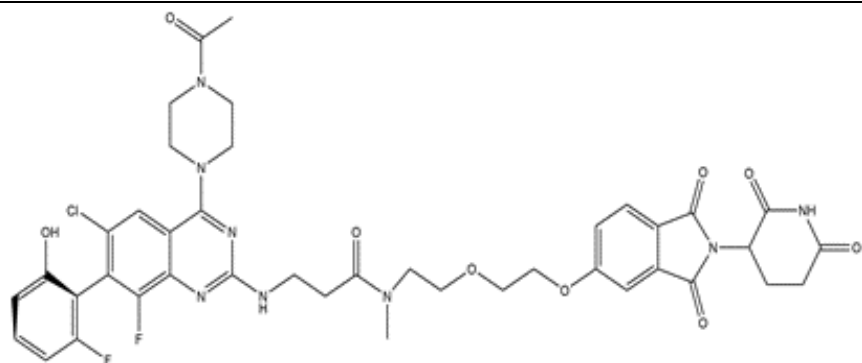
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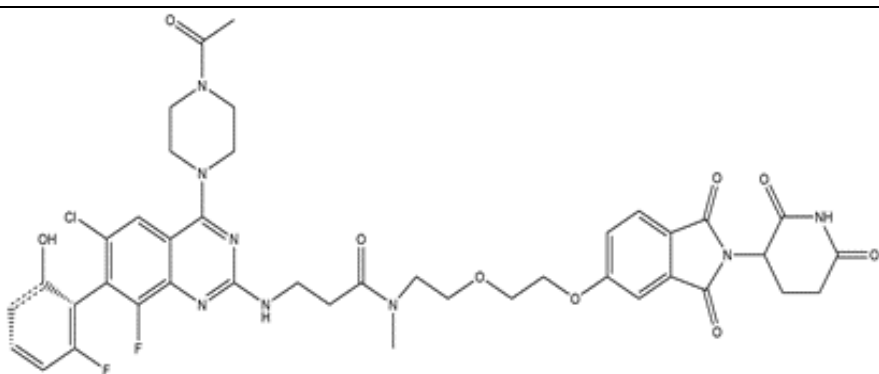
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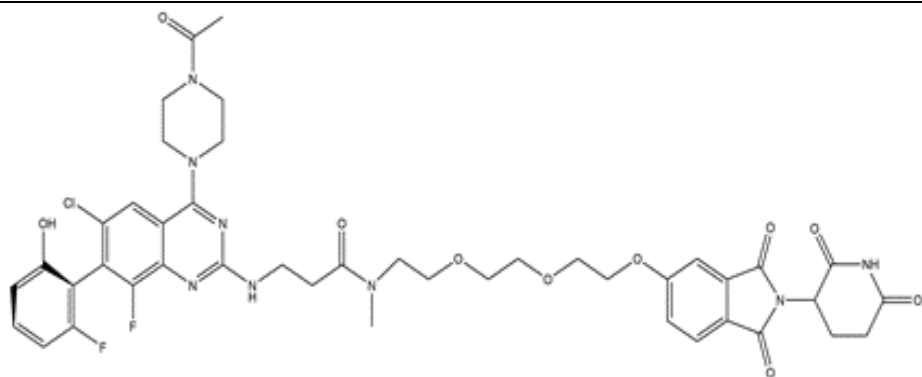
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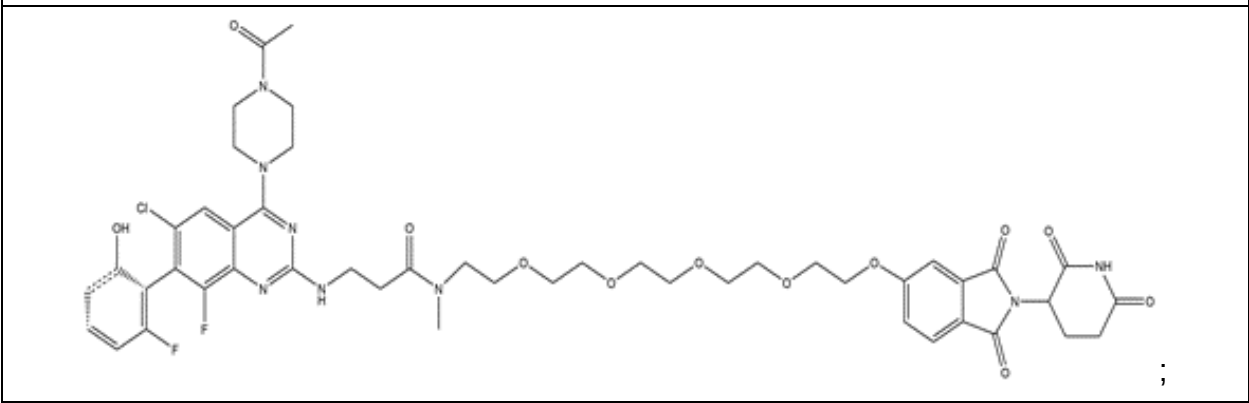
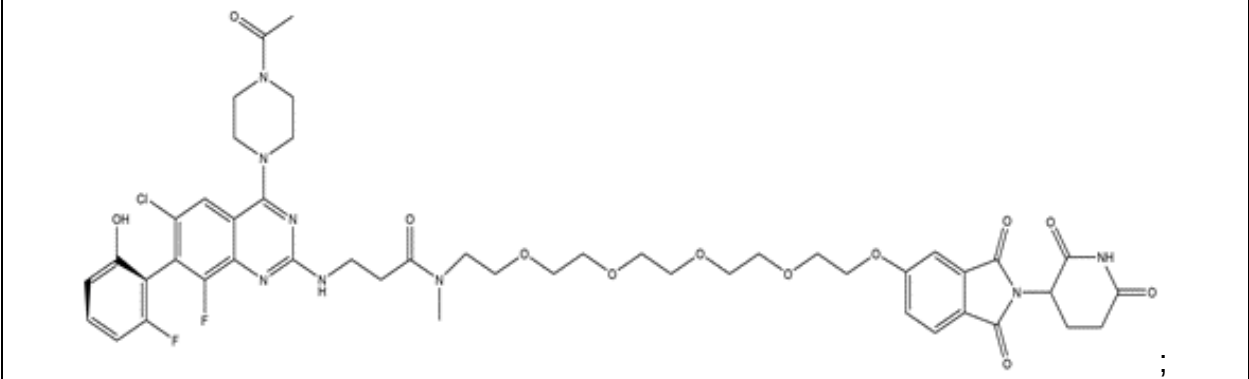
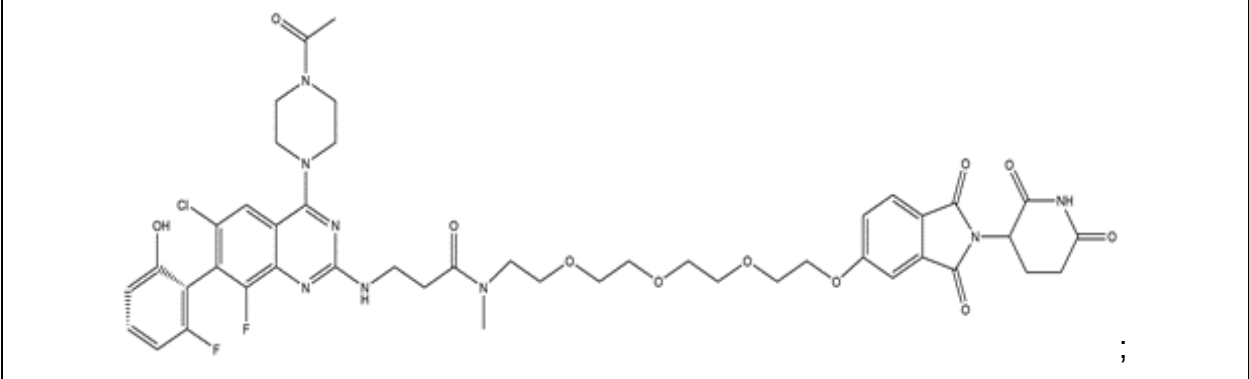
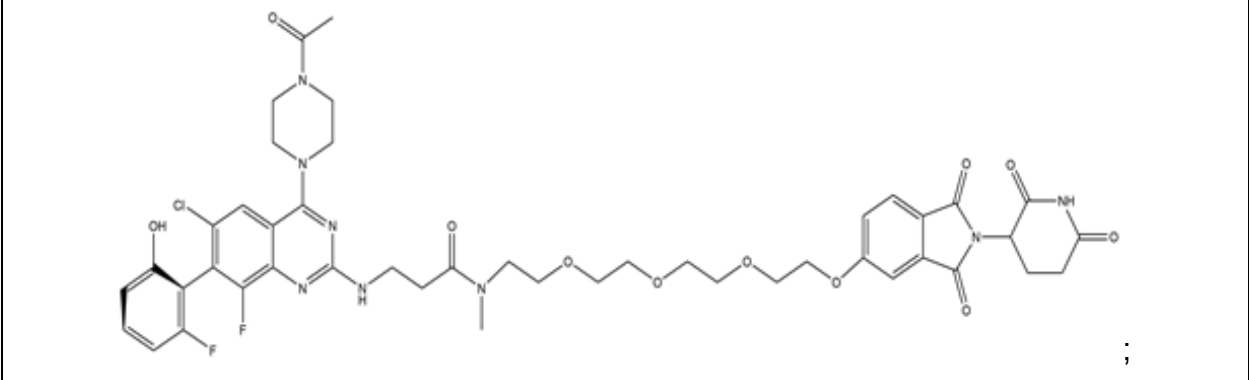
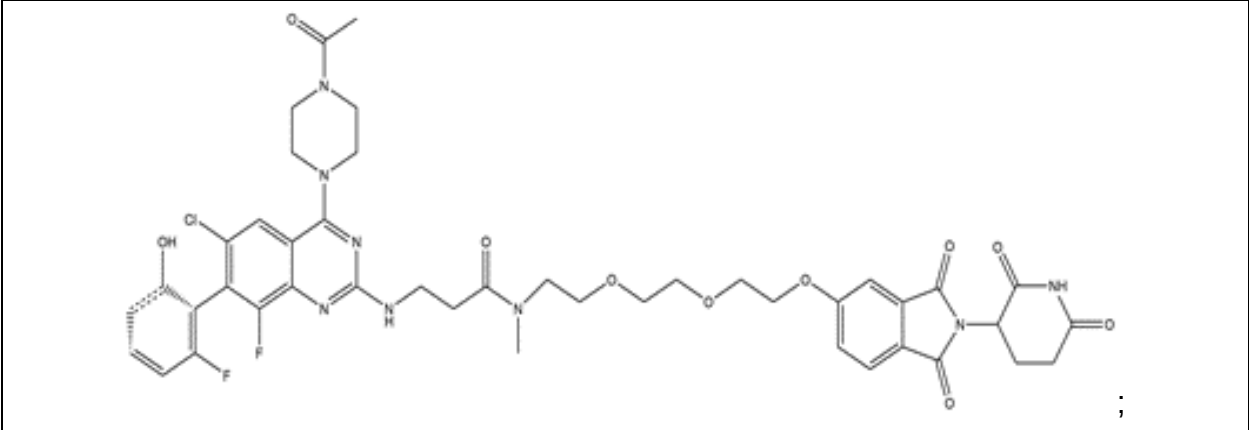
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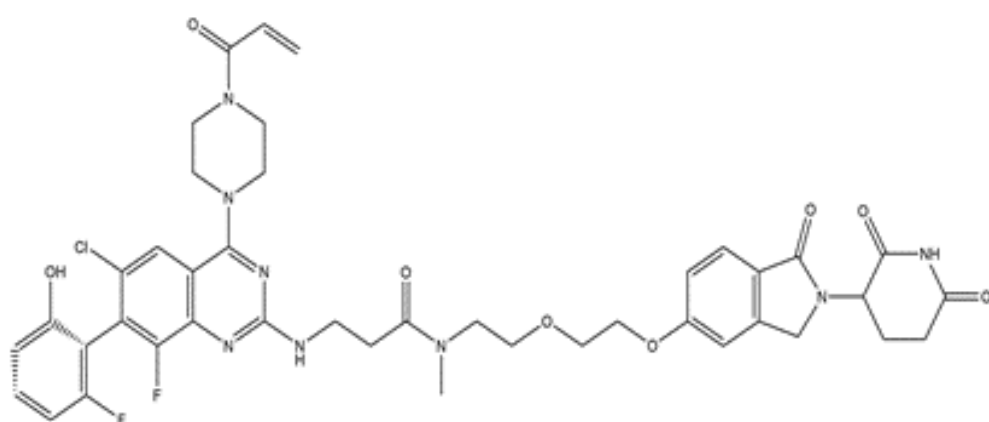
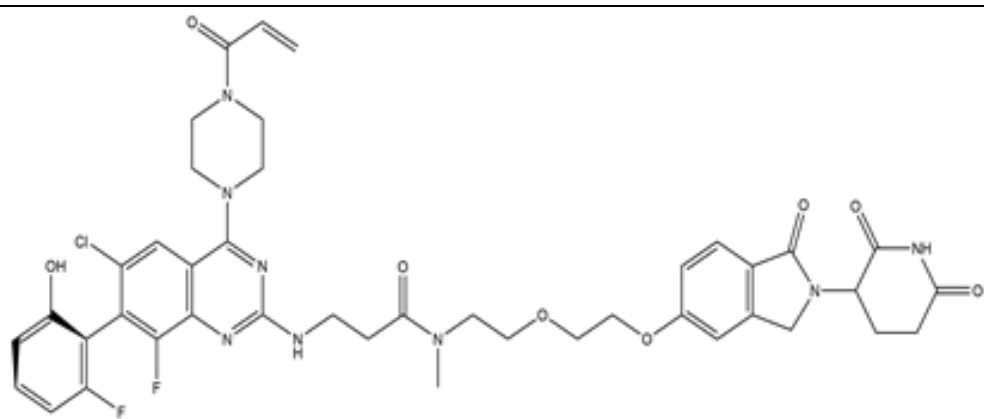
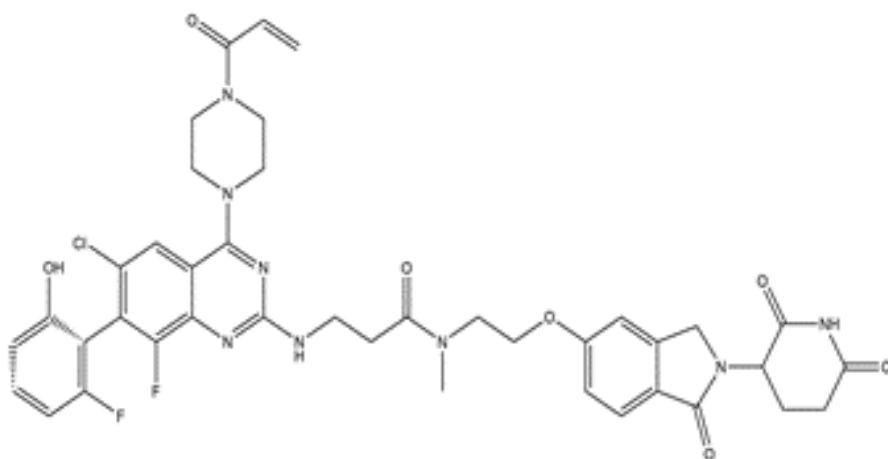
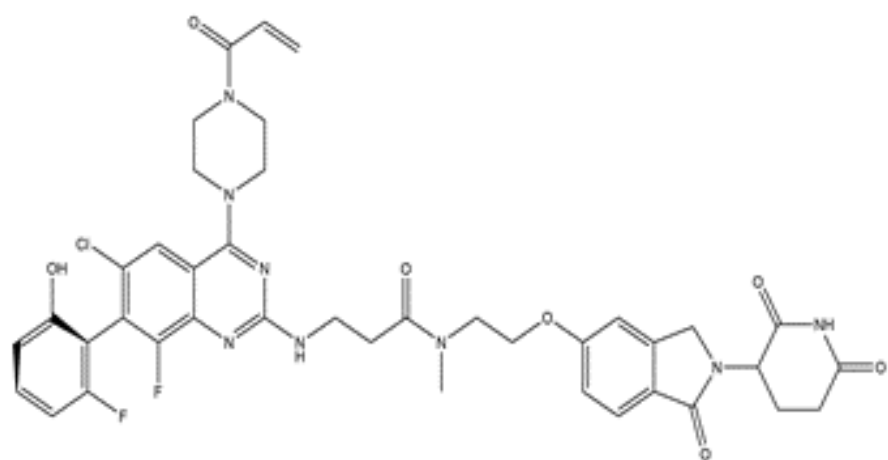


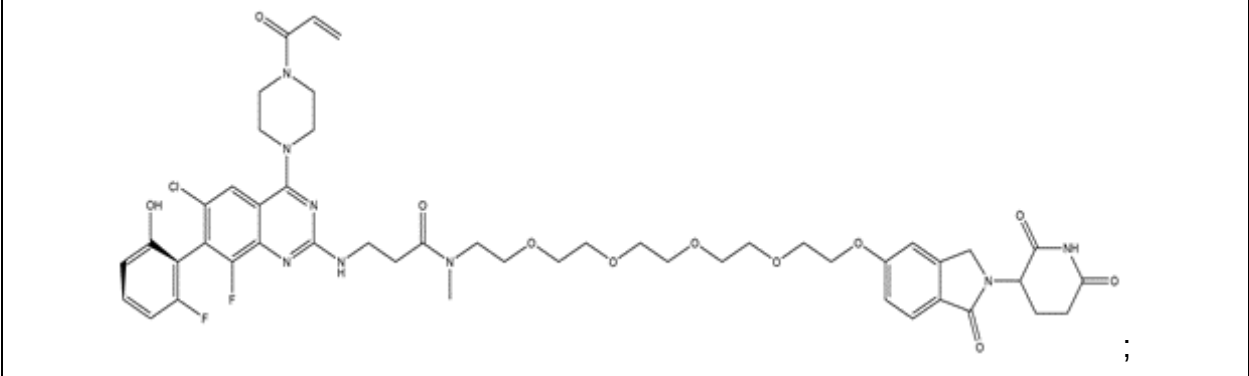
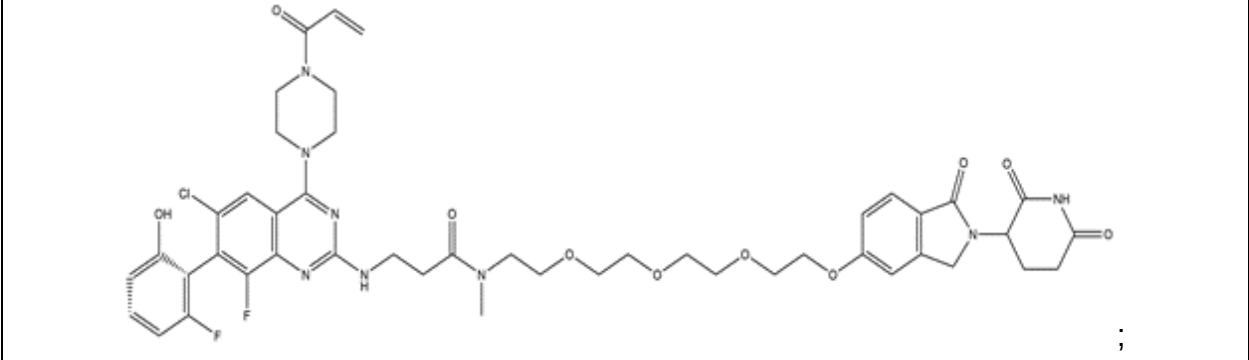
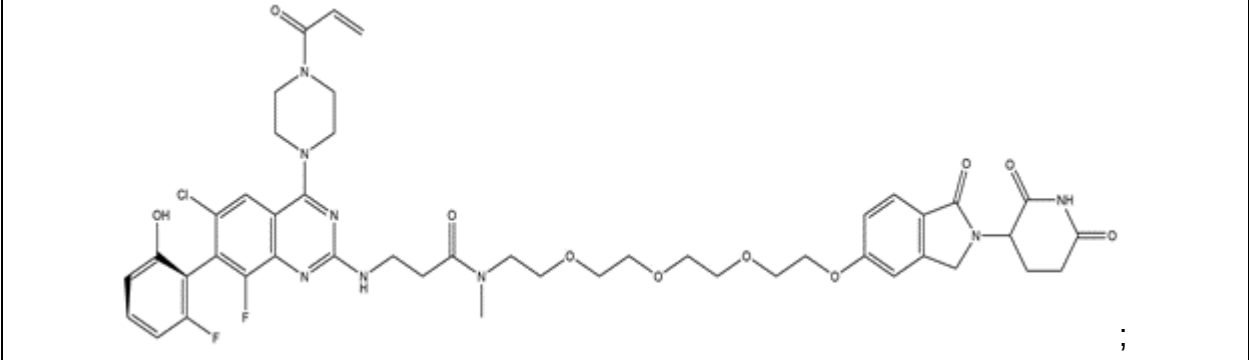
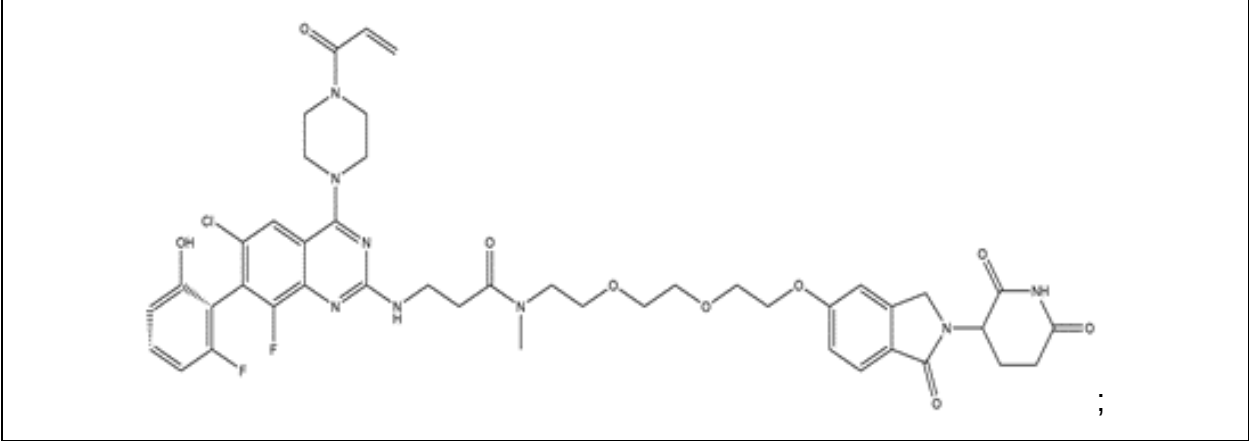
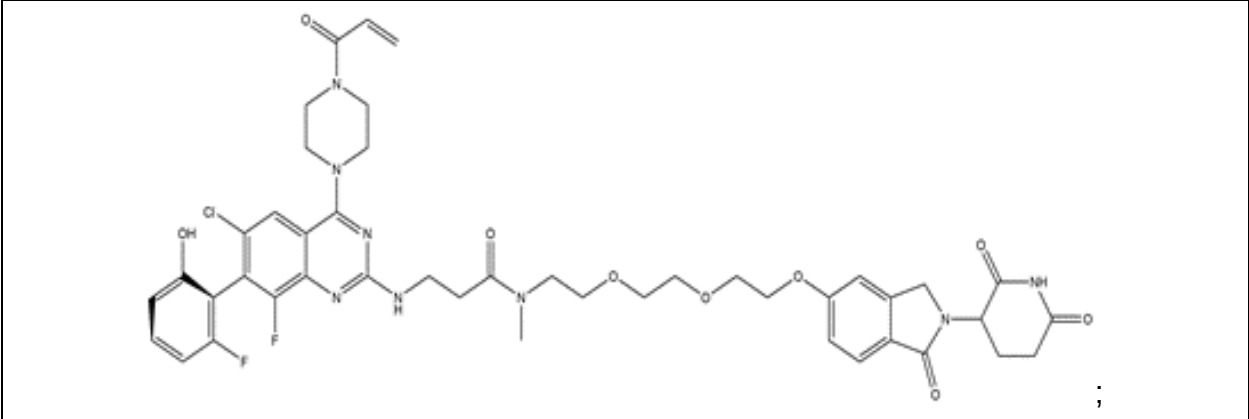
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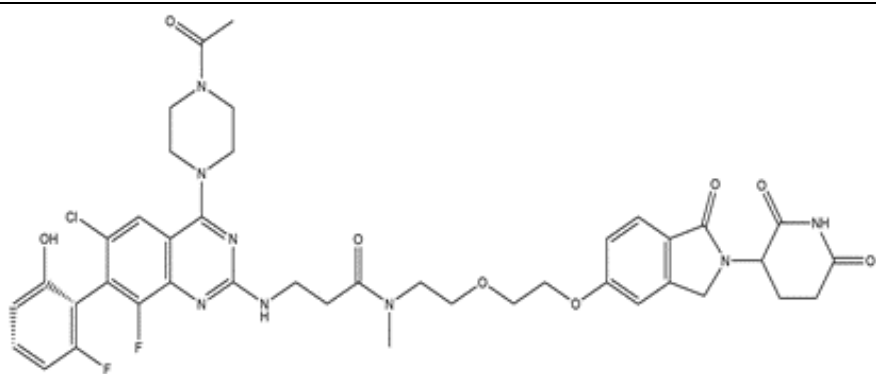
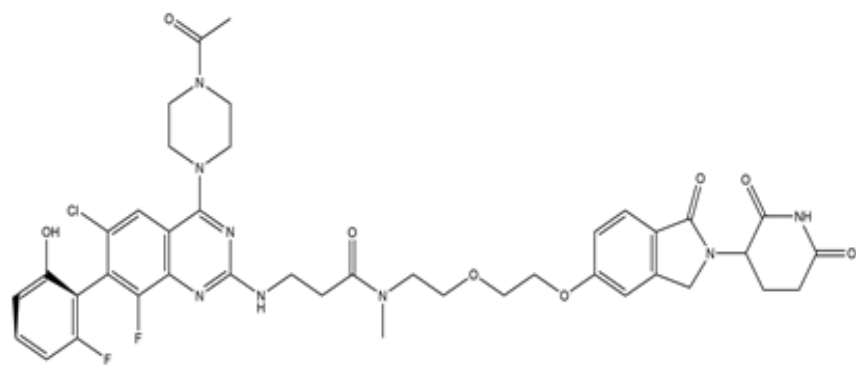
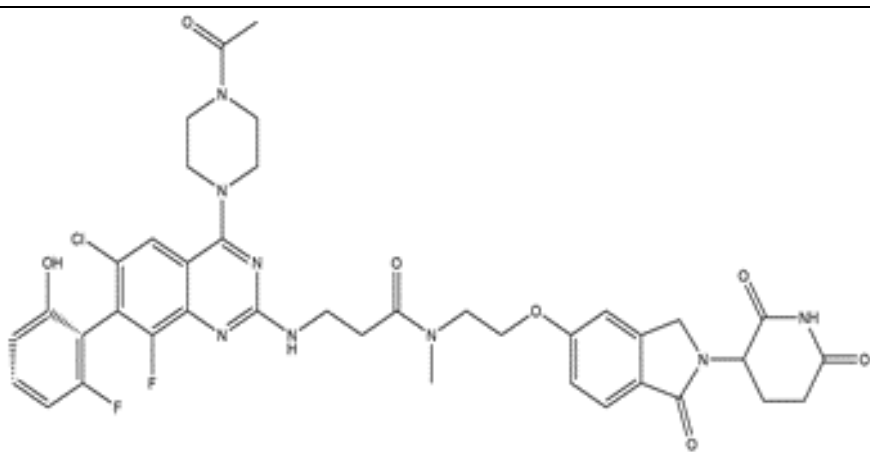
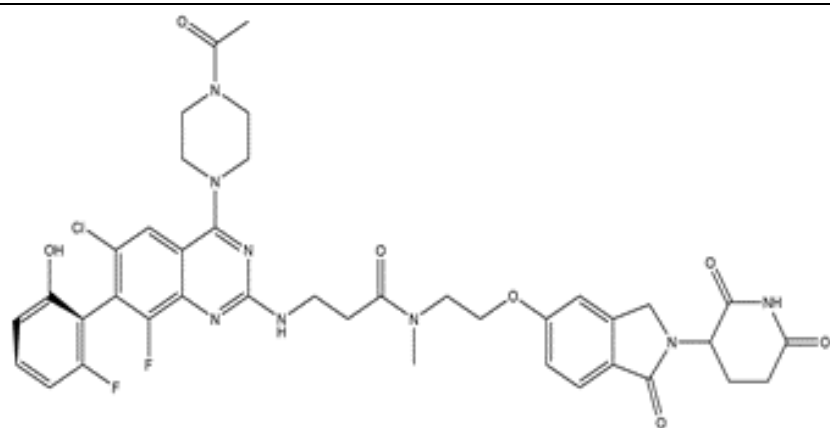
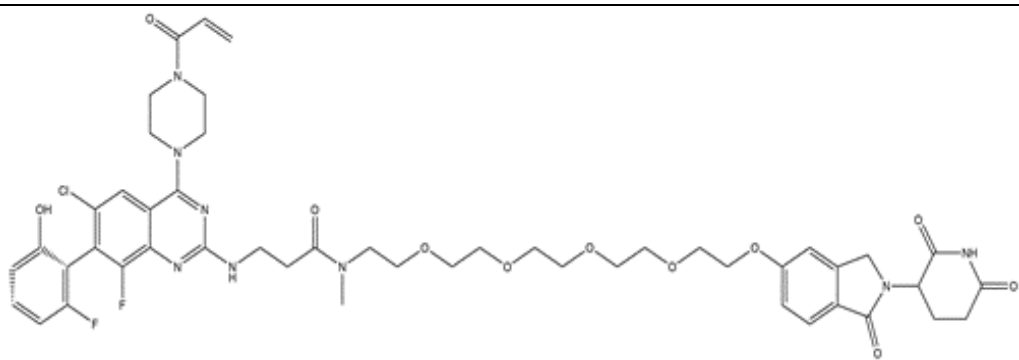


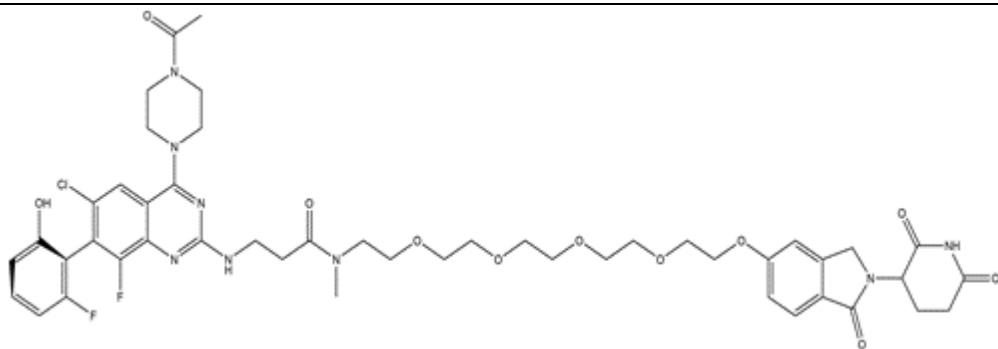
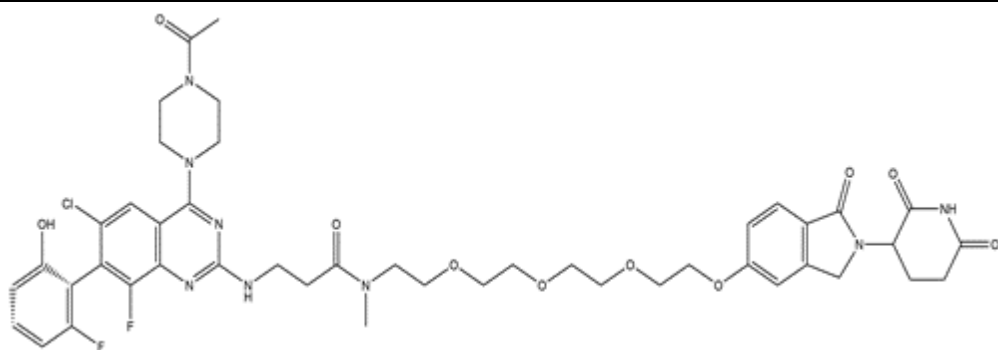
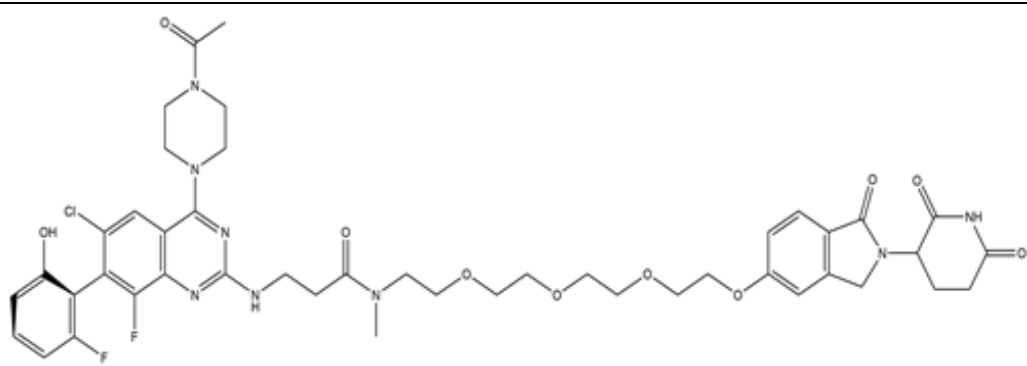
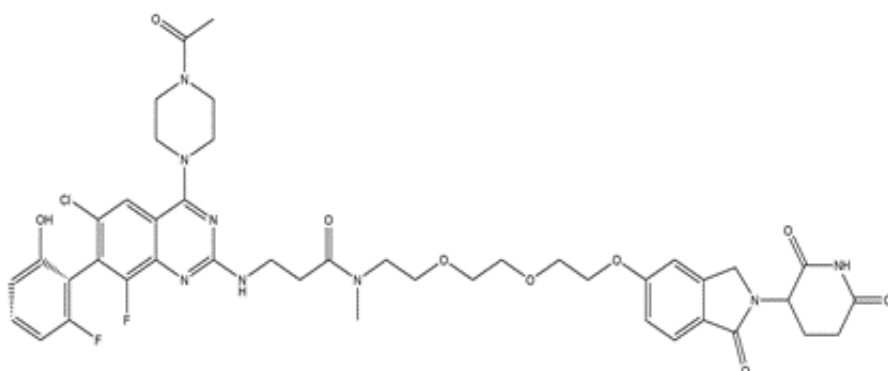
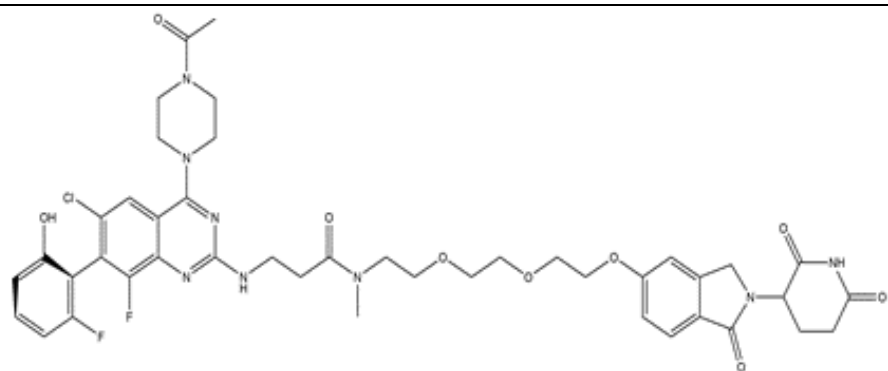
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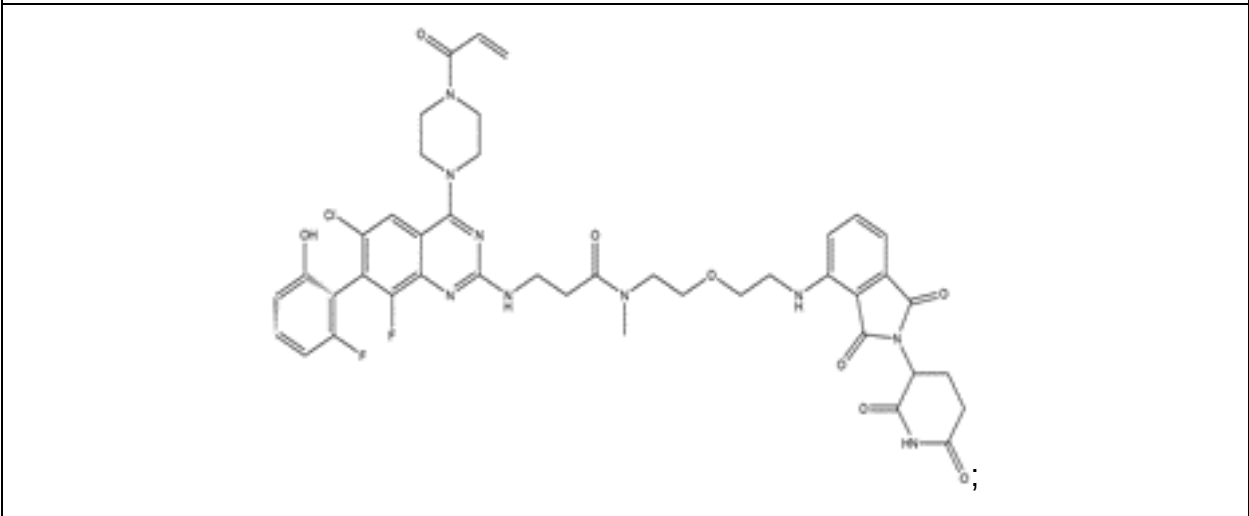
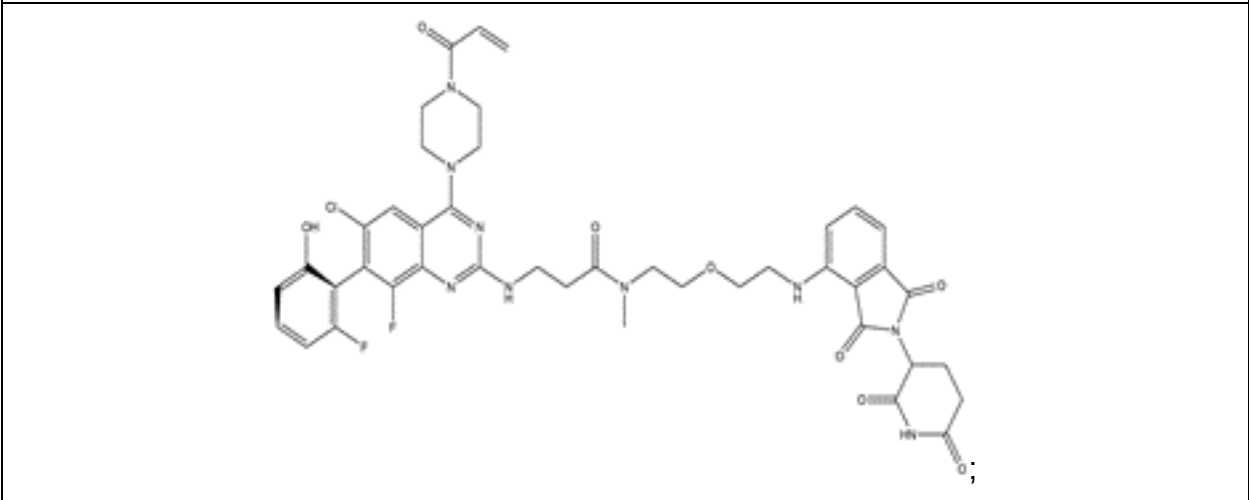
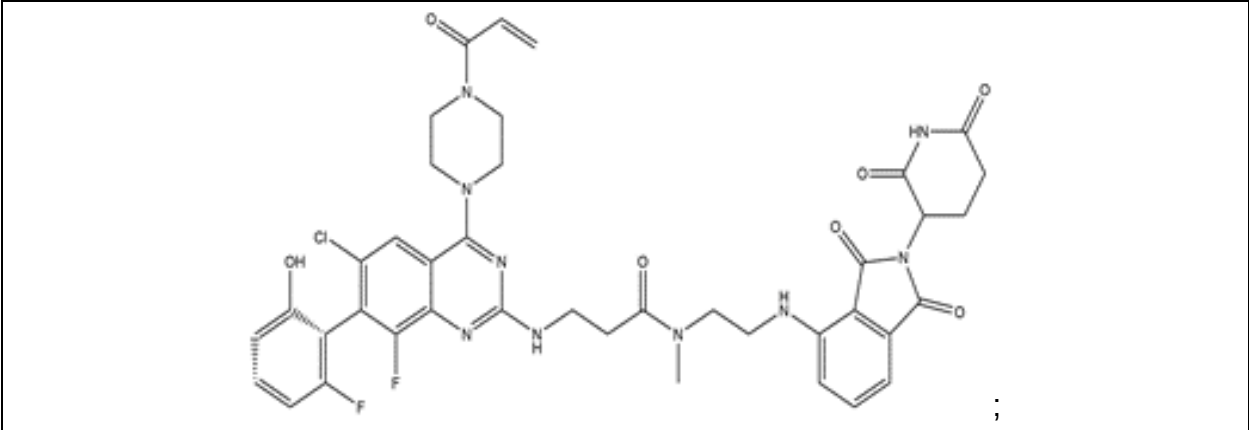
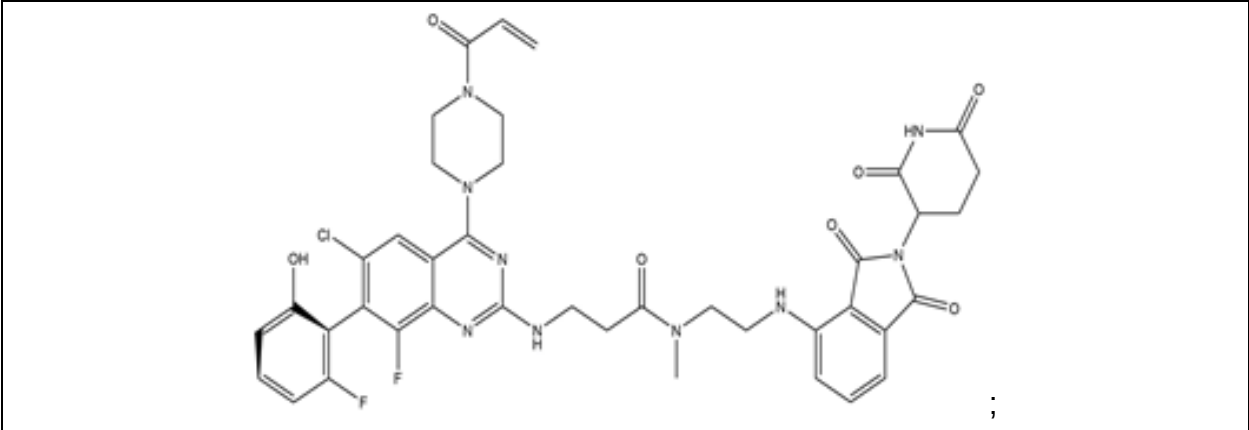
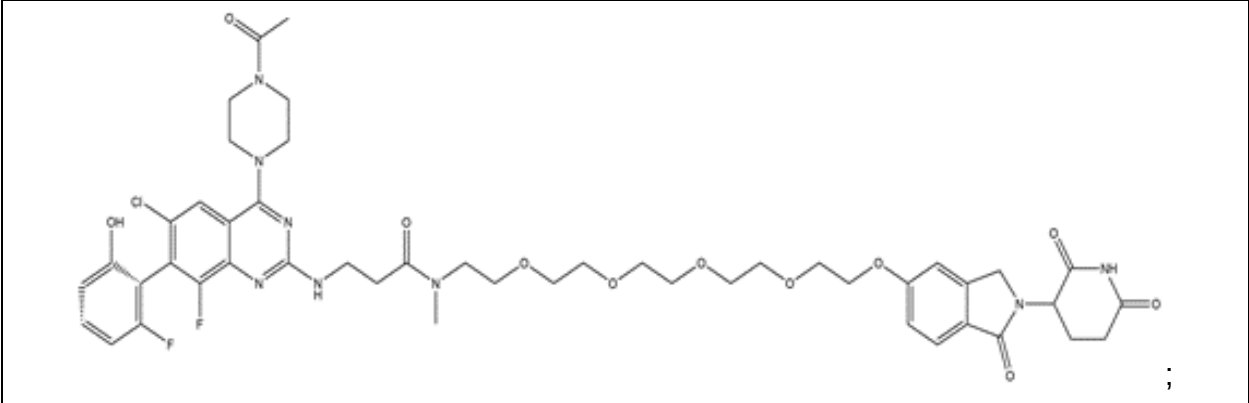


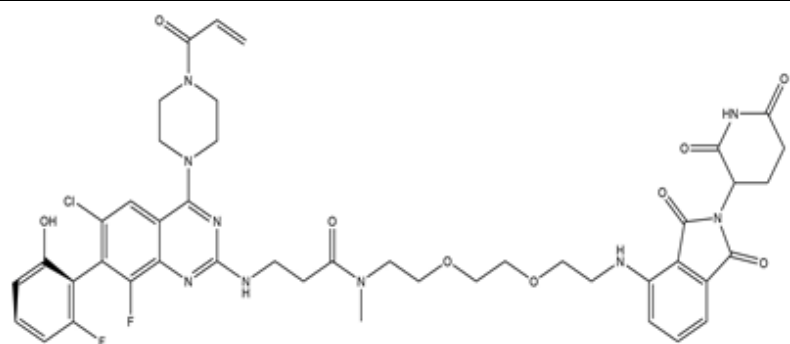




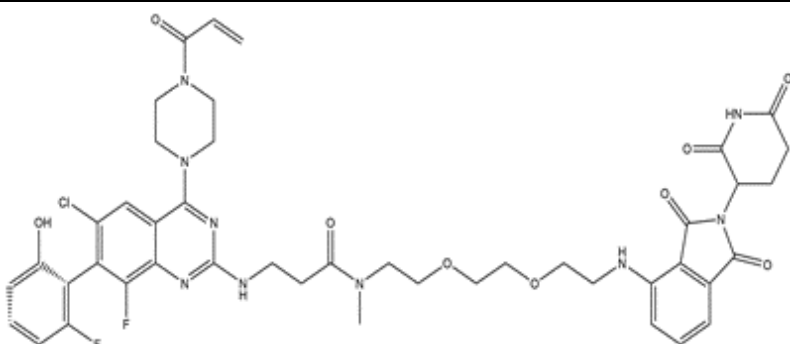




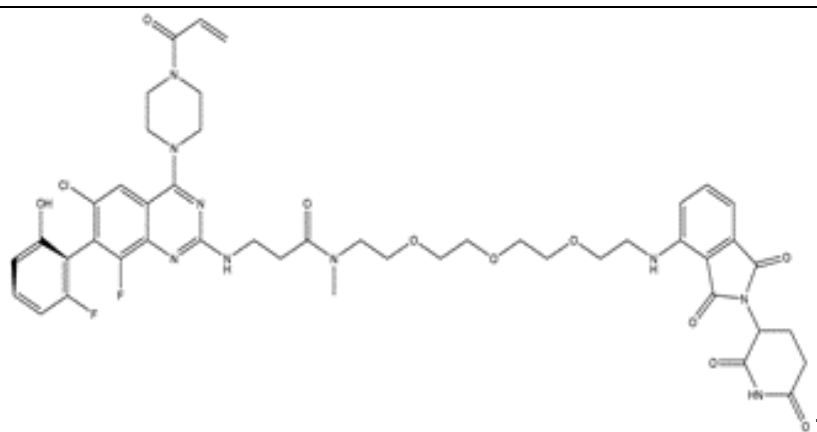




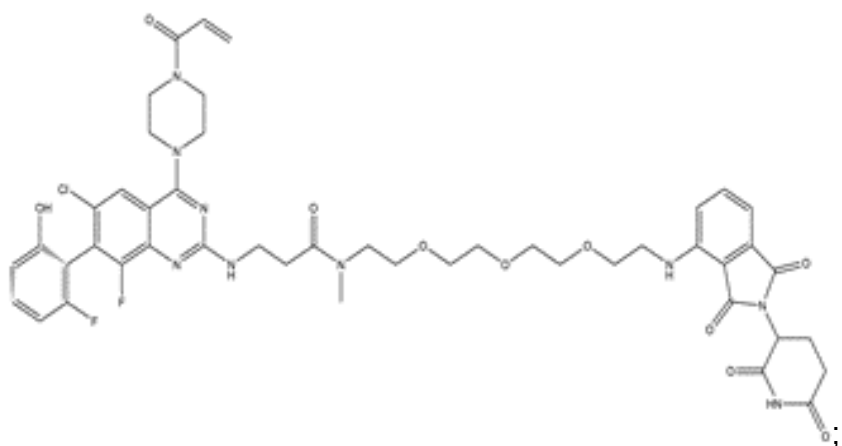
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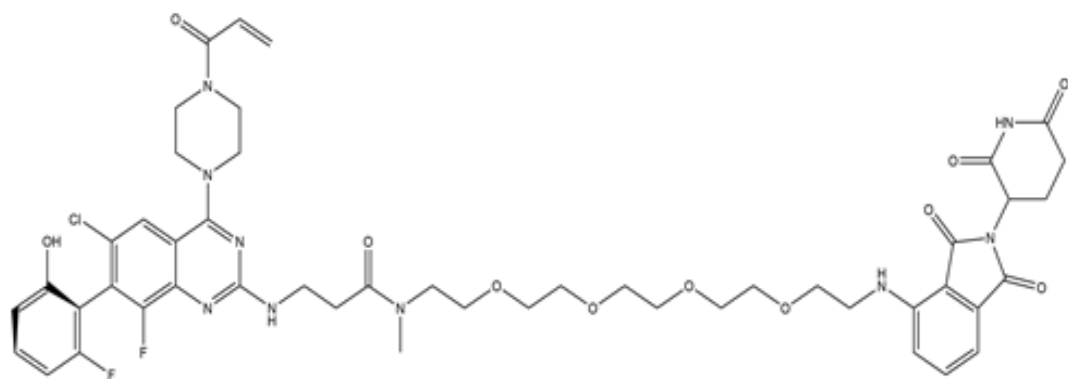
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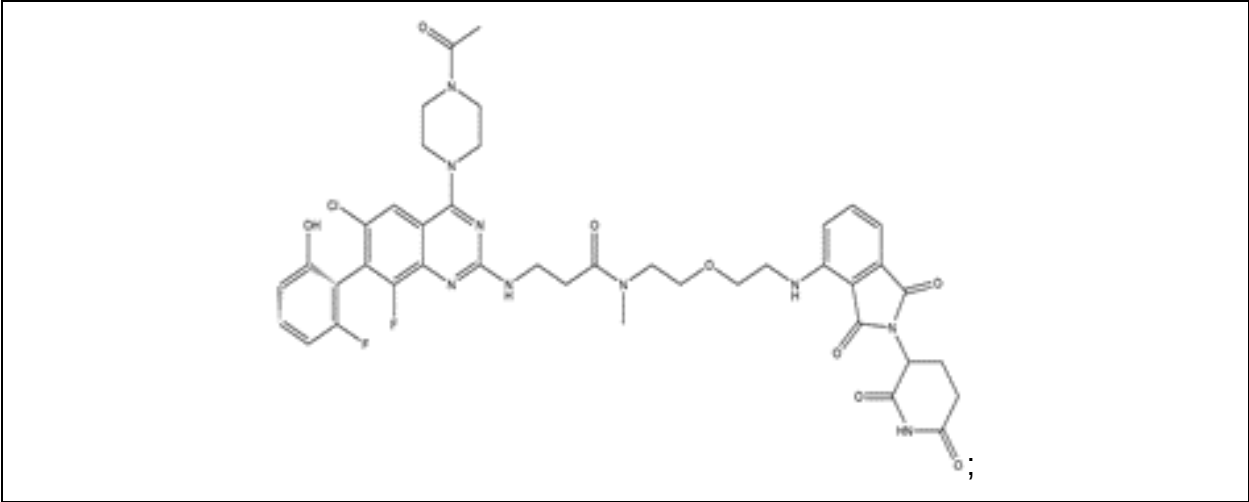
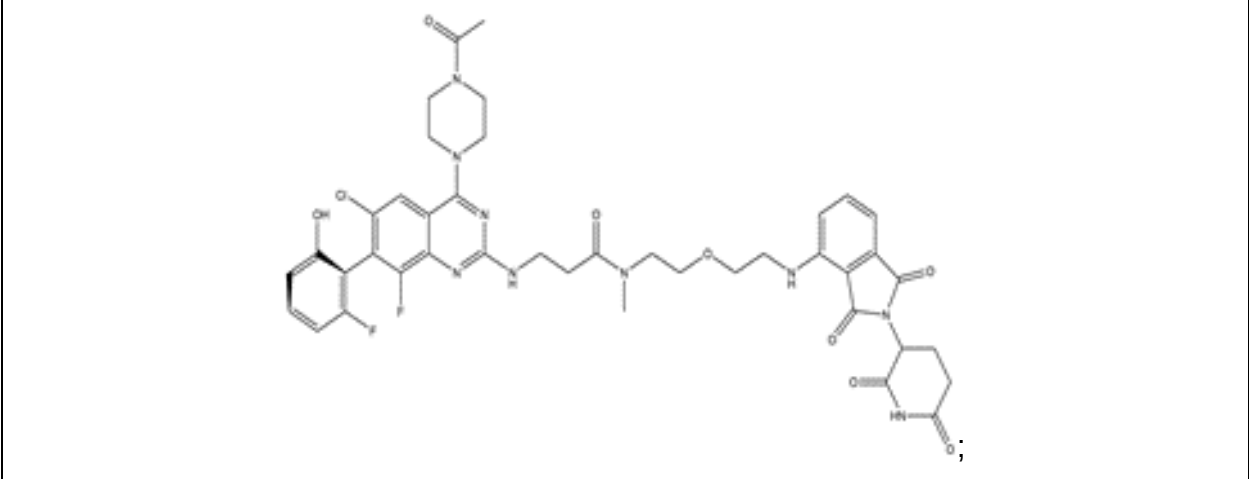
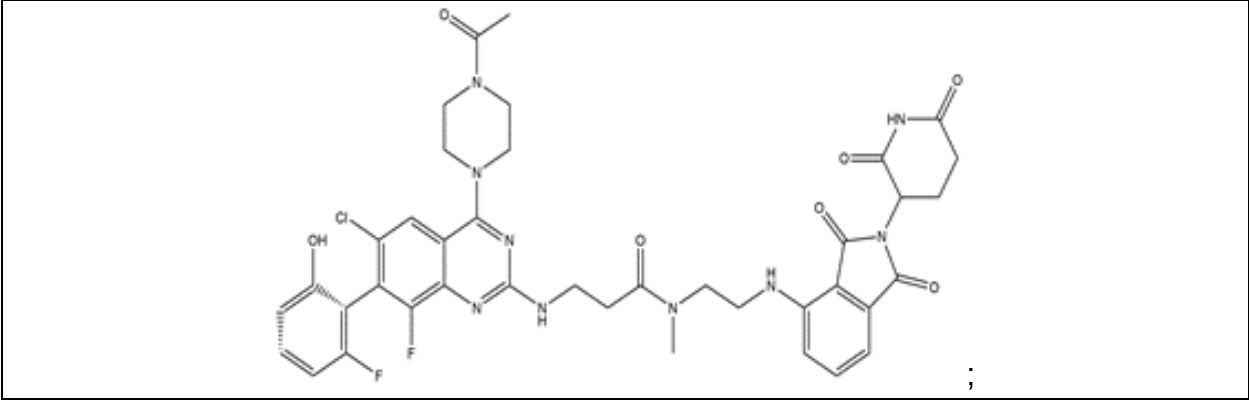
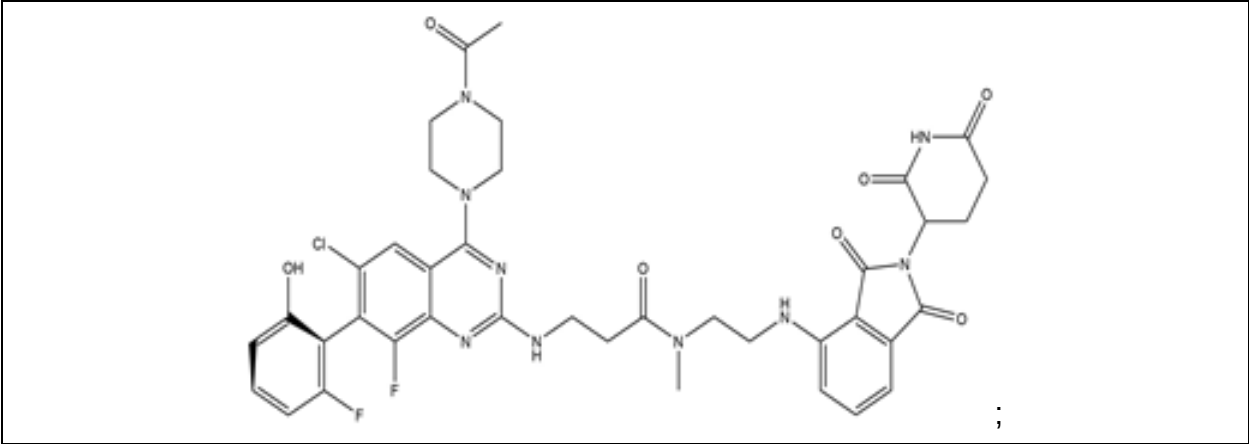
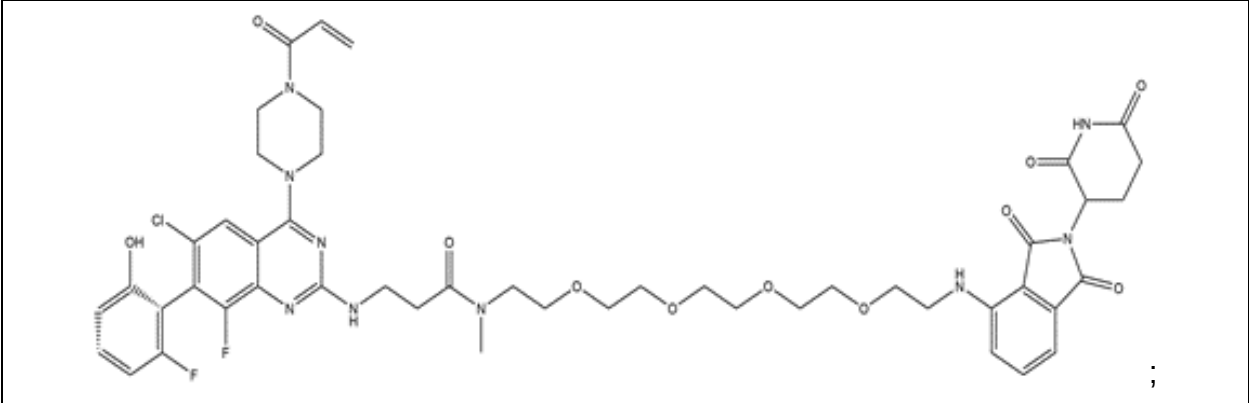
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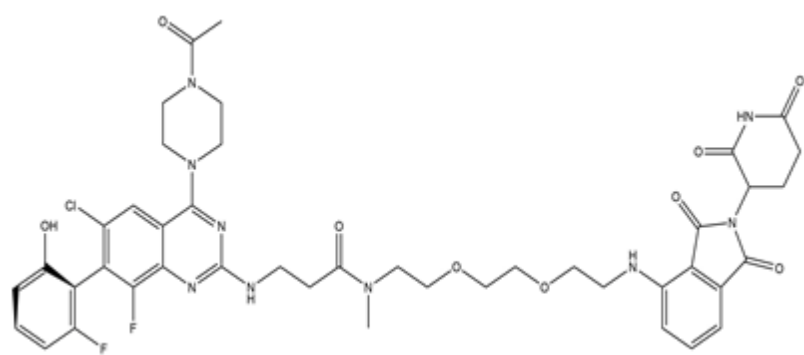


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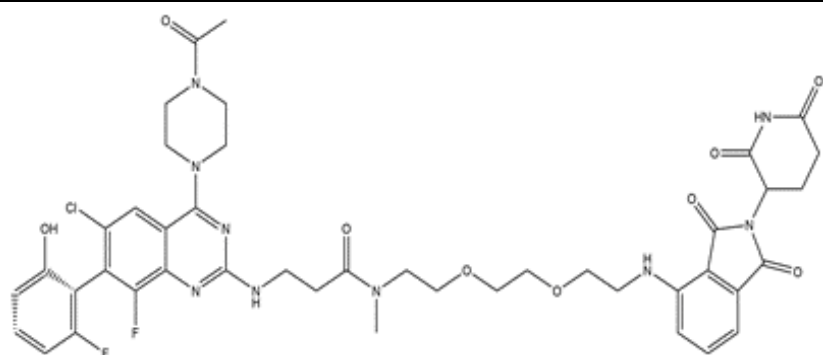


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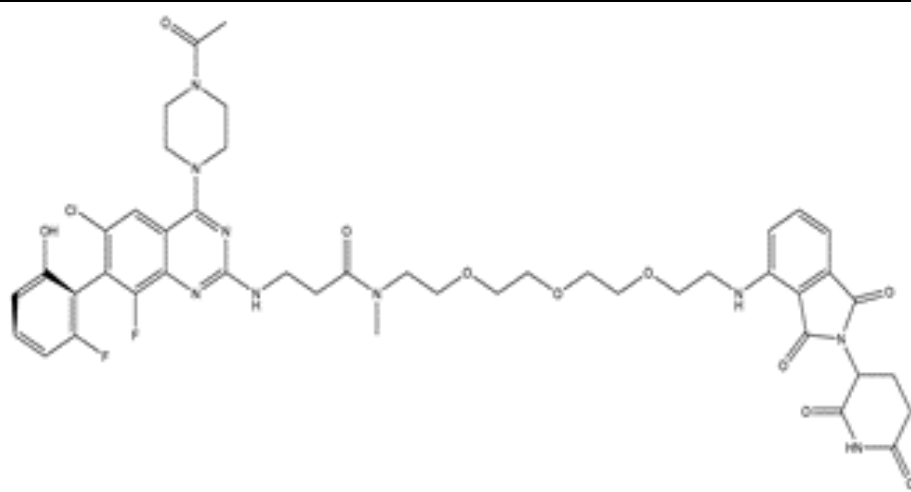




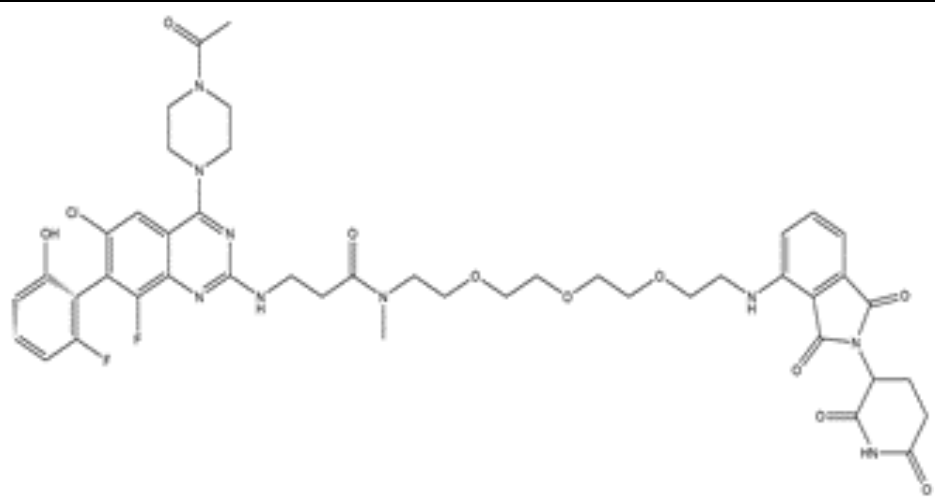
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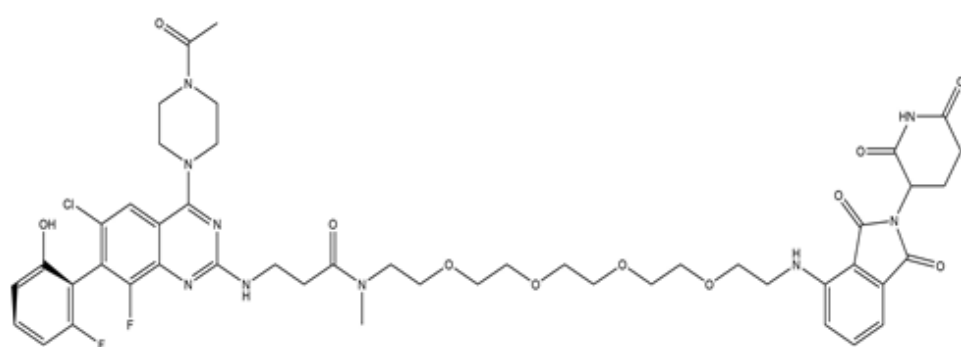
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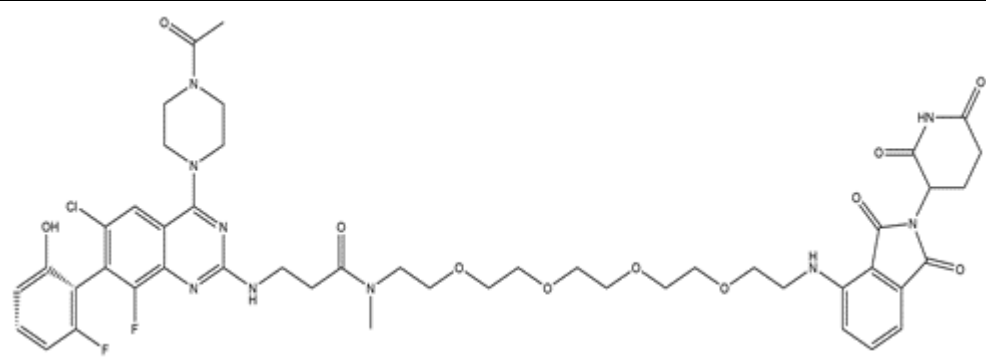
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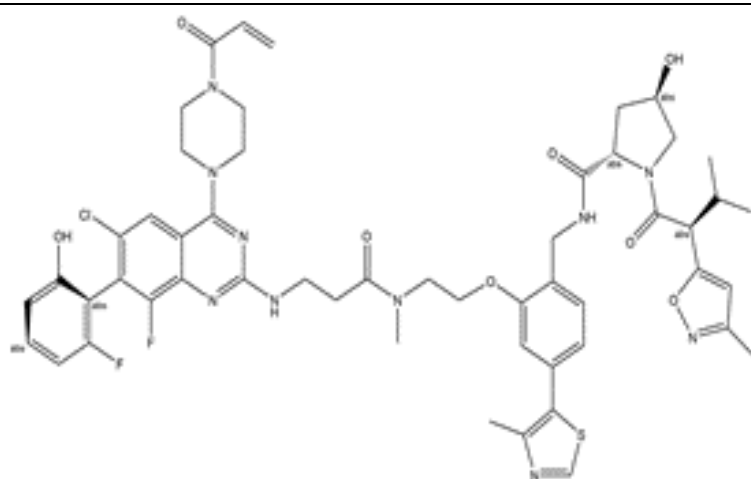
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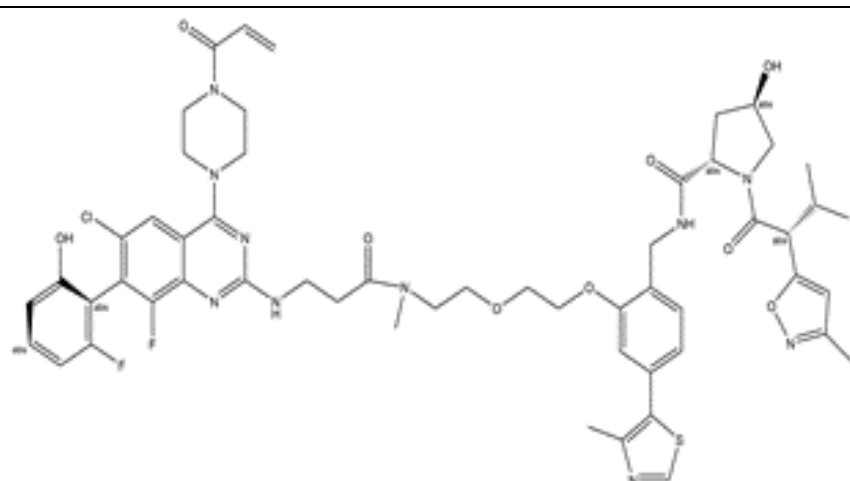
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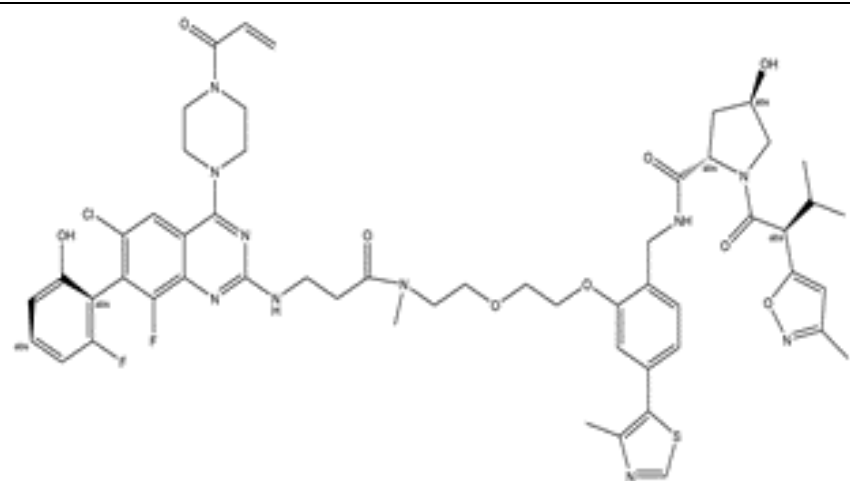
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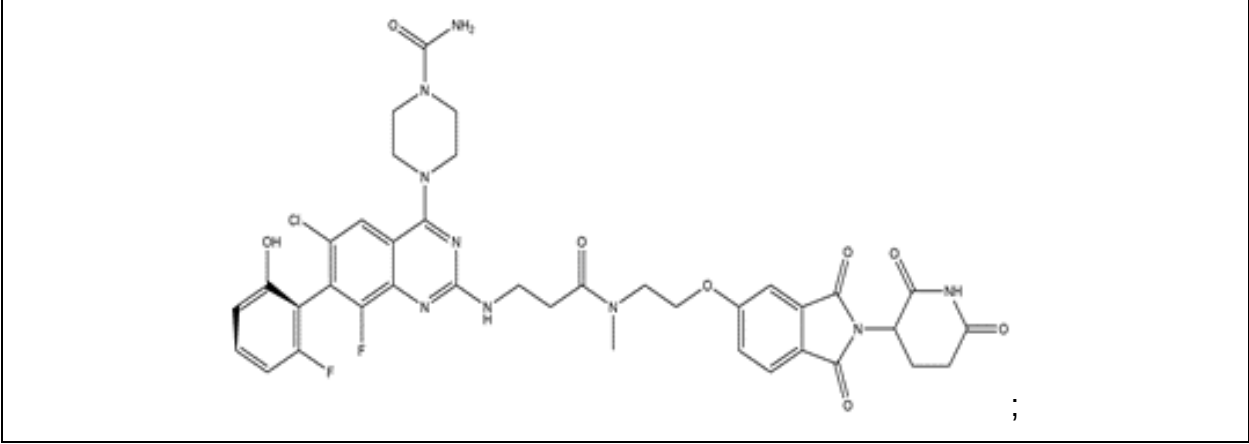
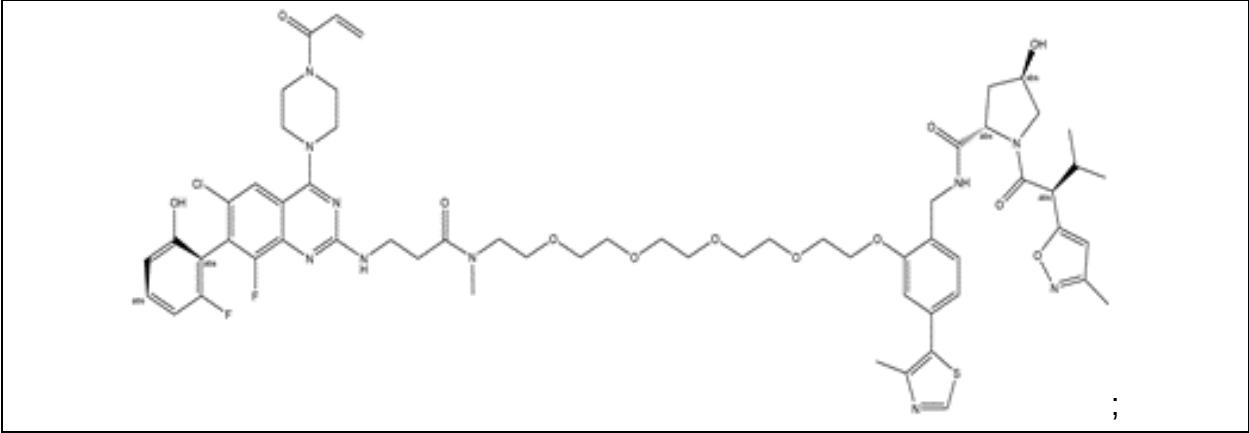
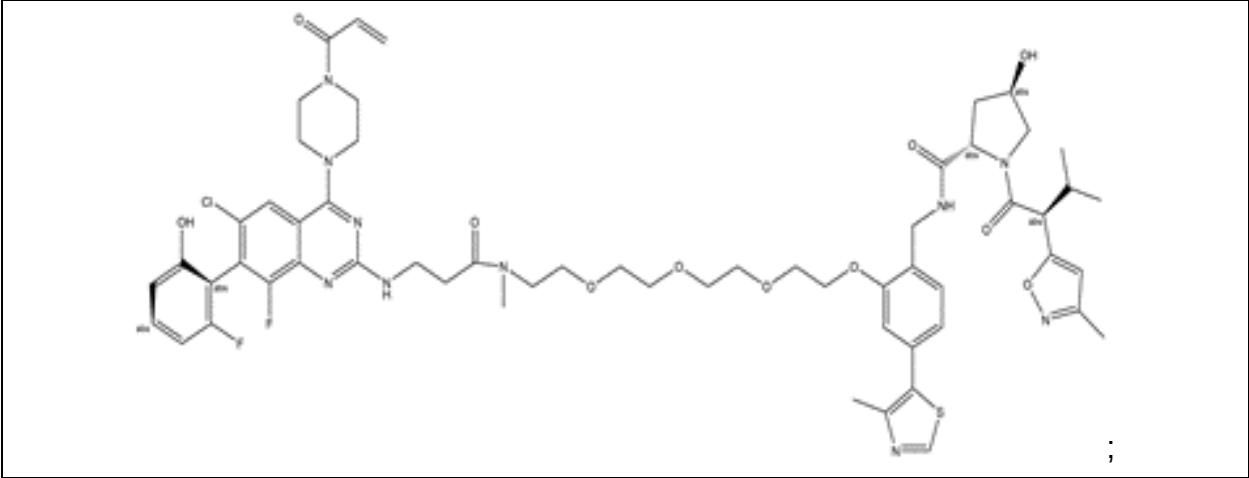
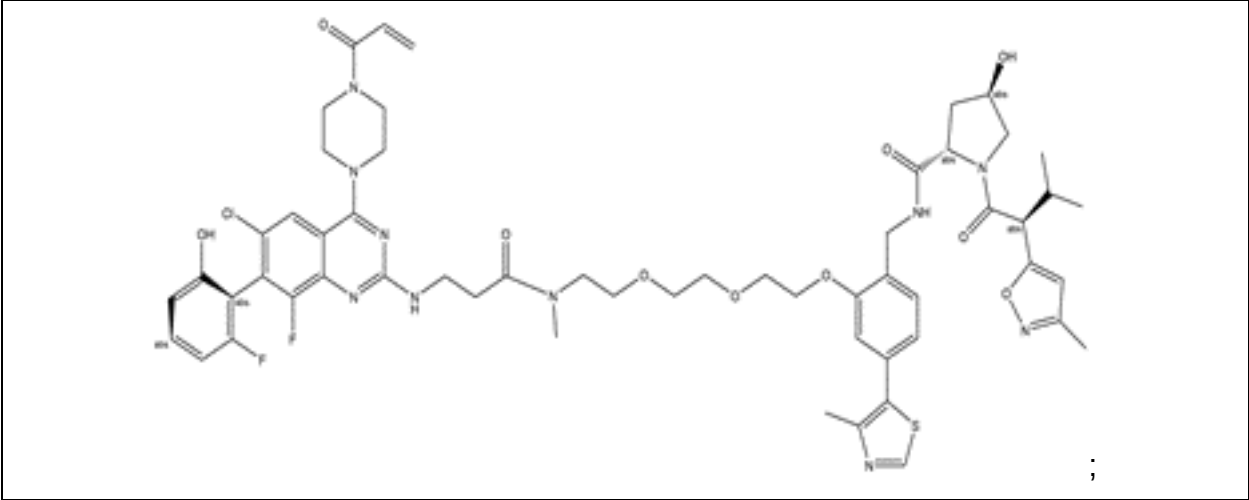
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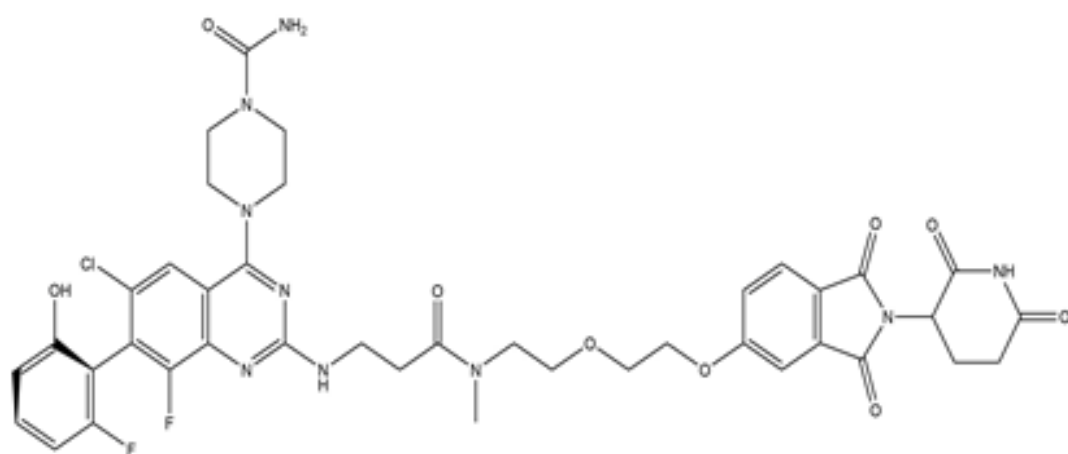


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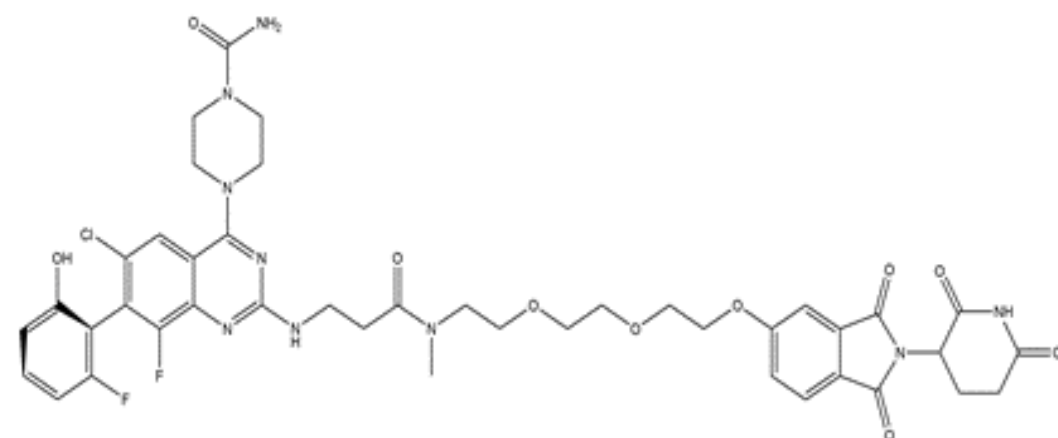


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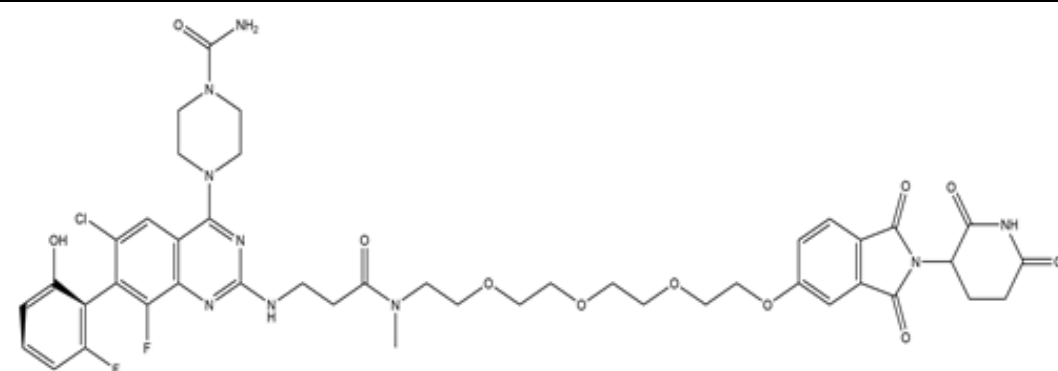




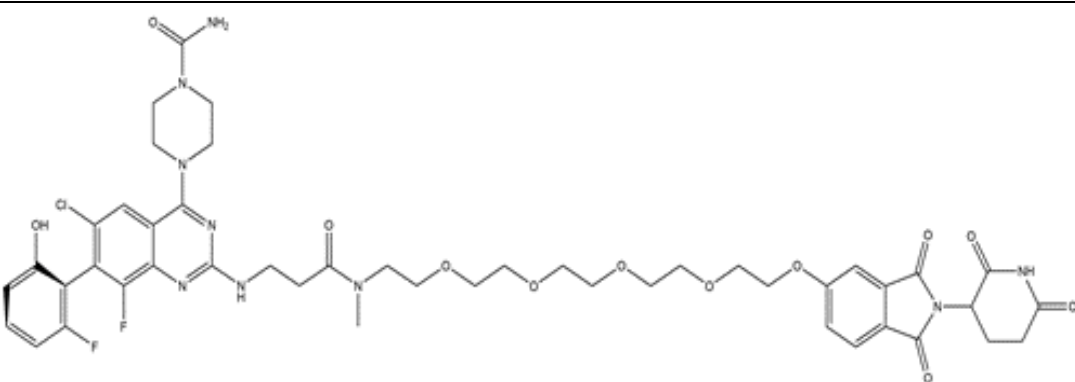
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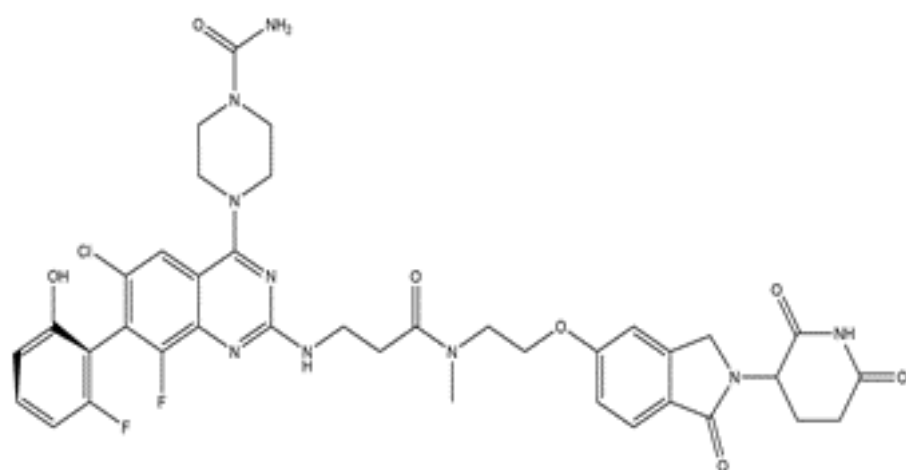
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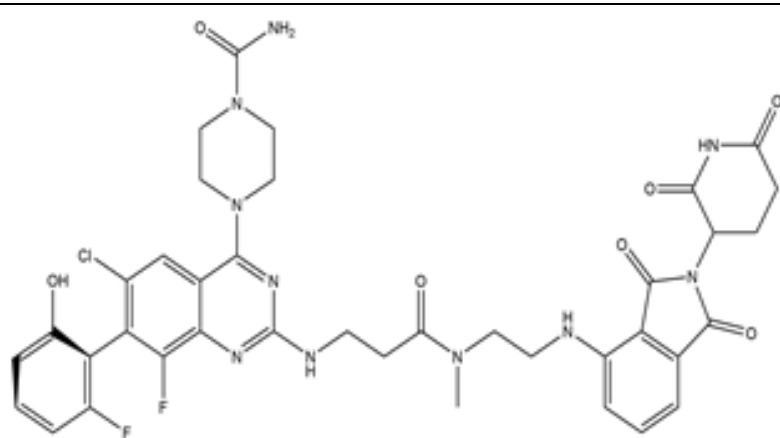
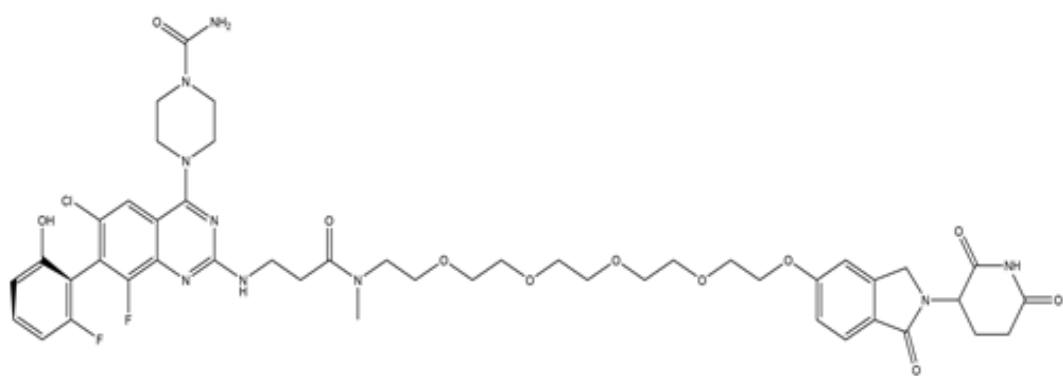
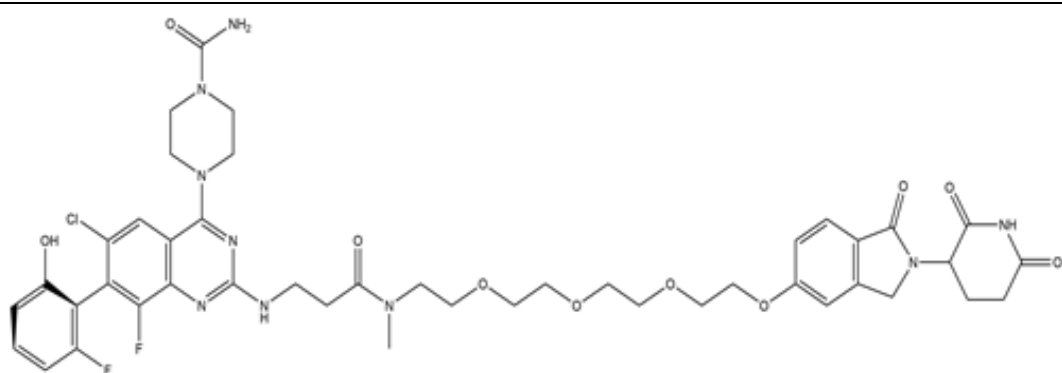
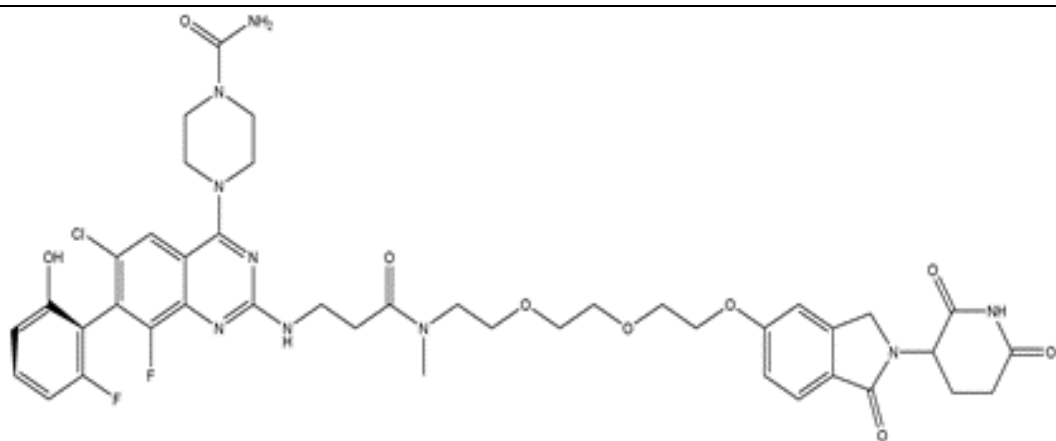
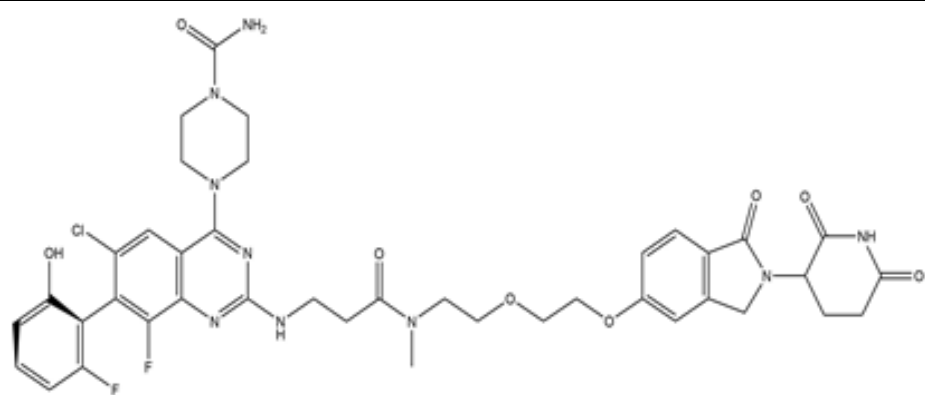
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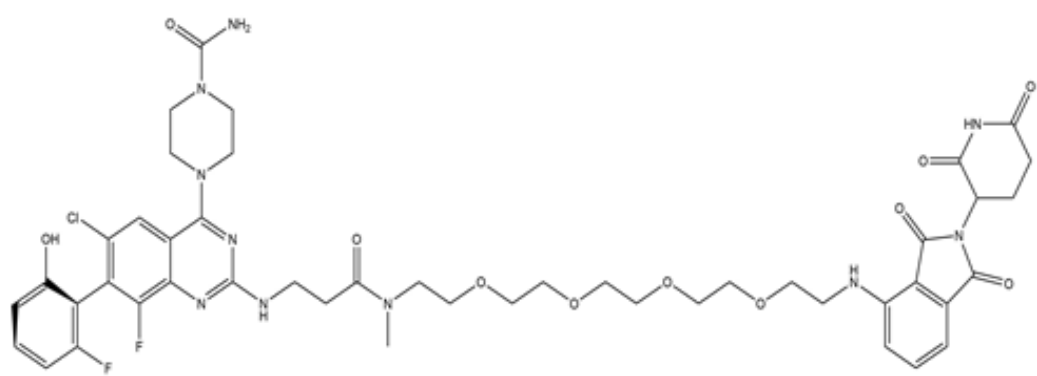
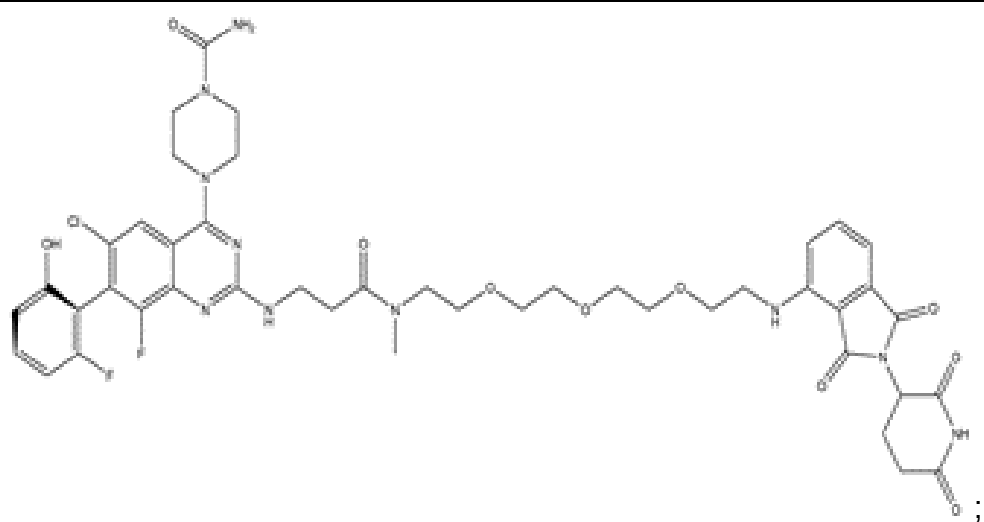
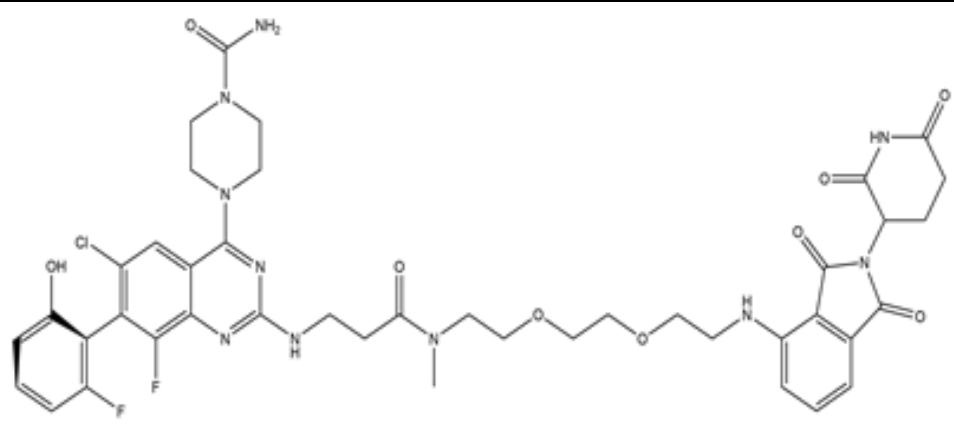
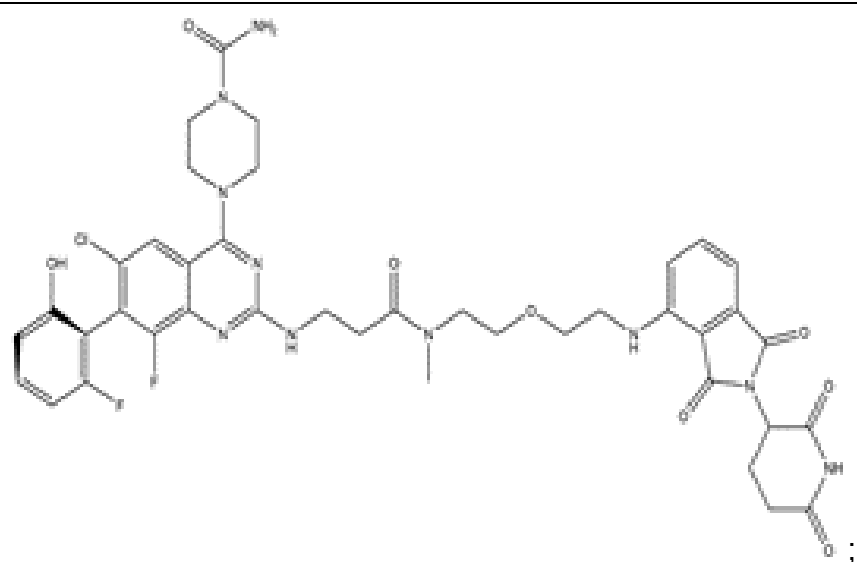


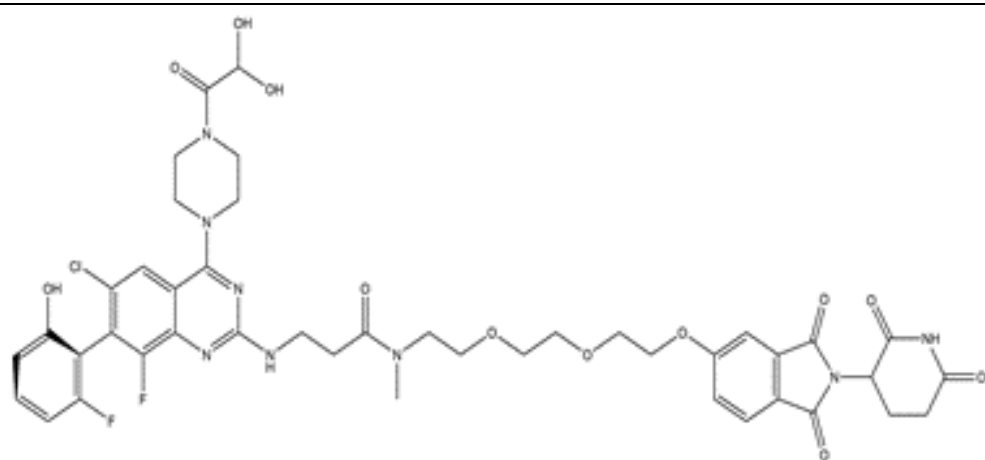
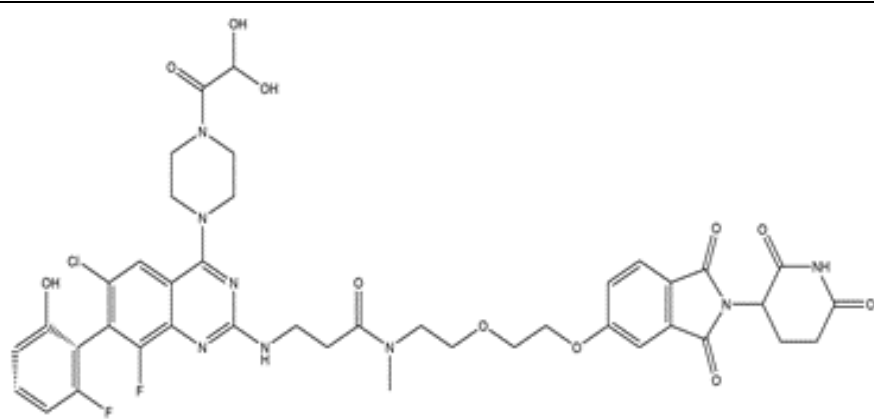
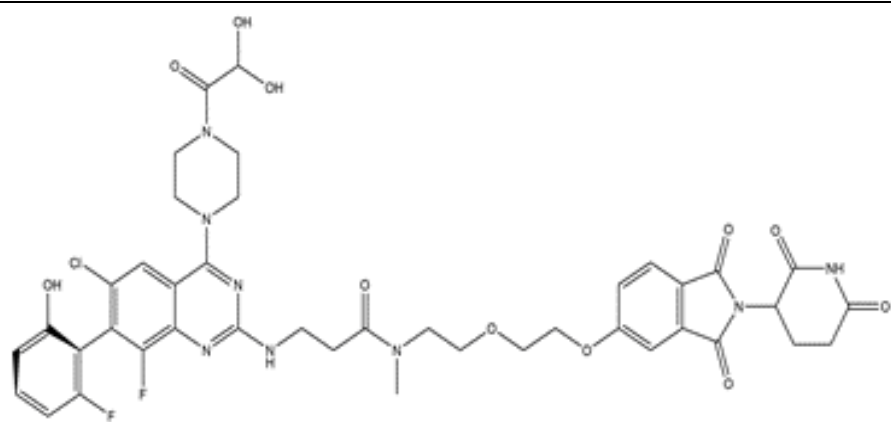
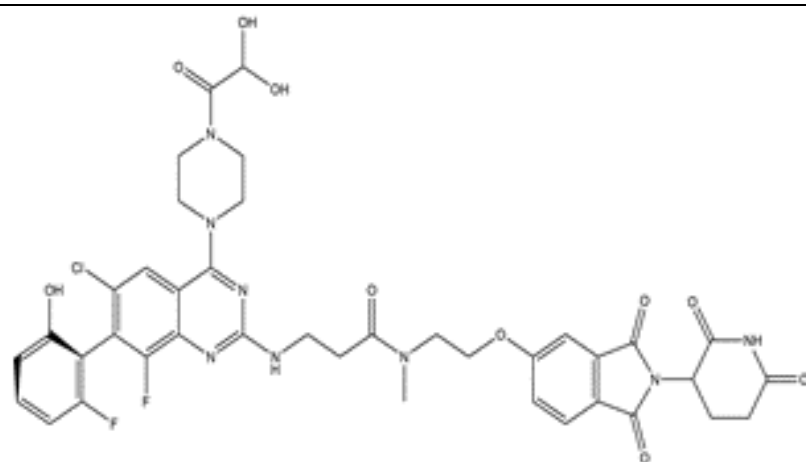
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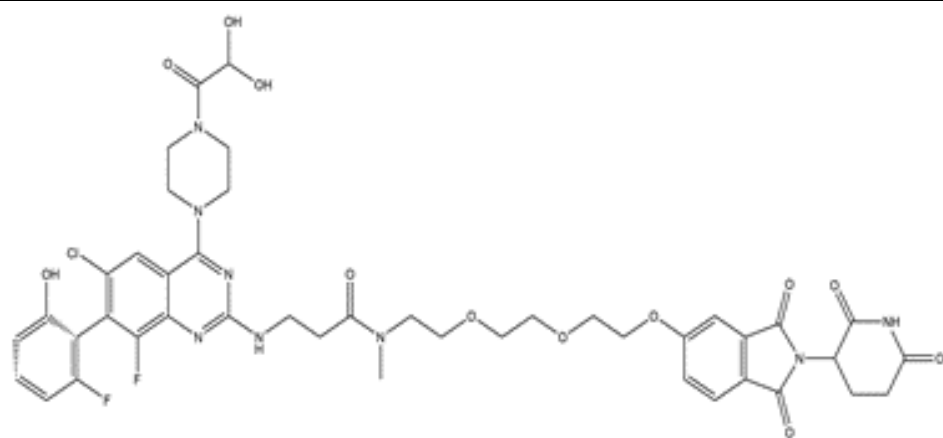


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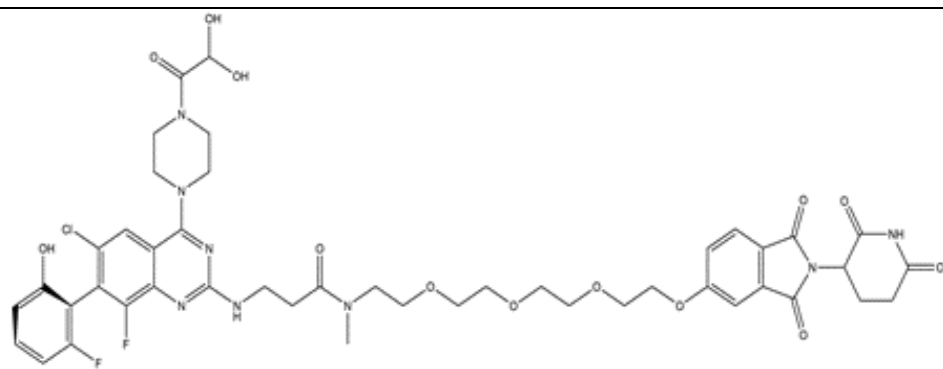




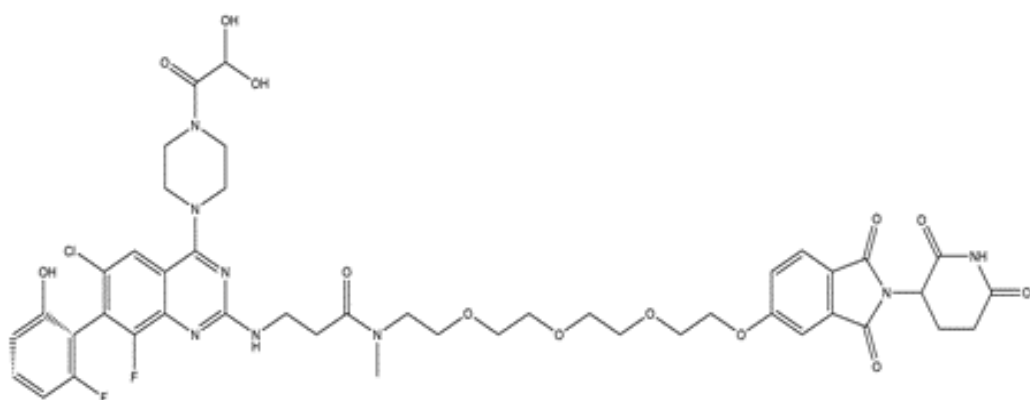




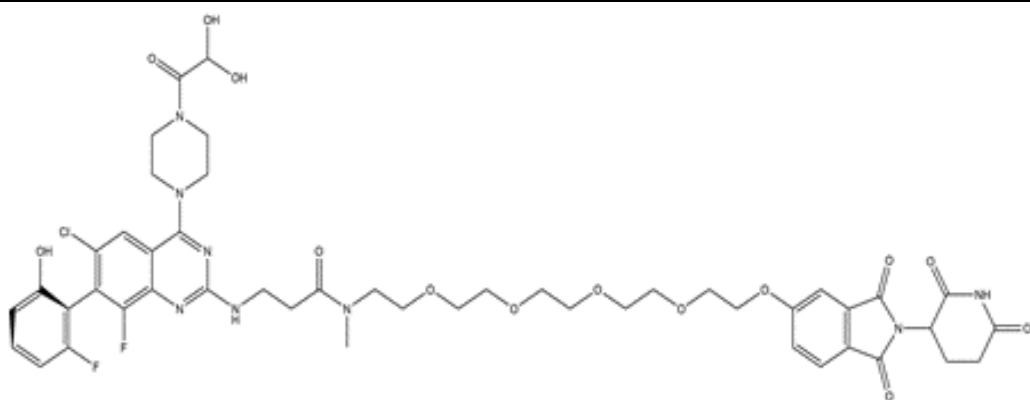
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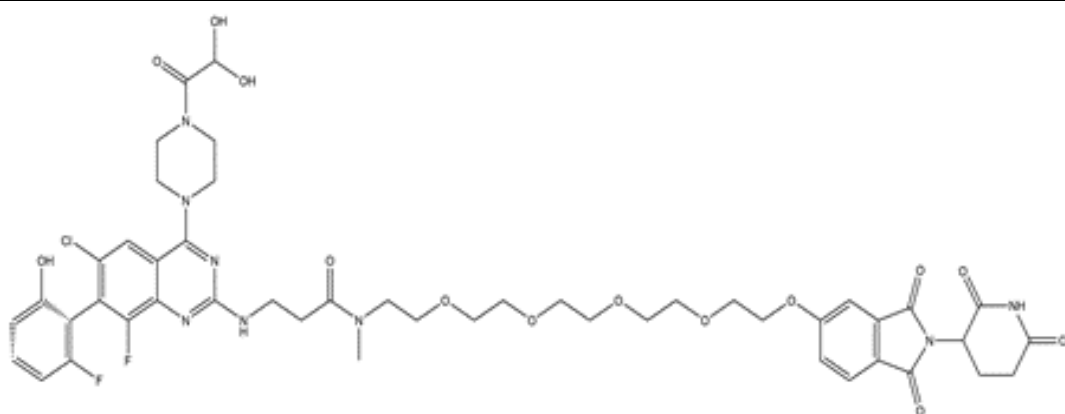
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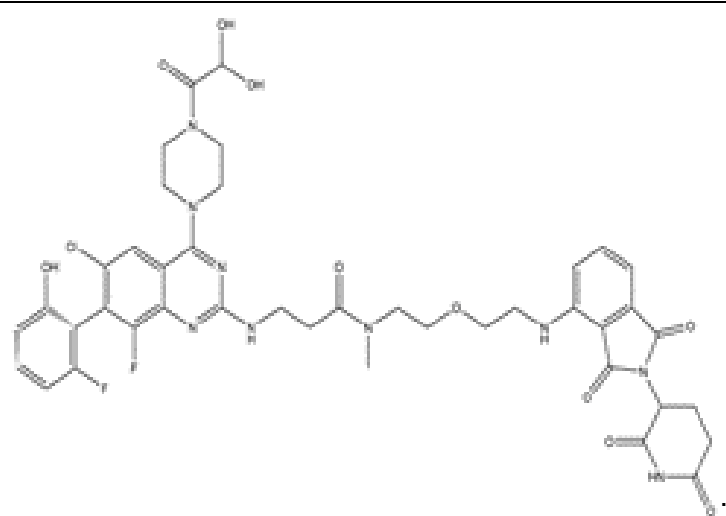
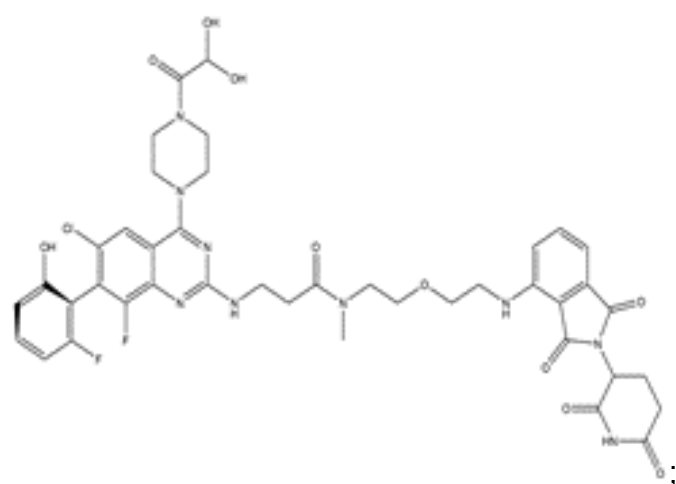
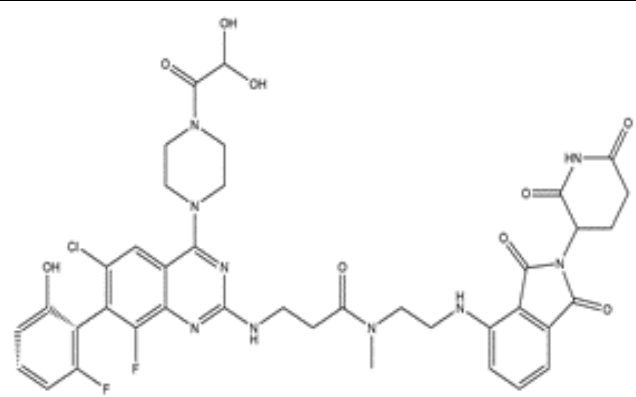
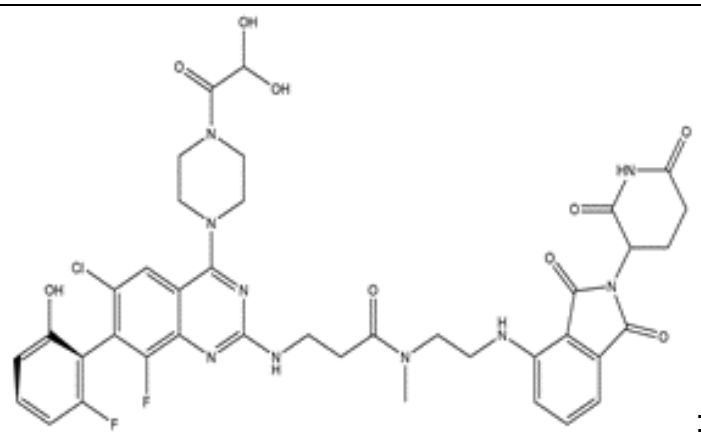
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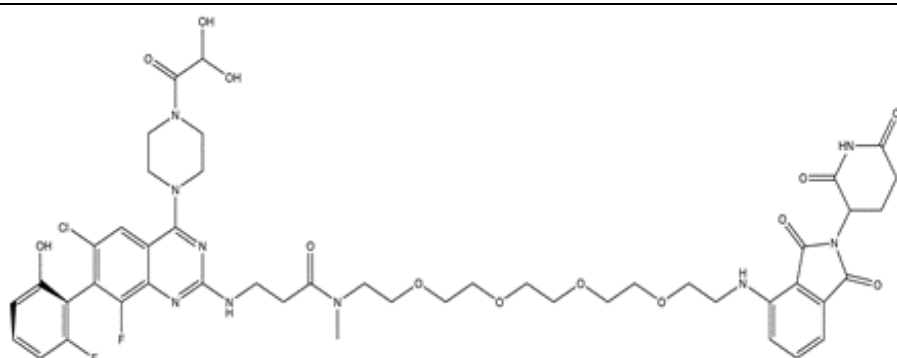
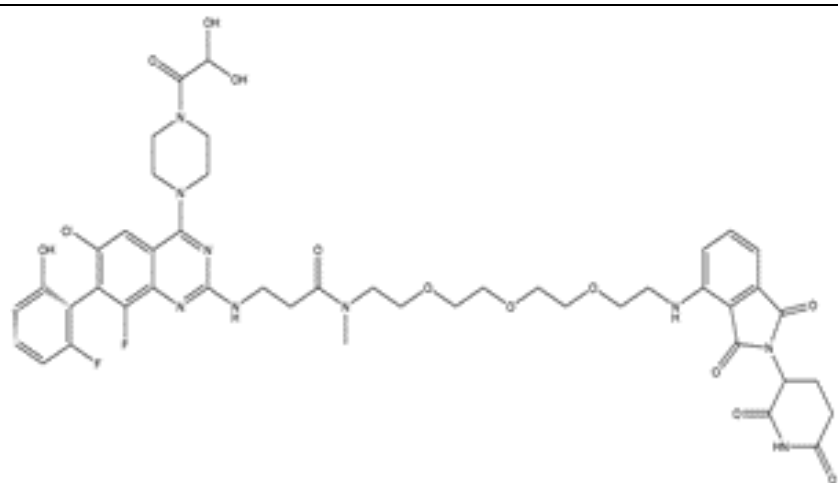
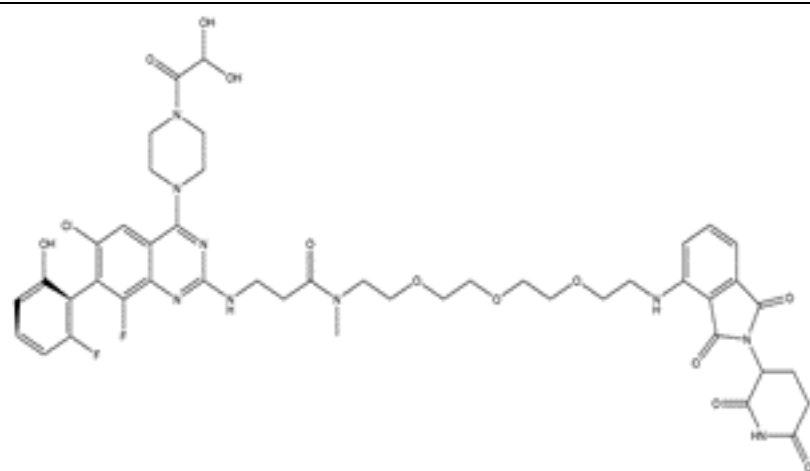
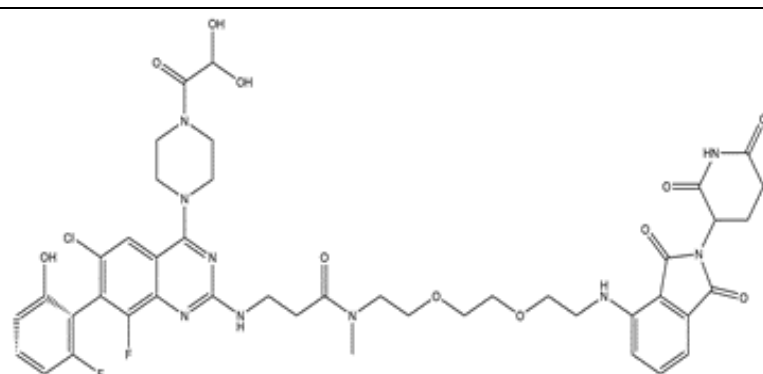
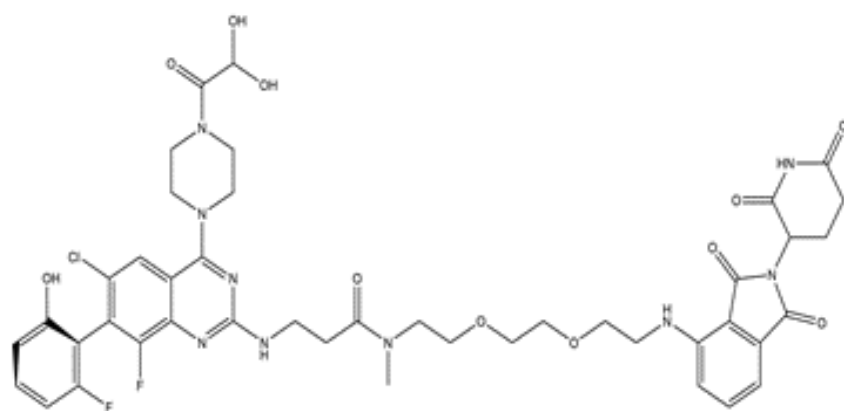


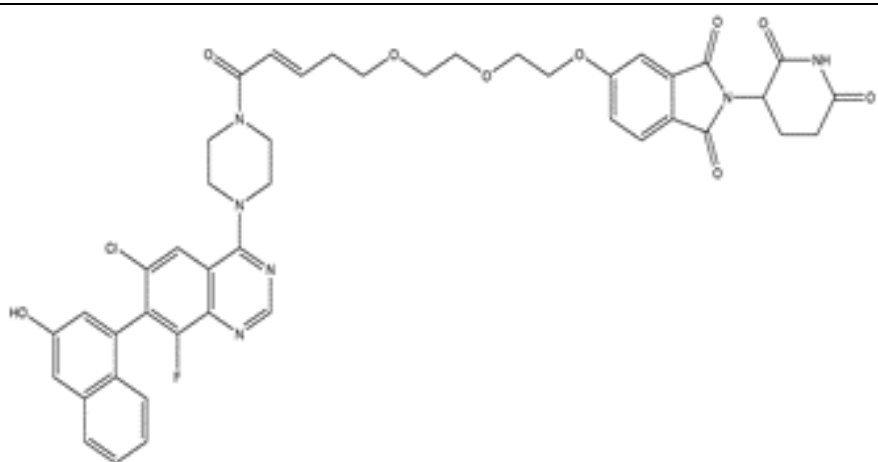
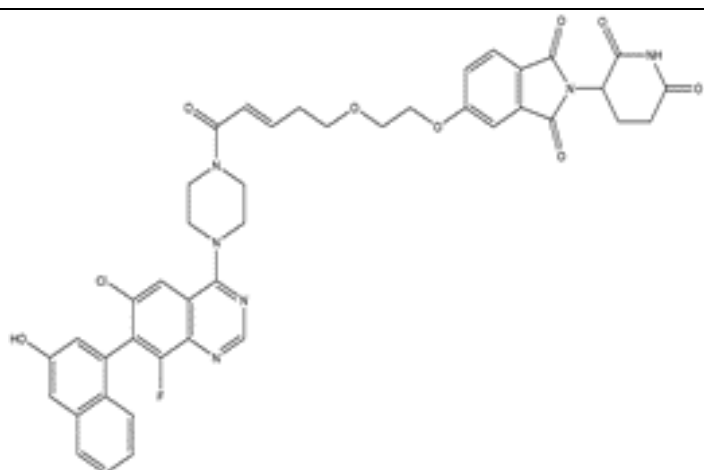
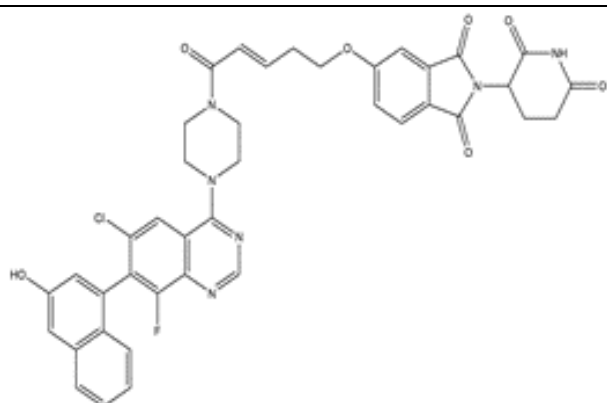
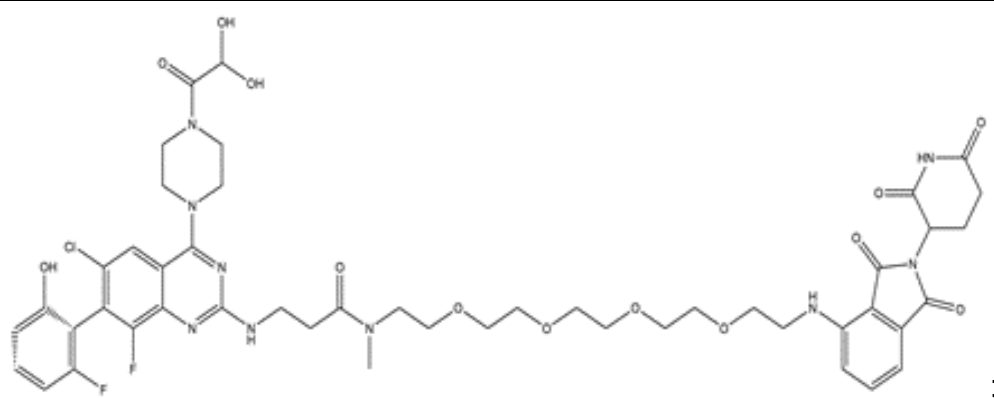
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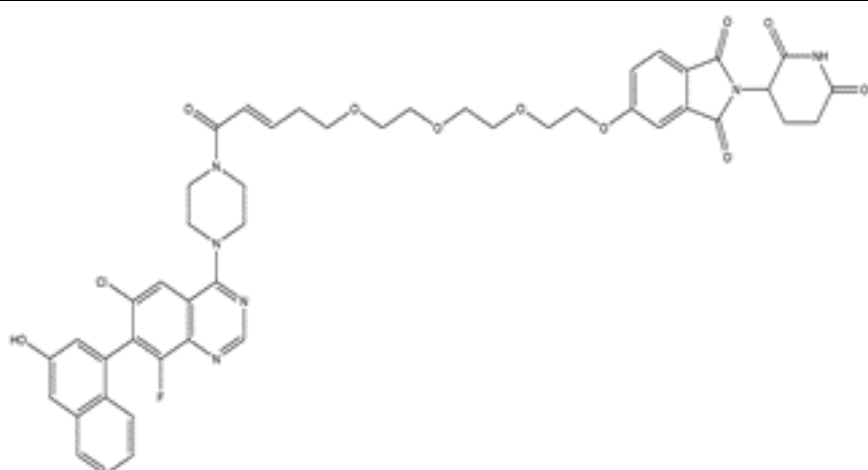


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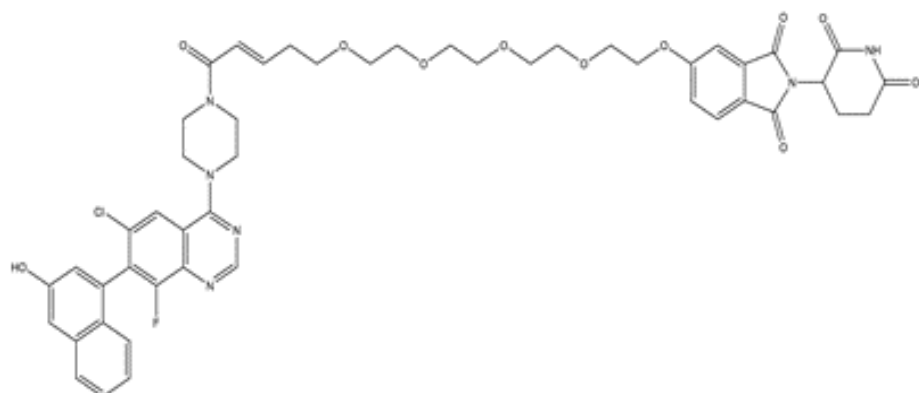




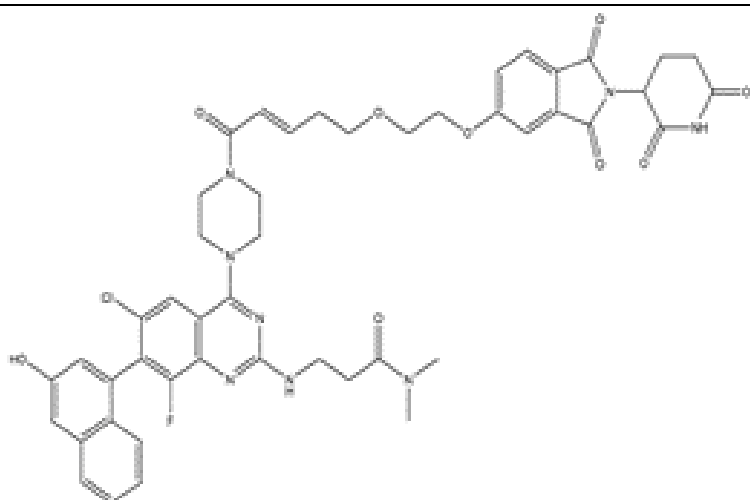




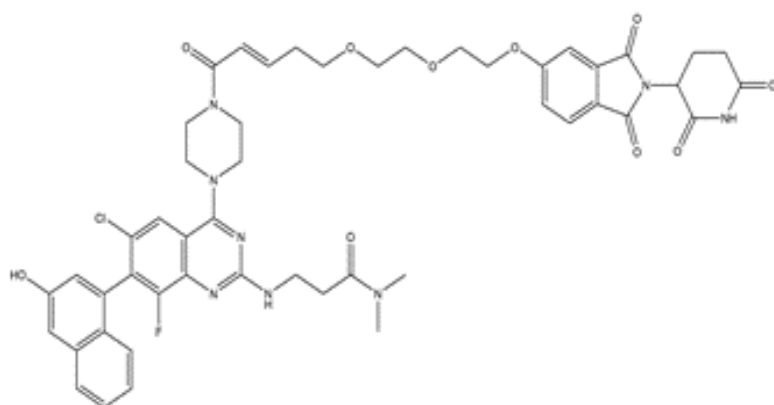
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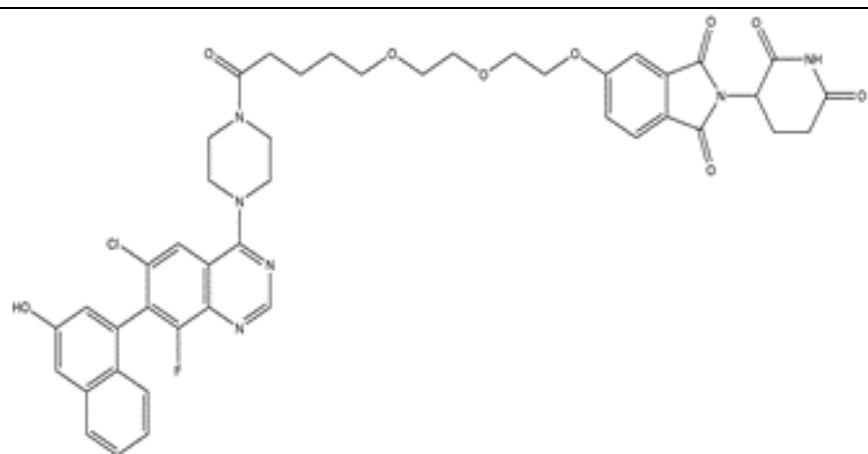
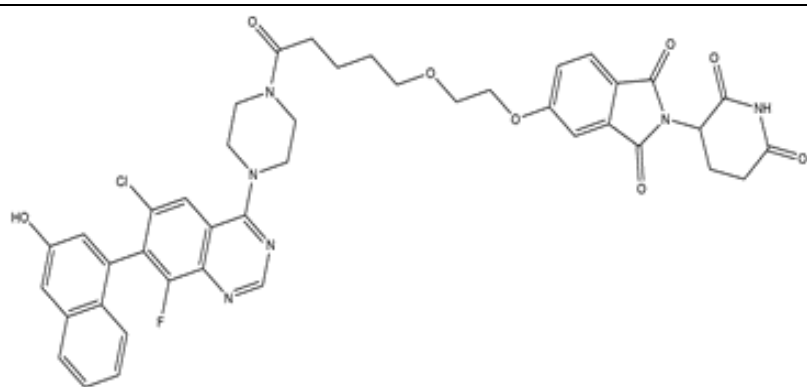
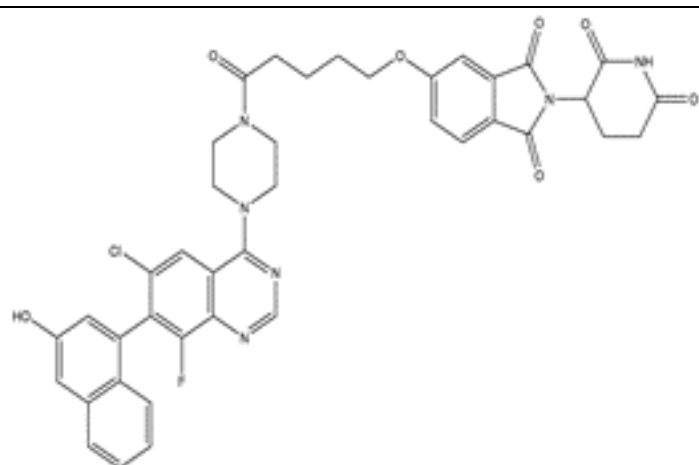
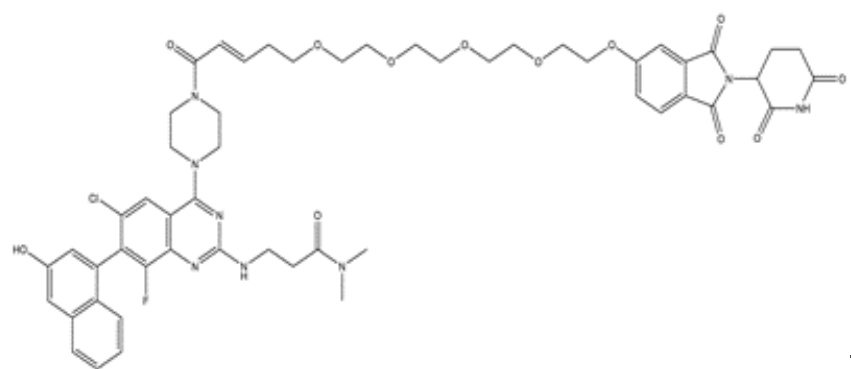
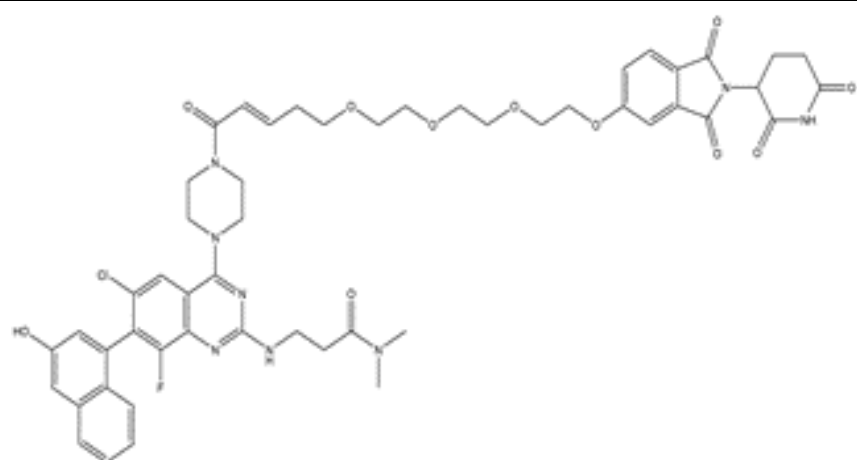
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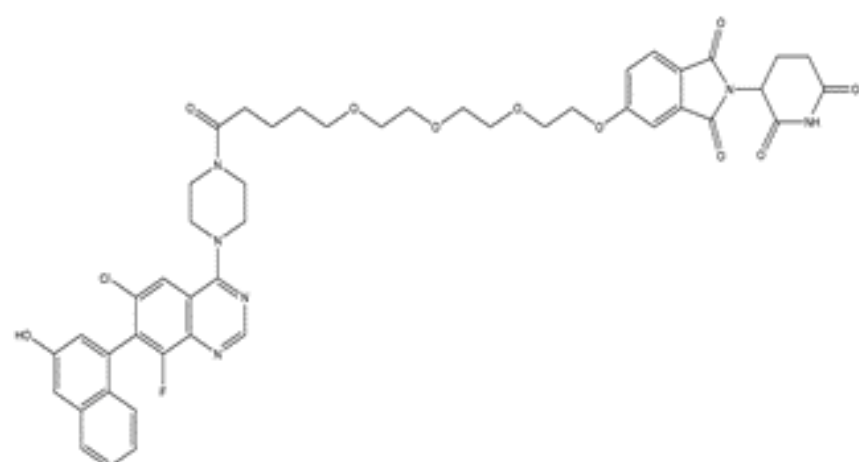


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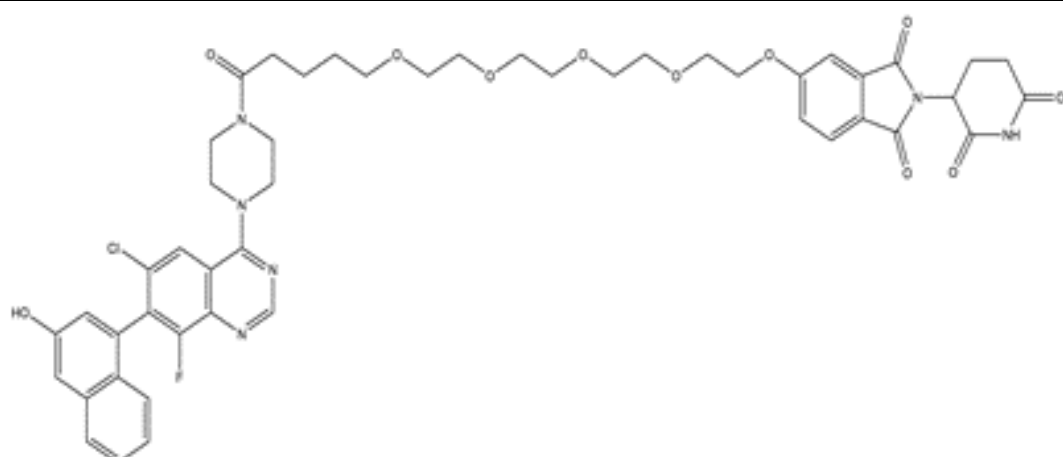


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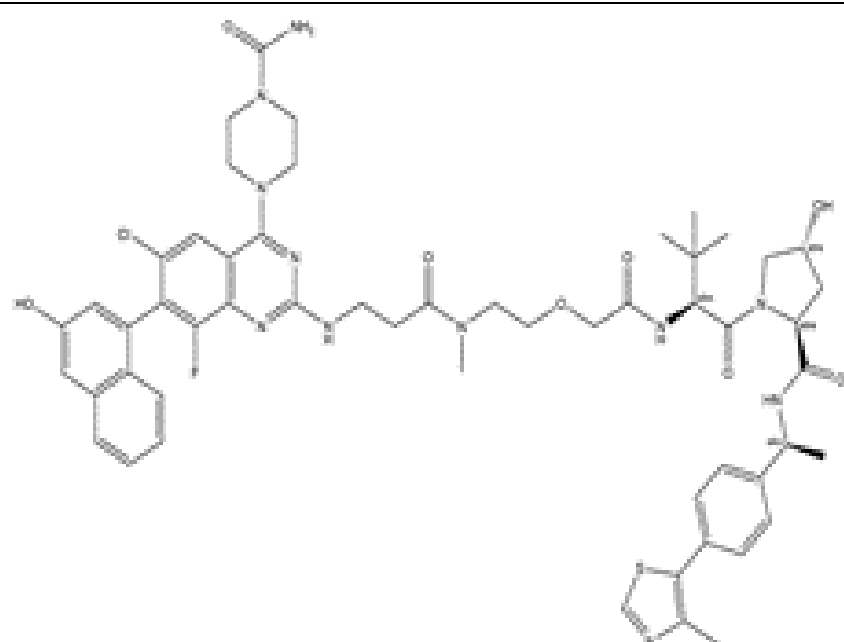




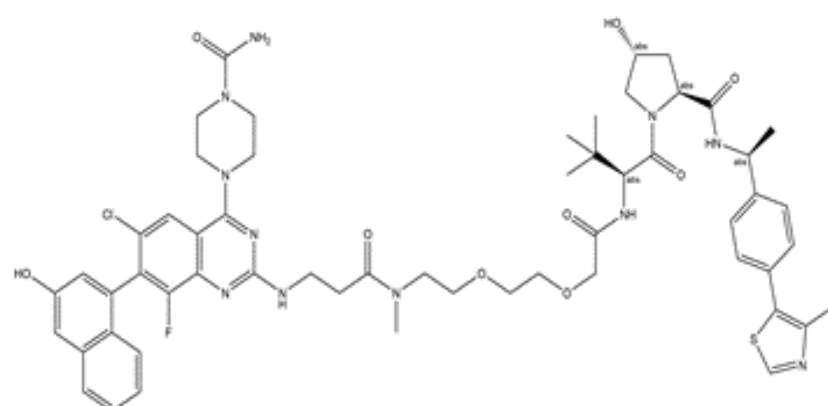
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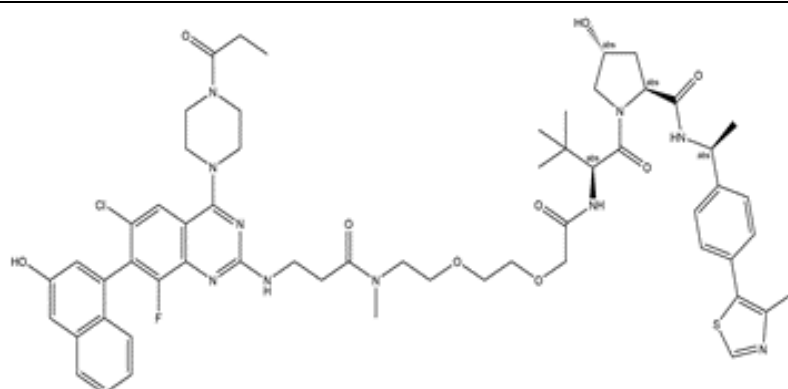
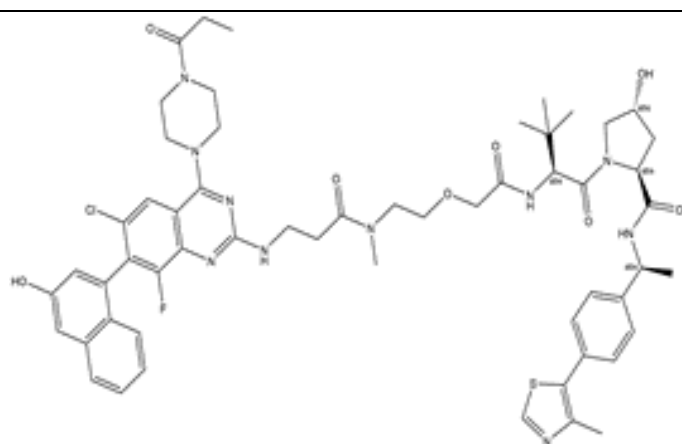
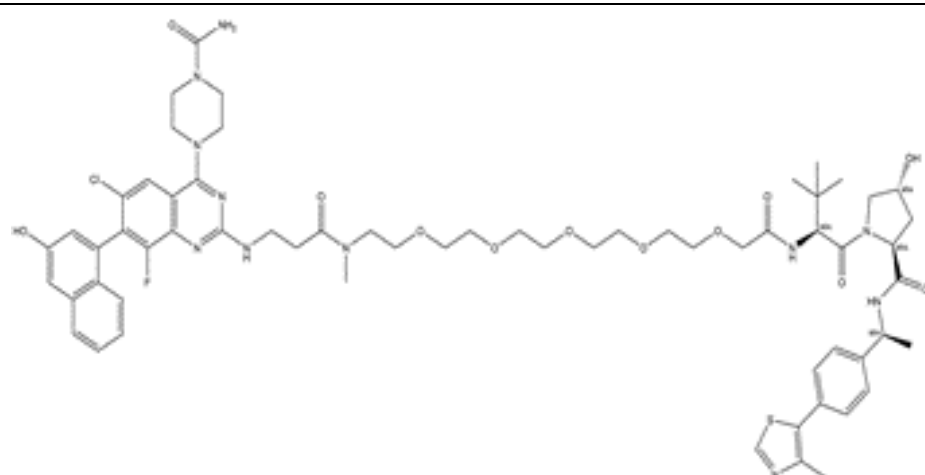
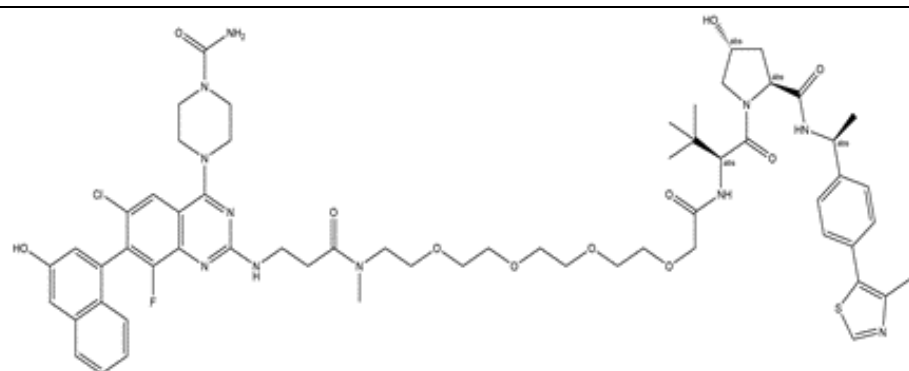
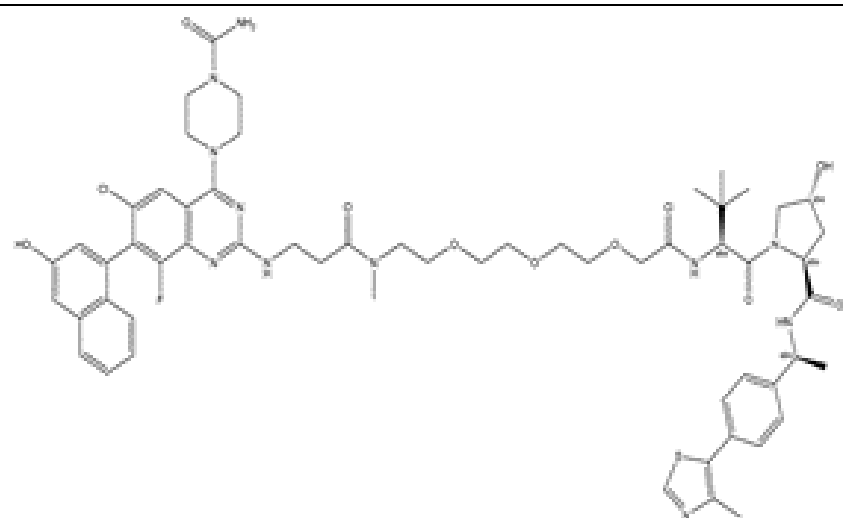
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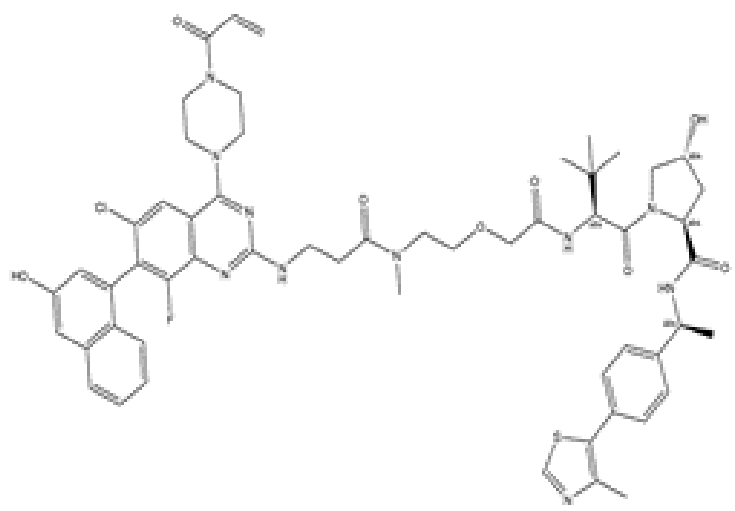
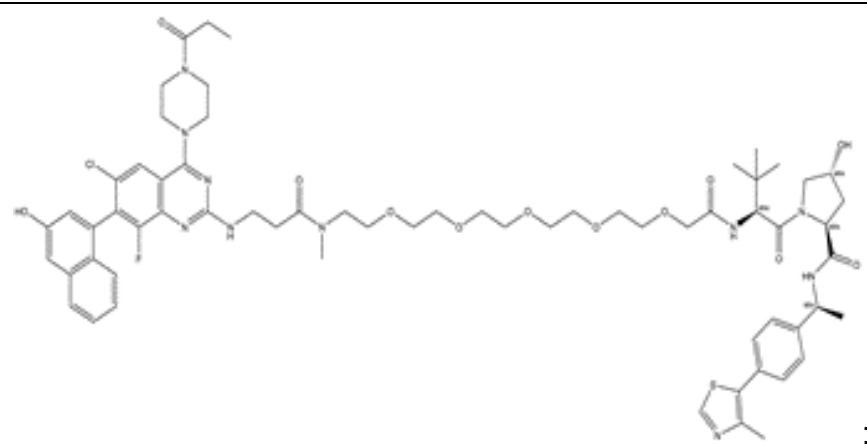
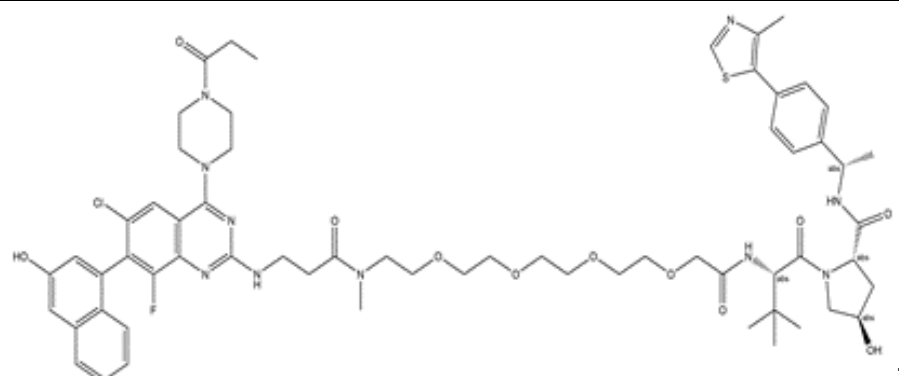
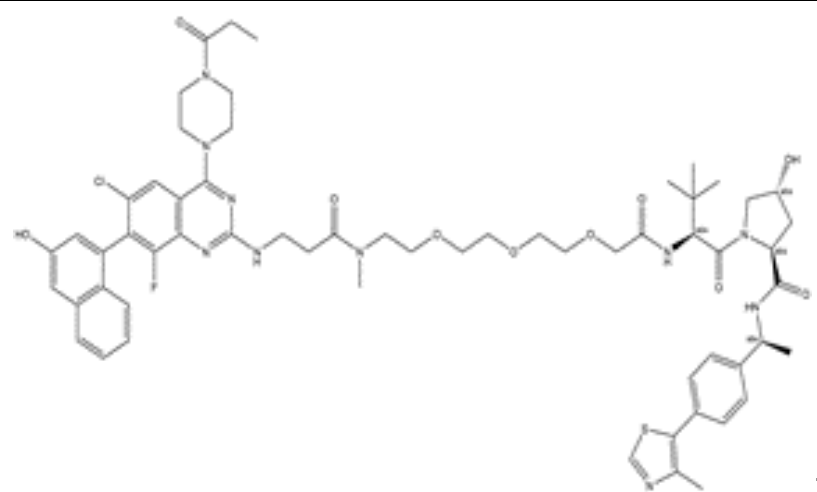


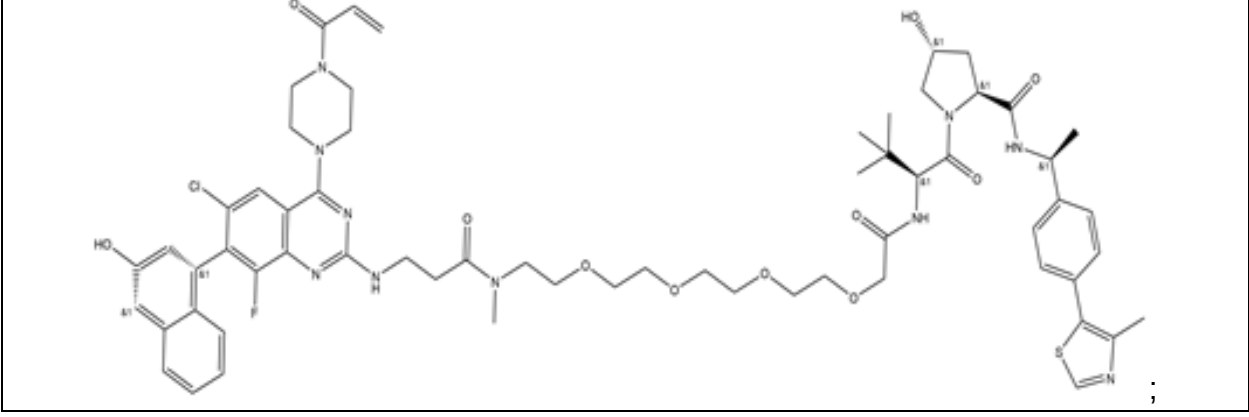
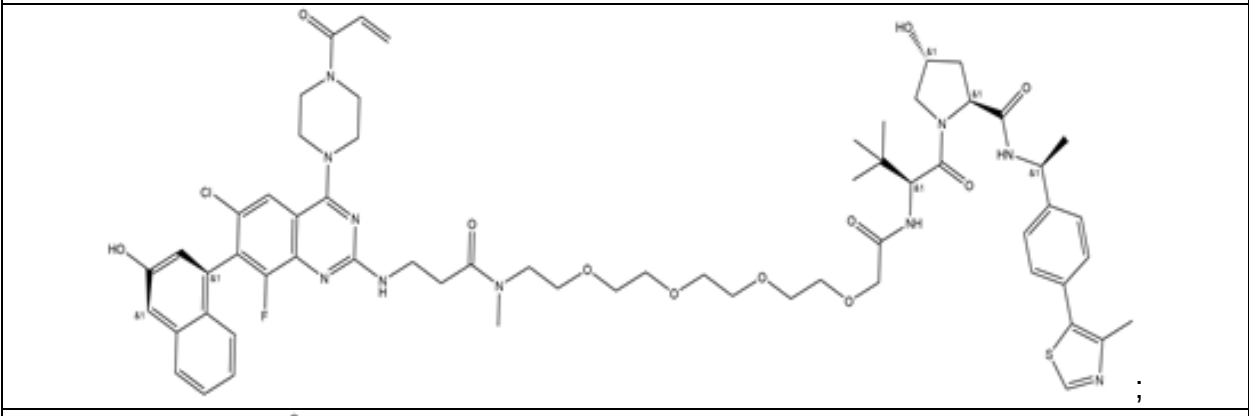
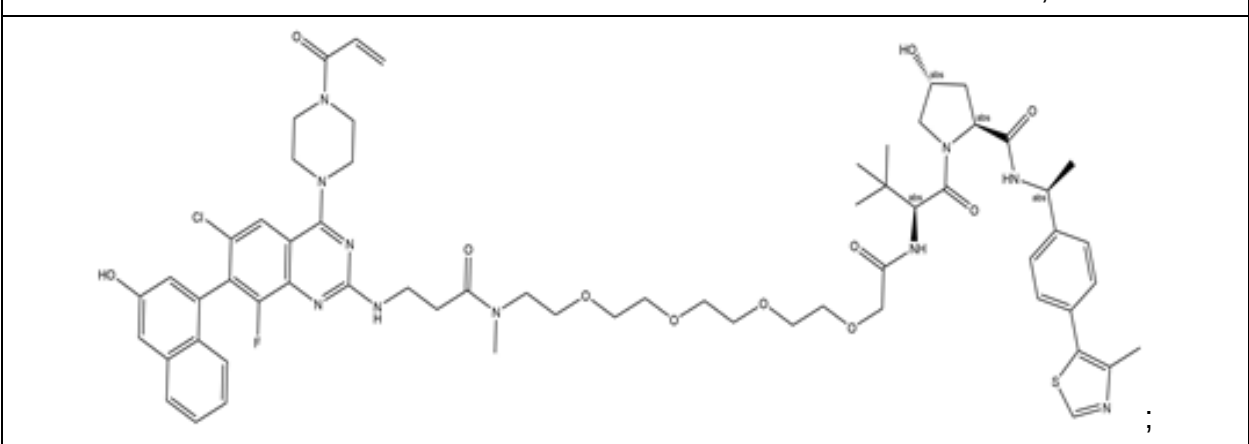
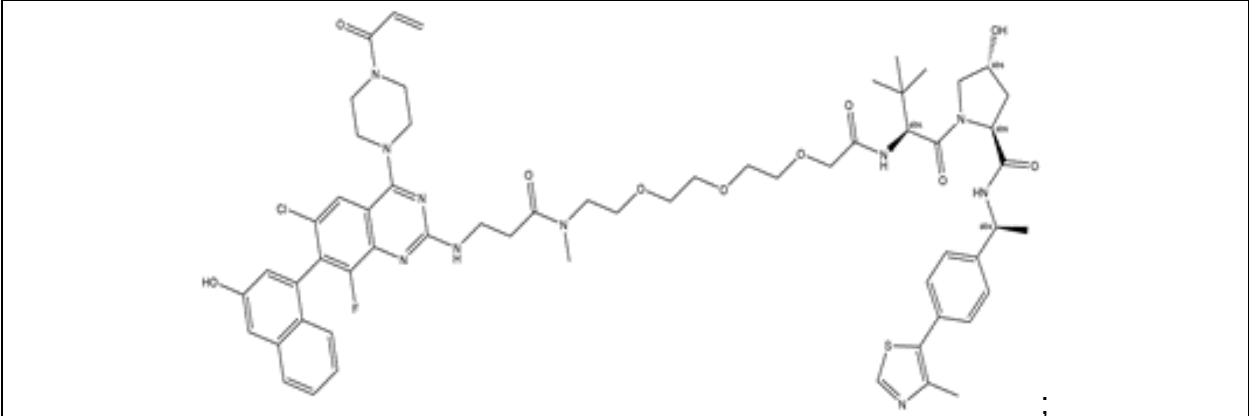
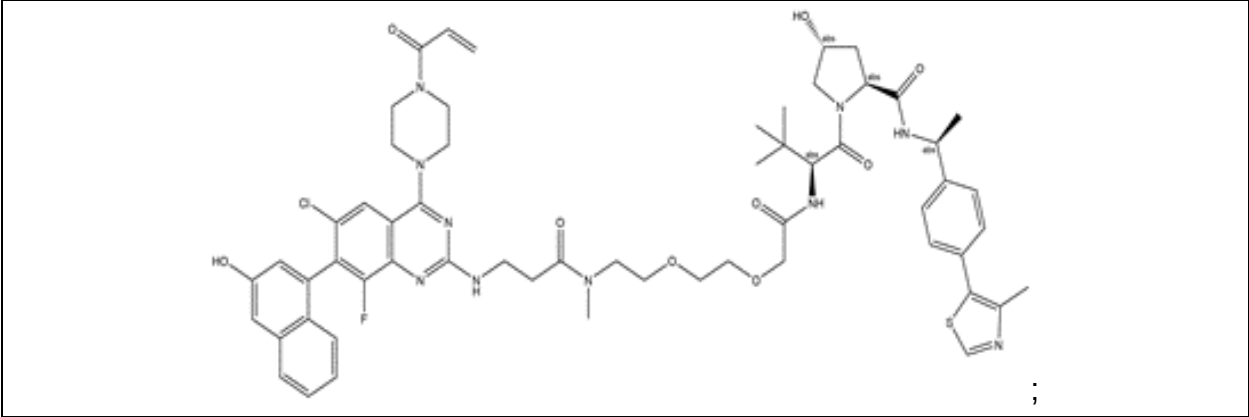
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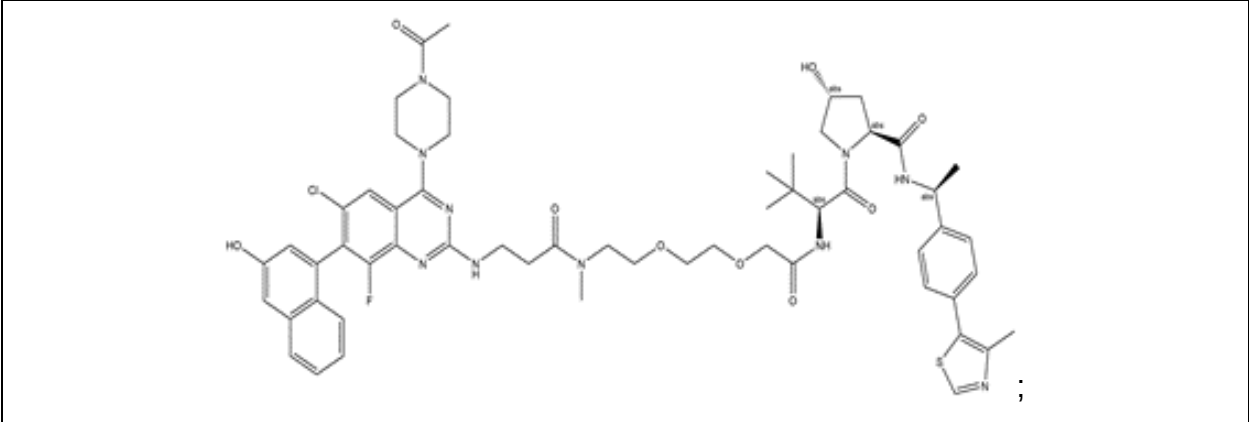
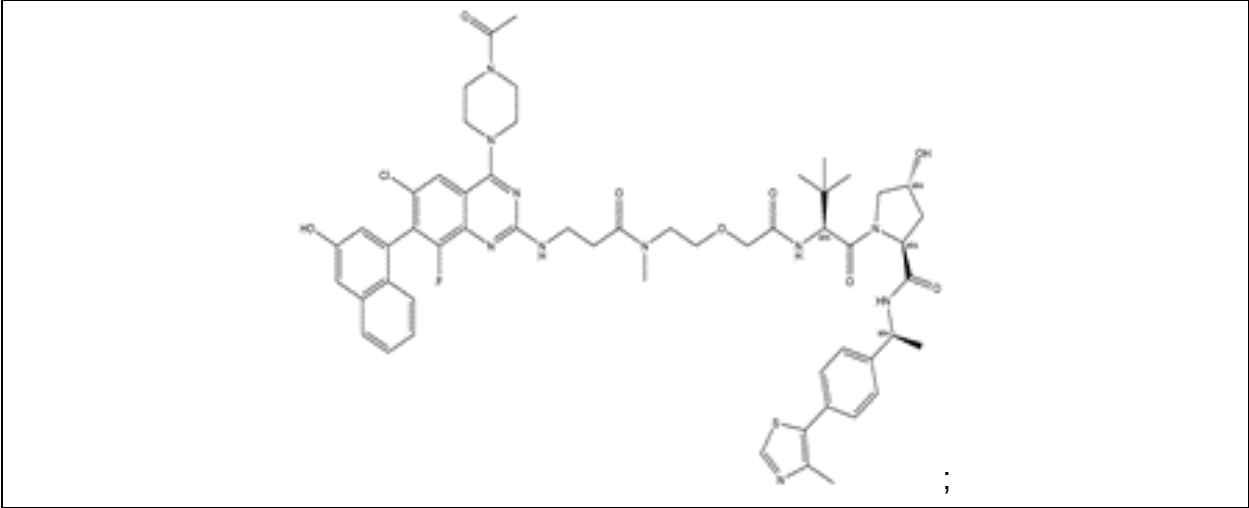
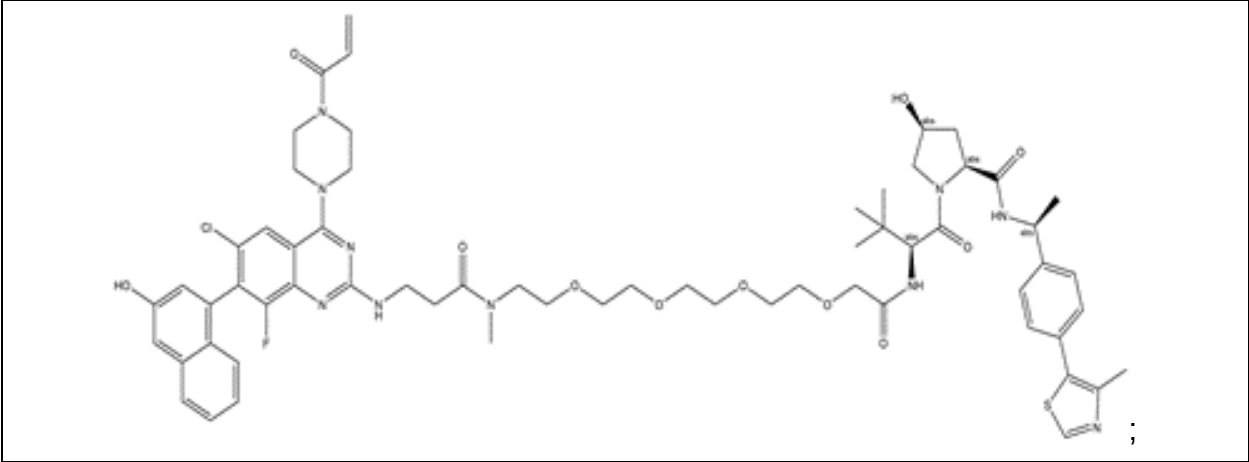
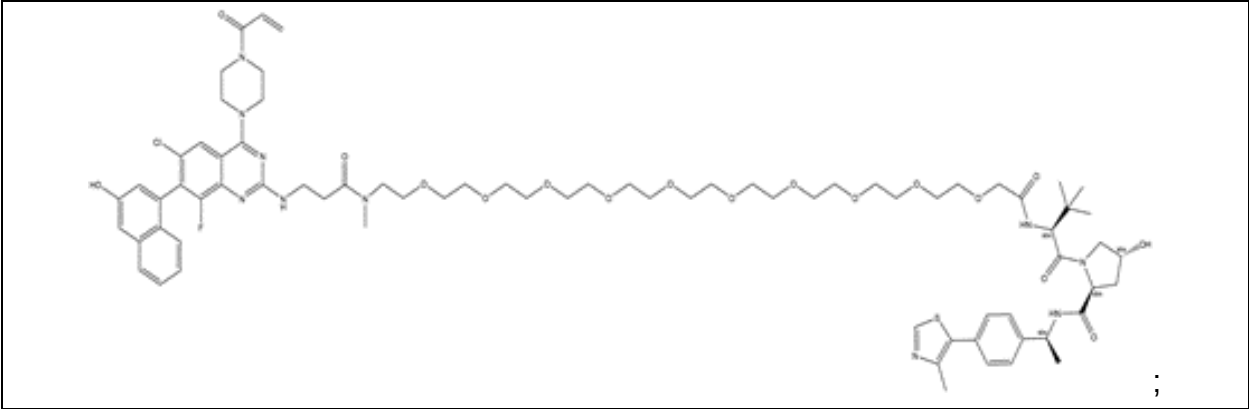
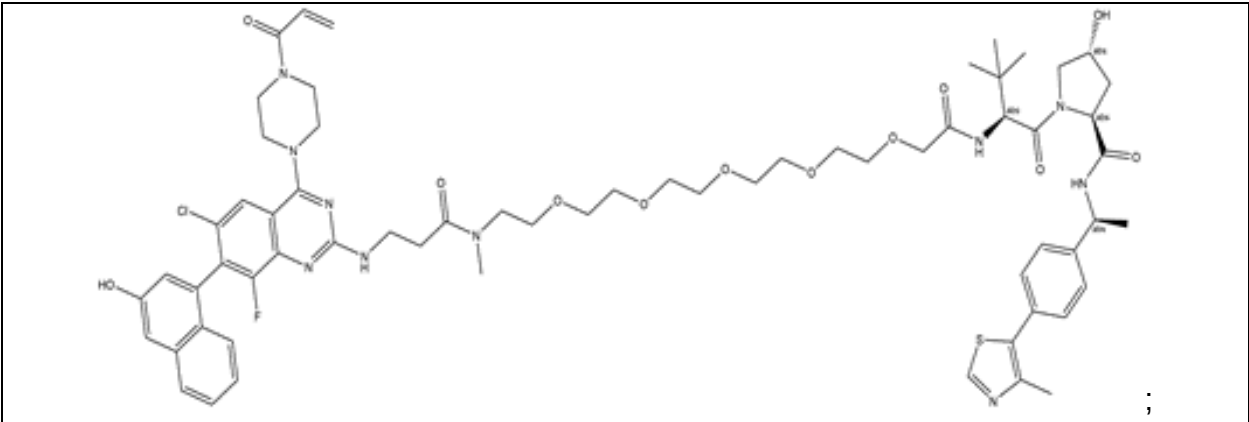


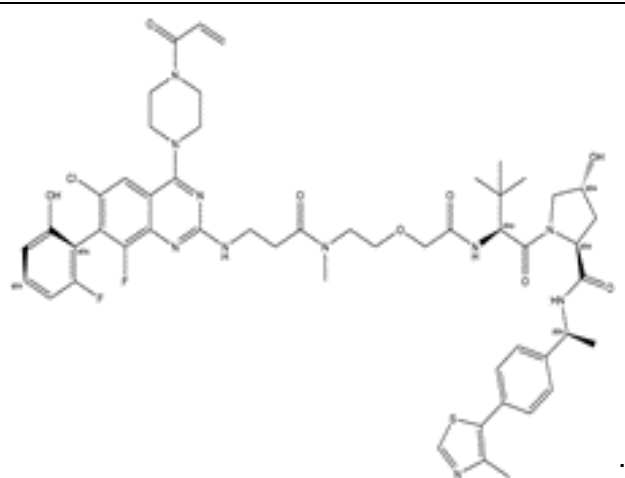
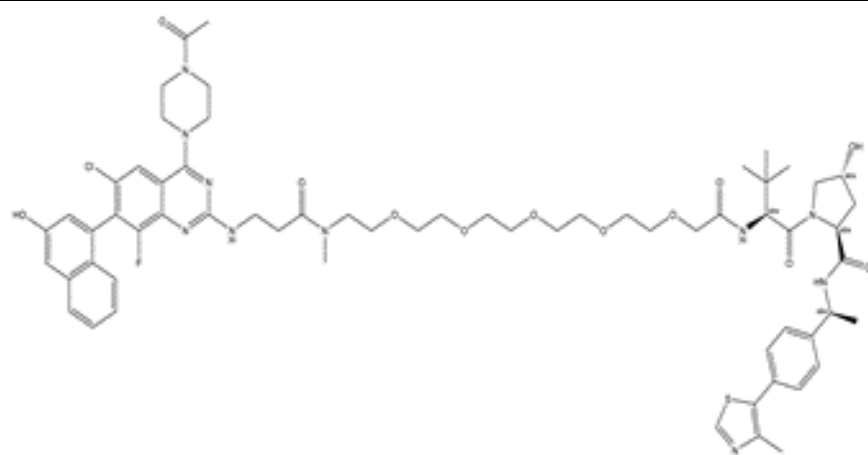
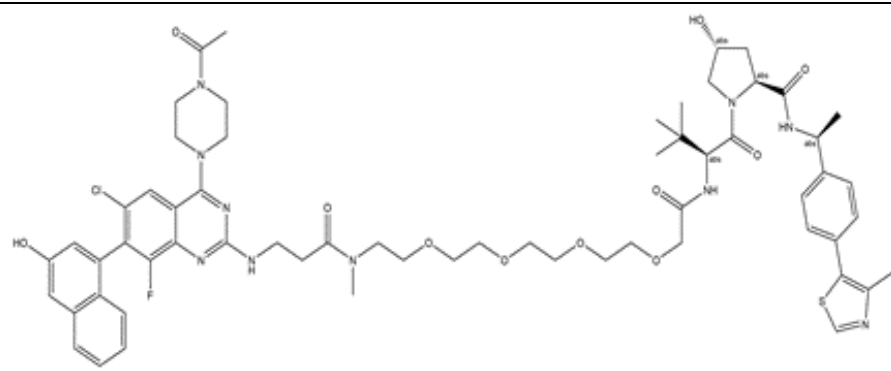
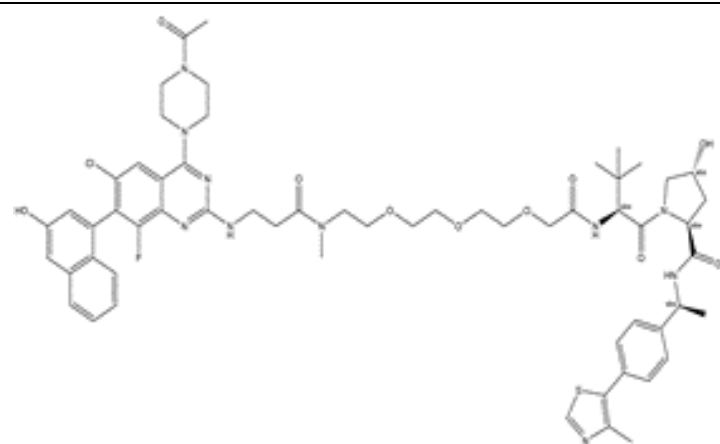
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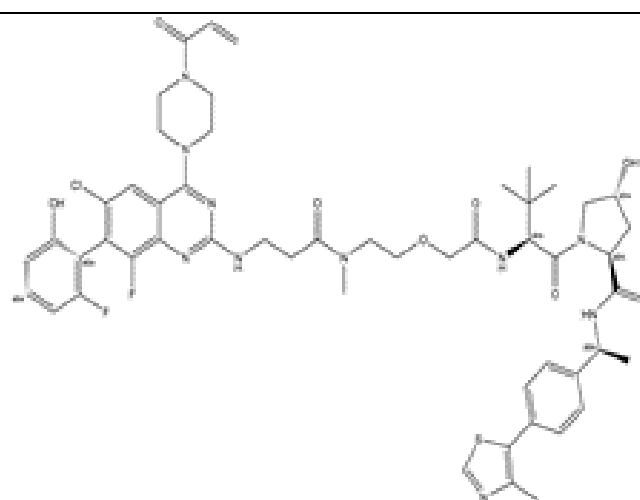




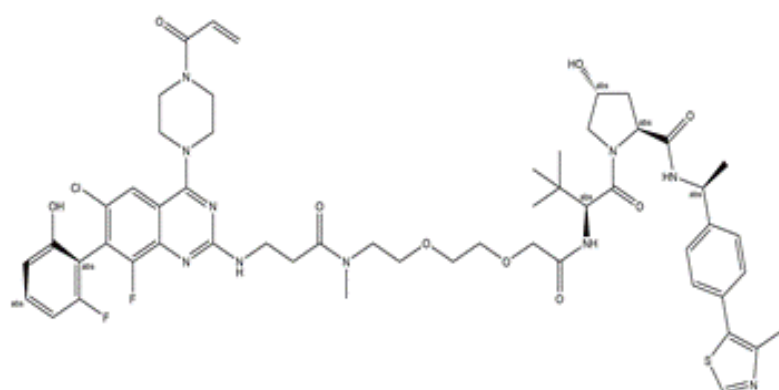




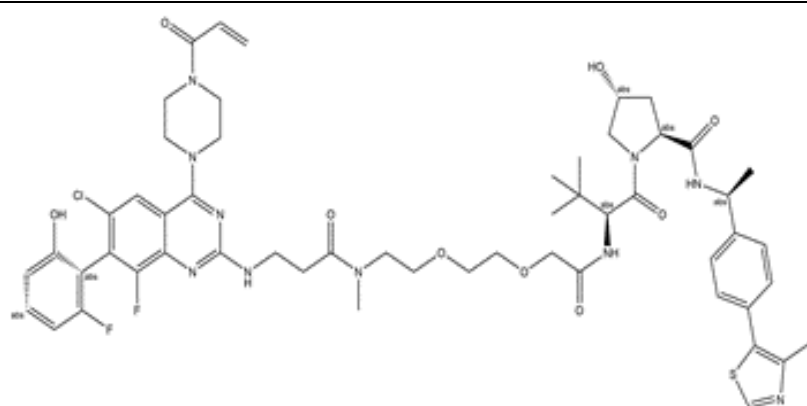




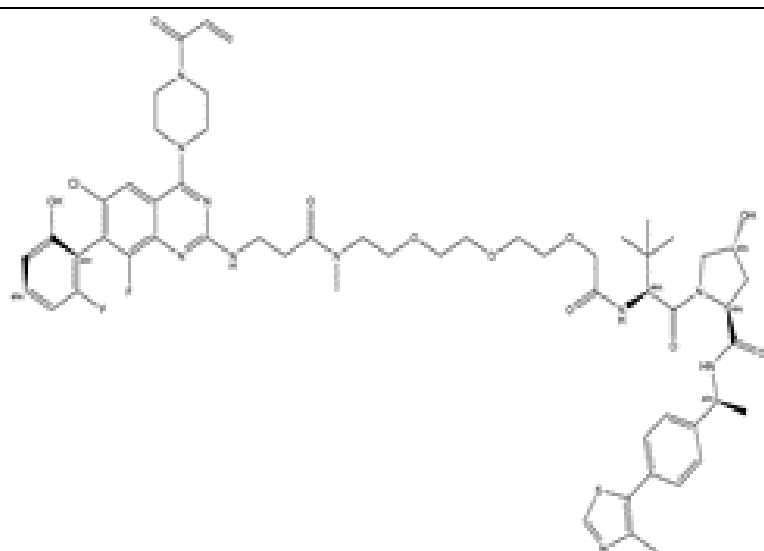
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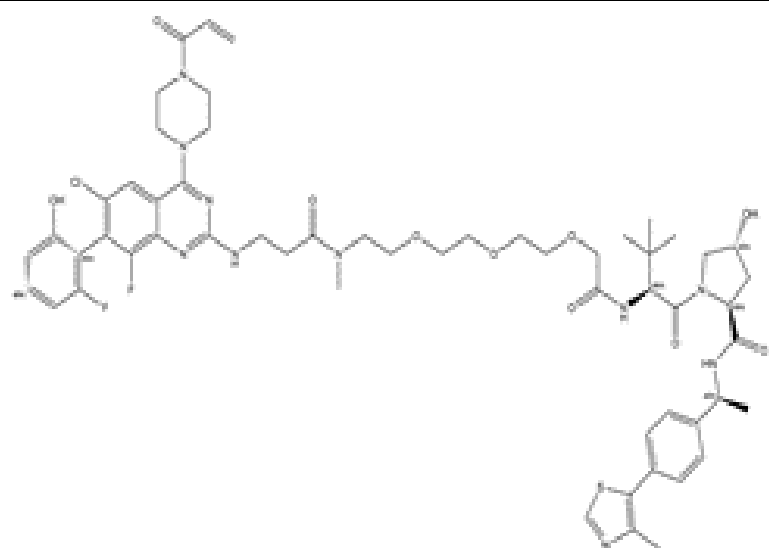
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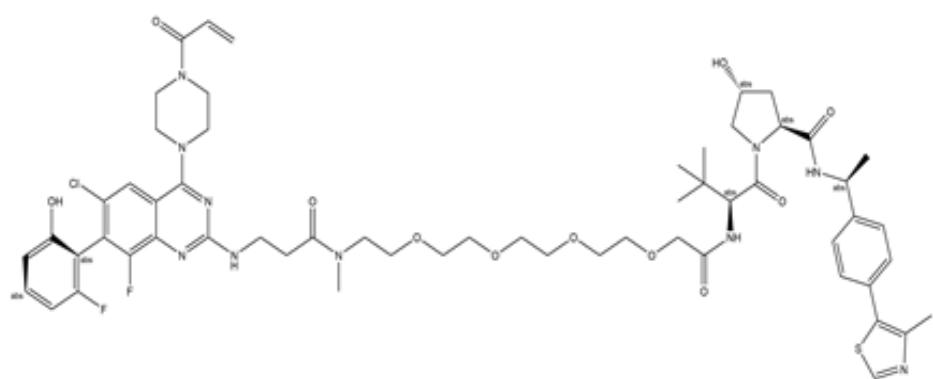
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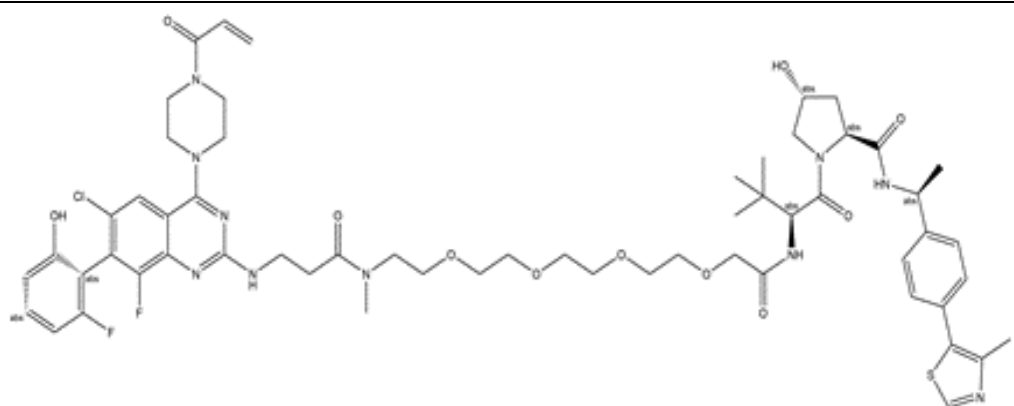
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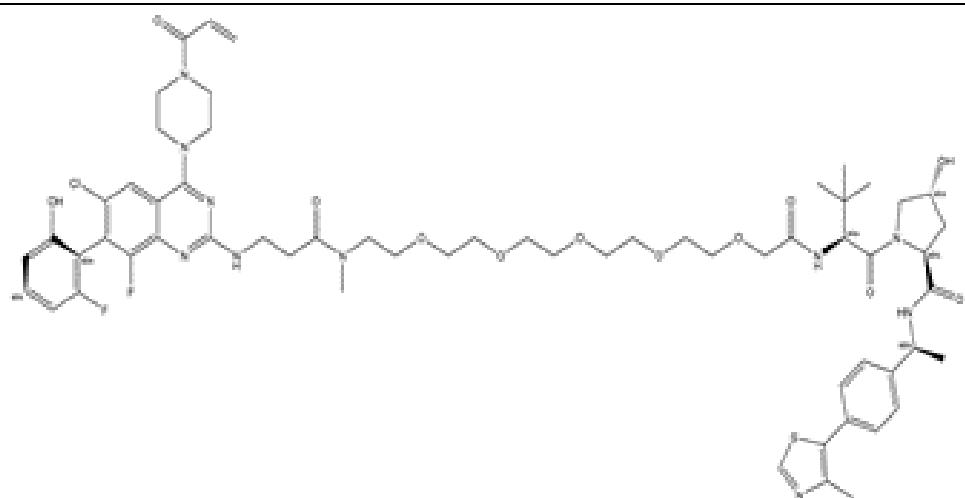
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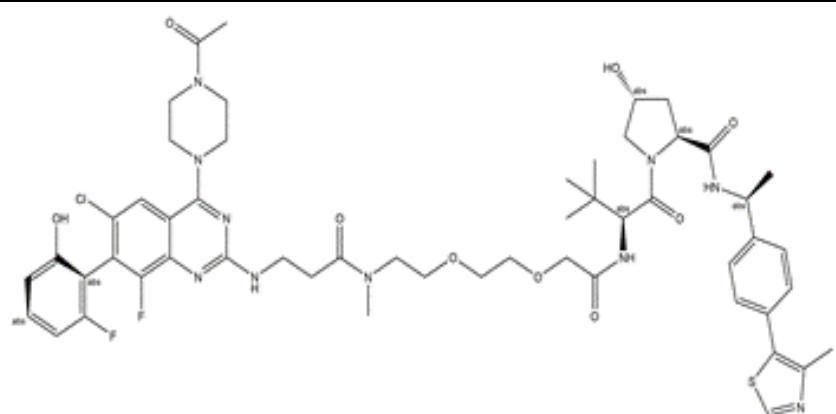
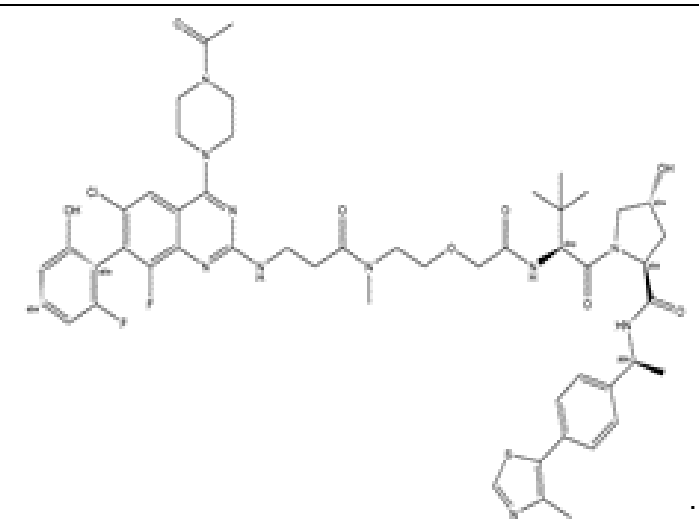
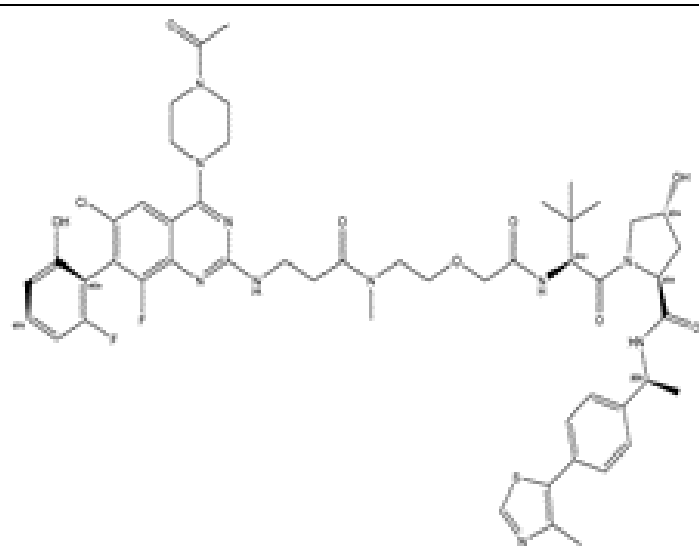
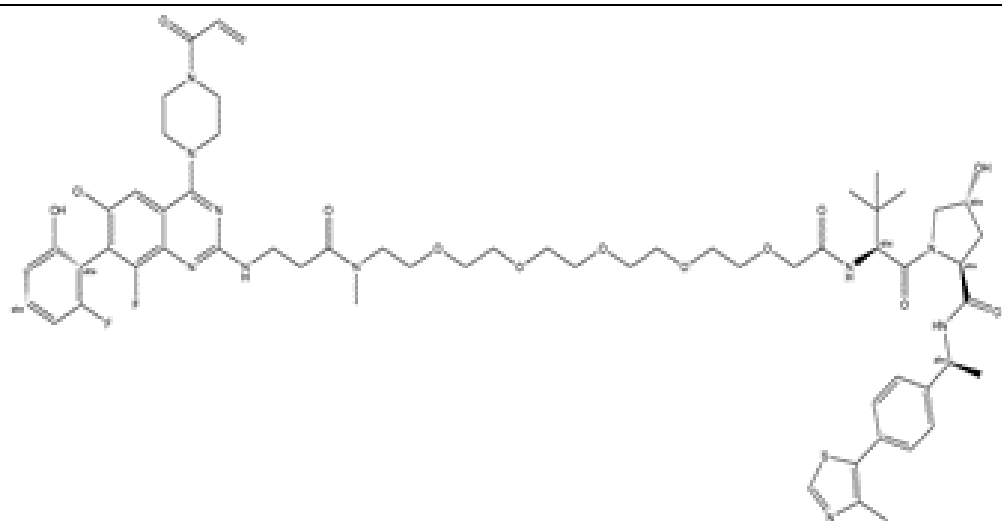
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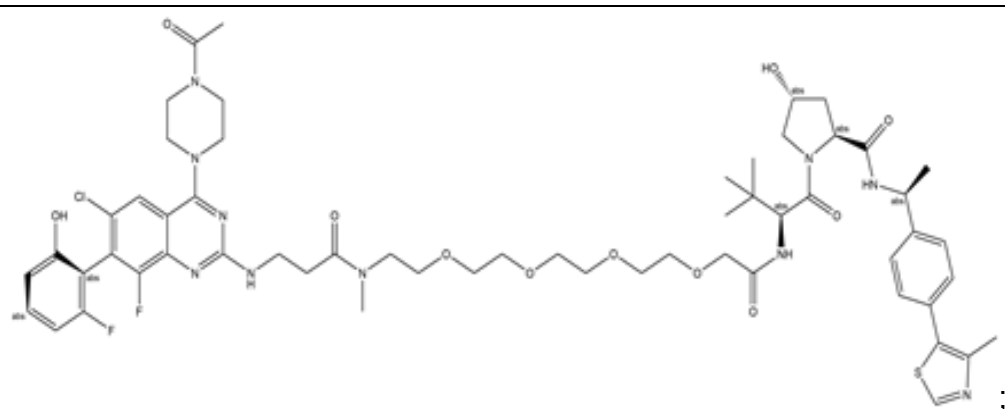
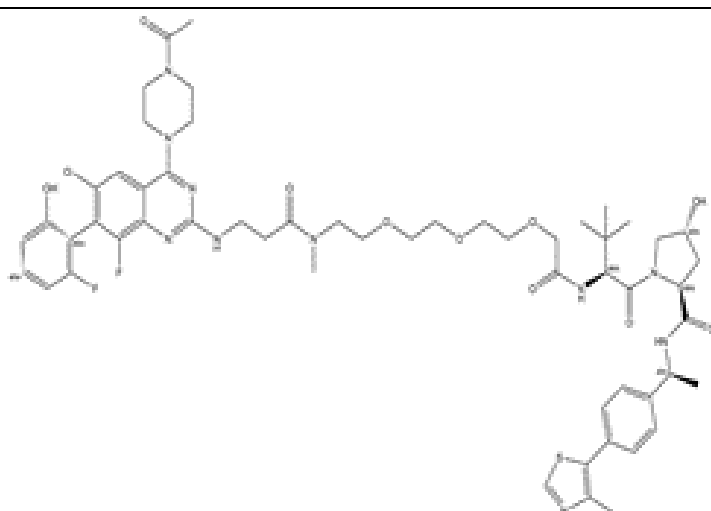
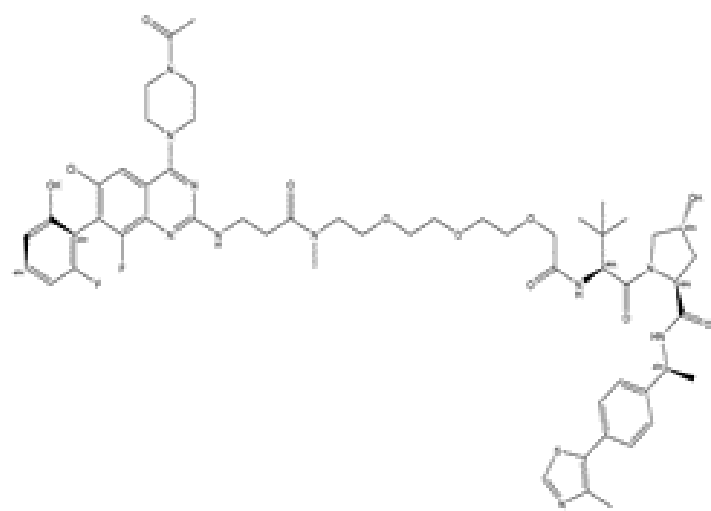
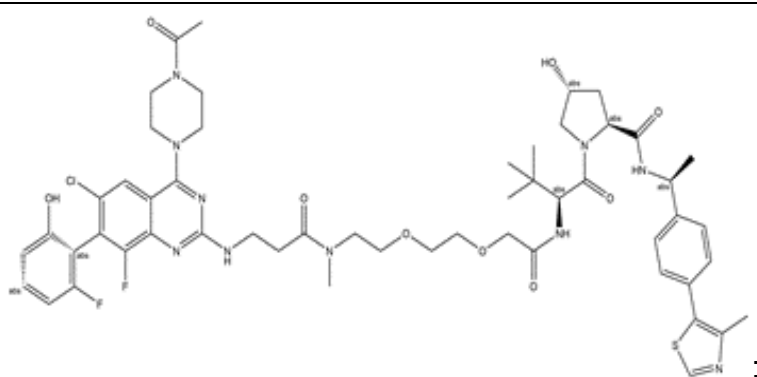


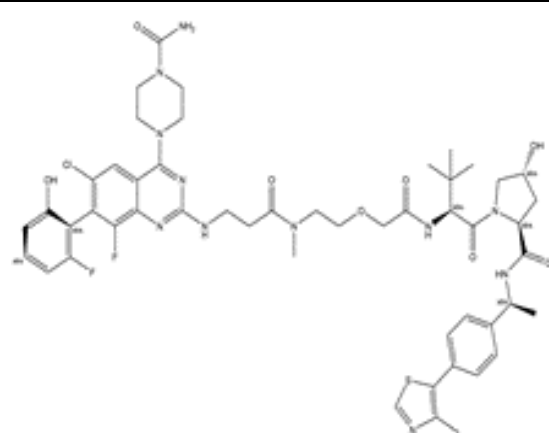
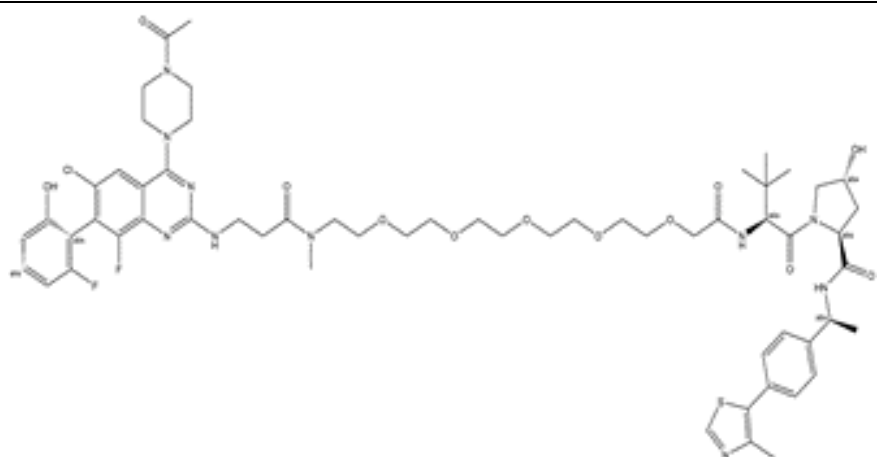
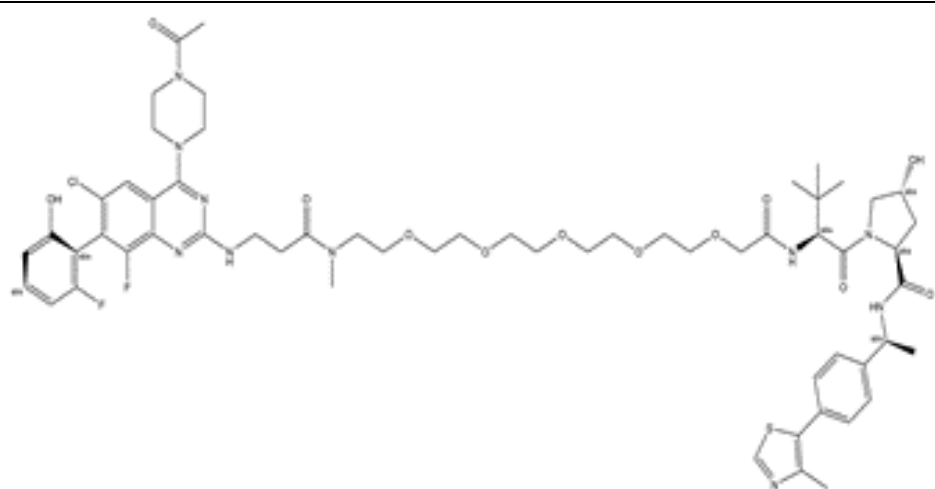
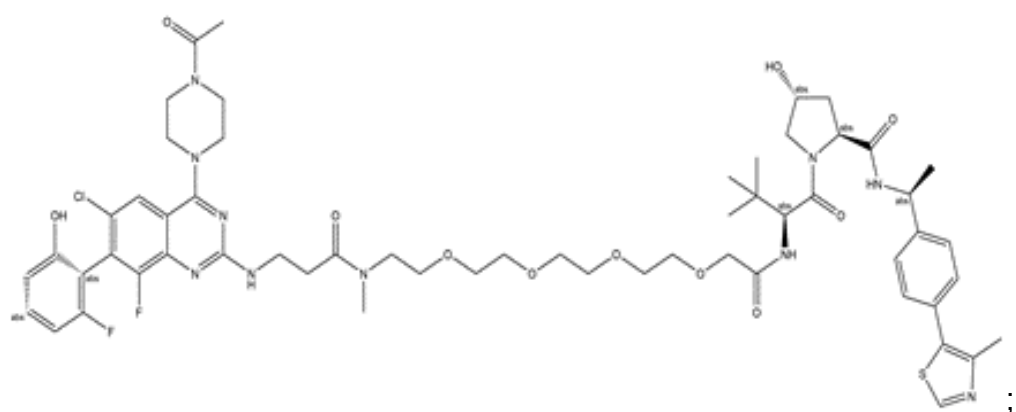
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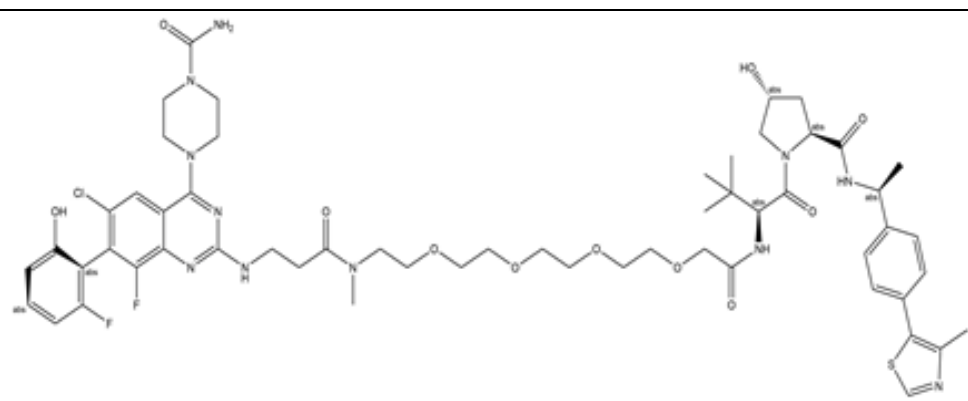
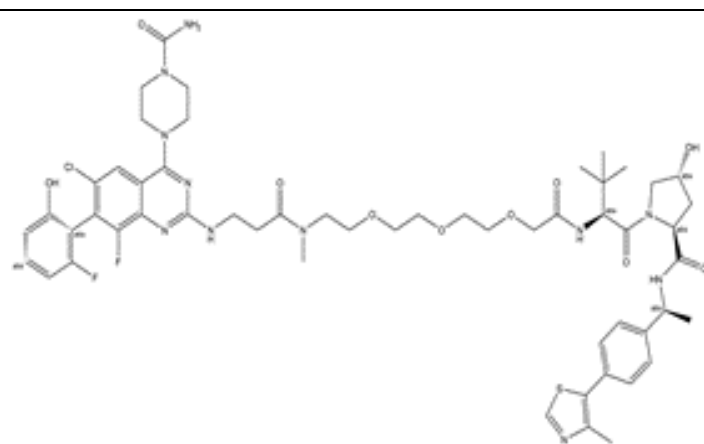
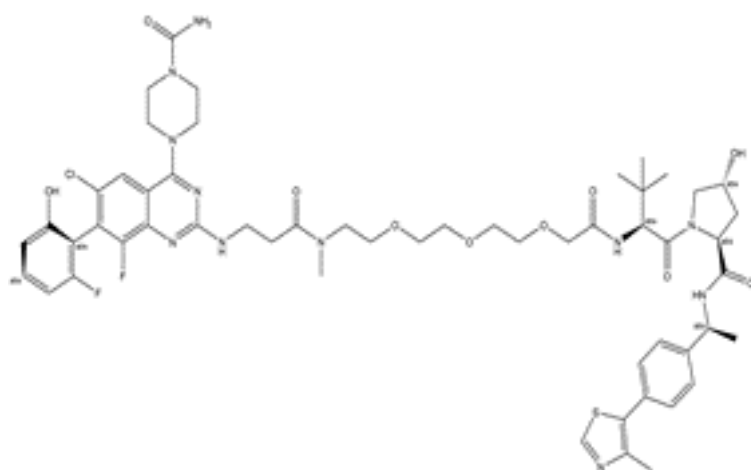
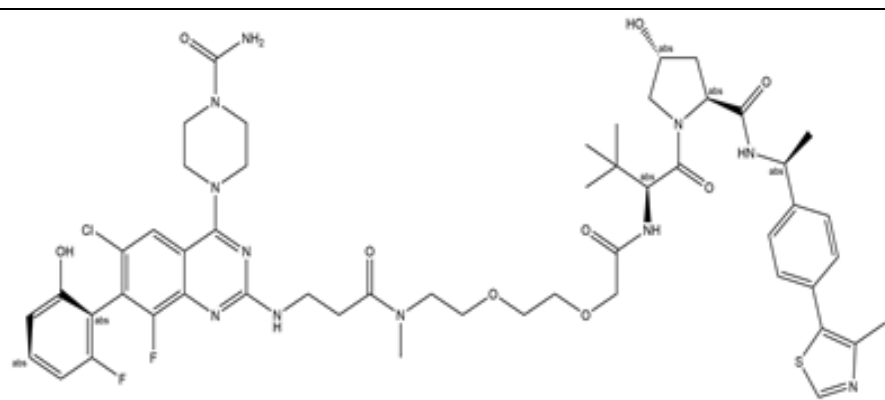
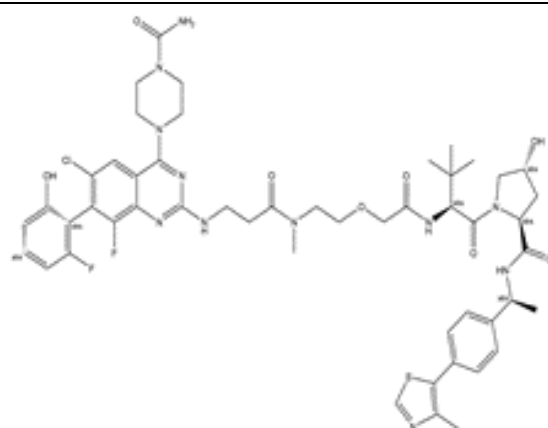


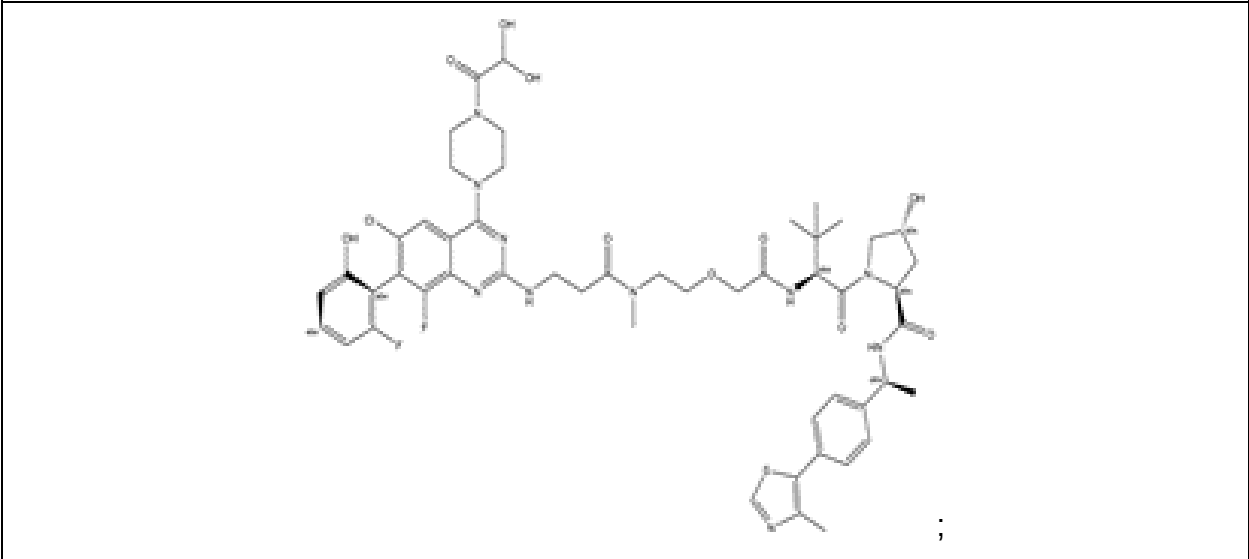
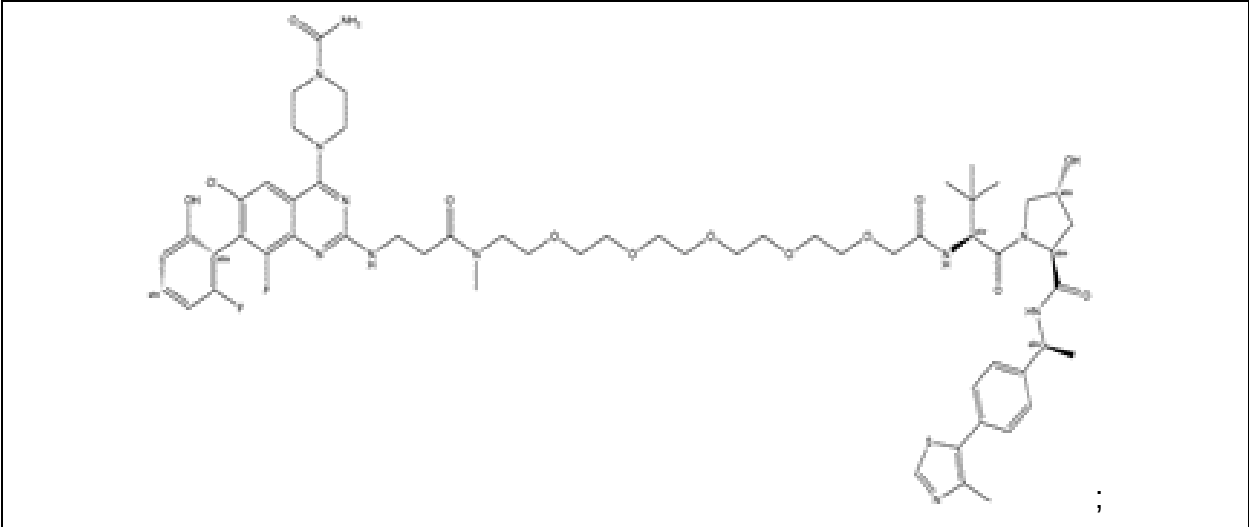
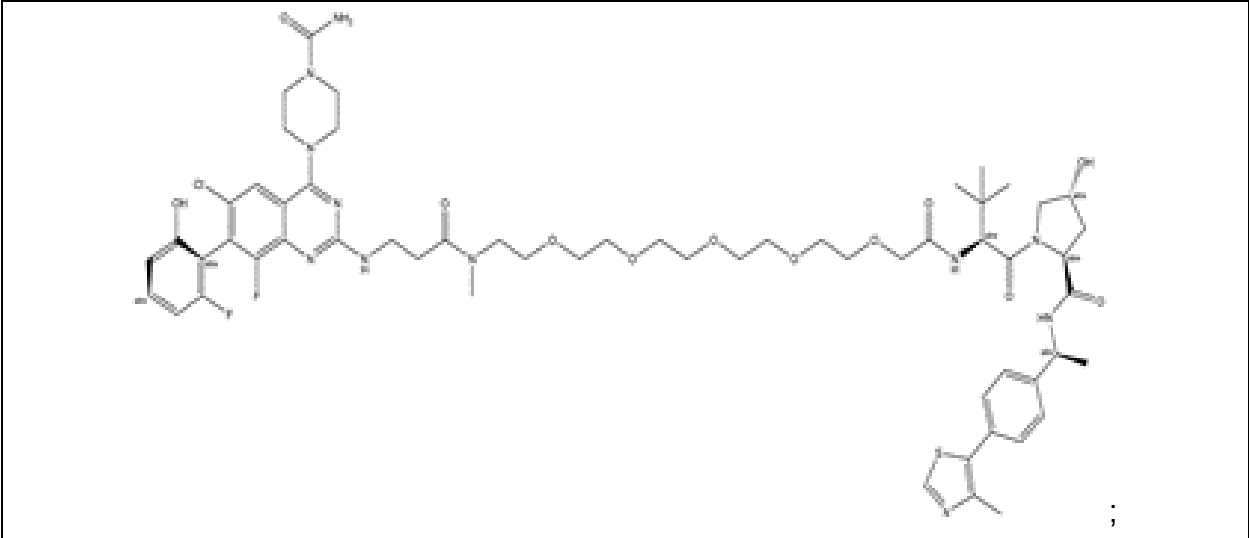
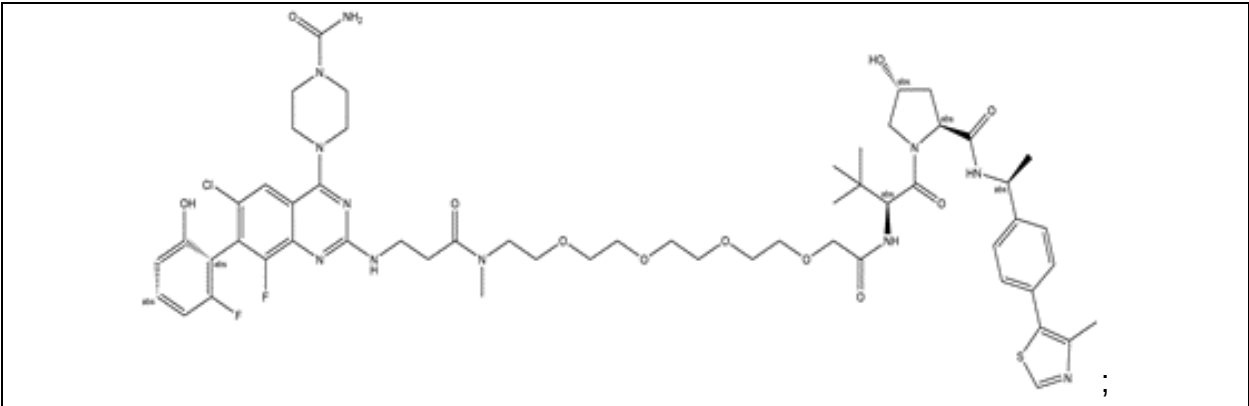
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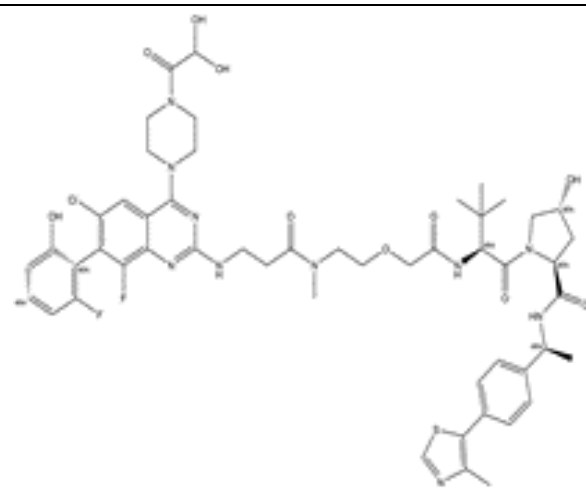




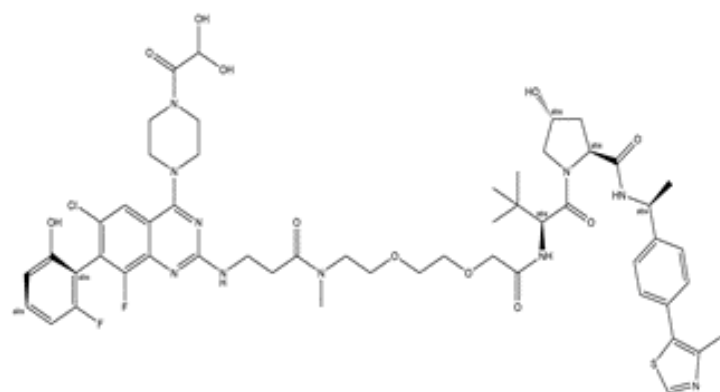




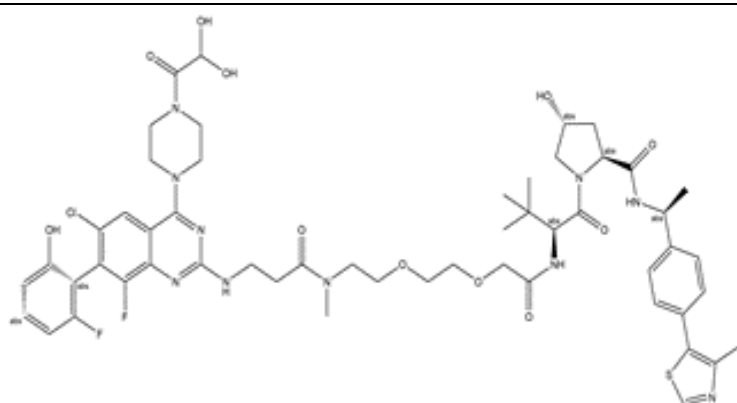




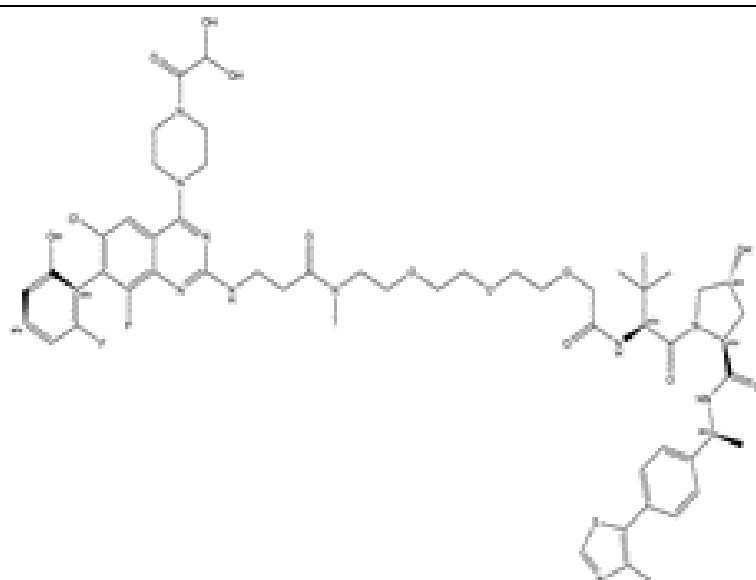
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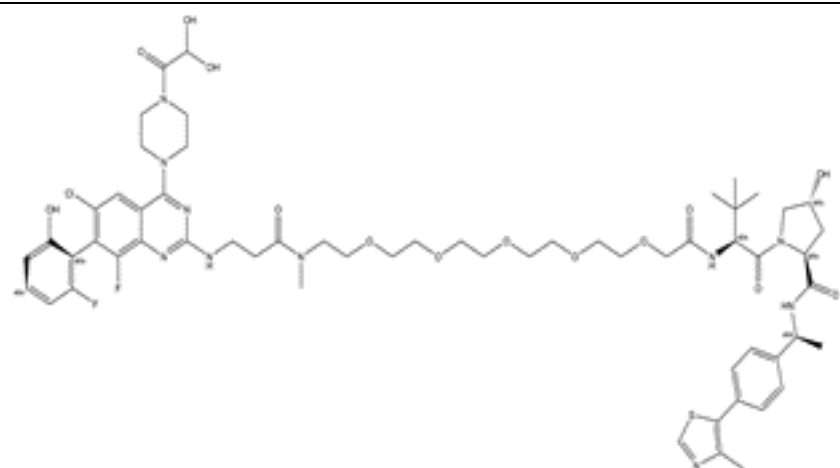
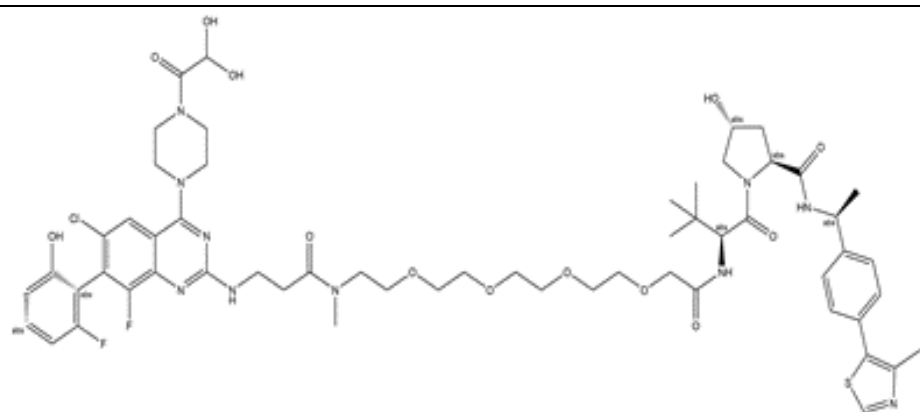
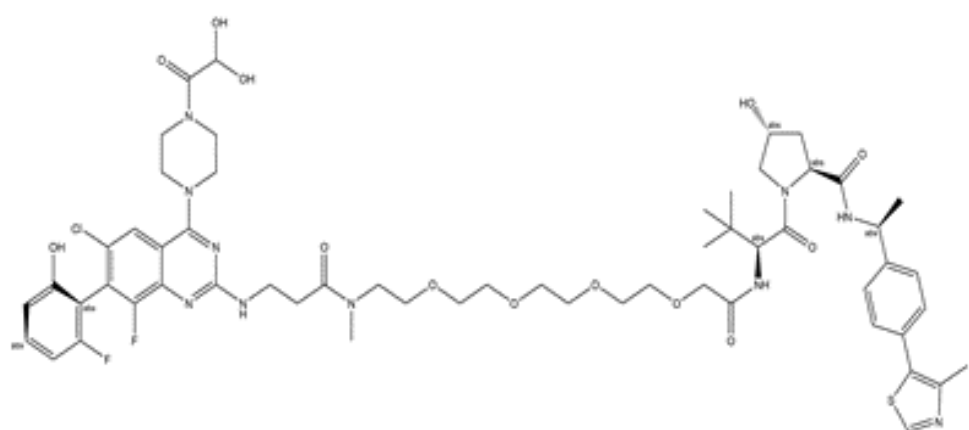
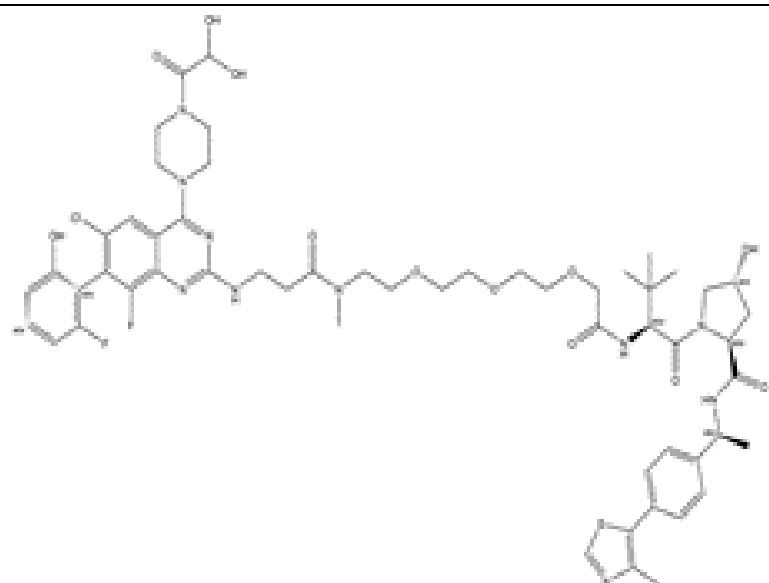
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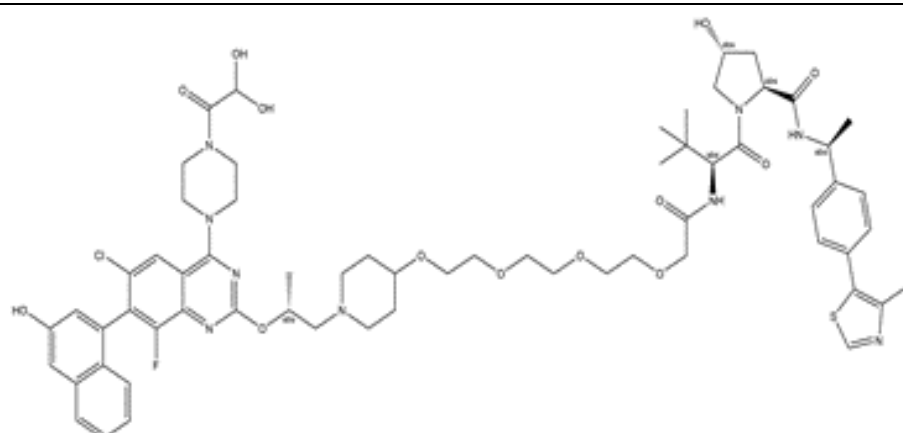
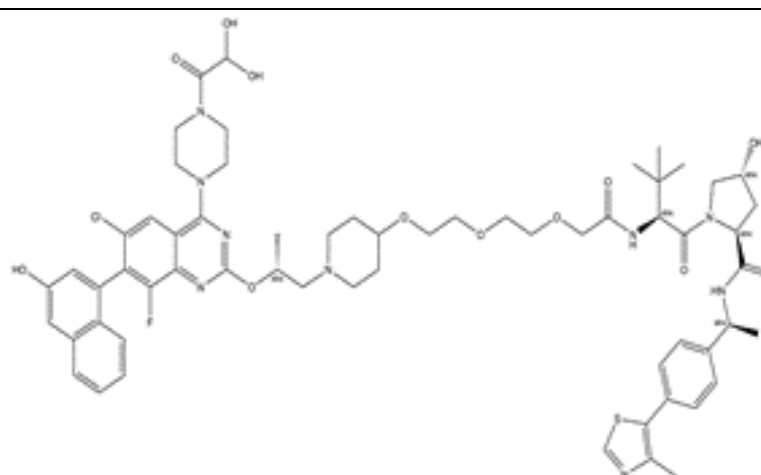
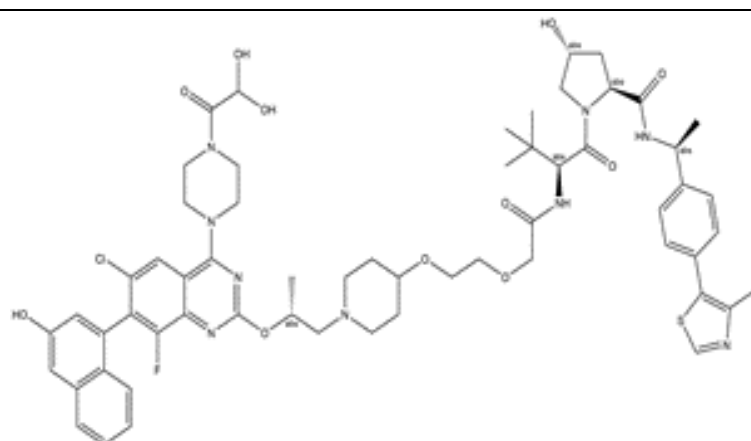
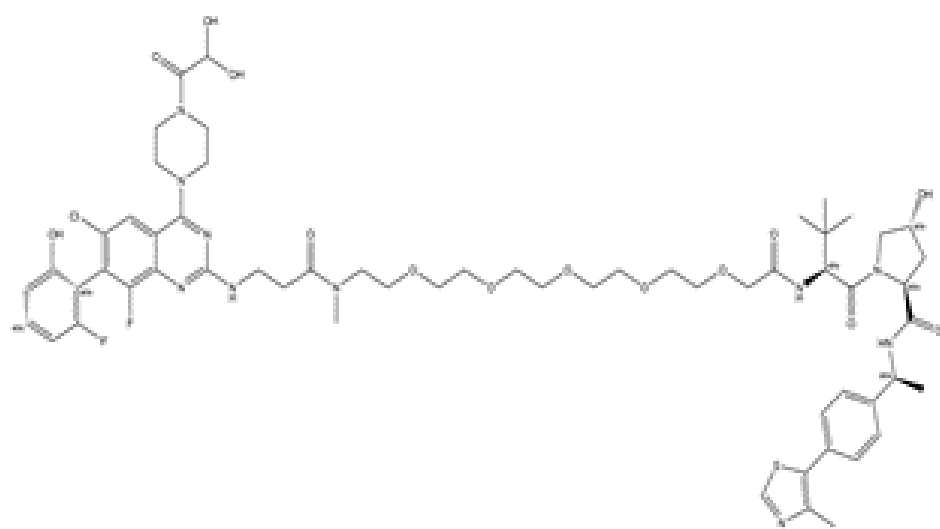


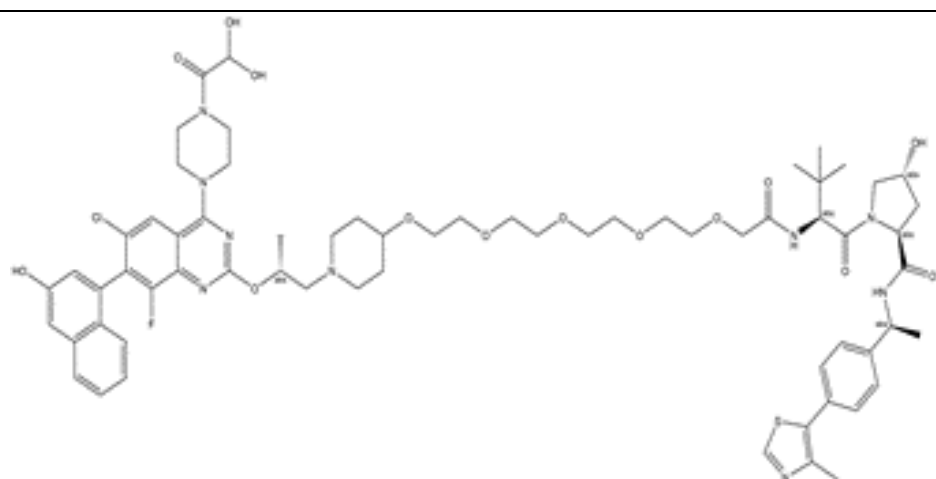
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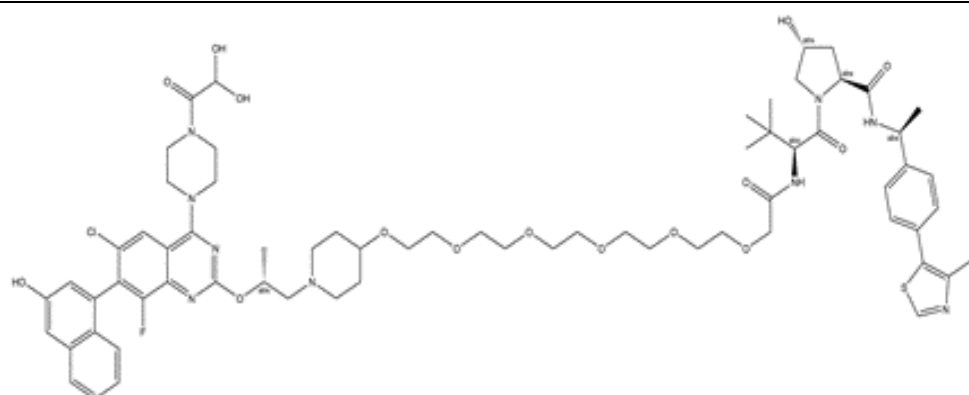
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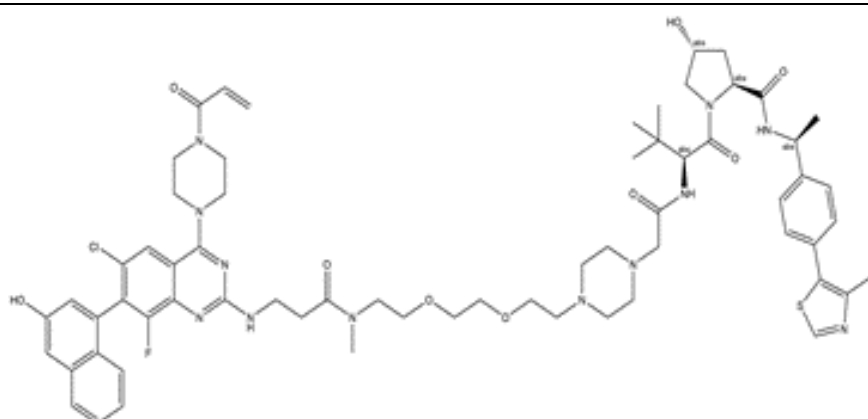




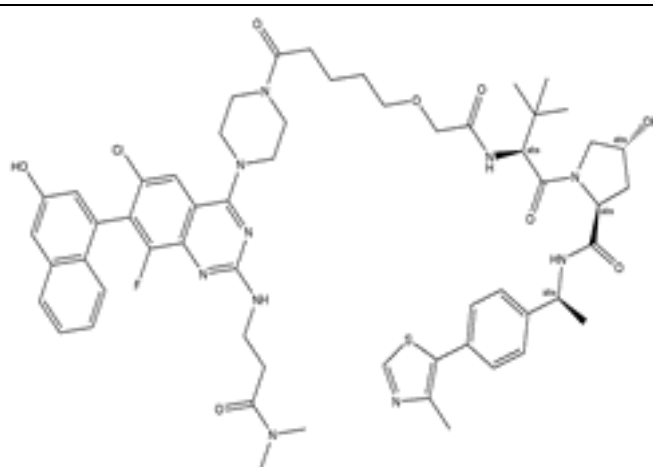
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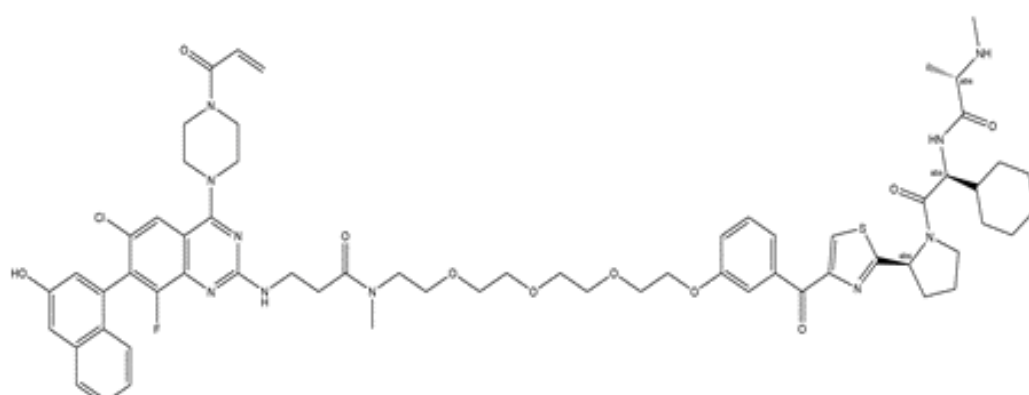
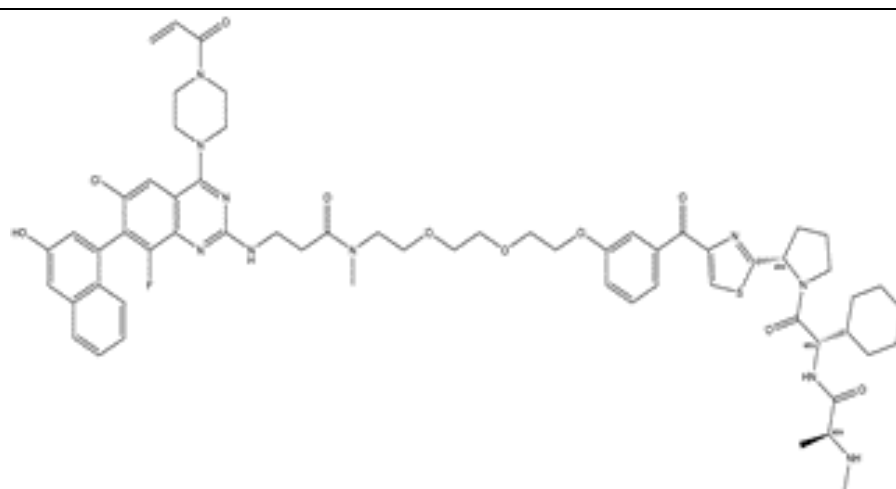
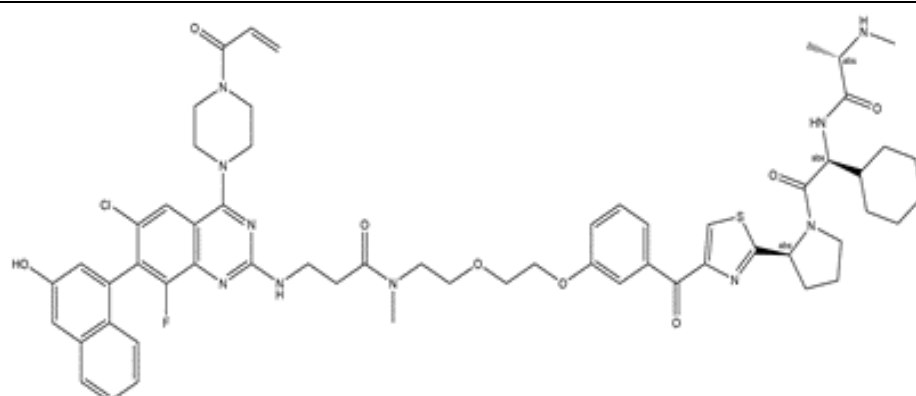
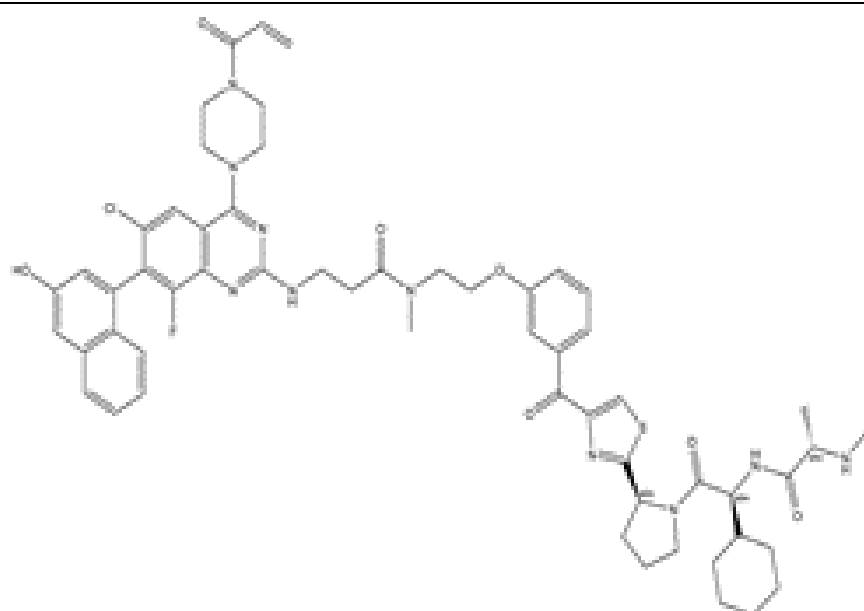
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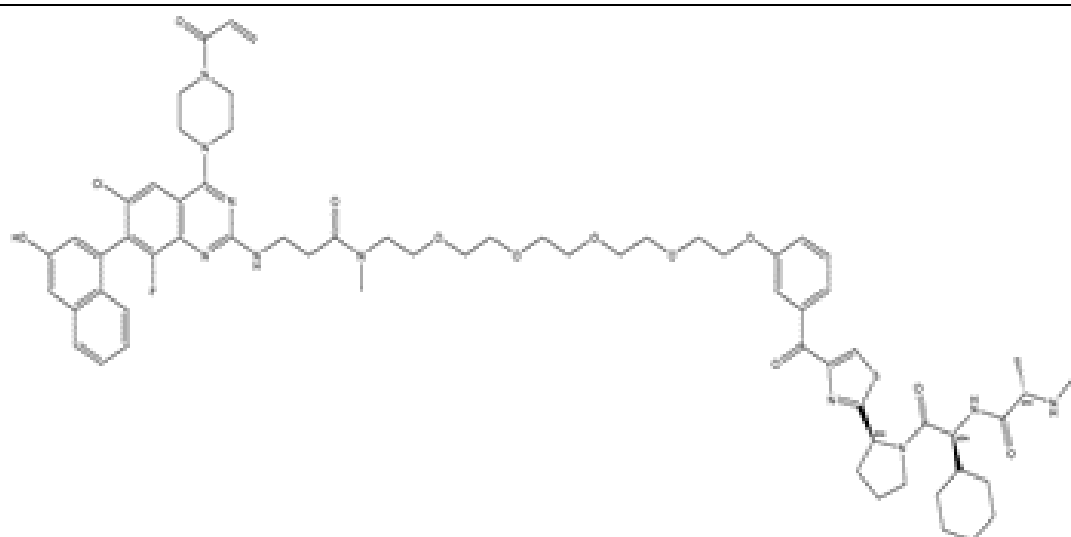


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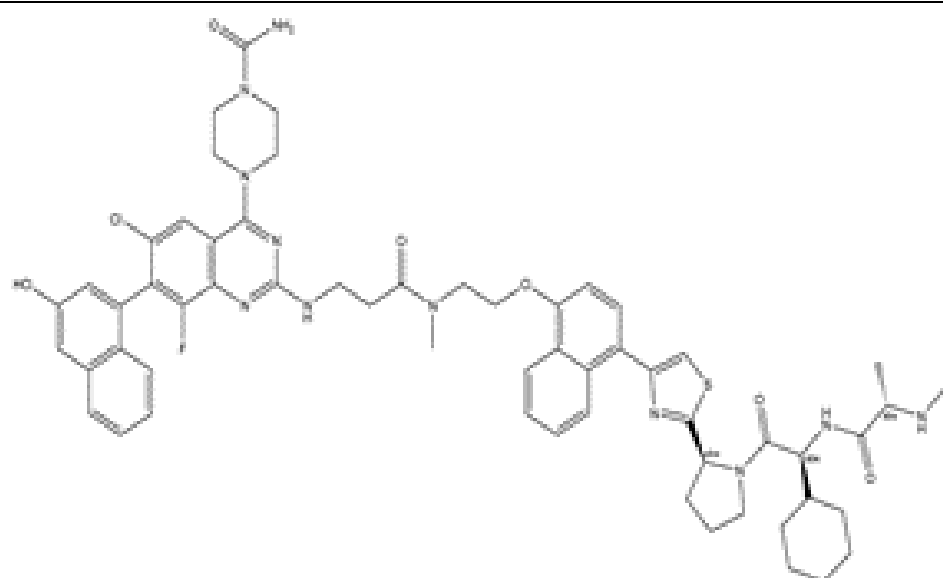


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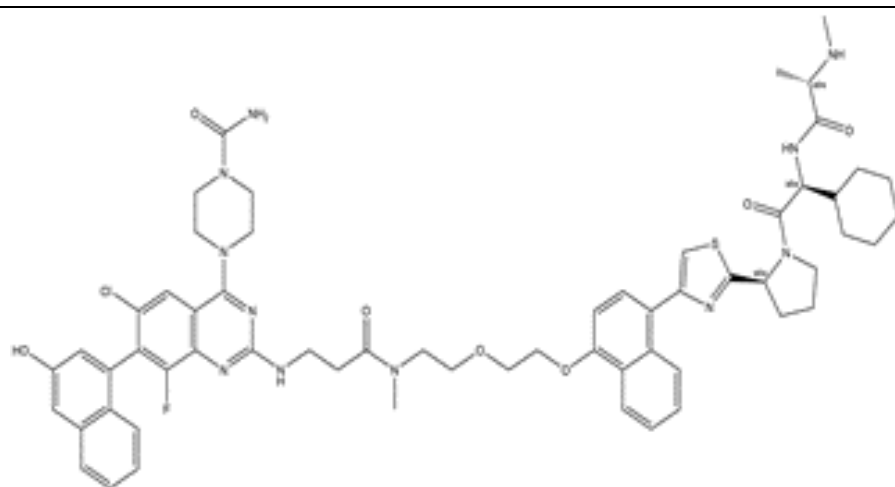




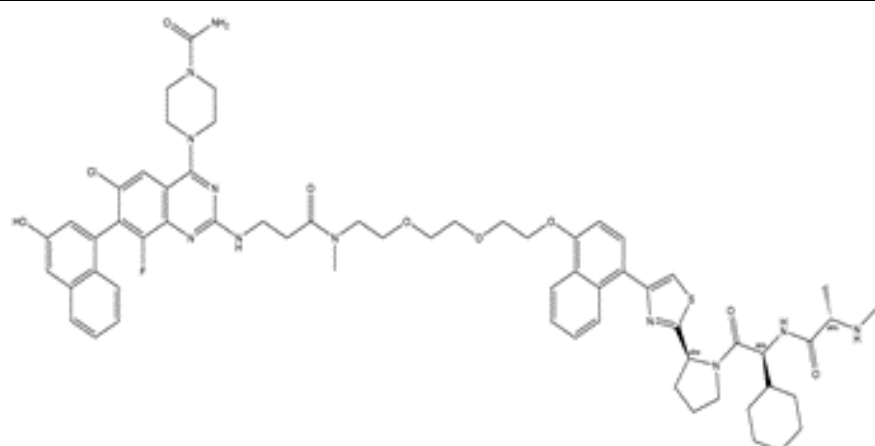
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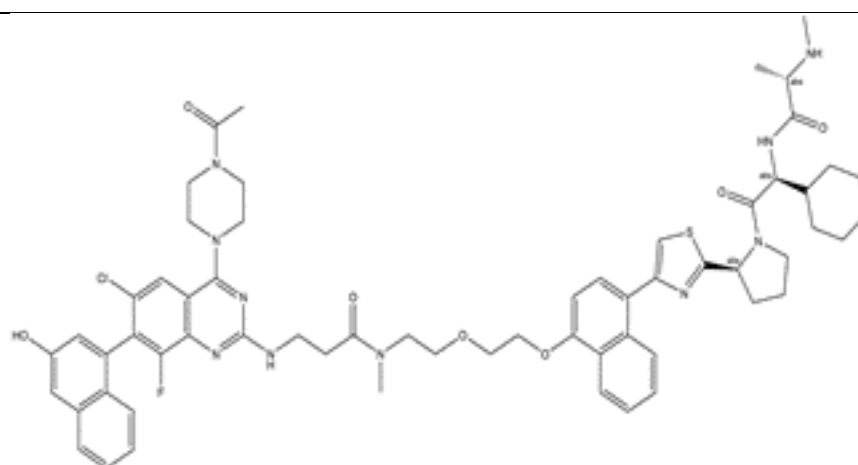
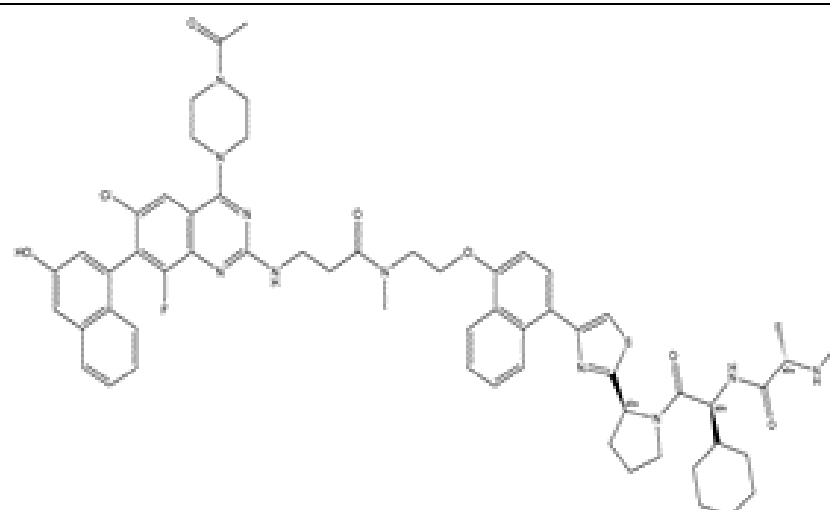
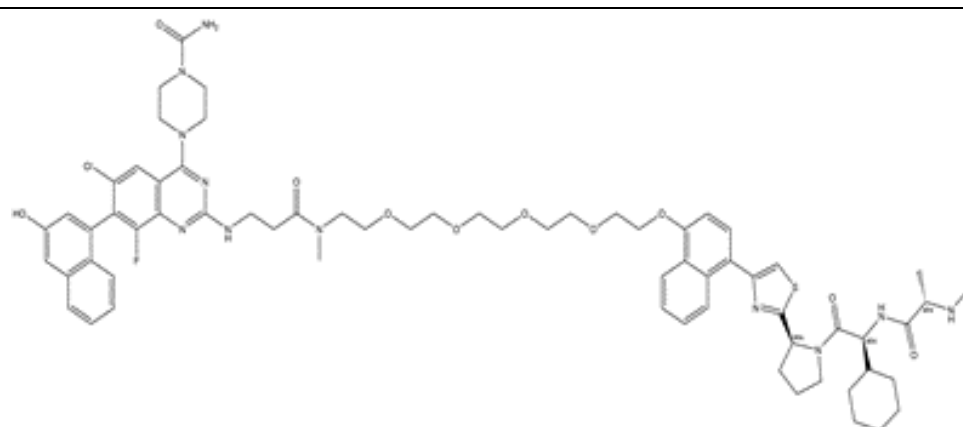
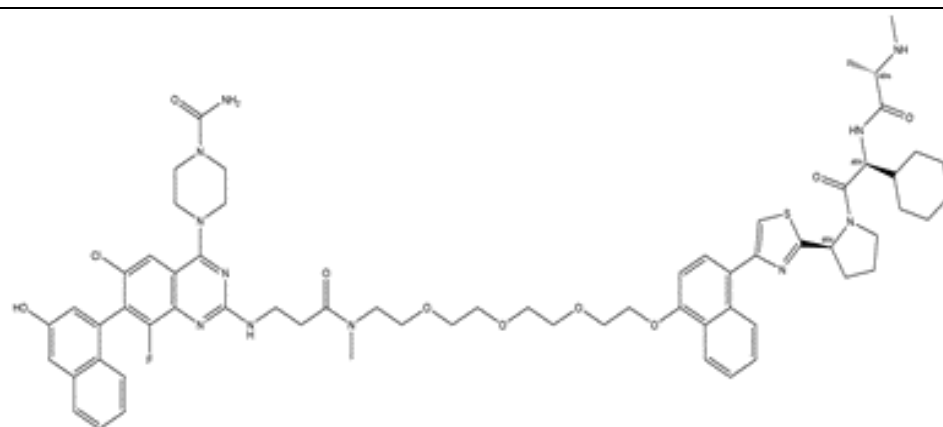
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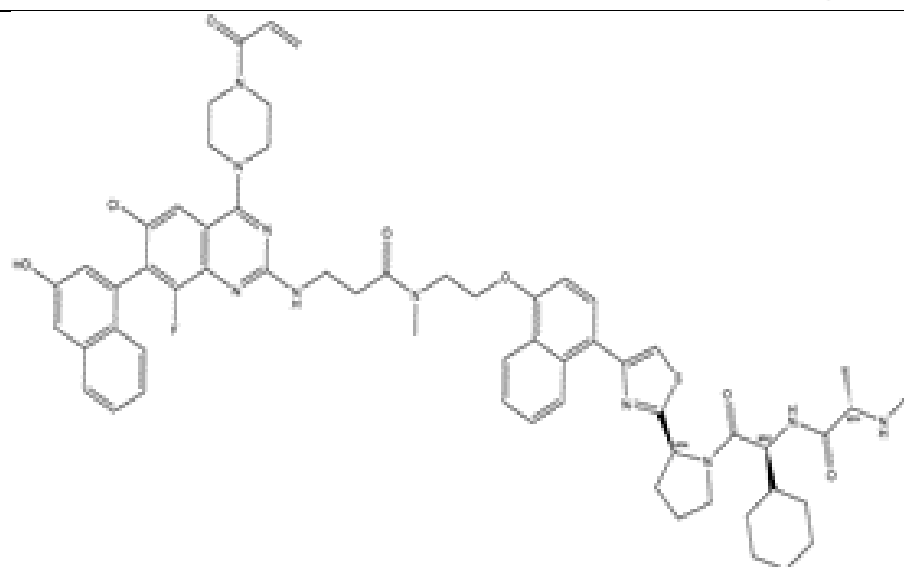
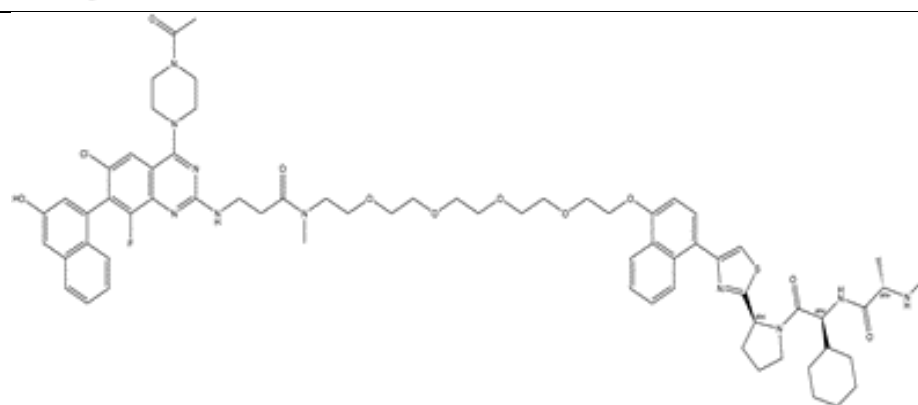
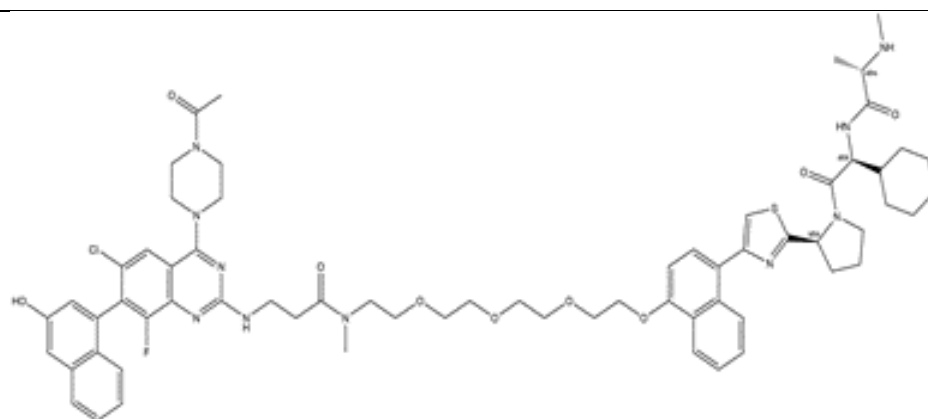
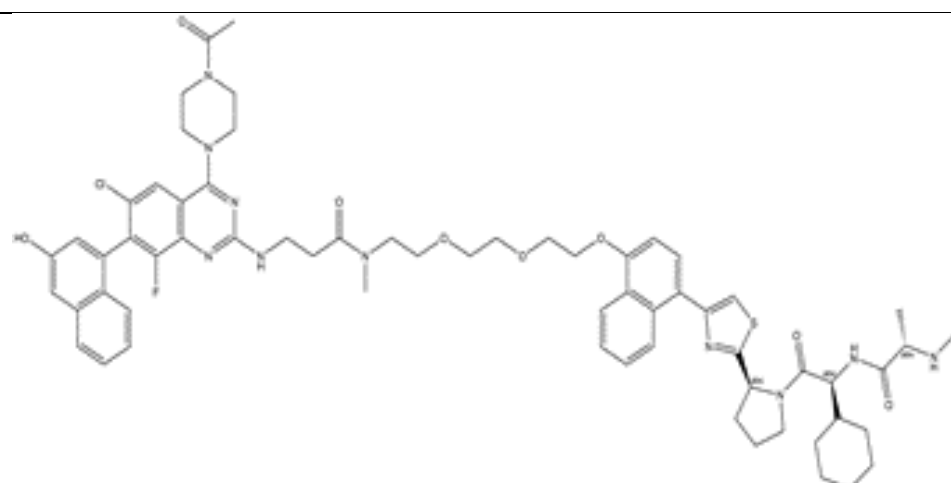


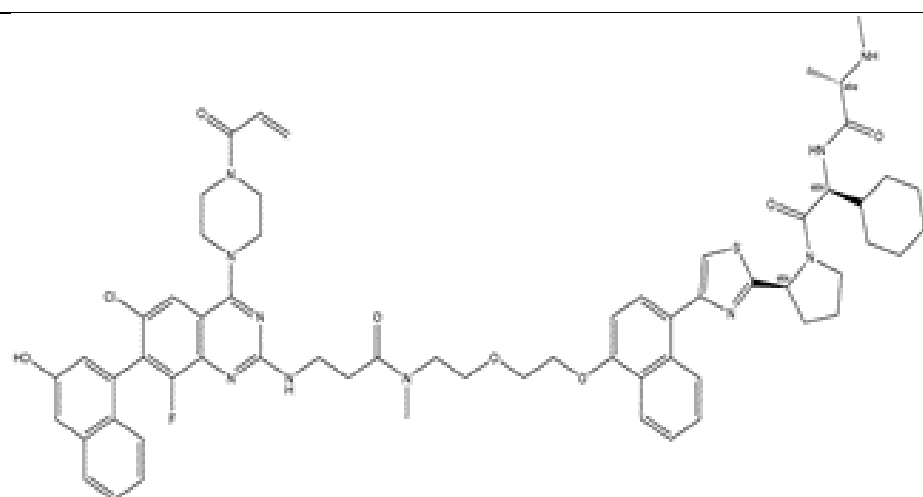
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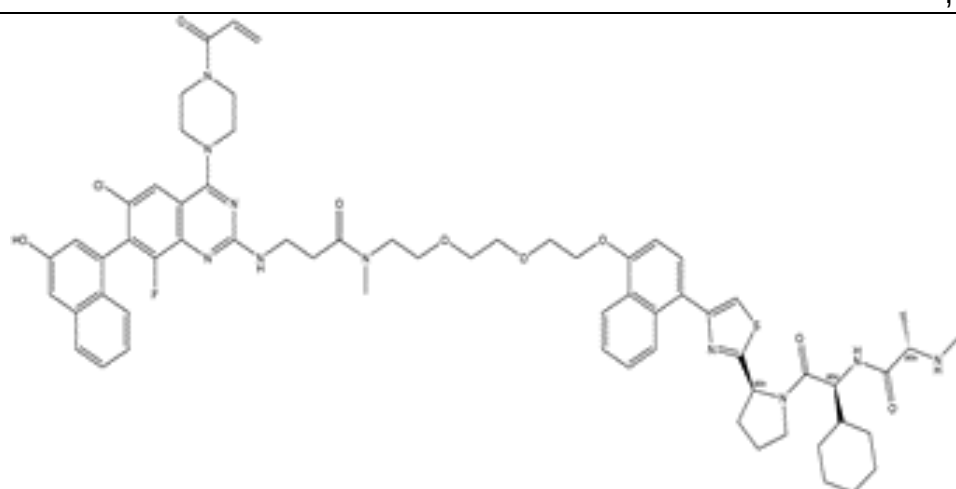
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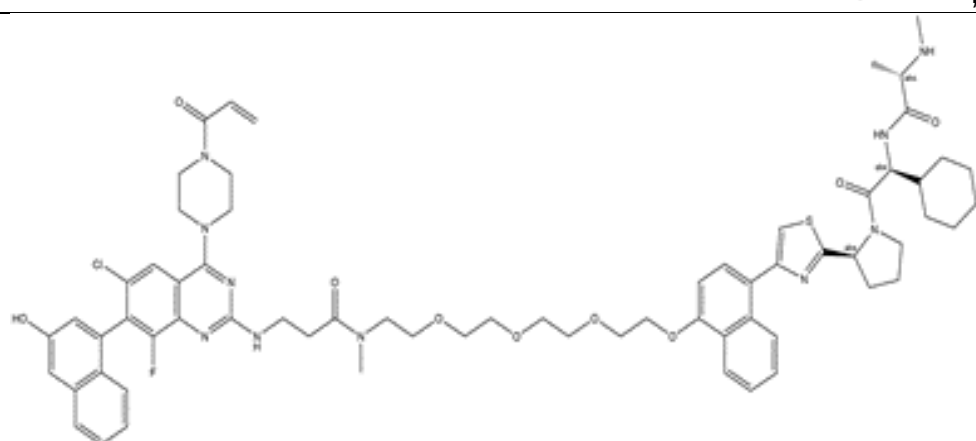




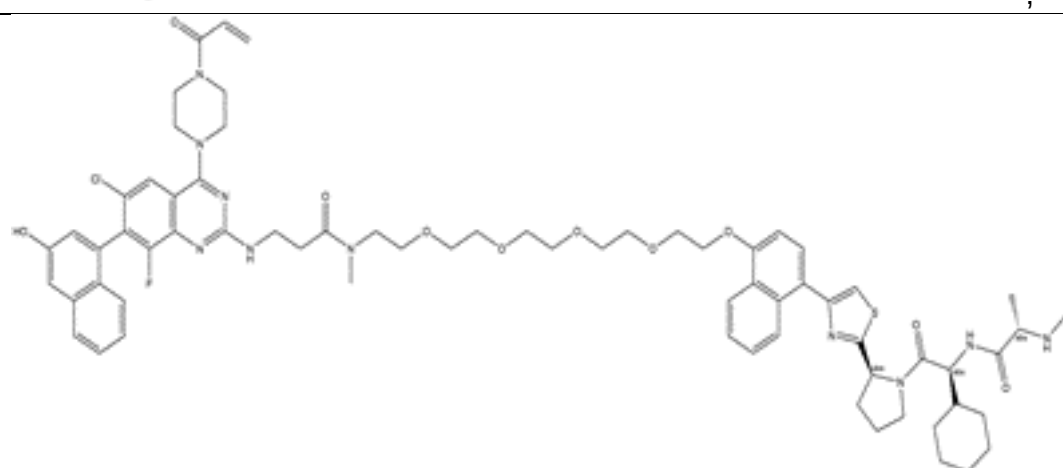
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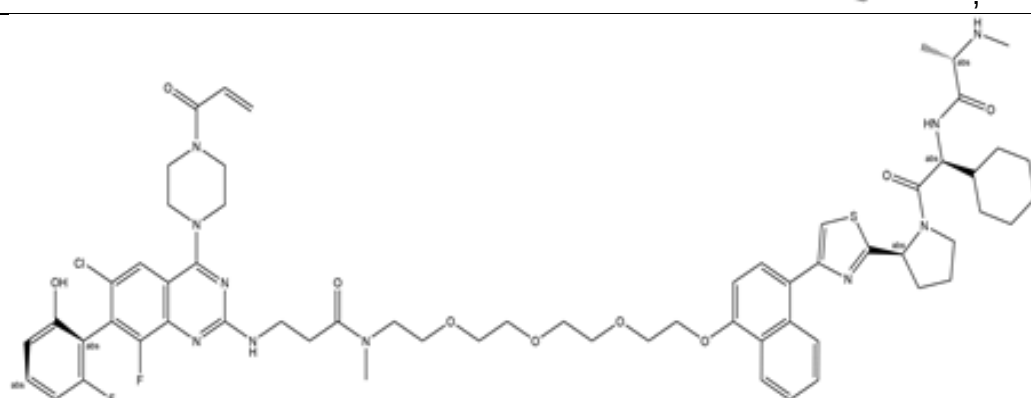
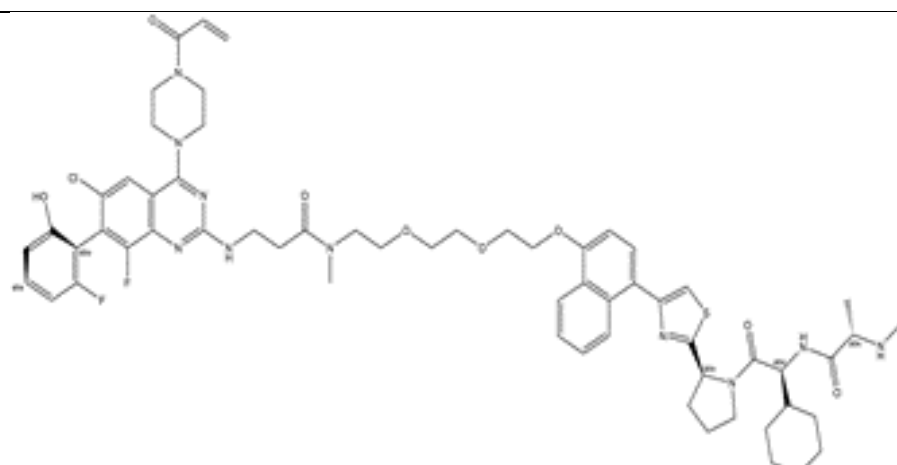
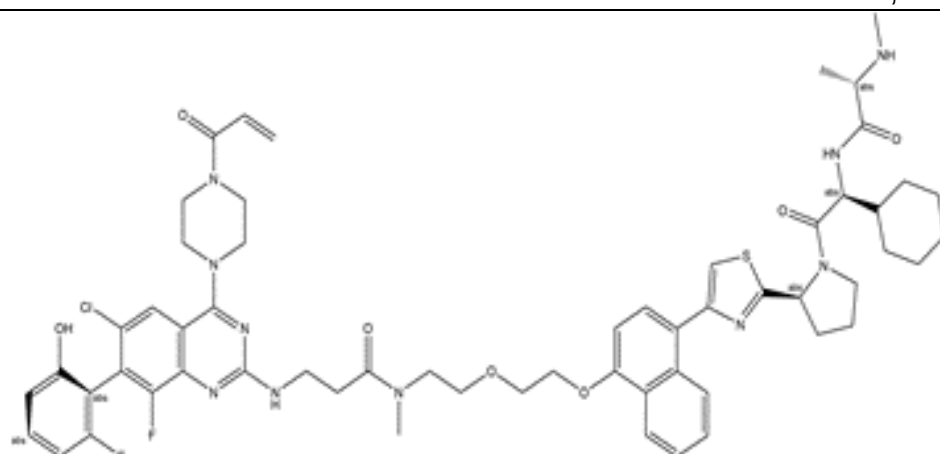
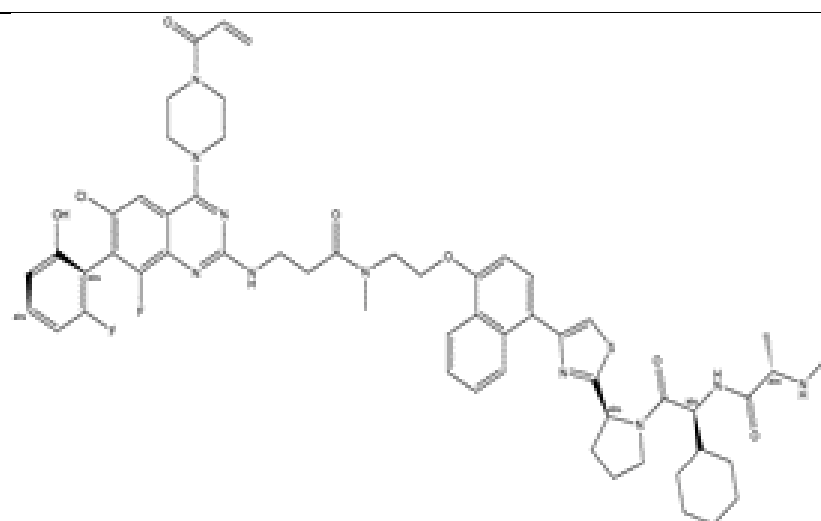
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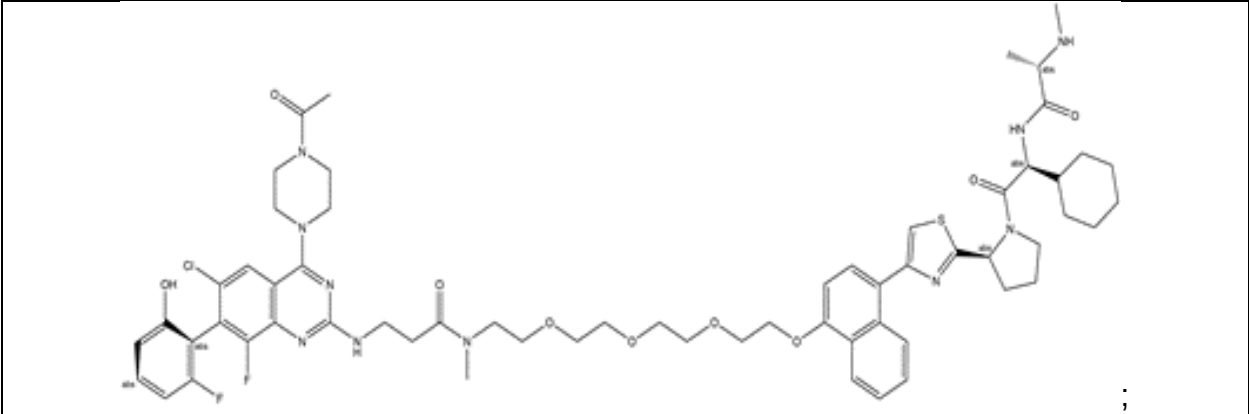
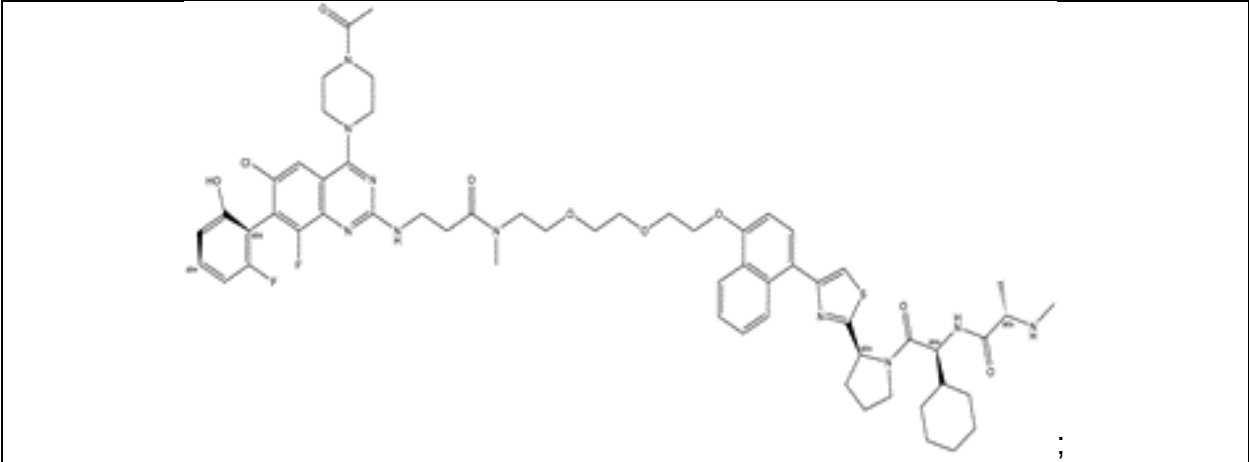
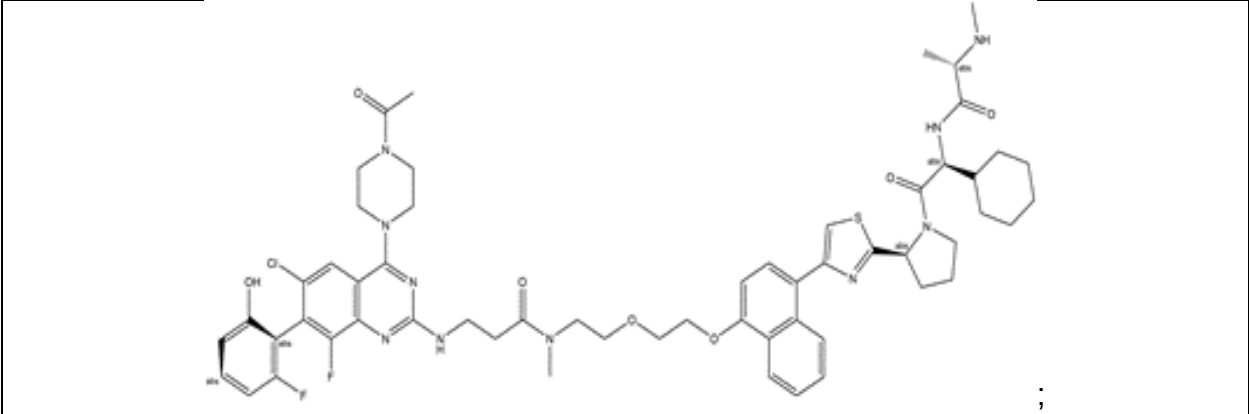
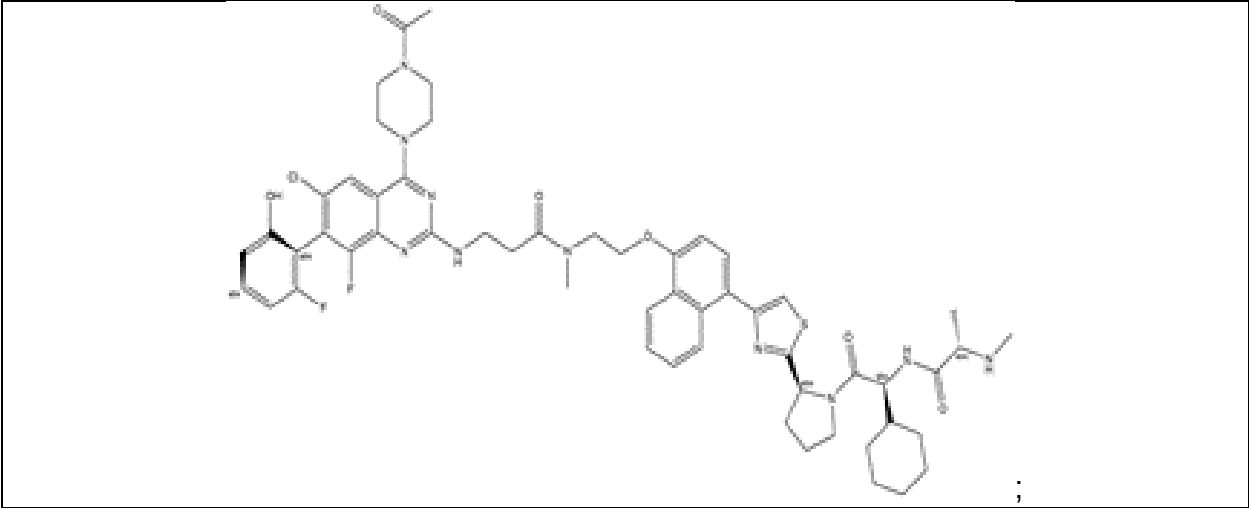
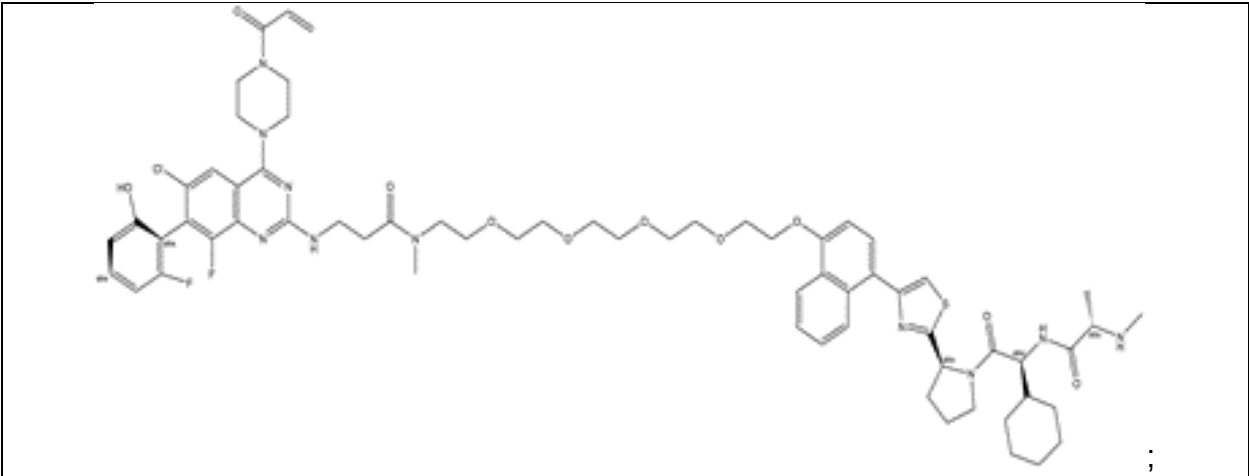


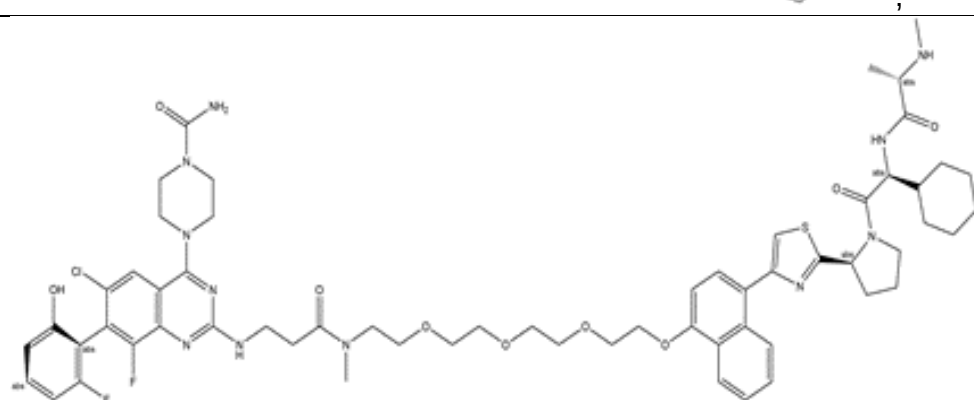
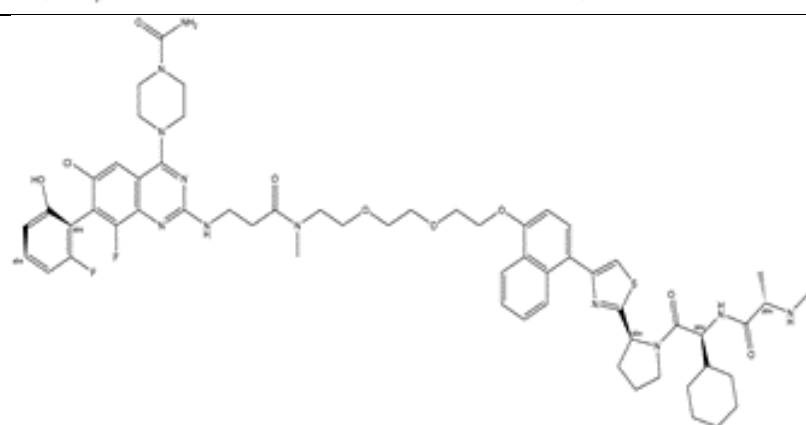
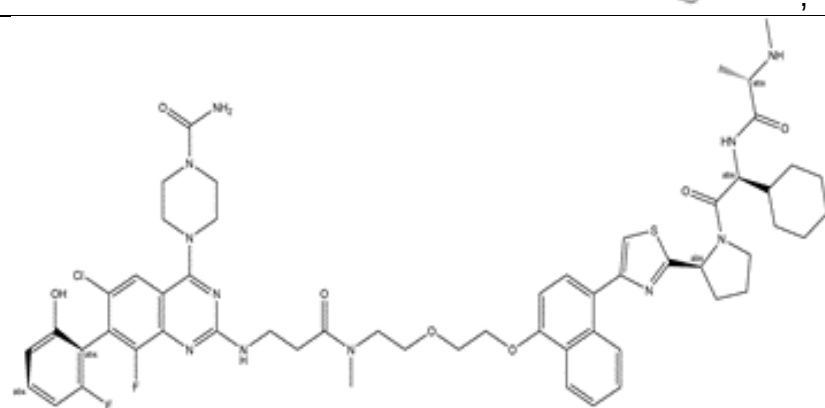
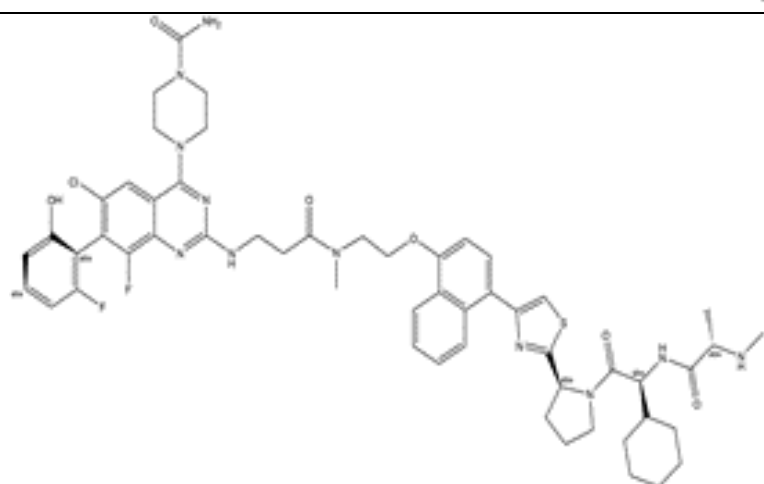
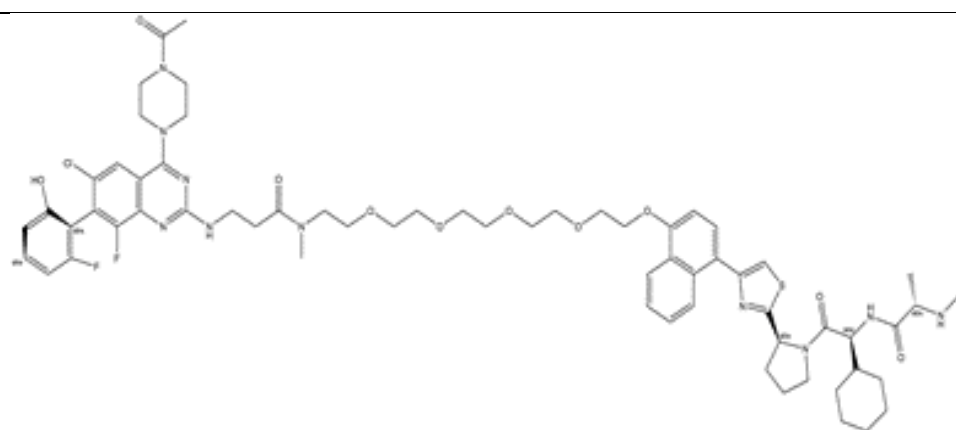
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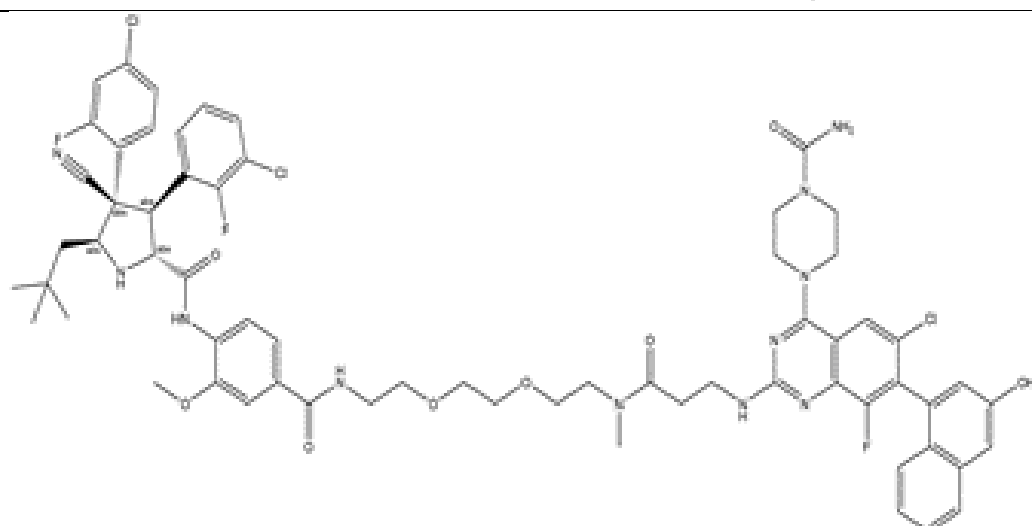
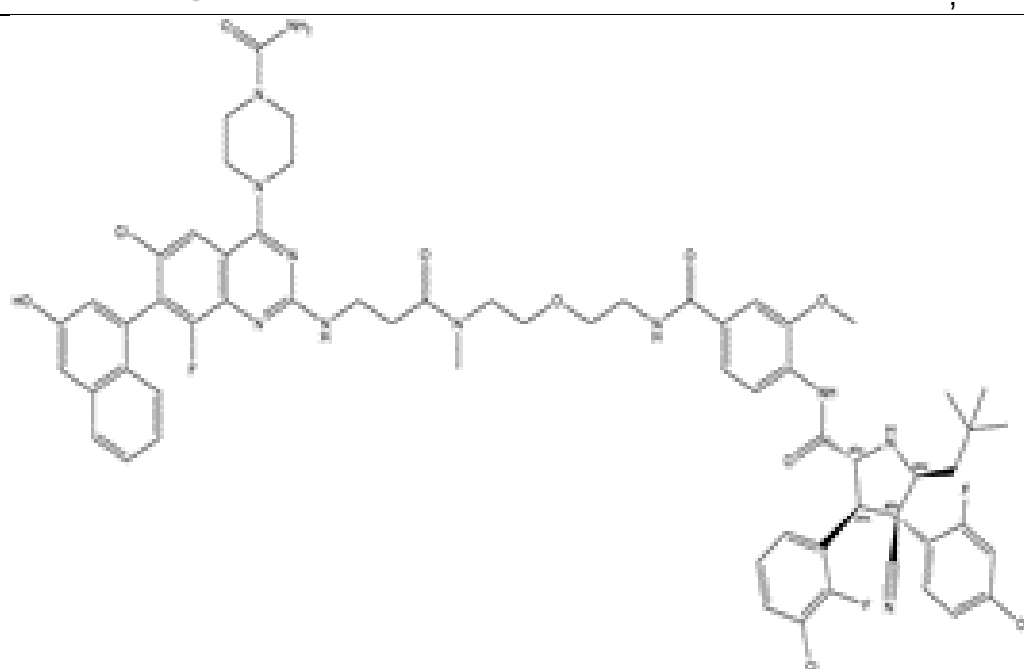
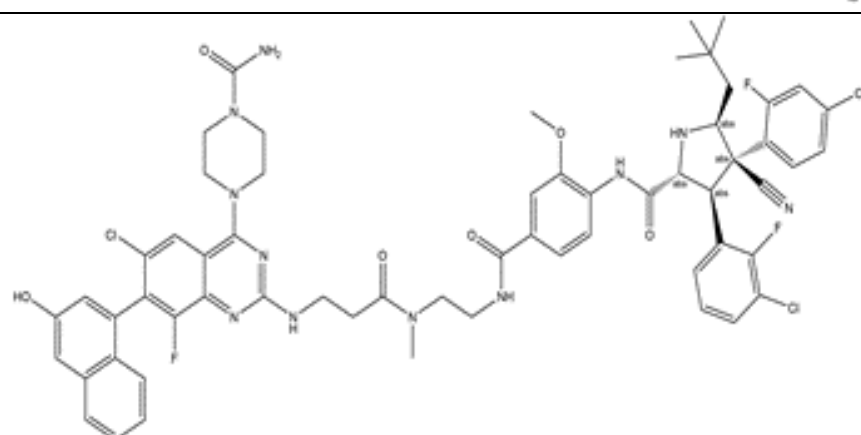
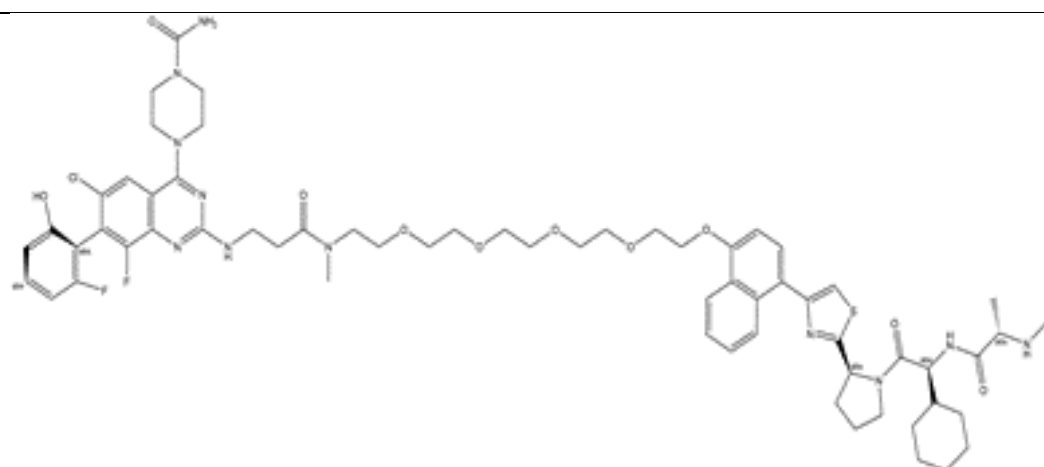


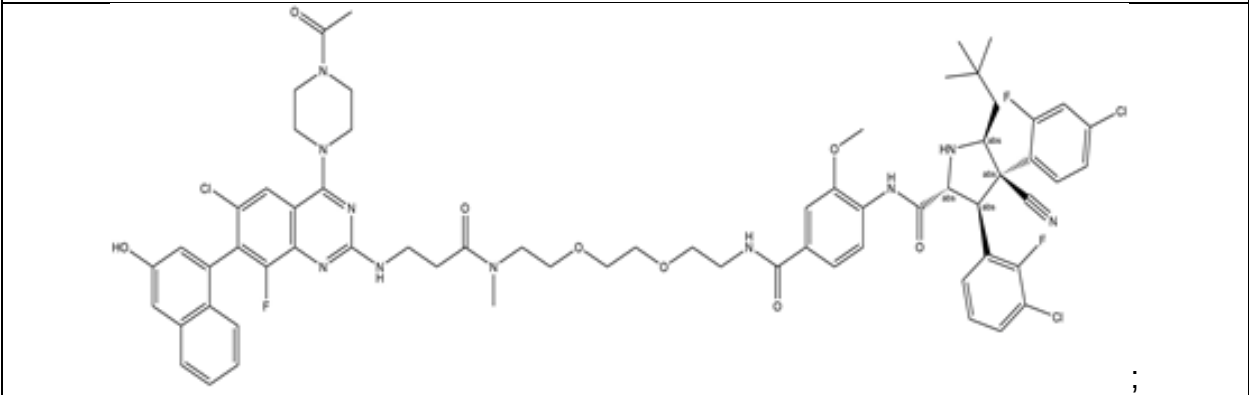
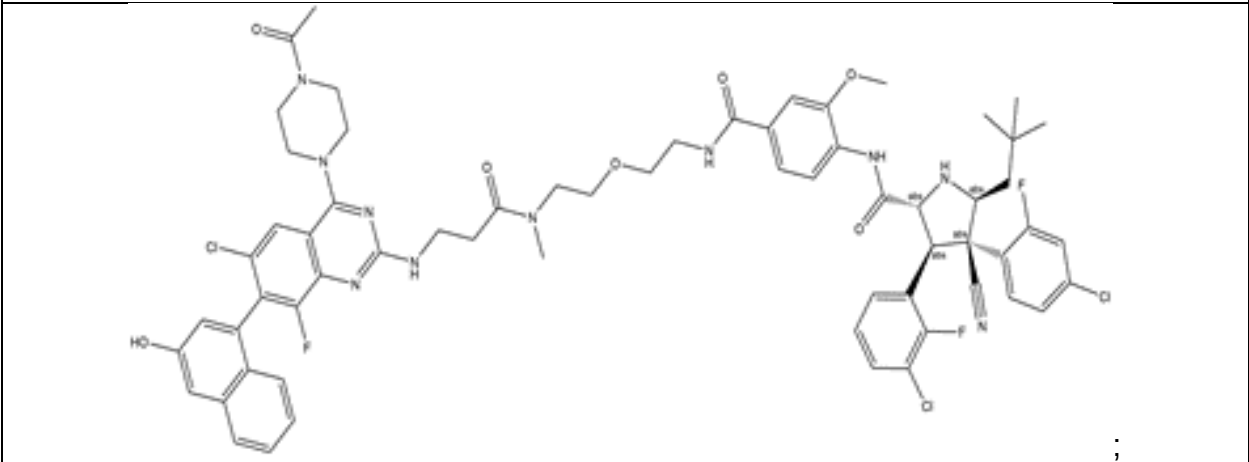
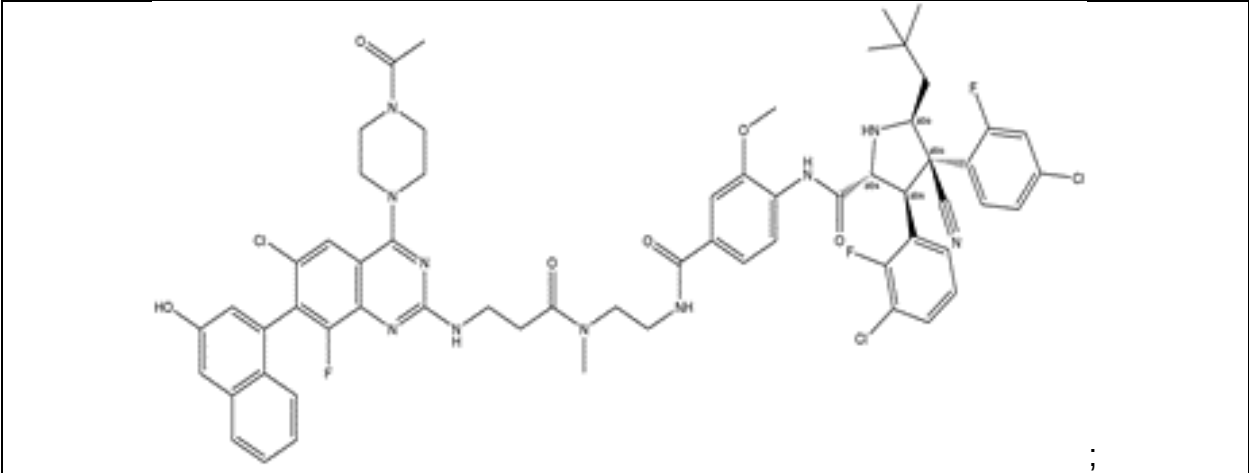
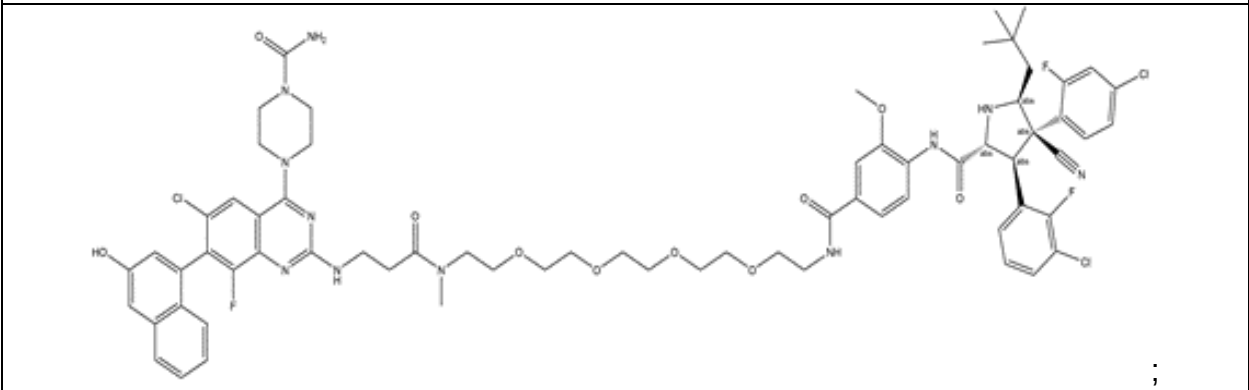
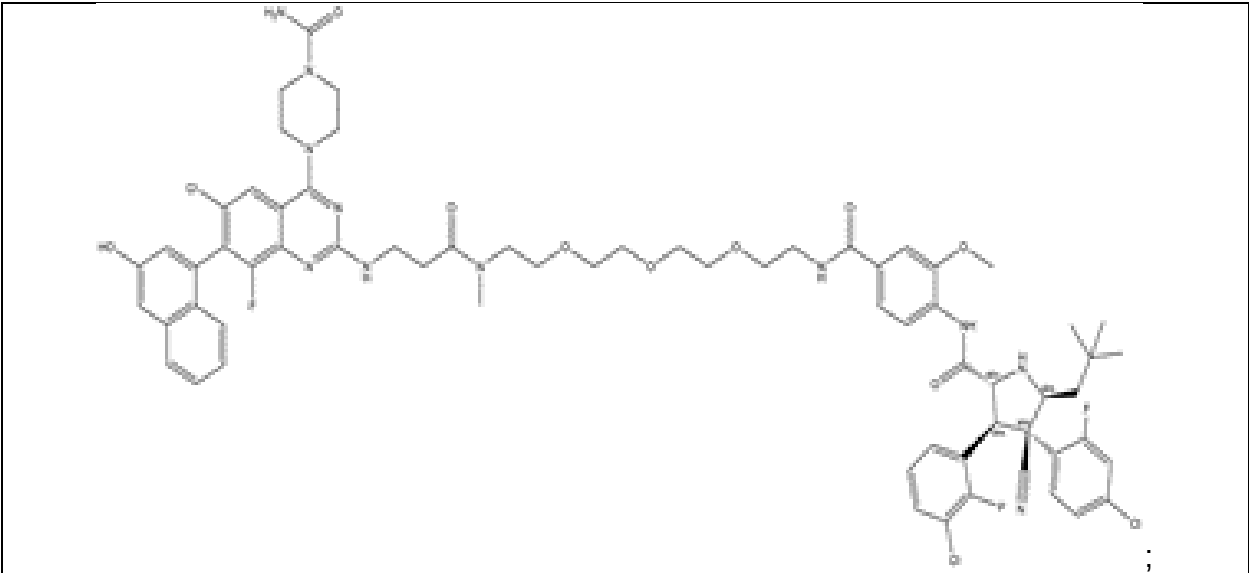
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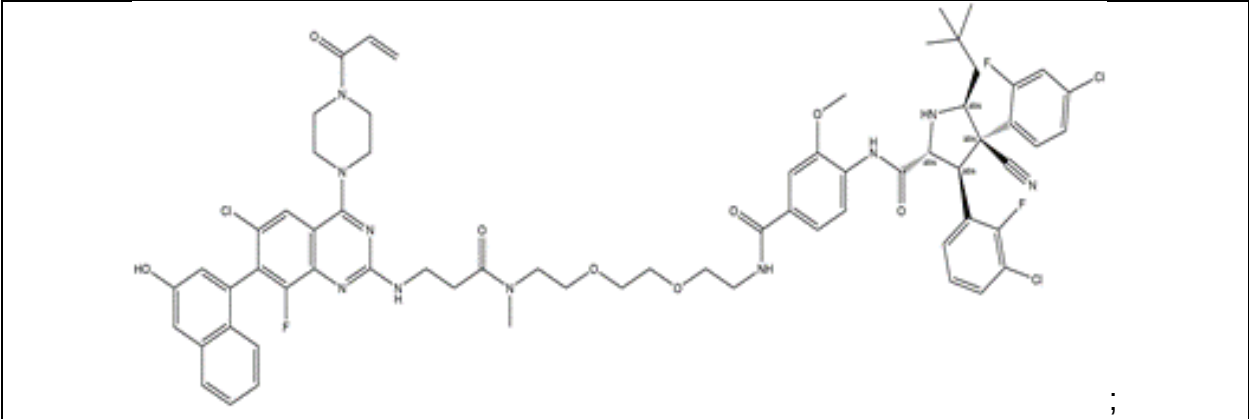
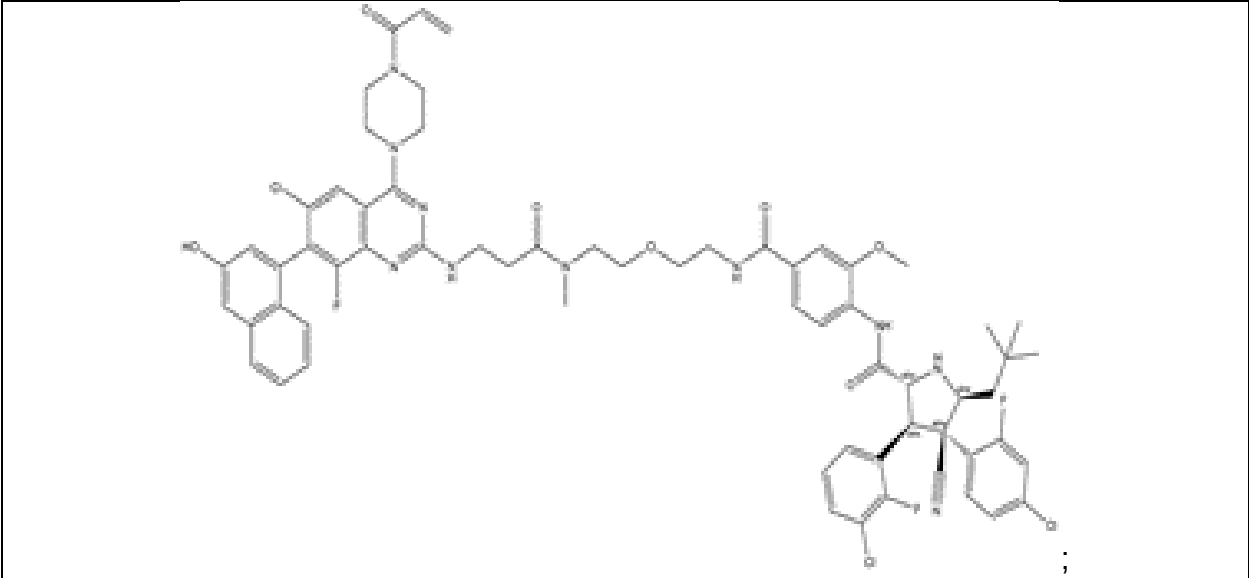
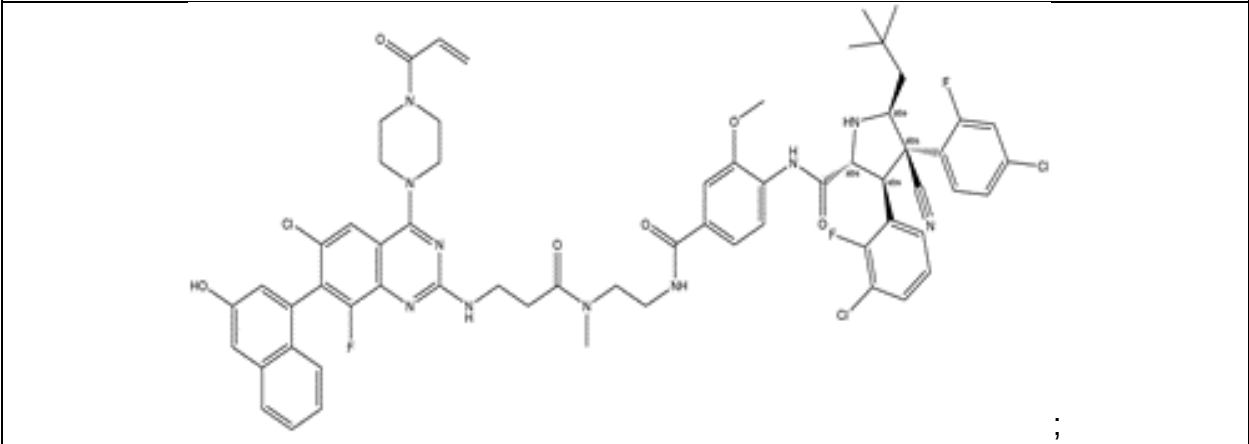
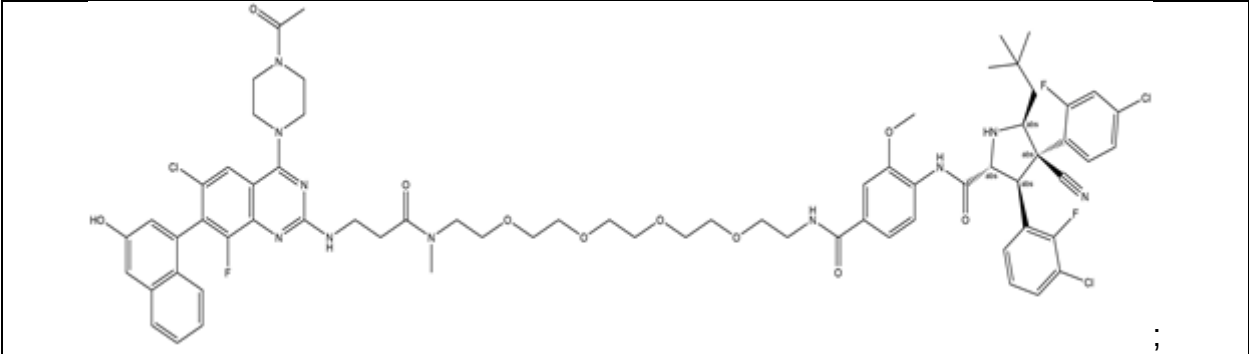
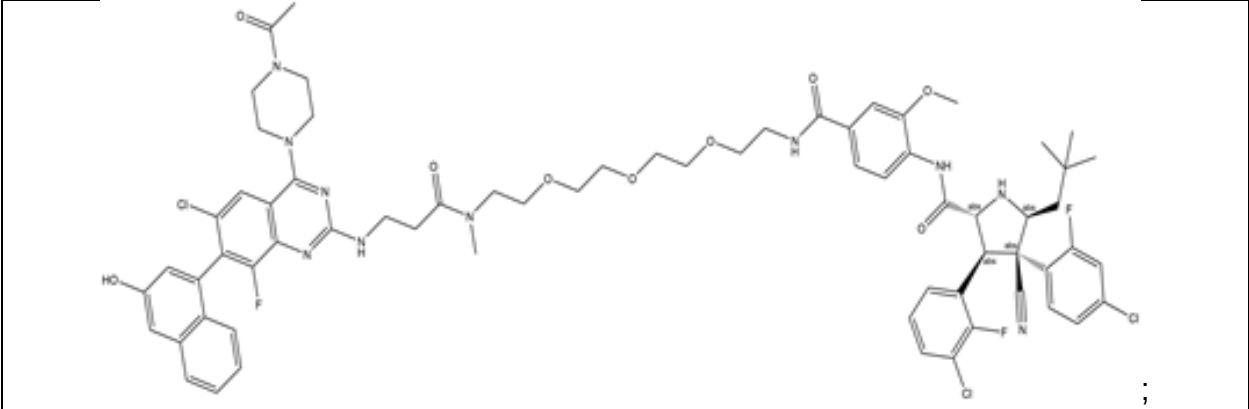


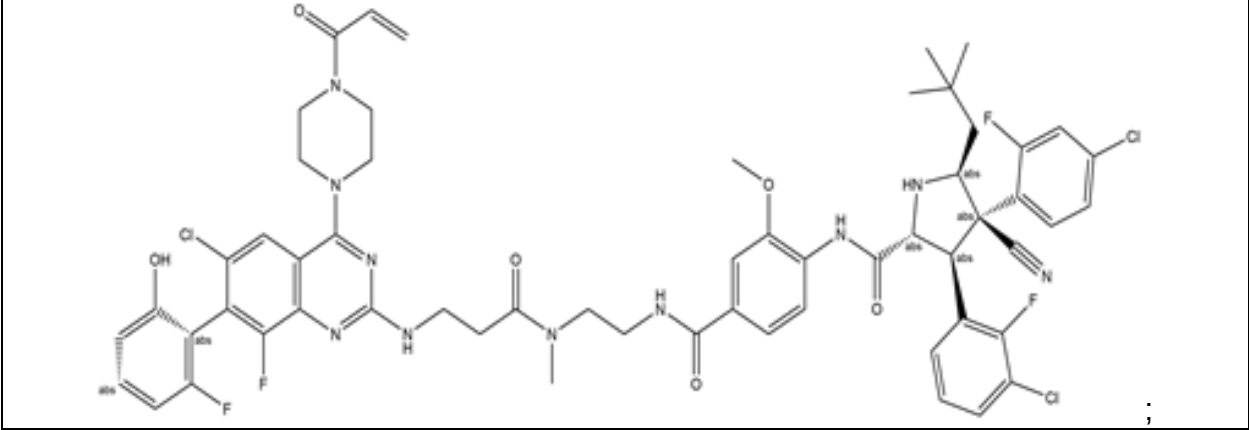
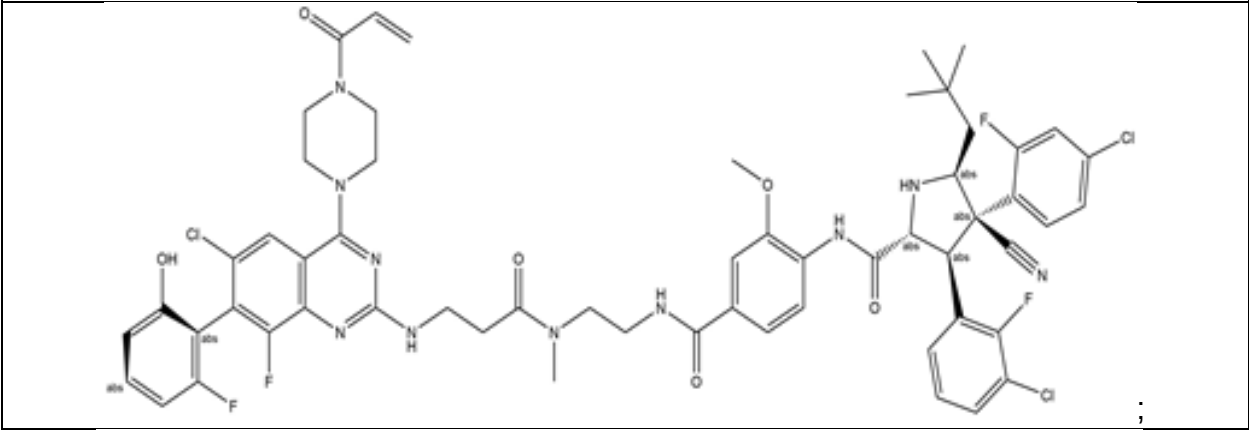
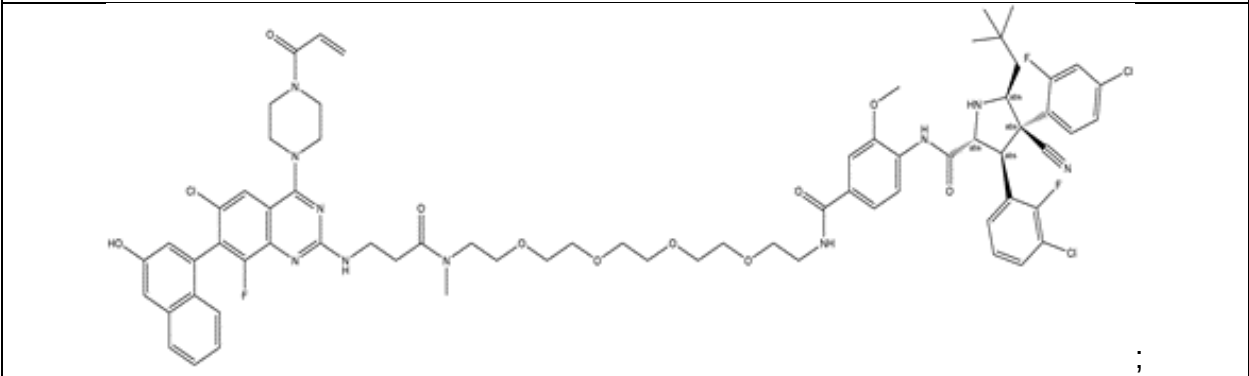
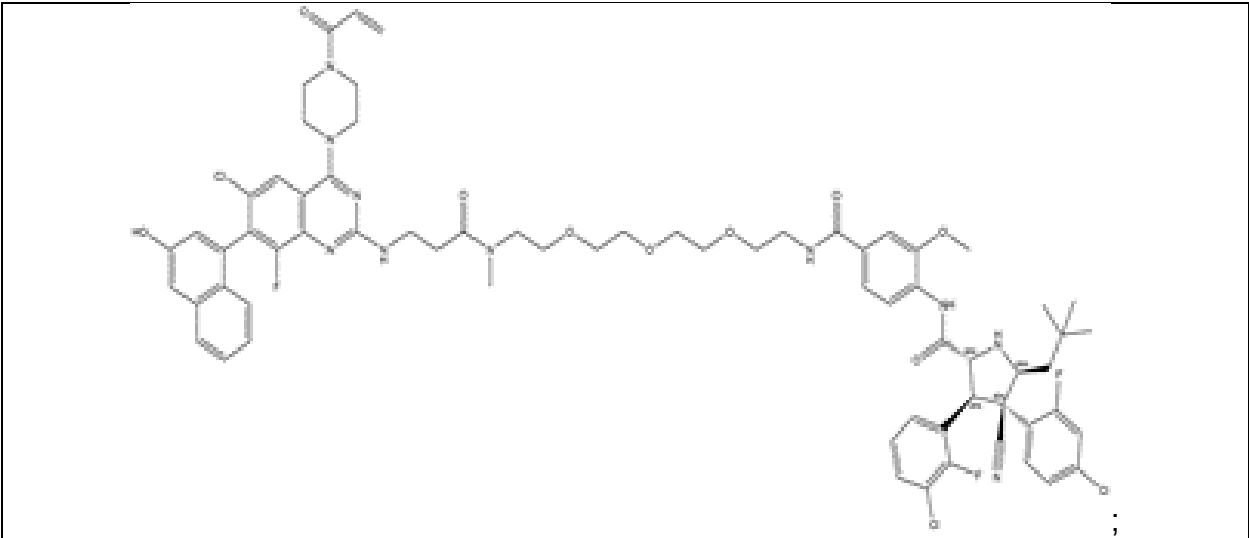


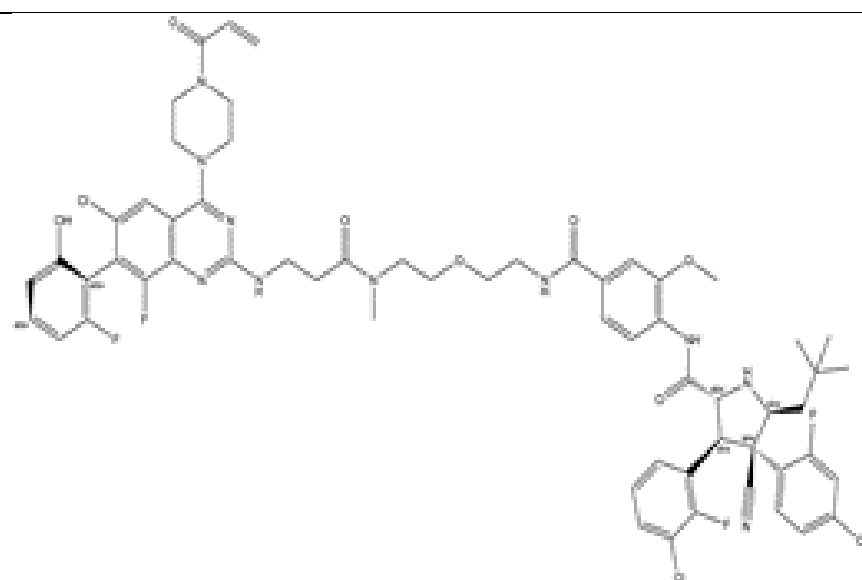




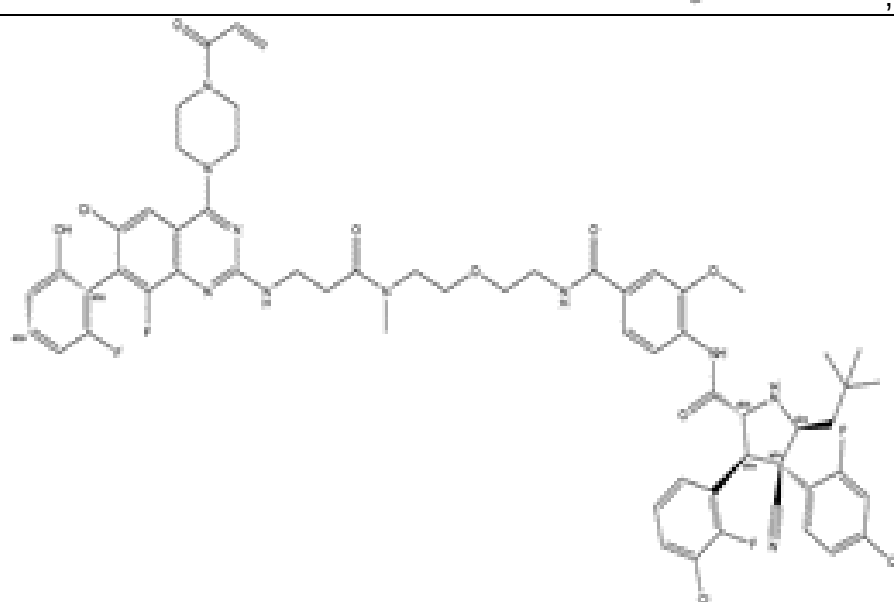




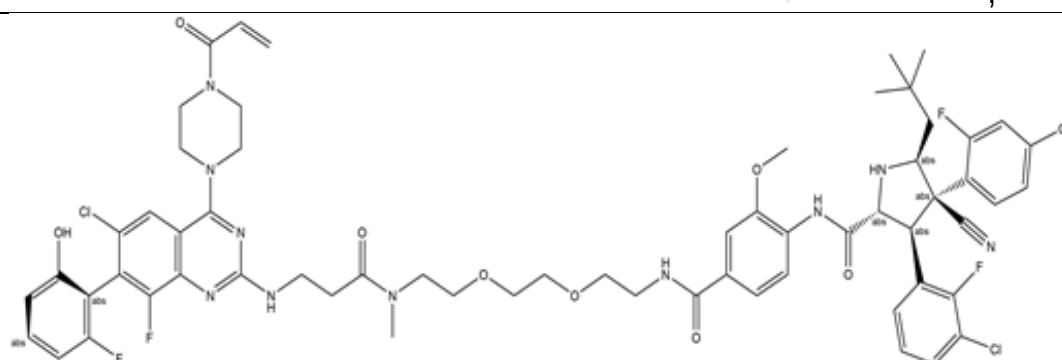




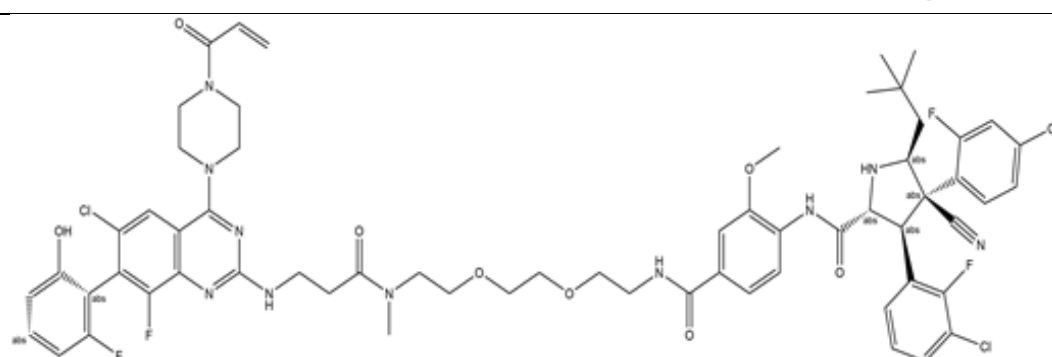
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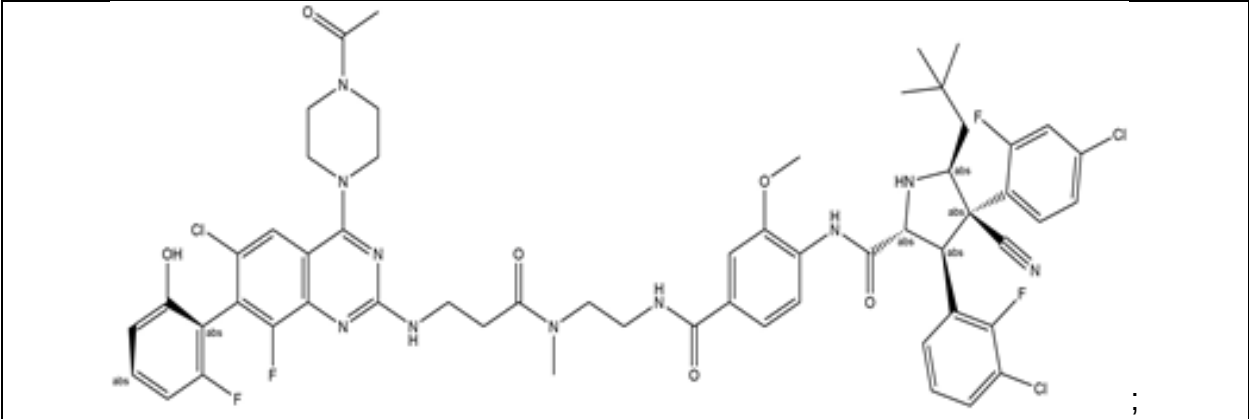
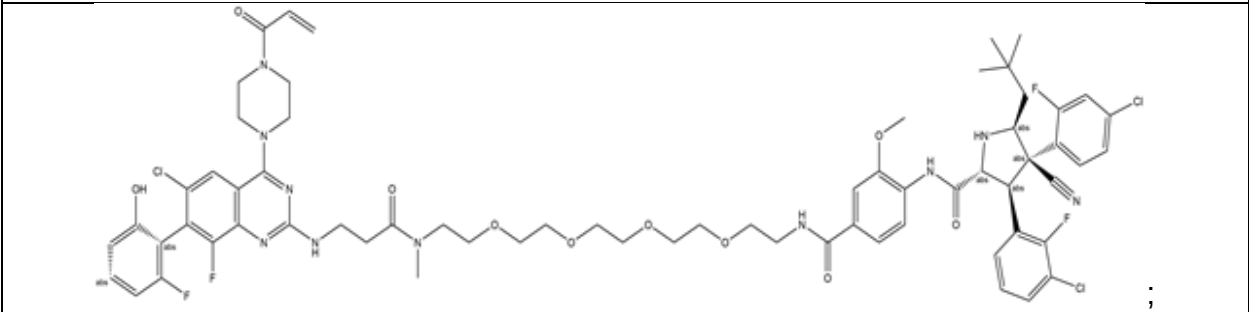
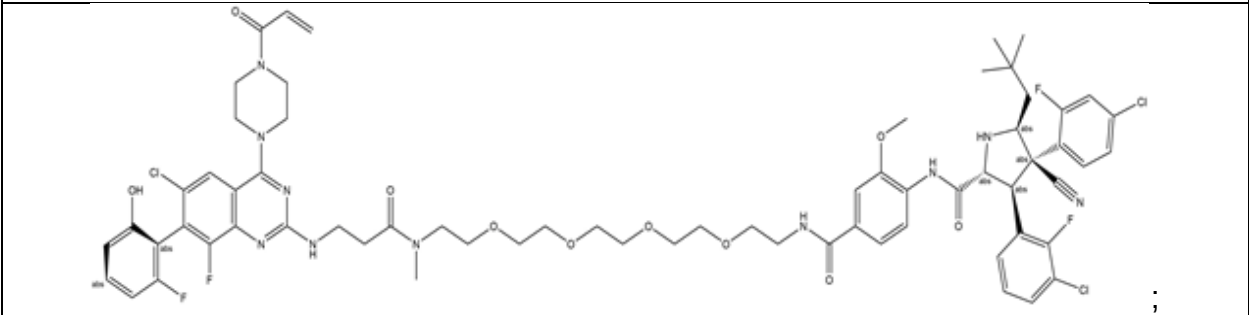
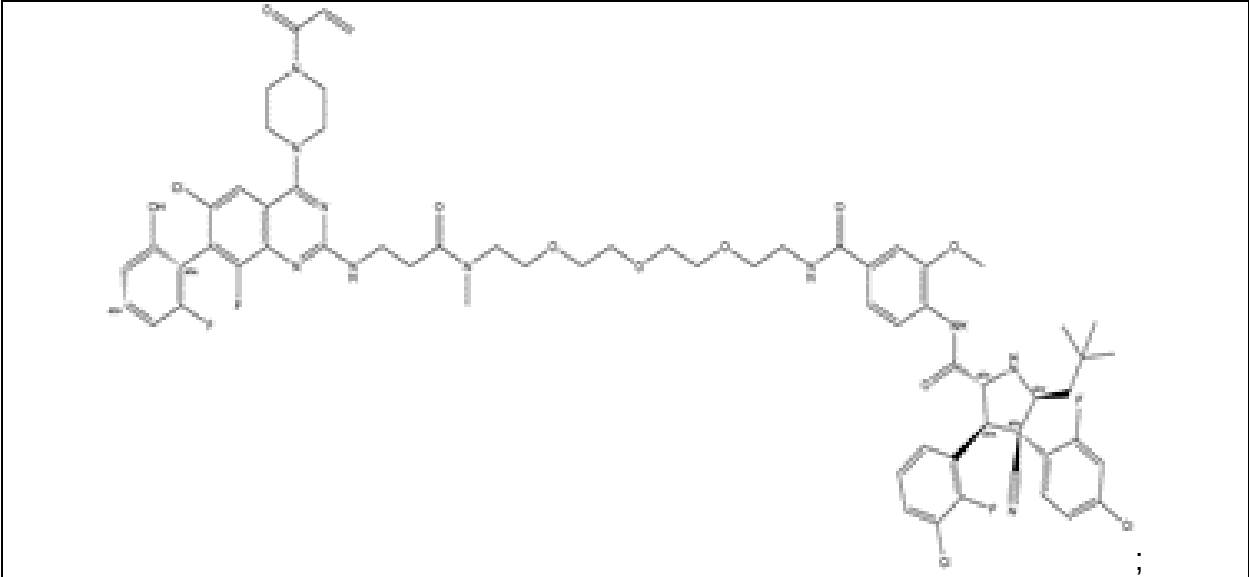
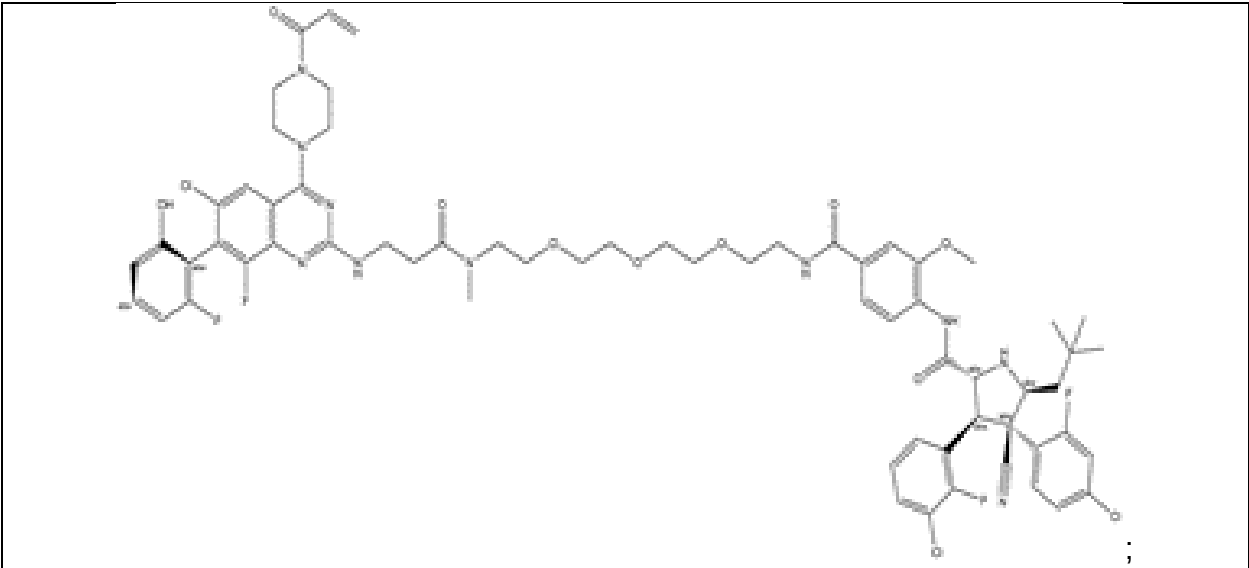
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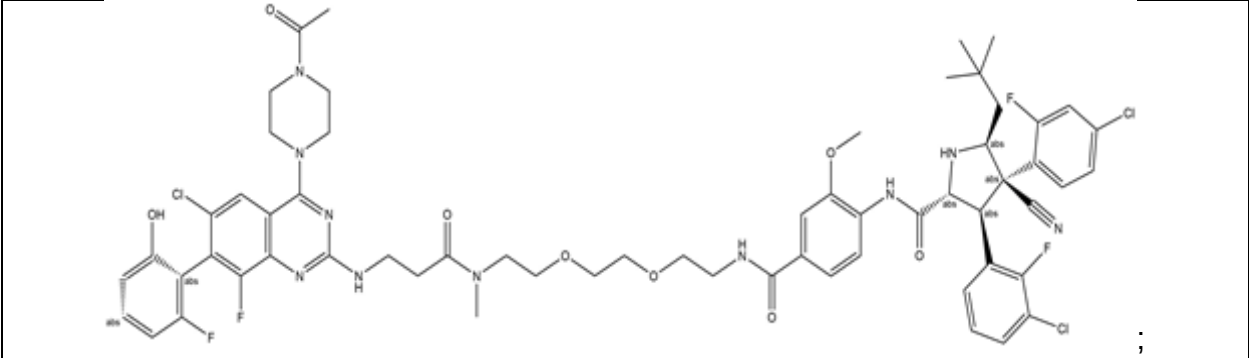
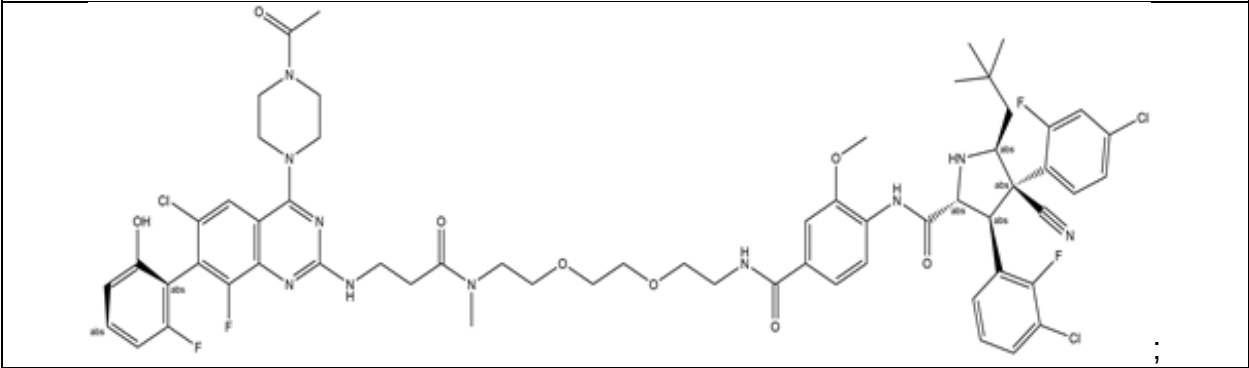
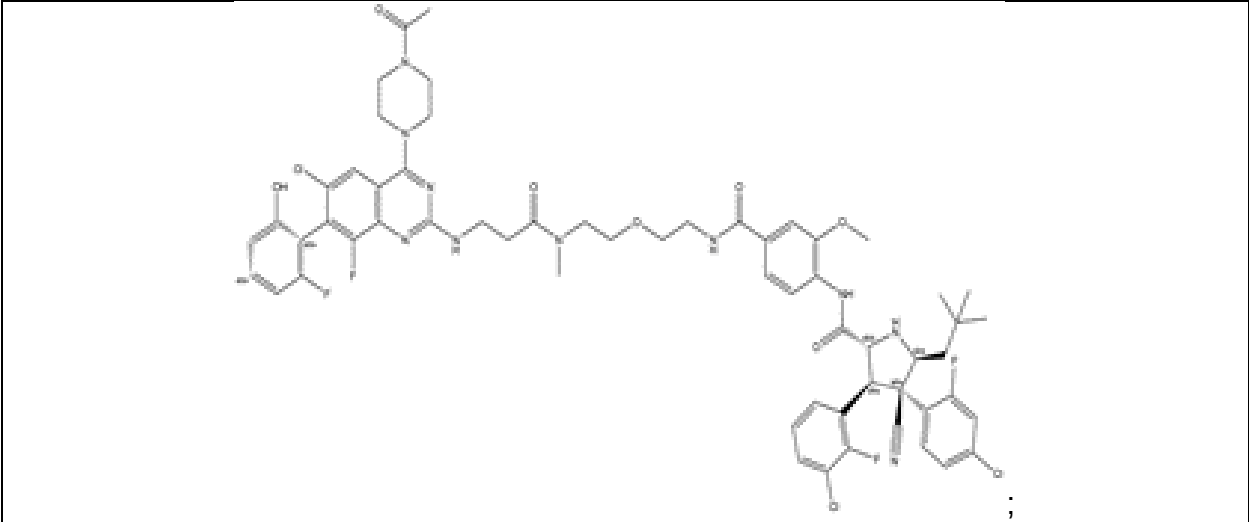
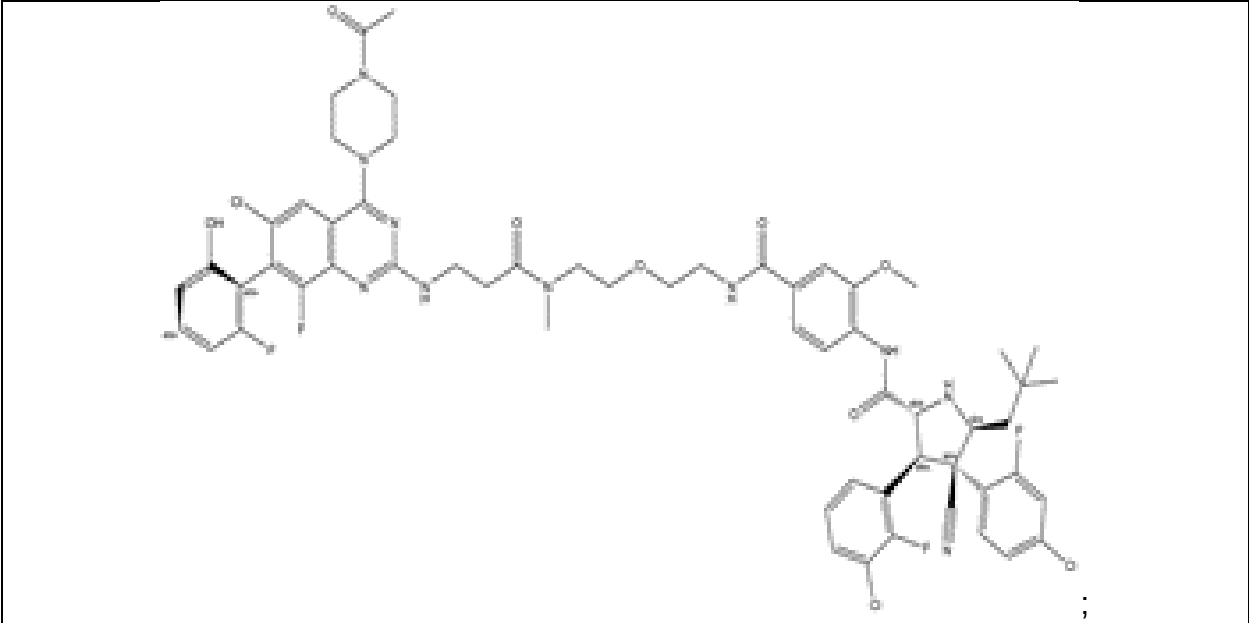
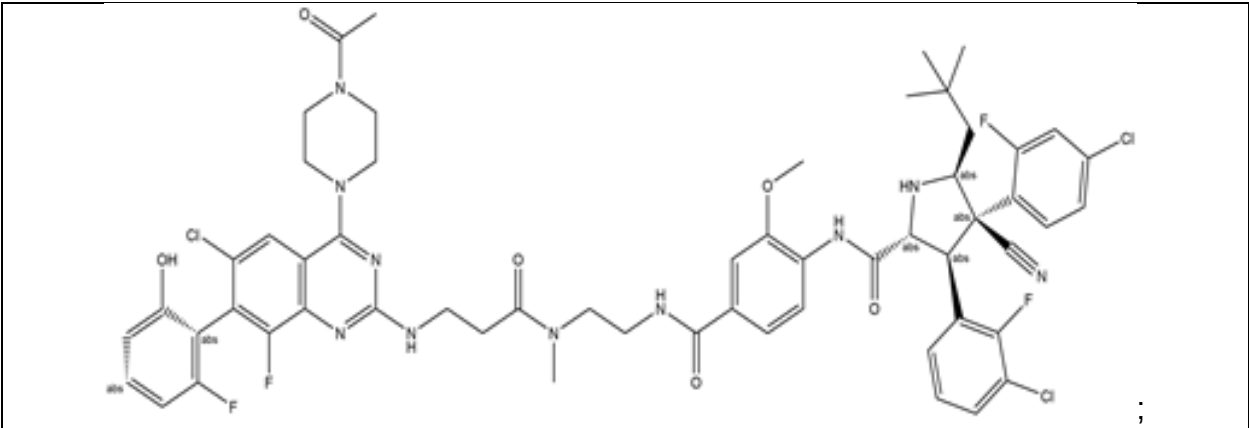


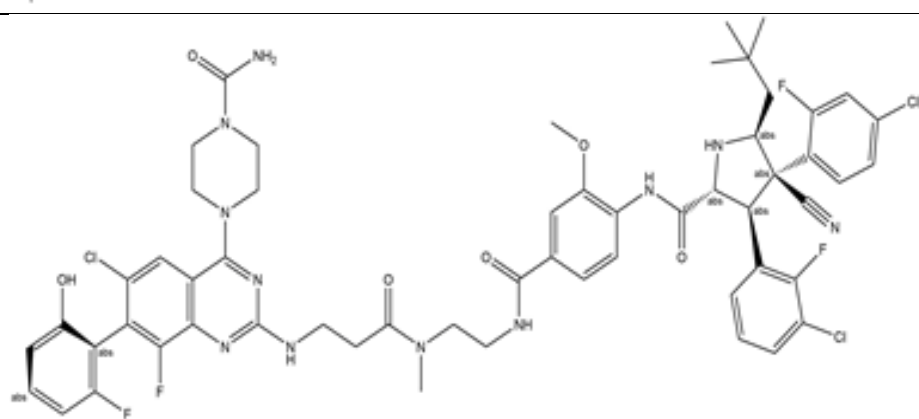
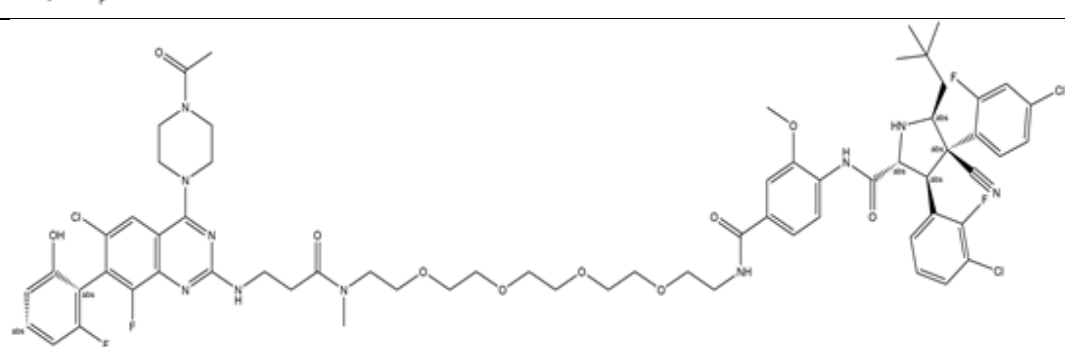
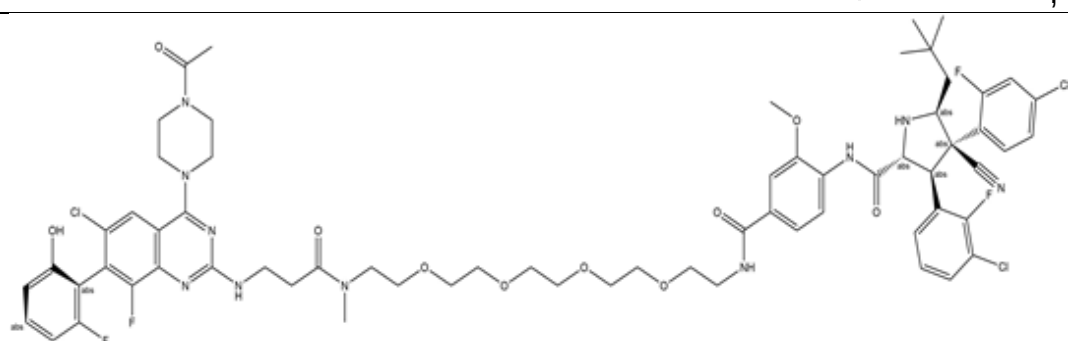
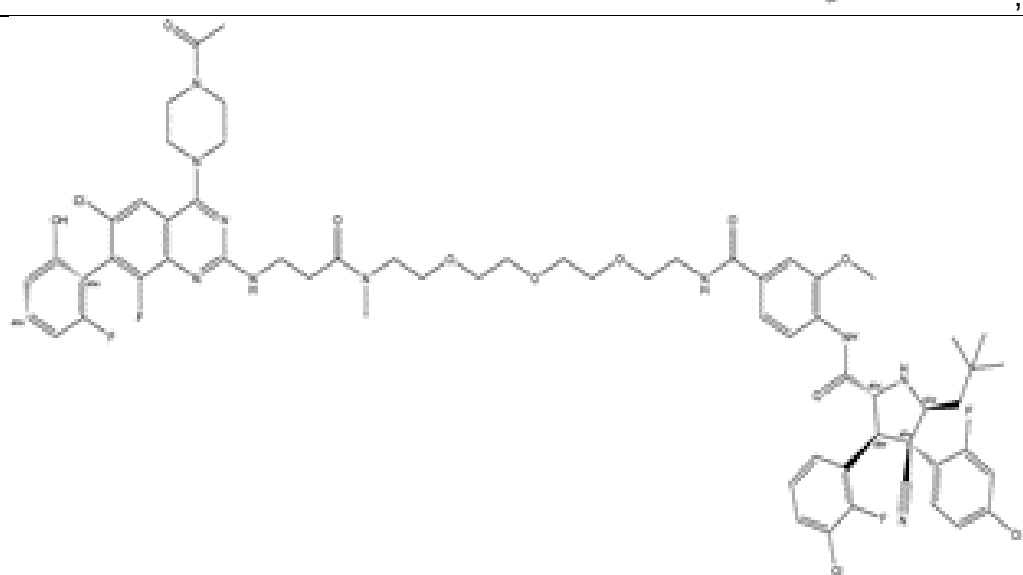
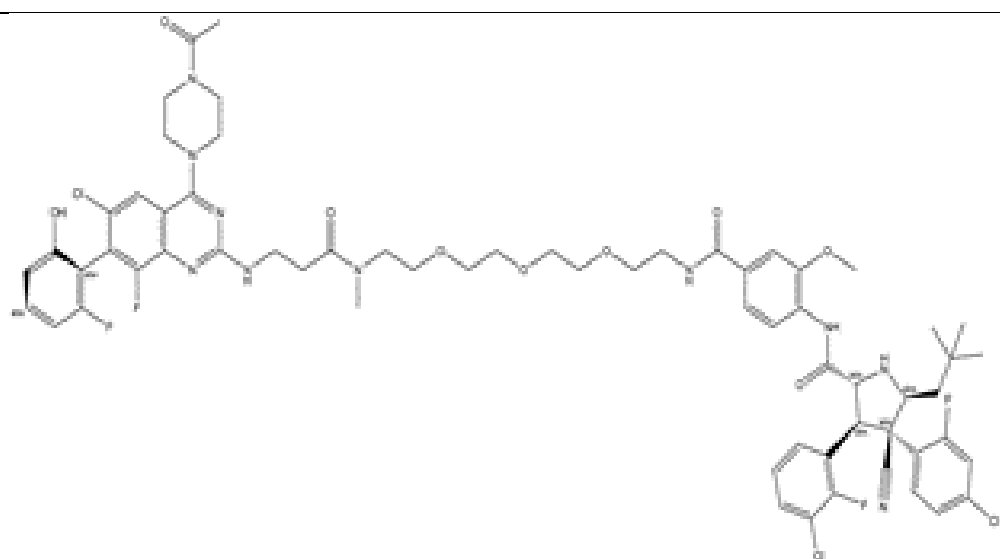
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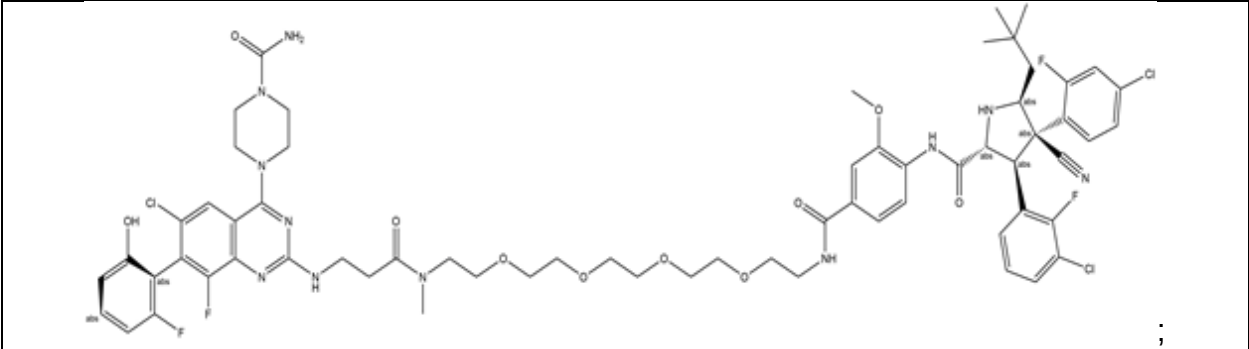
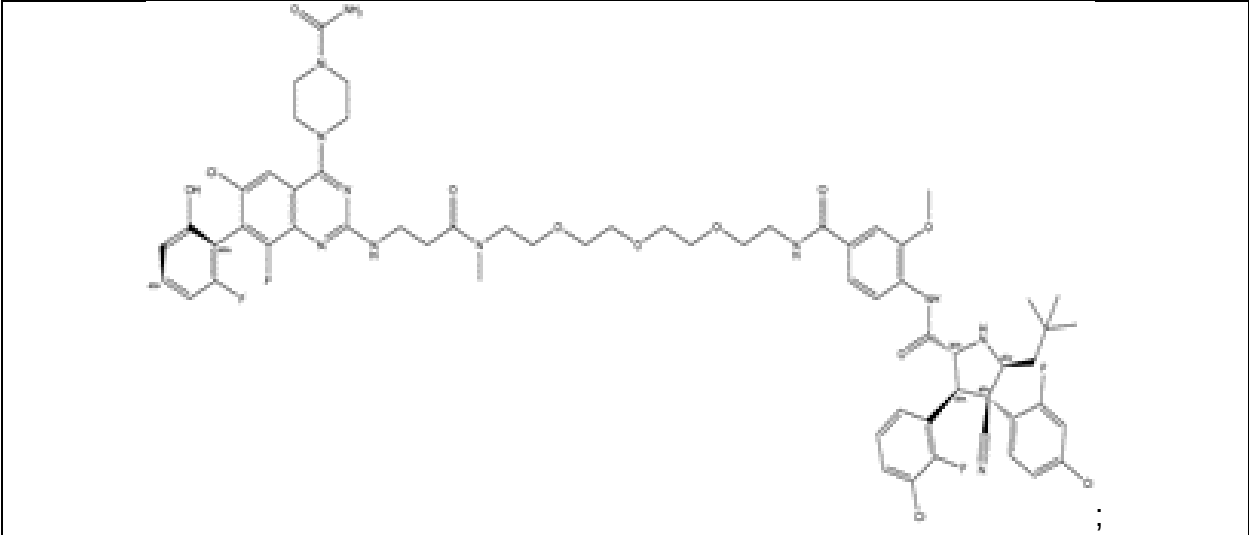
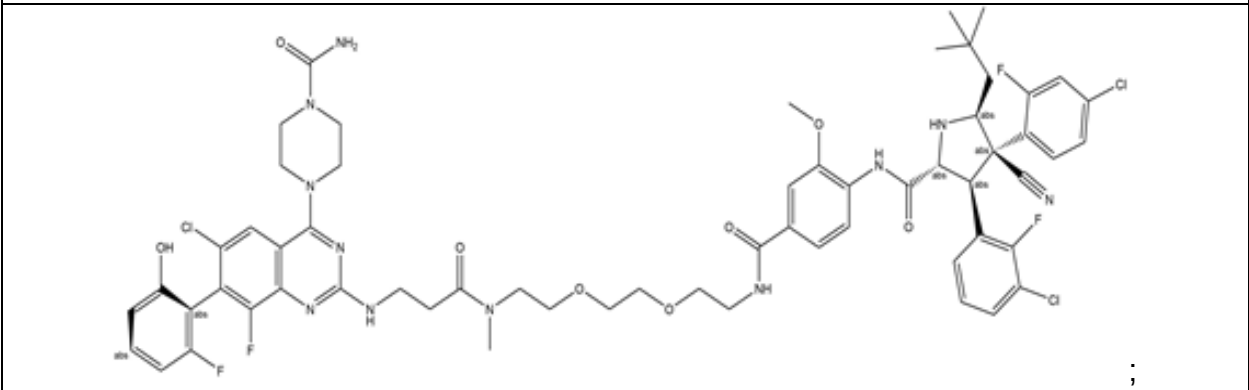
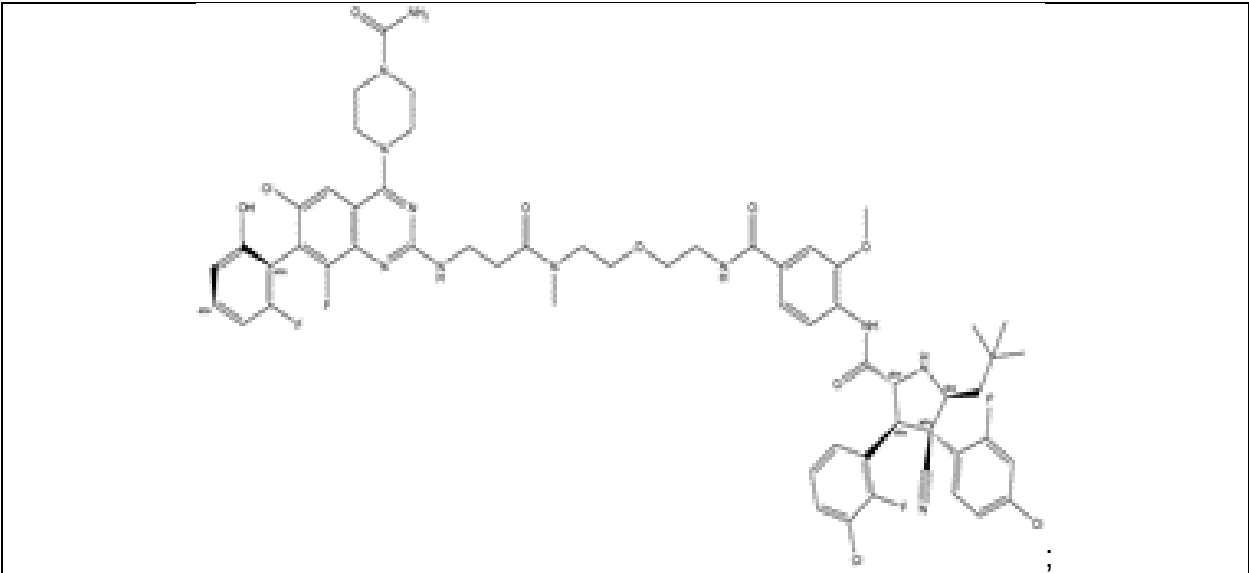


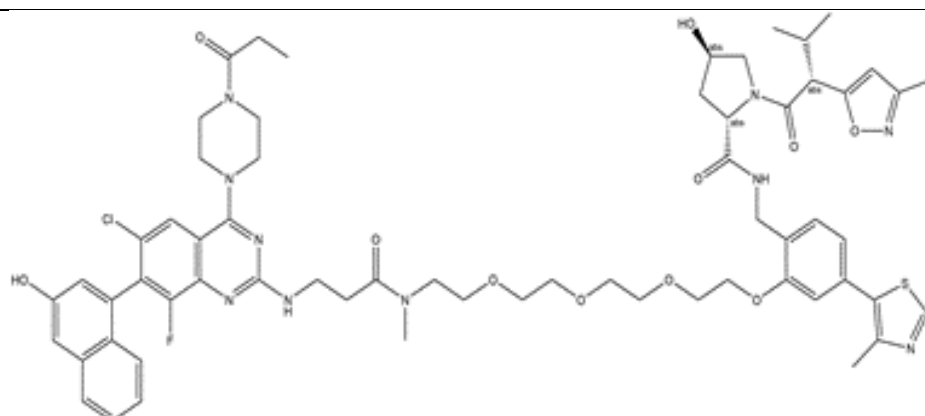
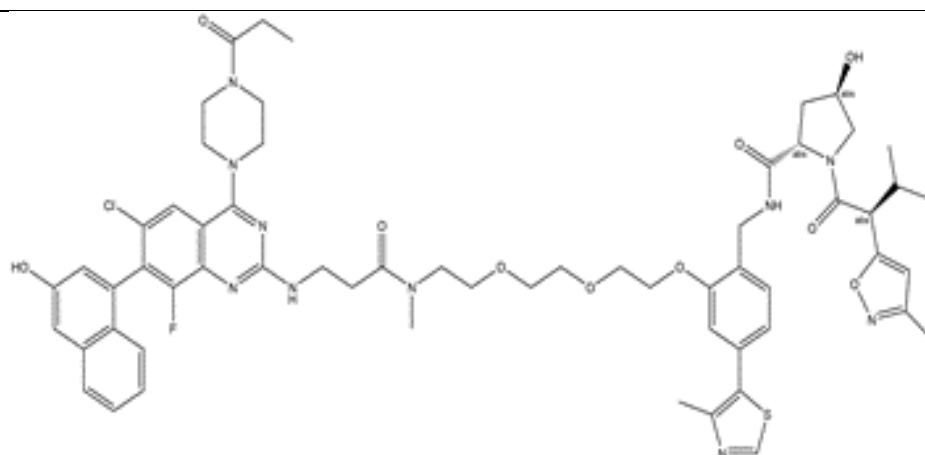
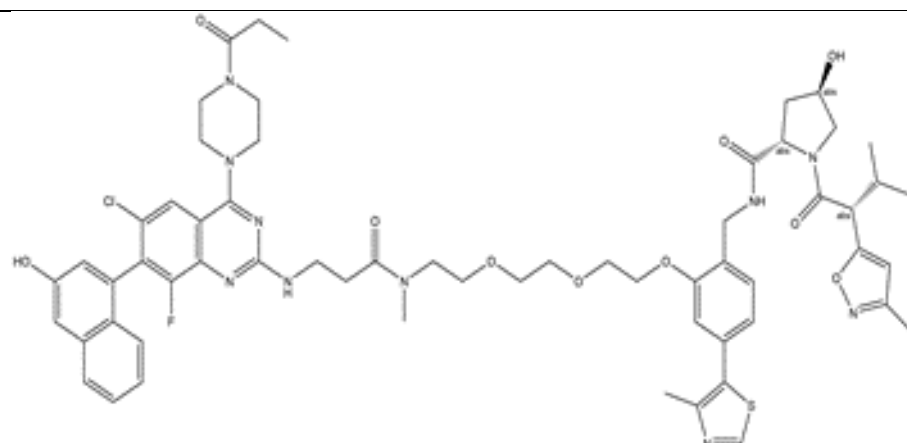
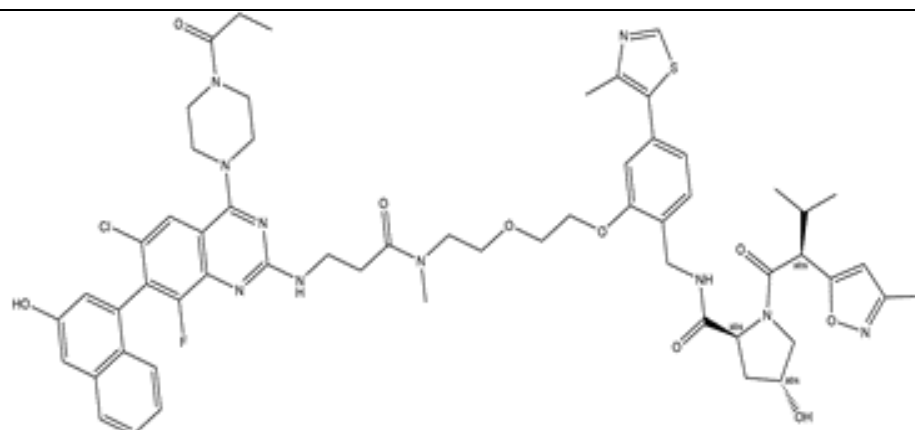
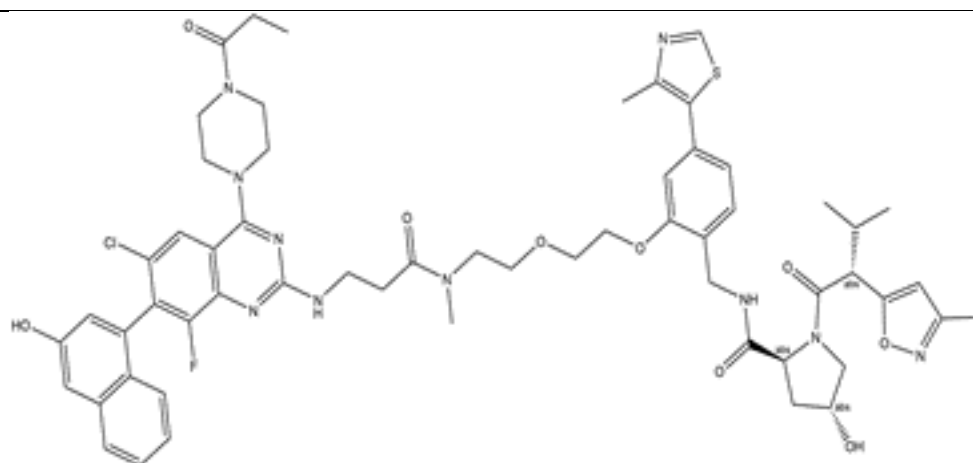
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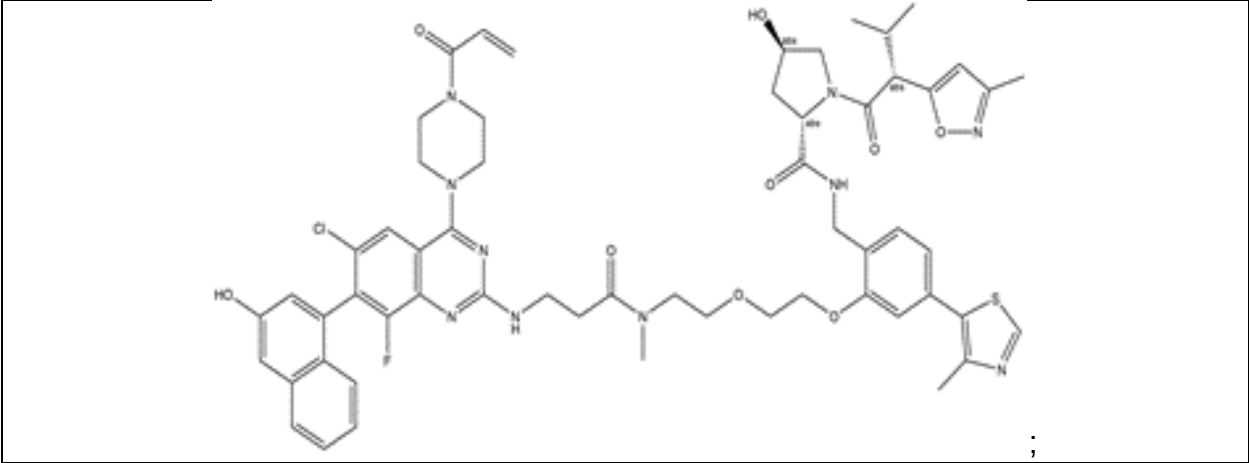
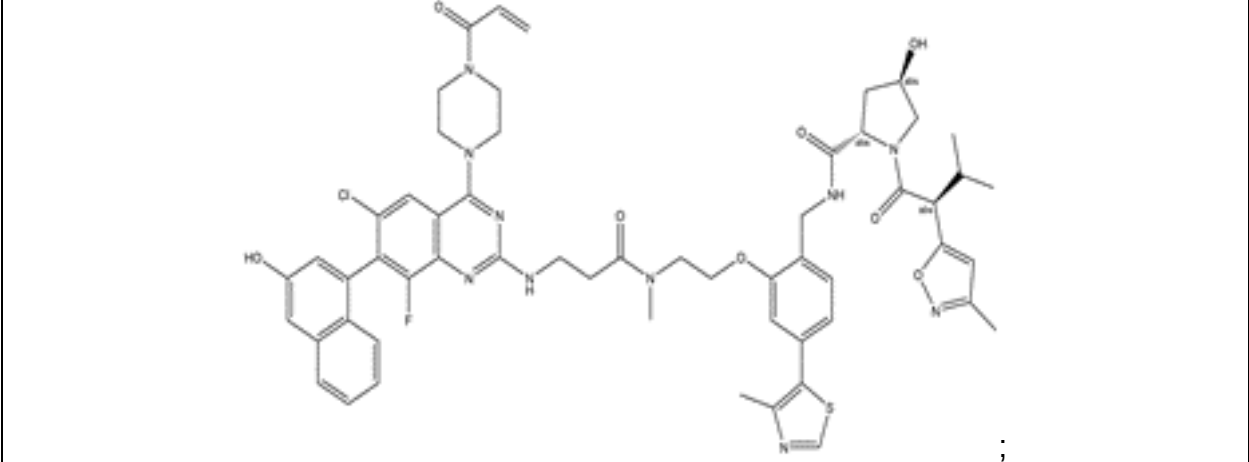
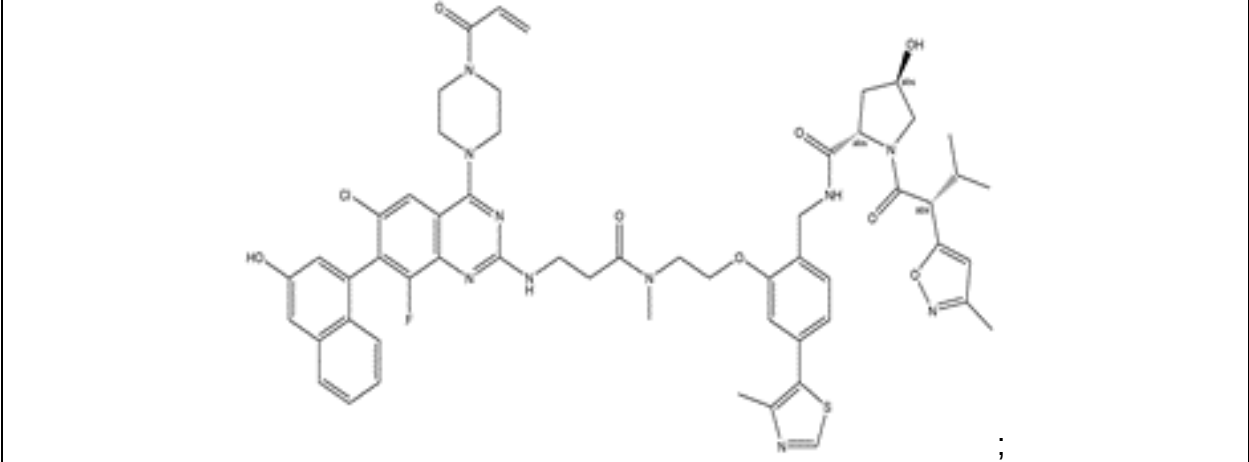
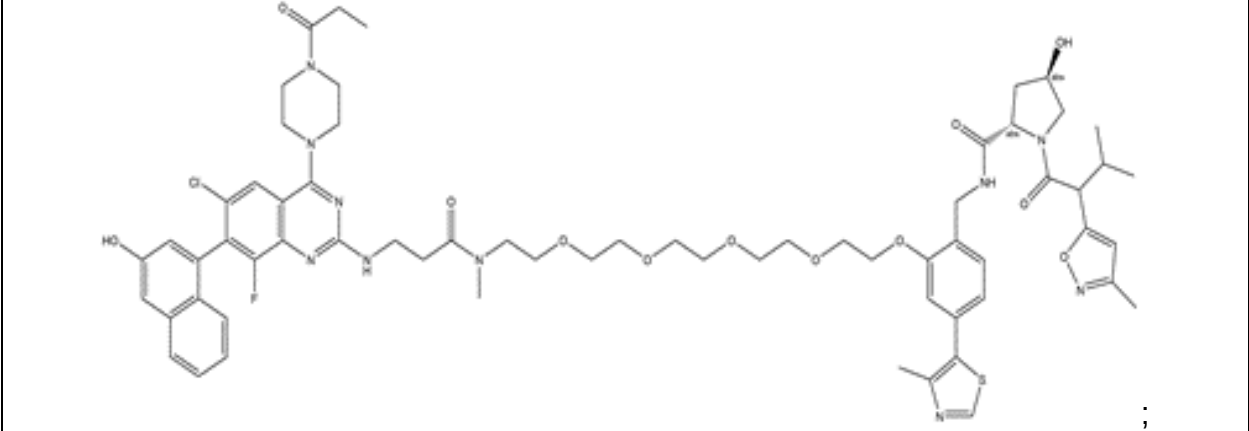
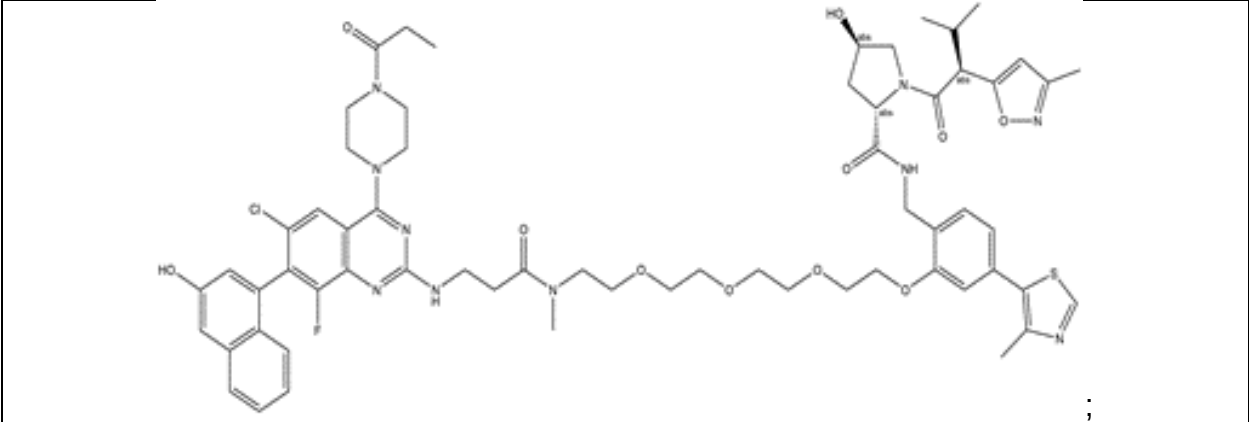


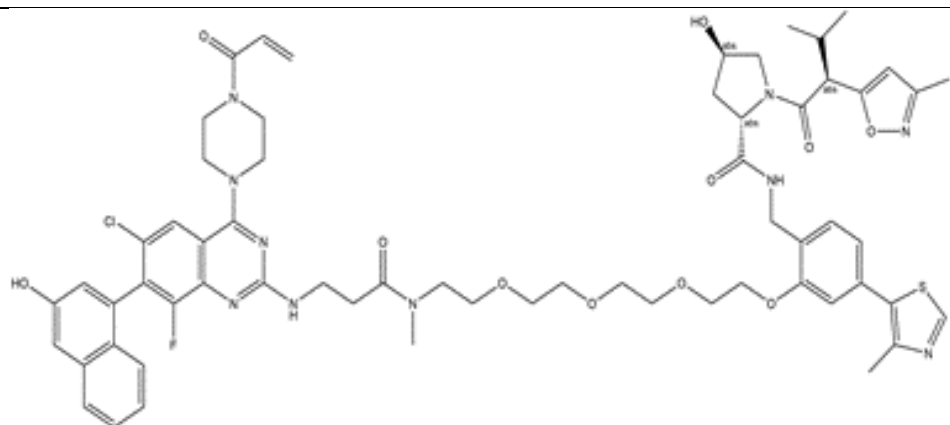
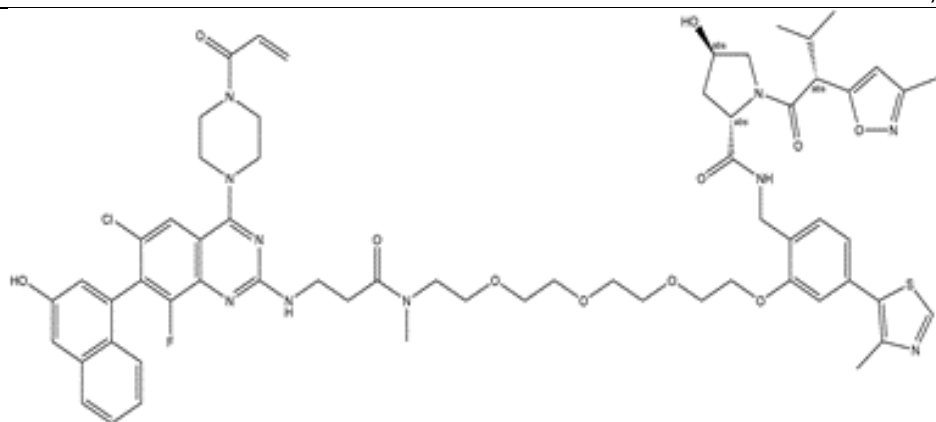
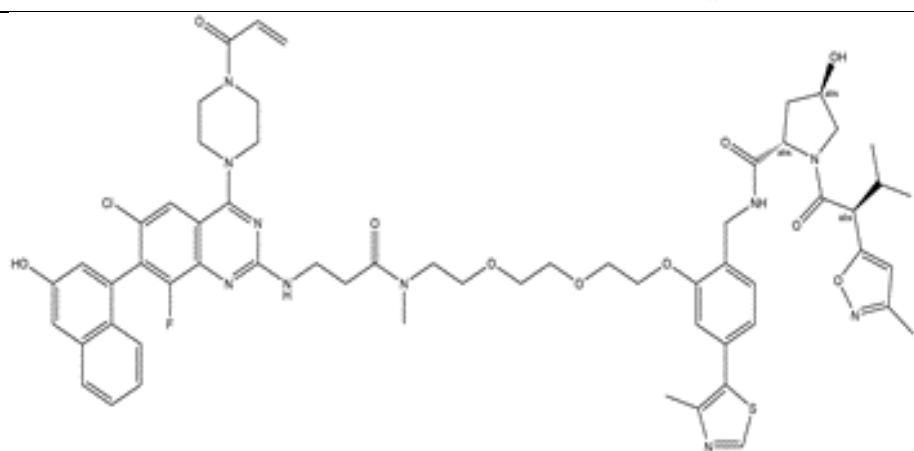
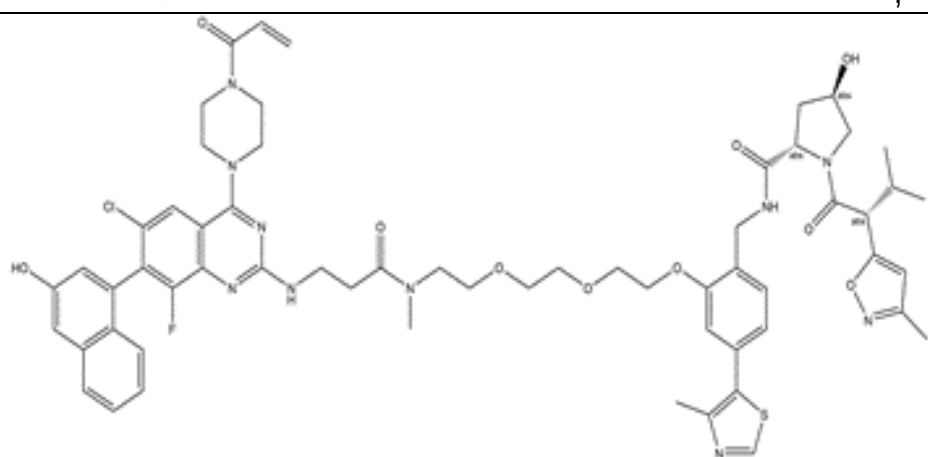
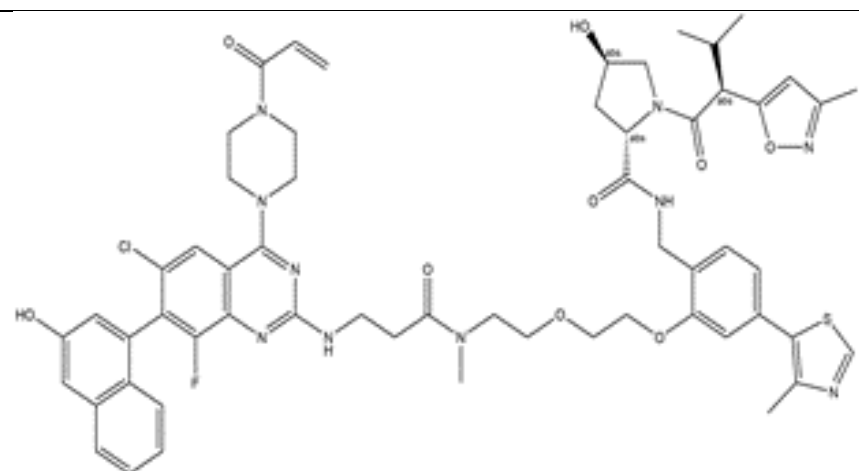


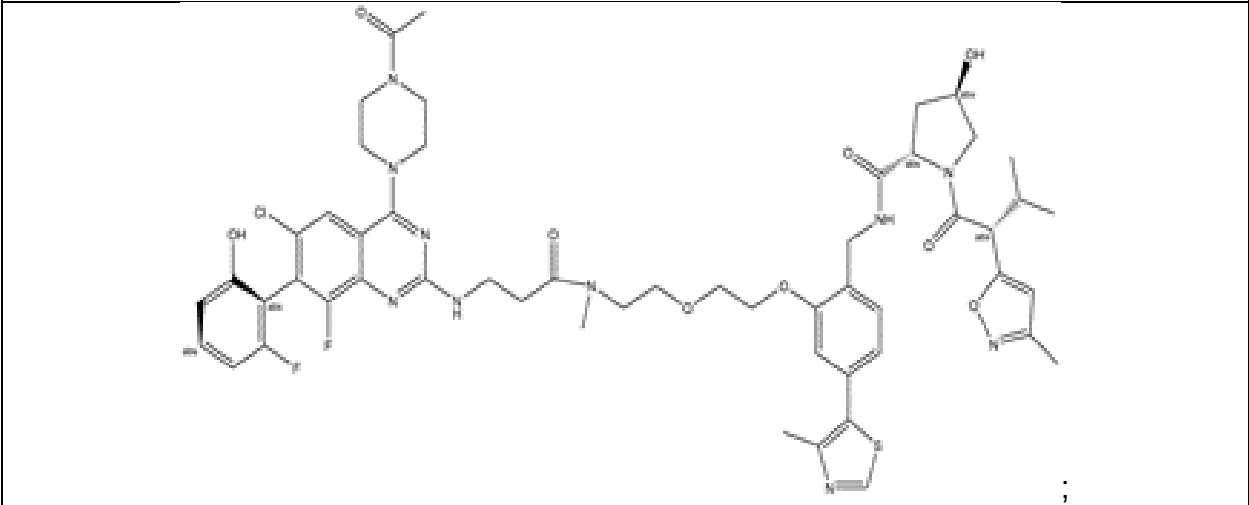
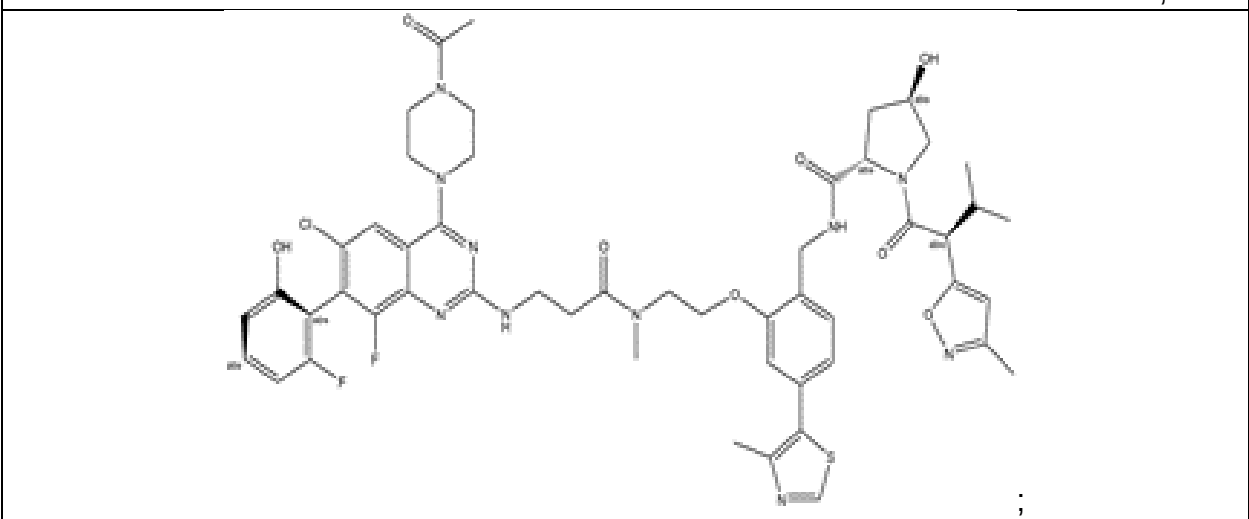
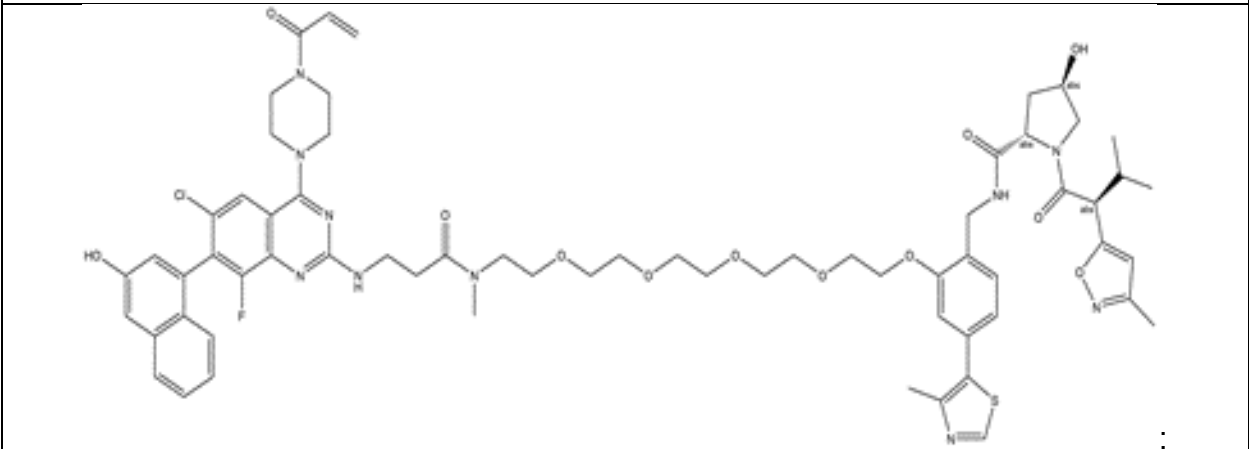
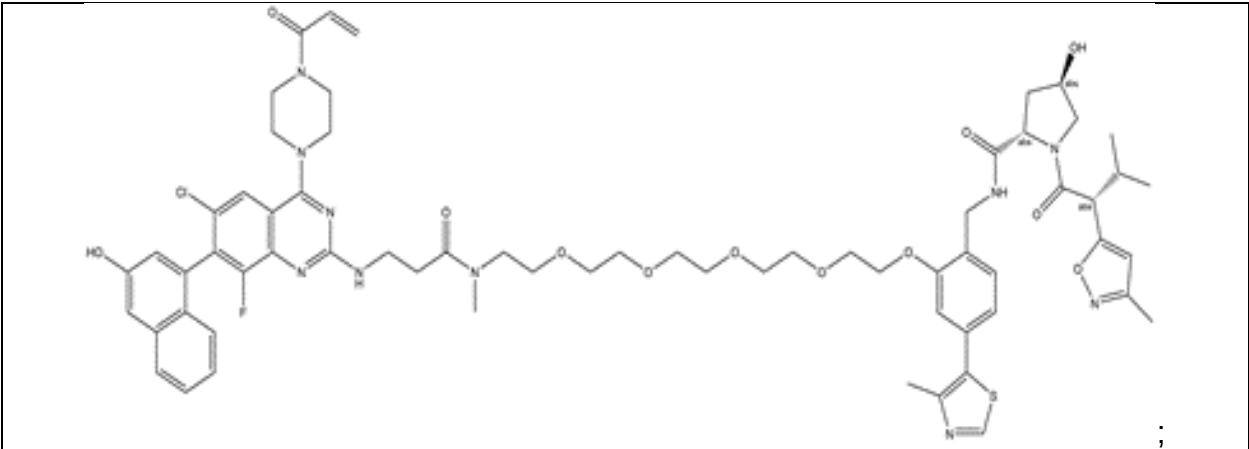


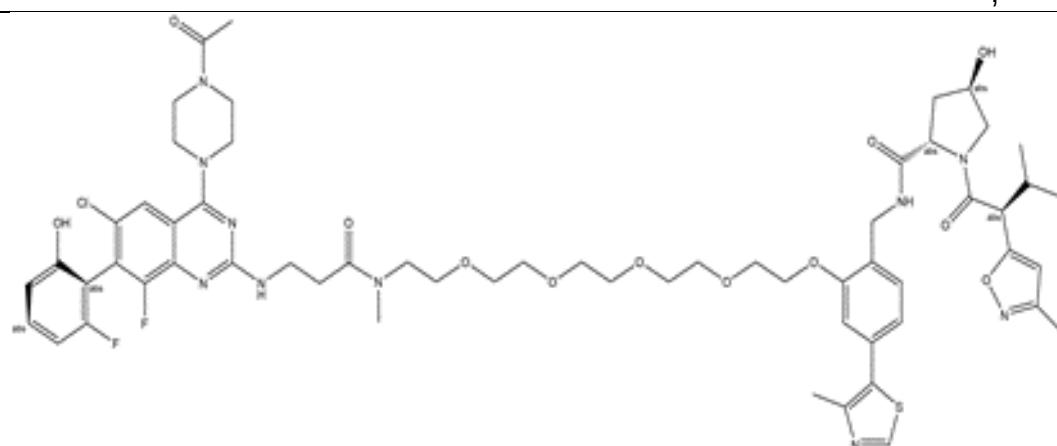
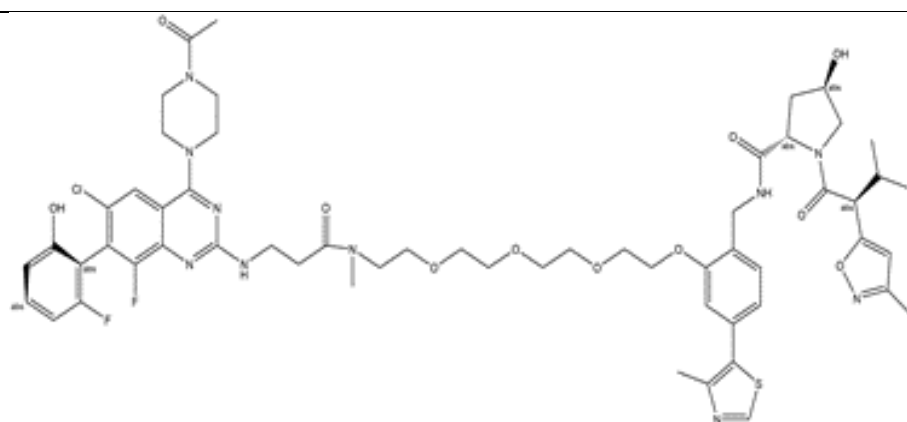
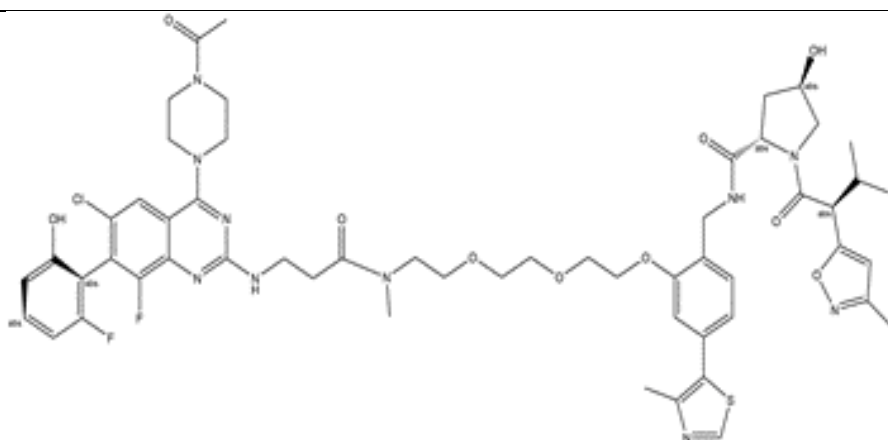
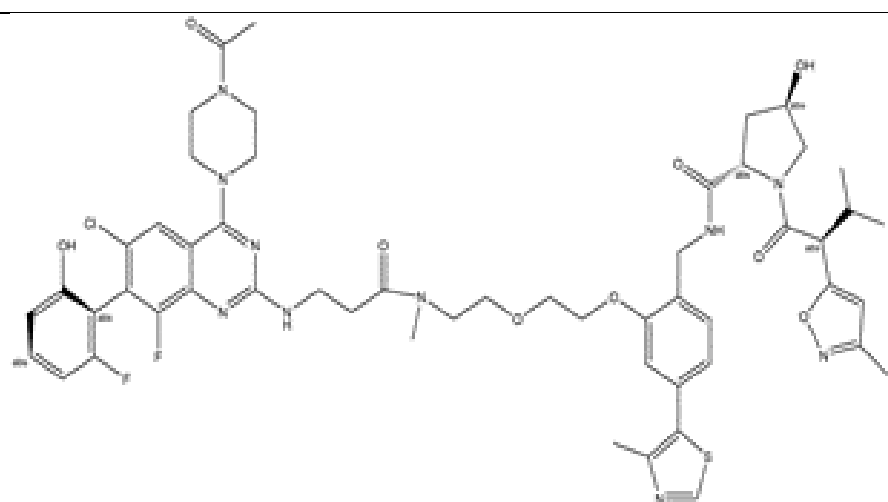


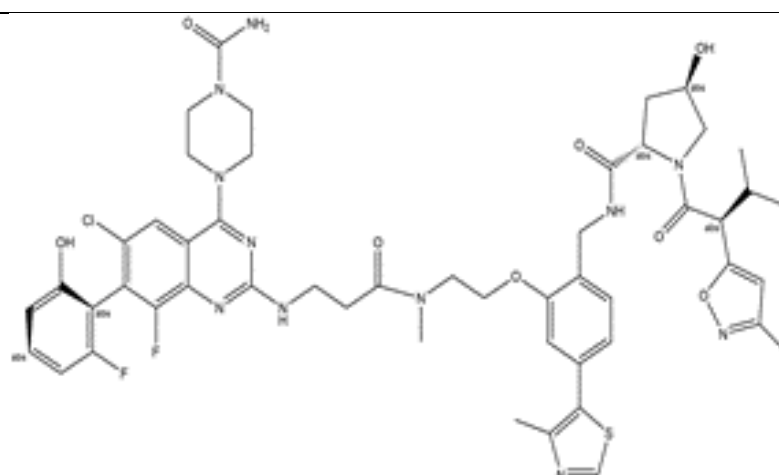




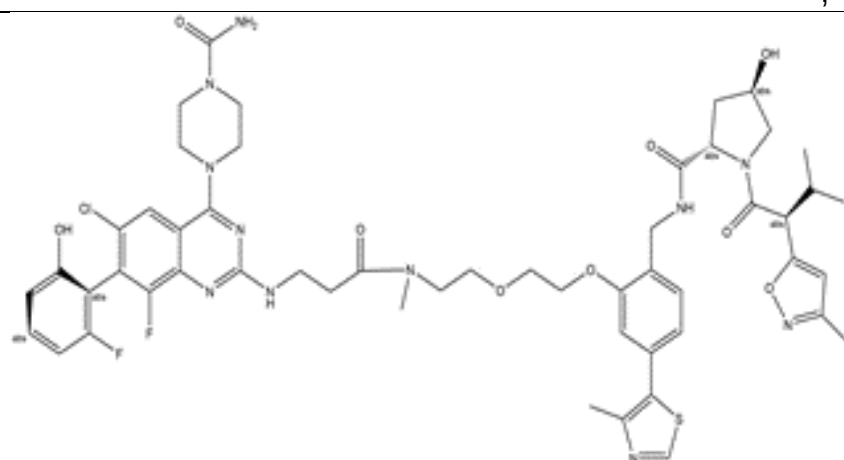




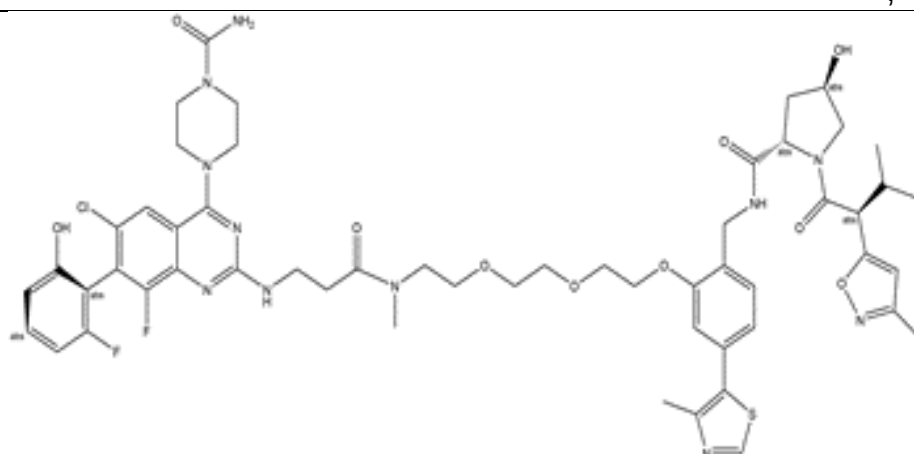




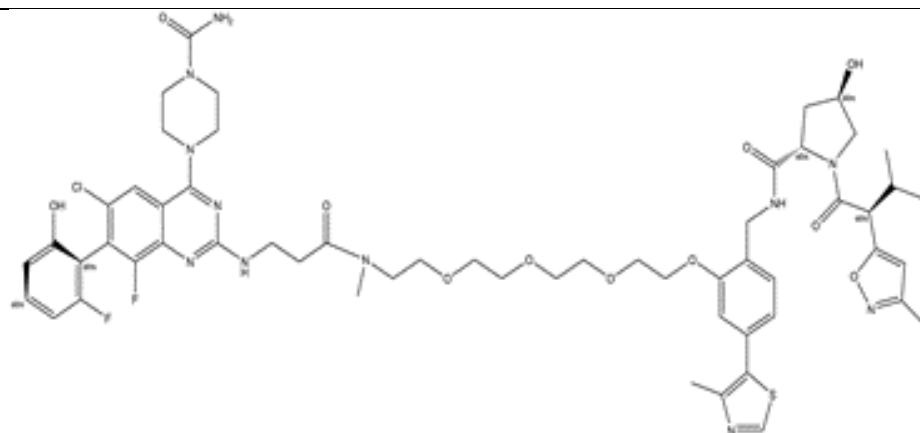
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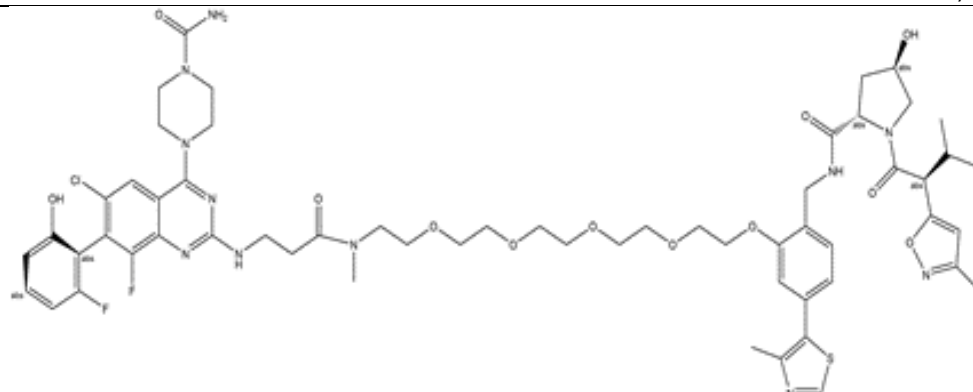
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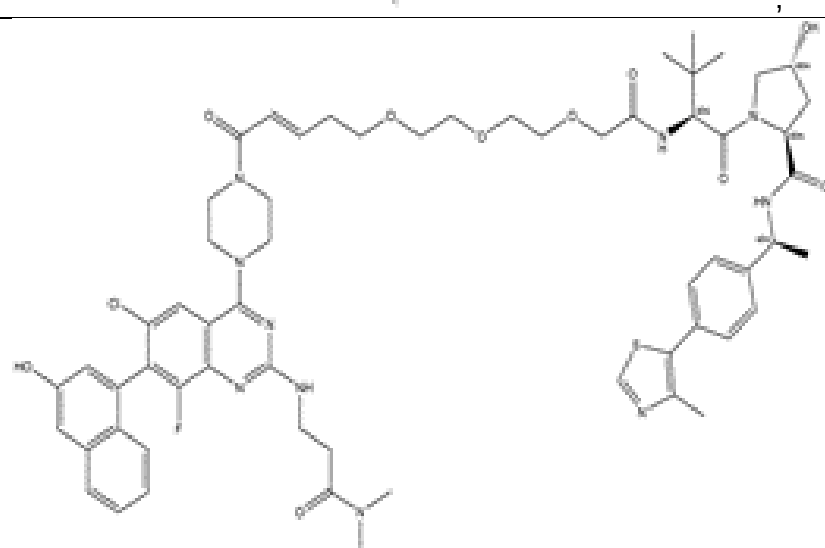
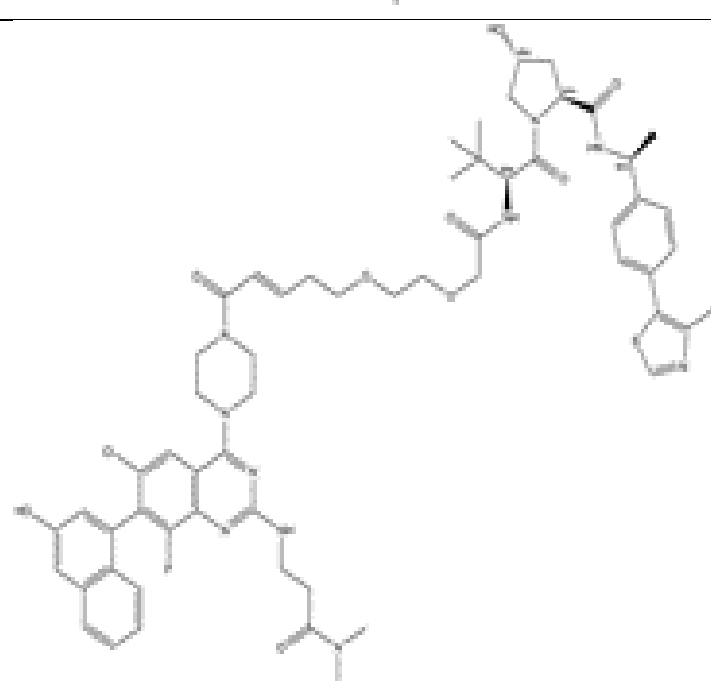
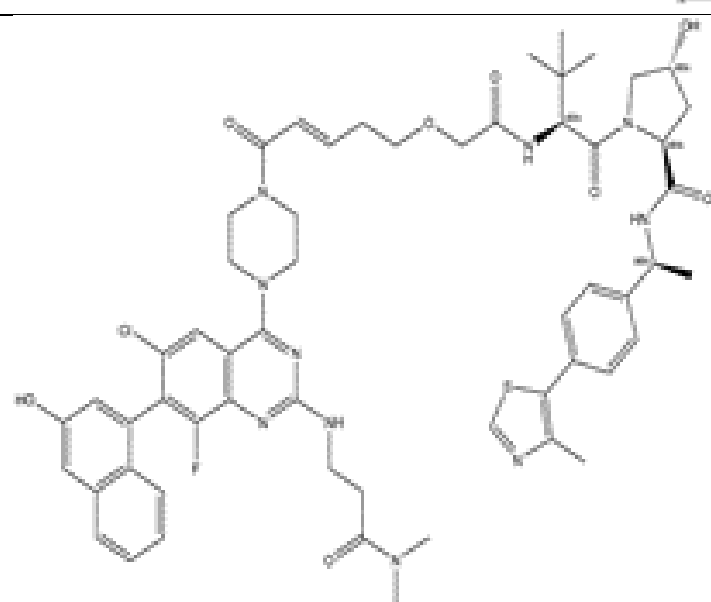
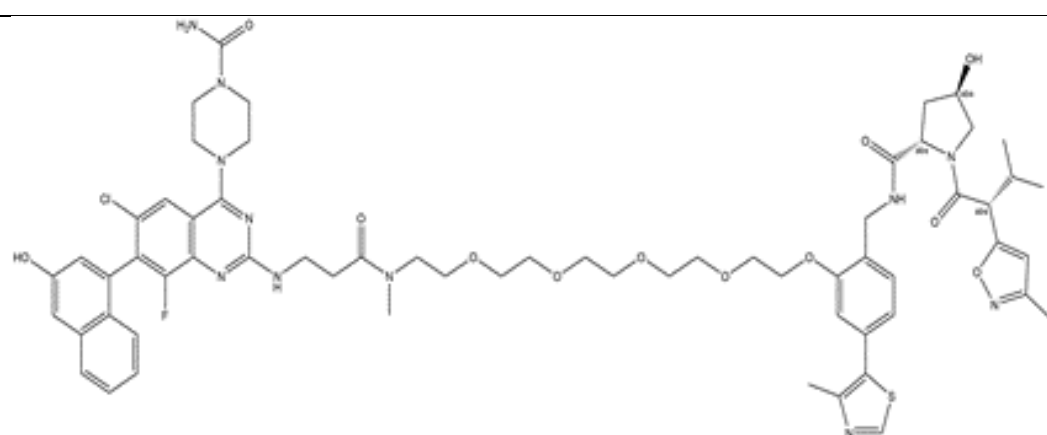


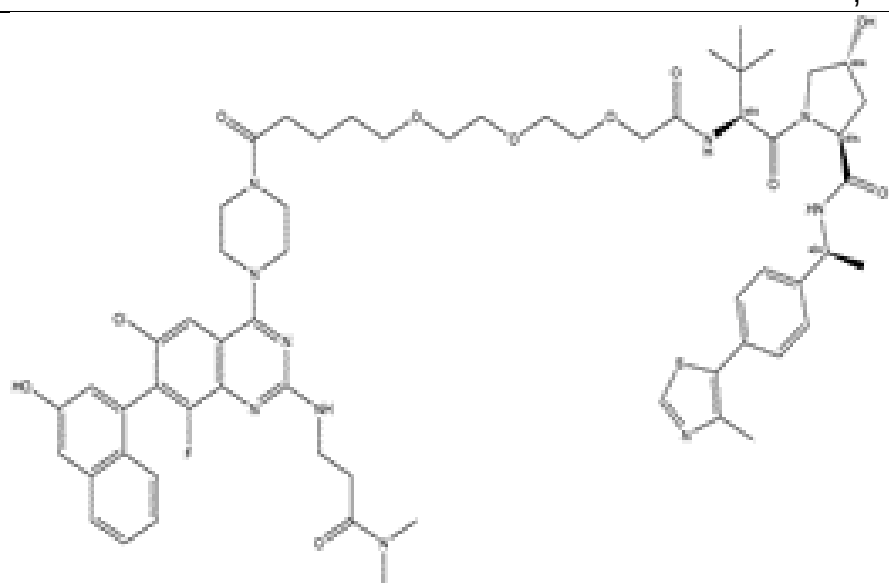
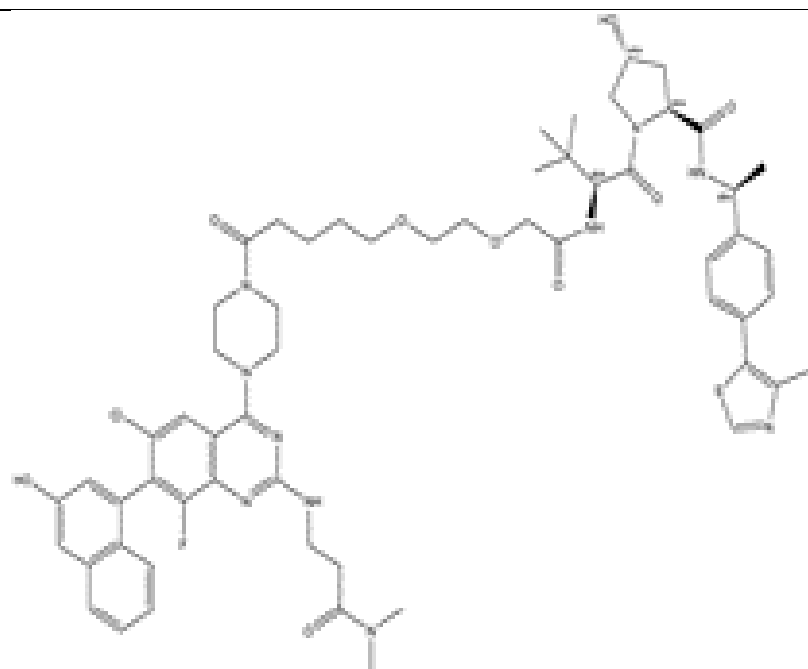
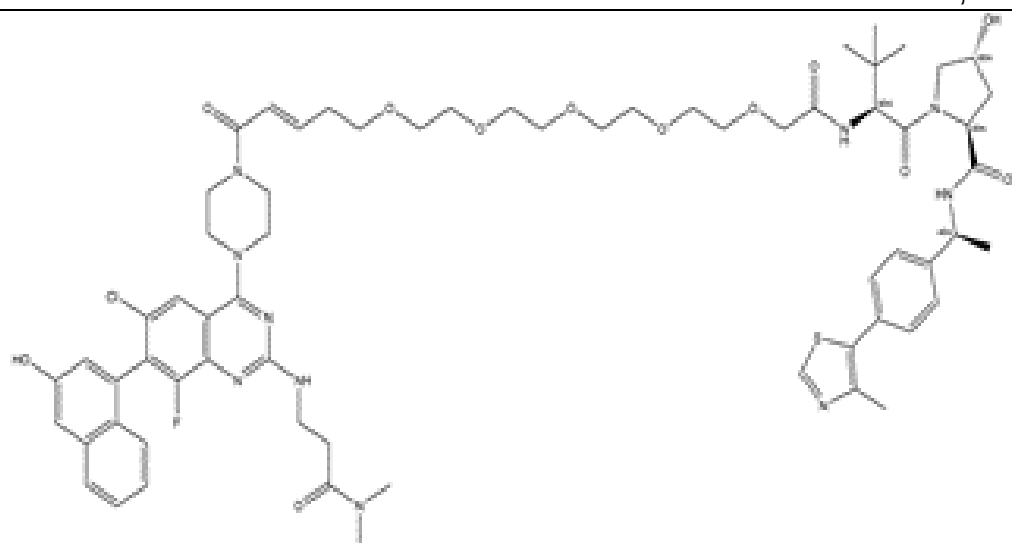
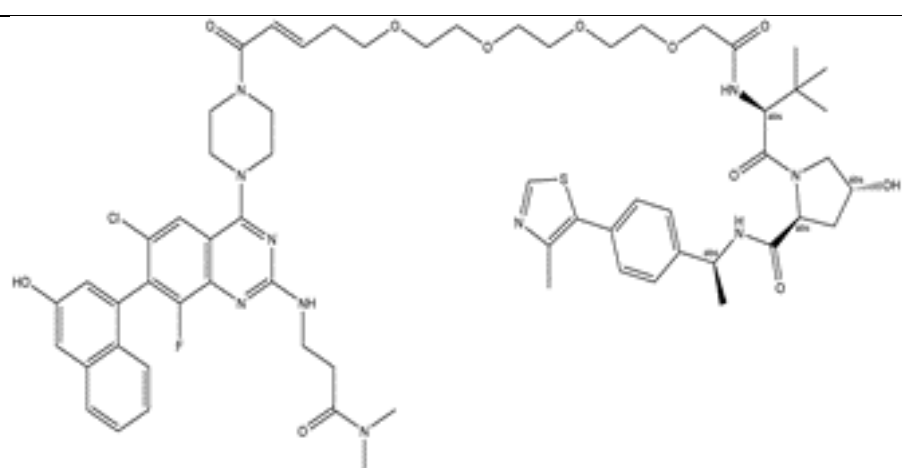
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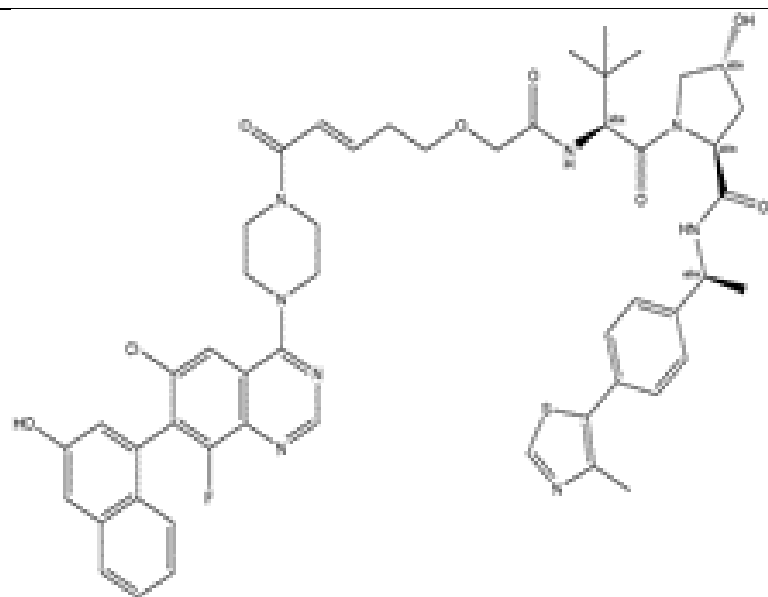
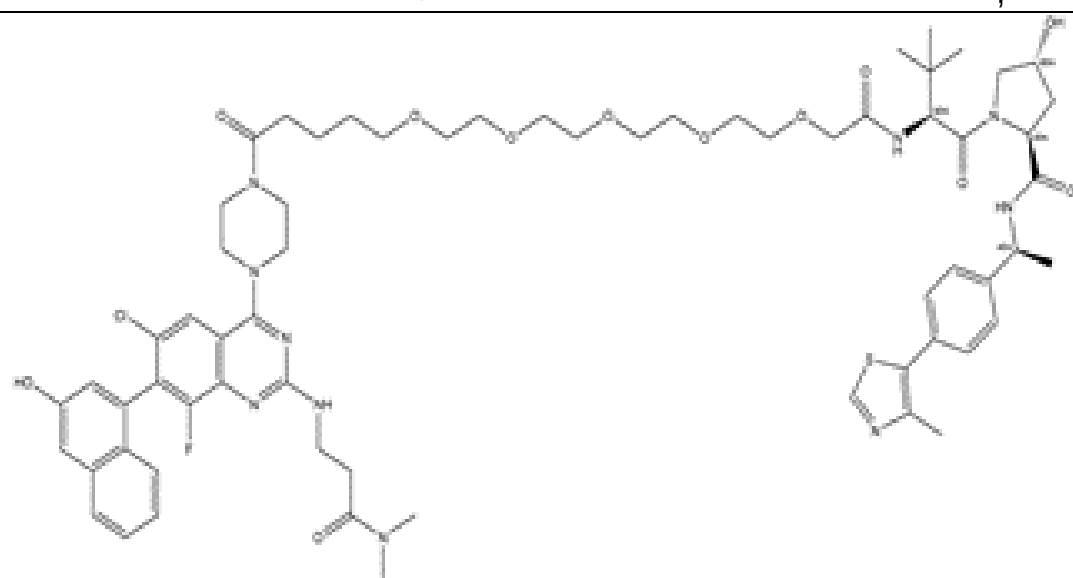
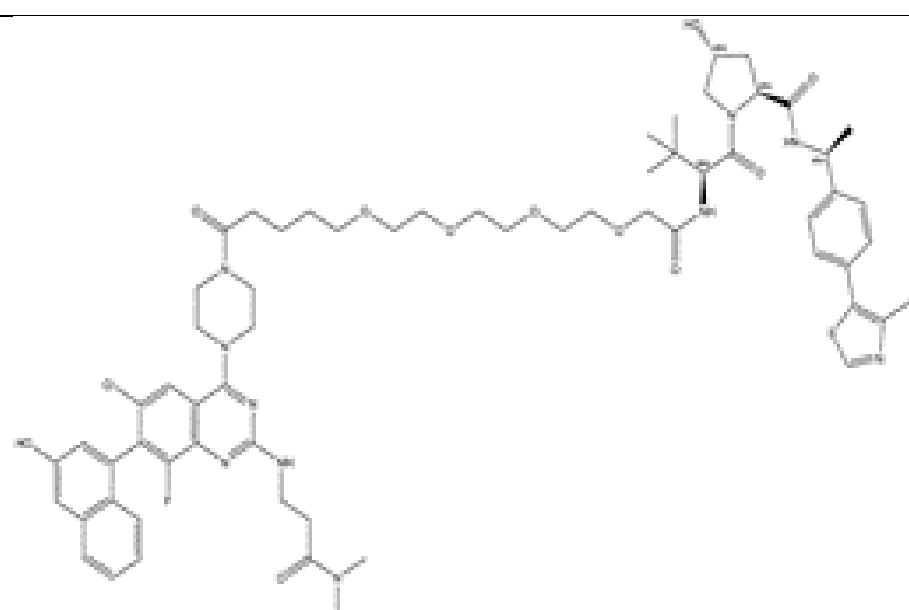


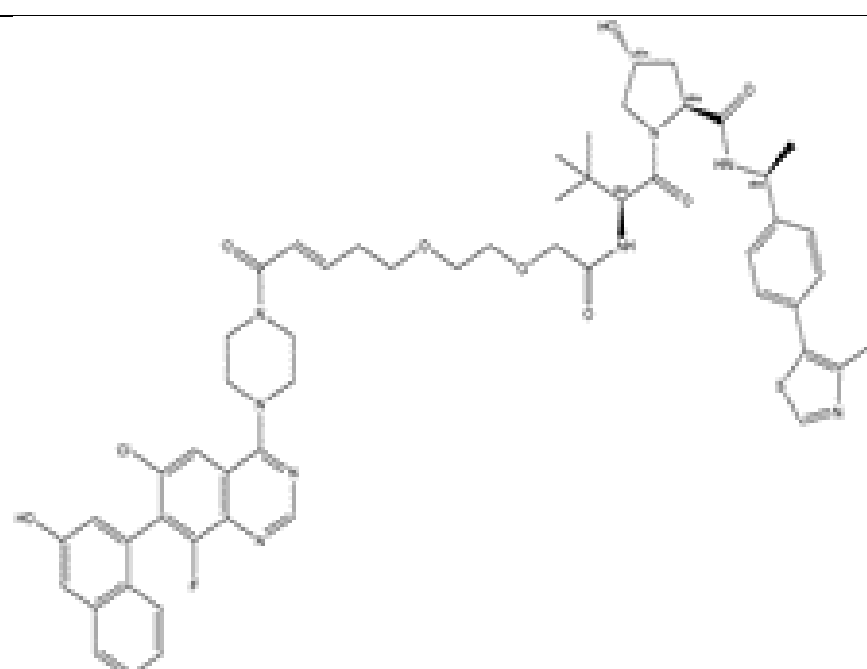
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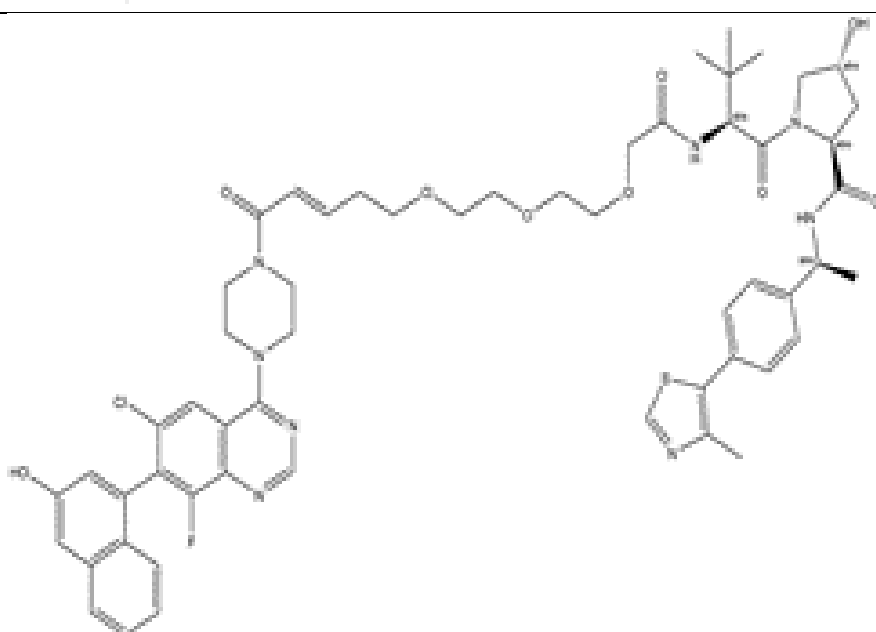




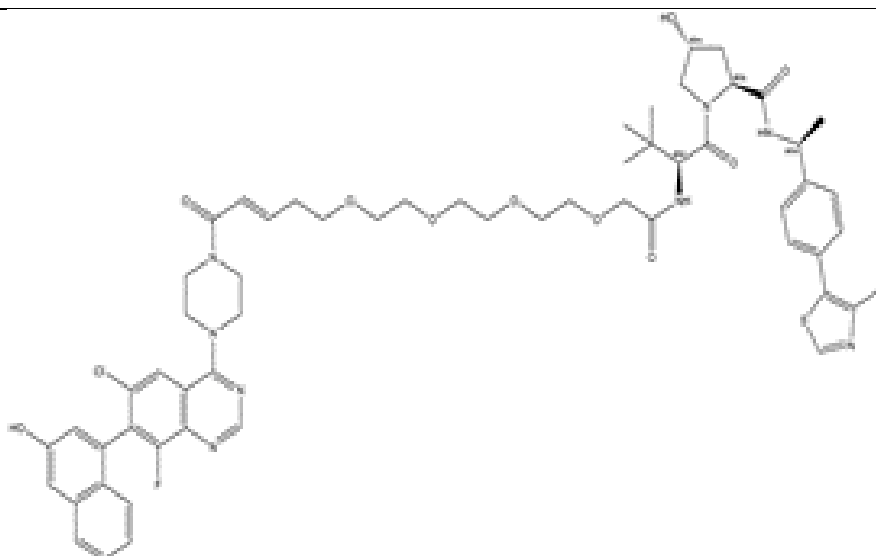




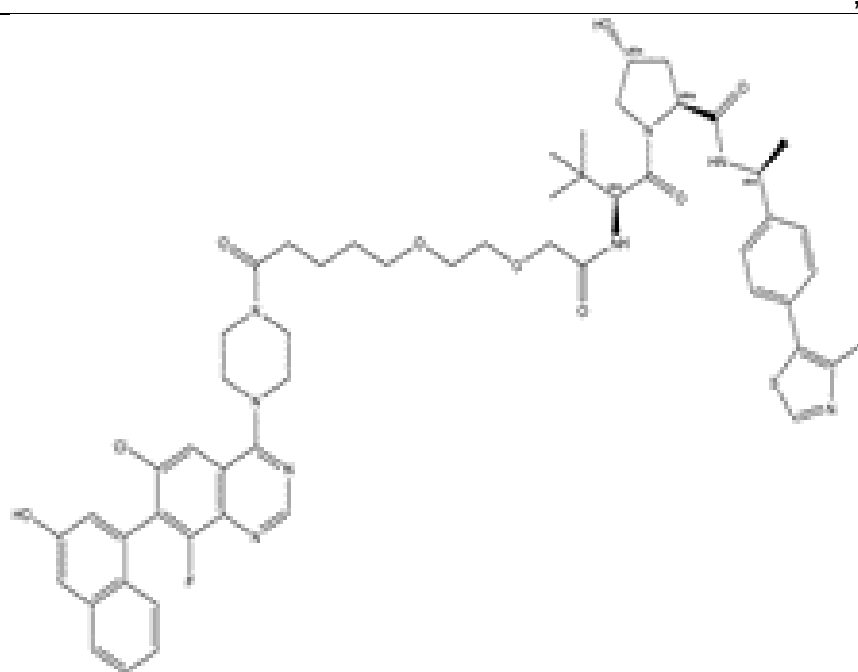
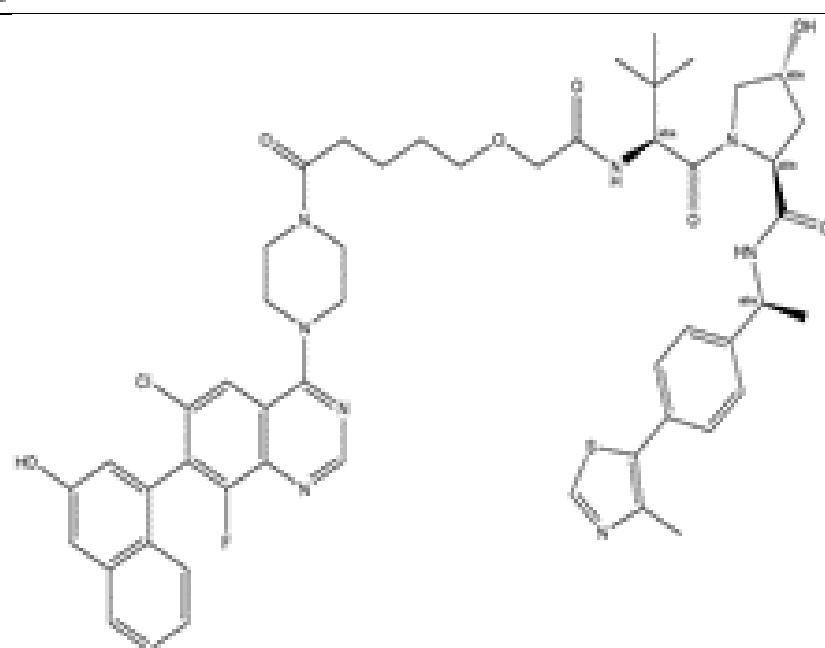
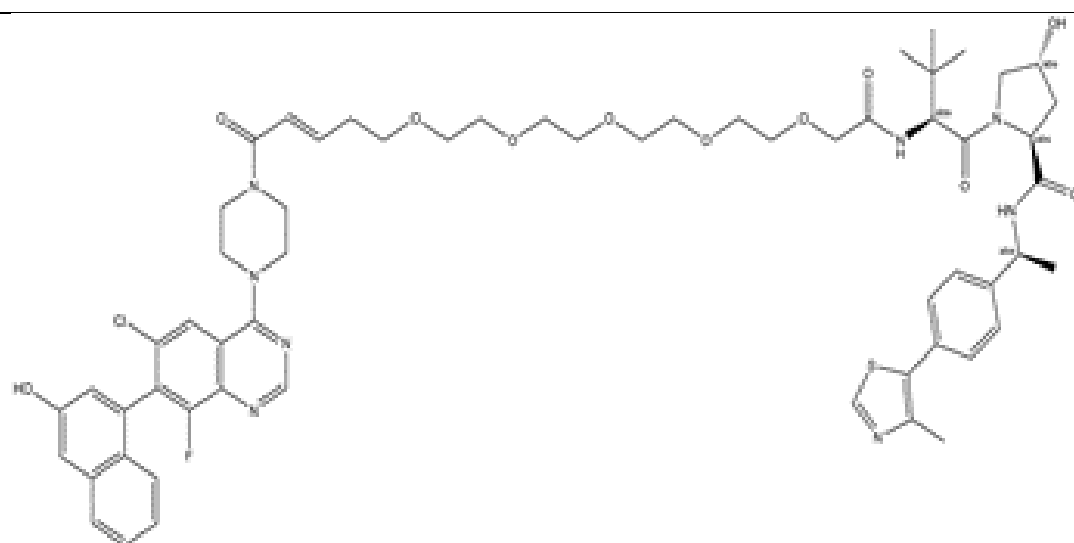
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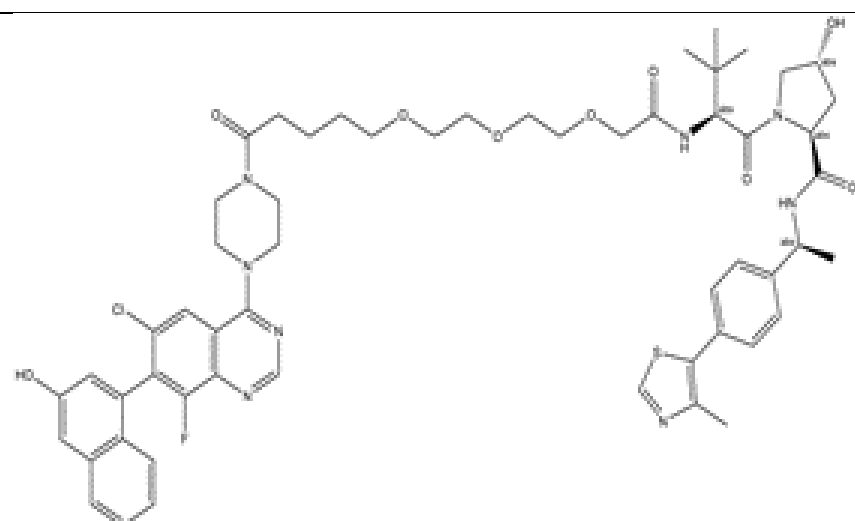


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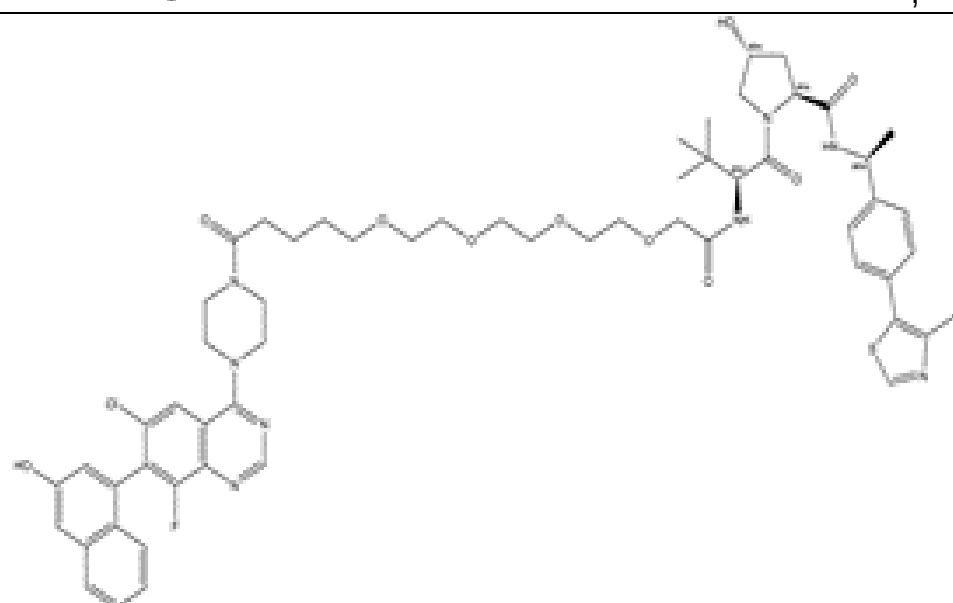


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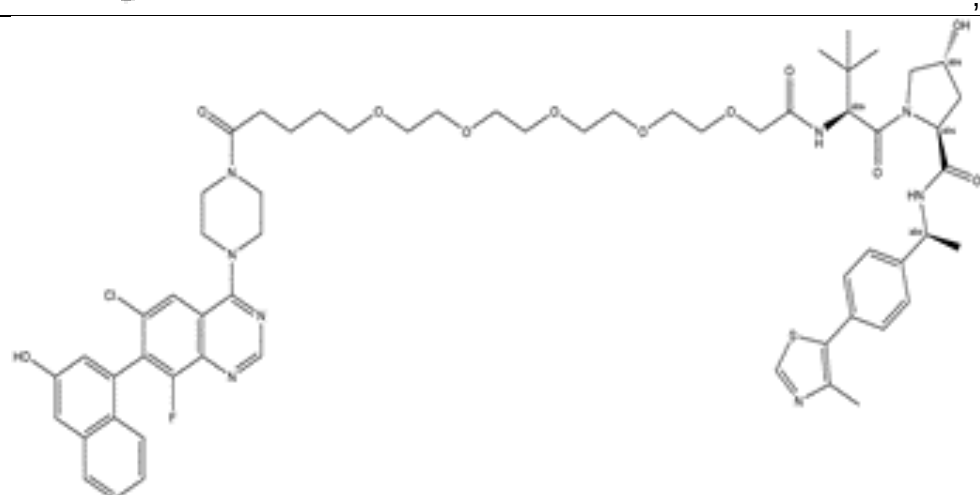




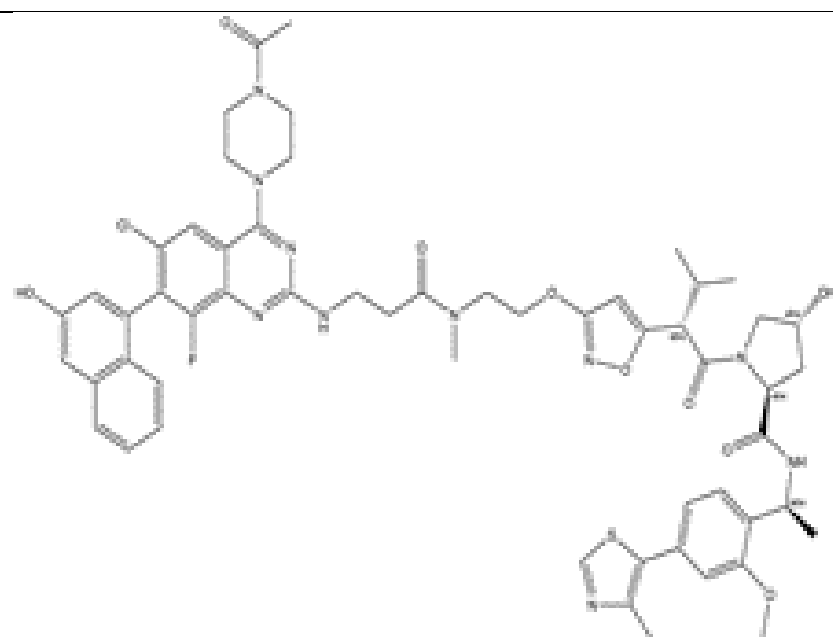
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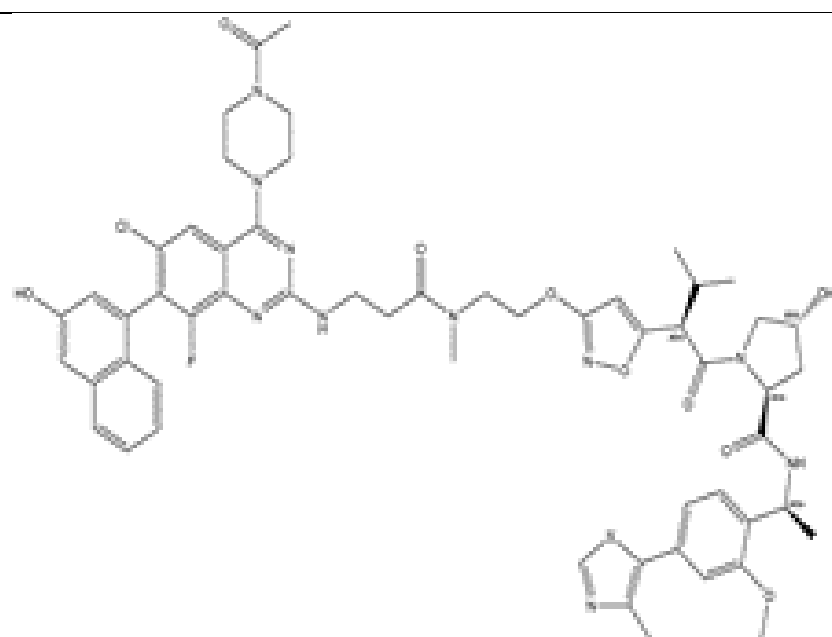
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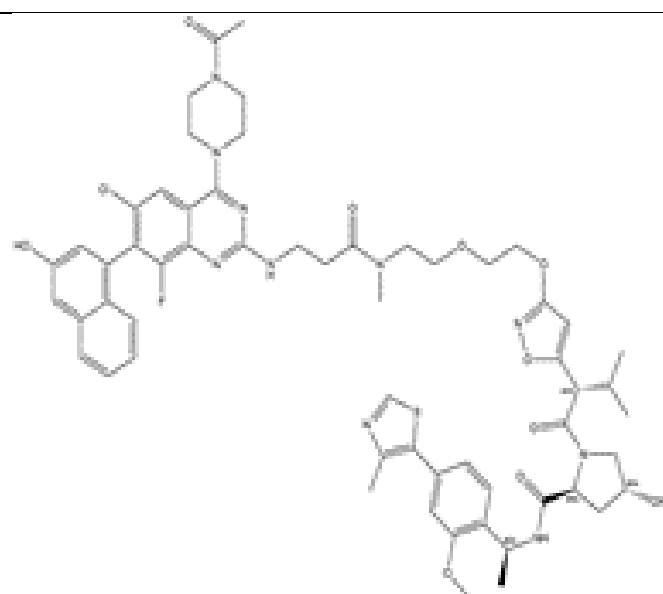
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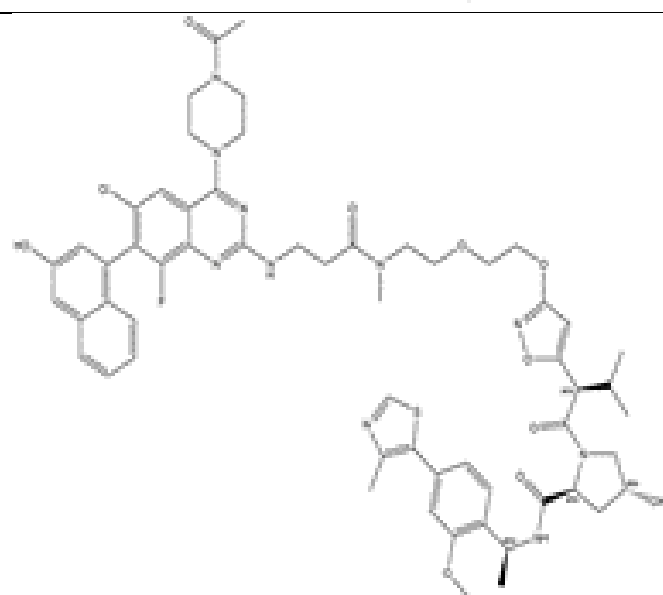
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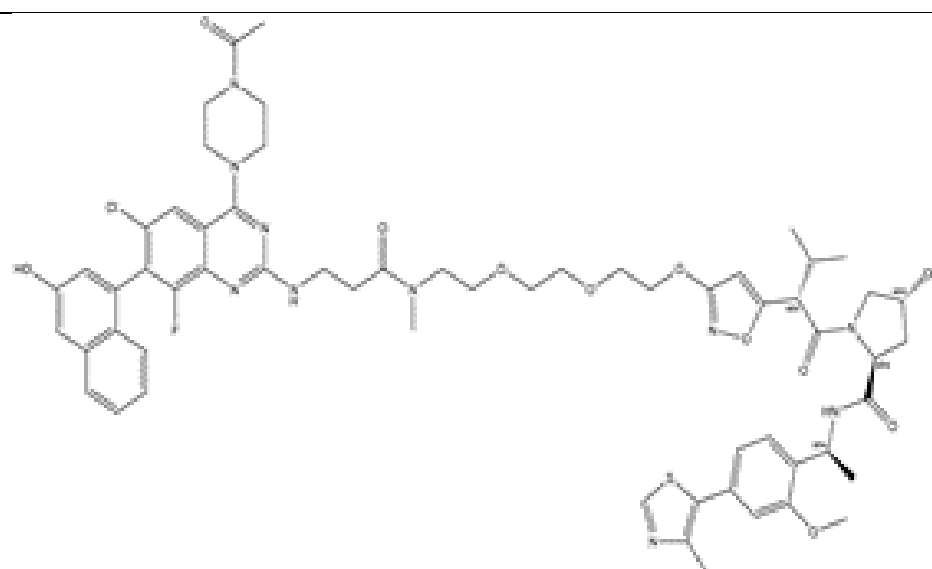
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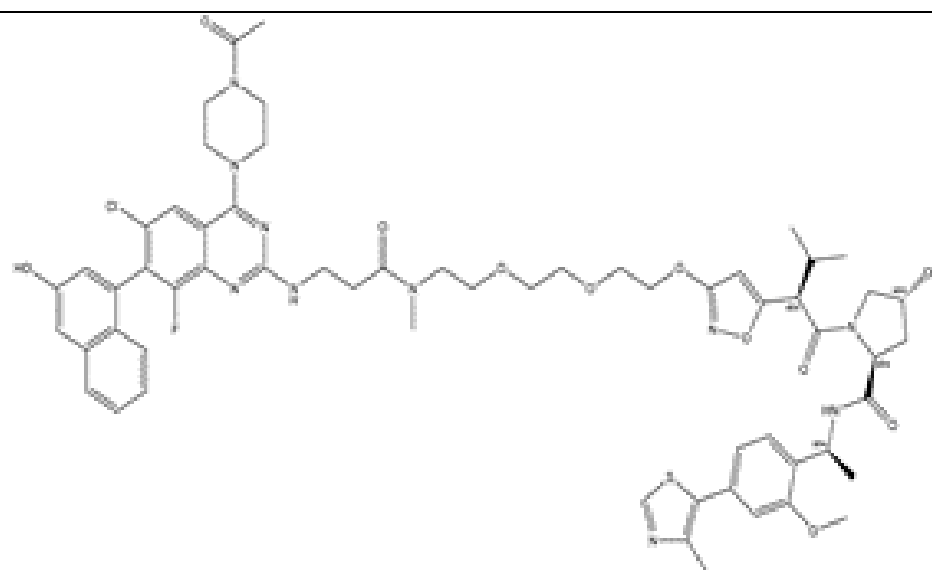
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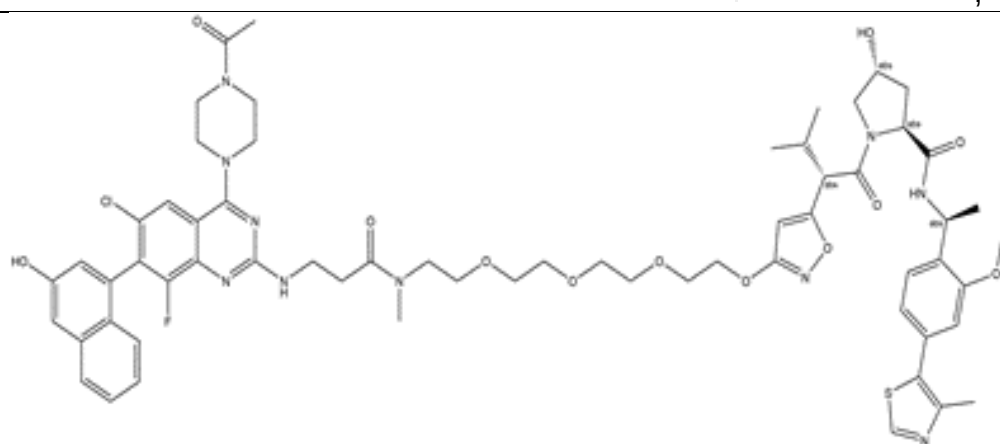
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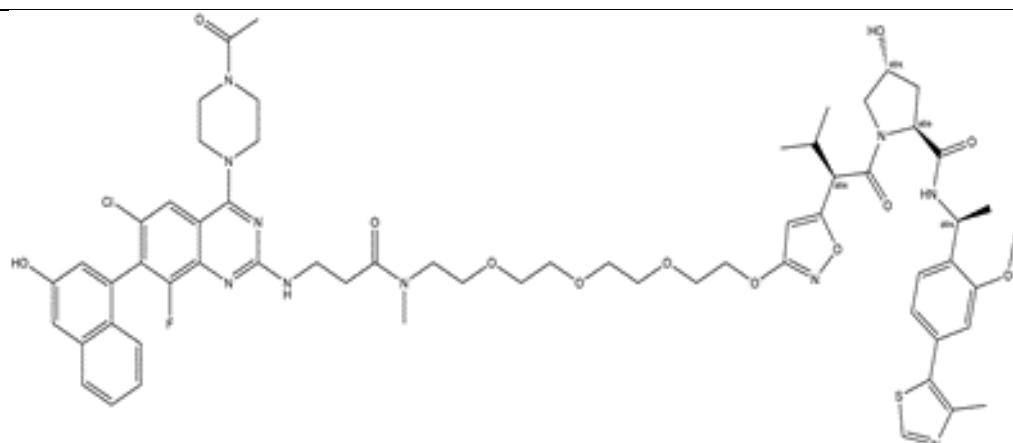
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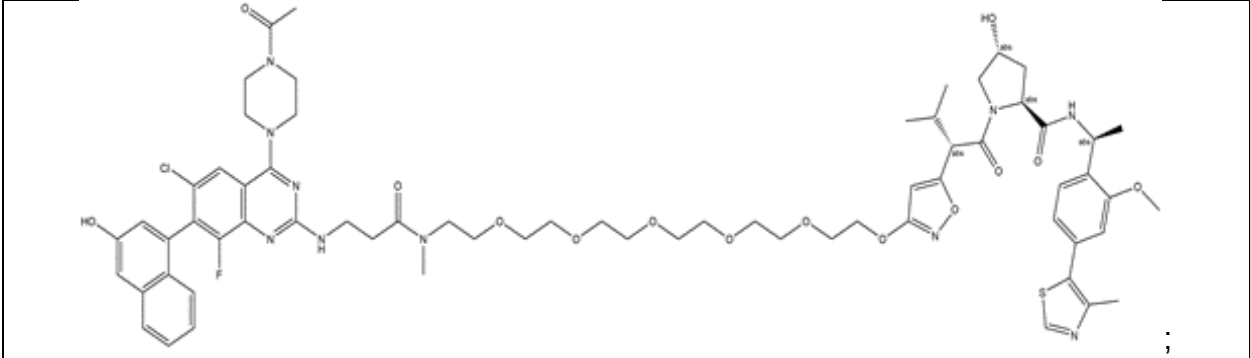
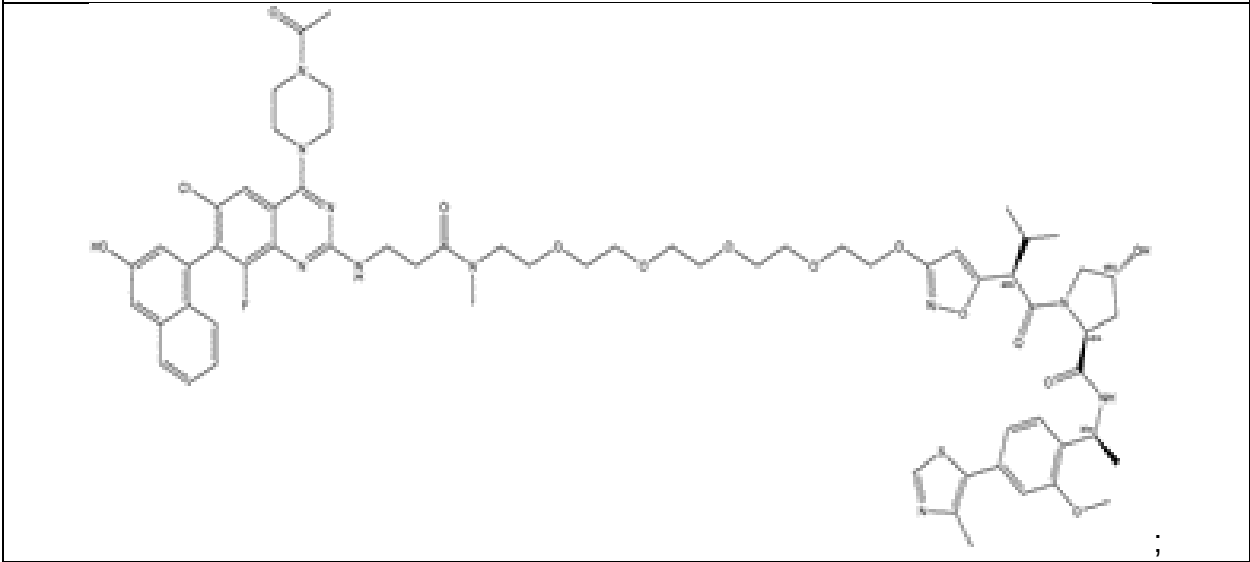
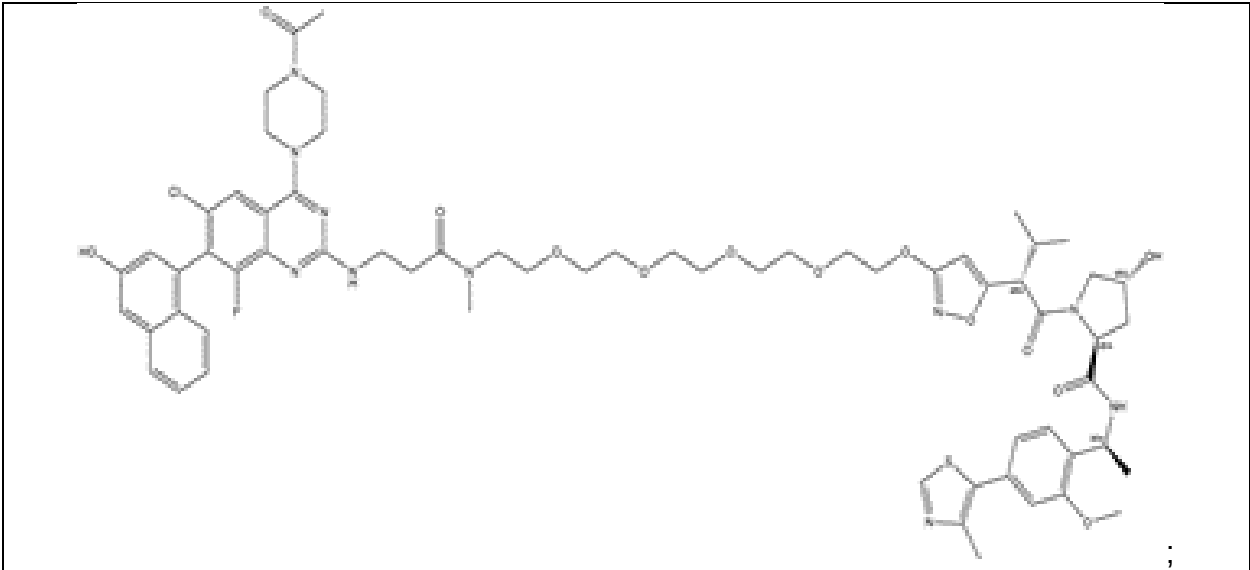
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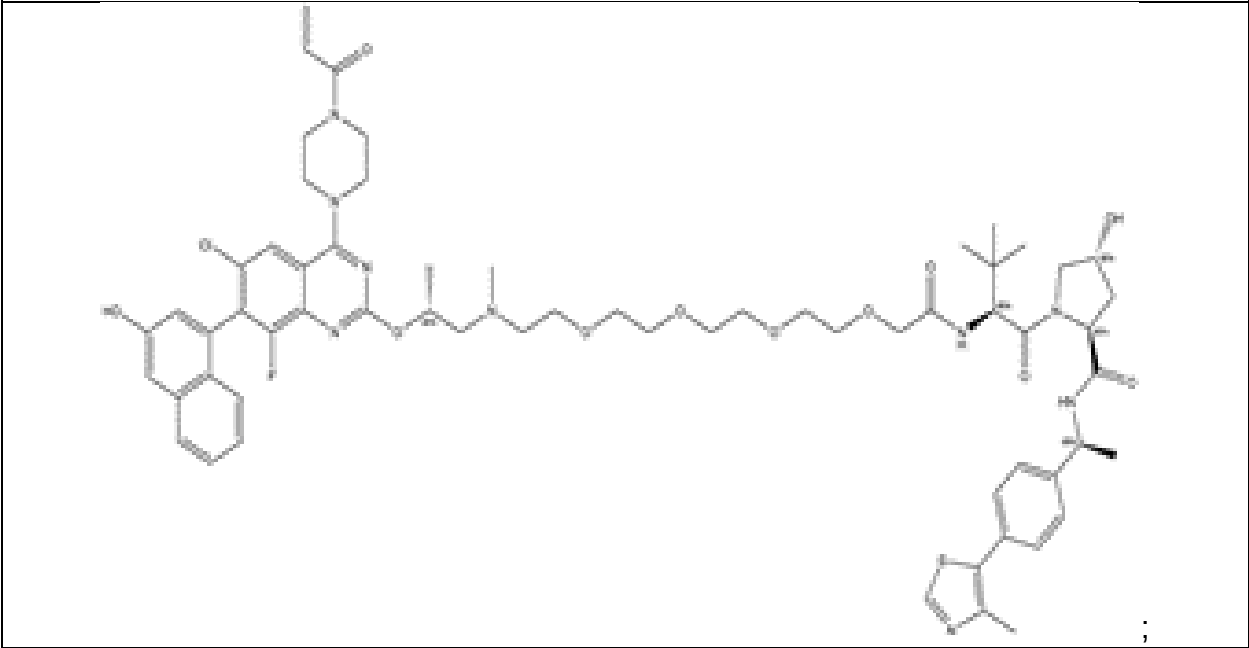
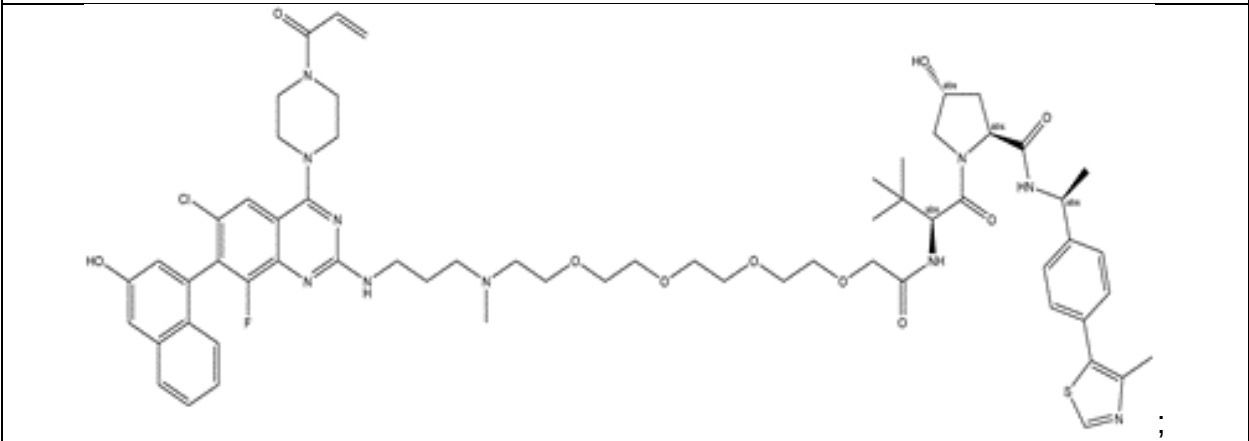
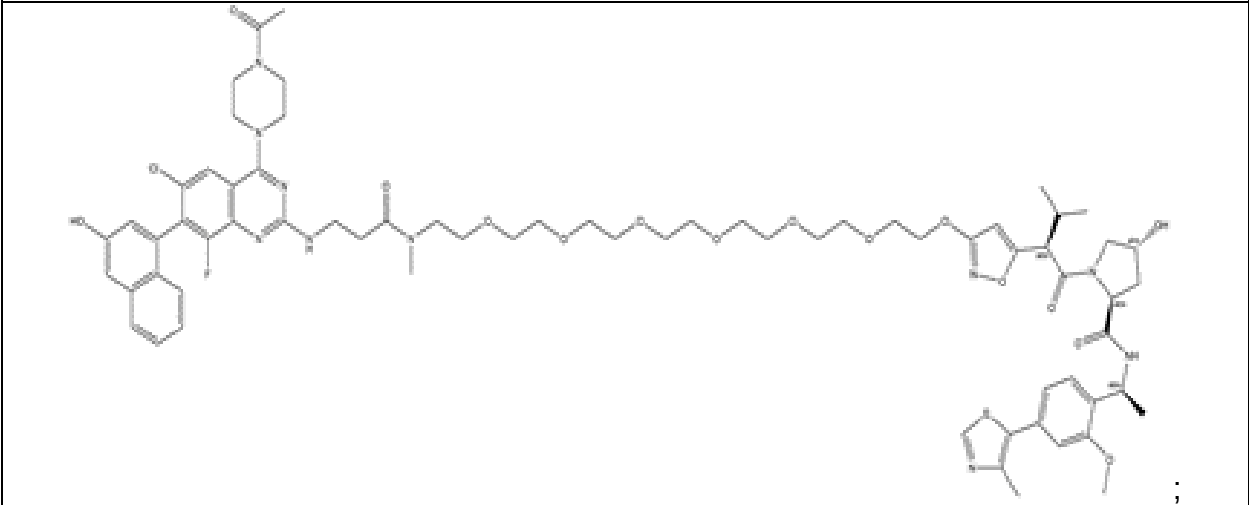
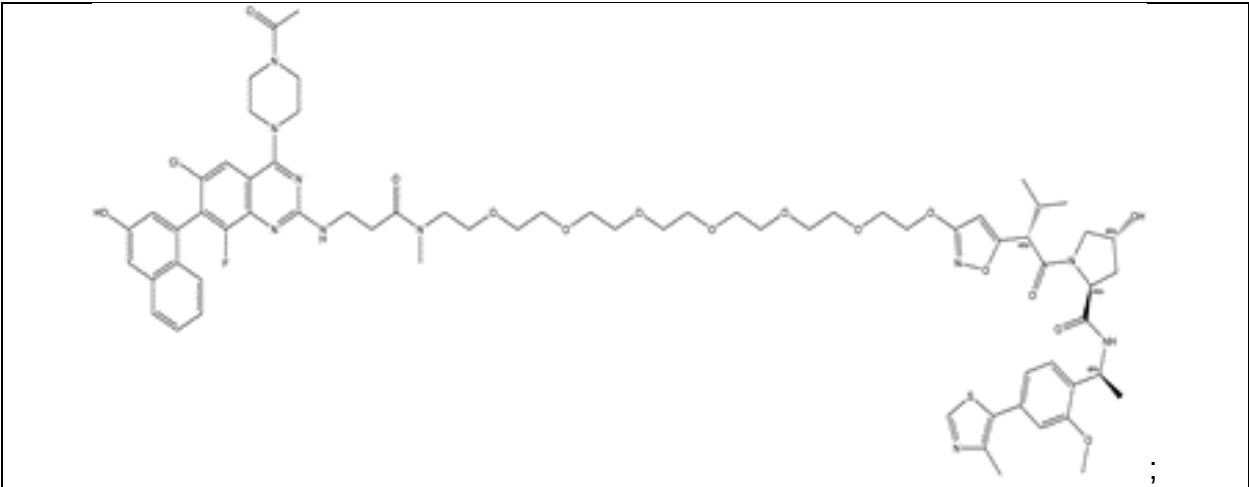


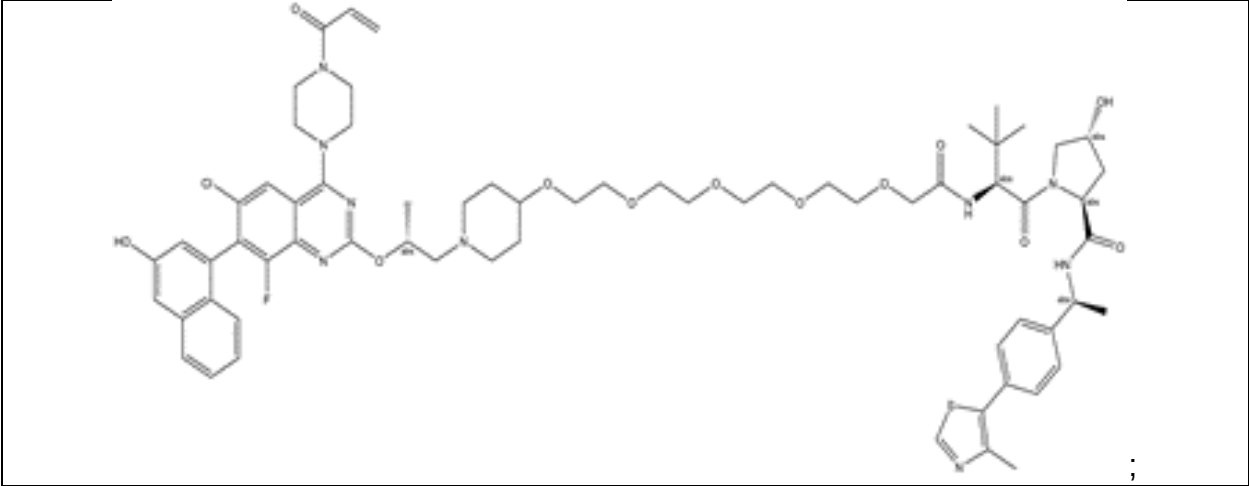
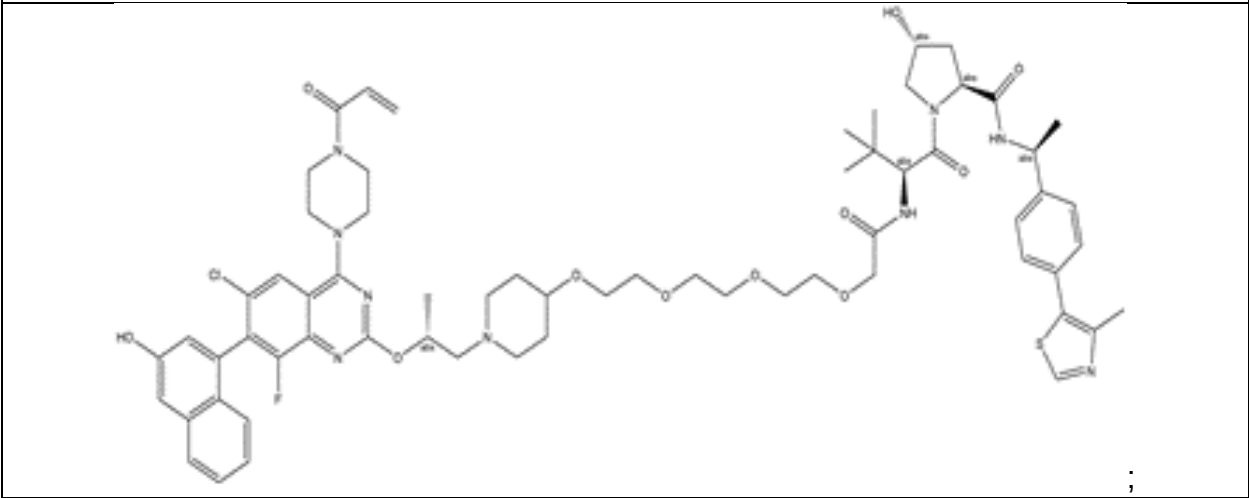
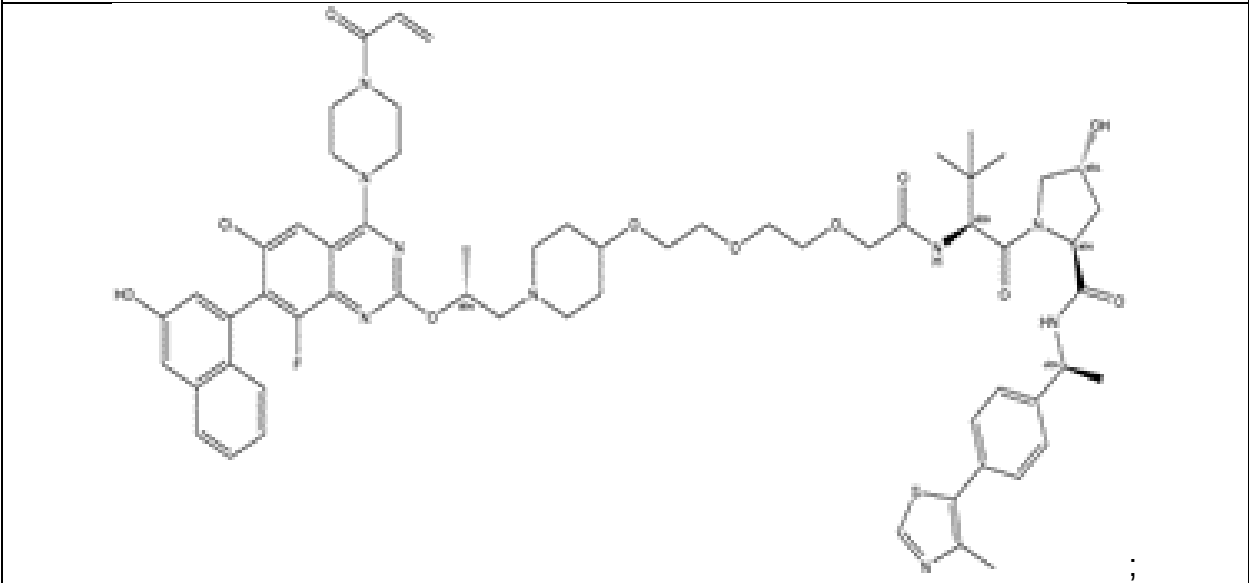
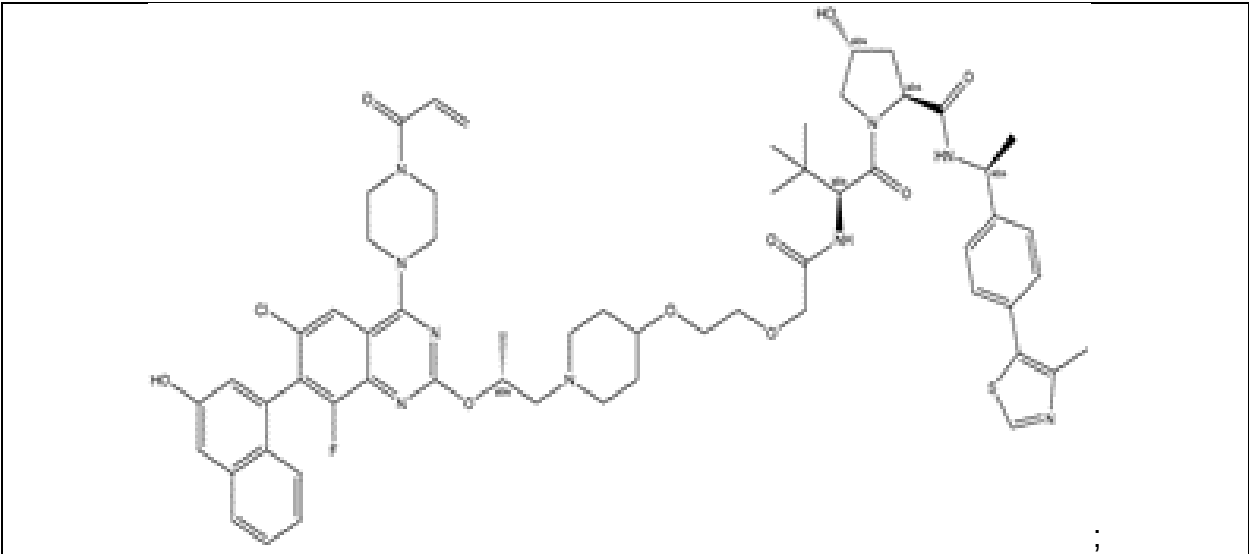
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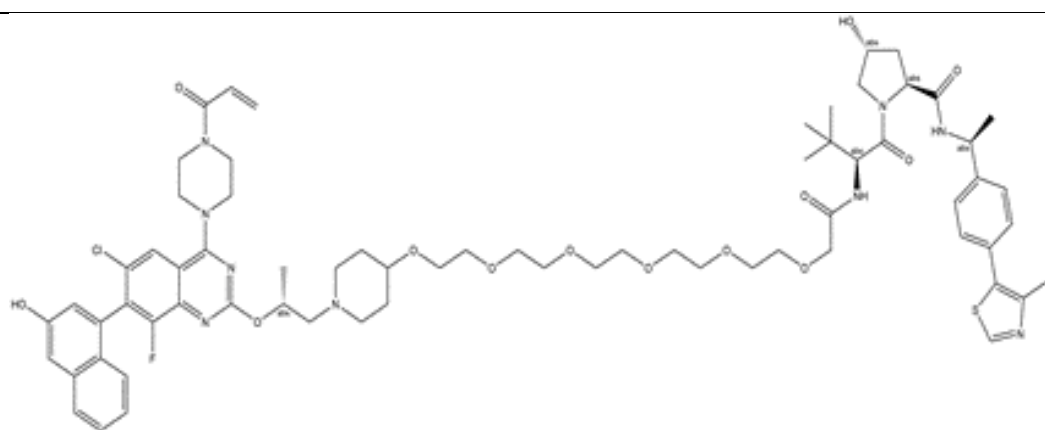


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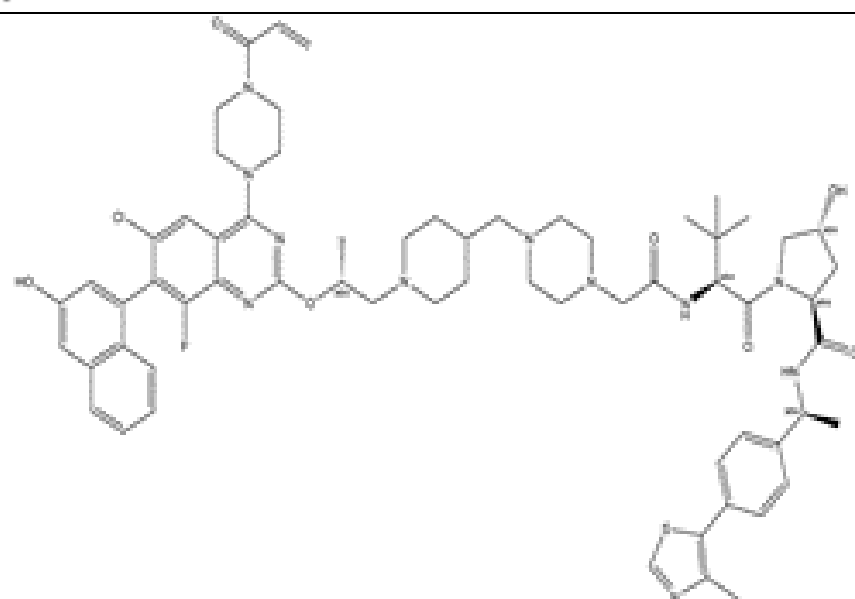




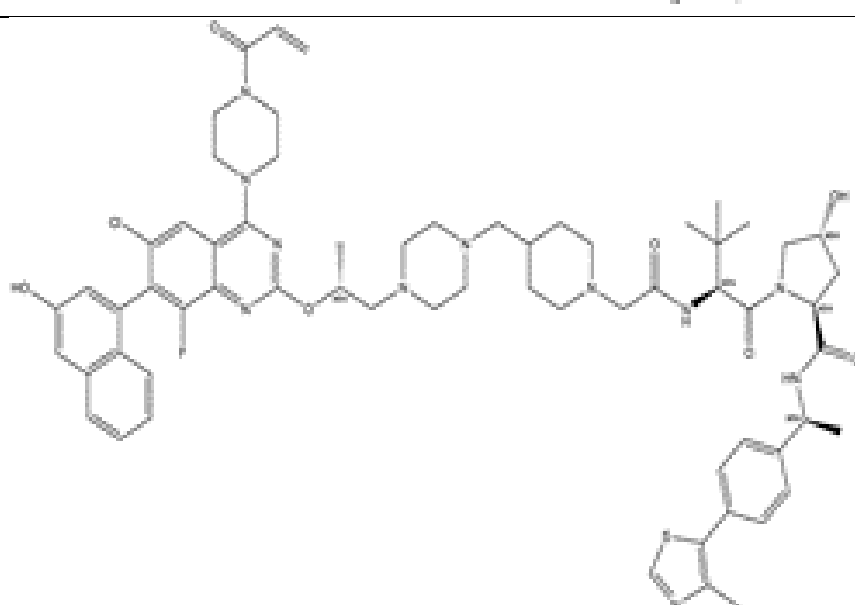




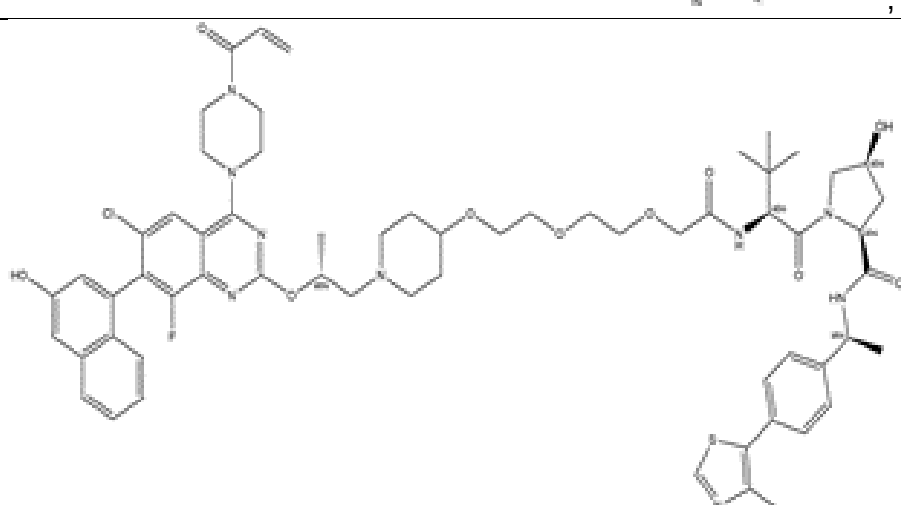
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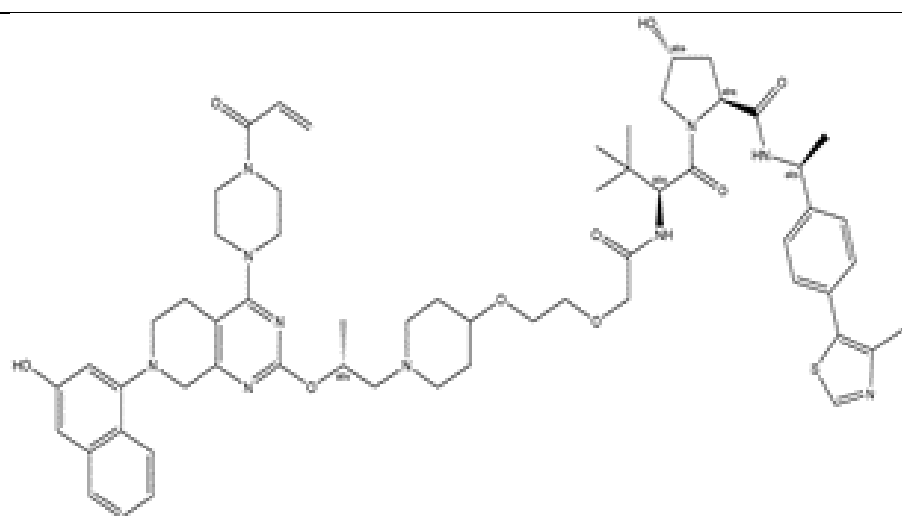
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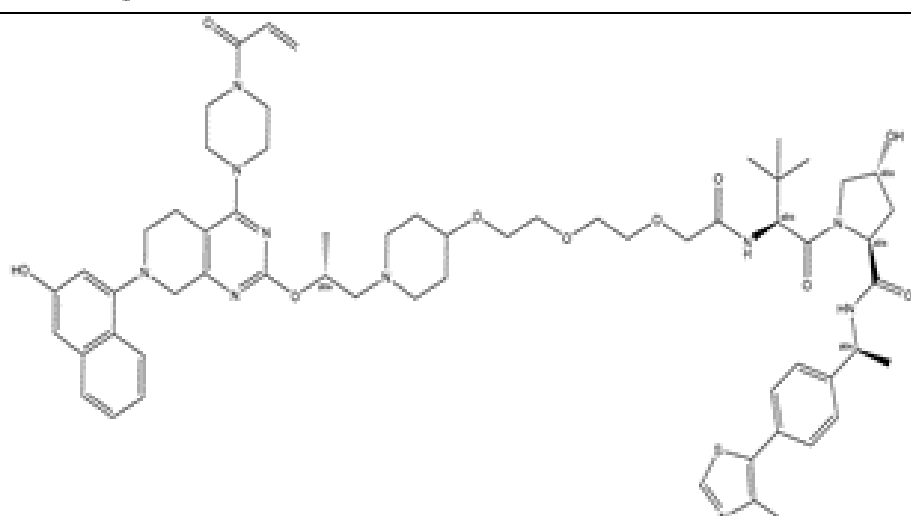
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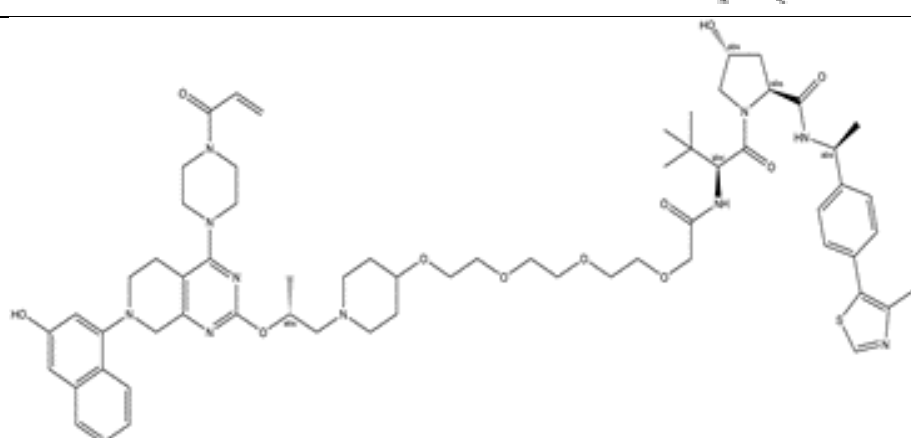
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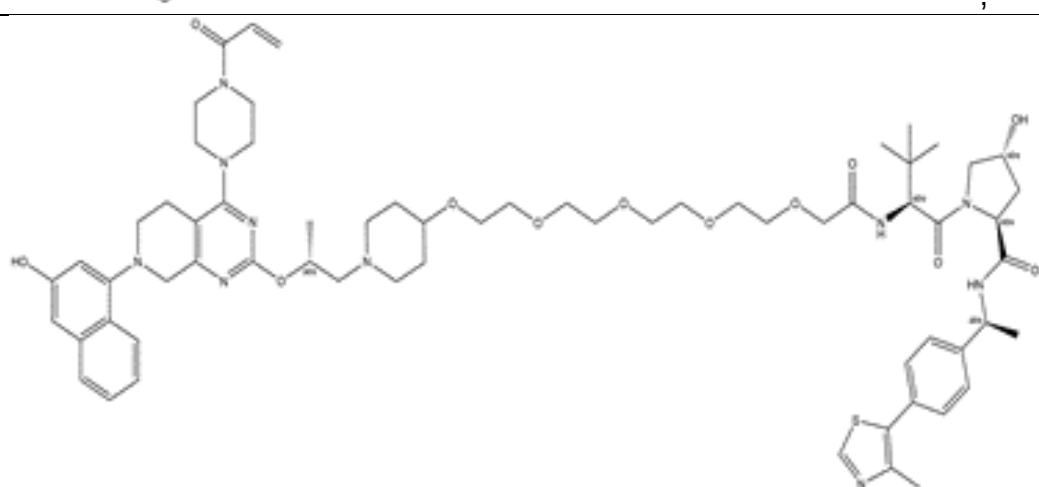
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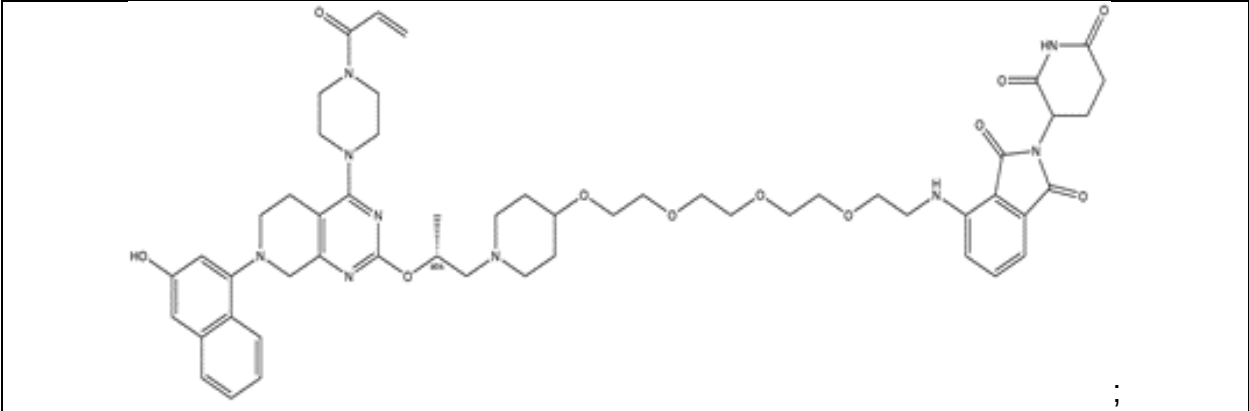
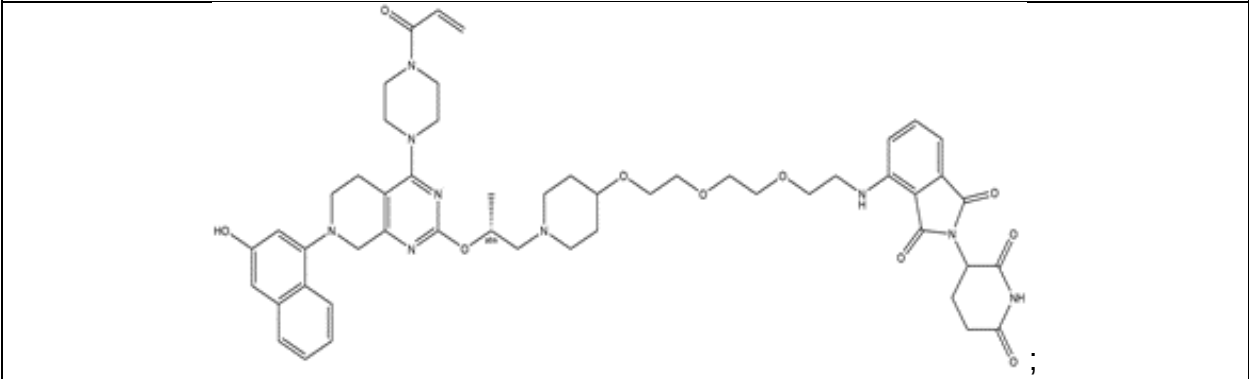
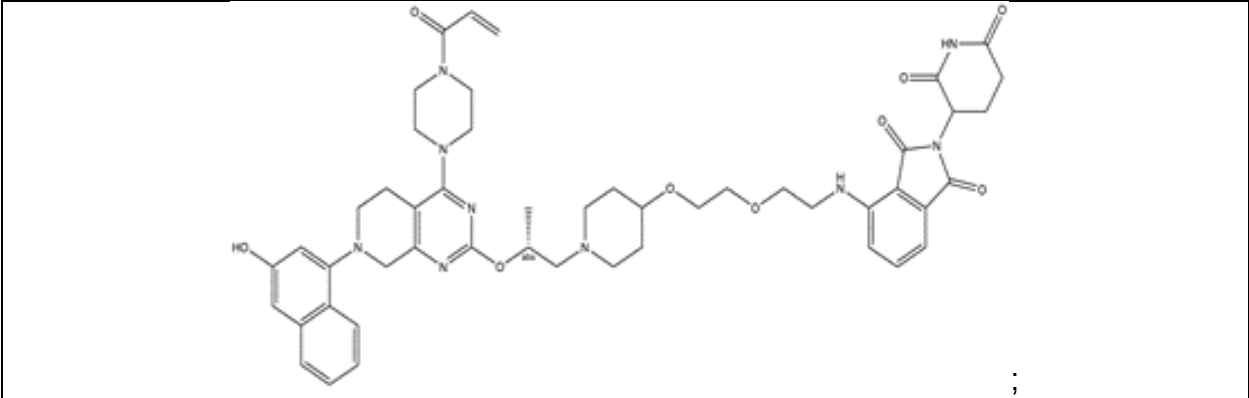
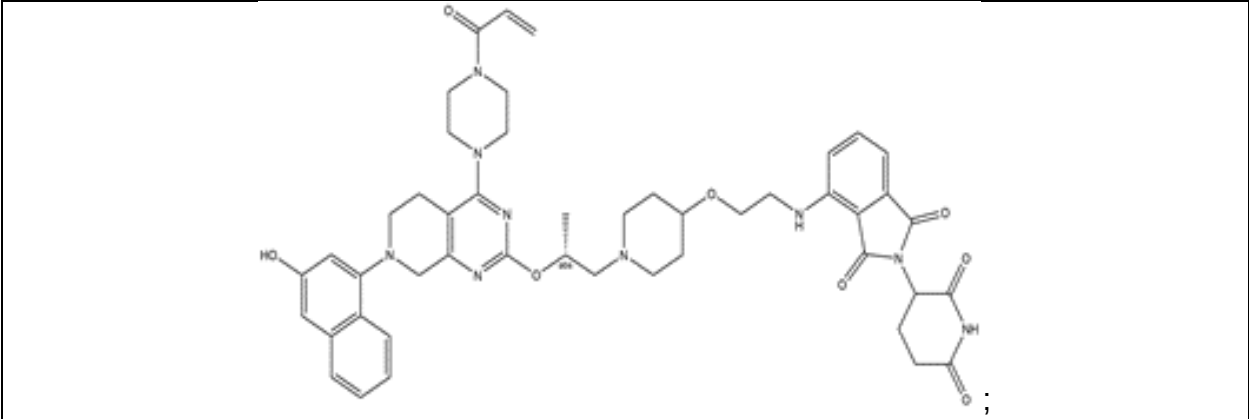
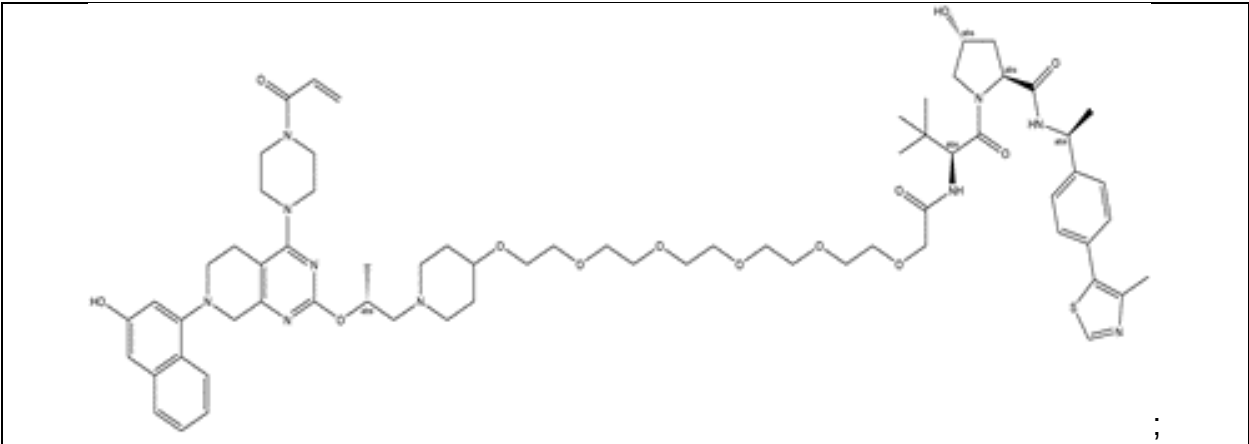
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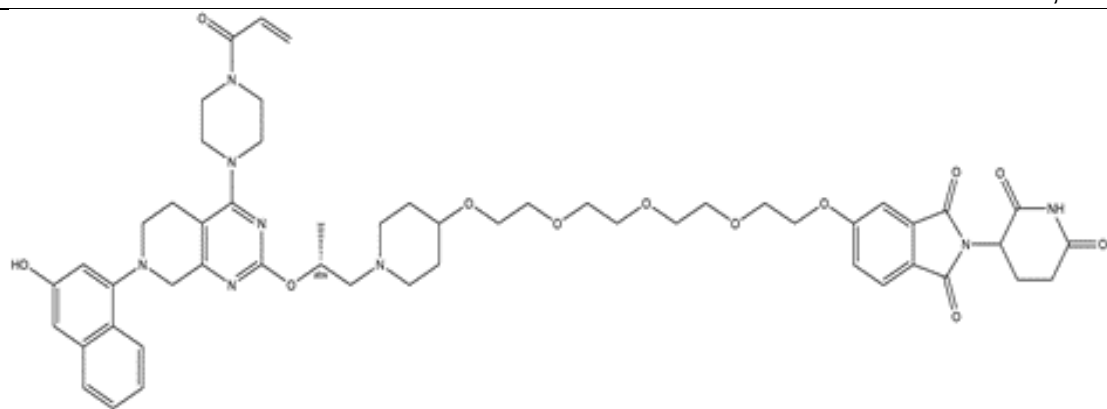
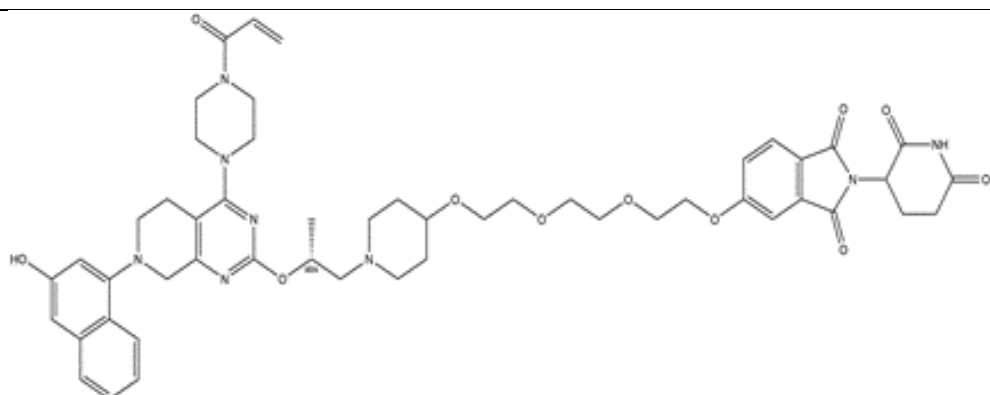
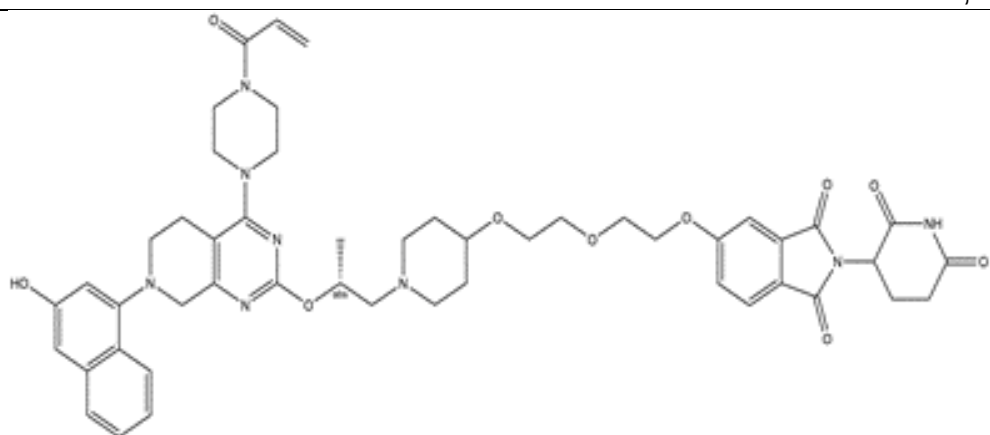
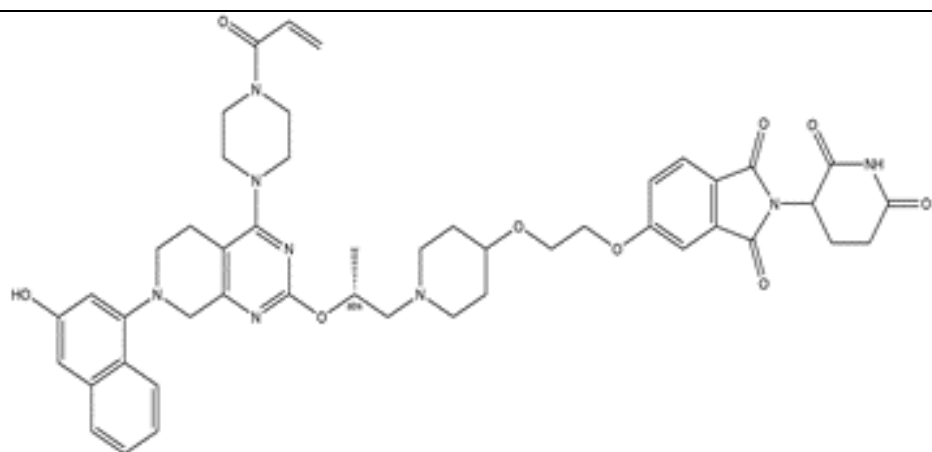
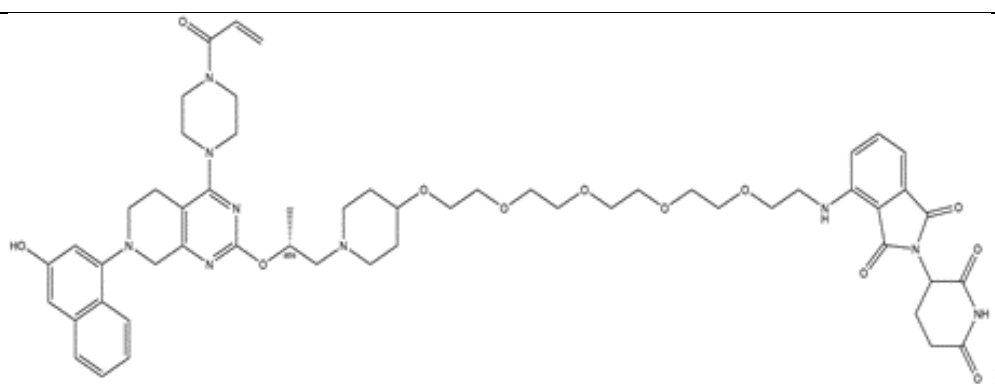


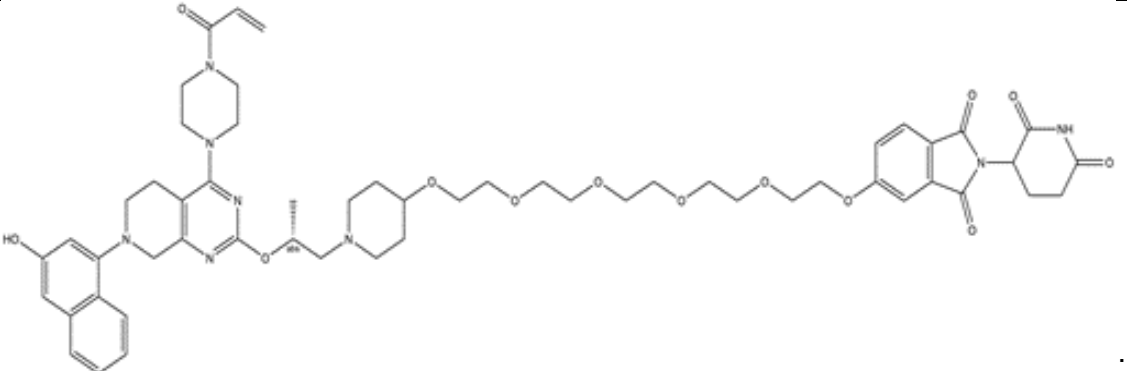
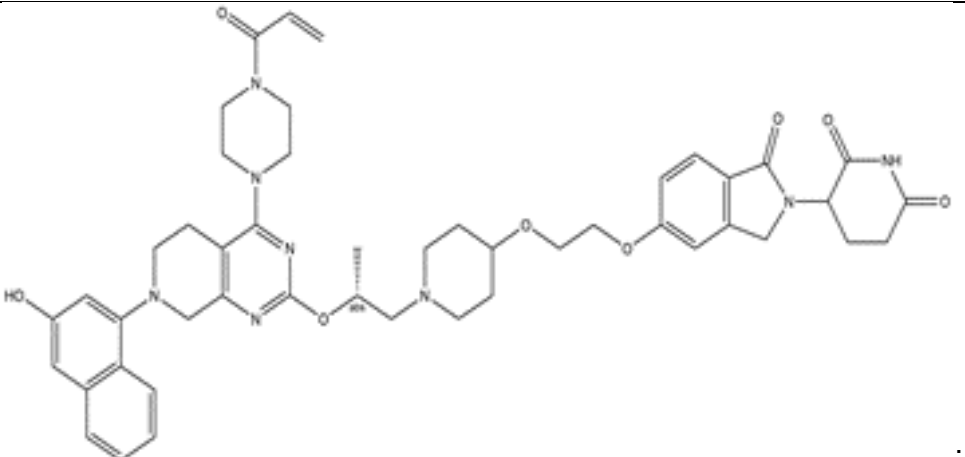
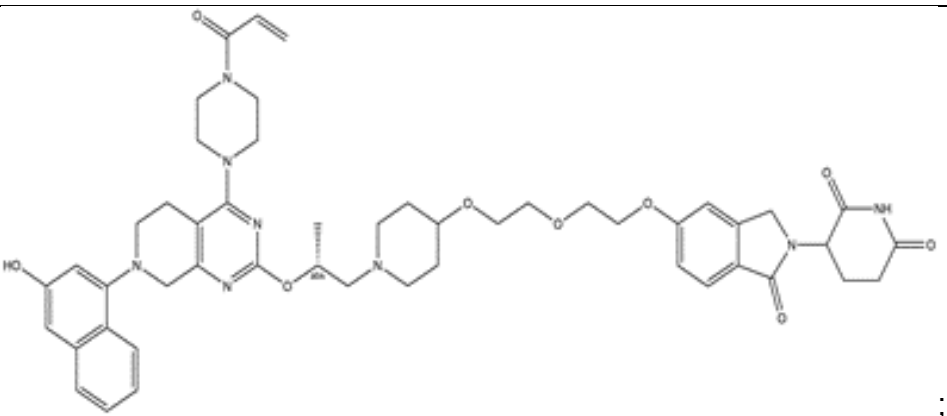
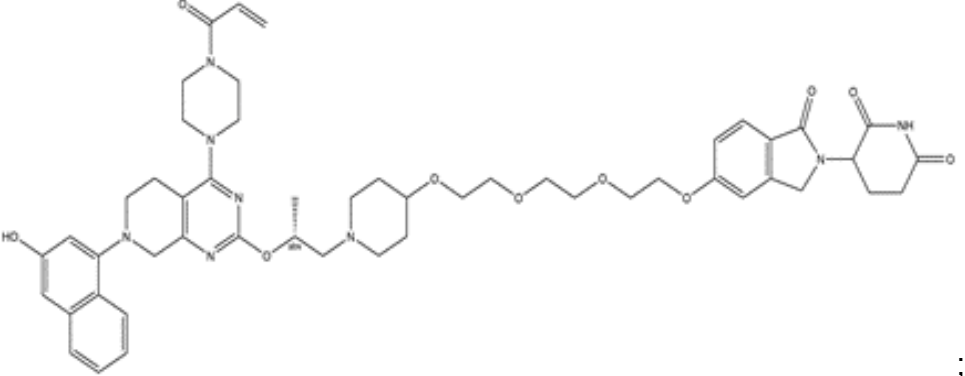
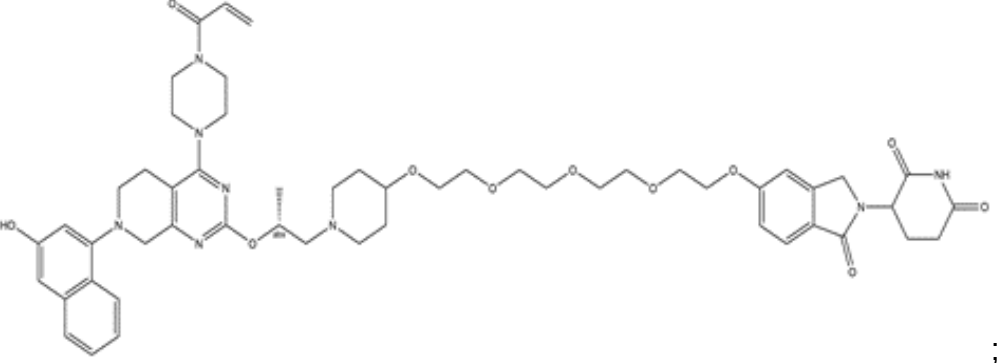
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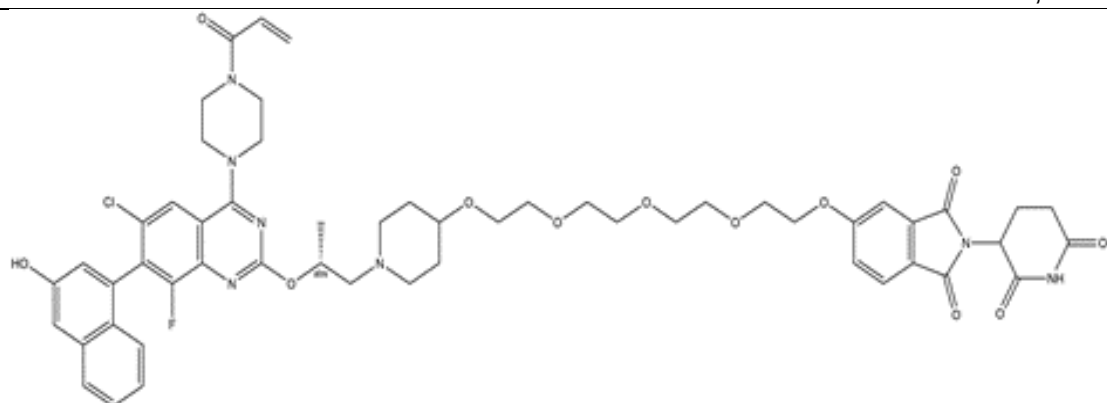
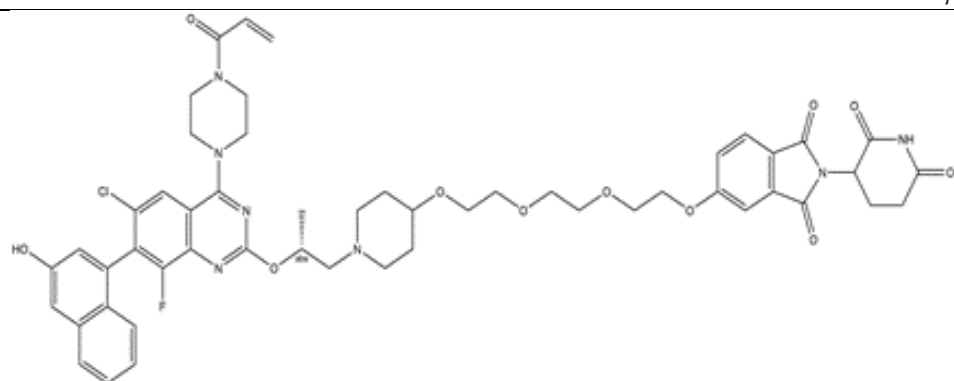
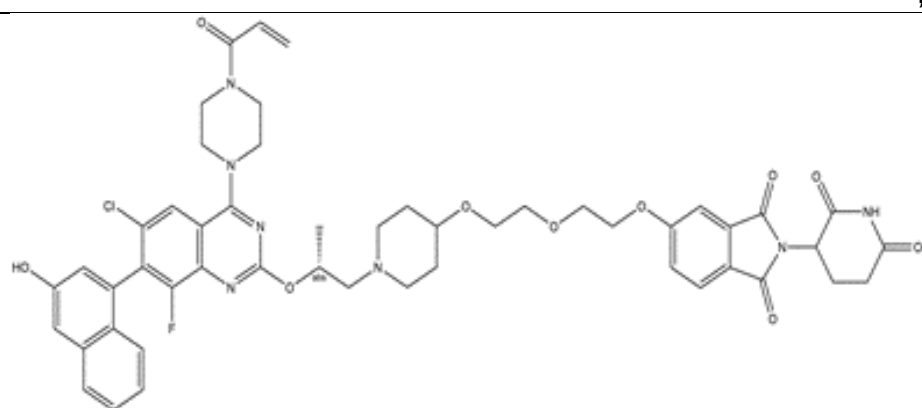
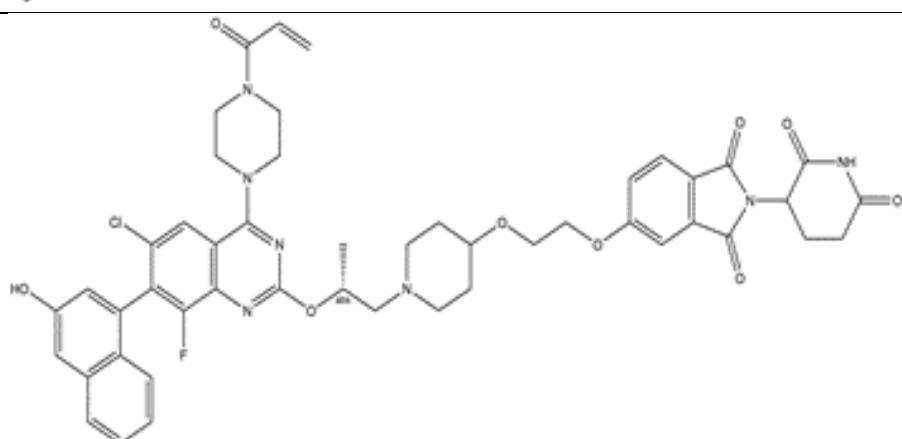
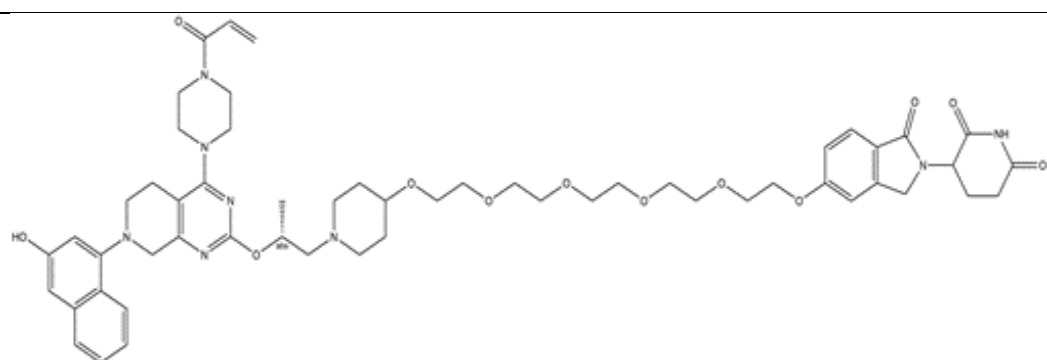


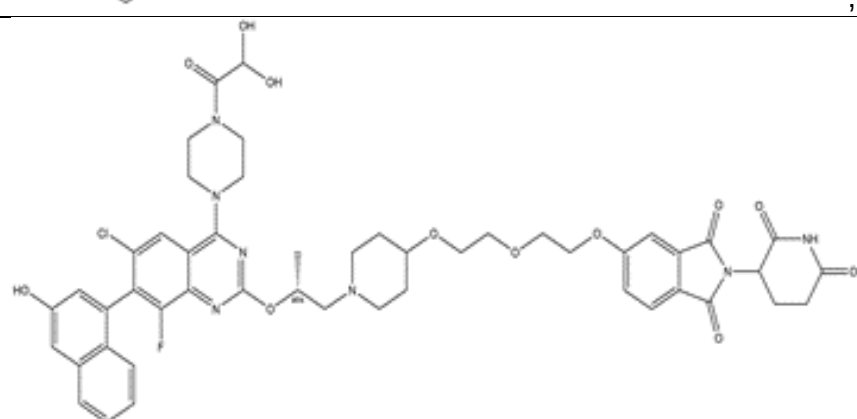
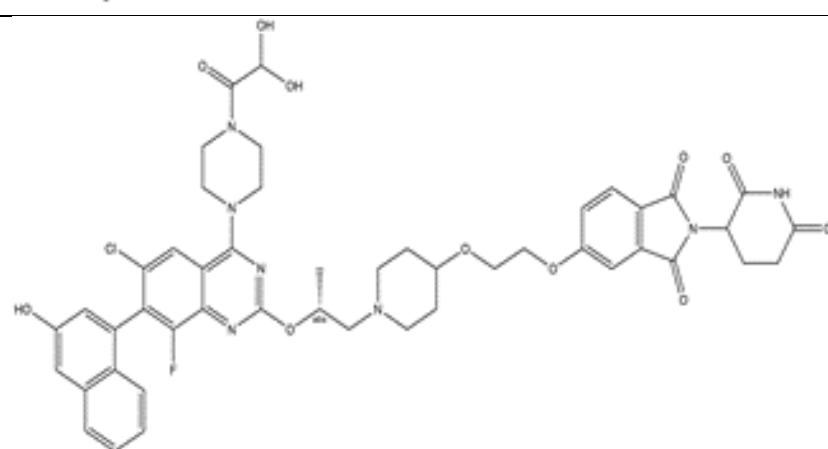
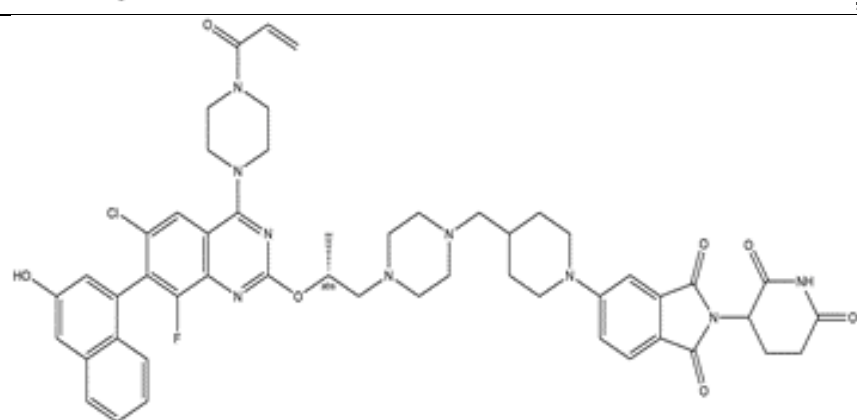
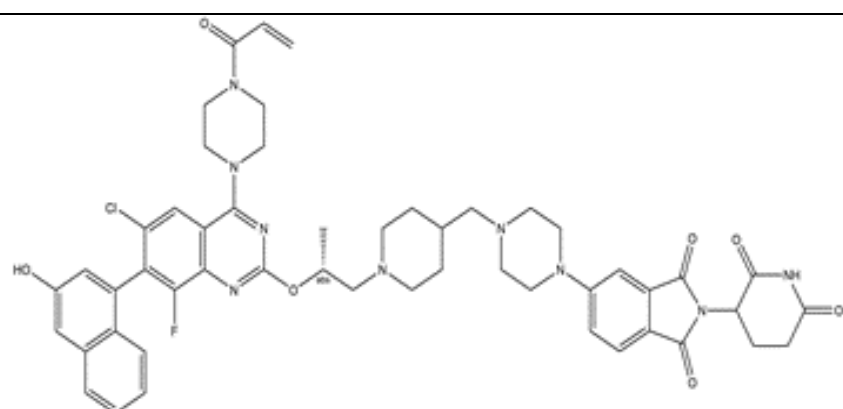
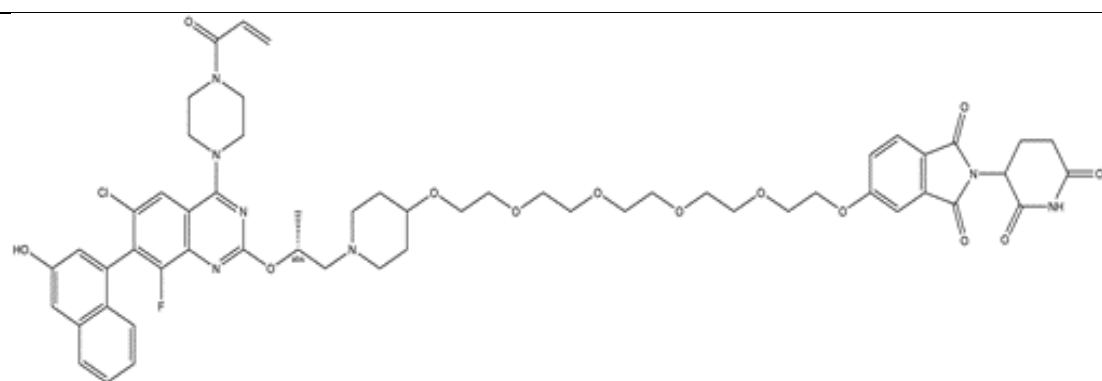
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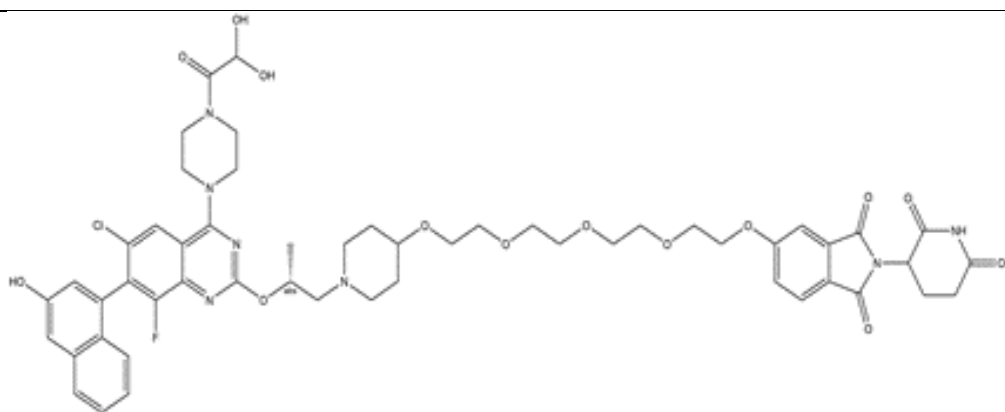




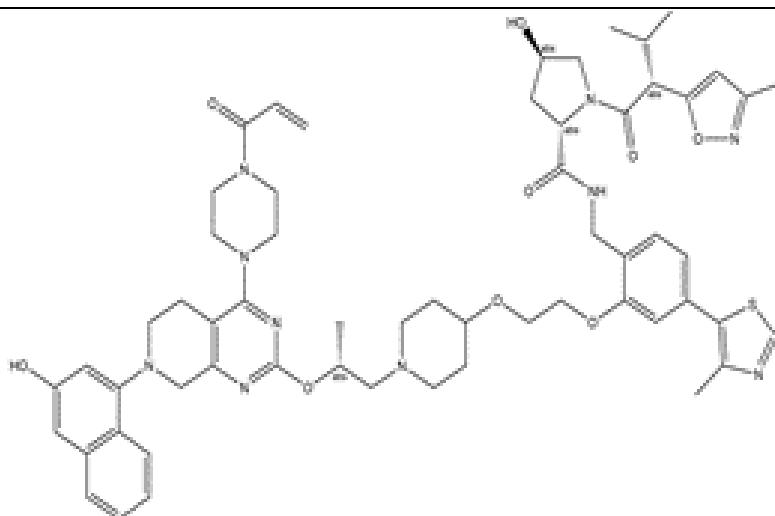
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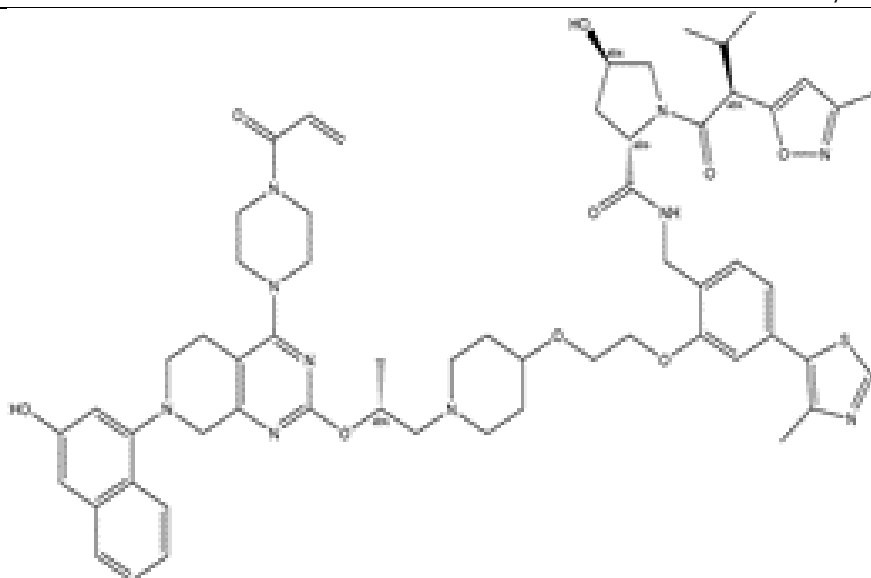




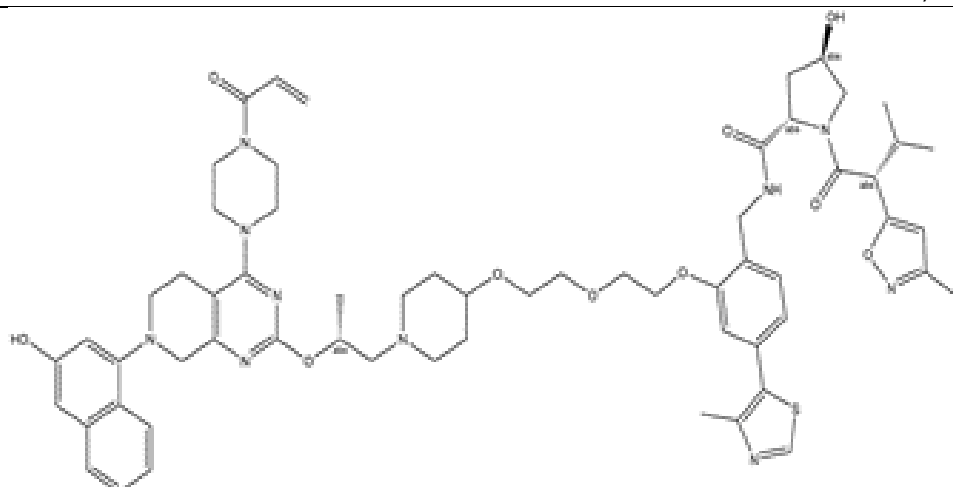
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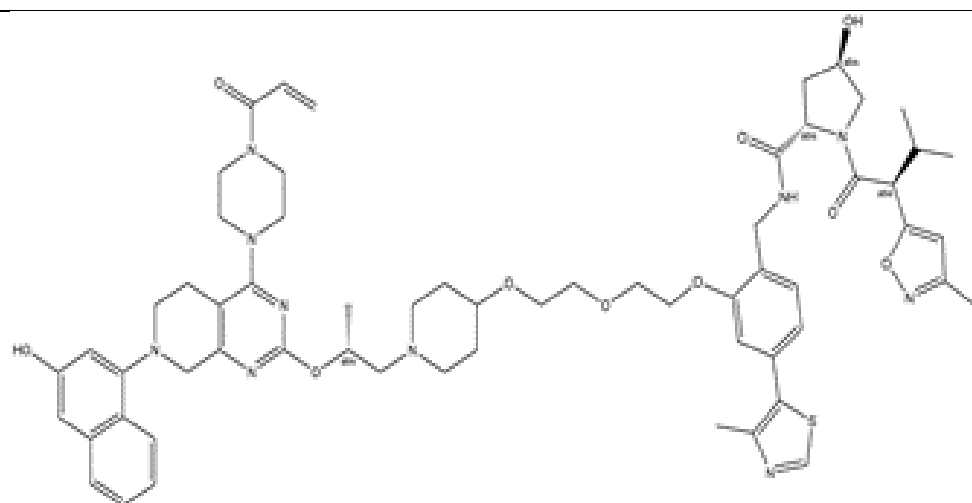
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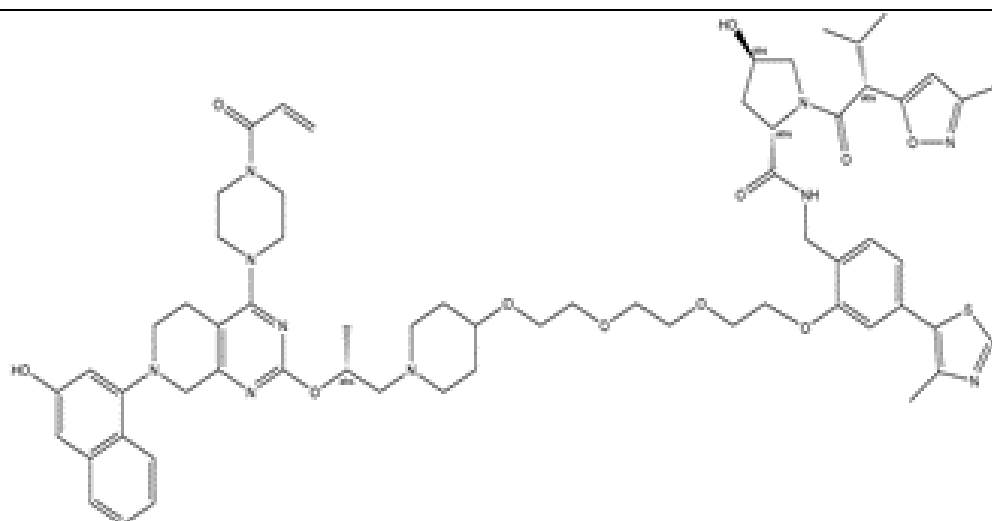
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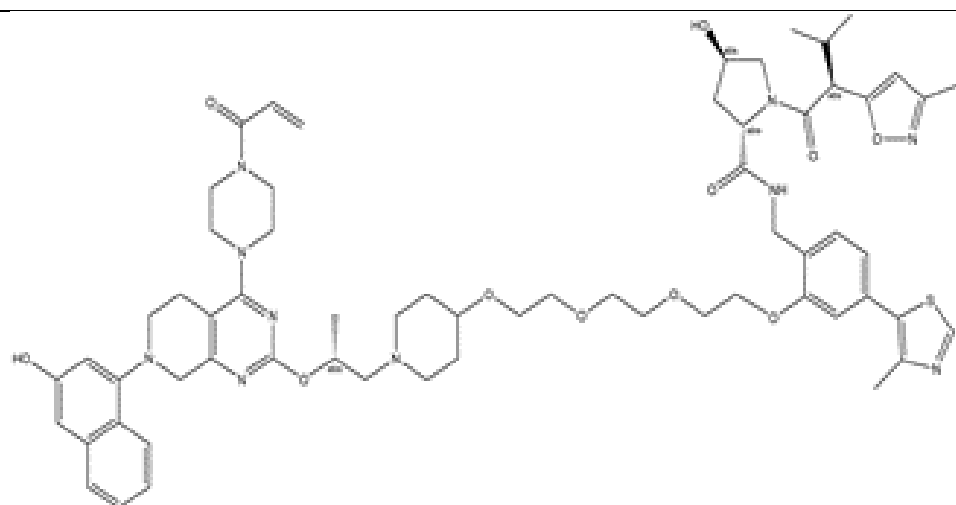
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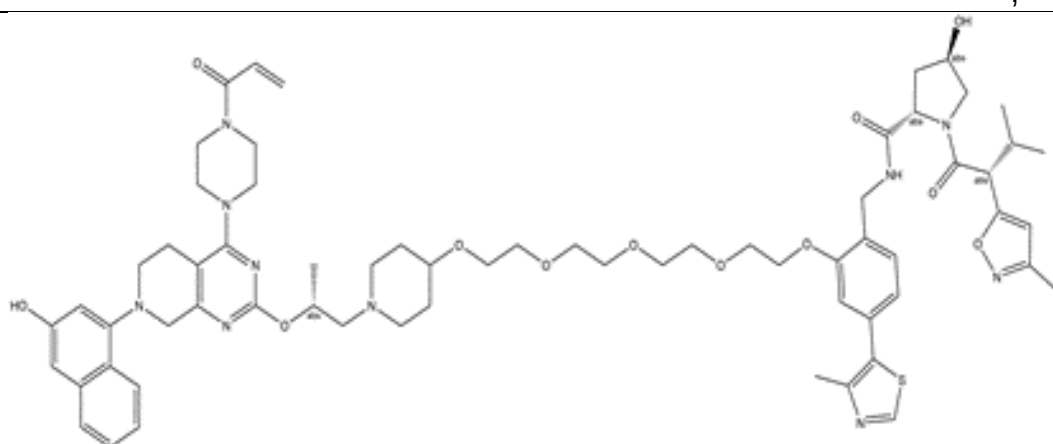
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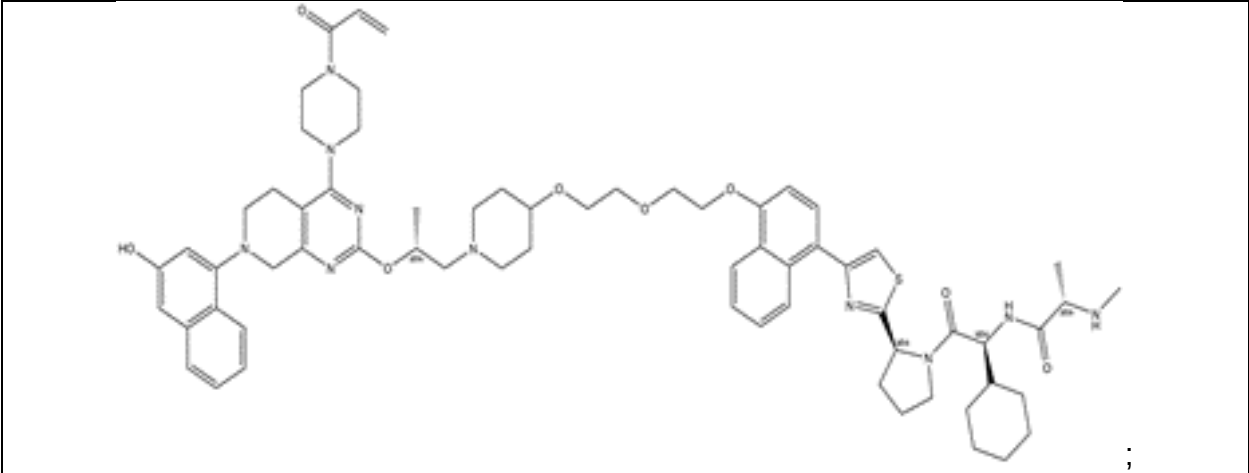
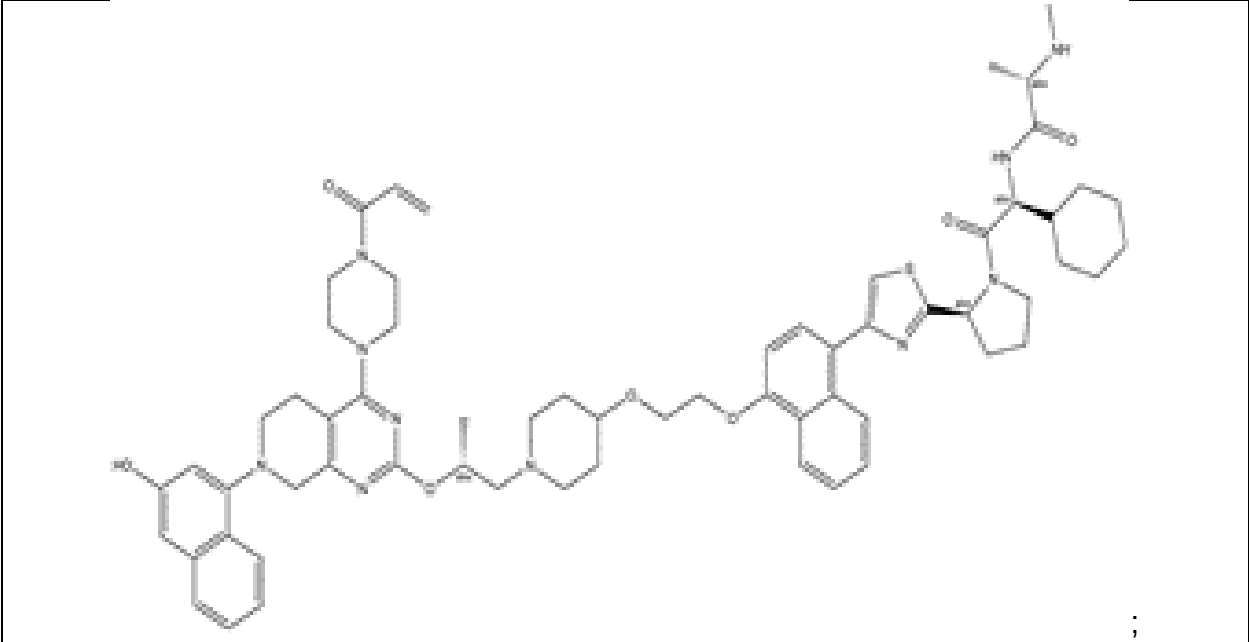
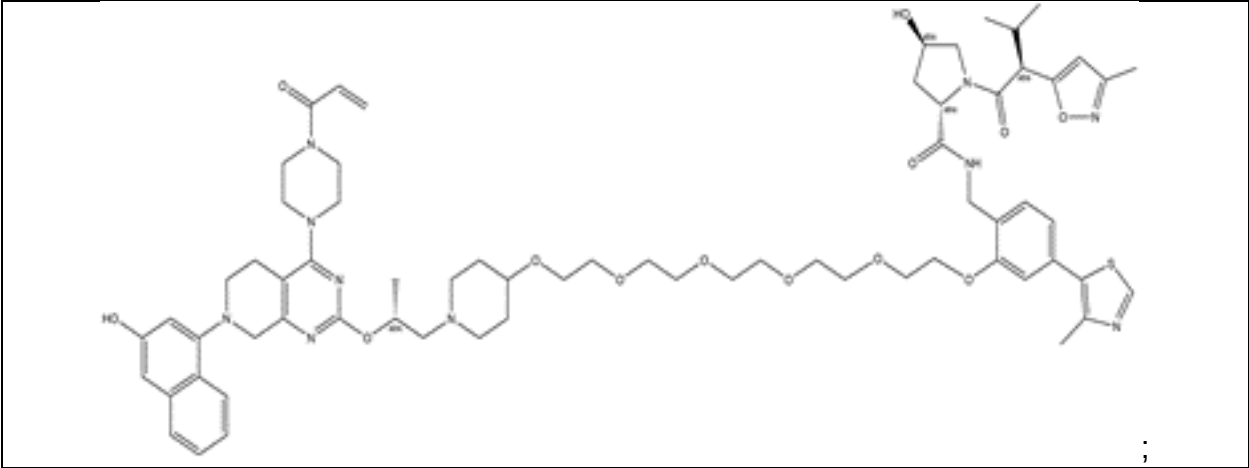
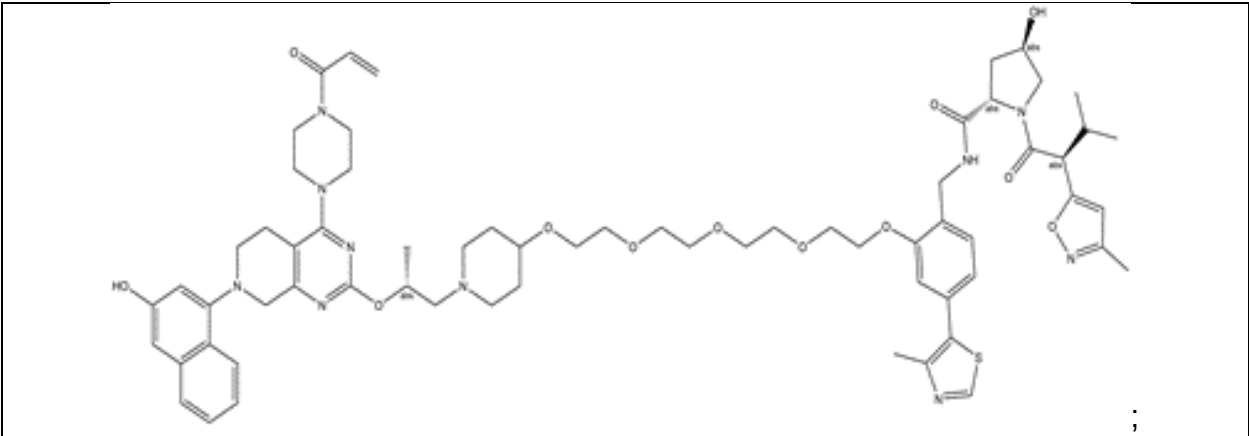
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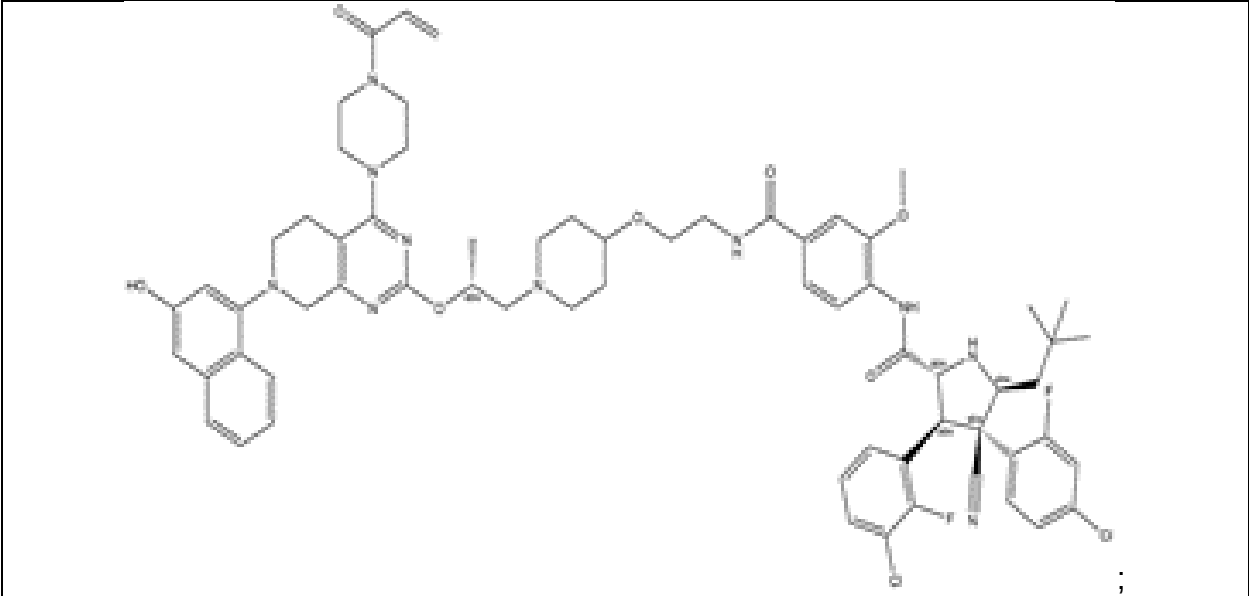
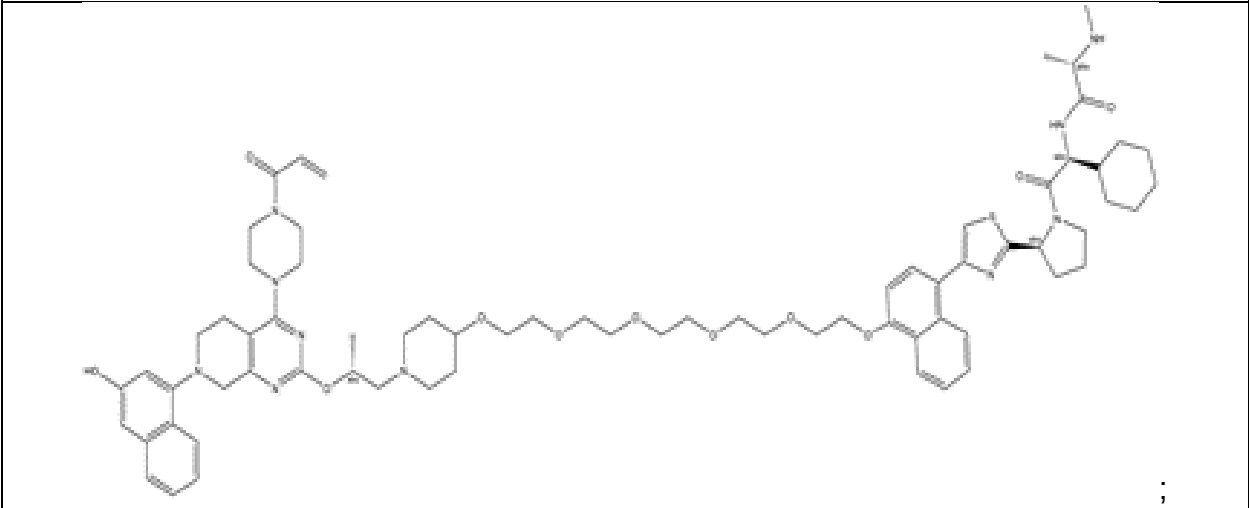
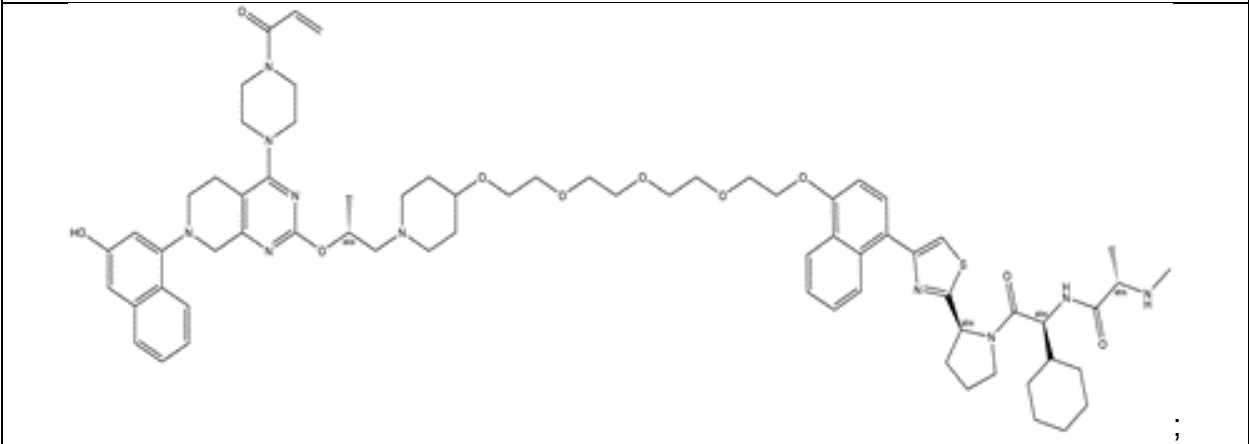
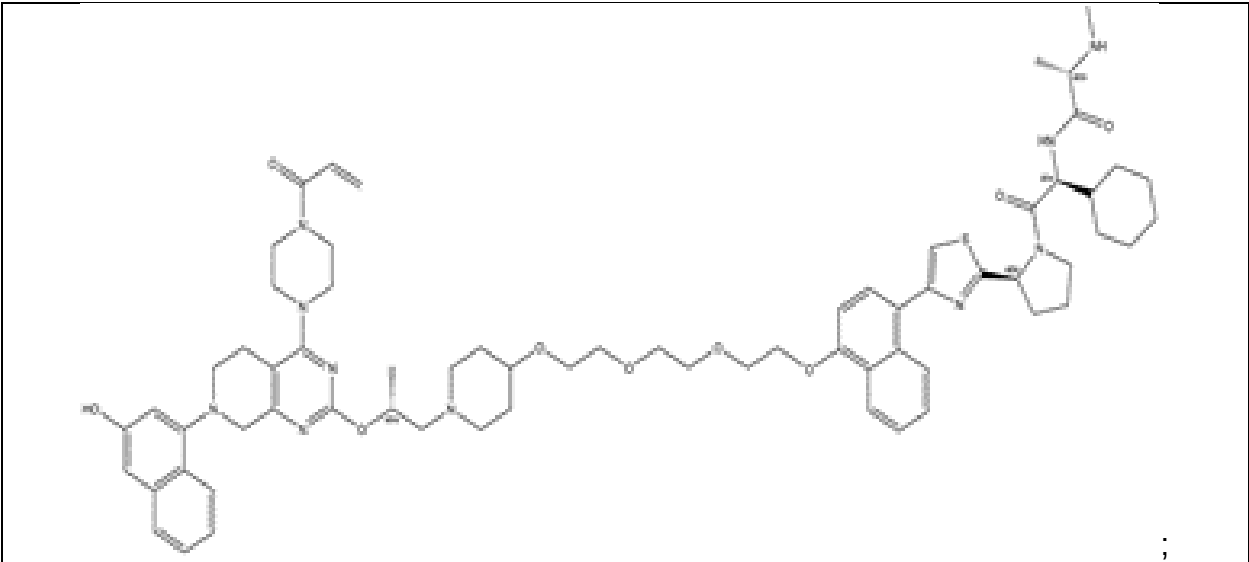


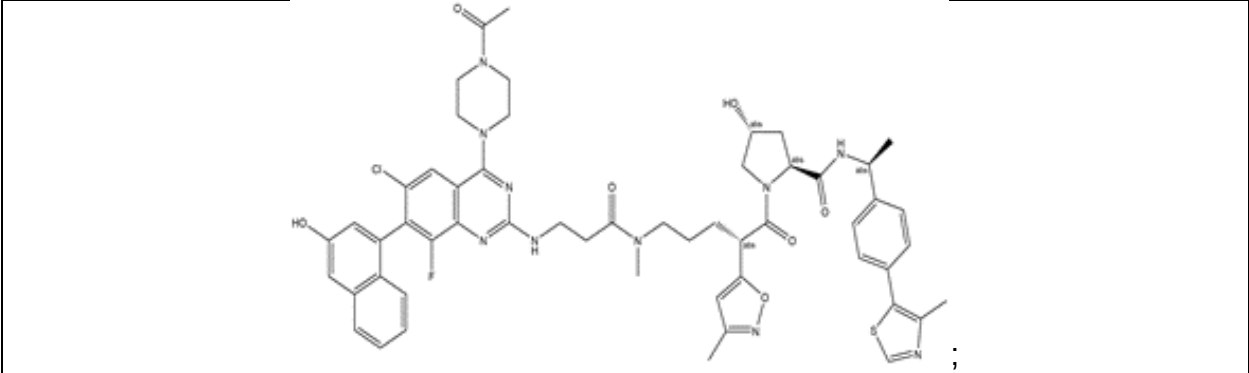
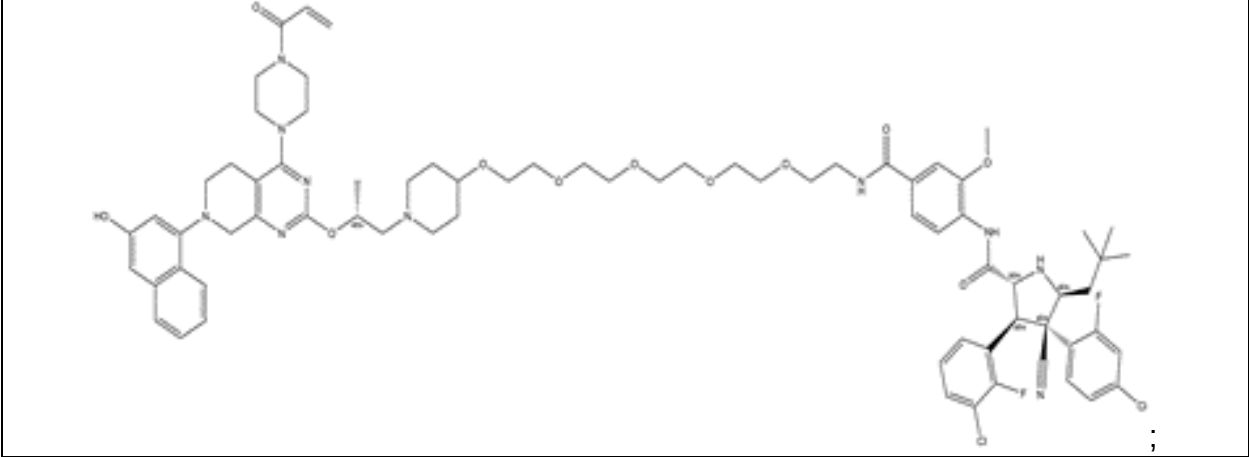
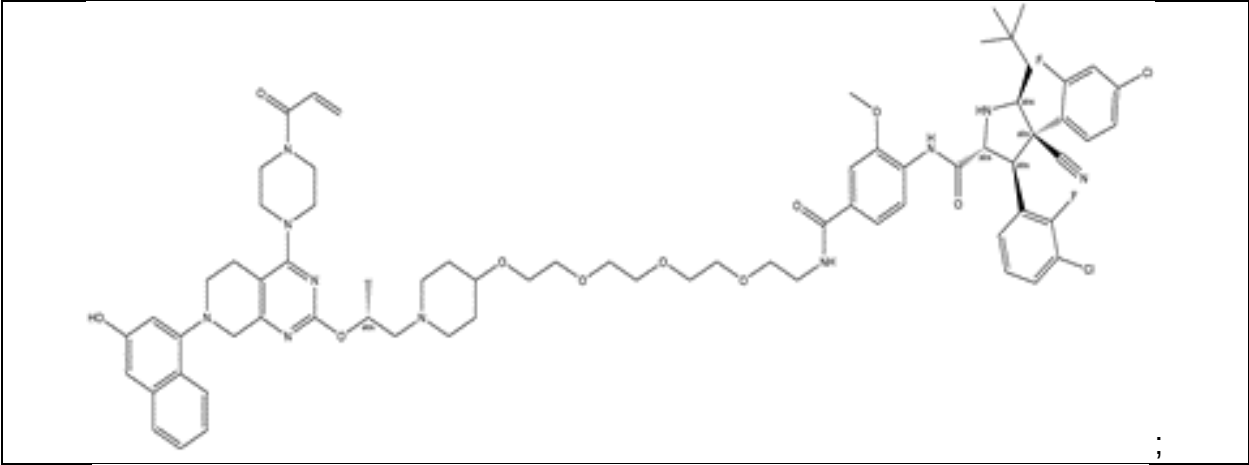
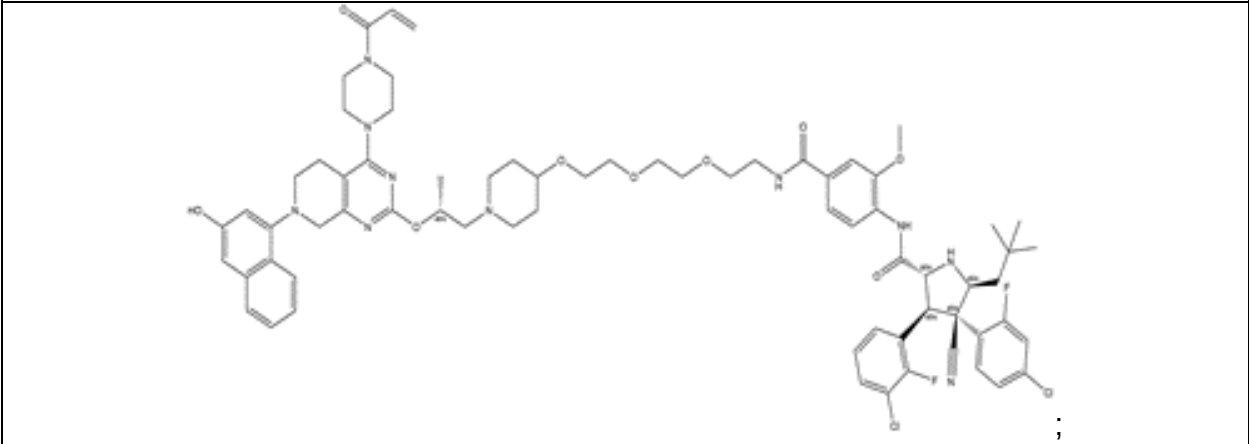
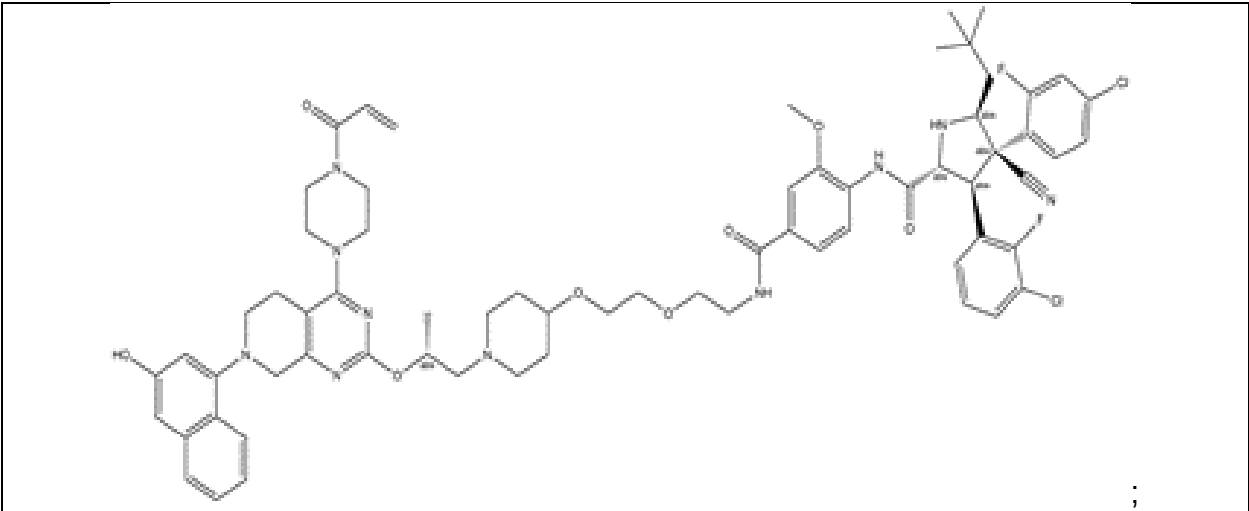
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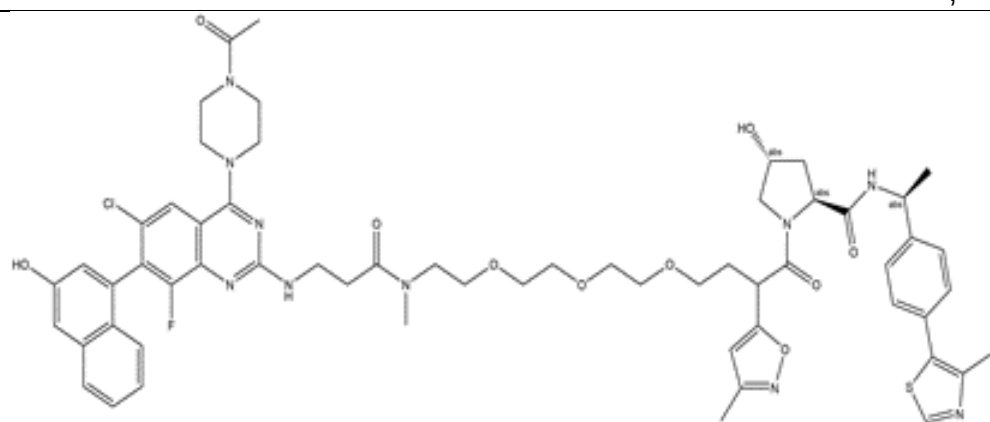
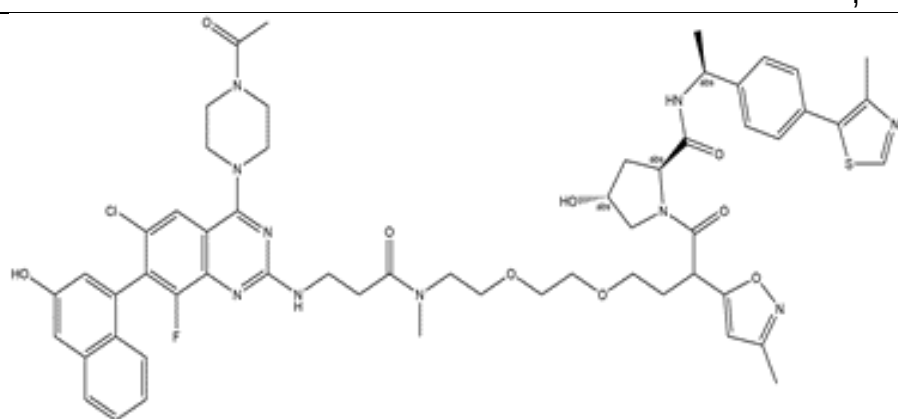
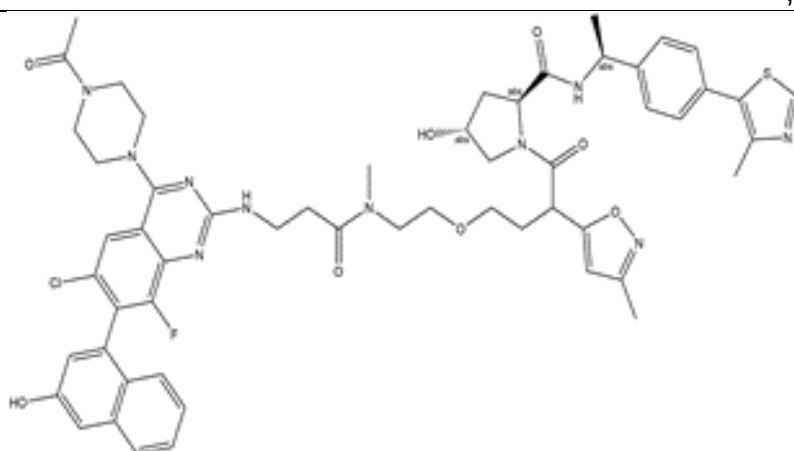
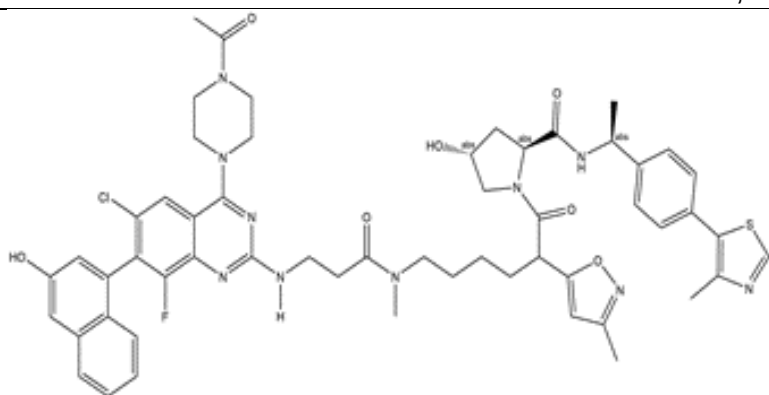
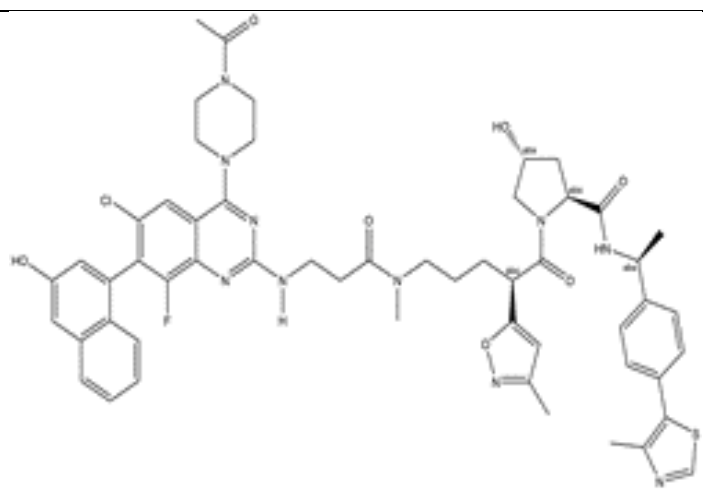


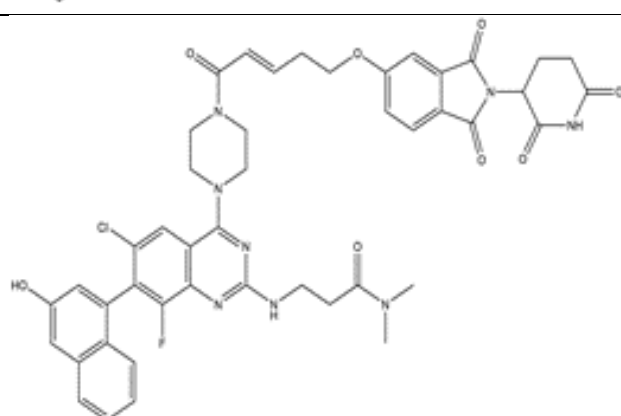
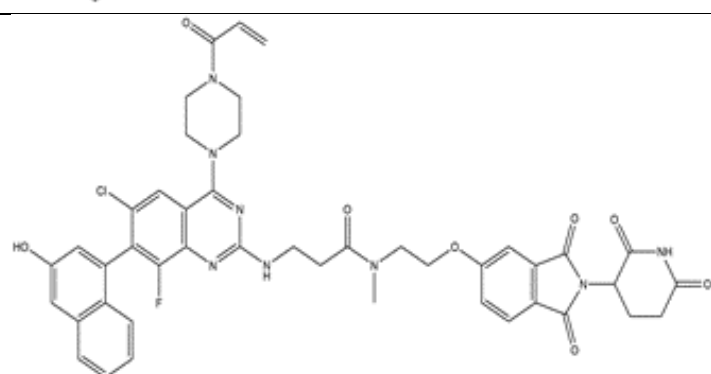
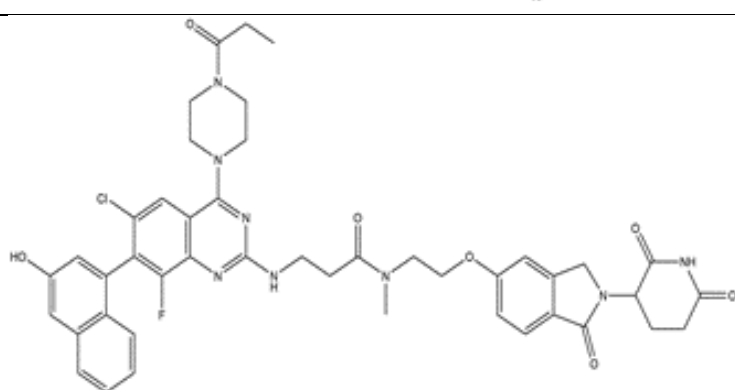
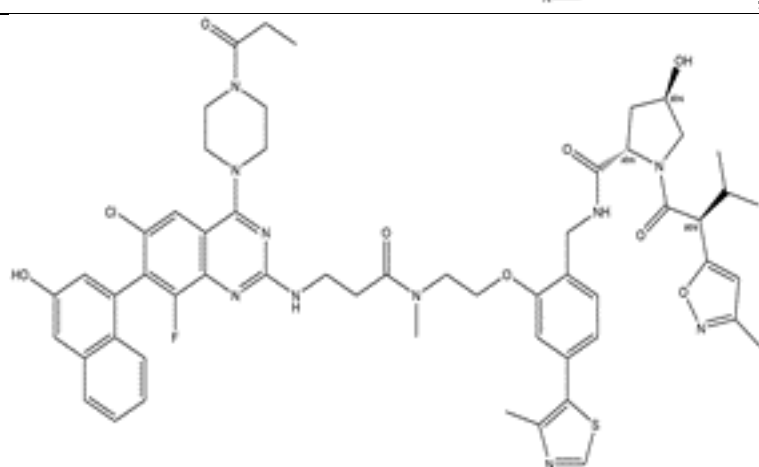
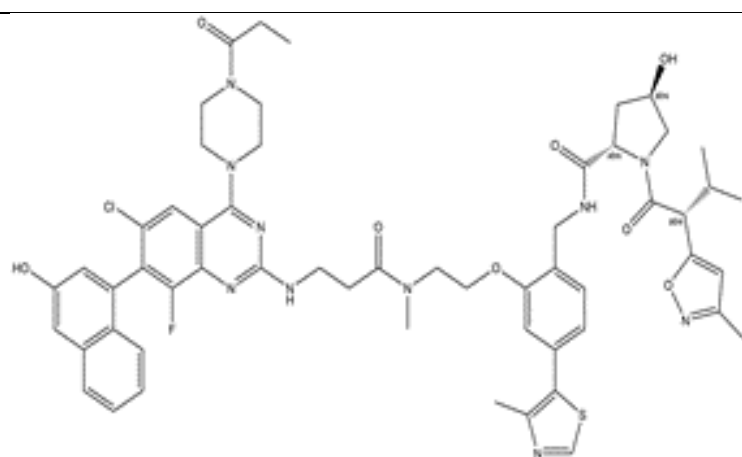
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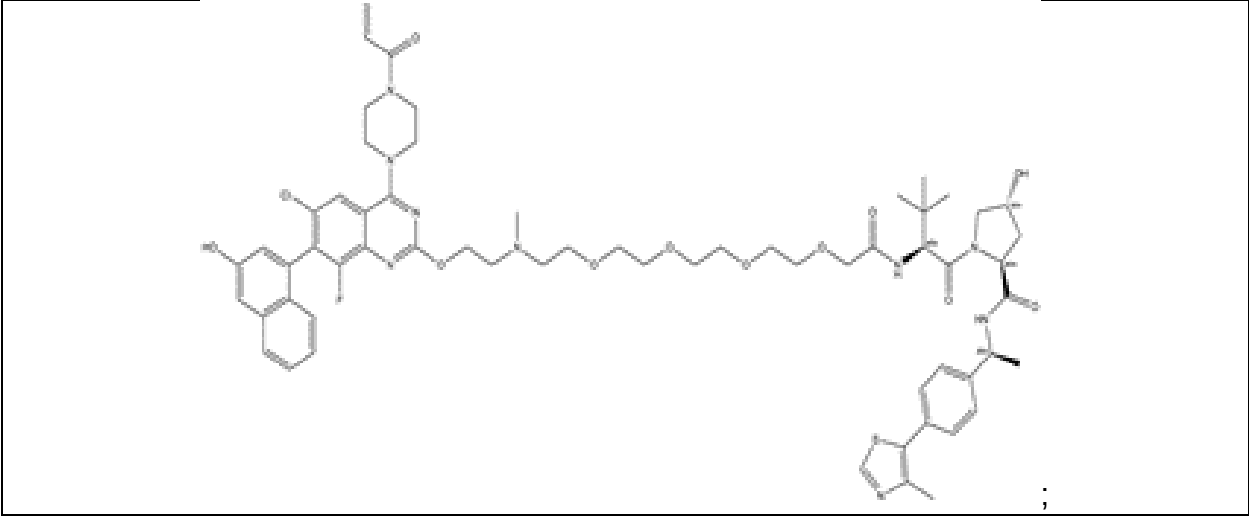
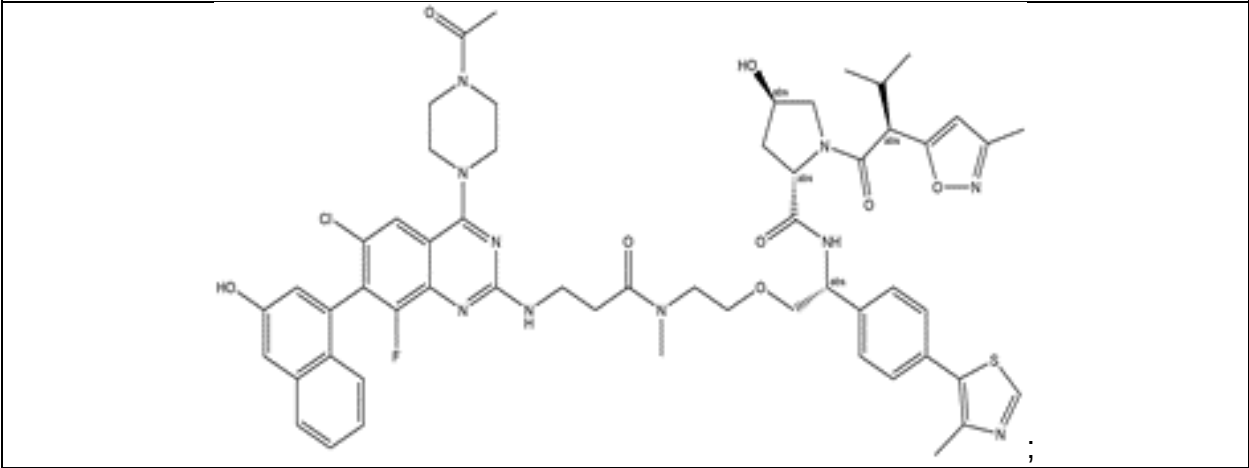
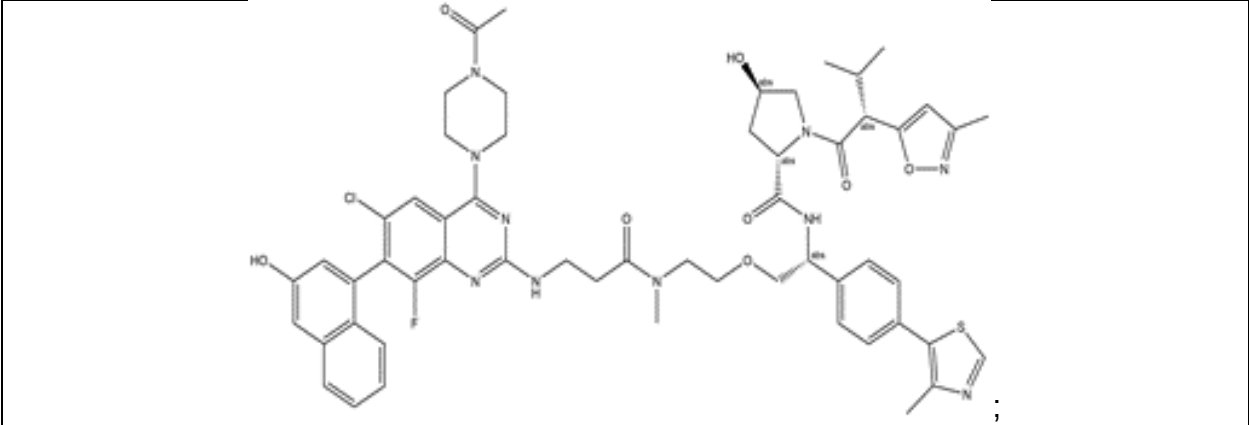
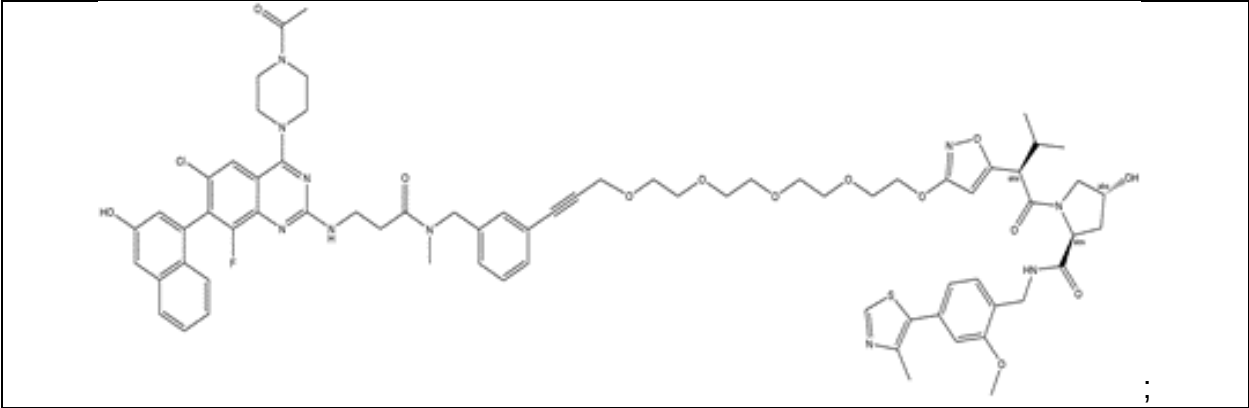
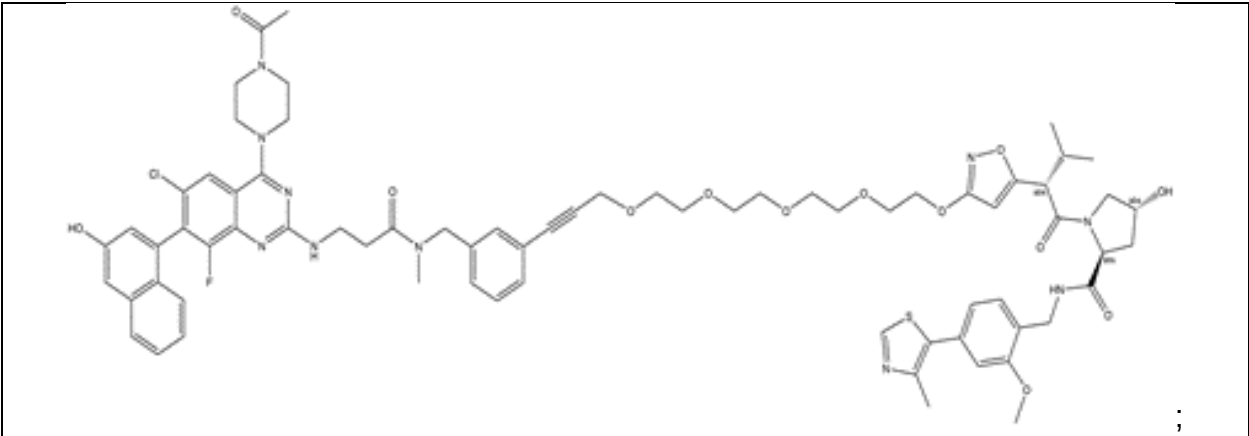


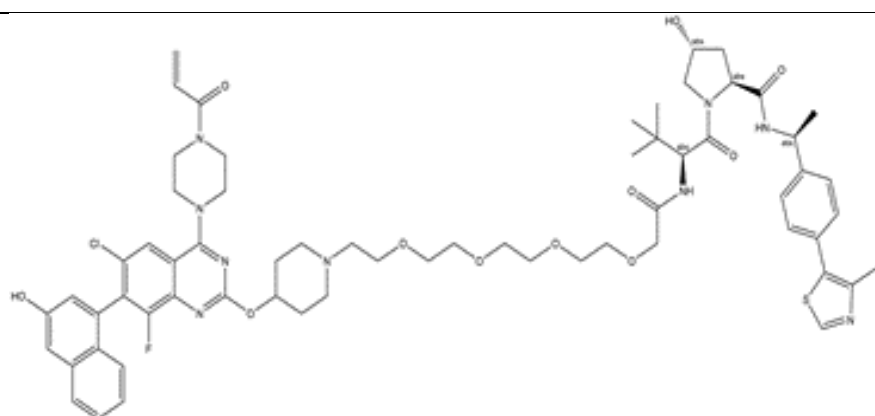




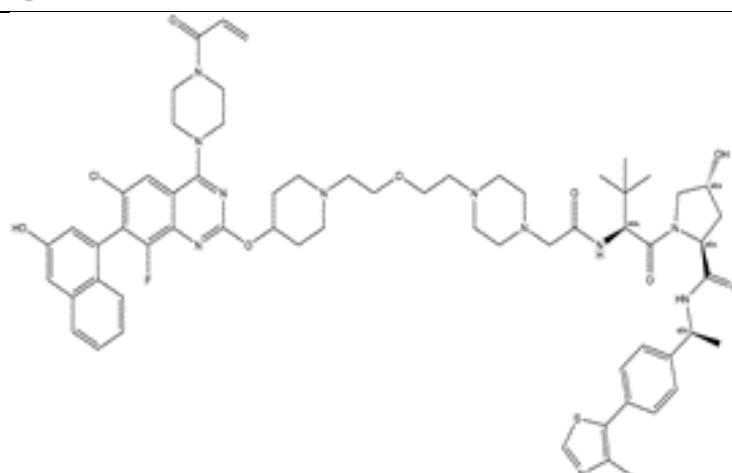




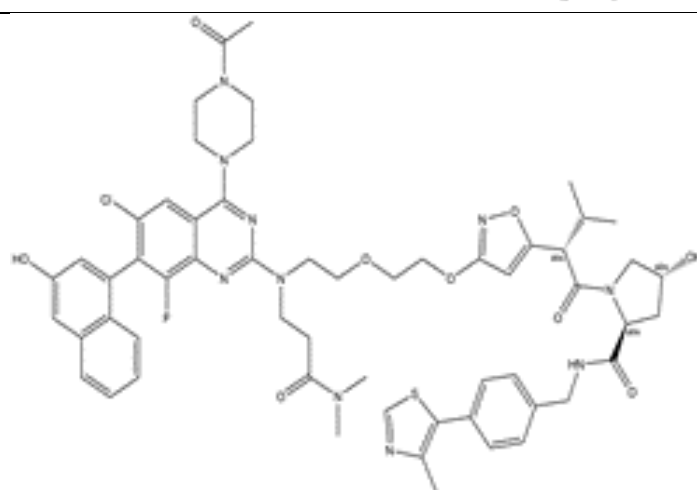




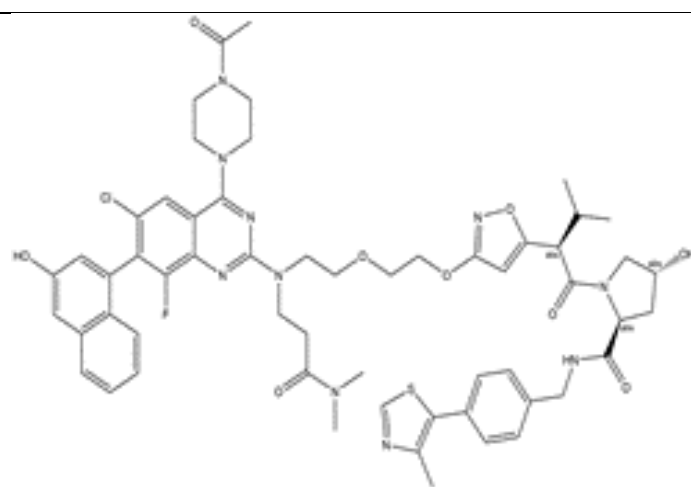
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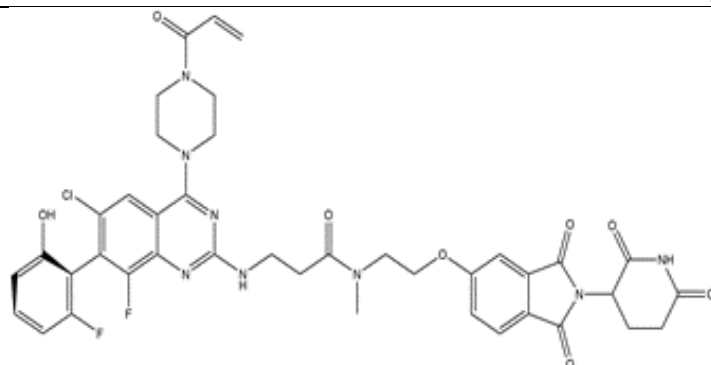
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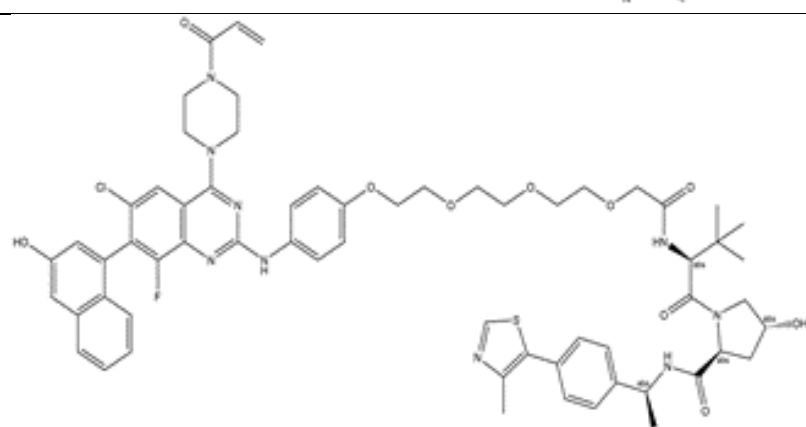
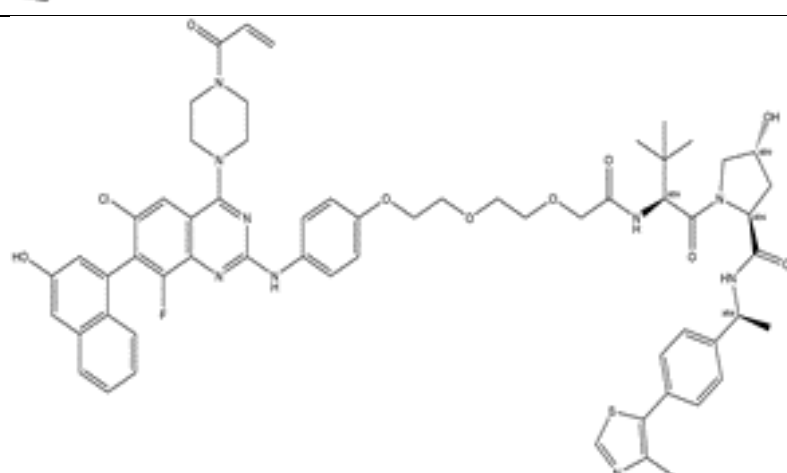
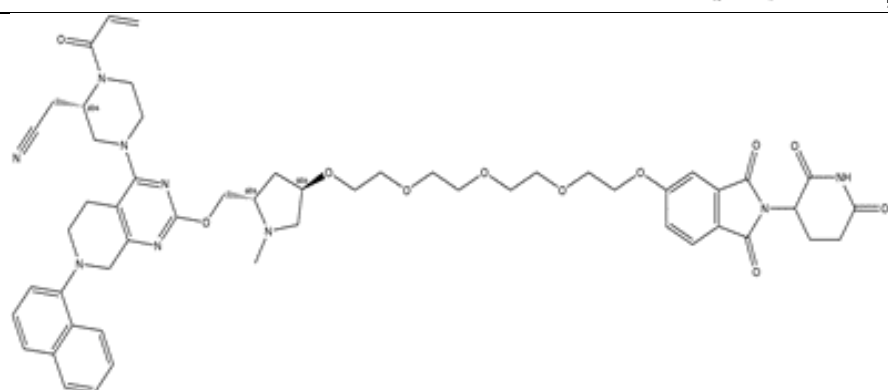
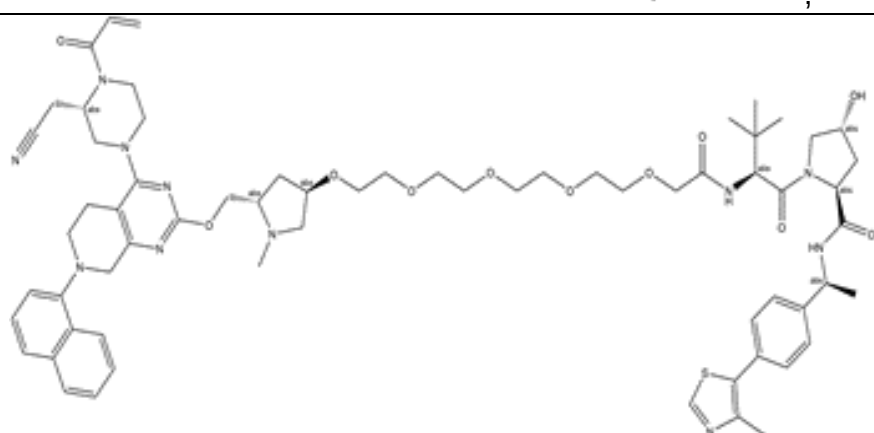
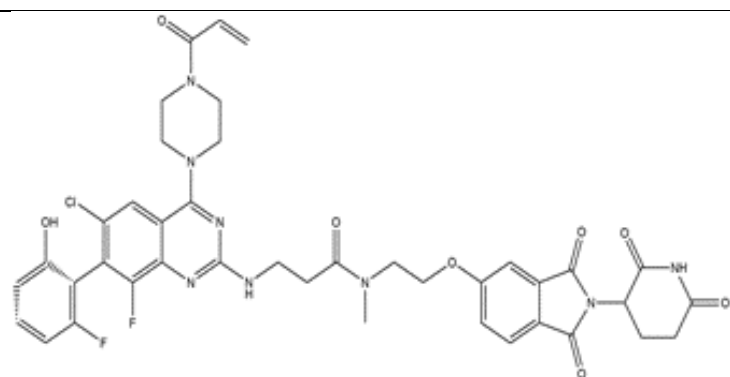
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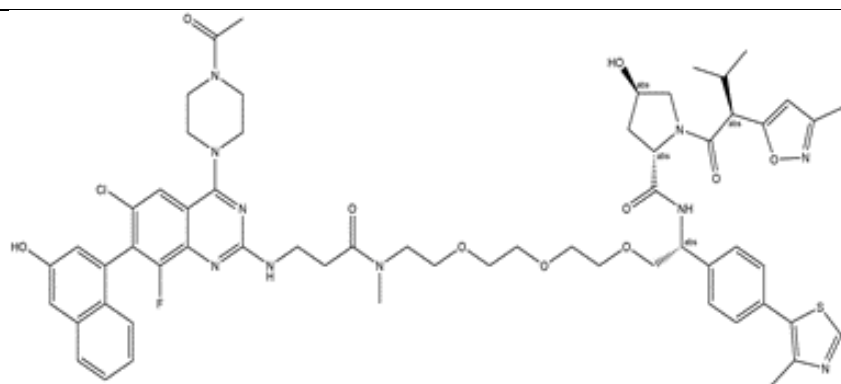
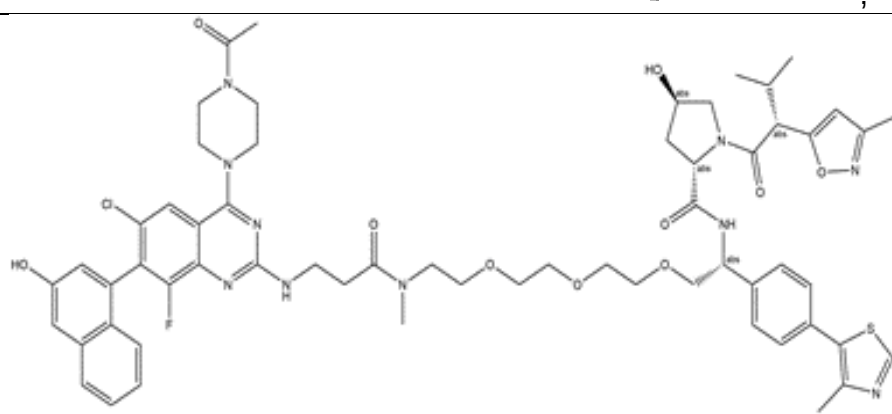
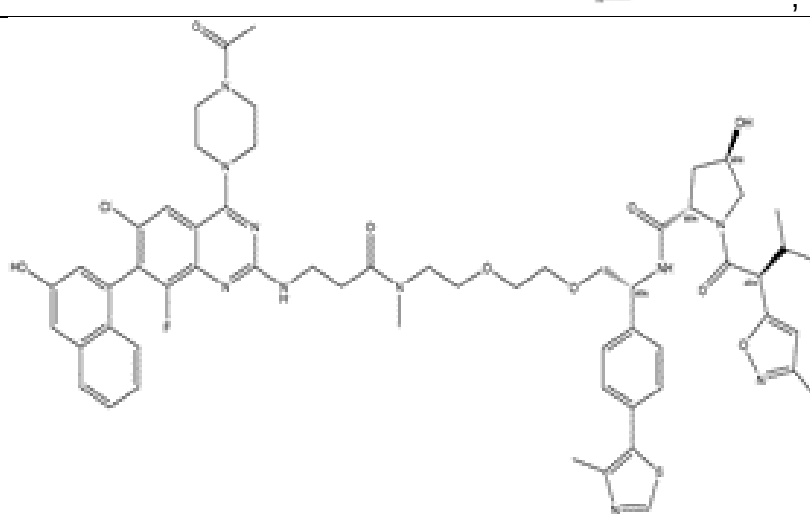
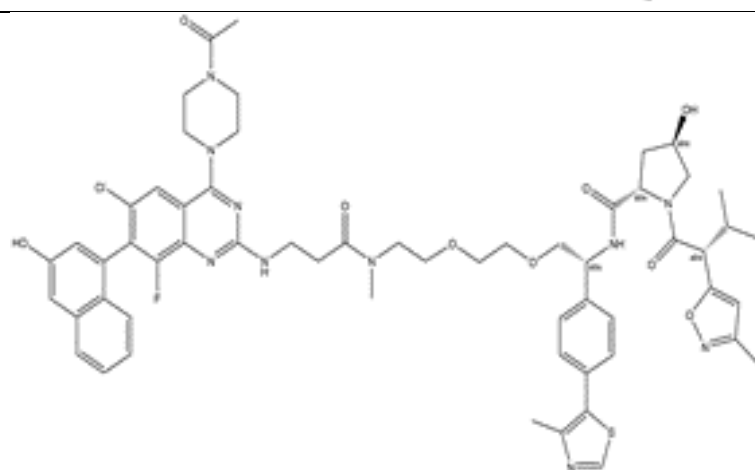
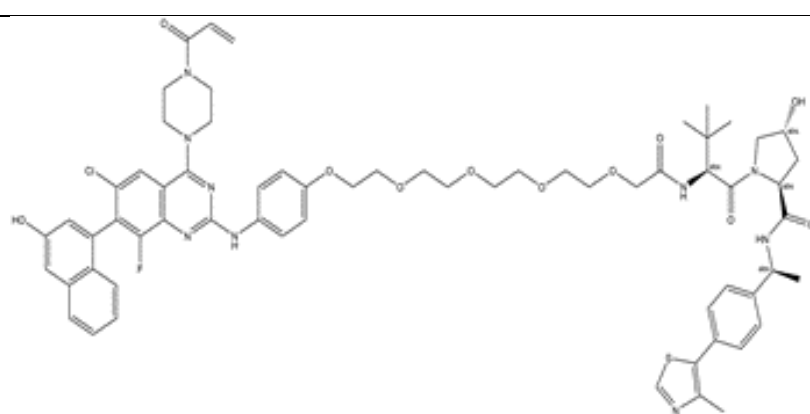


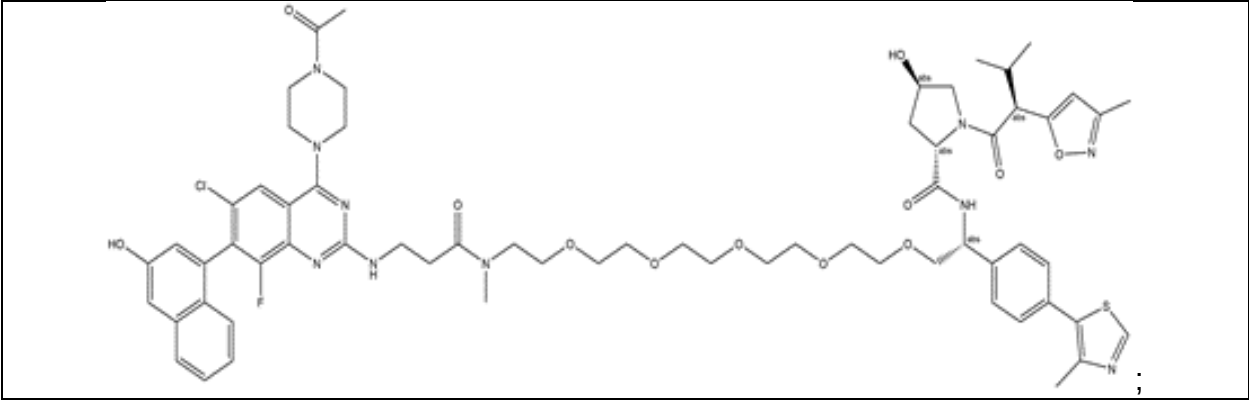
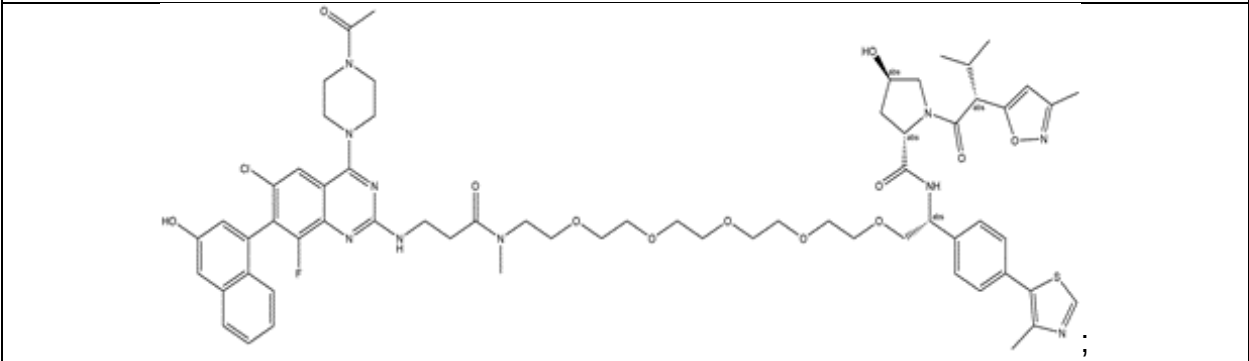
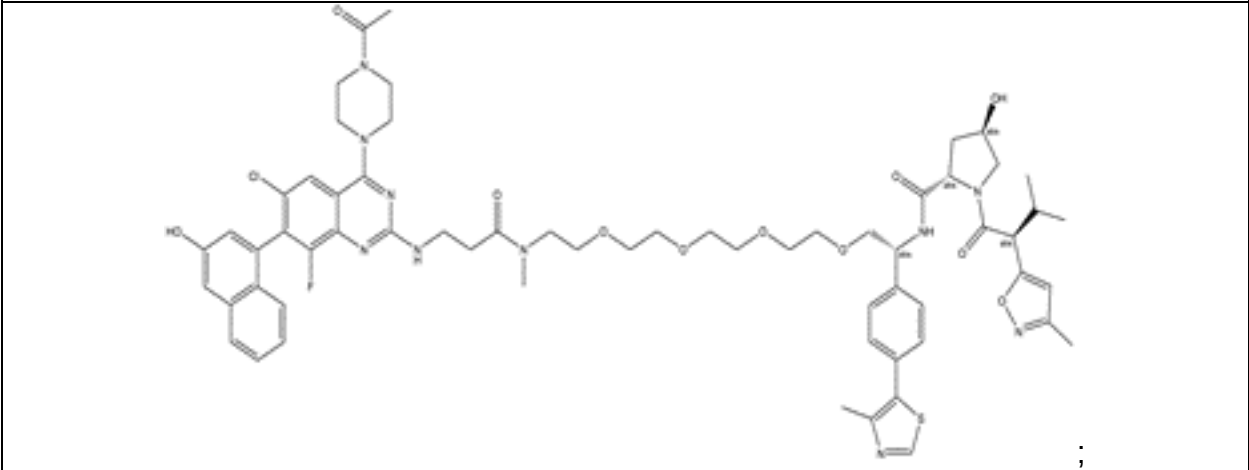
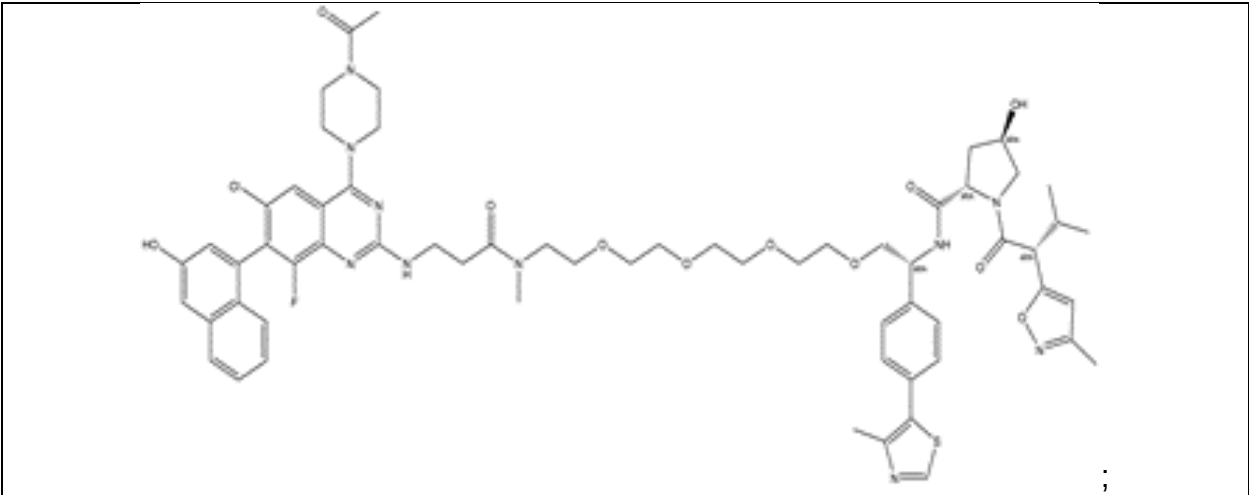
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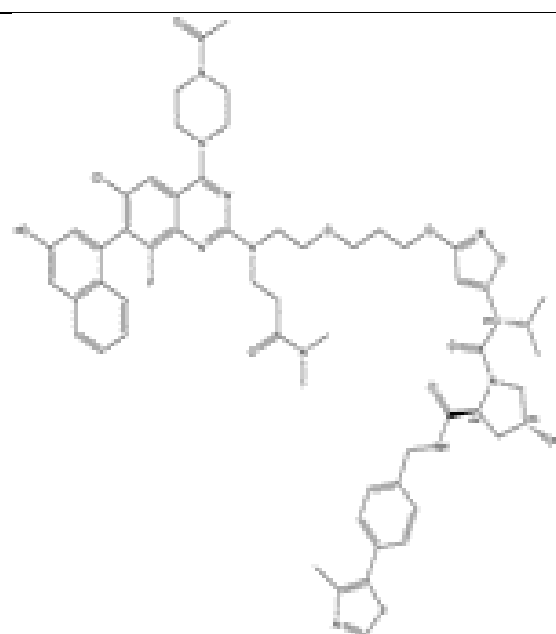


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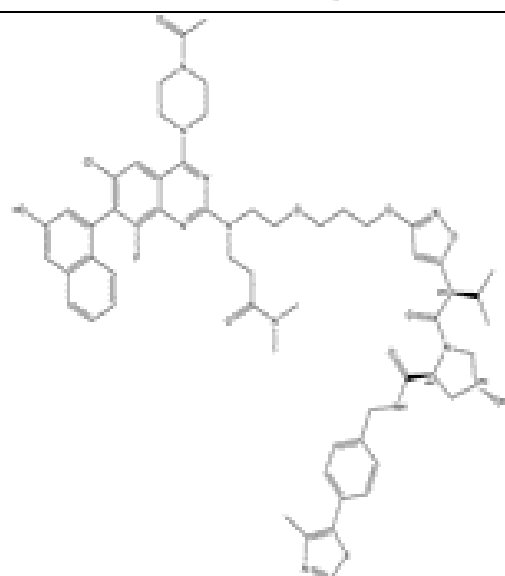




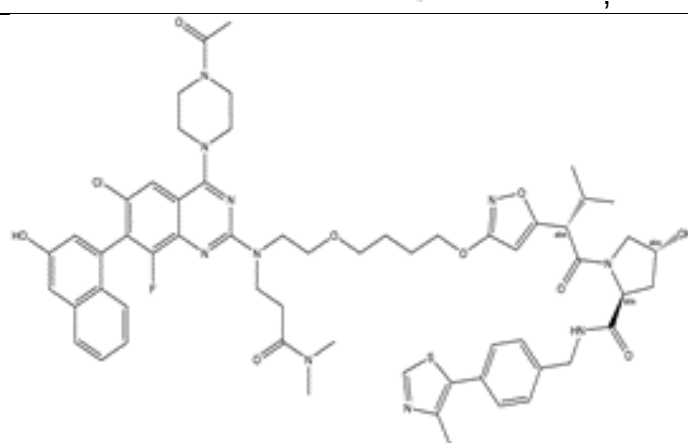




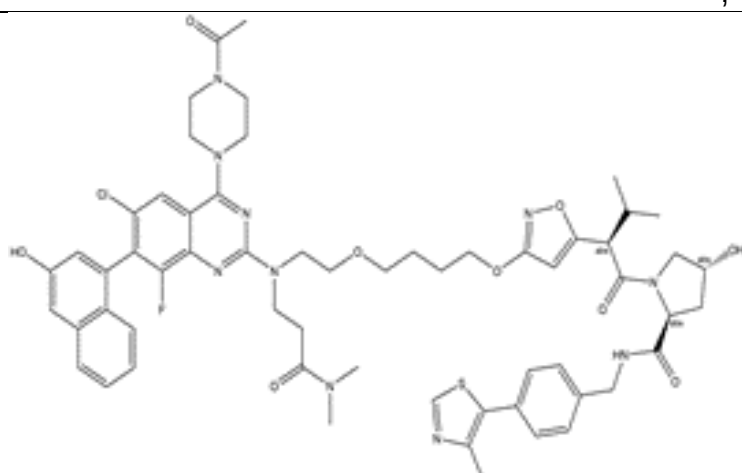
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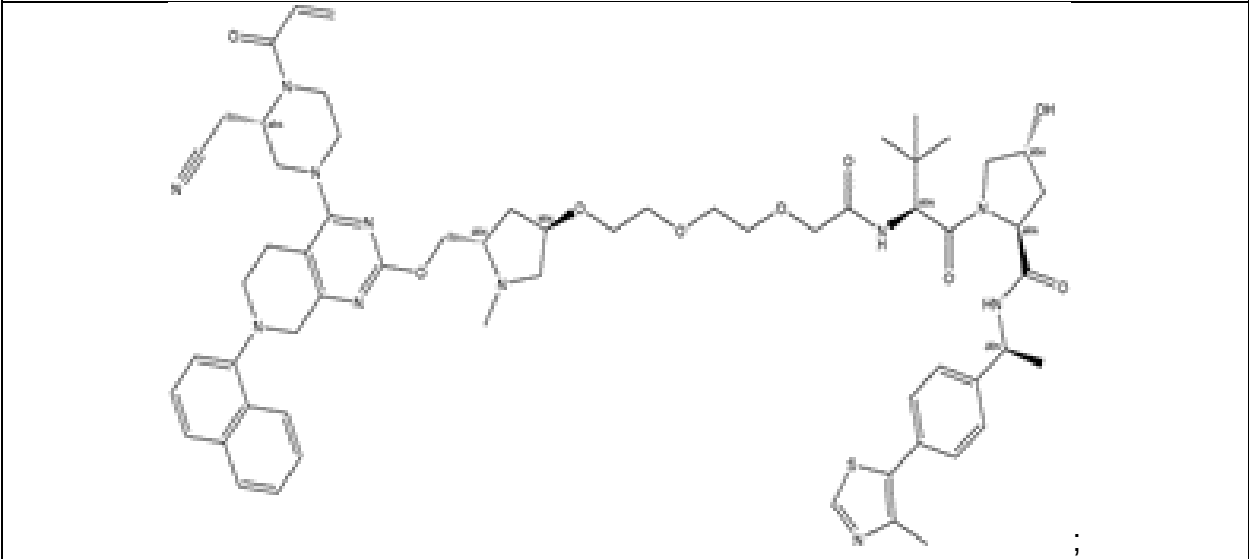
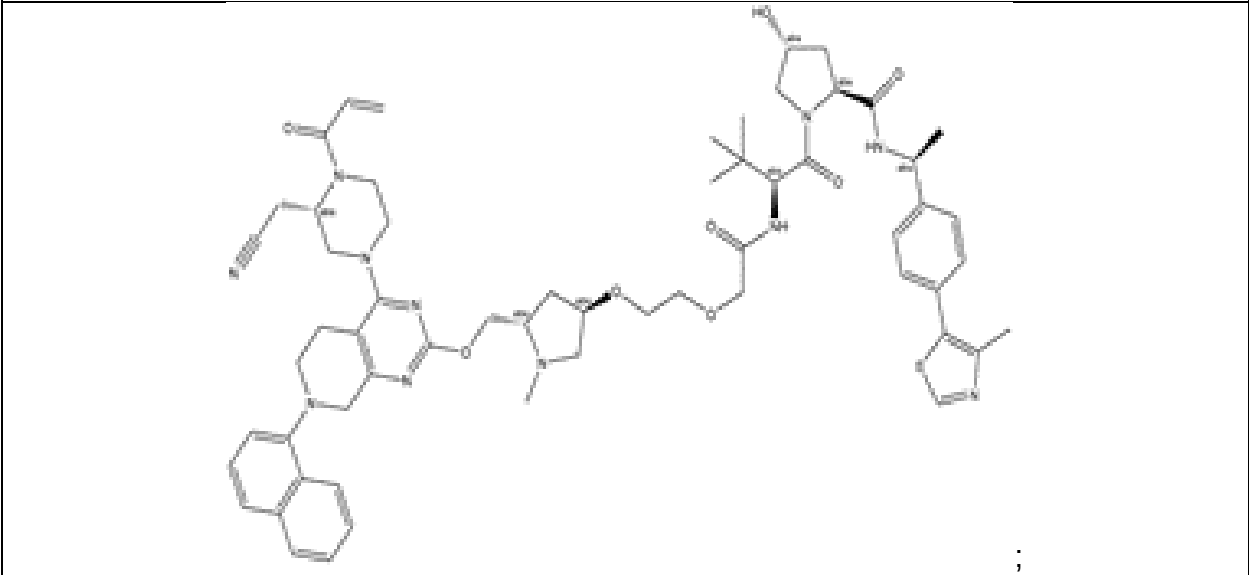
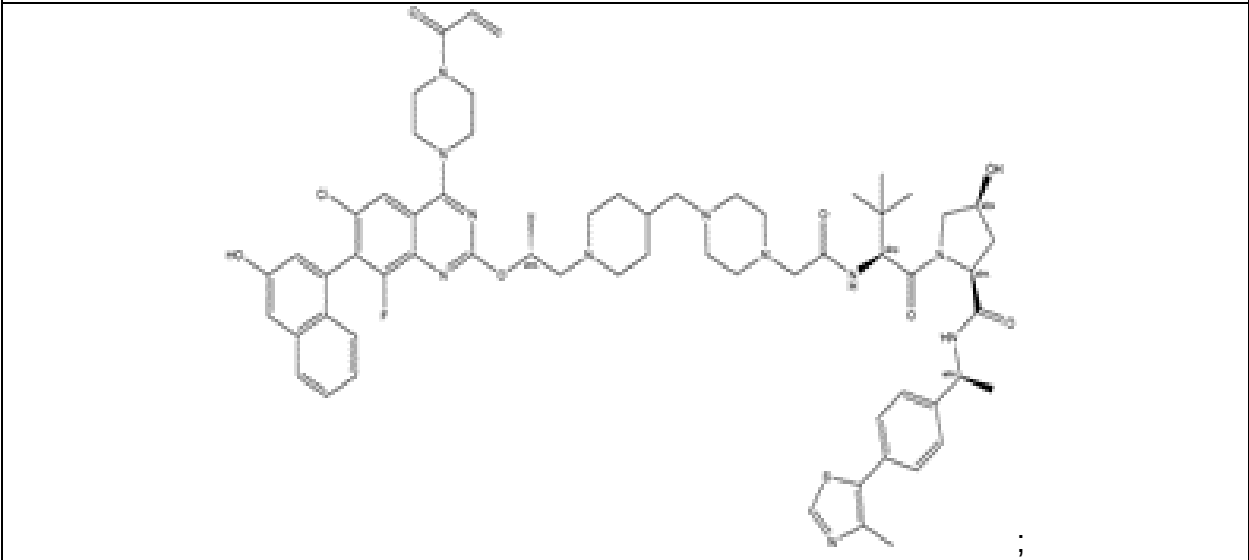
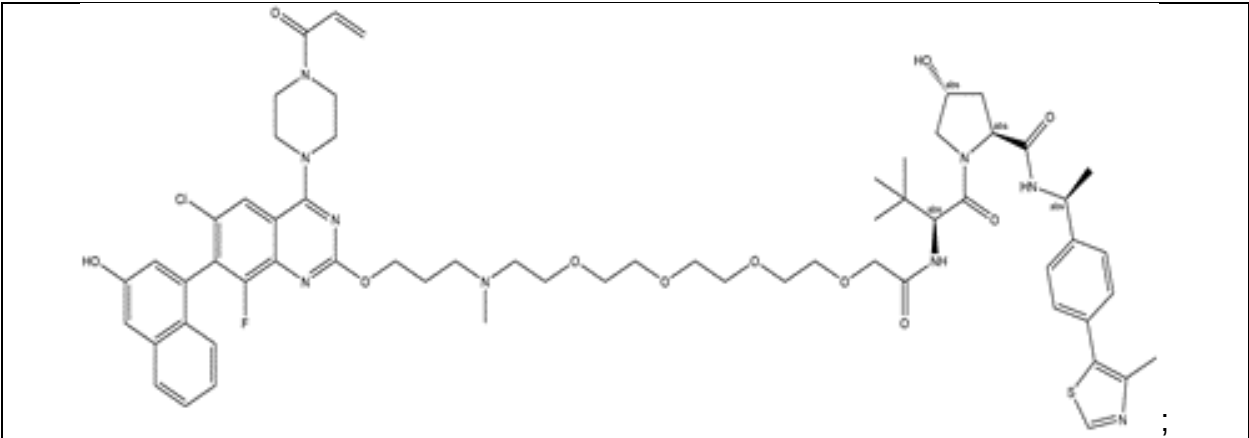
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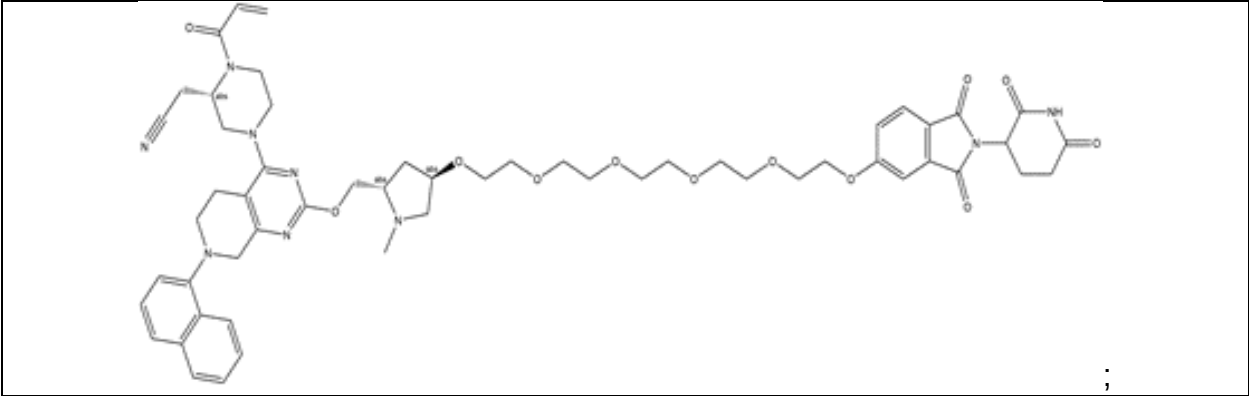
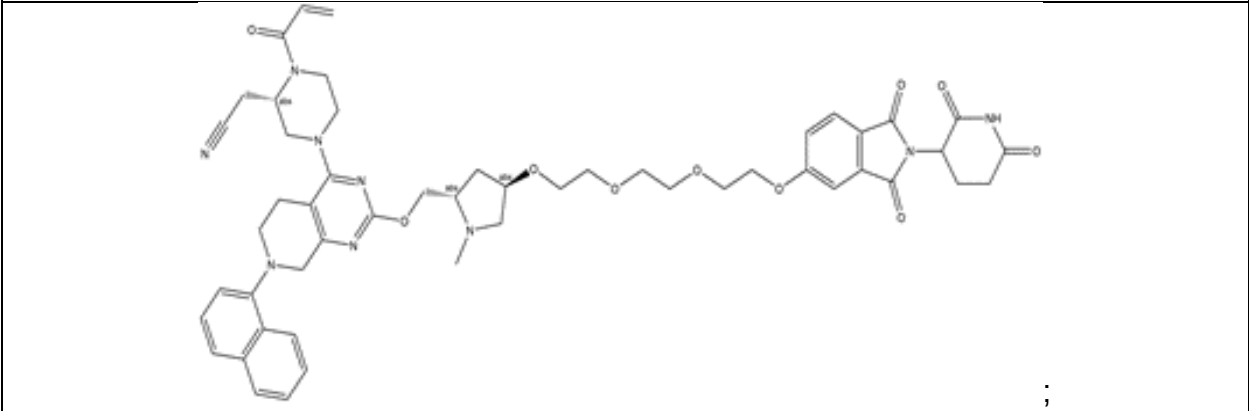
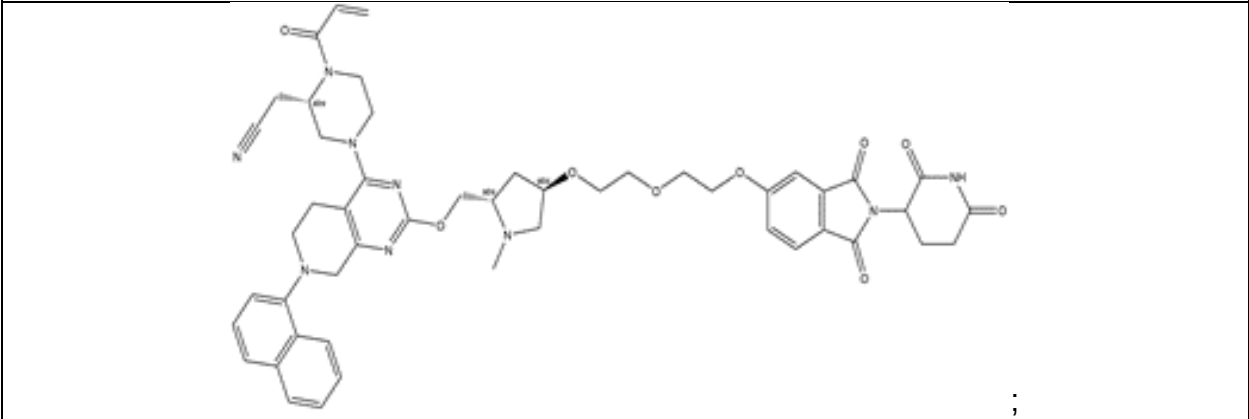
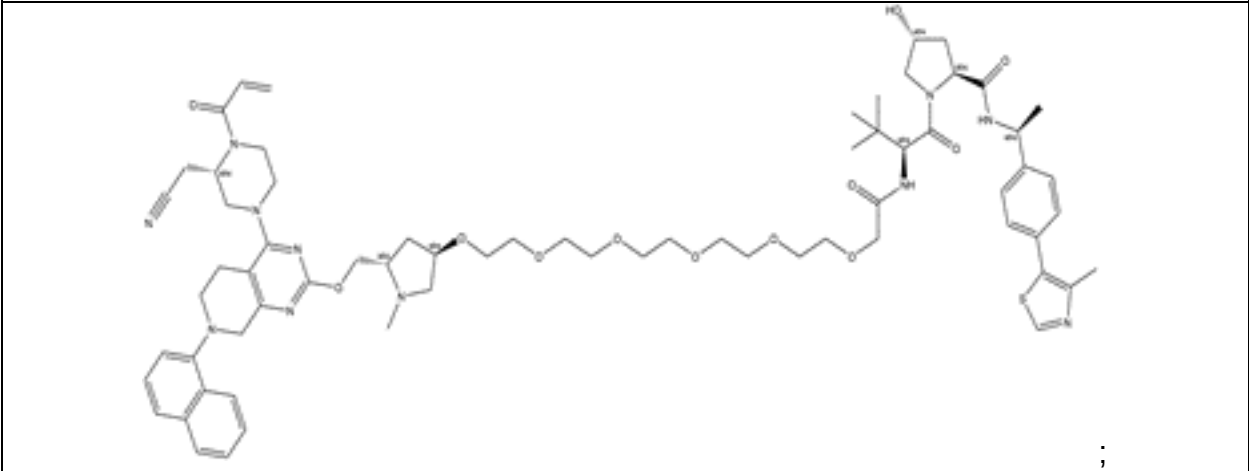
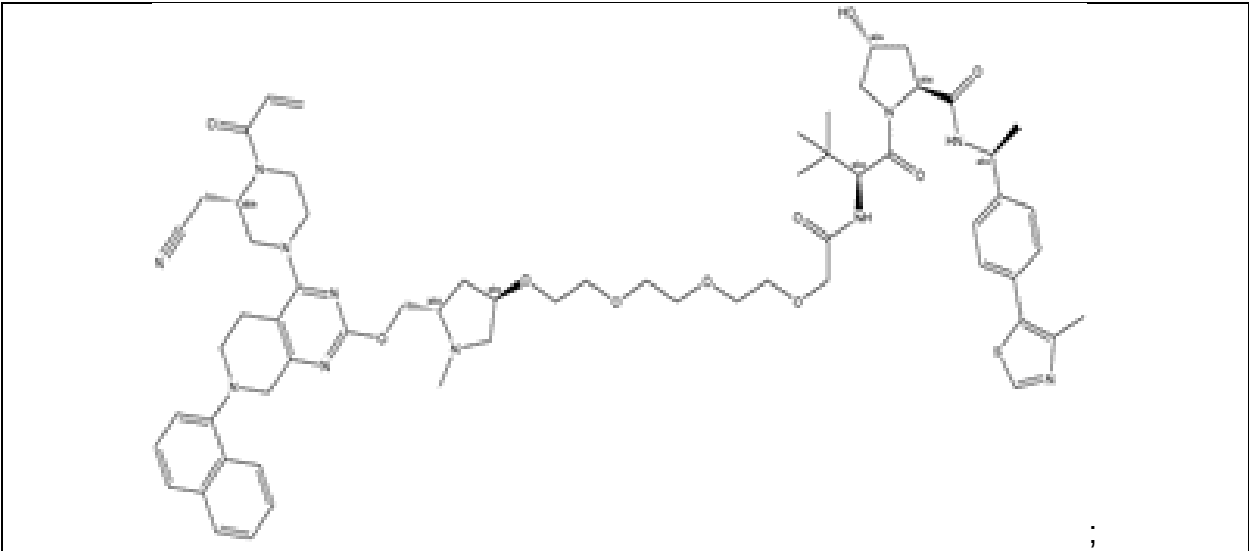


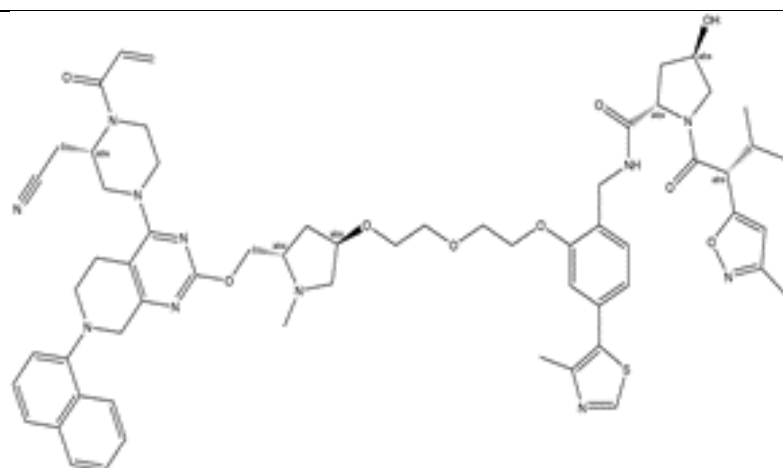
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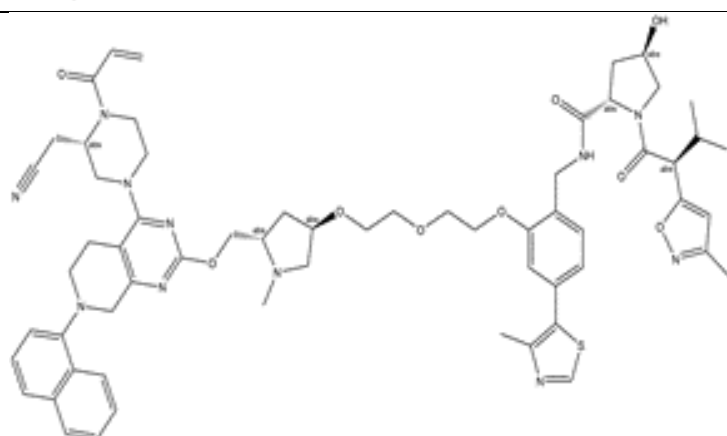
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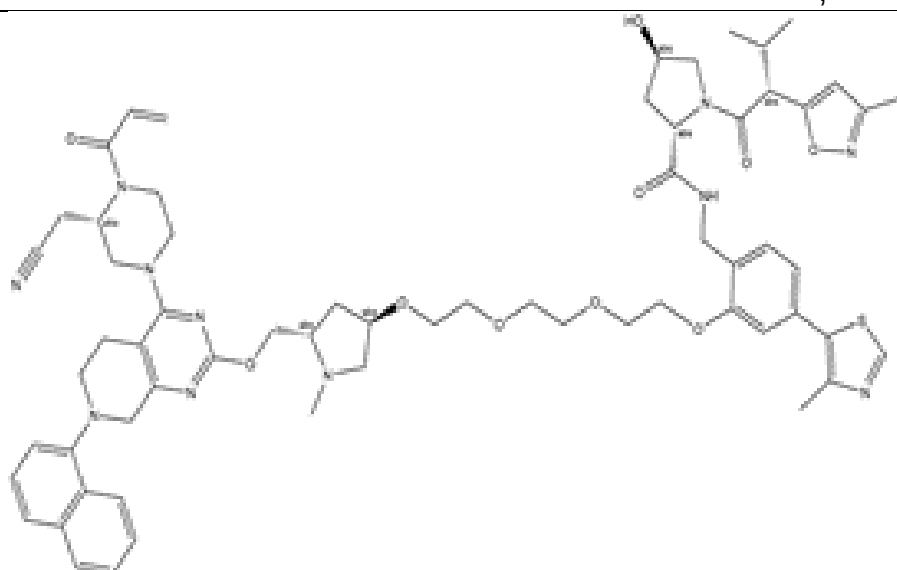




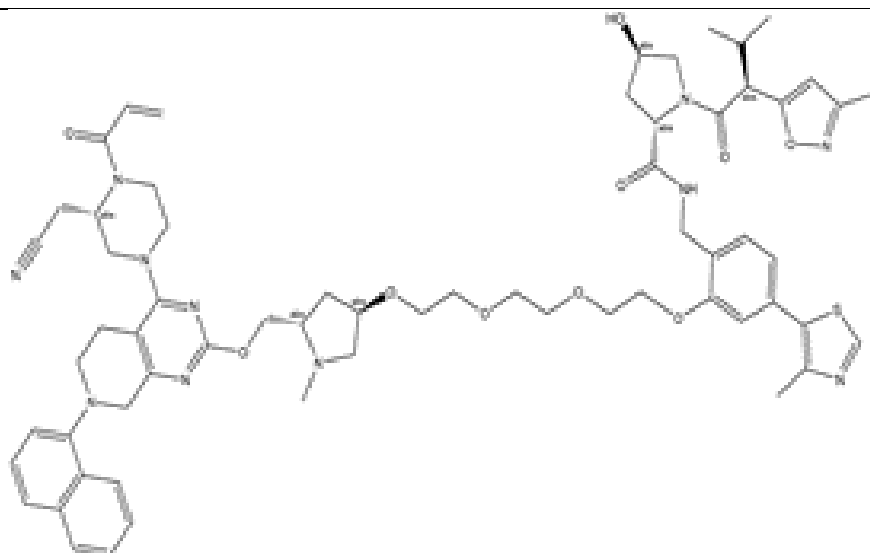
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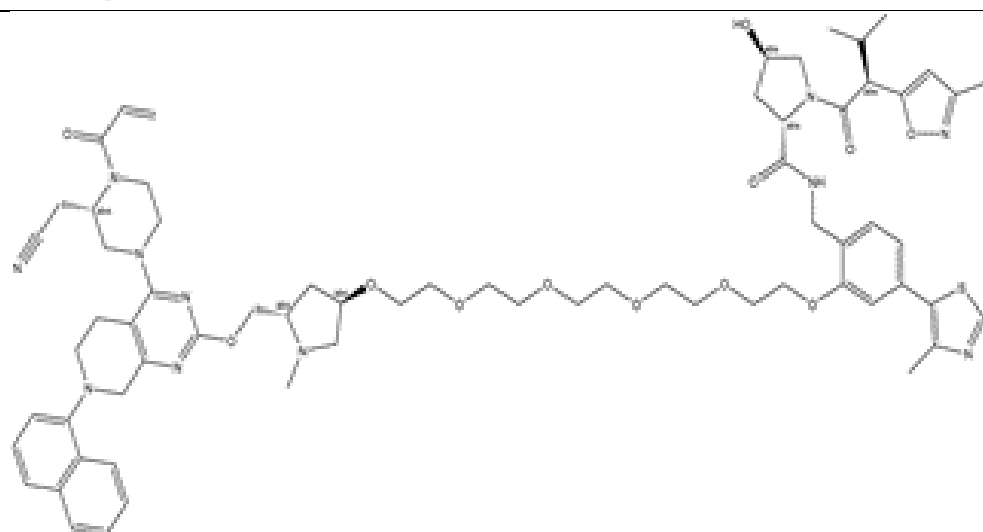
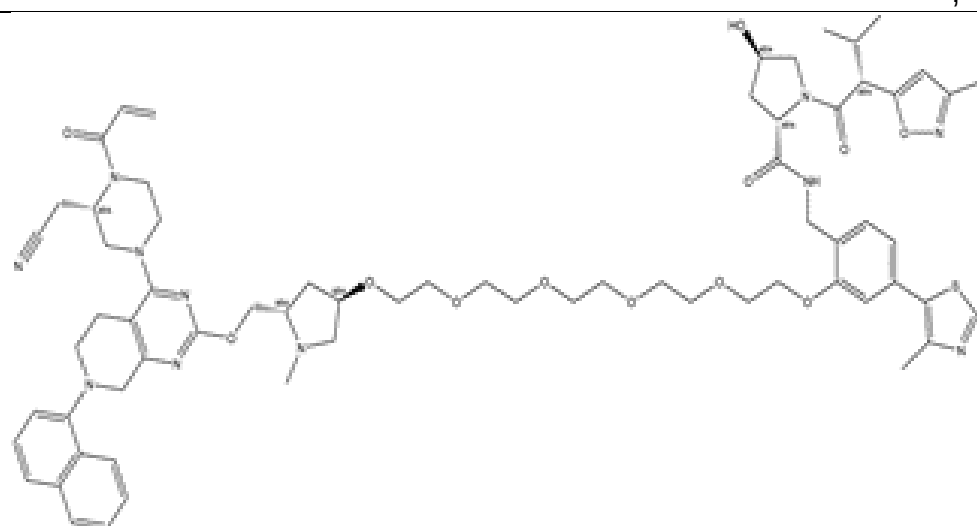
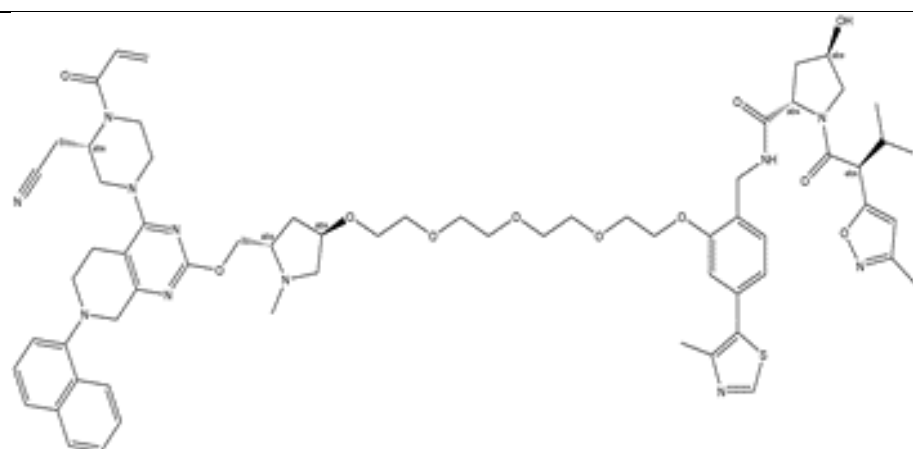
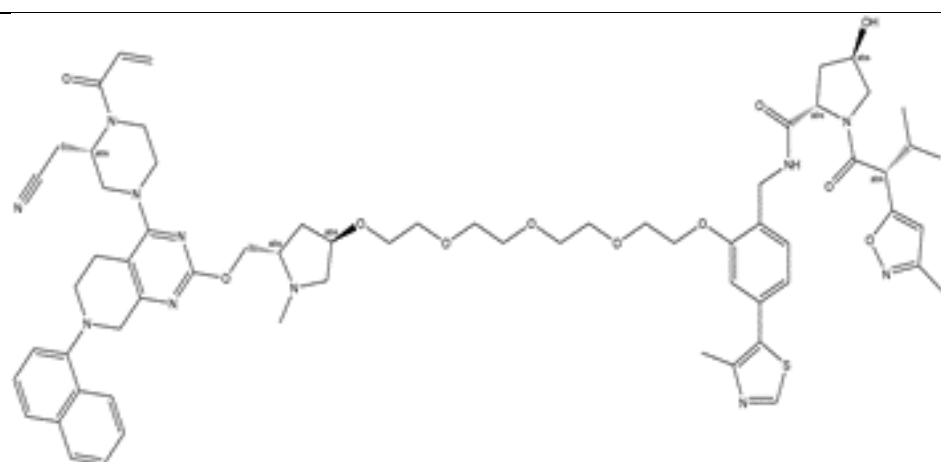
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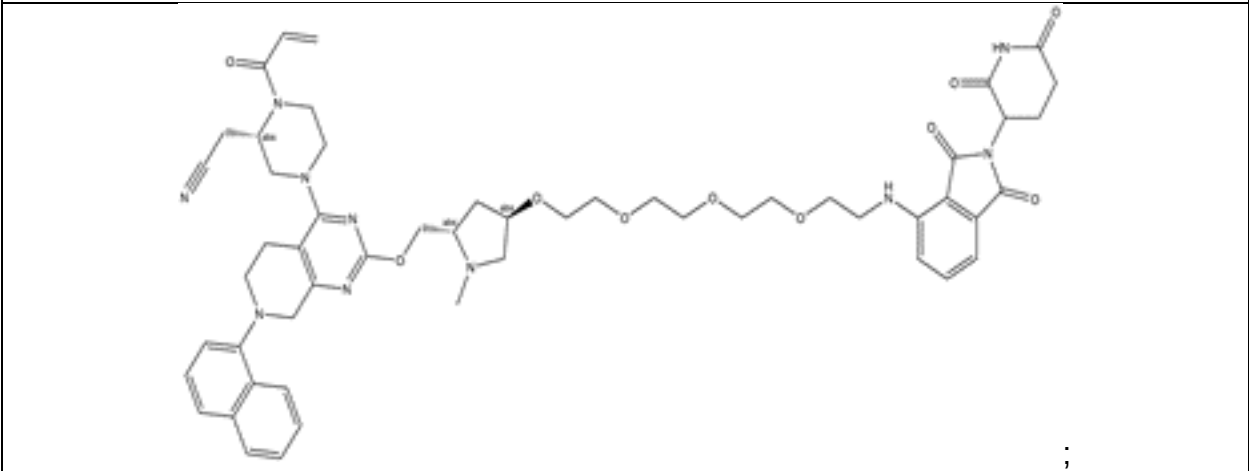
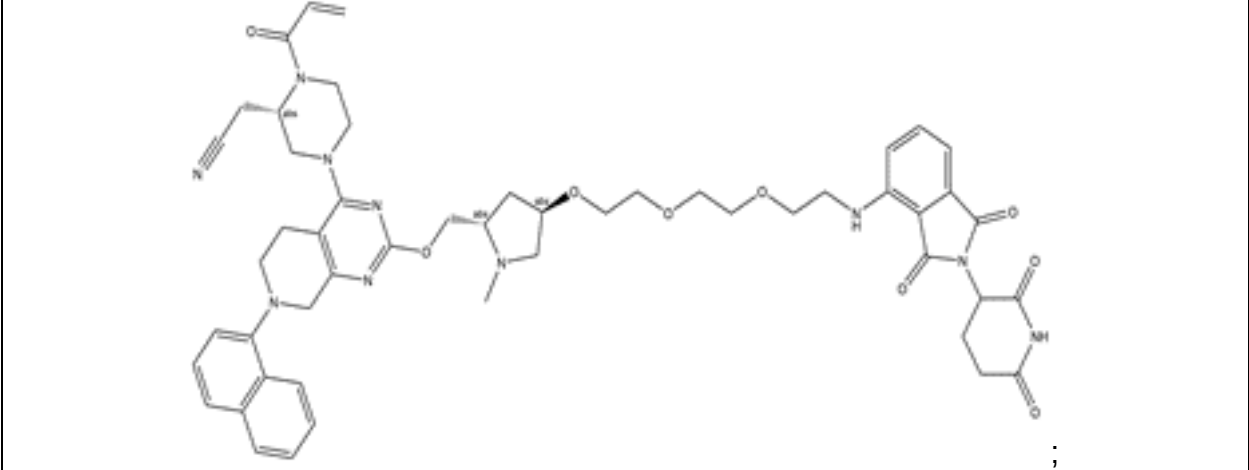
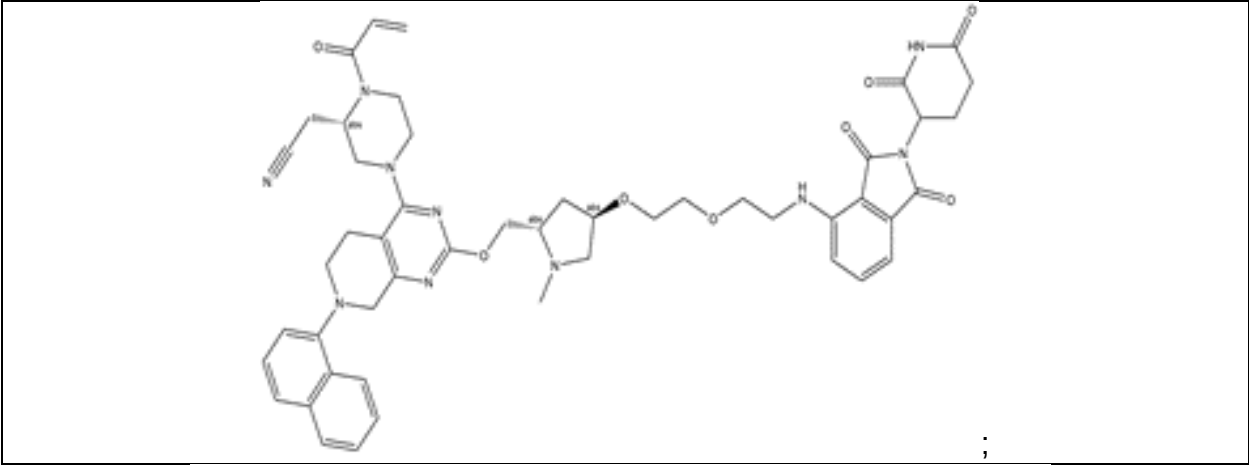
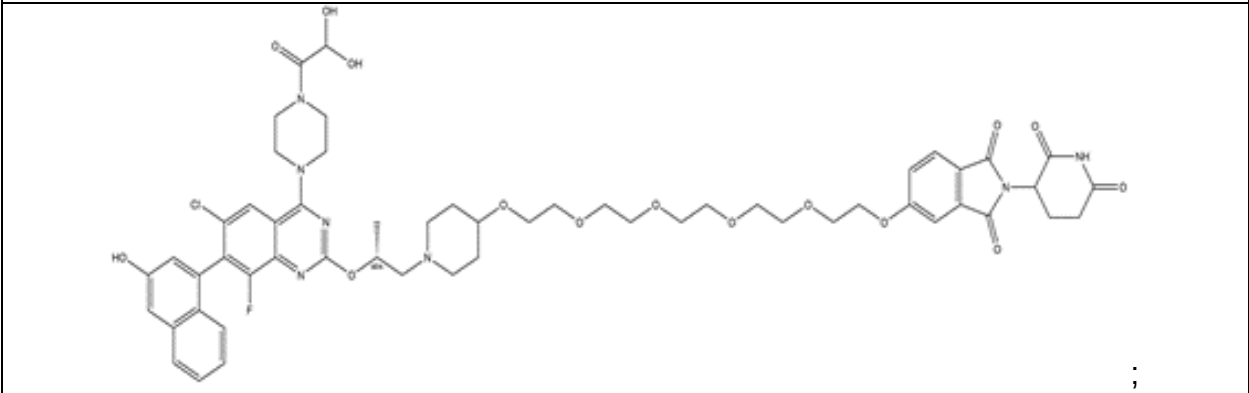
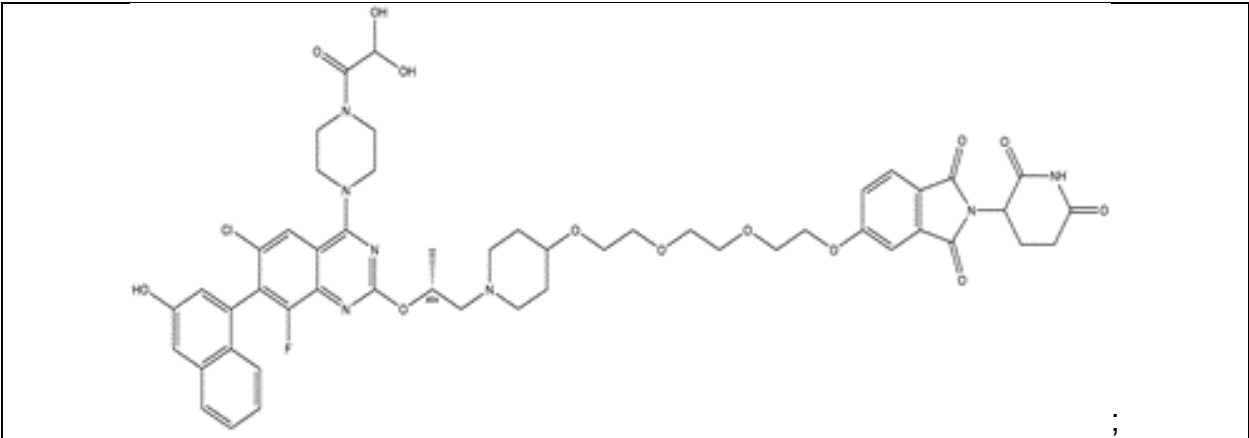


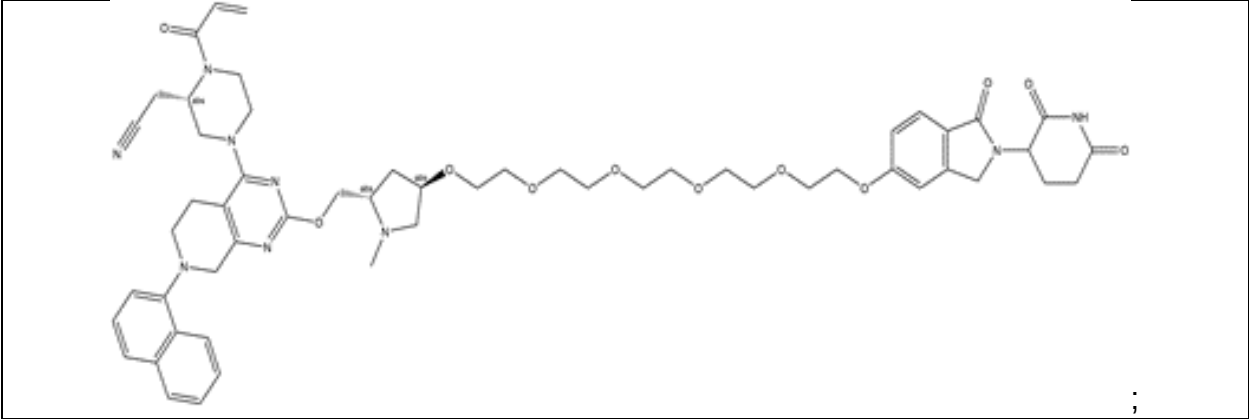
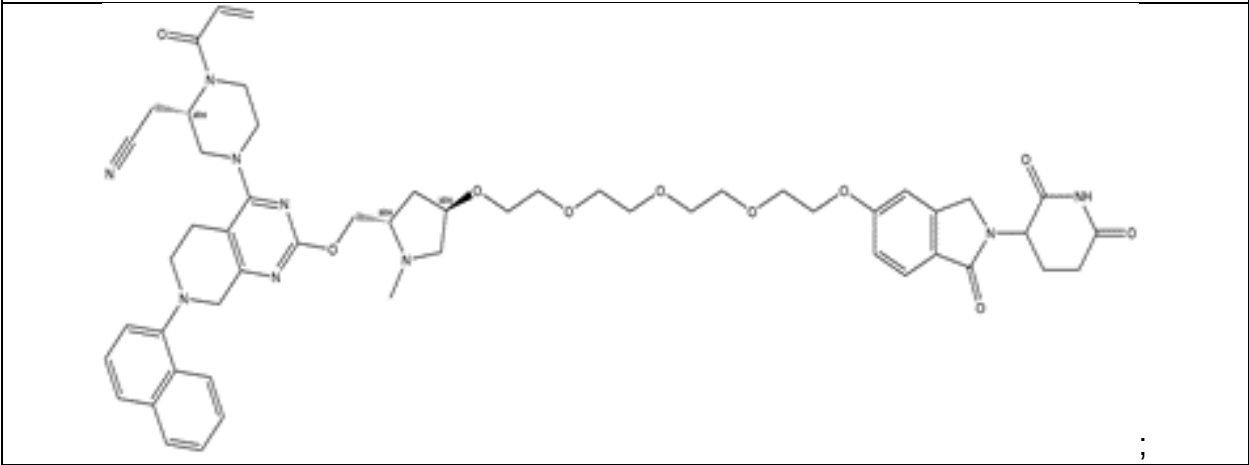
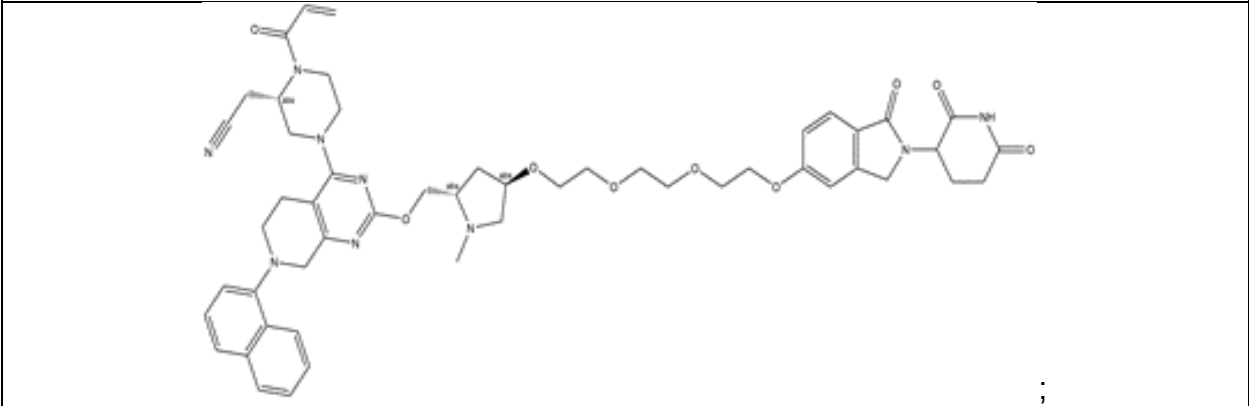
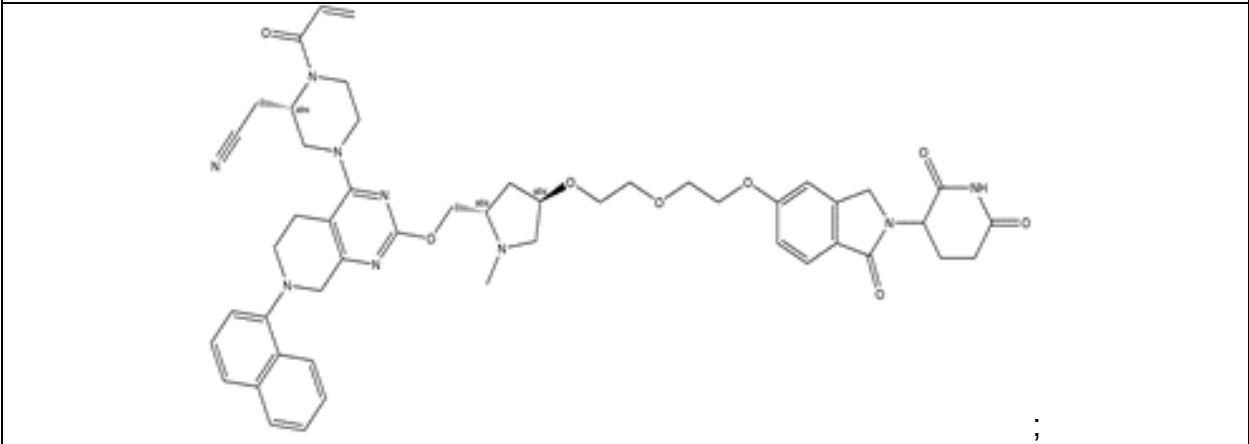
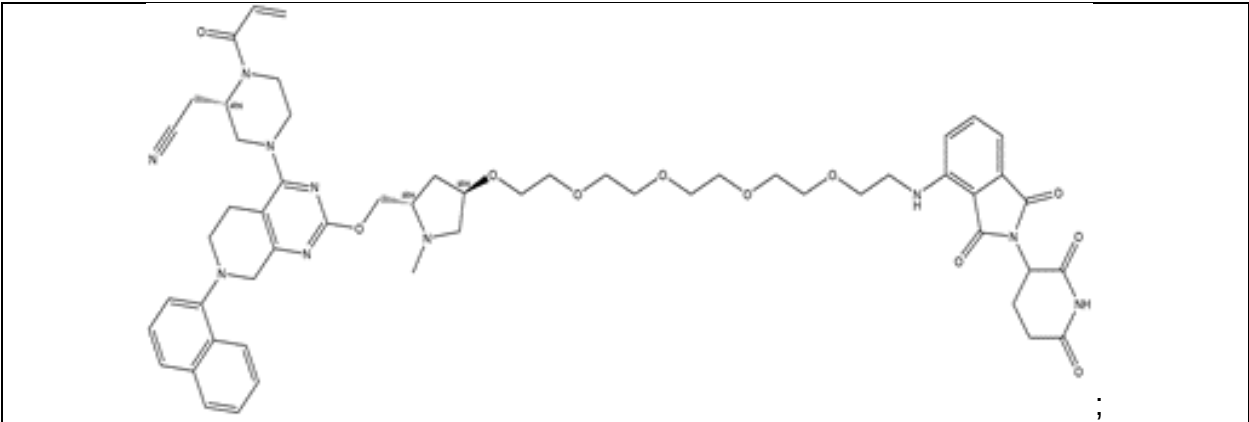
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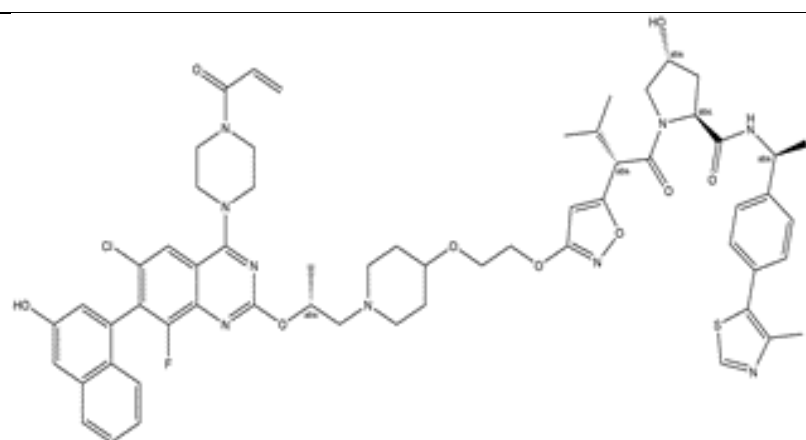


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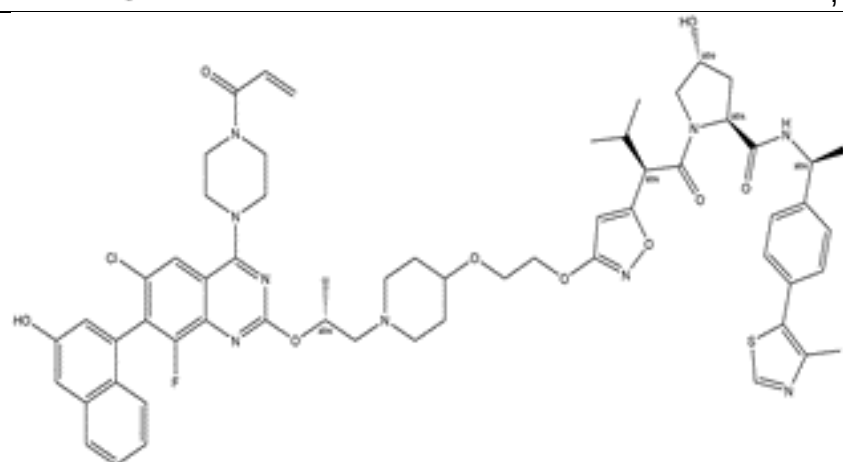




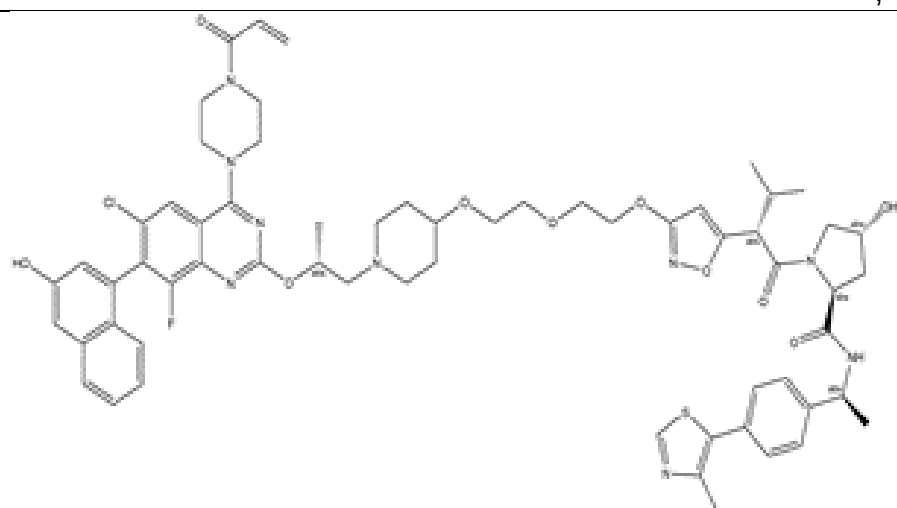




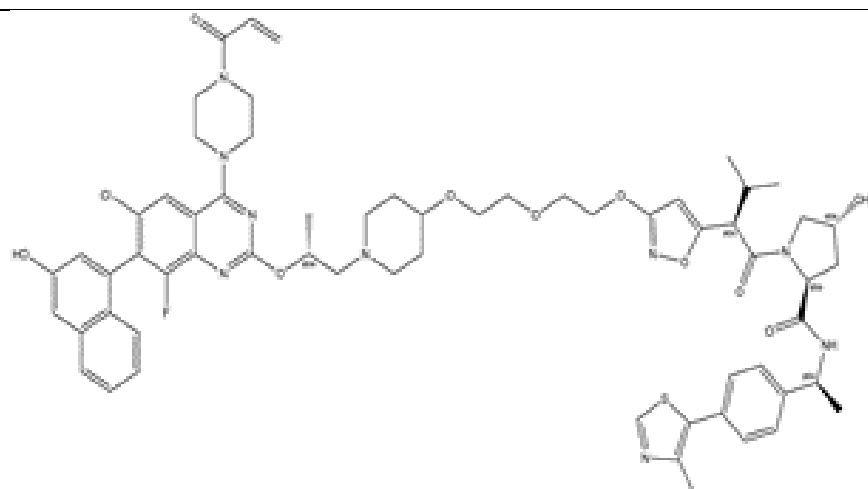
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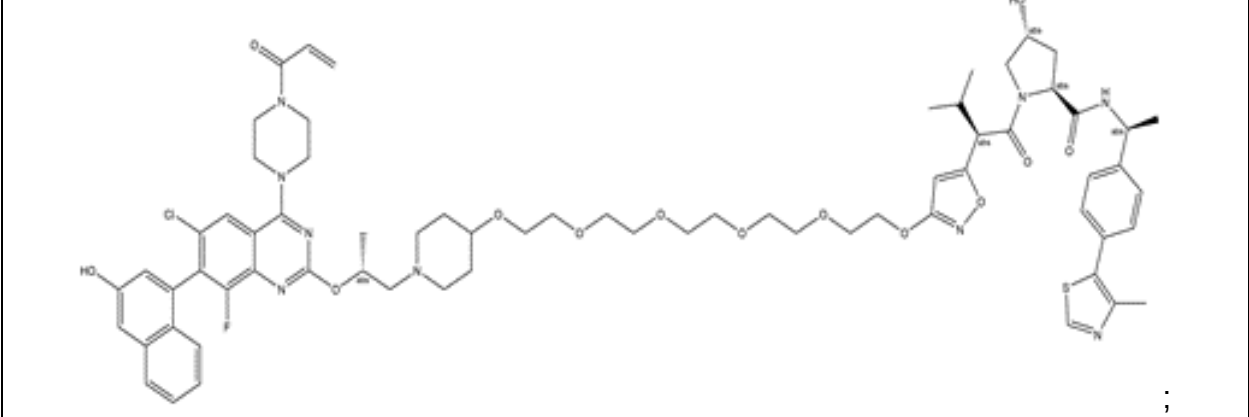
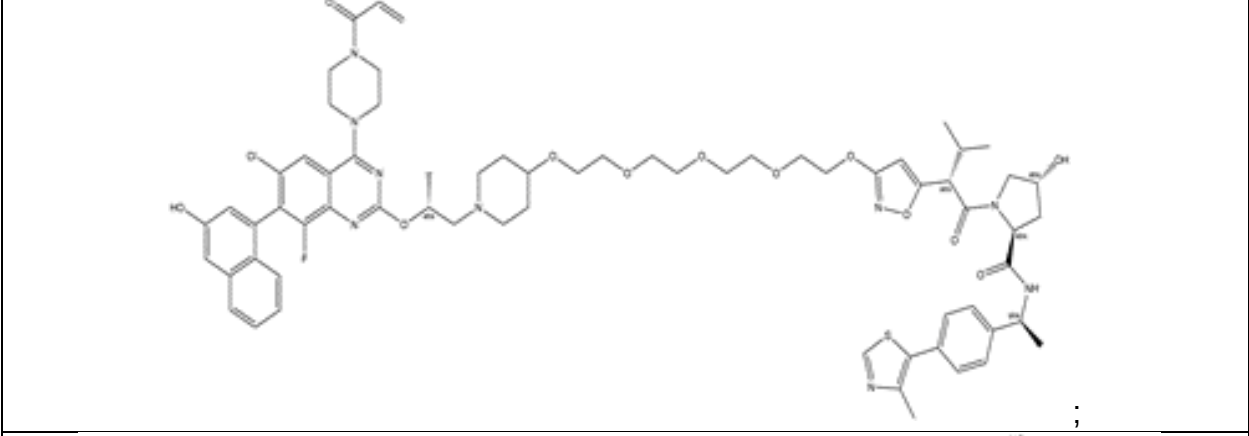
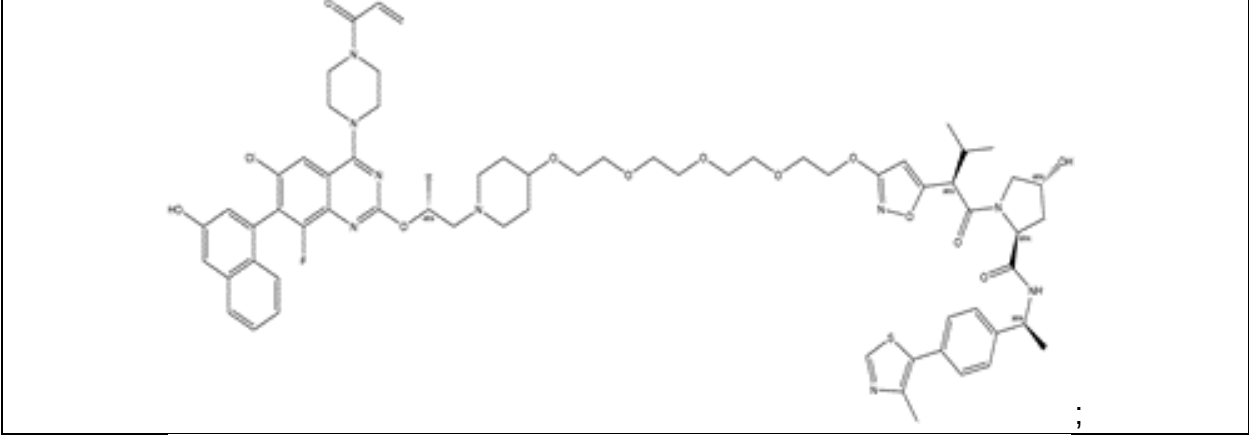
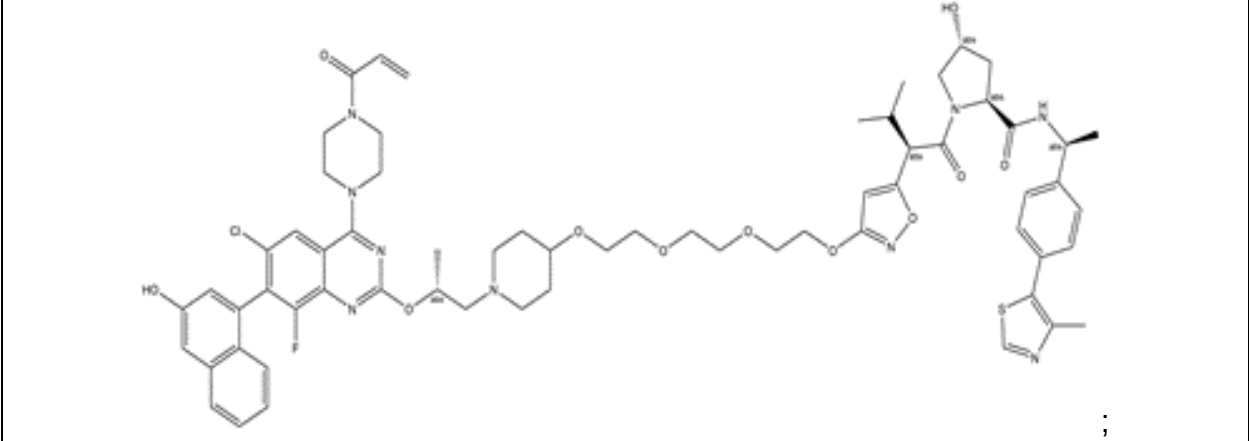
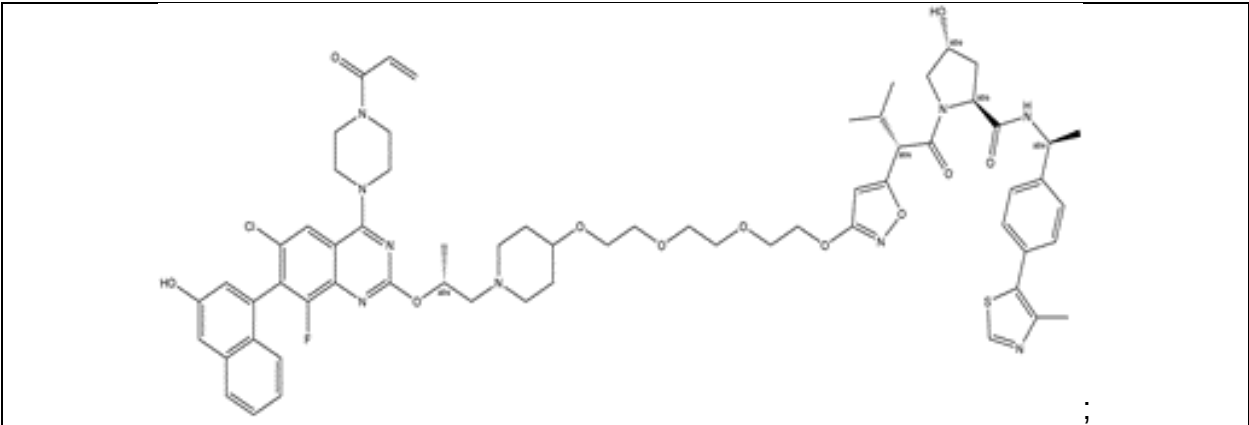
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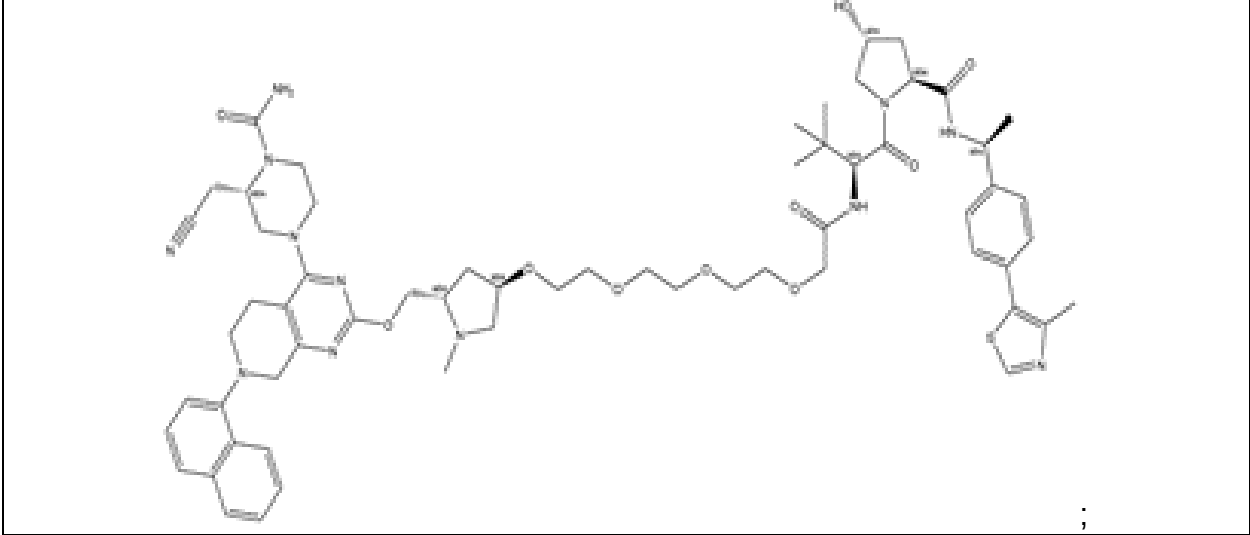
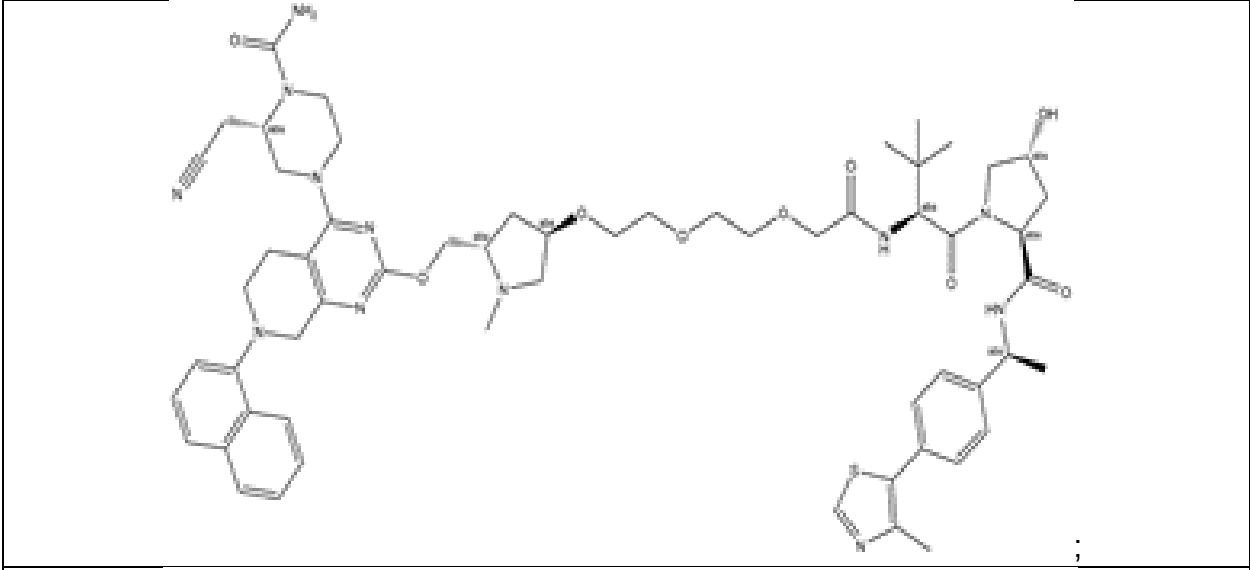
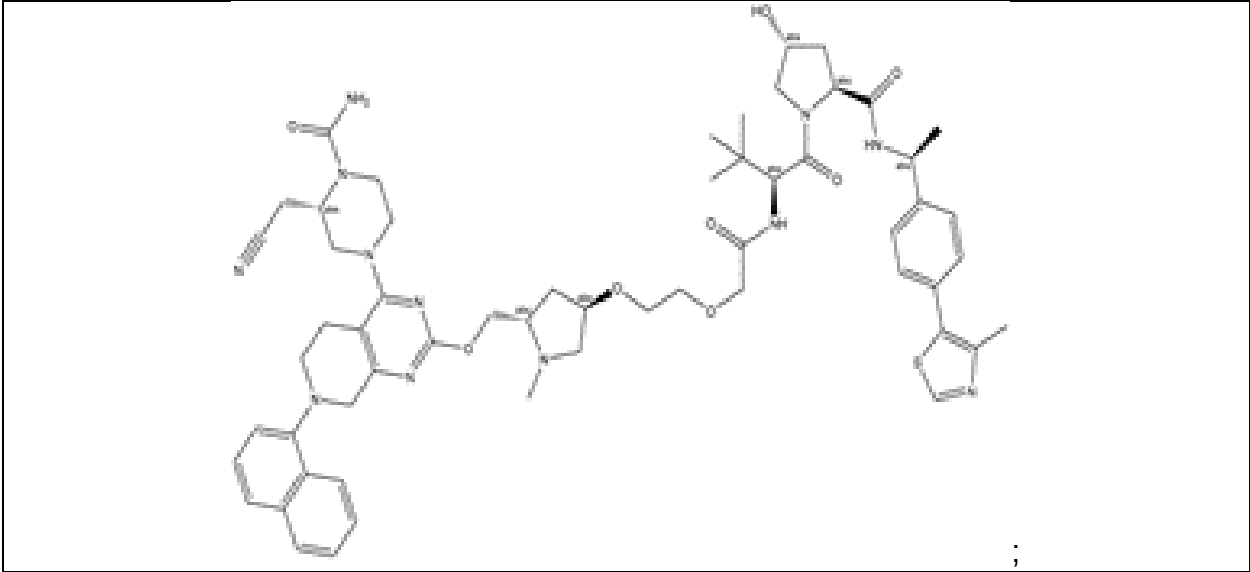
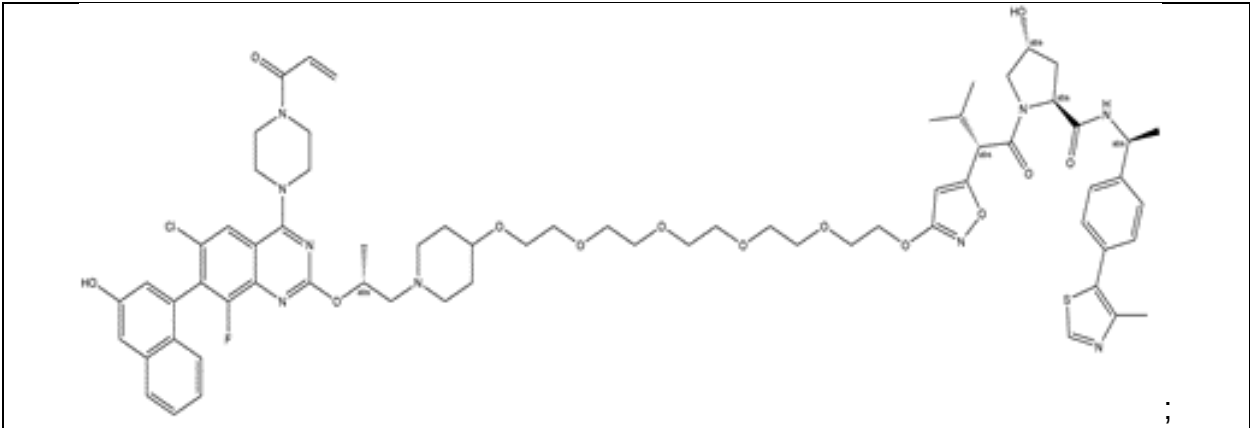


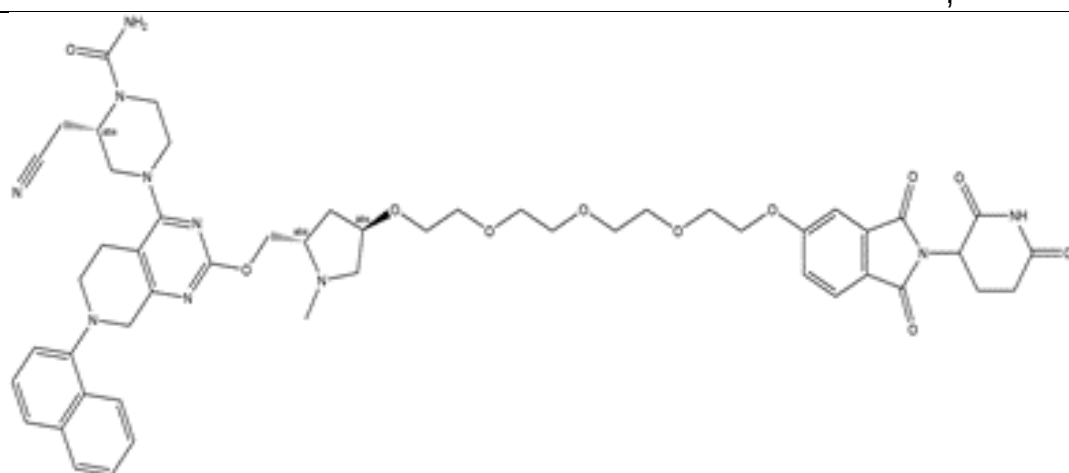
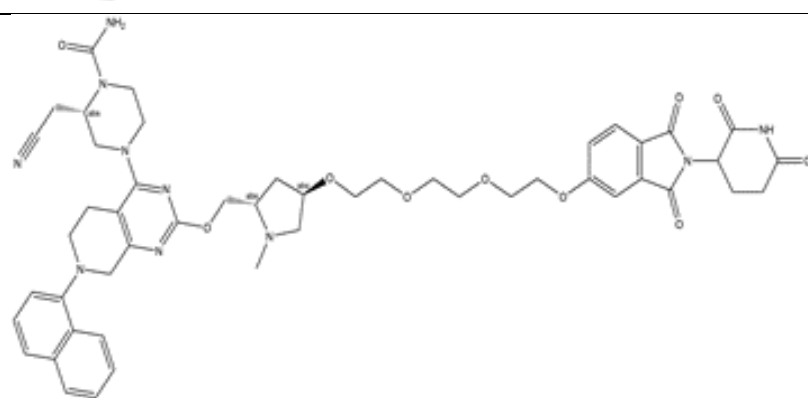
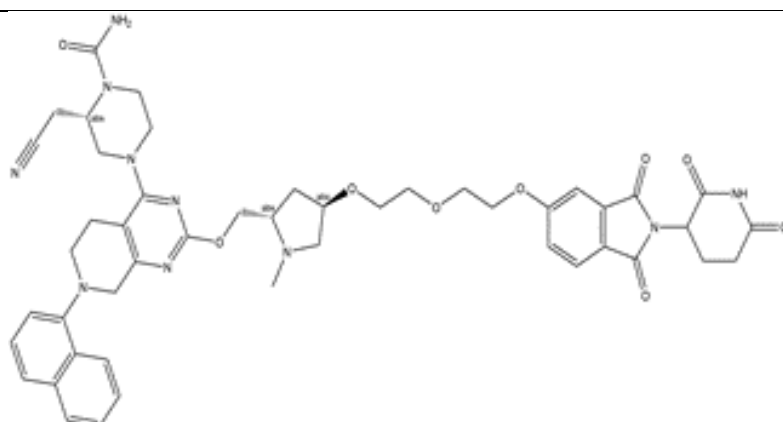
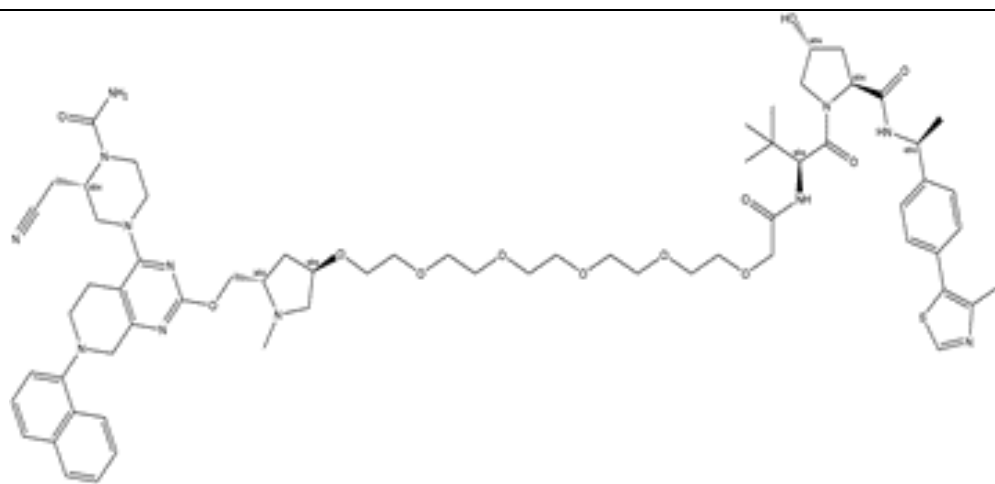
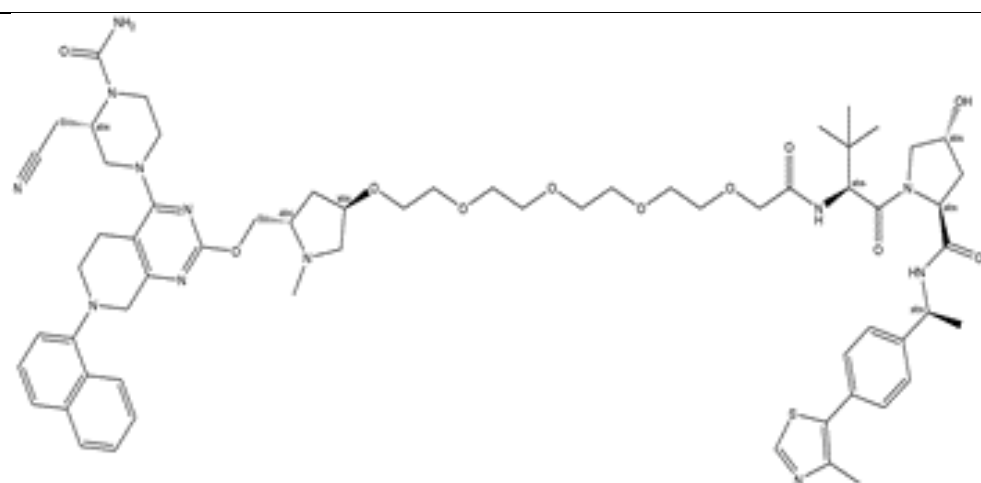
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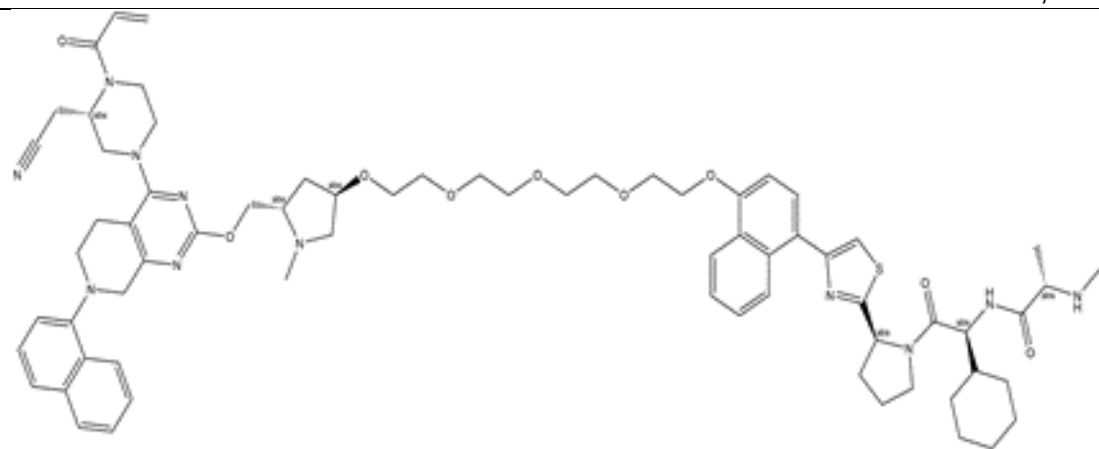
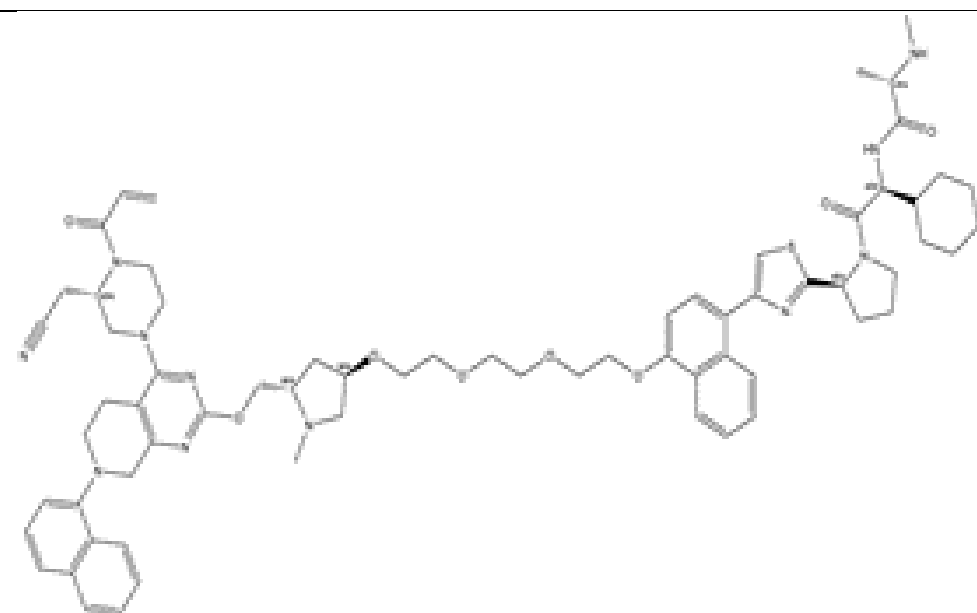
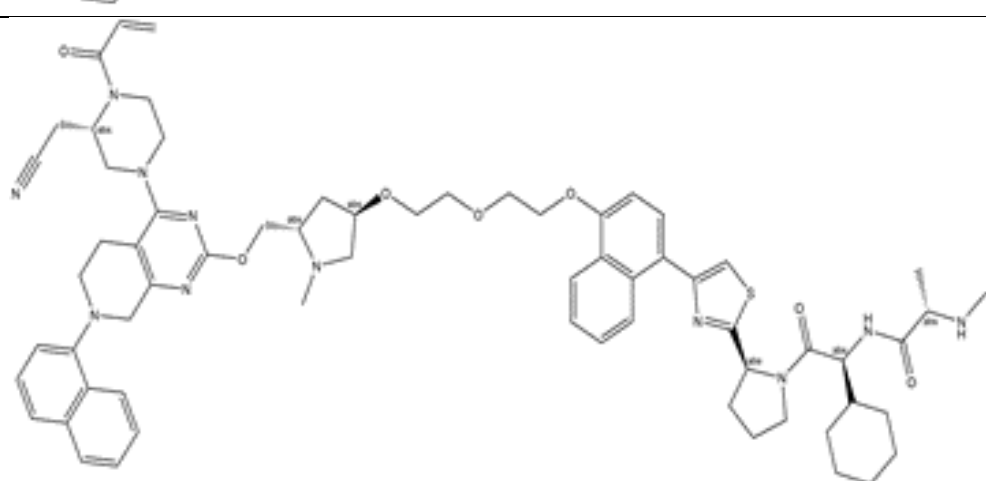
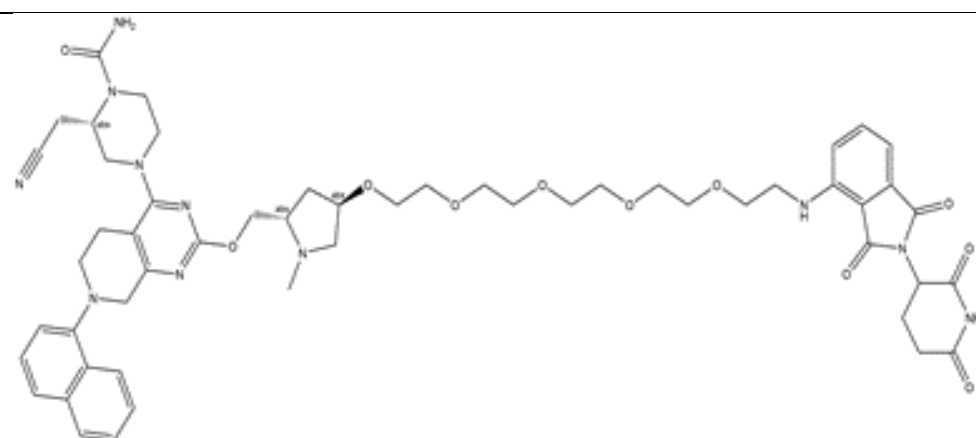


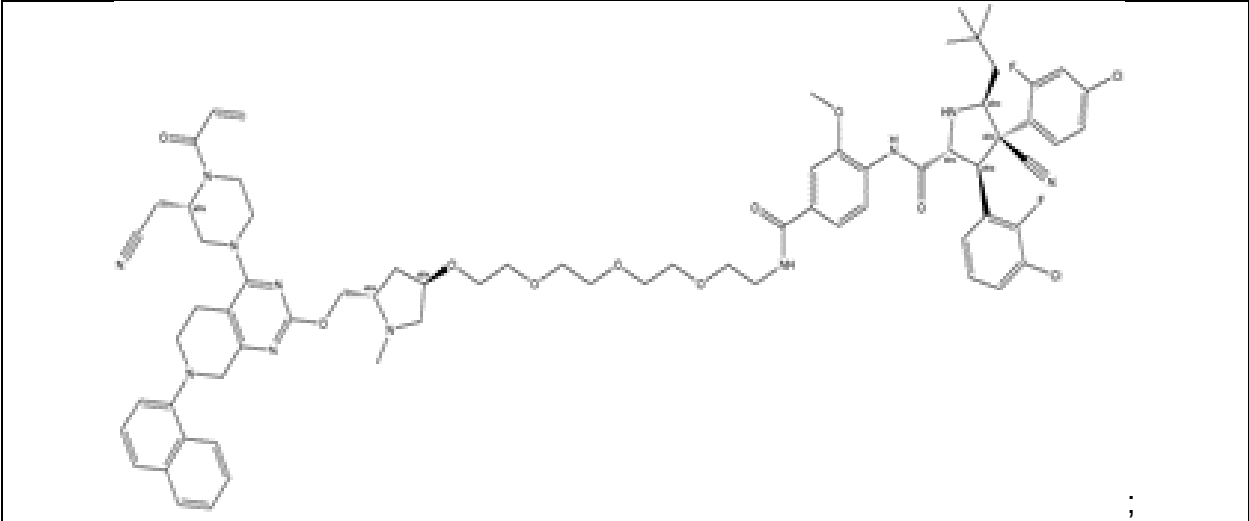
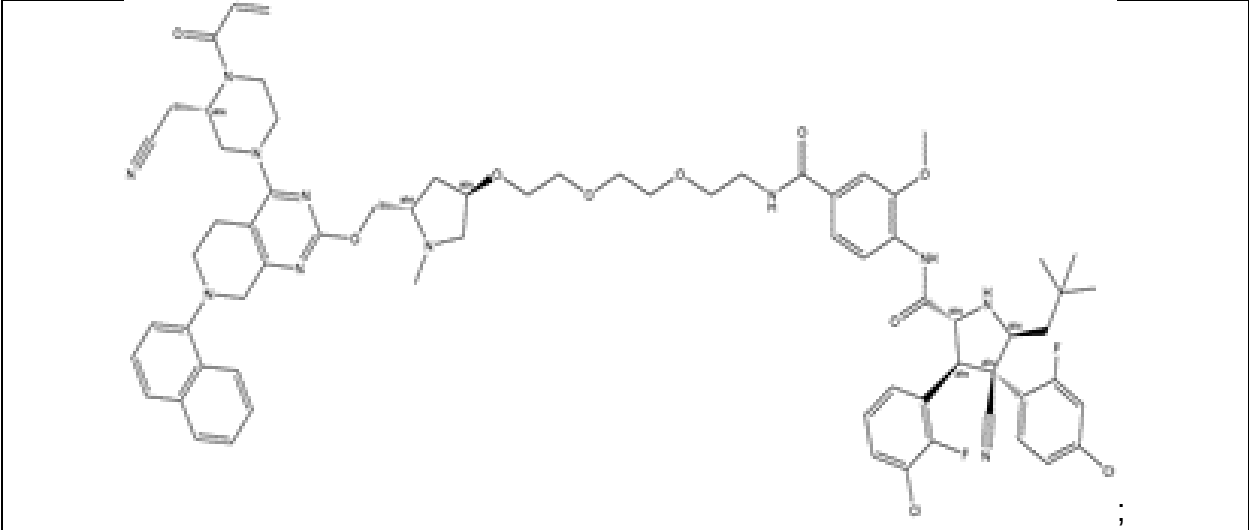
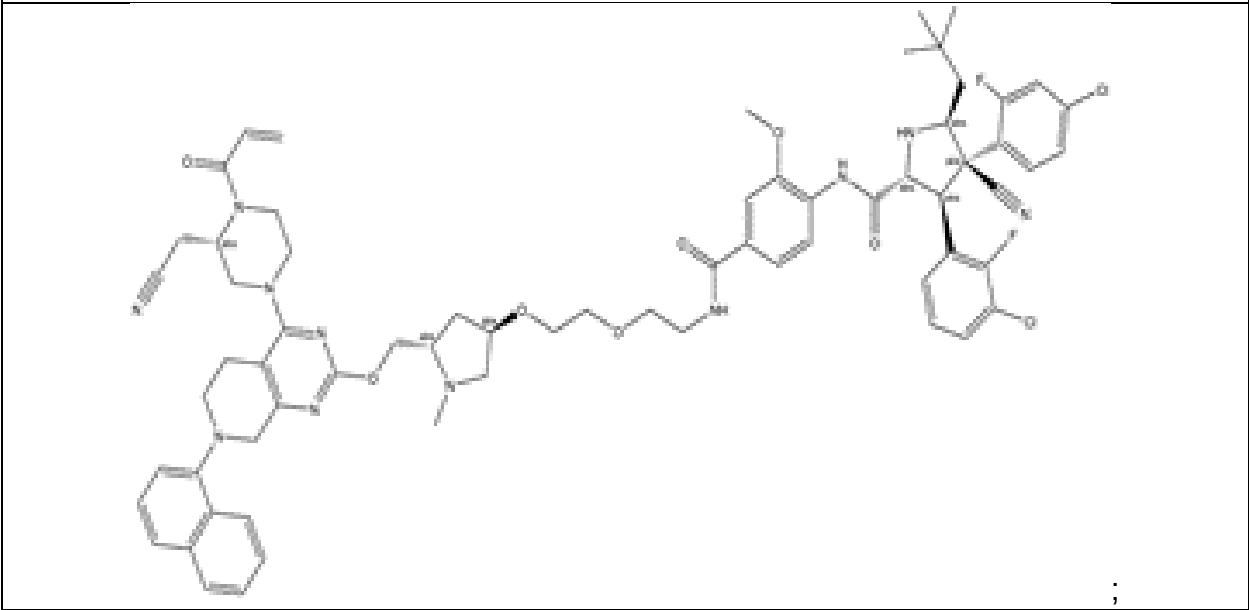
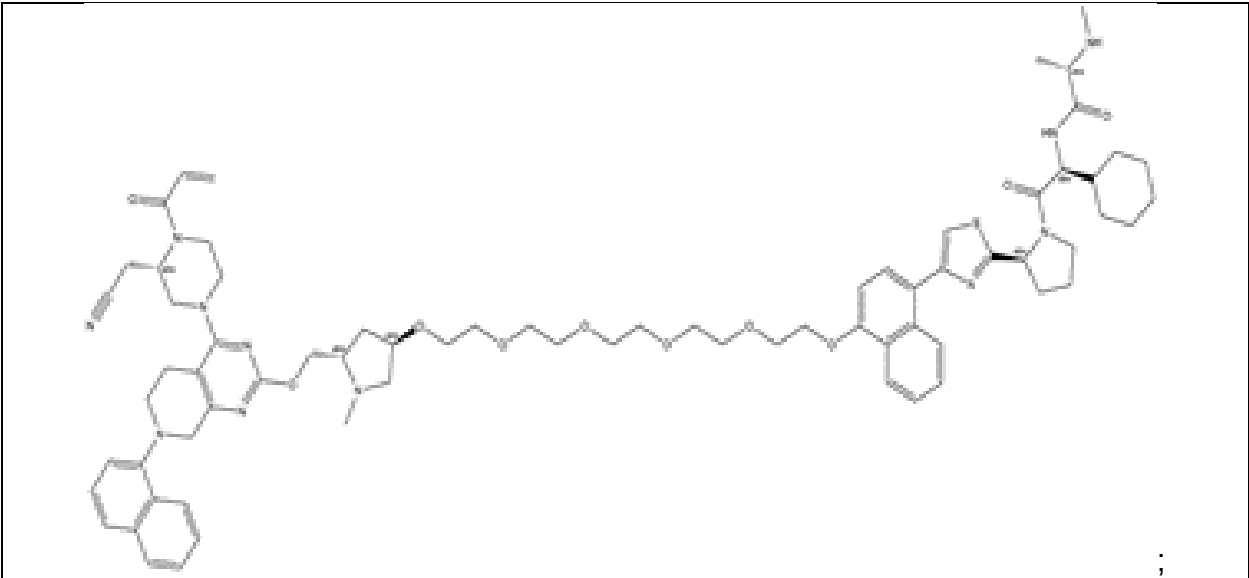
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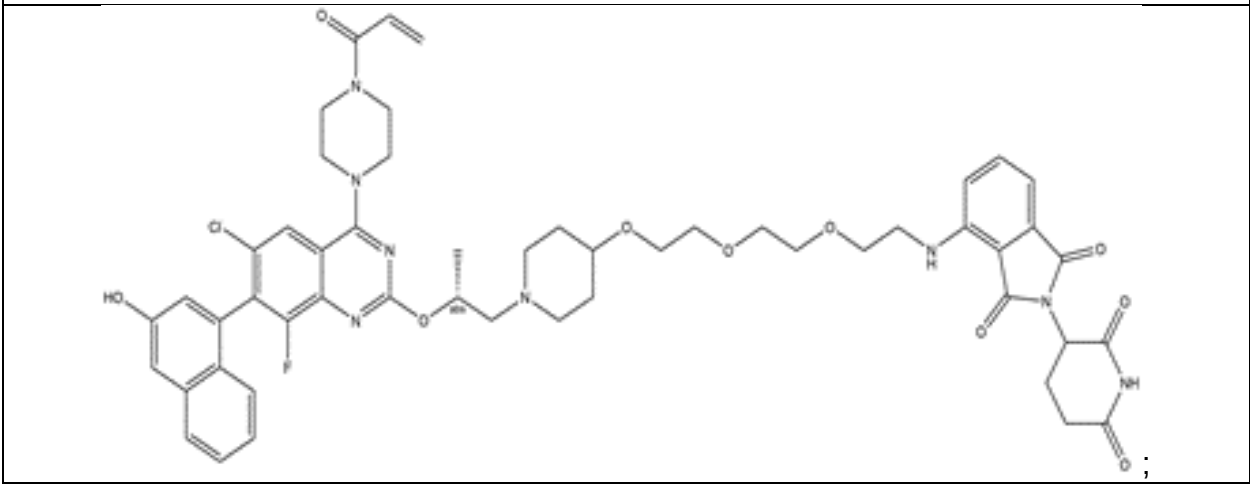
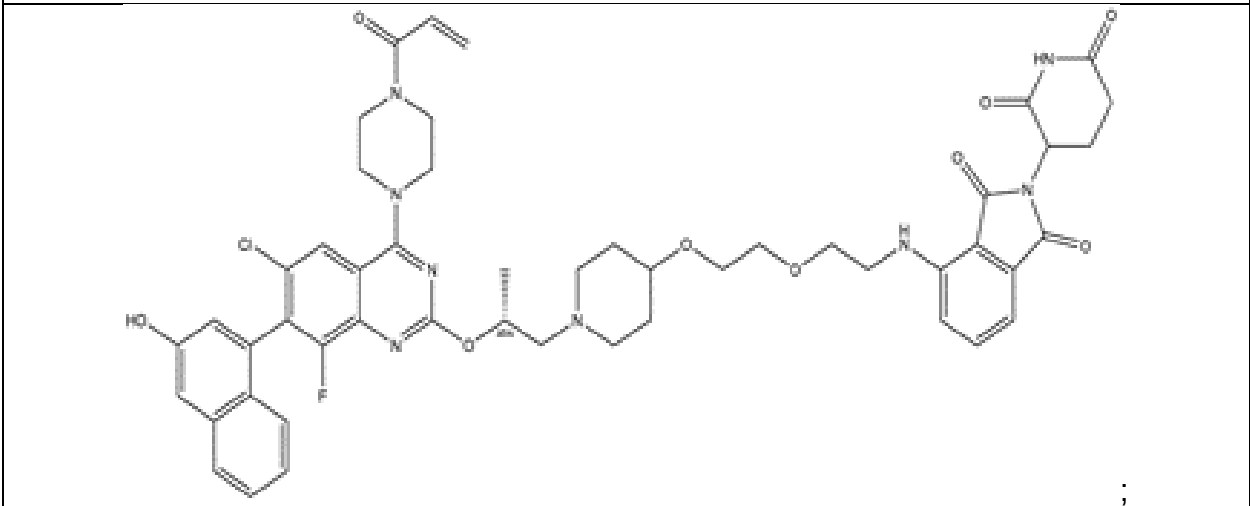
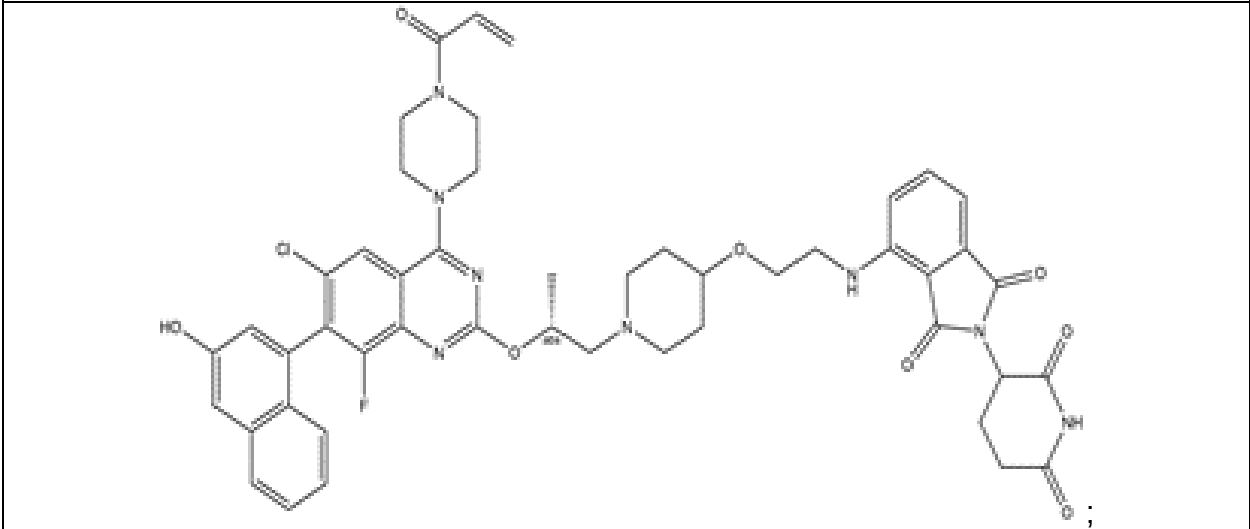
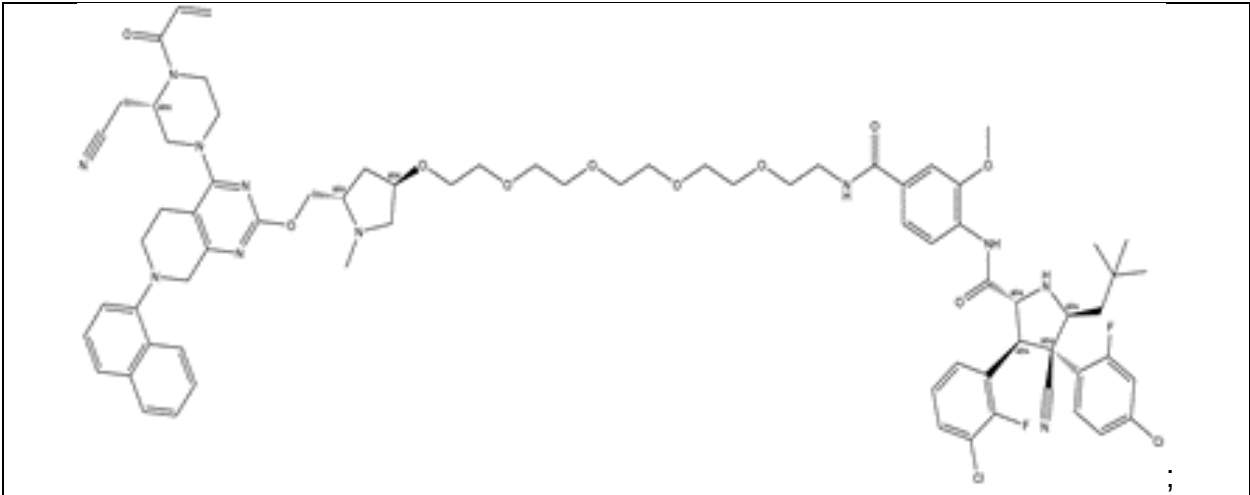


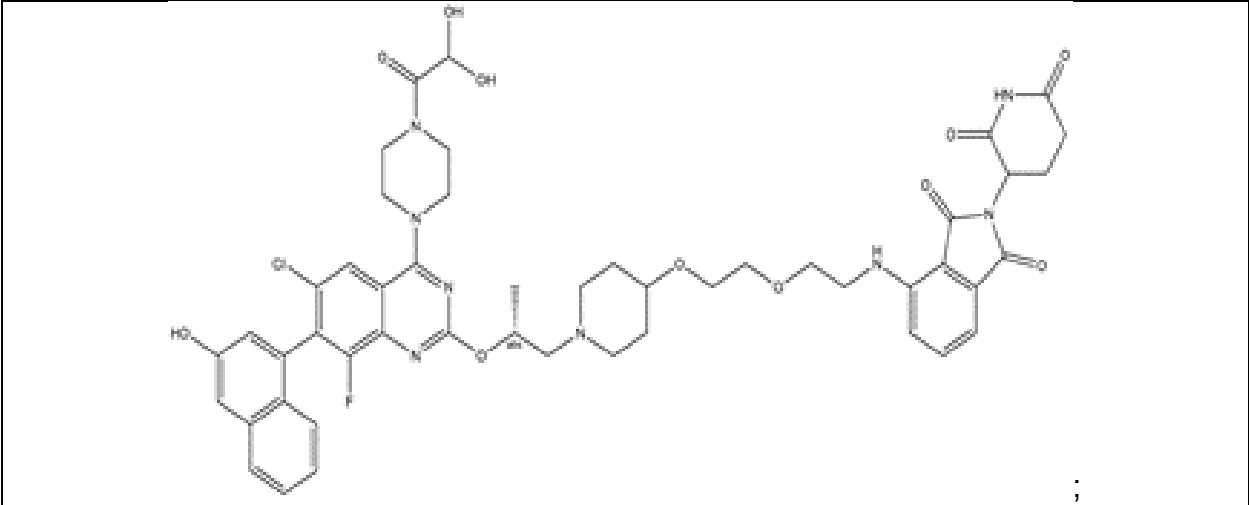
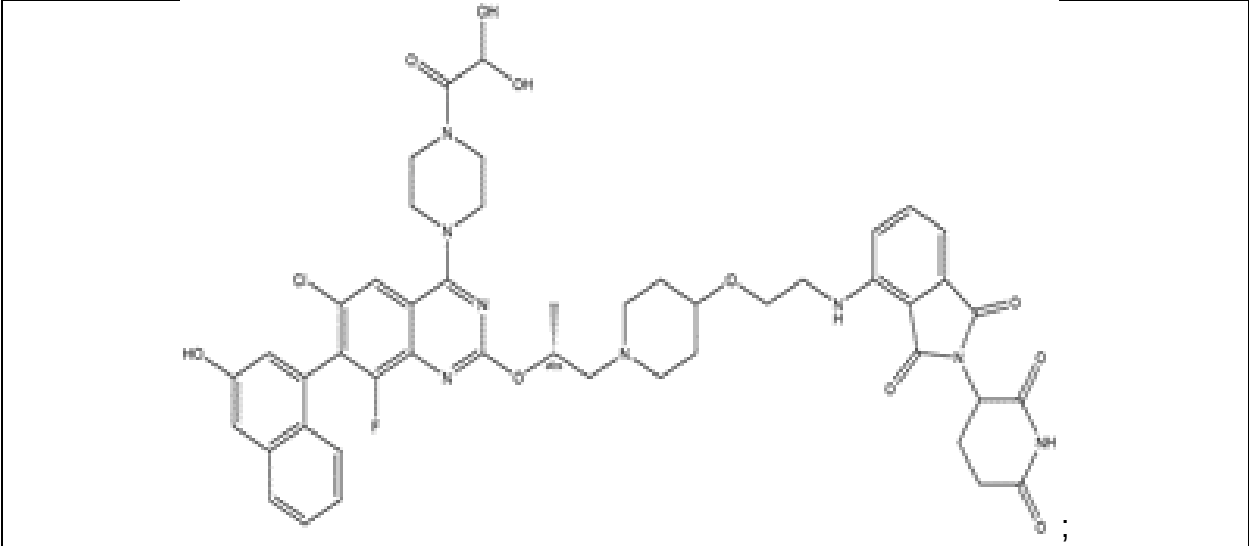
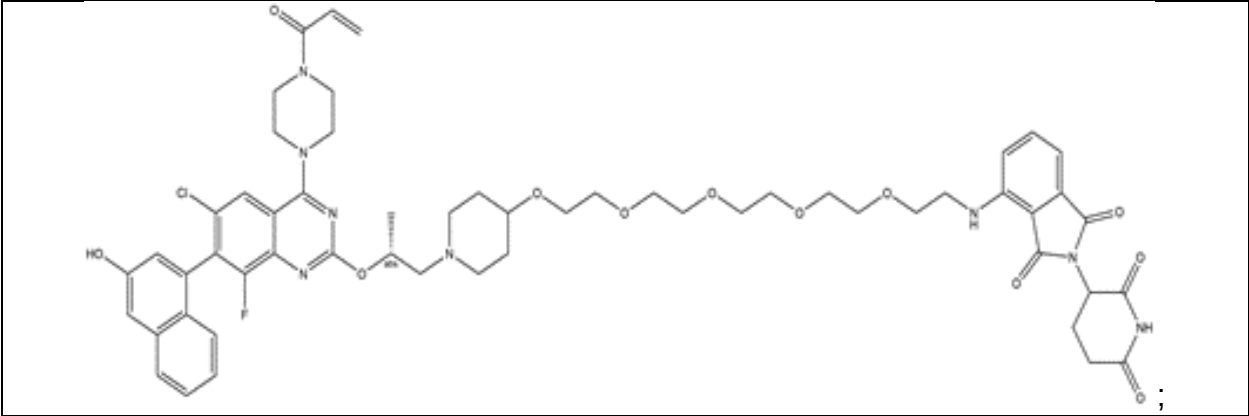
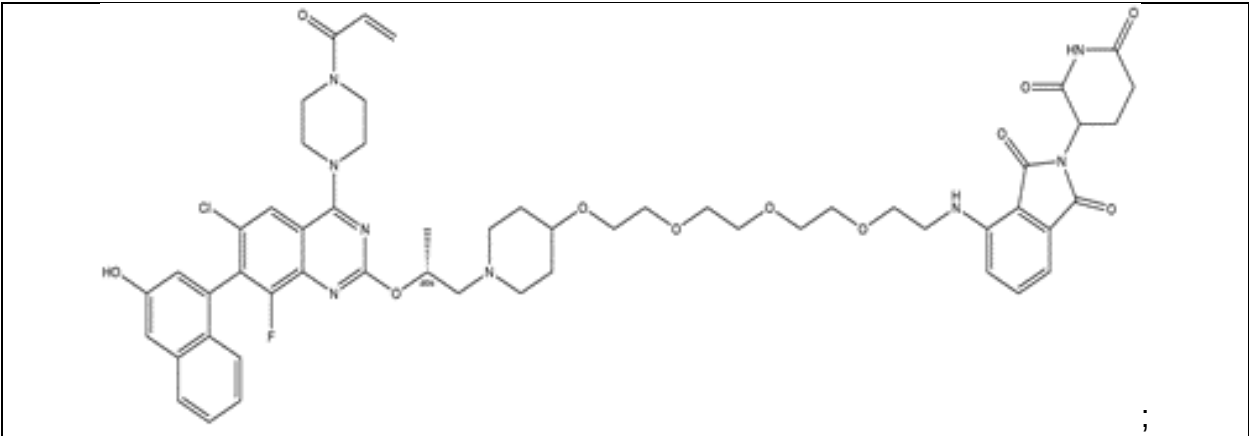


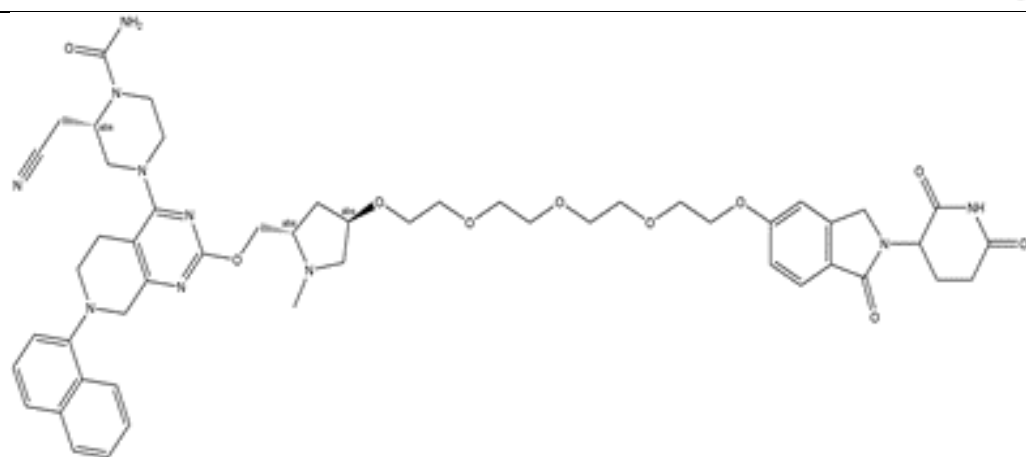
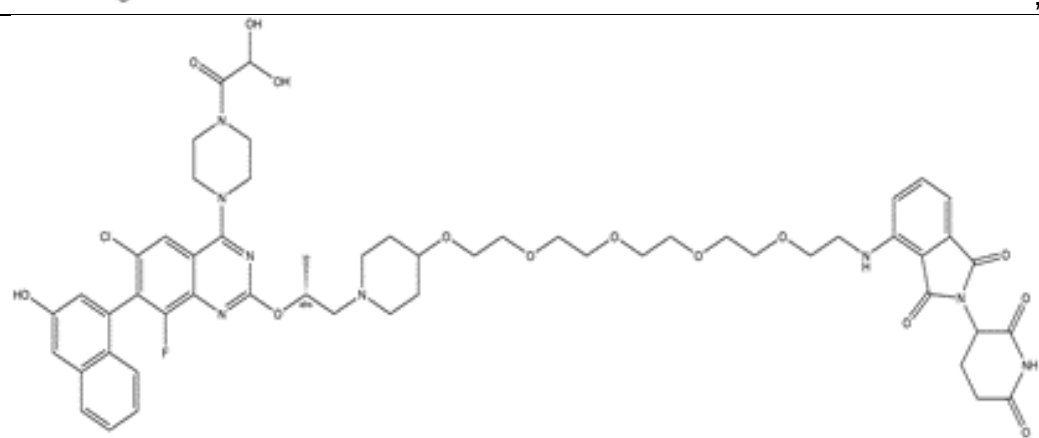
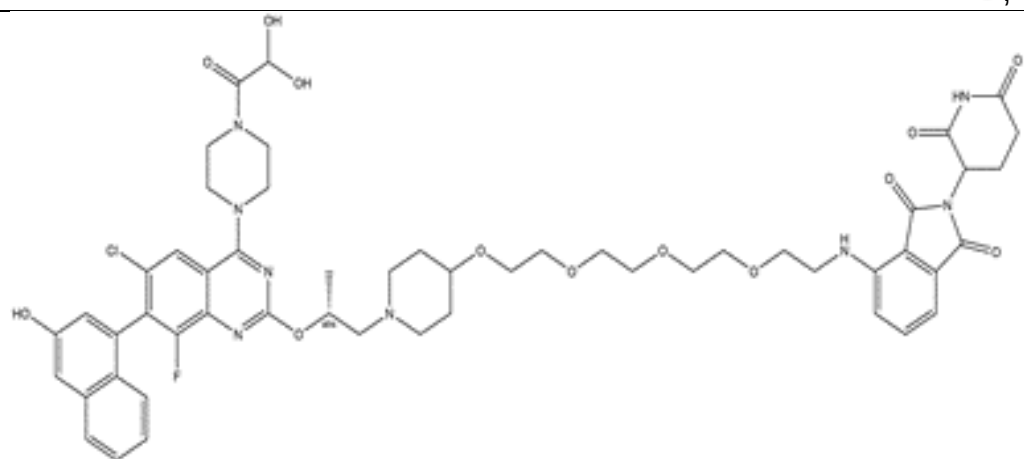
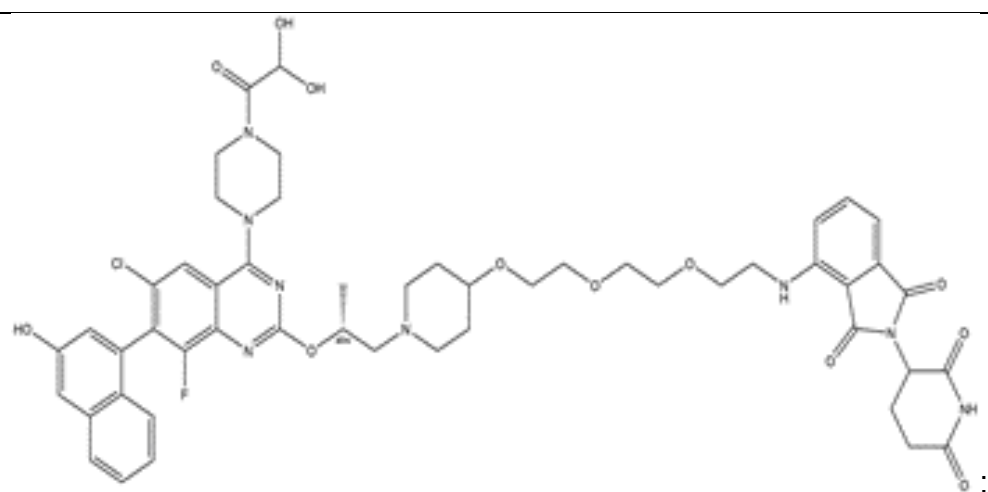


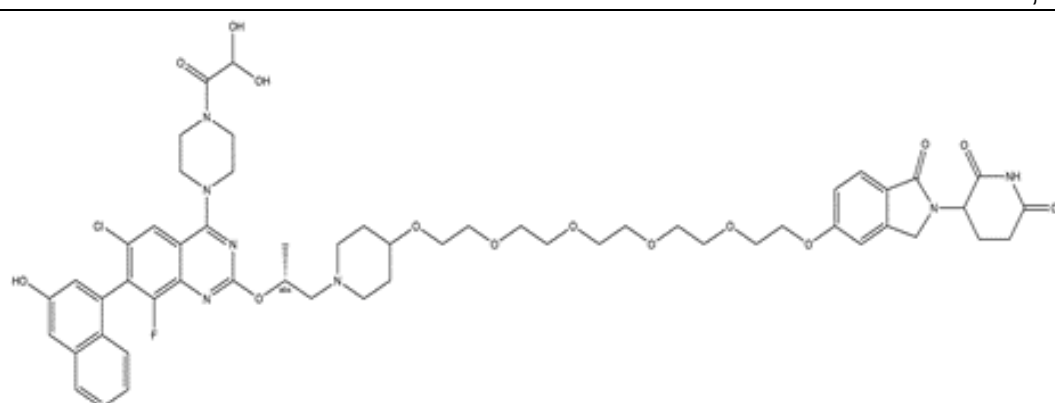
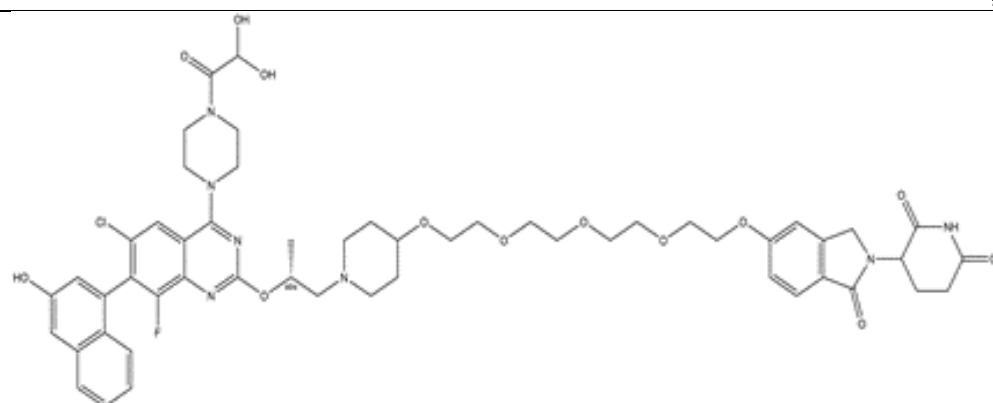
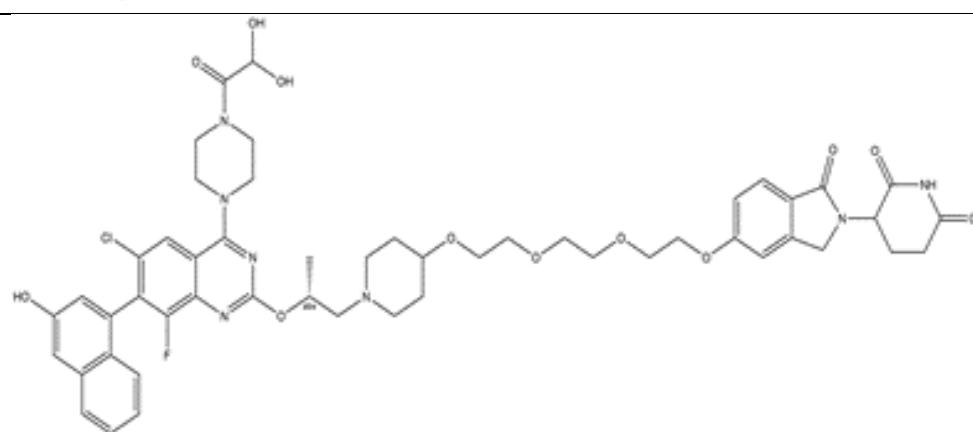
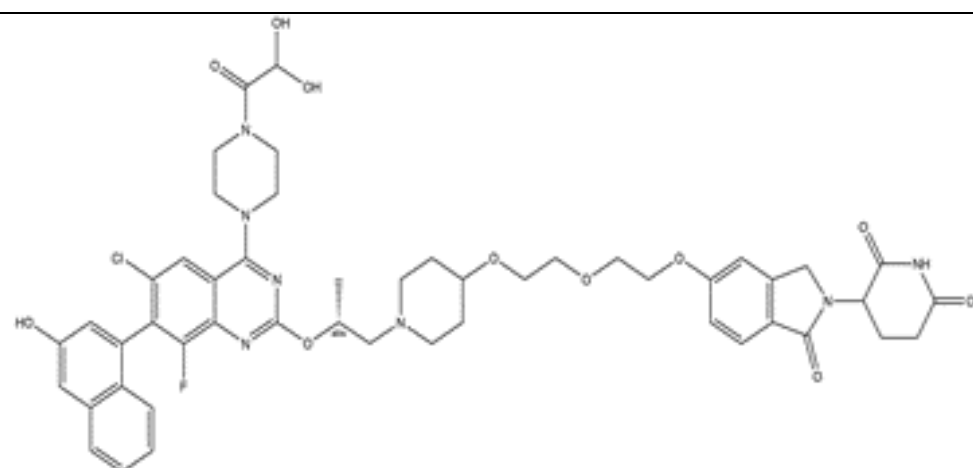
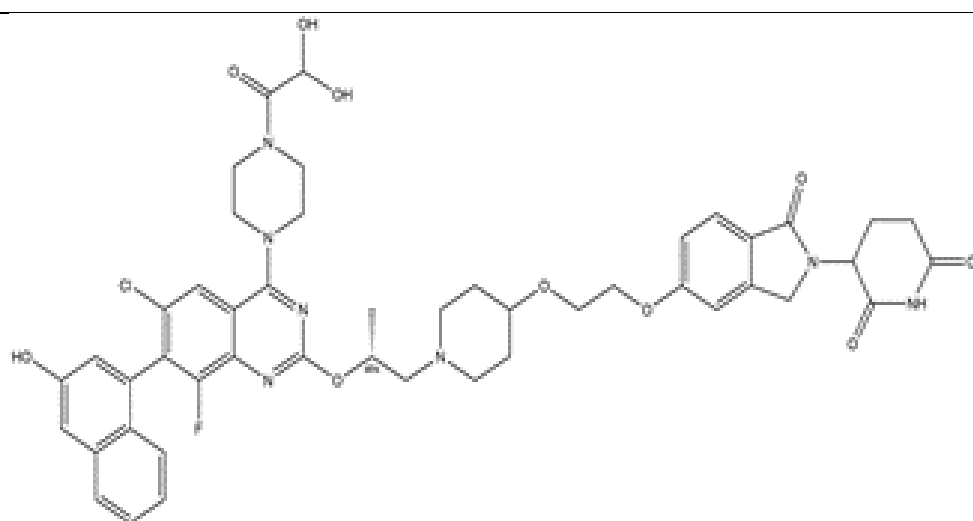


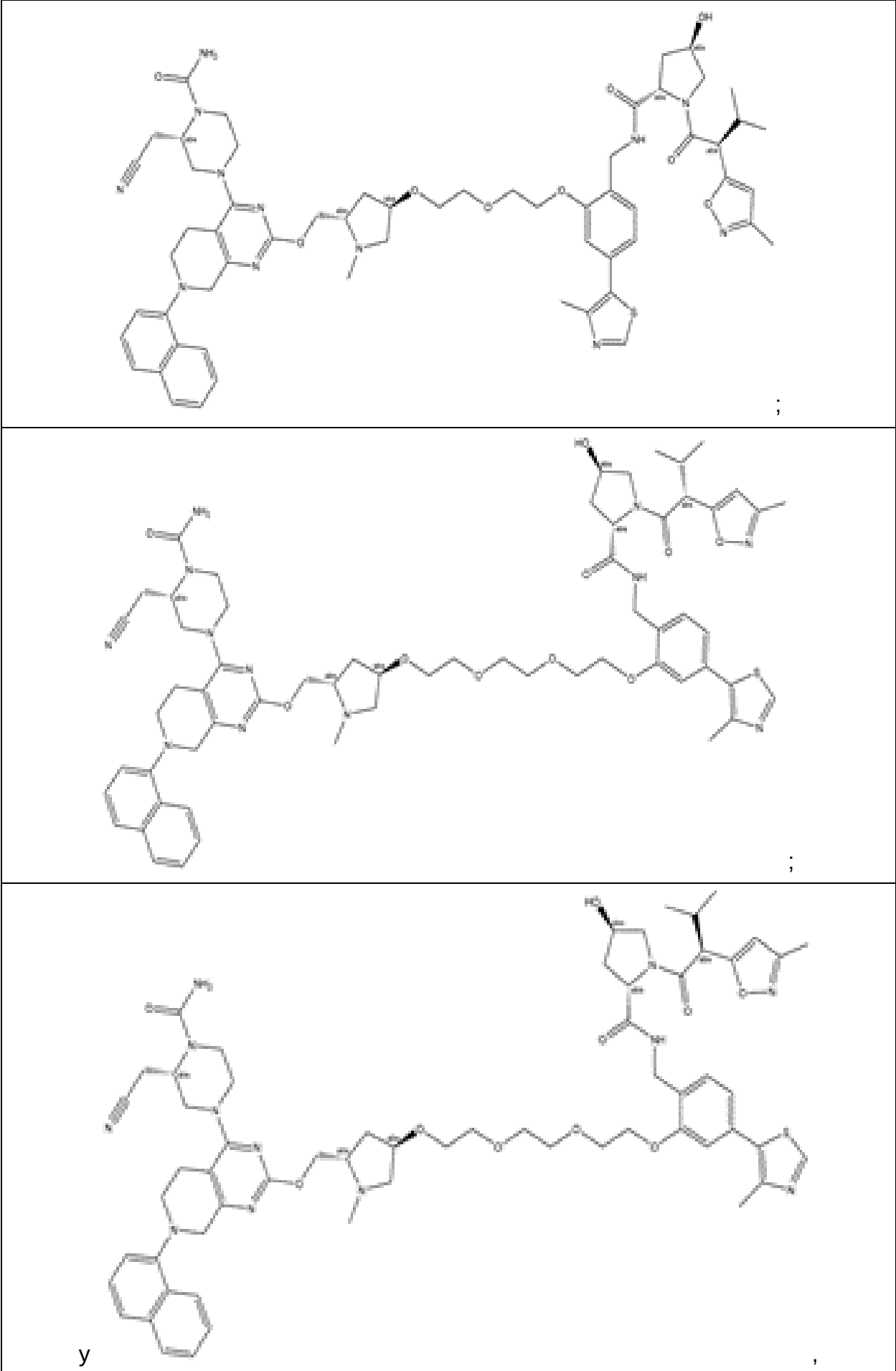












o una sal farmacéuticamente aceptable de este.

13. Una composición farmacéutica que comprende un compuesto bifuncional de cualquiera de las reivindicaciones 1 a 3, y 5 a 12 y un portador farmacéuticamente aceptable.
14. La composición farmacéutica de la reivindicación 13, donde la composición comprende además un agente bioactivo adicional.

15. La composición farmacéutica de la reivindicación 14, en donde el agente bioactivo adicional es un agente contra el cáncer.

16. La composición farmacéutica de la reivindicación 15, en donde el agente contra el cáncer es un inhibidor de receptores del factor de crecimiento epidérmico.