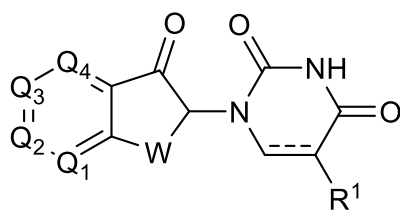
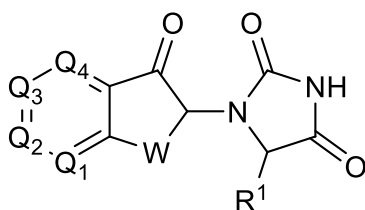


REIVINDICACIONES (con marcas de corrección)

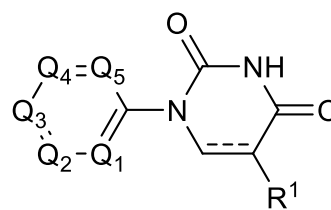
1. ~~Un compuesto de unión a la ligasa de ubiquitina E3 cereblon que tiene una estructura química seleccionada de:~~



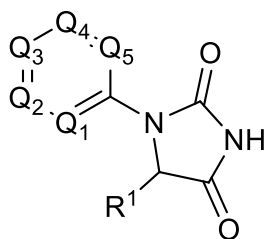
(a)



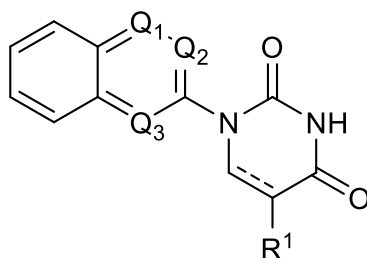
(b)



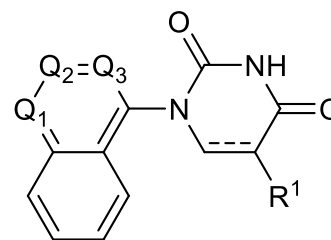
(c)



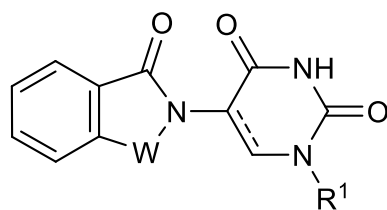
(d)



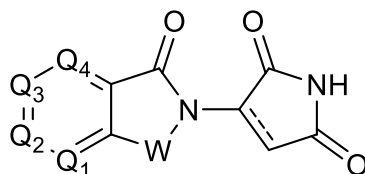
(e)



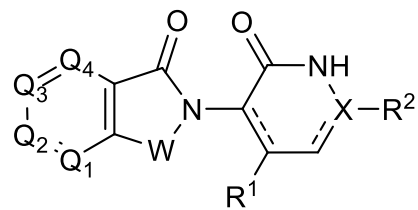
(f)



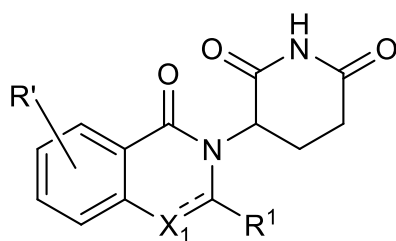
(g)



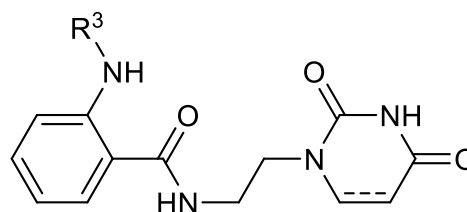
(h)



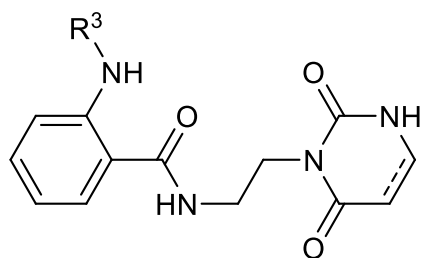
(i)



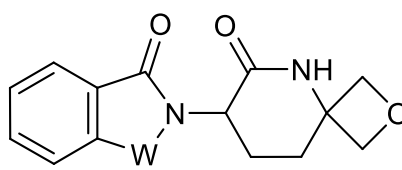
(j)



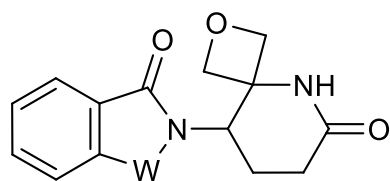
(k)



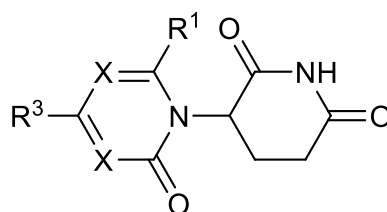
(l)



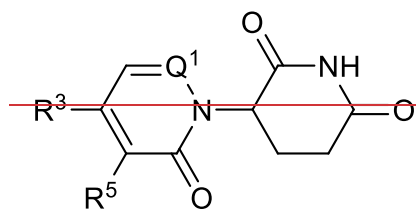
(m)



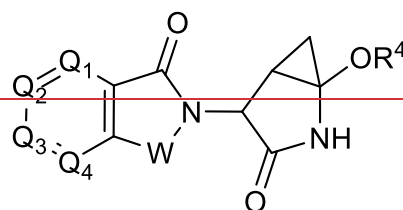
(n)



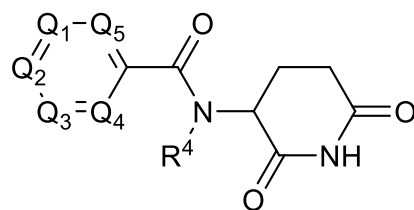
(o)



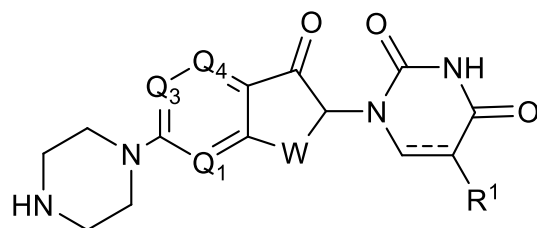
(p)



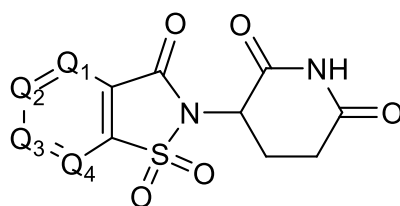
(q)



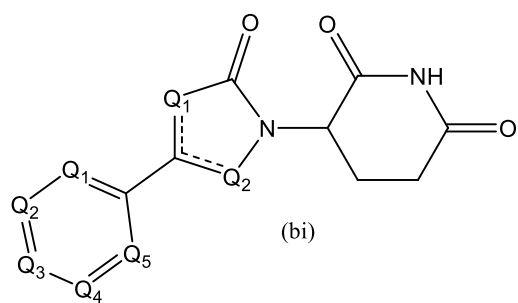
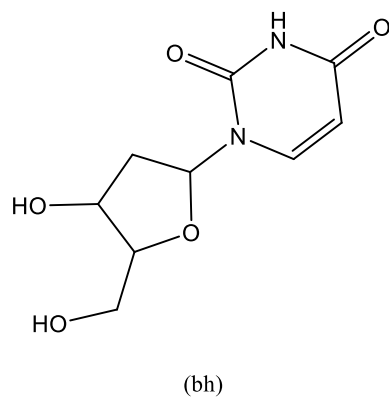
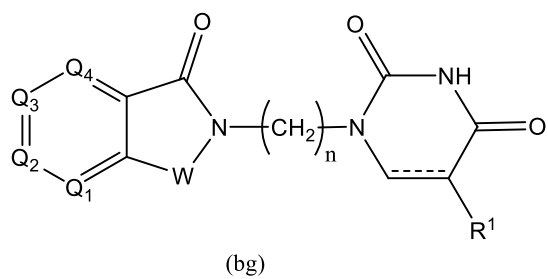
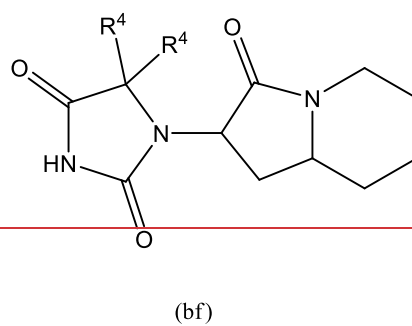
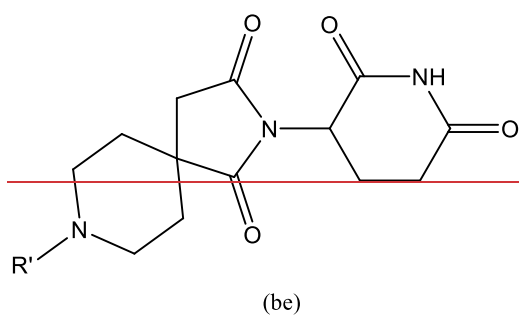
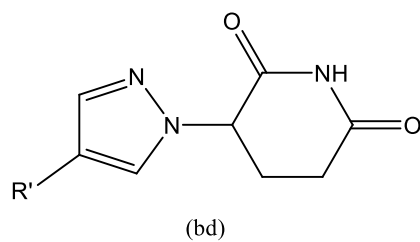
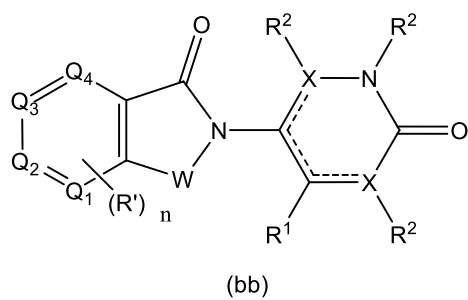
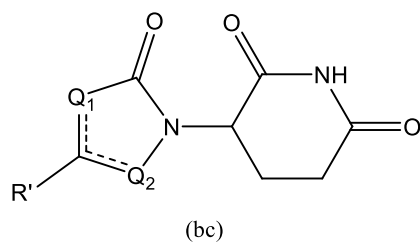
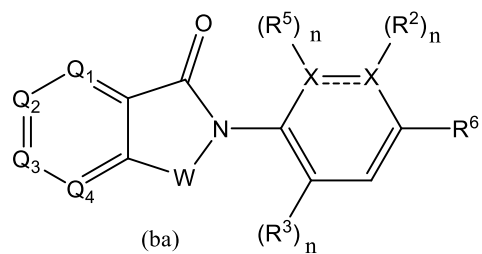
(r)

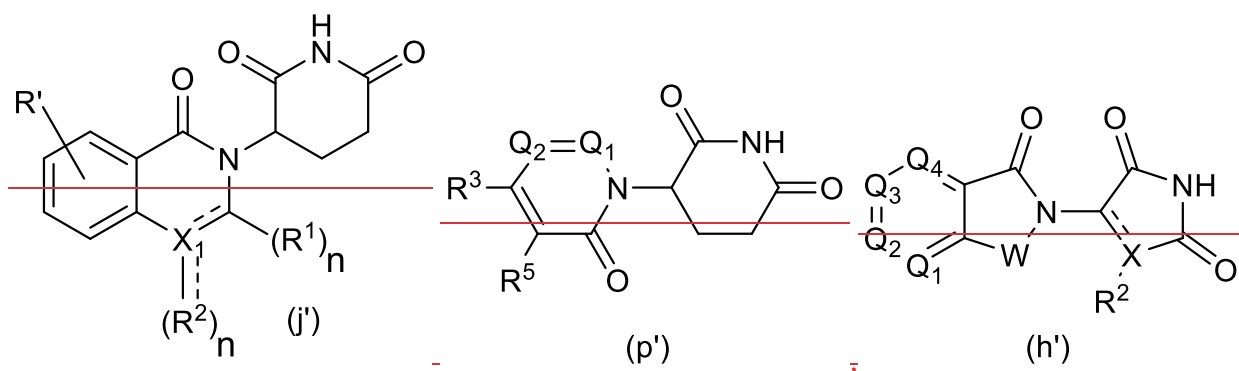


(s)



(t)





en donde:

~~W se selecciona independientemente de CH₂, CHR, C=O, SO₂, NH, y N alquilo;~~

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

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

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

~~R³ se selecciona de ausente, H, alquilo (por ejemplo, C1-C6 o C1-C3 alquilo), alquilo sustituido (por ejemplo, C1-C6 o C1-C3 alquilo sustituido), alcoxi (por ejemplo, C1-C6 o C1-C3 alcoxilo), alcoxi sustituido (por ejemplo, C1-C6 o C1-C3 alcoxilo sustituido);~~

~~R⁴ se selecciona de H, alquilo, alquilo sustituido;~~

~~R⁵ y R⁶ son cada uno independientemente H, halógeno, C(=O)R', CN, OH, CF₃;~~

~~X es C, CH, C=O, o N;~~

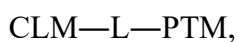
~~X₁ es C=O, N, CH, o CH₂;~~

~~R' se selecciona de H, halógeno, amina, alquilo (por ejemplo, C1-C3 alquilo), alquilo sustituido (por ejemplo, C1-C3 alquilo sustituido), alcoxi (por ejemplo, C1-C3 alcoxilo), alcoxi sustituido (por ejemplo, C1-C3 alcoxilo sustituido), NR²R³, C(=O)OR², fenilo opcionalmente sustituido;~~

~~n es 0-4; y~~

~~/ es un enlace simple o doble.~~

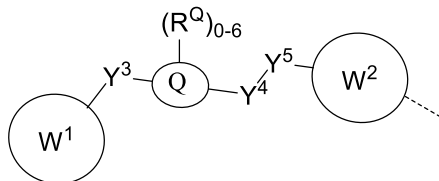
12. Un compuesto bifuncional que tiene la estructura química:



o una de sus sales, enantiómeros, o estereoisómeros, ~~solvatos, polimorfos o profármacos~~ aceptables farmacéuticamente,

en donde:

(a) la PTM es una porción de unión (ABM) al receptor de andrógenos (AR) que comprende



la estructura ;

en donde:

W¹ es arilo, heteroarilo, bicíclico, o biheterocíclico, cada uno independientemente sustituido con 1 o más H, halo, hidroxilo, nitro, CN, C≡CH, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), C₁₋₆ alcoxilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo), C₂₋₆ alquenilo, C₂₋₆ alquinilo, o CF₃;

Y³, Y⁴, Y⁵ son cada uno independientemente un enlace, O, NR^{Y2}, CR^{Y1}R^{Y2}, C=O, C=S, SO, SO₂, heteroarilo o arilo;

Q es un anillo de 3-6 miembros con 0-4 heteroátomos, opcionalmente sustituido con 0-6 R^Q, en donde cada R^Q, es independientemente H, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido, por ejemplo, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), halógeno, o C₁₋₆ alcoxi, o 2 grupos R^Q tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos);

R^{Y1}, R^{Y2} son cada uno independientemente H, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), halógeno, C₁₋₆ alcoxi, cíclico, o heterocíclico;

W² es un enlace, C₁₋₆ alquilo, C₁₋₆ heteroalquilo, O, arilo, heteroarilo, alicíclico, heterocíclico, biheterocíclico, biarilo, o biheteroarilo, cada uno opcionalmente sustituido con 1-10 R^{W2};

cada R^{W2} es independientemente H, halo, C₁₋₆ alquilo (lineal o ramificado opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más F), -OR^{W2A}, C₃₋₆ cicloalquilo, C₄₋₆ cicloheteroalquilo, C₁₋₆ alquilo (opcionalmente

sustituido), heterocíclico (opcionalmente sustituido), arilo (opcionalmente sustituido), o heteroarilo (opcionalmente sustituido), heteroarilo bicíclico, o arilo OC₁₋₃alquilo (opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más -F), OH, NH₂, NR^{Y1}R^{Y2}CN;

R^{W2A} es H, C₁₋₆ alquilo (lineal, ramificado), o C₁₋₆ heteroalquilo (lineal, ramificado), cada uno opcionalmente sustituido con un cicloalquilo, cicloheteroalquilo, arilo, heterocíclico, heteroarilo, halo, u OC₁₋₃alquilo; y

la línea discontinua indica el sitio de unión del enlazador;

una molécula pequeña que comprende una porción de direccionamiento a proteína;

(b) el L es ~~un enlace o~~ una porción de enlace químico que une covalentemente la CLM y la PTM, y comprende una unidad estructural química representada por la Fórmula -(A^L)_q- en donde:

(A^L)_q se conecta a la CLM y la PTM;

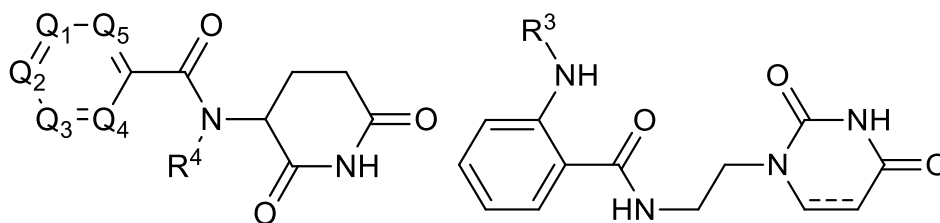
q es un número mayor que o igual a 1;

cada A^L se selecciona independientemente 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}, C₃₋₁₁cicloalquilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, C₃₋₁₁heterociclilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, arilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, heteroarilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, donde R^{L1} o R^{L2}, cada uno independientemente se unen opcionalmente a otros grupos para formar porciones 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 independientemente, H, halo, C₁₋₈ alquilo, OC₁₋₈alquilo, SC₁₋₈alquilo, NHC₁₋₈alquilo, N(C₁₋₈alquilo)₂, C₃₋₁₁cicloalquilo, arilo, heteroarilo, C₃₋₁₁heterociclilo, OC₁₋₈cicloalquilo, SC₁₋₈cicloalquilo, NHC₁₋₈cicloalquilo, N(C₁₋₈cicloalquilo)₂, N(C₁₋₈cicloalquilo)(C₁₋₈alquilo), OH, NH₂, SH, SO₂C₁₋₈alquilo, P(O)(OC₁₋₈alquilo)(C₁₋₈alquilo), P(O)(OC₁₋₈alquilo)₂, CC-C₁₋₈alquilo, CCH, CH=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=C(C₁₋₈alquilo)₂, Si(OH)₃, Si(C₁₋₈alquilo)₃, Si(OH)(C₁₋₈alquilo)₂, COC₁₋₈alquilo, CO₂H, halógeno, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO₂NHC₁₋₈alquilo, SO₂N(C₁₋₈alquilo)₂, SONHC₁₋₈alquilo, SON(C₁₋₈alquilo)₂,

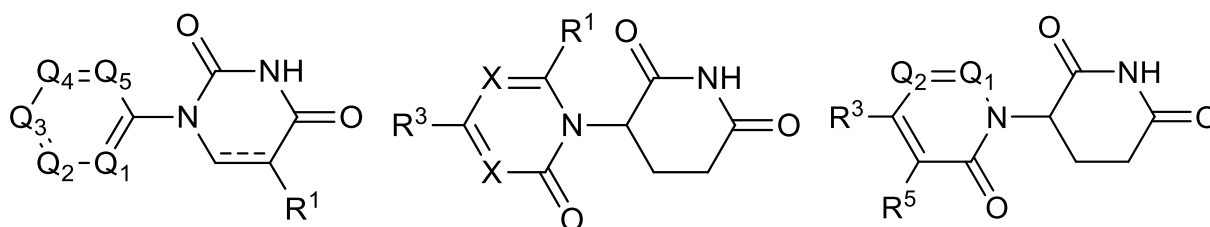
CONHC₁₋₈alquilo, CON(C₁₋₈alquilo)₂, N(C₁₋₈alquilo)CONH(C₁₋₈alquilo), N(C₁₋₈alquilo)CON(C₁₋₈alquilo)₂, NHCONH(C₁₋₈alquilo), NHCON(C₁₋₈alquilo)₂, NHCONH₂, N(C₁₋₈alquilo)SO₂NH(C₁₋₈alquilo), N(C₁₋₈alquilo) SO₂N(C₁₋₈alquilo)₂, NH SO₂NH(C₁₋₈alquilo), NH SO₂N(C₁₋₈alquilo)₂, NH SO₂NH₂; y

(c) la CLM es una porción de unión a la ligasa de ubiquitinaE3 cereblon de molécula pequeña que se une o se dirige a una ligasa de ubiquitina E3 cereblon y tiene una estructura química seleccionada del grupo que consiste en:



(r)

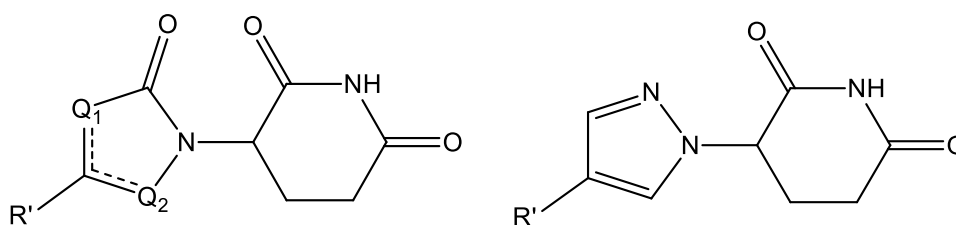
(k)



(c)

(o)

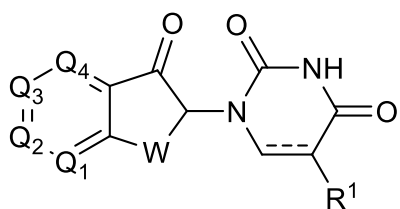
(p')



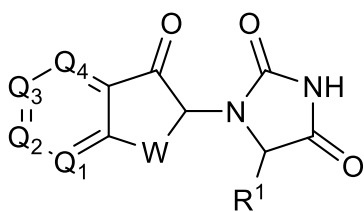
(bc)

(bd)

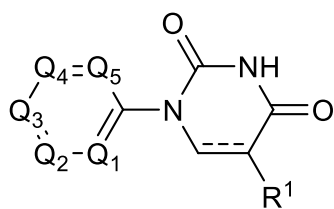
, y



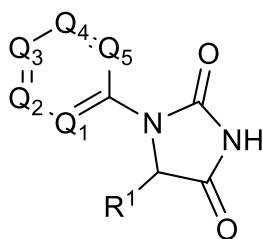
(a)



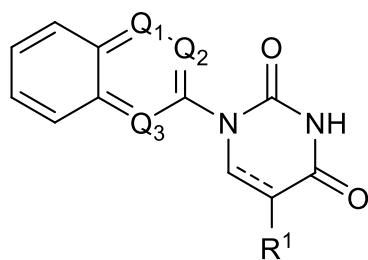
(b)



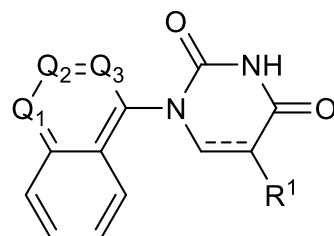
(c)



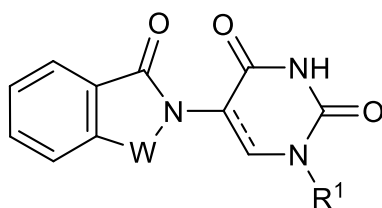
(d)



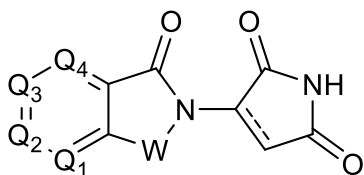
(e)



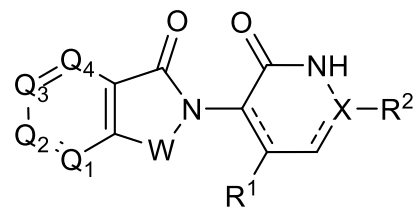
(f)



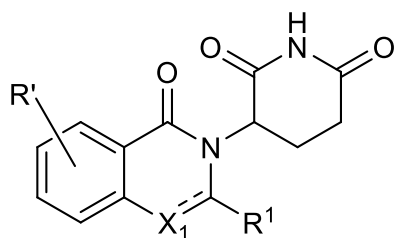
(g)



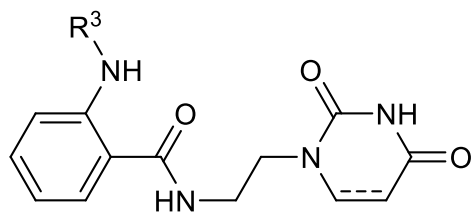
(h)



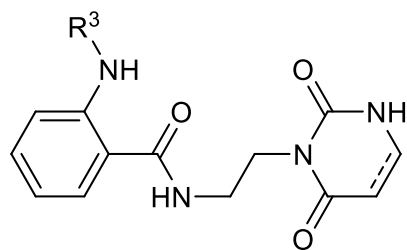
(i)



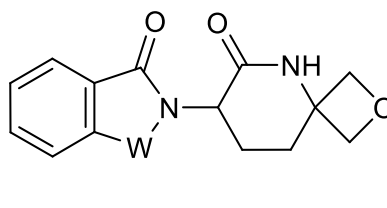
(j)



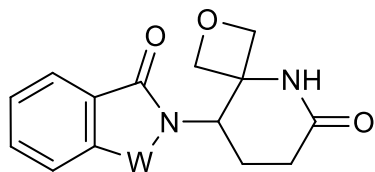
(k)



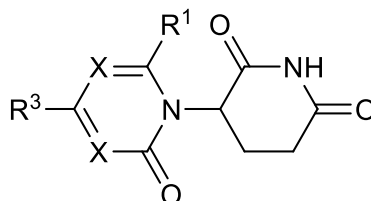
(l)



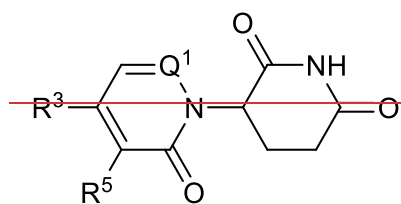
(m)



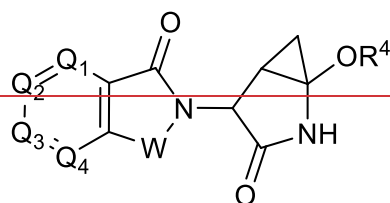
(n)



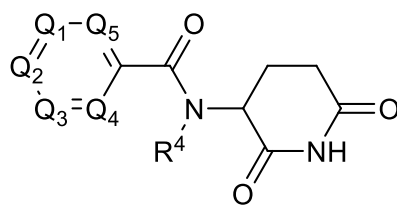
(o)



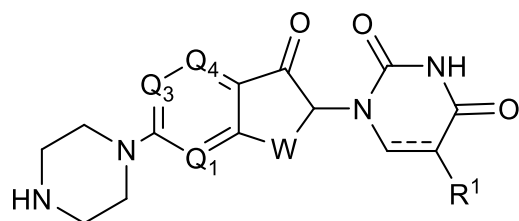
(p)



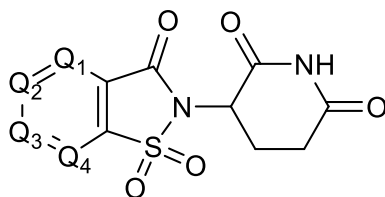
(q)



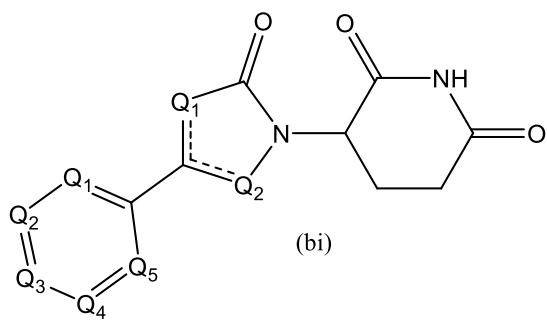
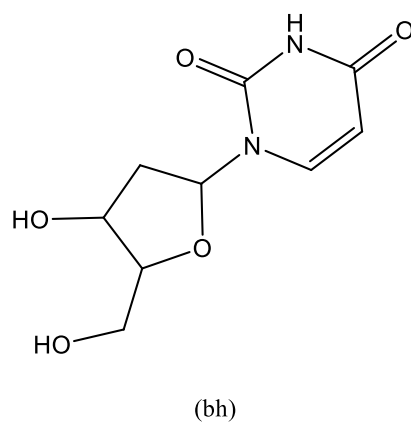
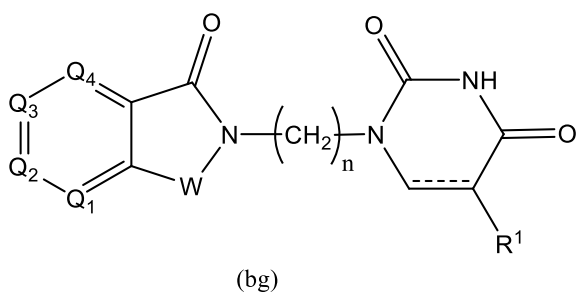
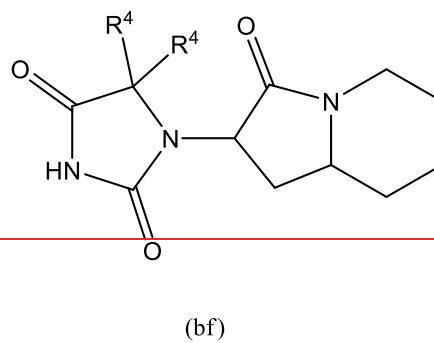
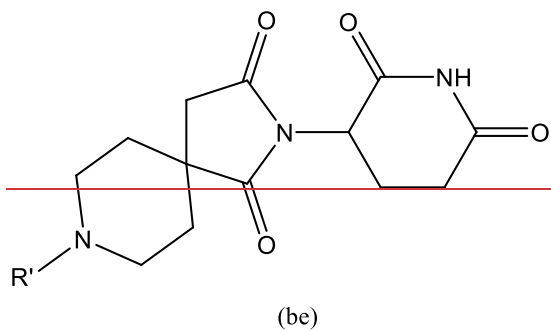
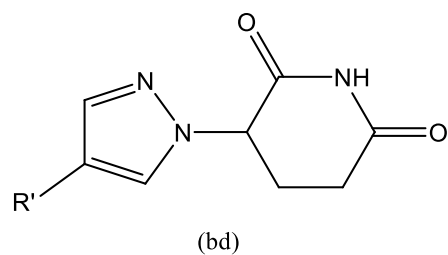
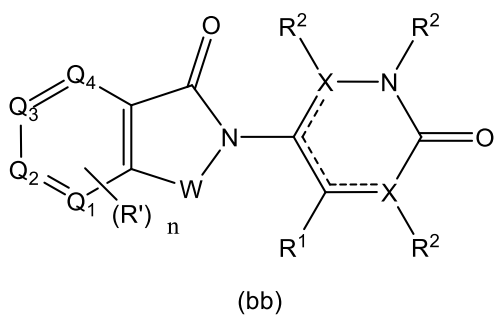
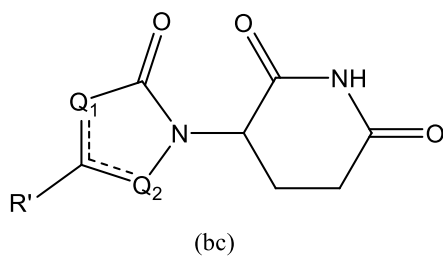
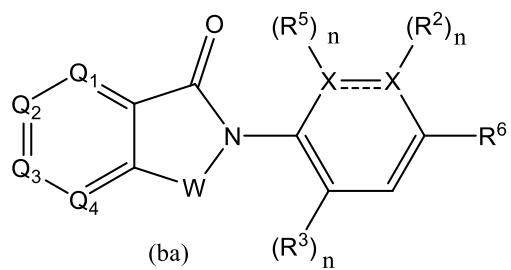
(r)

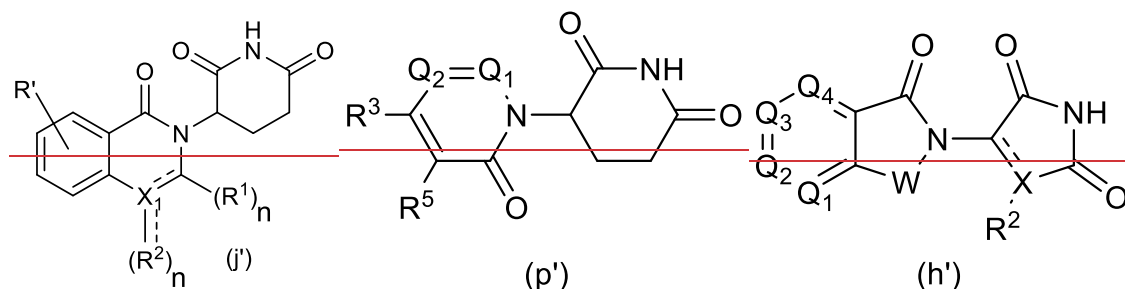


(s)



(t)





en donde:

~~W~~ se selecciona independientemente de CH_2 , CHR , $\text{C}=\text{O}$, SO_2 , NH , y N -alquilo;

Q_1 , Q_2 , Q_3 , Q_4 , Q_5 representan cada uno independientemente un ~~carbono~~-C o N sustituido con un grupo seleccionado independientemente de R' , N o N-óxido;

R^1 ~~se selecciona de~~ ausente, H, OH, CN, C1-C3 alquilo, C $\text{C}=\text{O}$;

R^2 ~~se selecciona del grupo~~ ausente, H, OH, CN, C1-3 alquilo, CHF_2 , CF_3 , CHO, $\text{C}(=\text{O})\text{NH}_2$;

R^3 ~~se selecciona de~~ ausente, H, alquilo (~~por ejemplo, preferiblemente un~~ C1-C6 o C1-C3 alquilo), alquilo sustituido (~~por ejemplo, preferiblemente~~ C1-C6 o C1-C3 alquilo sustituido), alcoxi (~~por ejemplo, preferiblemente un~~ C1-C6 o C1-C3 alcoxilo), alcoxi sustituido (por ejemplo, C1-C6 o C1-C3 alcoxilo sustituido);

R^4 se selecciona de H, alquilo, alquilo sustituido;

R^5 ~~y R^6 son cada uno independientemente~~ H, halógeno, $\text{C}(=\text{O})\text{R}'$; CN, OH, C CF_3 ;

X es C, CH, $\text{C}=\text{O}$, o N;

~~X_1 es $\text{C}=\text{O}$, N, CH, o CH_2 ;~~

R' se selecciona de H, halógeno, amina, alquilo (~~por ejemplo, preferiblemente~~ C1-C3 alquilo), alquilo sustituido (~~por ejemplo, preferiblemente un~~ C1-C3 alquilo sustituido), alcoxi (~~preferiblemente un~~ ~~por ejemplo,~~ C1-C3 alcoxilo), alcoxi sustituido (~~preferiblemente un~~ ~~por ejemplo,~~ C1-C3 alcoxilo sustituido), NR^2R^3 , $\text{C}(=\text{O})\text{OR}^2$, fenilo opcionalmente sustituido;

~~n es 0-4~~; y

// es un enlace simple o doble.

32. El compuesto bifuncional de conformidad con la reivindicación **21**, en donde la CLM se une ~~a la PTM~~, al grupo enlazador químico (L), ~~o una combinación de estos~~ a través de ~~W~~, X, R^1 , R^2 , R^3 , R^4 , R' , Q_1 , Q_2 , Q_3 , Q_4 , ~~y~~ C Q_5 .

~~43.~~ El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1 o 2 o 3, en donde: ~~la PTM es una porción que se une a Brd4, Proteína Tau, Receptor de Estrógenos (ER), o Receptor de Andrógenos (AR)~~

W¹ es arilo, o heteroarilo, cada uno independientemente sustituido con 1 o más H, halo, hidroxilo, nitro, CN, C≡CH, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), C₁₋₆ alcoxilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo), C₂₋₆ alqueno, C₂₋₆ alquino, o CF₃;

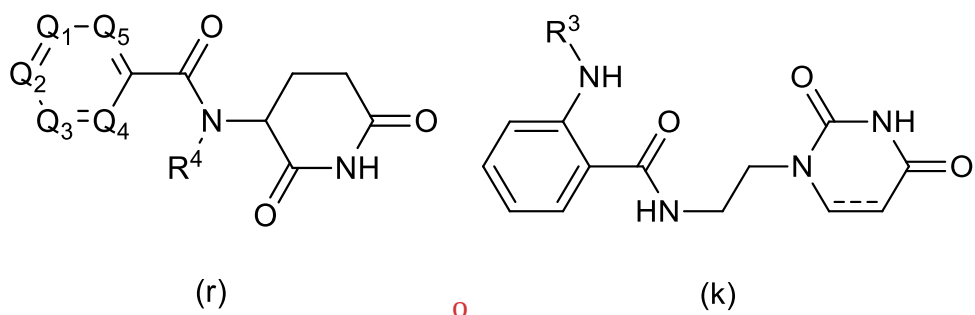
Q es un anillo alicíclico de 4 miembros con 0-2 heteroátomos, opcionalmente sustituido con 0-6 R^Q, cada R^Q es independientemente H, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), o 2 grupos R^Q tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos);

R^{Y1}, R^{Y2} son cada uno independientemente H, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo);

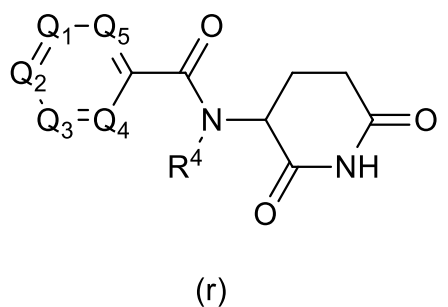
W² es un enlace, C₁₋₆ alquilo, C₁₋₆ heteroalquilo, O, C₁₋₆ alicíclico, heterocíclico, arilo, biheterocíclico, biarilo, o biheteroarilo, o heteroarilo, cada uno opcionalmente sustituido con 1, 2 o 3 R^{W2}; y

cada R^{W2} es independientemente H, halo, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más F), C₁₋₆ heteroalquilo (lineal, ramificado, opcionalmente sustituido), -OR^{W2A} OC₁₋₃alquilo (opcionalmente sustituido con 1 o más -F), C₃₋₆ cicloalquilo, C₄₋₆ cicloheteroalquilo (opcionalmente sustituido), heterocíclico (opcionalmente sustituido), arilo (opcionalmente sustituido), heteroarilo (opcionalmente sustituido), heteroarilo bicíclico (opcionalmente sustituido), arilo bicíclico, OH, NH₂, NR^{Y1}R^{Y2}, o CN.

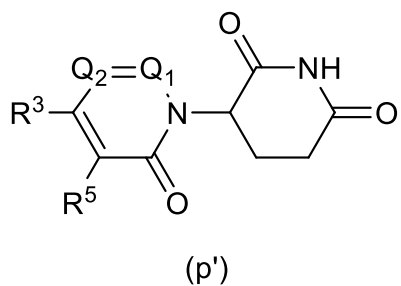
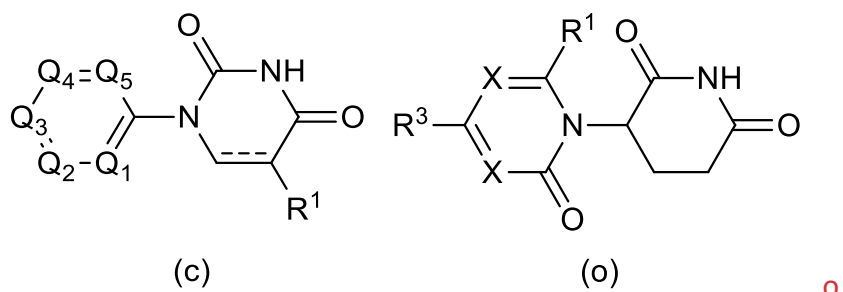
~~54.~~ El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones ~~21-43~~, en donde el ~~compuesto comprende, además, una segunda porción de unión a la ligasa de ubiquitina E3 acoplada a través de un grupo enlazador~~CLM tiene la estructura



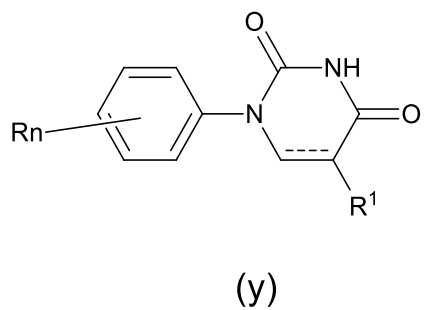
65. El compuesto bifuncional de conformidad con la reivindicación 54, en donde la ~~segunda CLM tiene la estructura porción de unión a la ligasa de ubiquitina E3 se une o se dirige a una ligasa de ubiquitina E3 seleccionada del grupo que consiste en Von Hippel-Lindau (VLM); cereblon (CLM), homólogo 2 de doble minuto de ratón (MLM), e inhibidores de las proteínas de apoptosis (ILM)~~

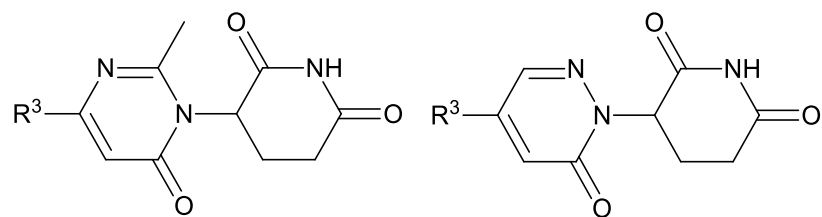


6. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-3, en donde la CLM tiene la estructura



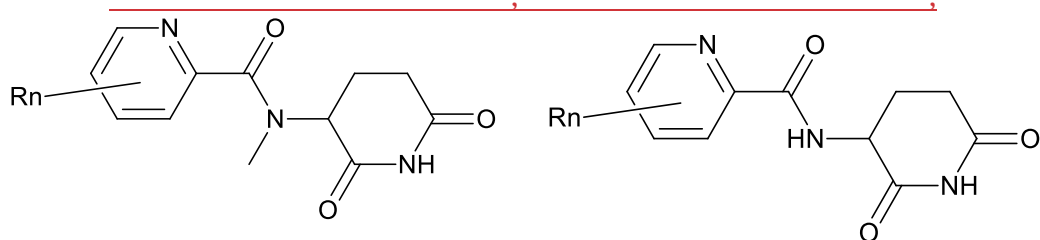
7. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 21-6, en donde la CLM se representa por una estructura química seleccionada del grupo que consiste en:





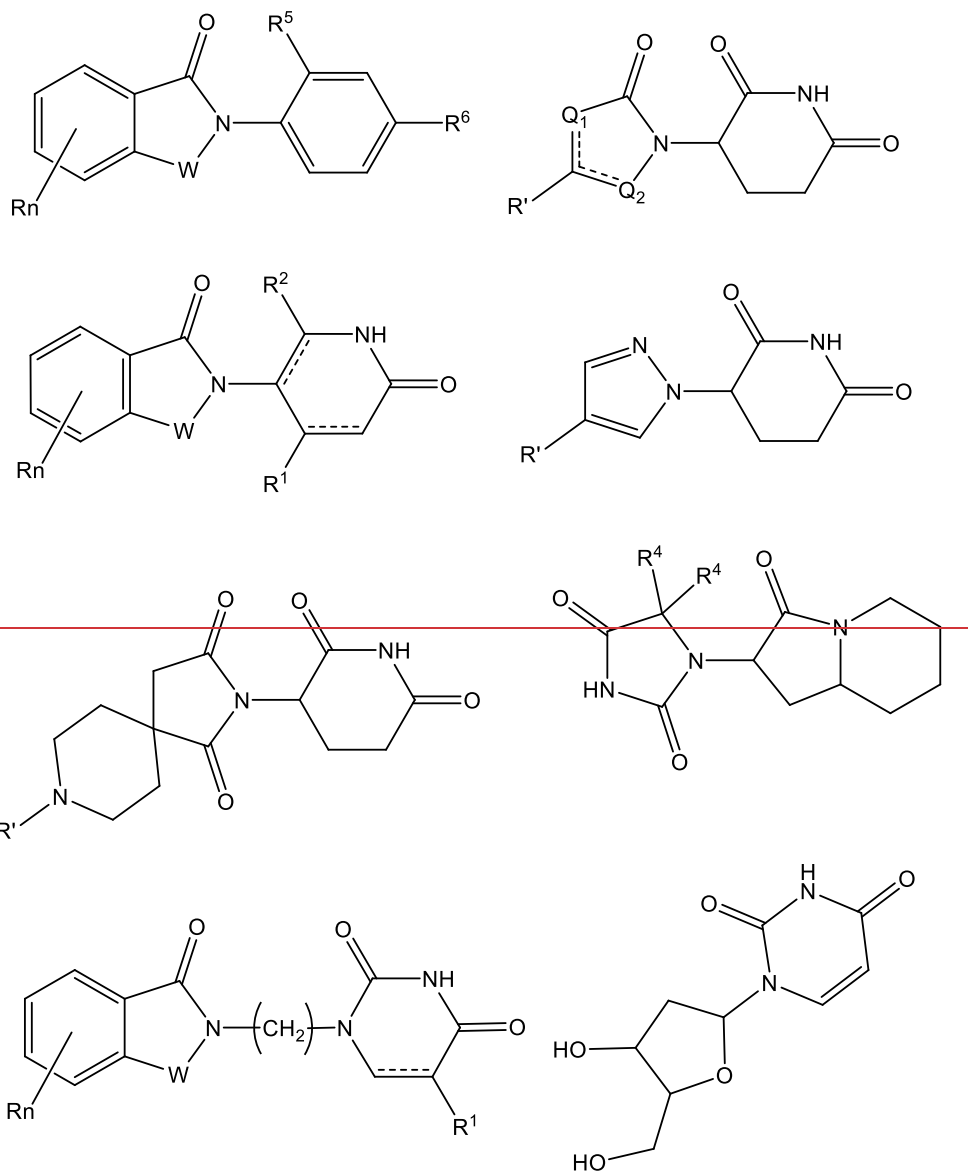
(ad)

(ae)



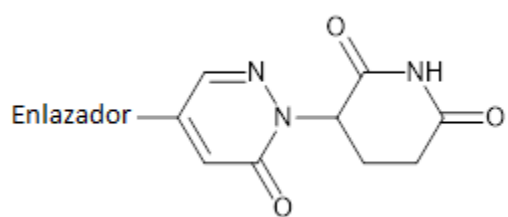
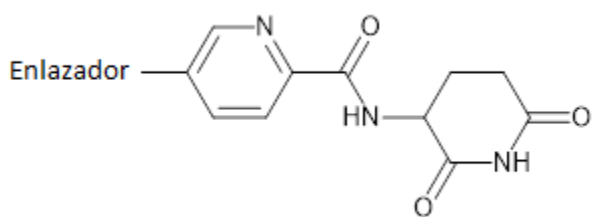
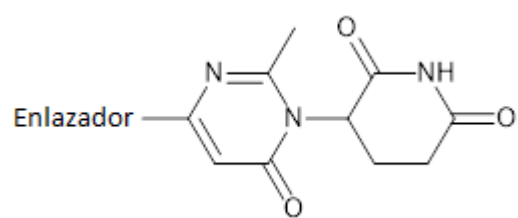
(af)

(ag)

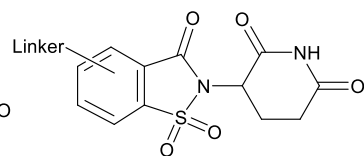
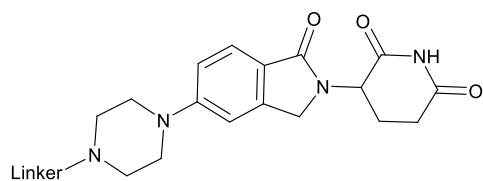
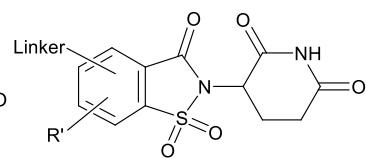
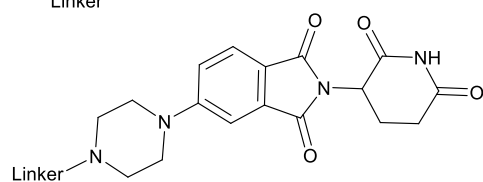
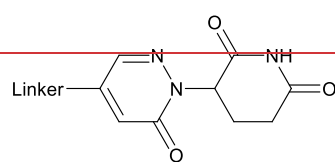
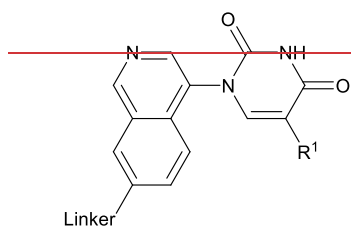
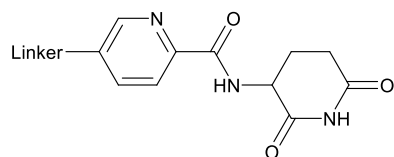
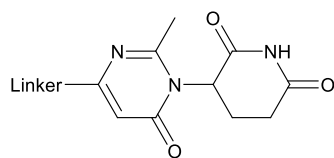
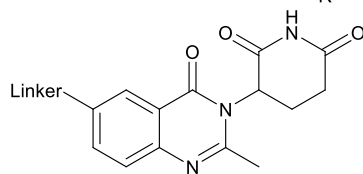
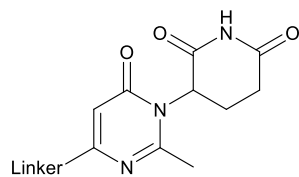
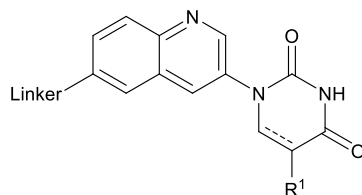
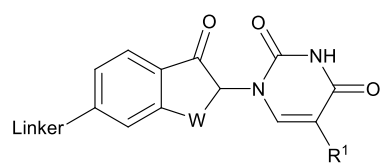


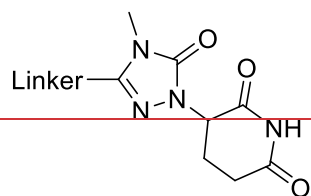
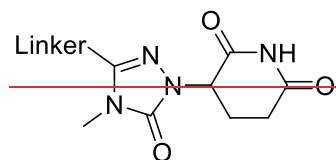
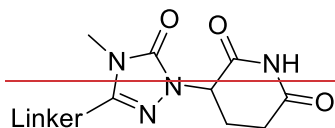
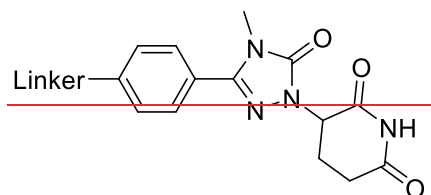
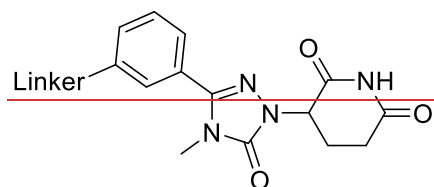
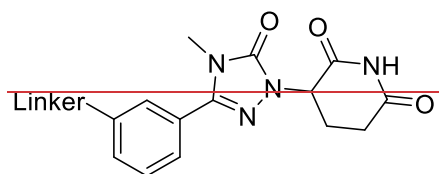
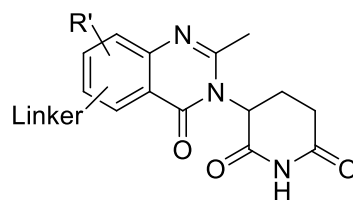
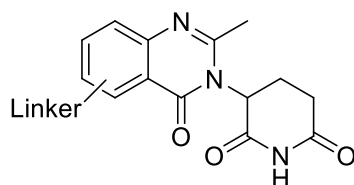
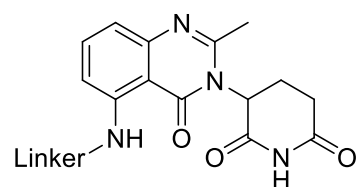
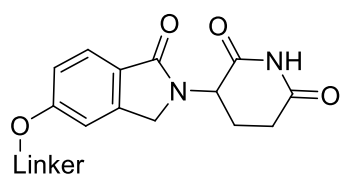
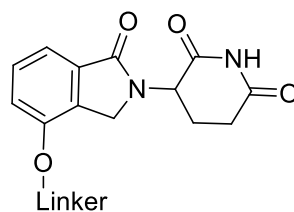
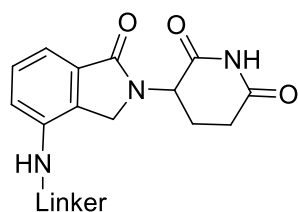
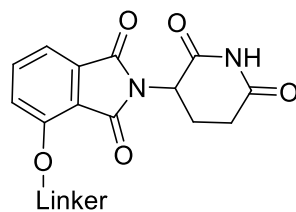
en donde R_n comprende un grupo funcional o un átomo.

8. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 21-7, en donde la CLM se representa por una estructura química seleccionada por:



y





9. — El compuesto de conformidad con cualquiera de las reivindicaciones 2-8, en donde el enlazador (L) comprende una unidad estructural química representada por la Fórmula:



en donde:

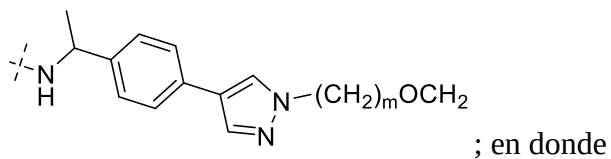
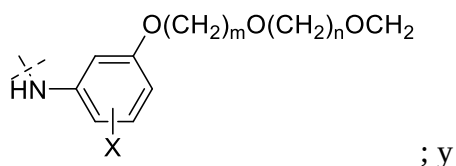
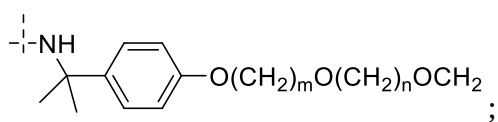
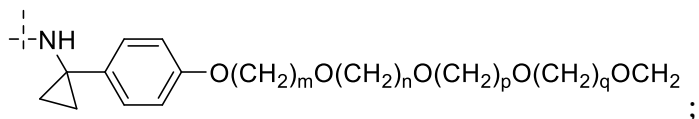
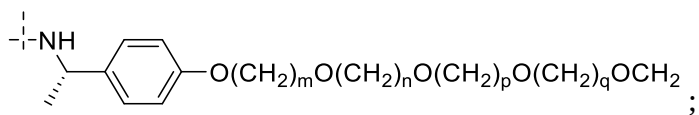
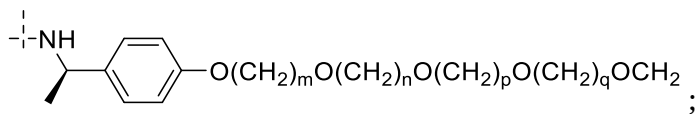
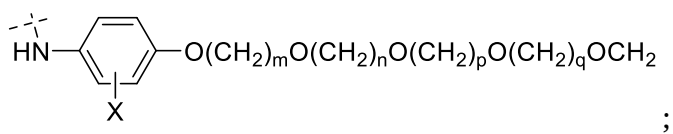
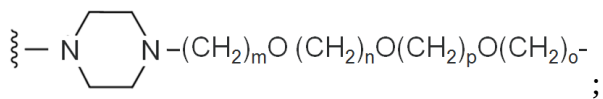
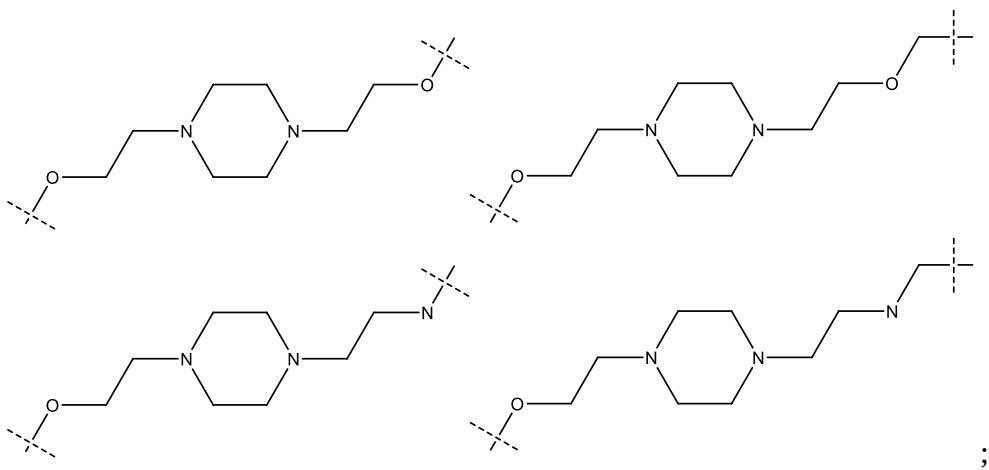
$(A^L)_q$ es un grupo que se conecta al menos a uno de la CLM, la PTM o una combinación de estos;

q es un número mayor que o igual a 1;

cada A^L se selecciona independientemente 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, $CR^{L1}=CR^{L2}$, $C\equiv C$, SiR^{L1}R^{L2}, P(O)R^{L1}, P(O)OR^{L1}, NR^{L3}C(=NCN)NR^{L4}, NR^{L3}C(=NCN), NR^{L3}C(=CNO₂)NR^{L4}, C₃₋₁₁cicloalquilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, C₃₋₁₁heterociclilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, arilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, heteroarilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2}, donde R^{L1} o R^{L2}, cada uno independientemente se unen opcionalmente a otros grupos para formar porciones 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 independientemente, H, halo, C₁₋₈alquilo, OC₁₋₈alquilo, SC₁₋₈alquilo, NHC₁₋₈alquilo, N(C₁₋₈alquilo)₂, C₃₋₁₁cicloalquilo, arilo, heteroarilo, C₃₋₁₁heterociclilo, OC₁₋₈cicloalquilo, SC₁₋₈cicloalquilo, NHC₁₋₈cicloalquilo, N(C₁₋₈cicloalquilo)₂, N(C₁₋₈cicloalquilo)(C₁₋₈alquilo), OH, NH₂, SH, SO₂C₁₋₈alquilo, P(O)(OC₁₋₈alquilo)(C₁₋₈alquilo), P(O)(OC₁₋₈alquilo)₂, CC-C₁₋₈alquilo, CCH, CH=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=C(C₁₋₈alquilo)₂, Si(OH)₃, Si(C₁₋₈alquilo)₃, Si(OH)(C₁₋₈alquilo)₂, COC₁₋₈alquilo, CO₂H, halógeno, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO₂NHC₁₋₈alquilo, SO₂N(C₁₋₈alquilo)₂, SONHC₁₋₈alquilo, SON(C₁₋₈alquilo)₂, CONHC₁₋₈alquilo, CON(C₁₋₈alquilo)₂, N(C₁₋₈alquilo)CONH(C₁₋₈alquilo), N(C₁₋₈alquilo)CON(C₁₋₈alquilo)₂, NHCONH(C₁₋₈alquilo), NHCON(C₁₋₈alquilo)₂, NHCONH₂, N(C₁₋₈alquilo)SO₂NH(C₁₋₈alquilo), N(C₁₋₈alquilo)SO₂N(C₁₋₈alquilo)₂, NH SO₂NH(C₁₋₈alquilo), NH SO₂N(C₁₋₈alquilo)₂, NH SO₂NH₂.

109. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 21-98, en donde L se selecciona del grupo que consiste en:

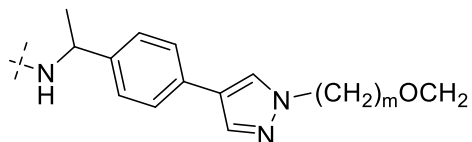


m, n, o, p, q, y r del enlazador son independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,
14, 15, 16, 17, 18, 19, 20;

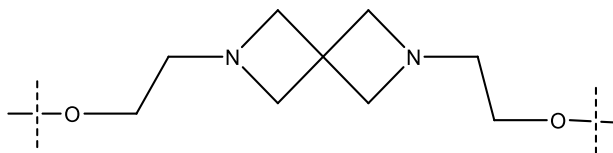
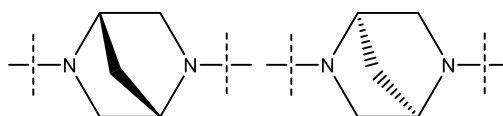
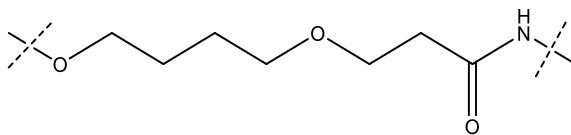
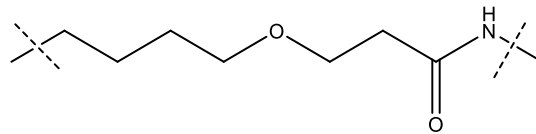
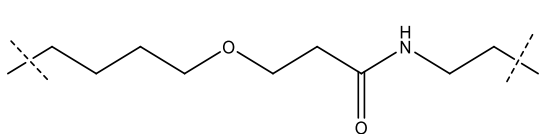
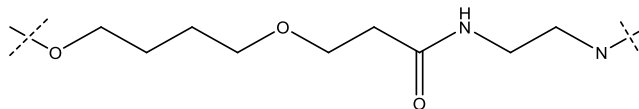
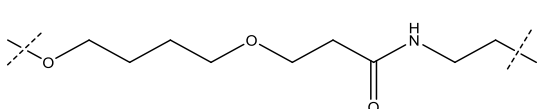
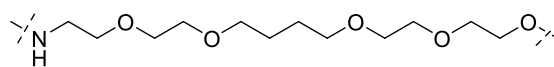
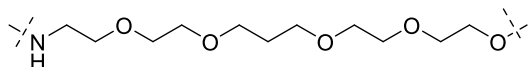
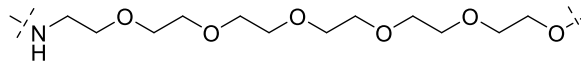
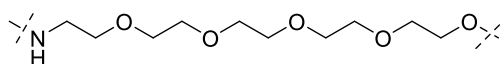
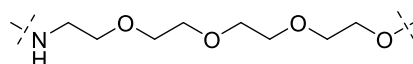
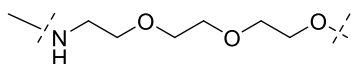
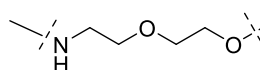
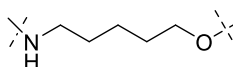
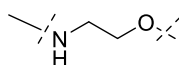
cuando el número es cero, no hay enlace N-O u O-O

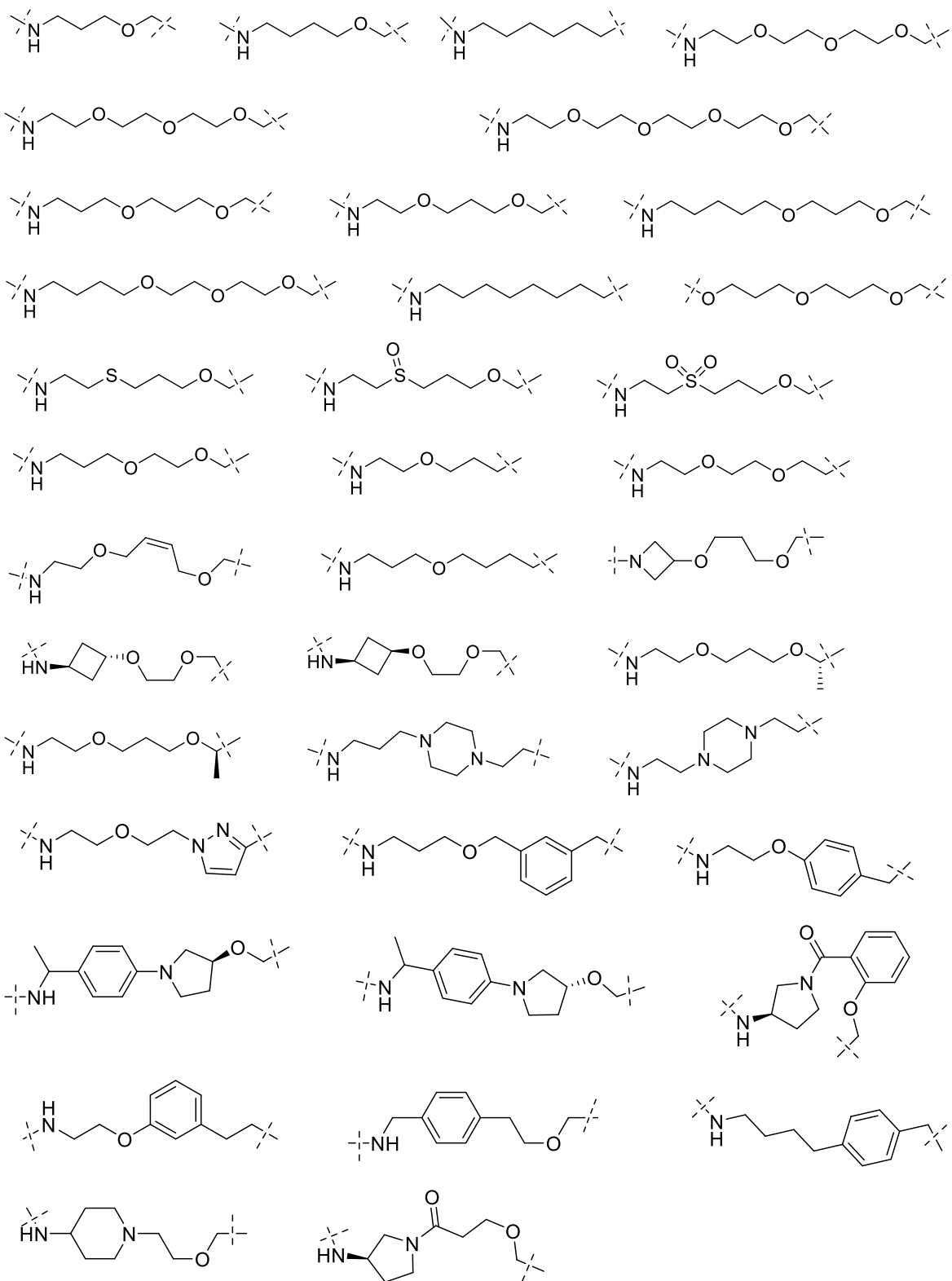
R del enlazador es H, metilo y etilo;

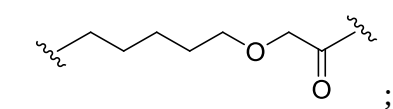
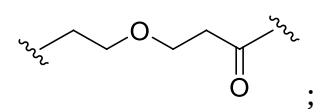
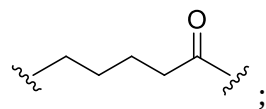
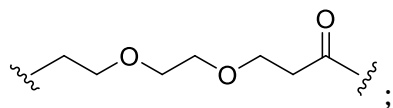
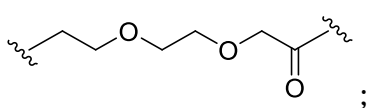
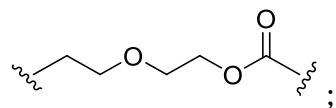
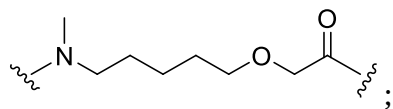
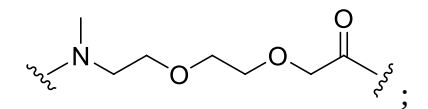
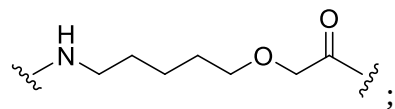
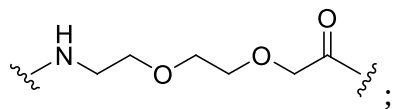
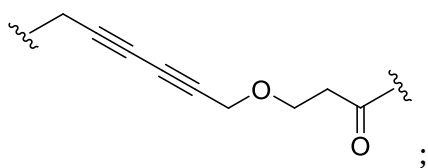
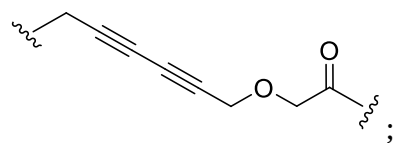
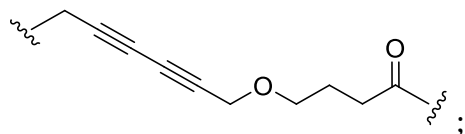
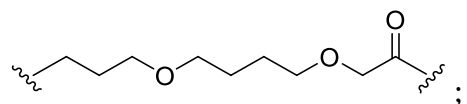
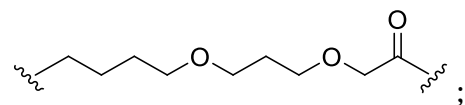
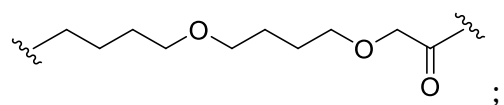
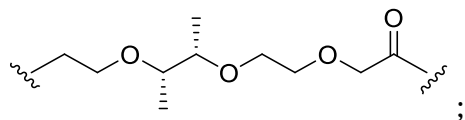
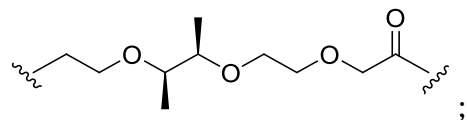
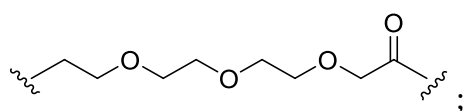
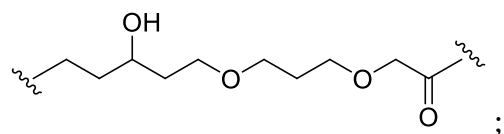
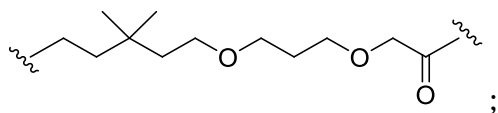
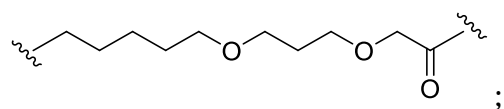
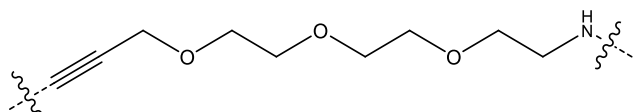
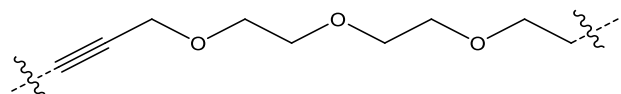
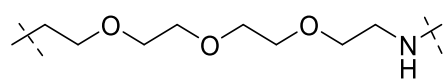
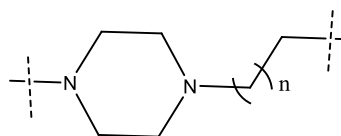
X del enlazador es H y F

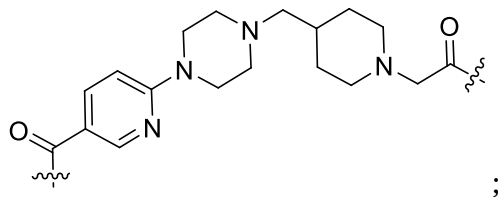
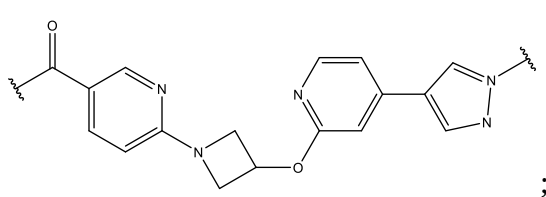
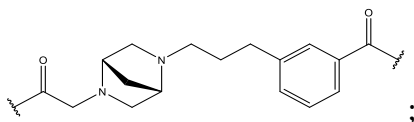
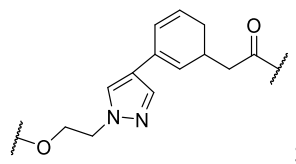
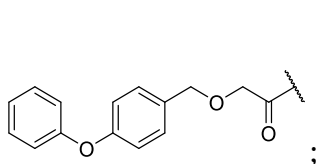
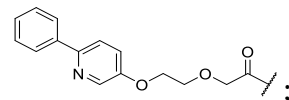
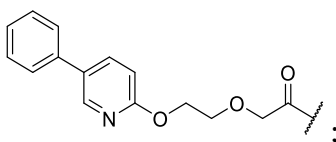
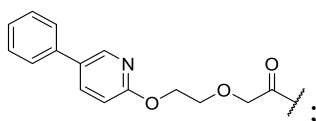
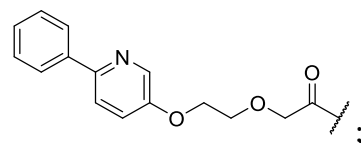
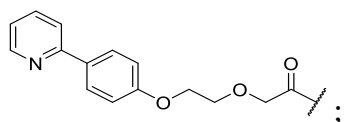
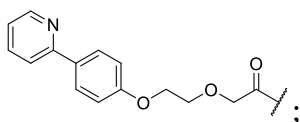
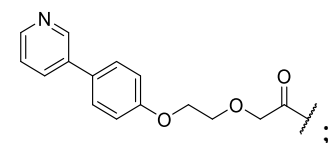
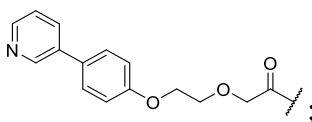
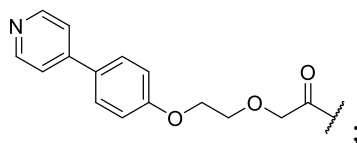
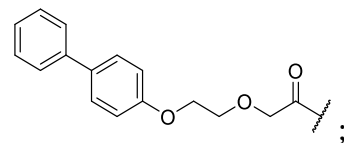
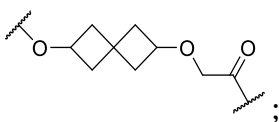
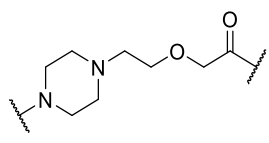
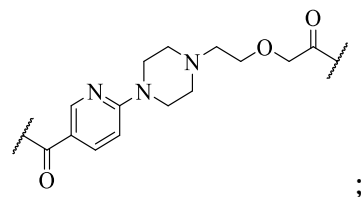
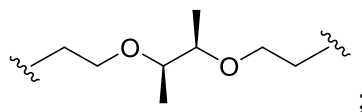
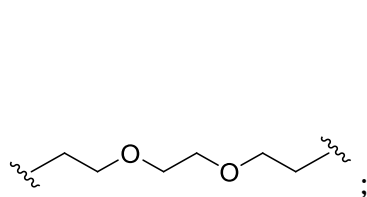
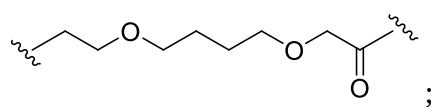
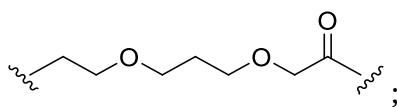
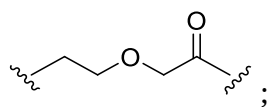
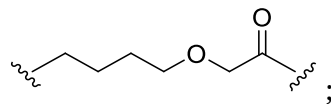
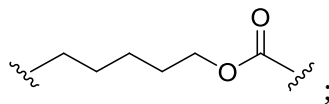
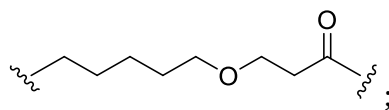


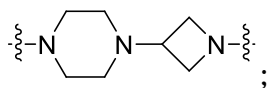
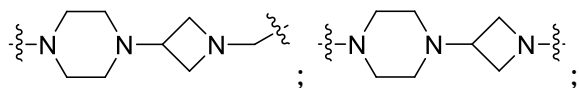
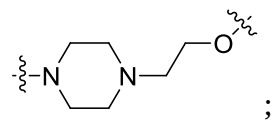
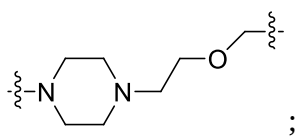
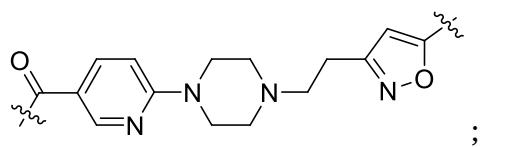
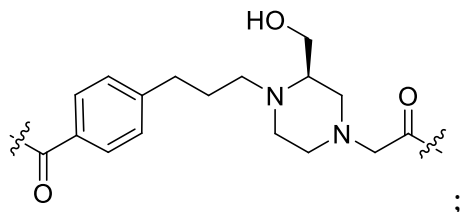
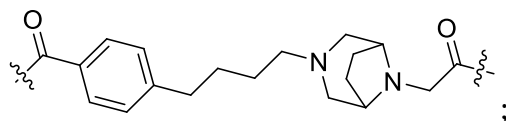
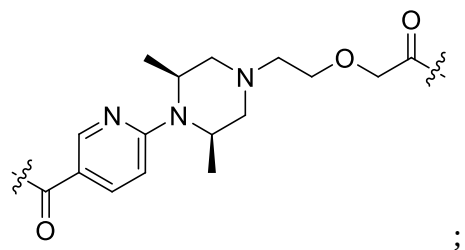
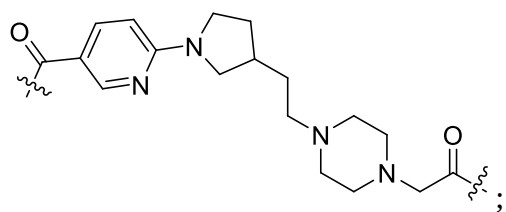
donde m del enlazador puede ser 2, 3, 4, 5

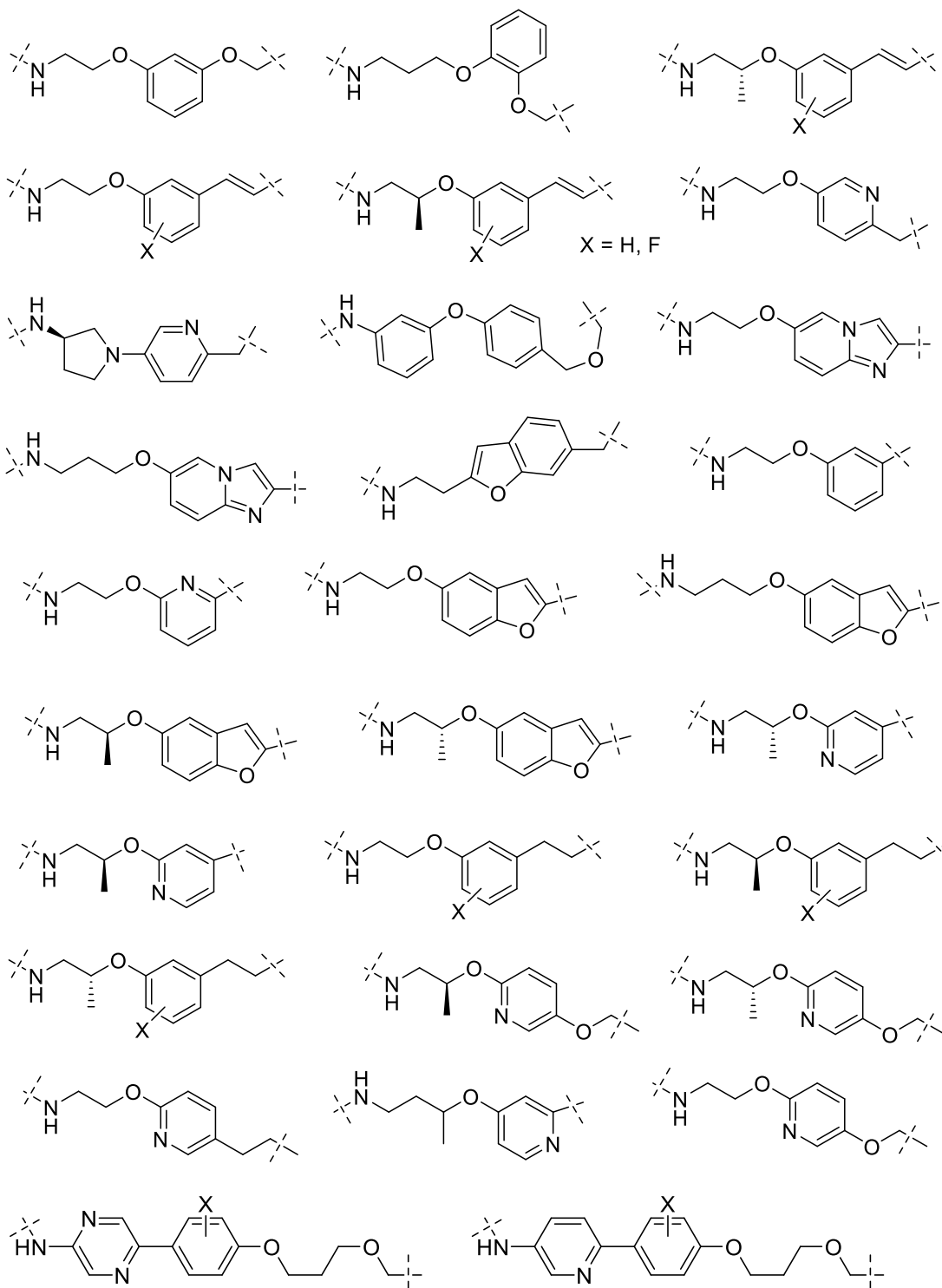


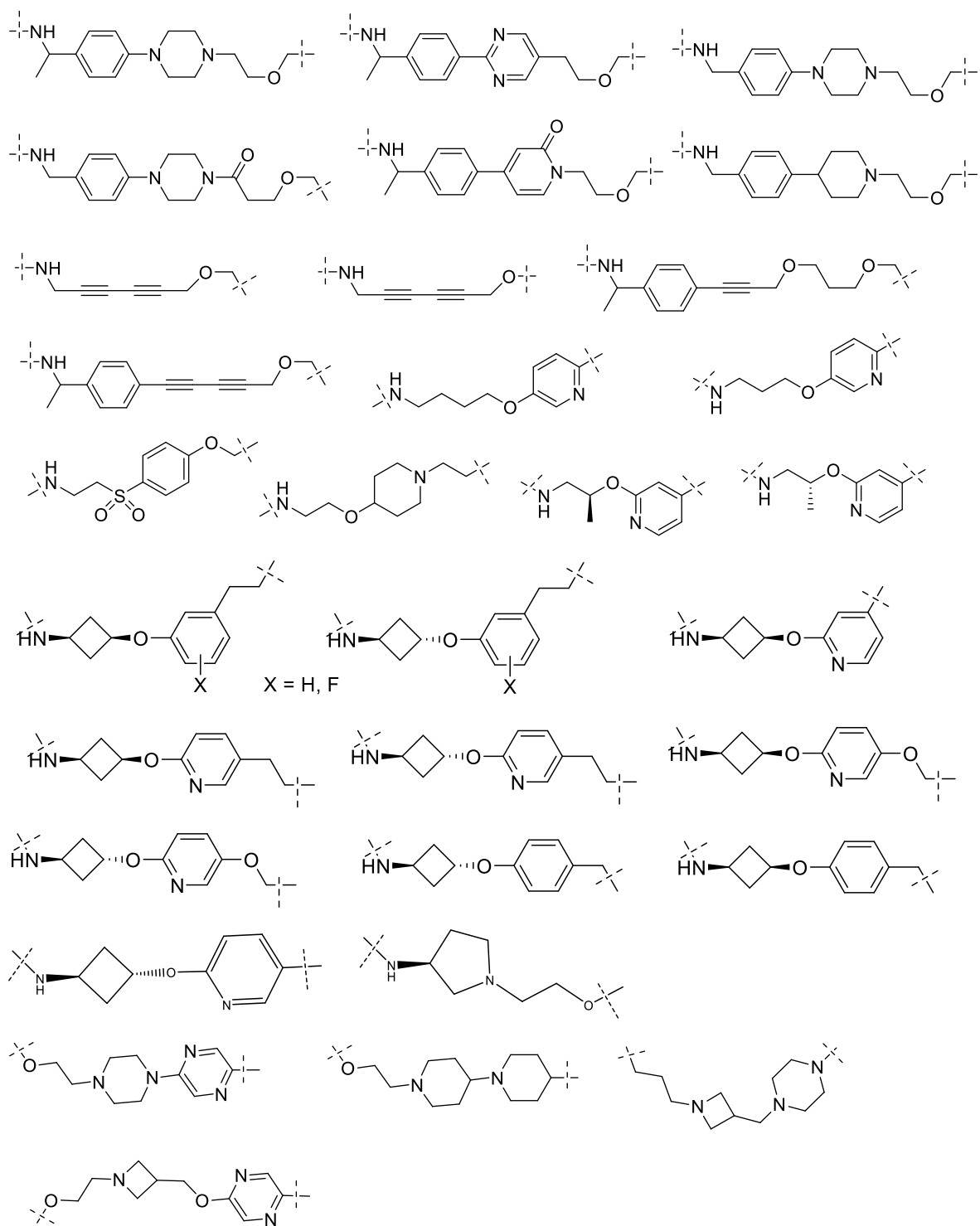


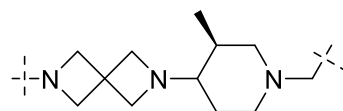
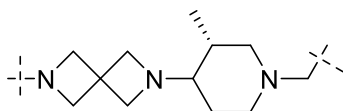
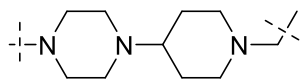
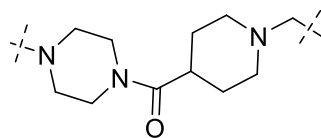
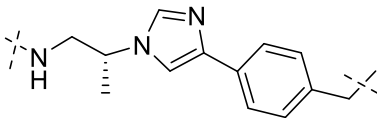
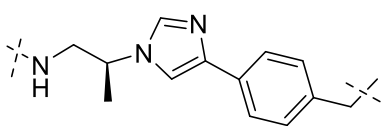
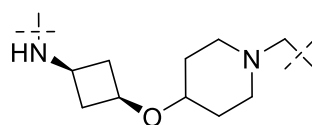
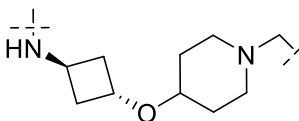
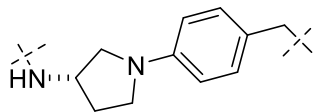
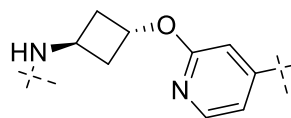
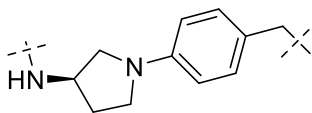
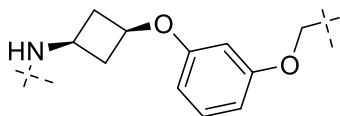
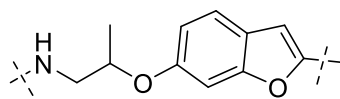
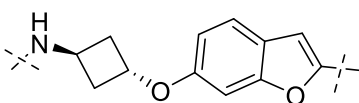
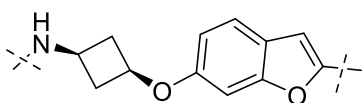
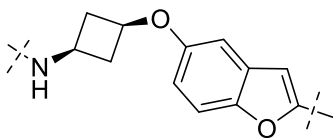
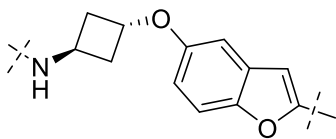
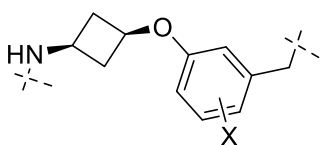
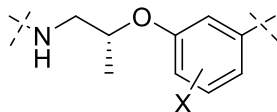
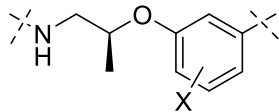
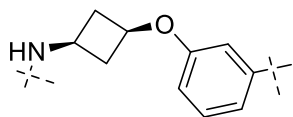
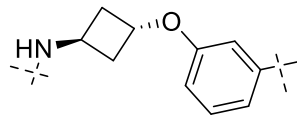
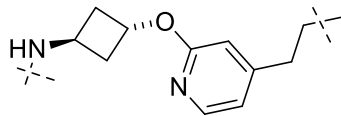
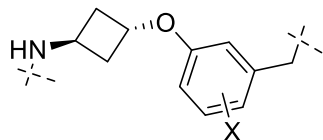
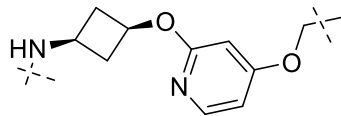
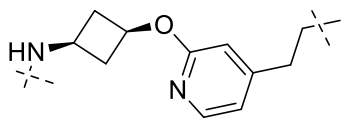
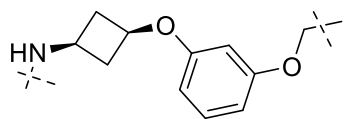




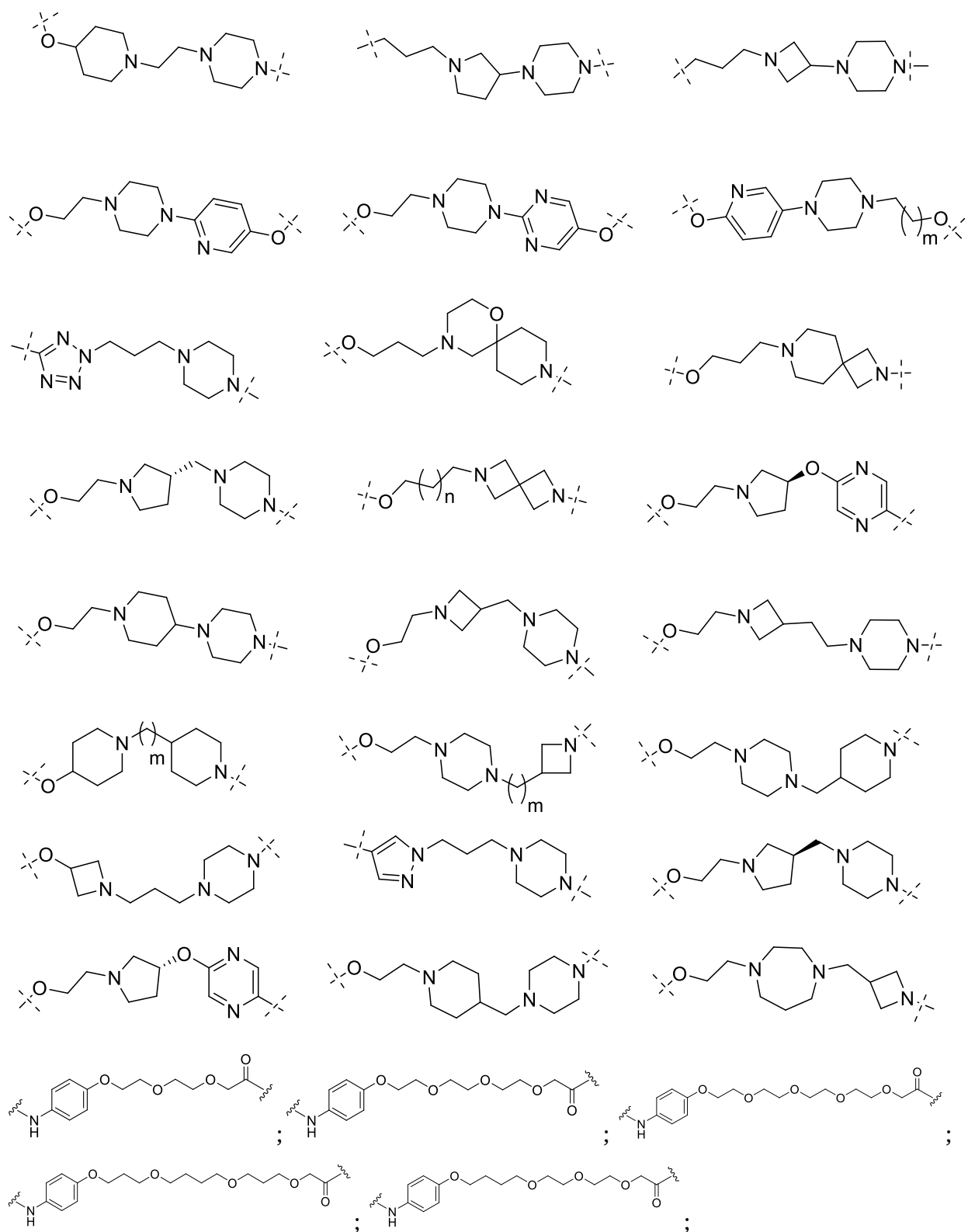


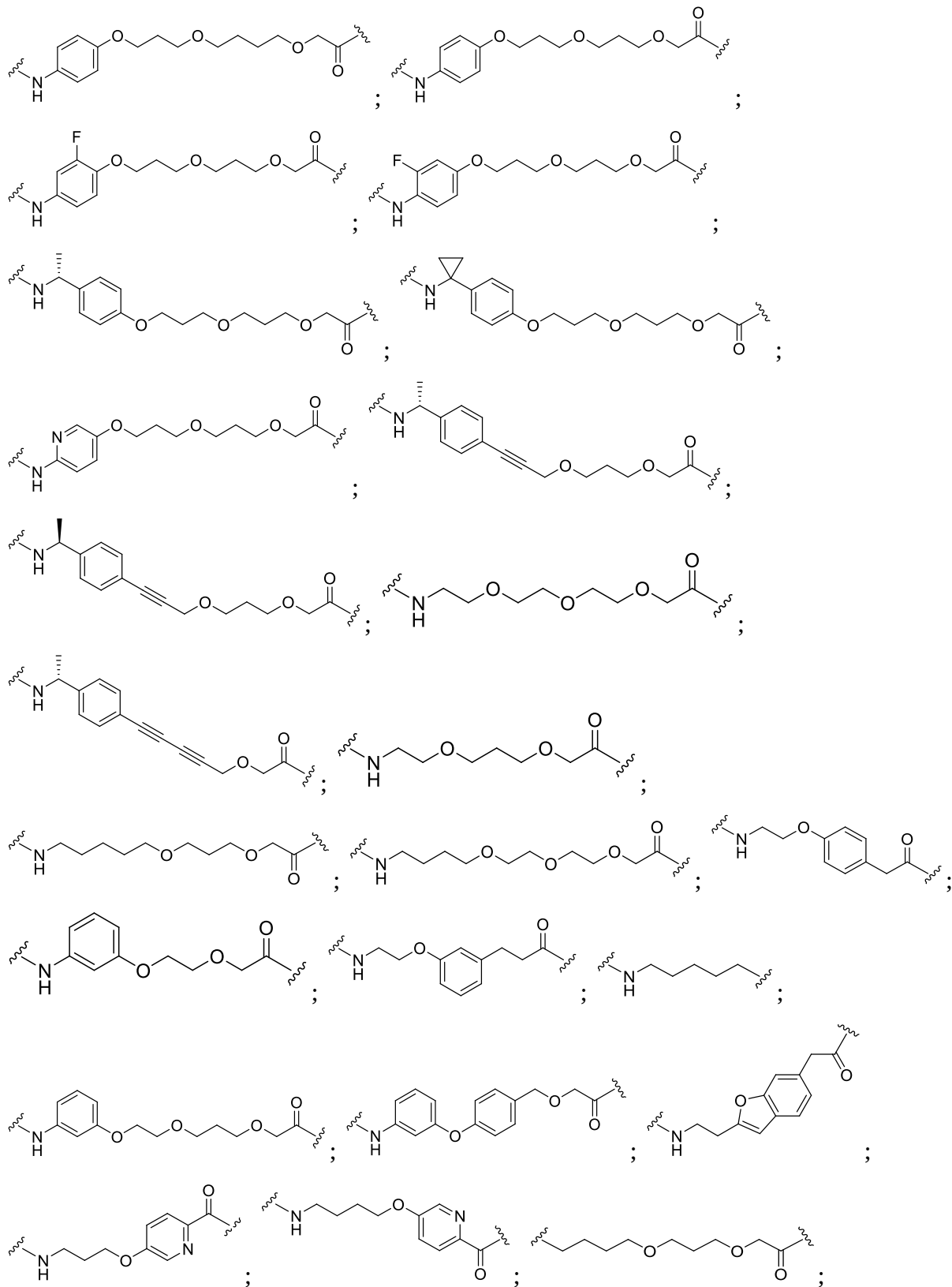


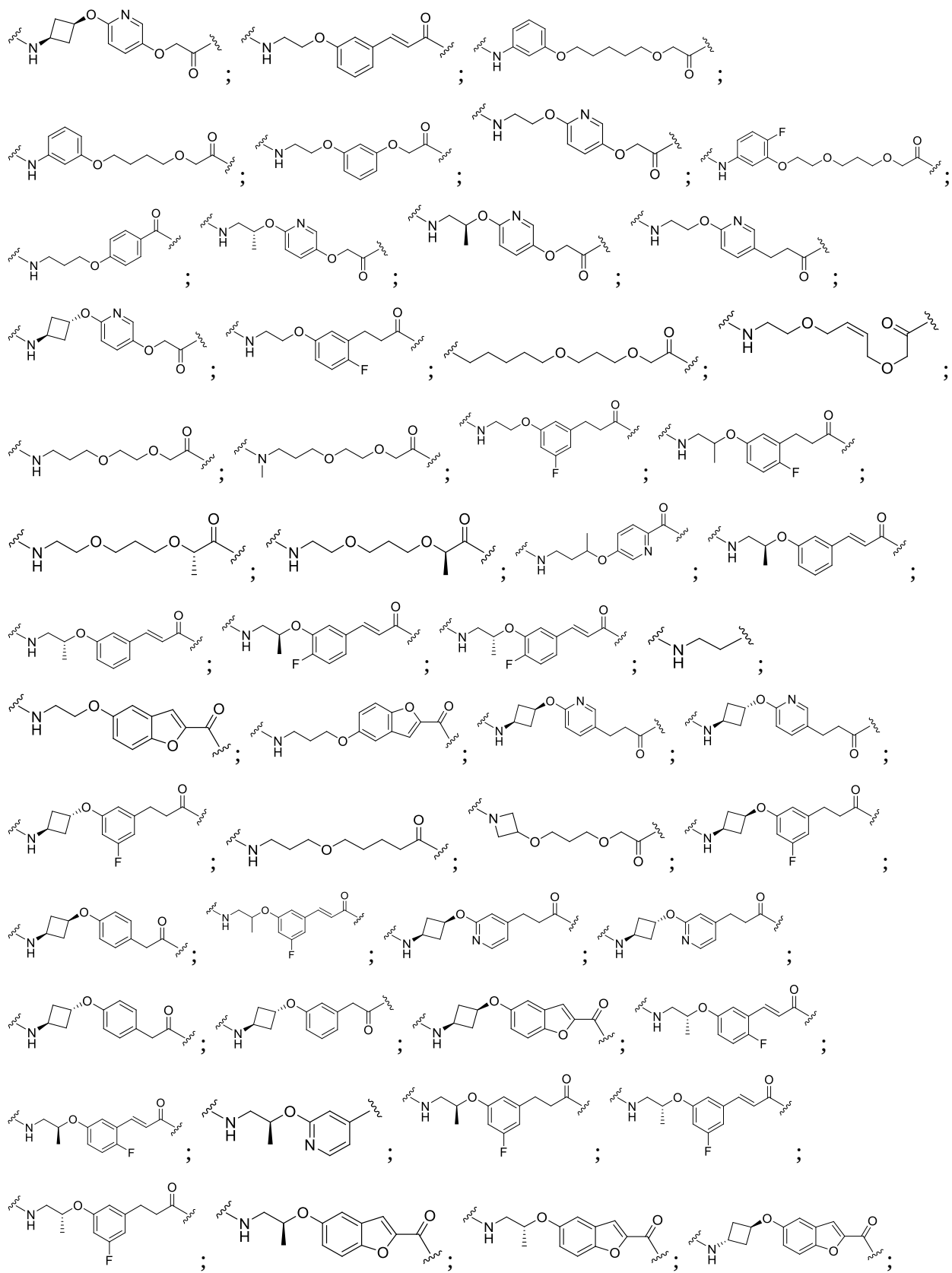


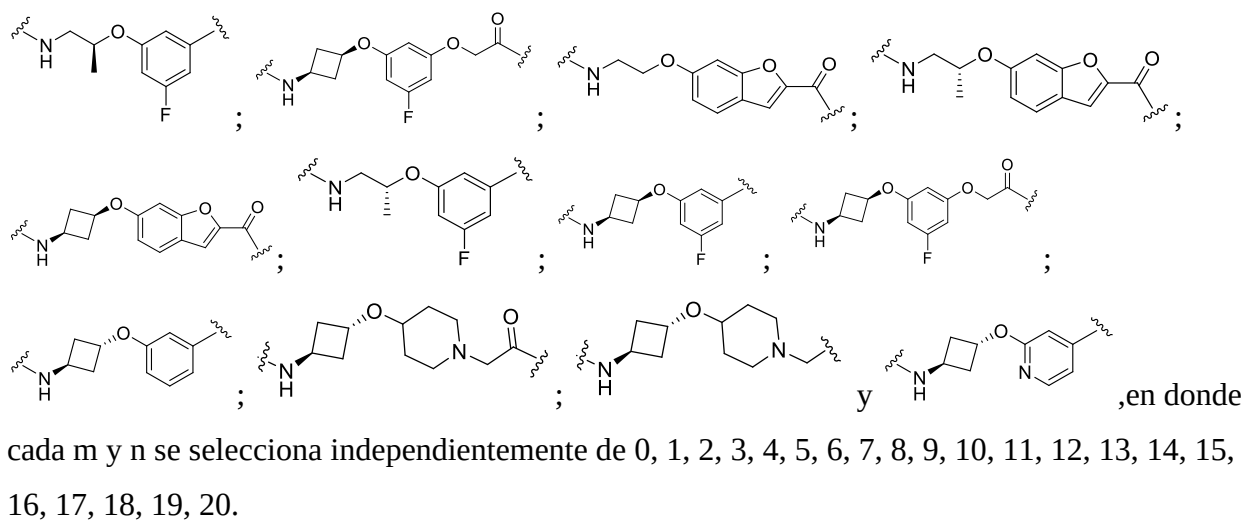


~~44~~10. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones ~~21~~9, en donde L se selecciona del grupo que consiste en:

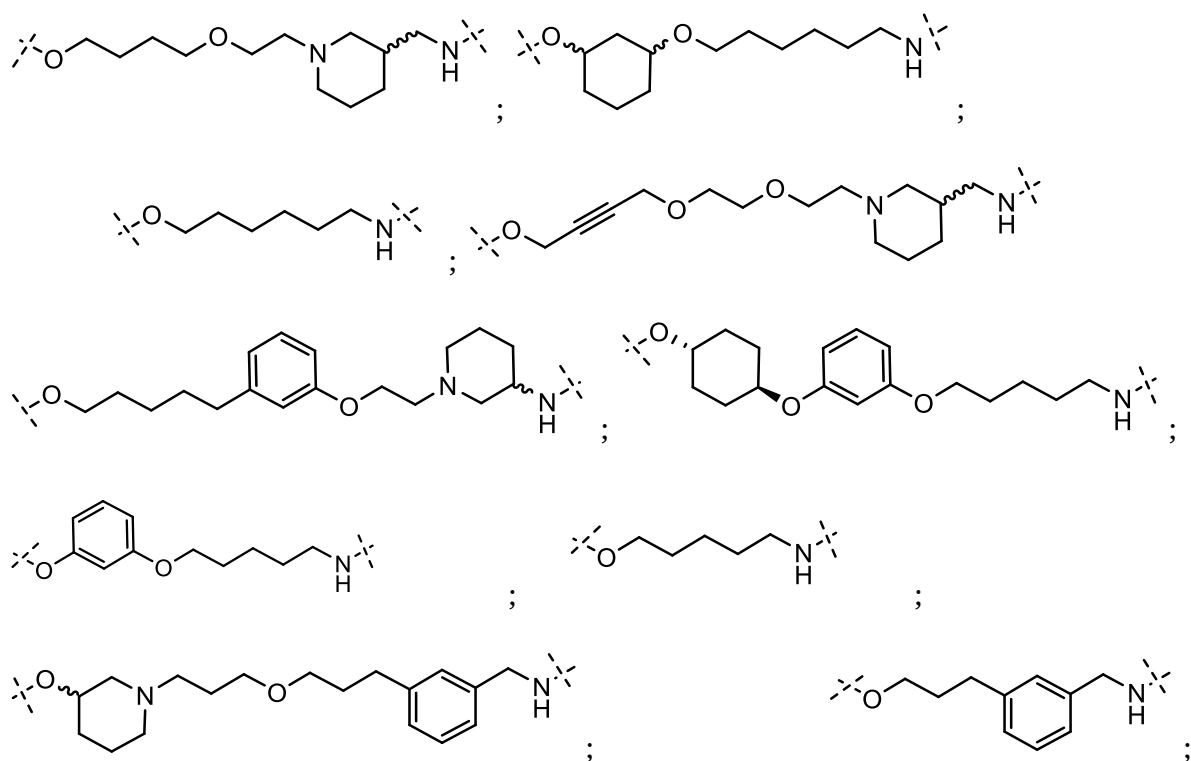


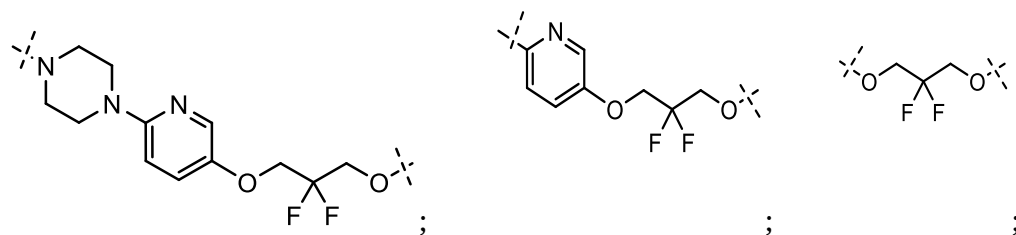
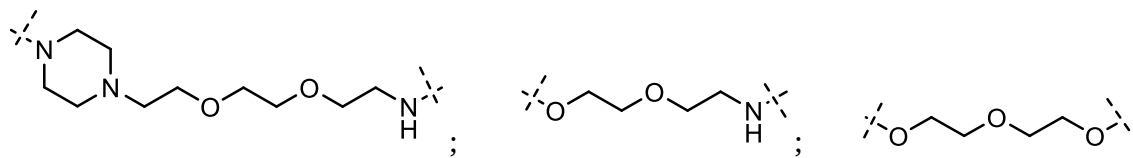
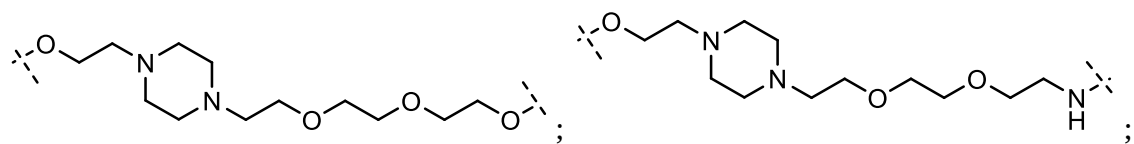
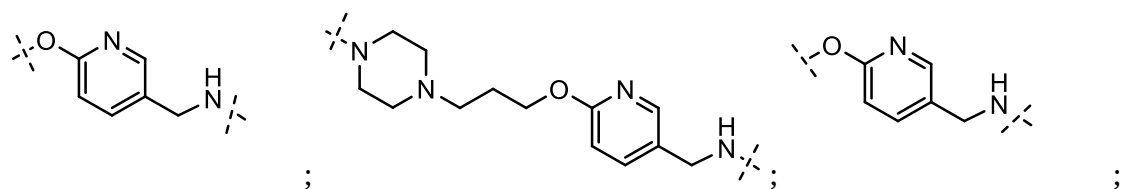
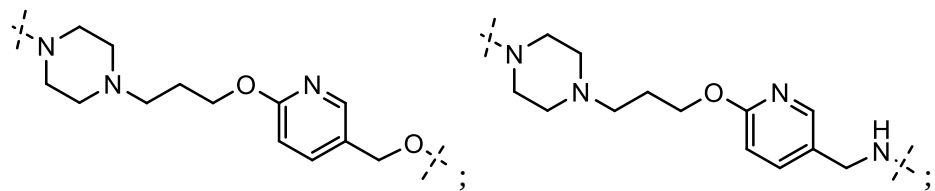
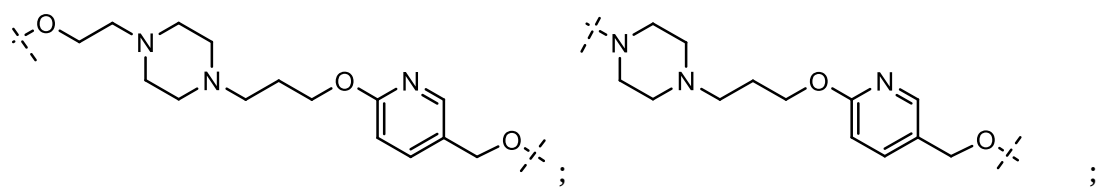
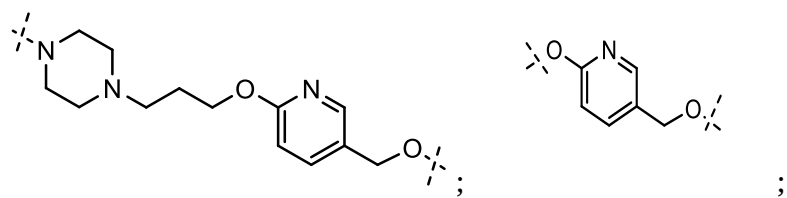


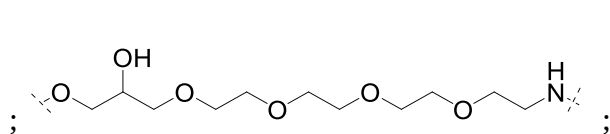
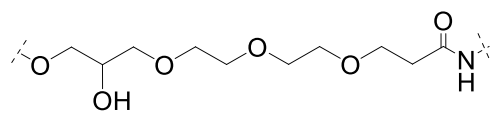
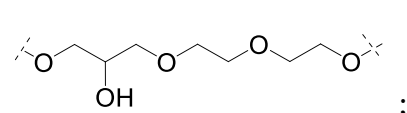
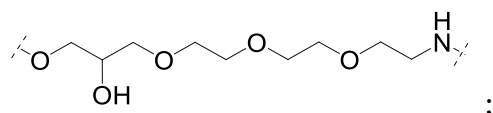
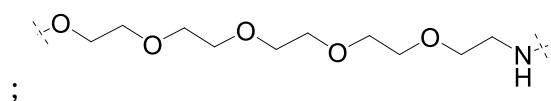
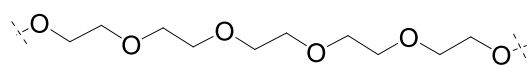
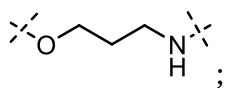
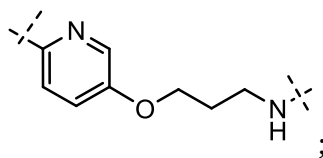
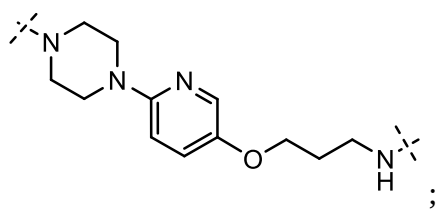
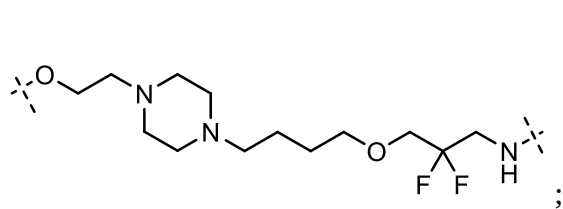
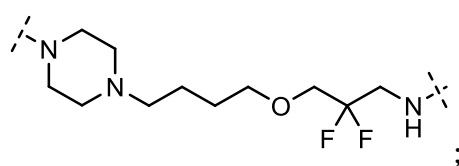
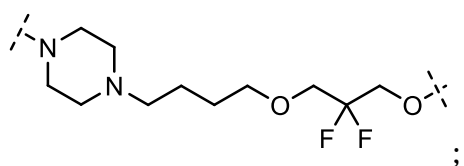
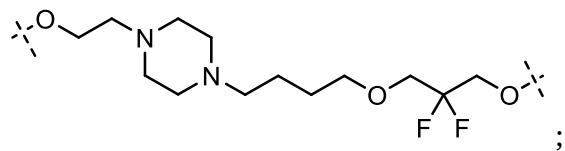
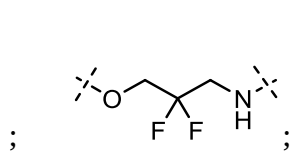
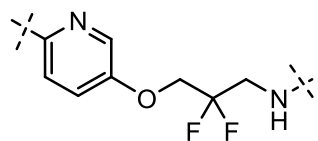
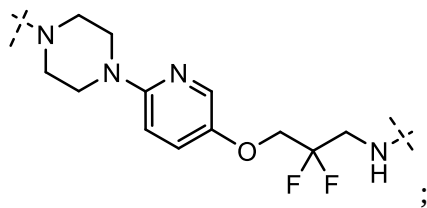
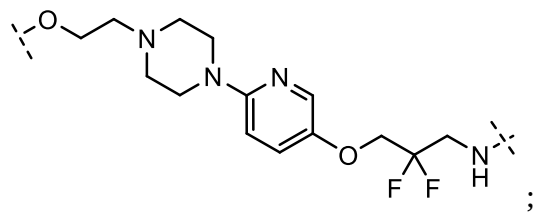


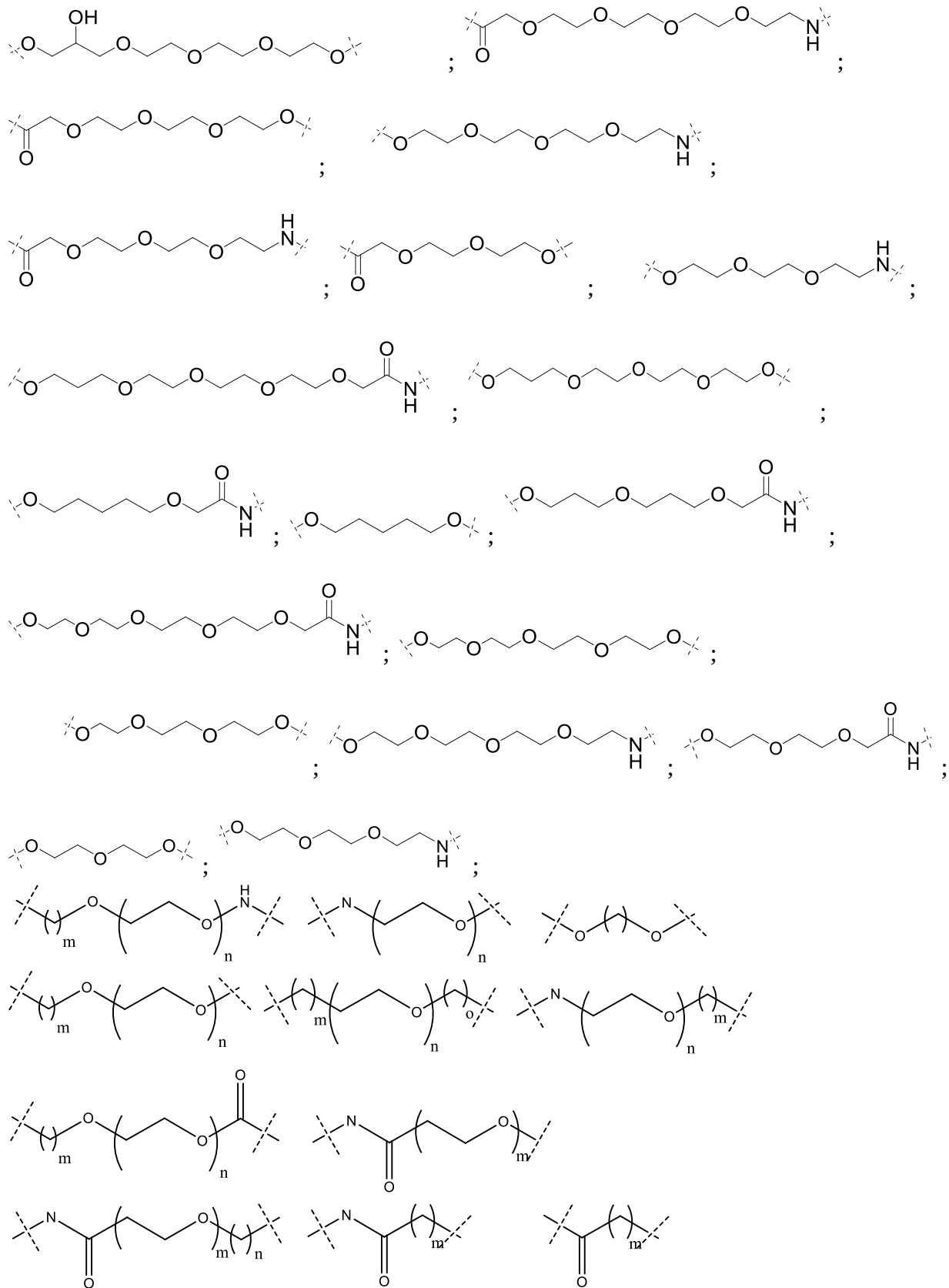


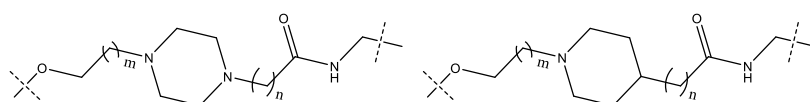
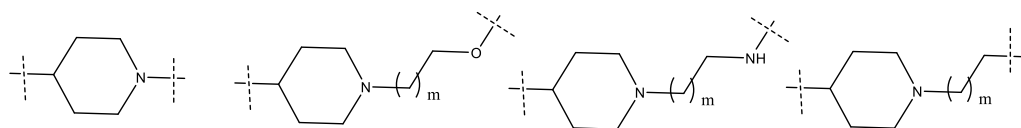
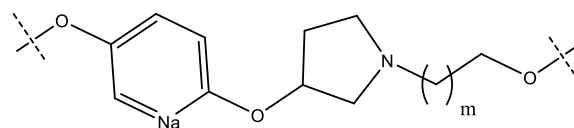
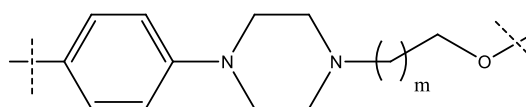
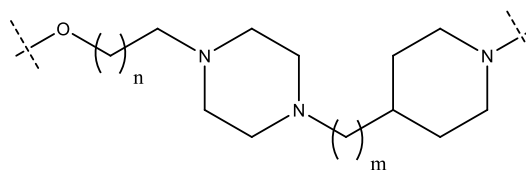
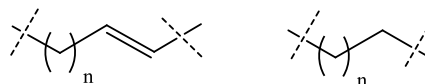
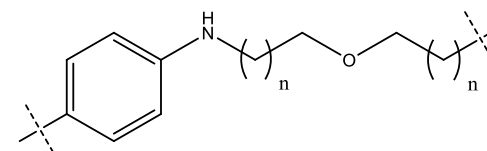
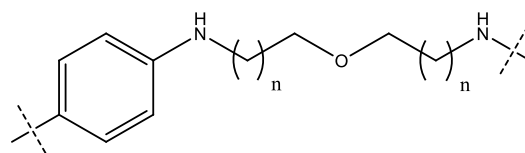
1211. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones **21-9**, en donde el enlazador (L) se selecciona del grupo que consiste en:

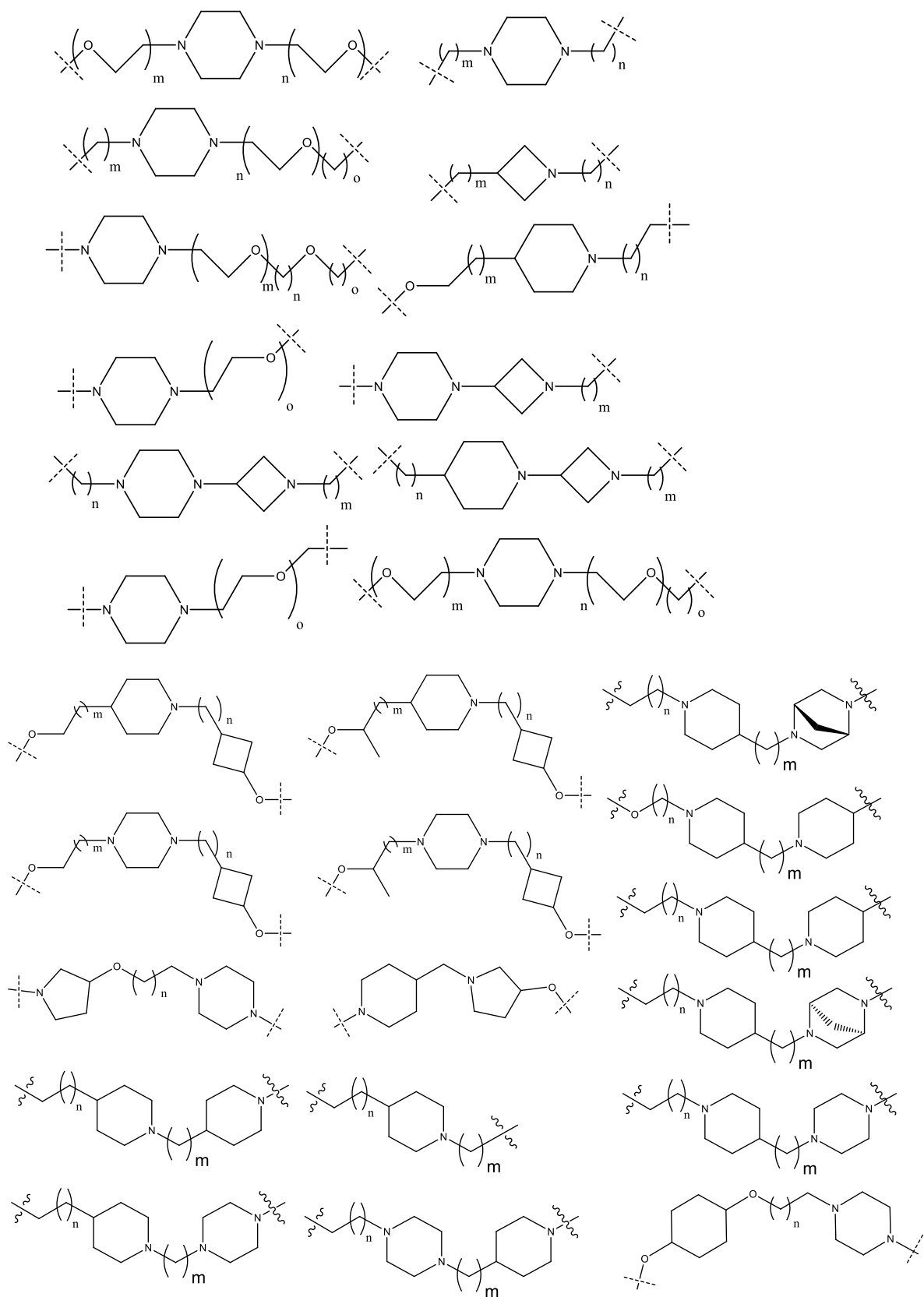


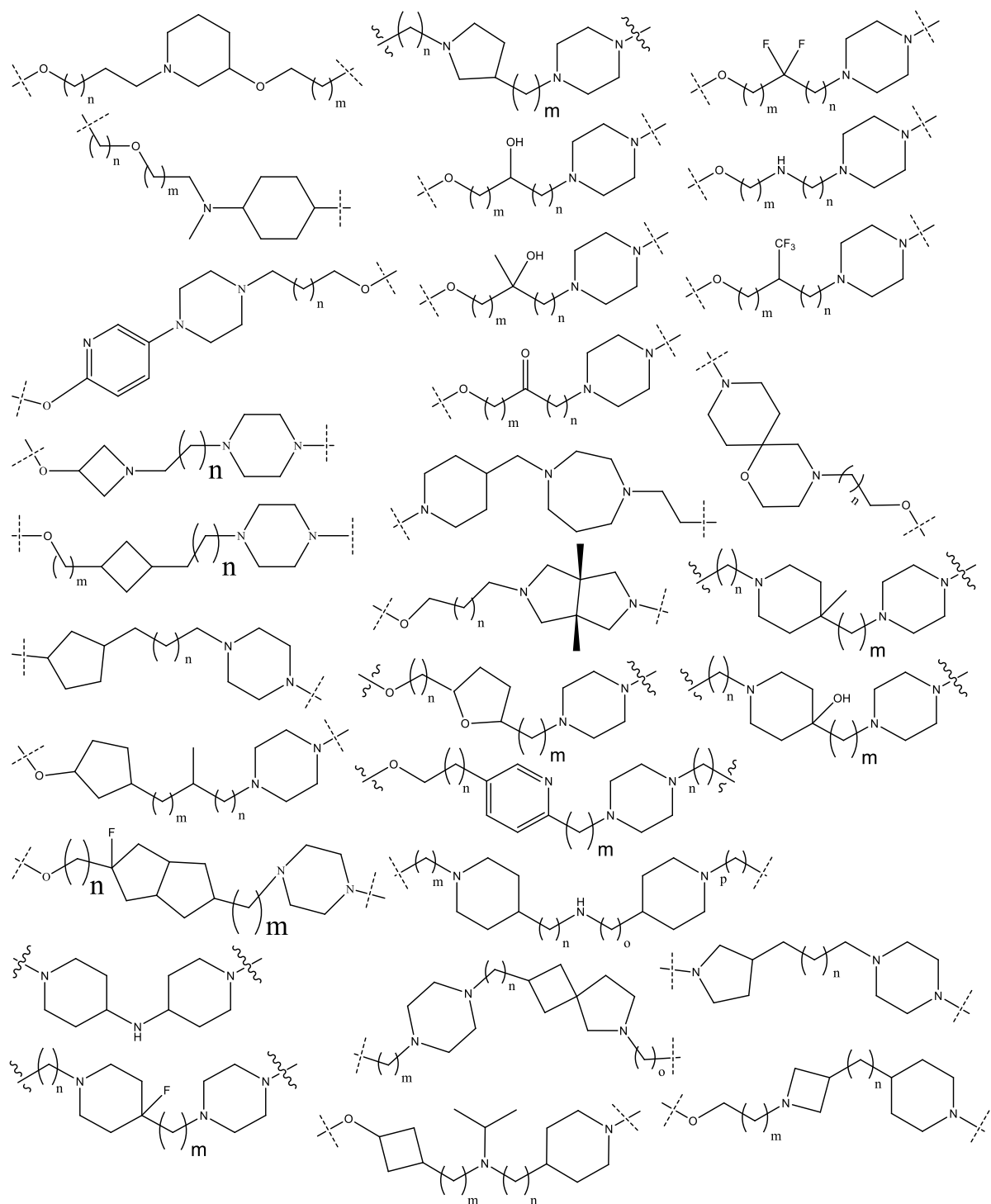


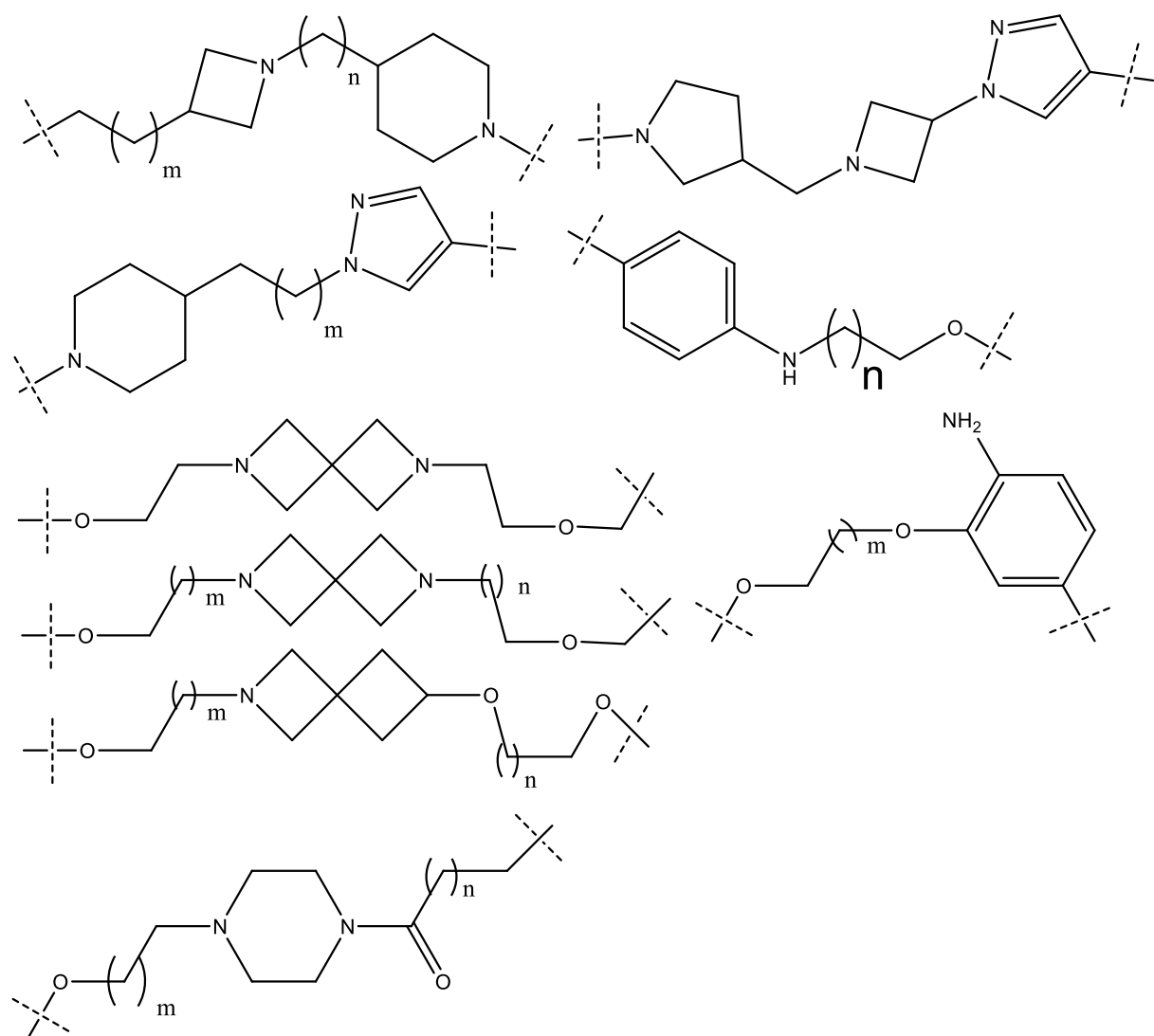


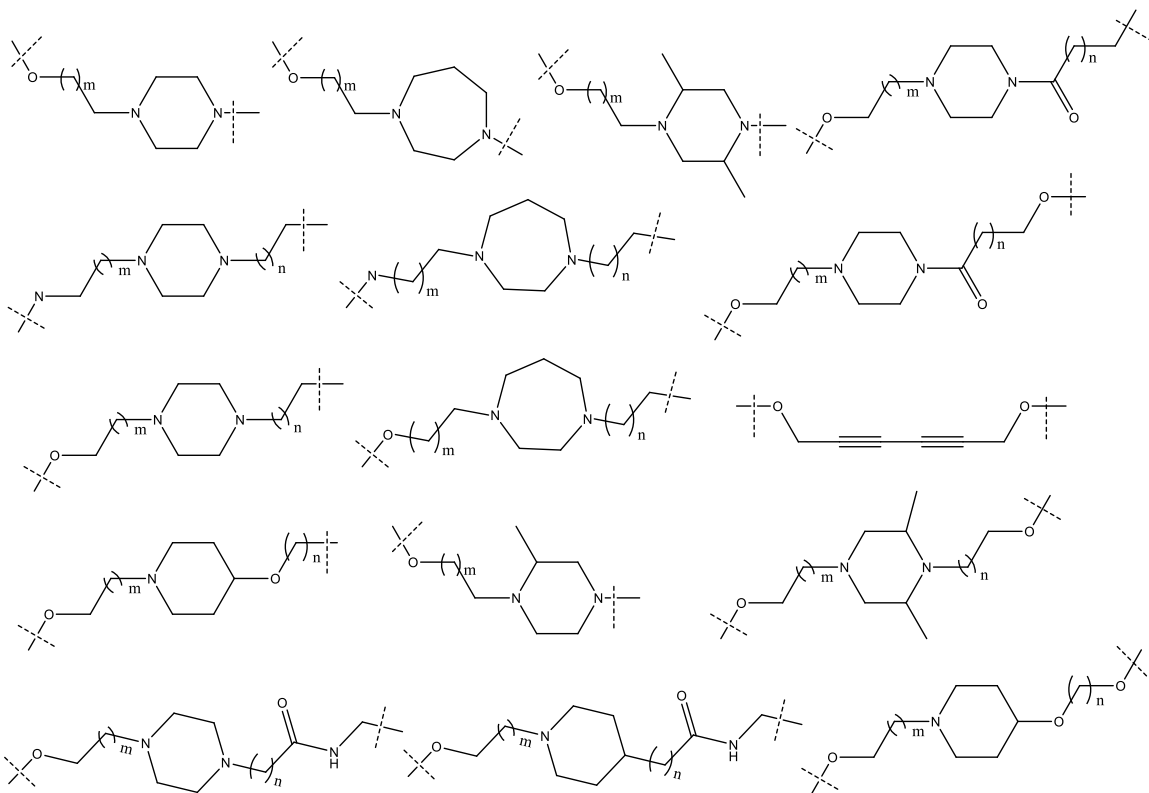
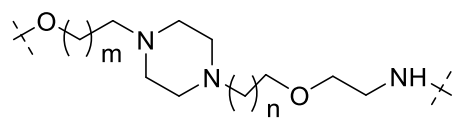
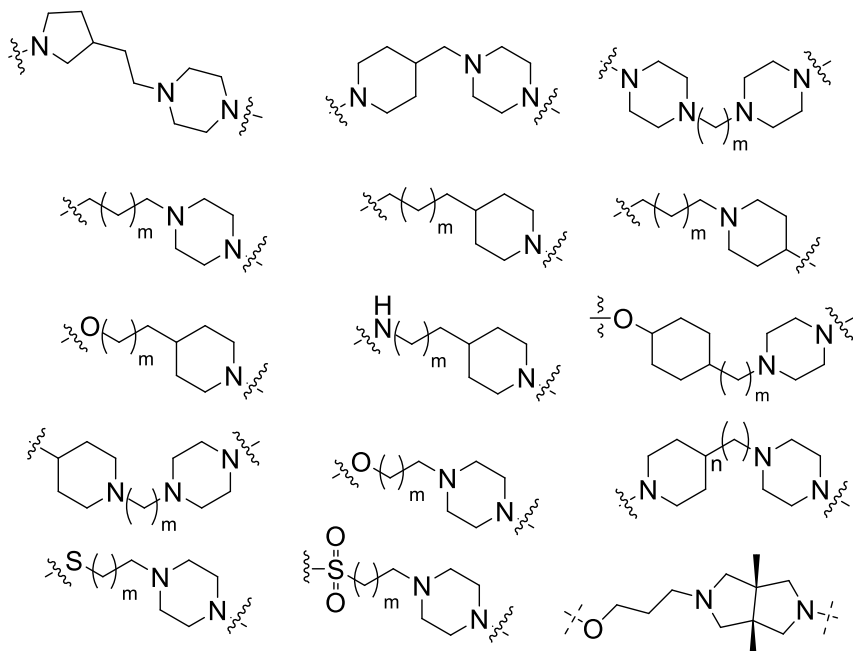


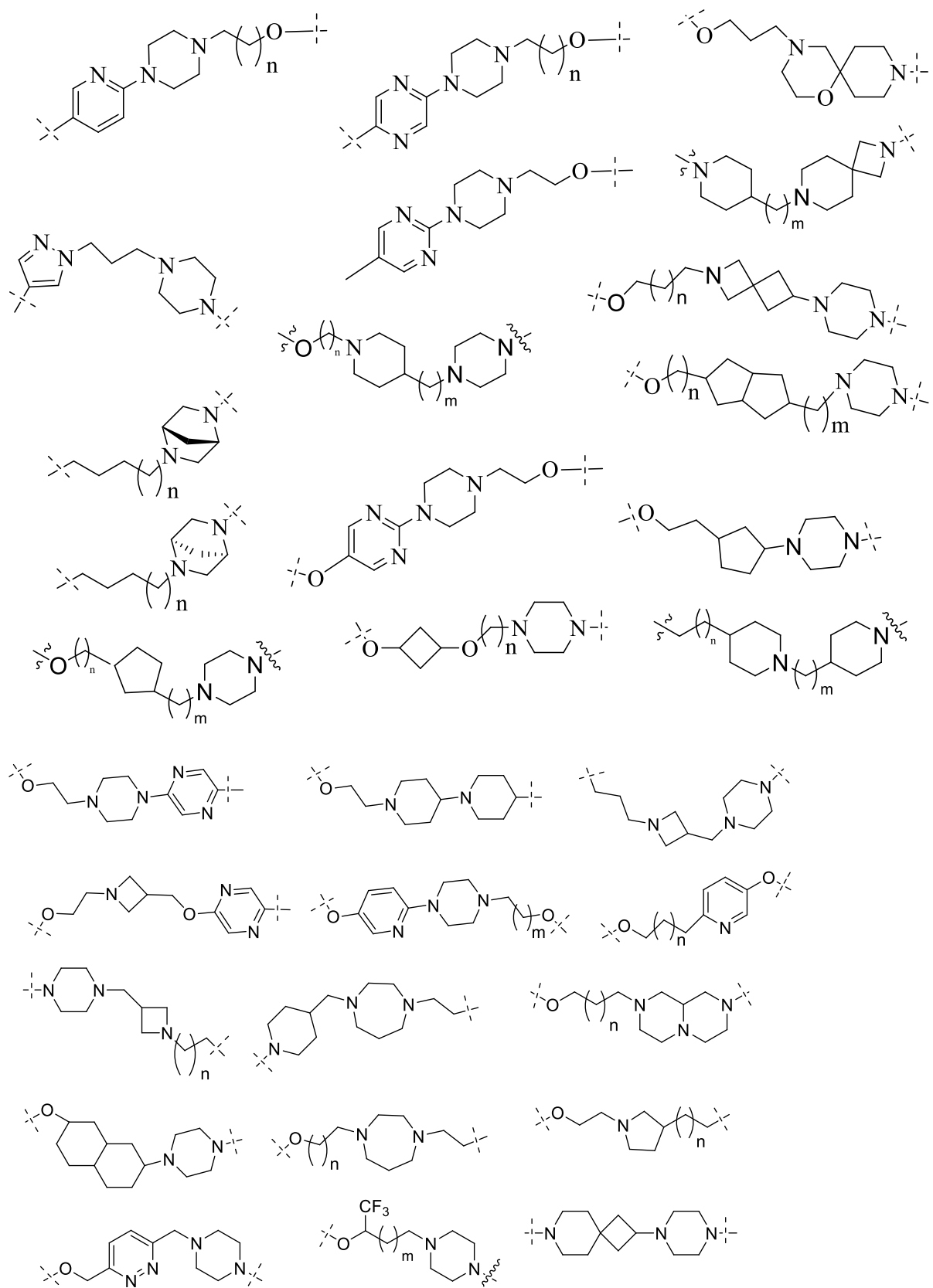


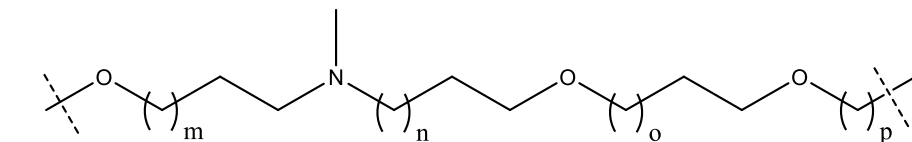


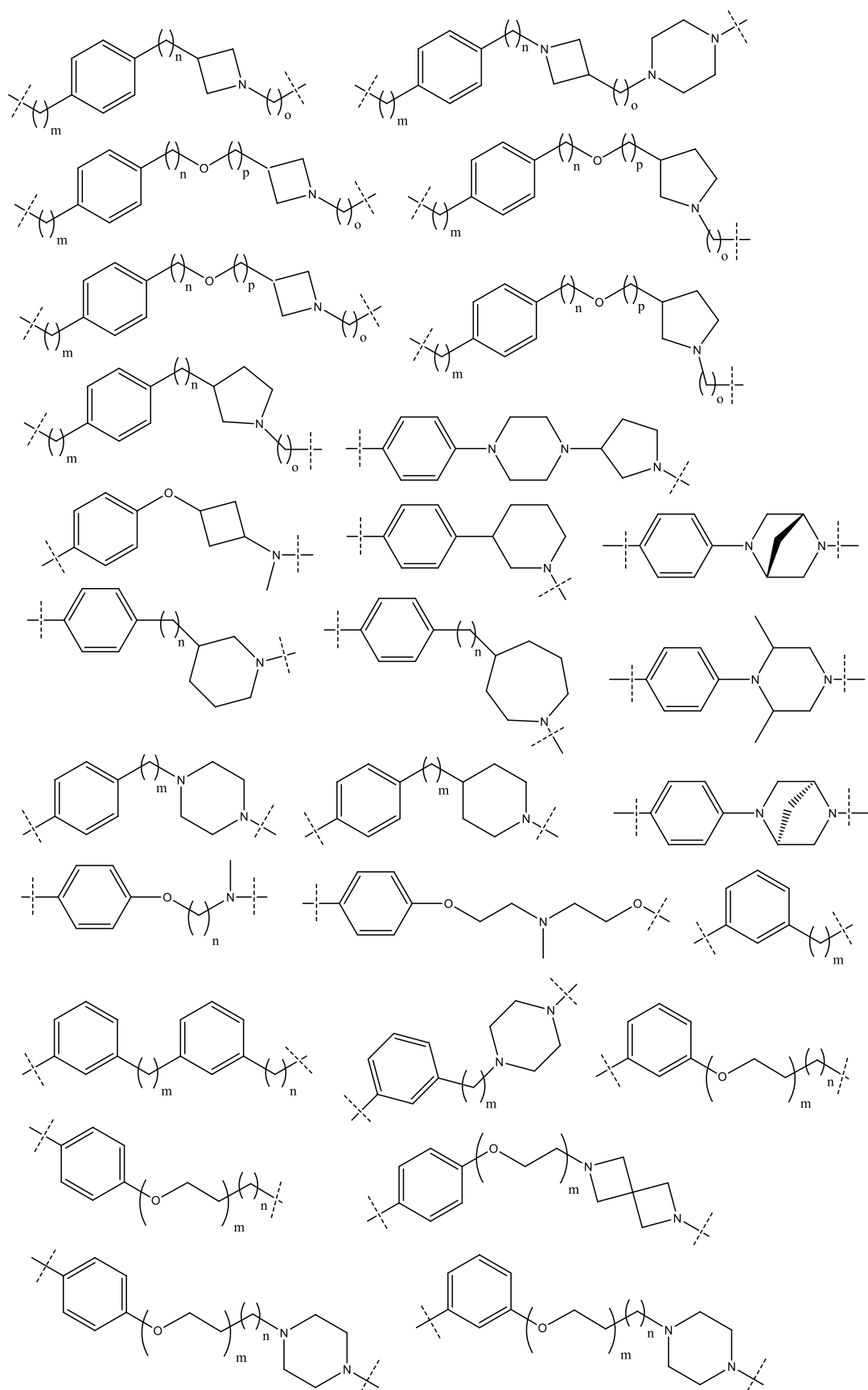


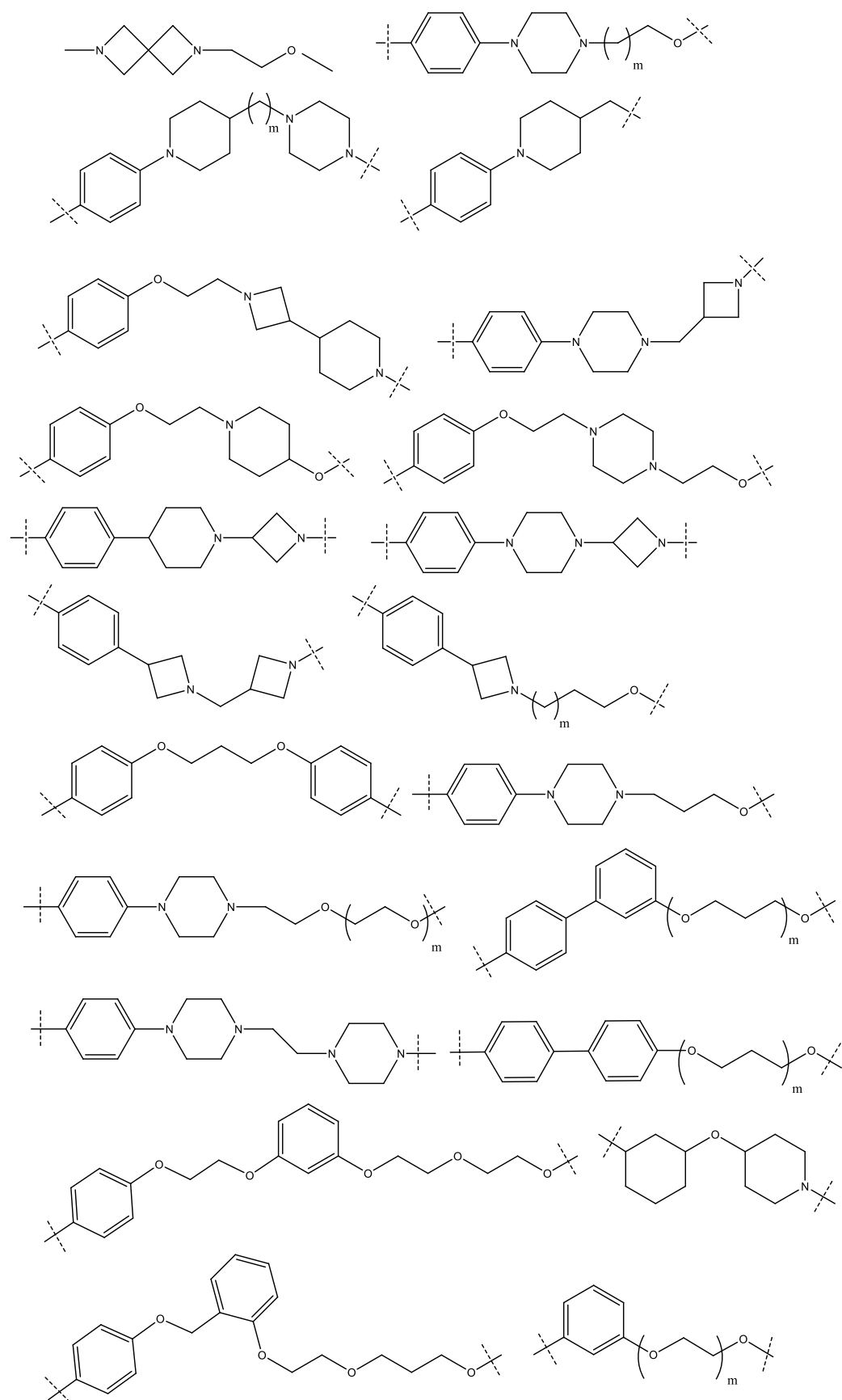


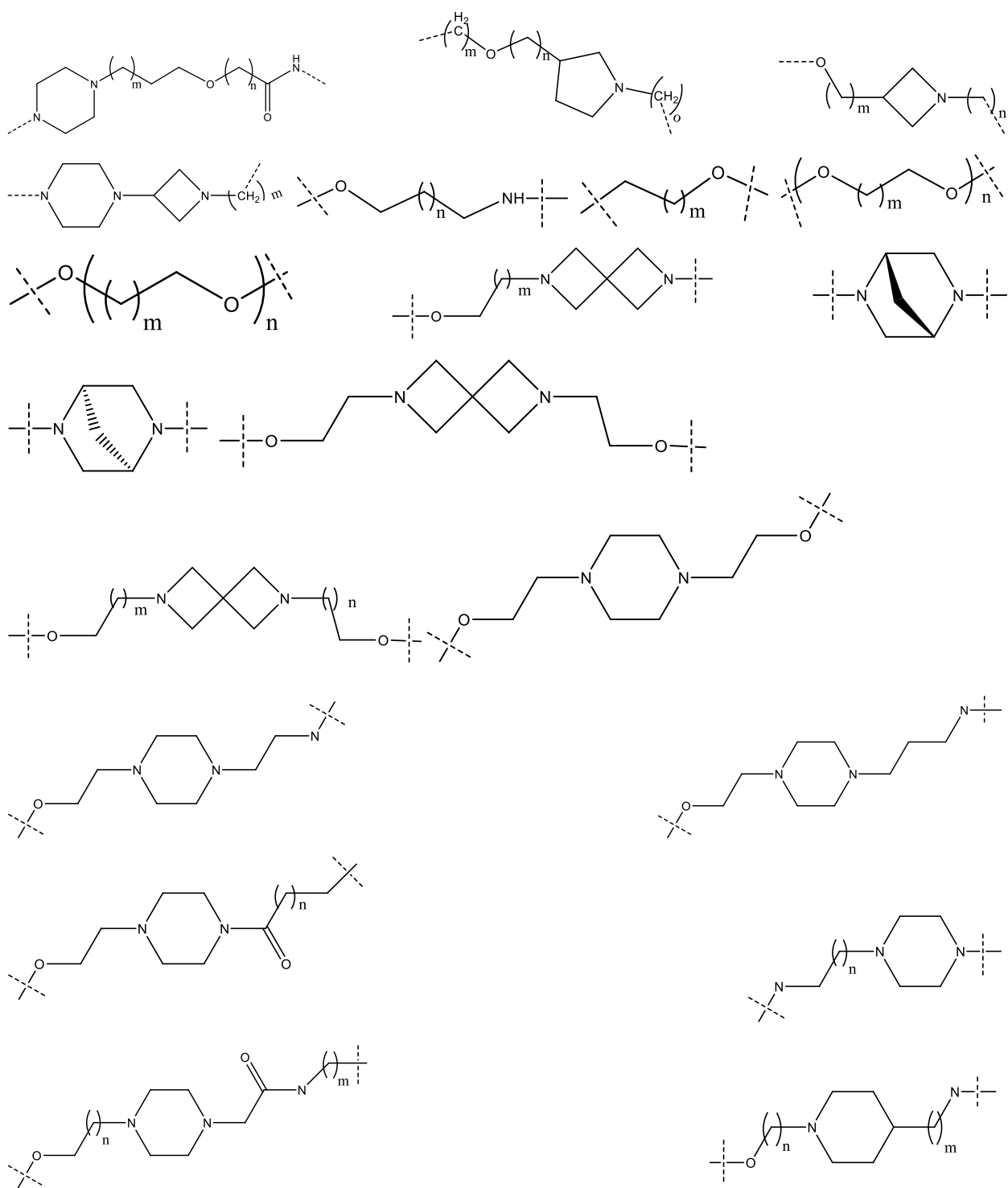


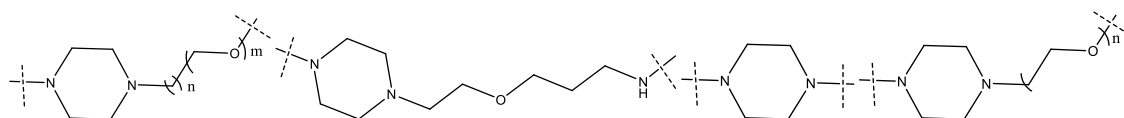
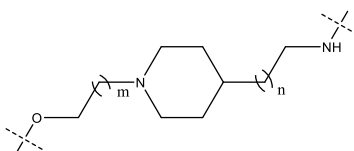
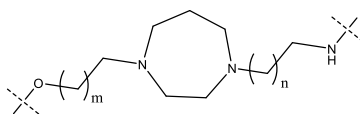
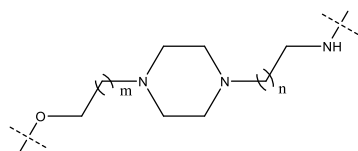
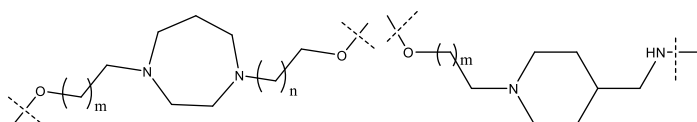
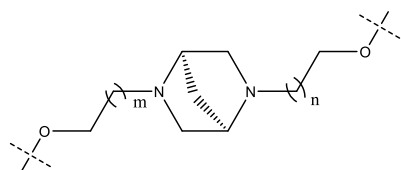
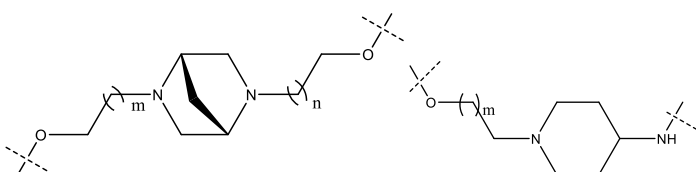
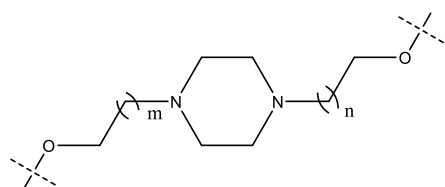
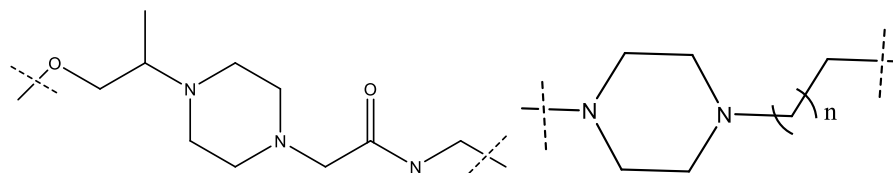
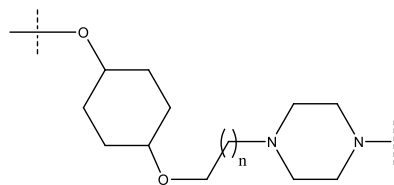
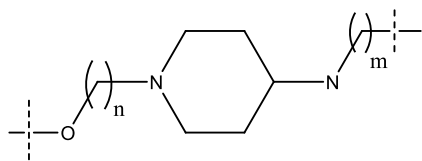


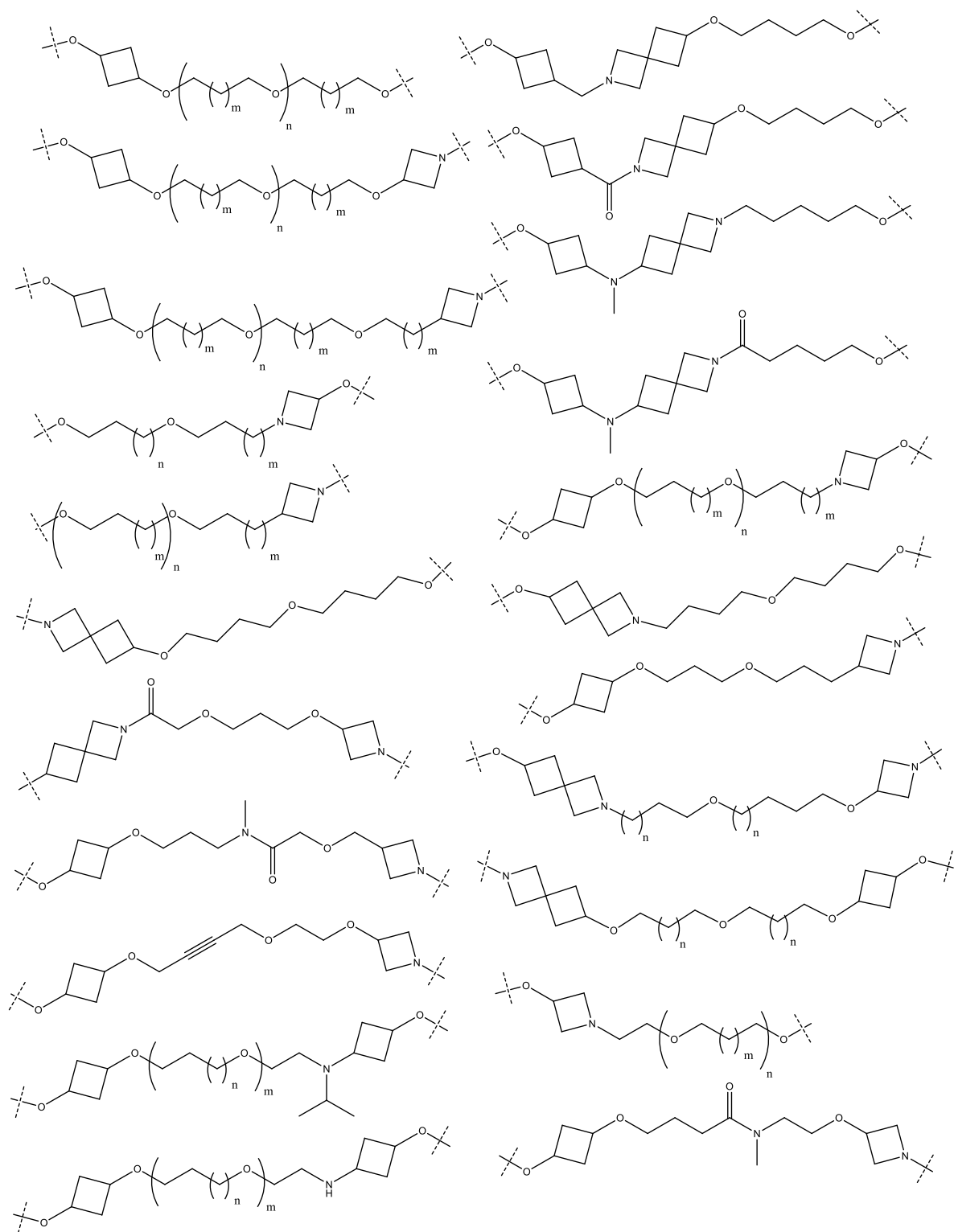


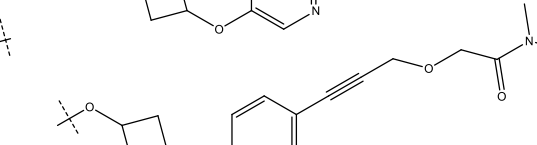
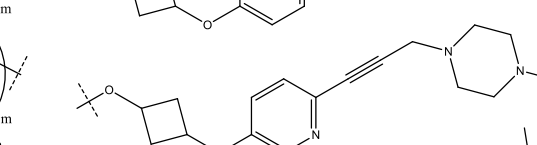
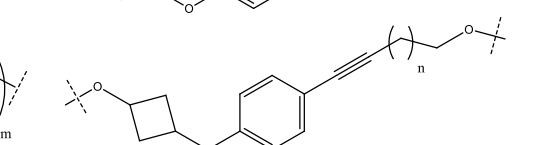
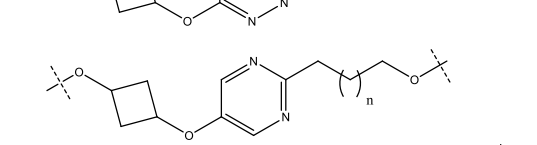
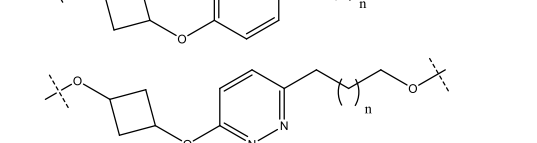
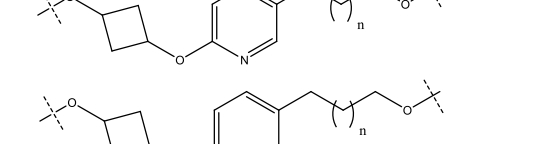
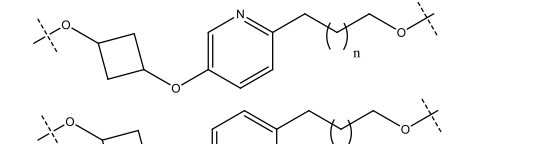
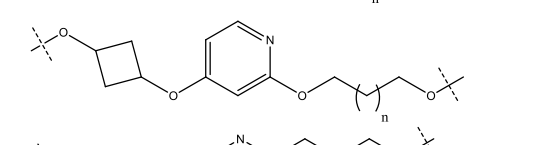
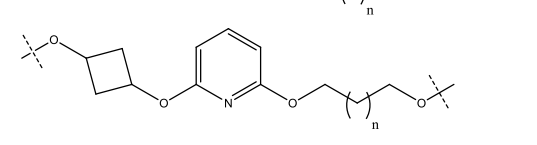
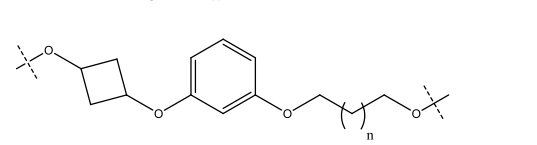
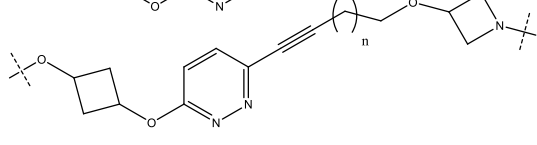
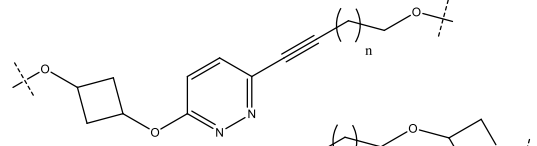
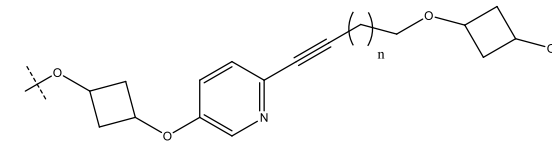
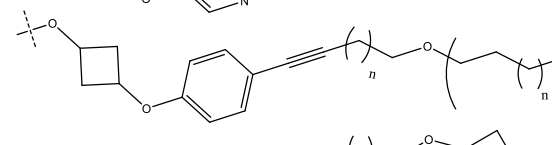
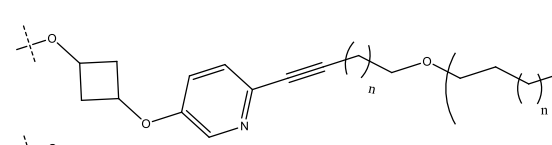
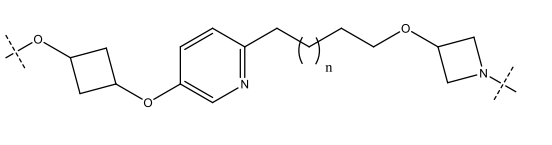
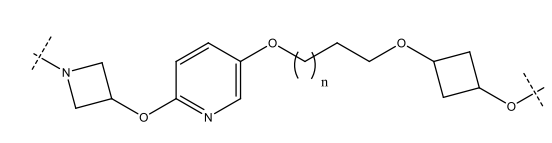
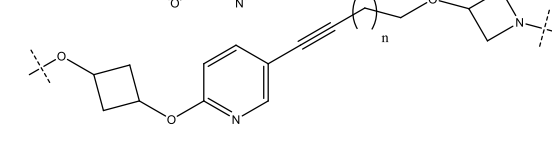
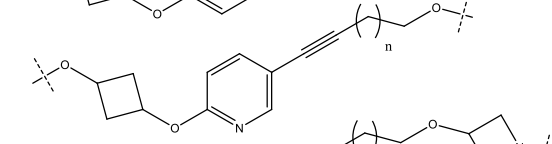
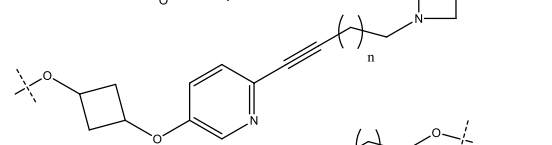
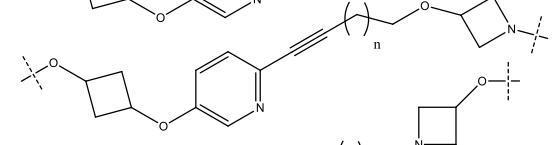
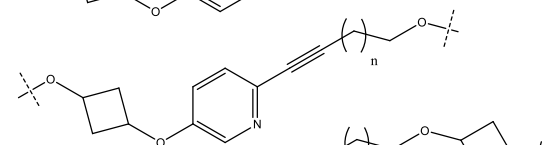
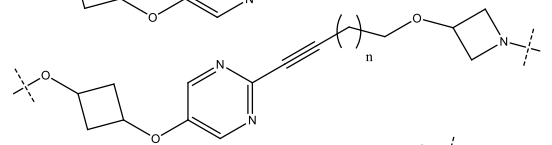
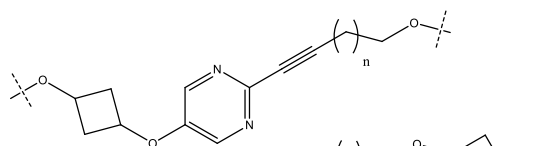


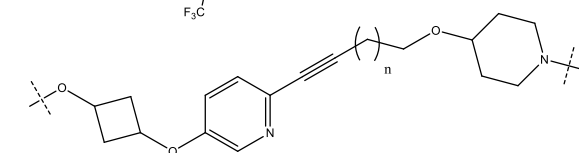
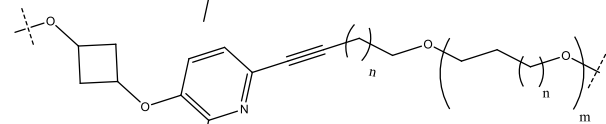
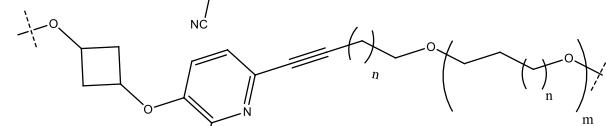
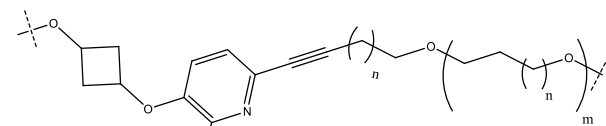
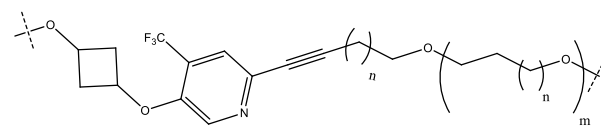
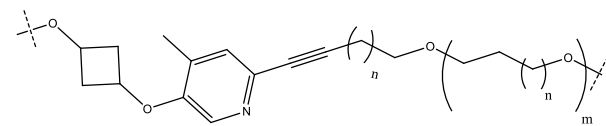
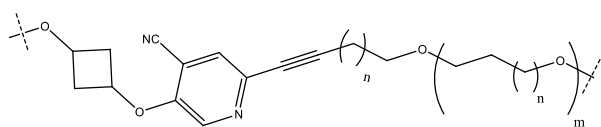
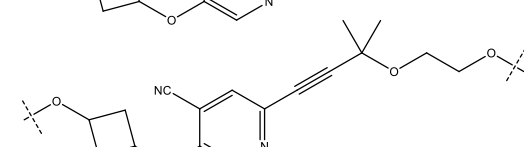
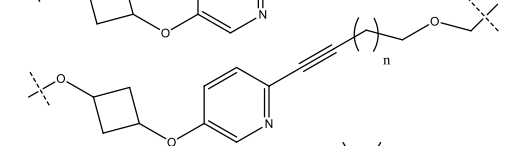
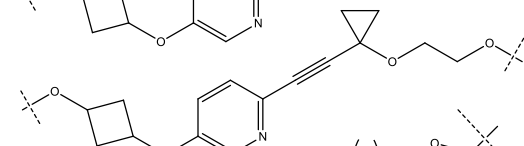
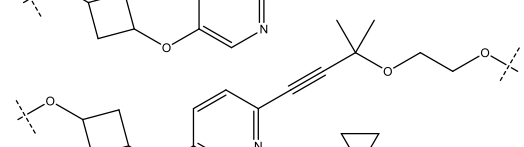
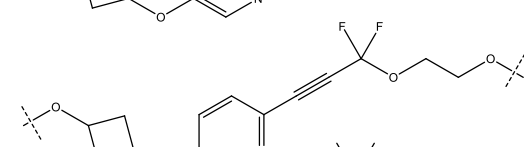
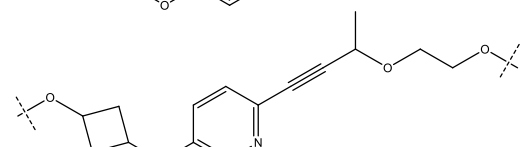
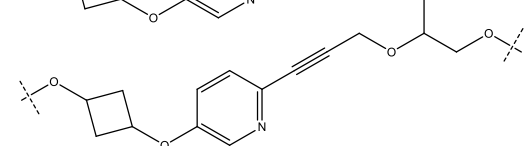
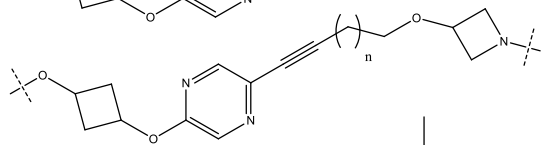
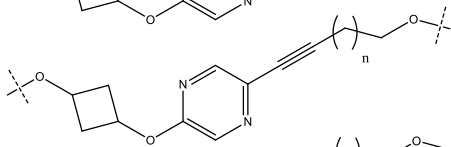
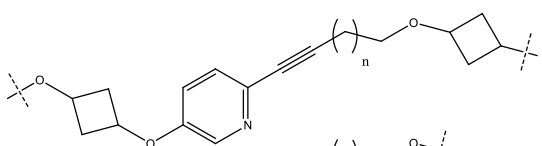


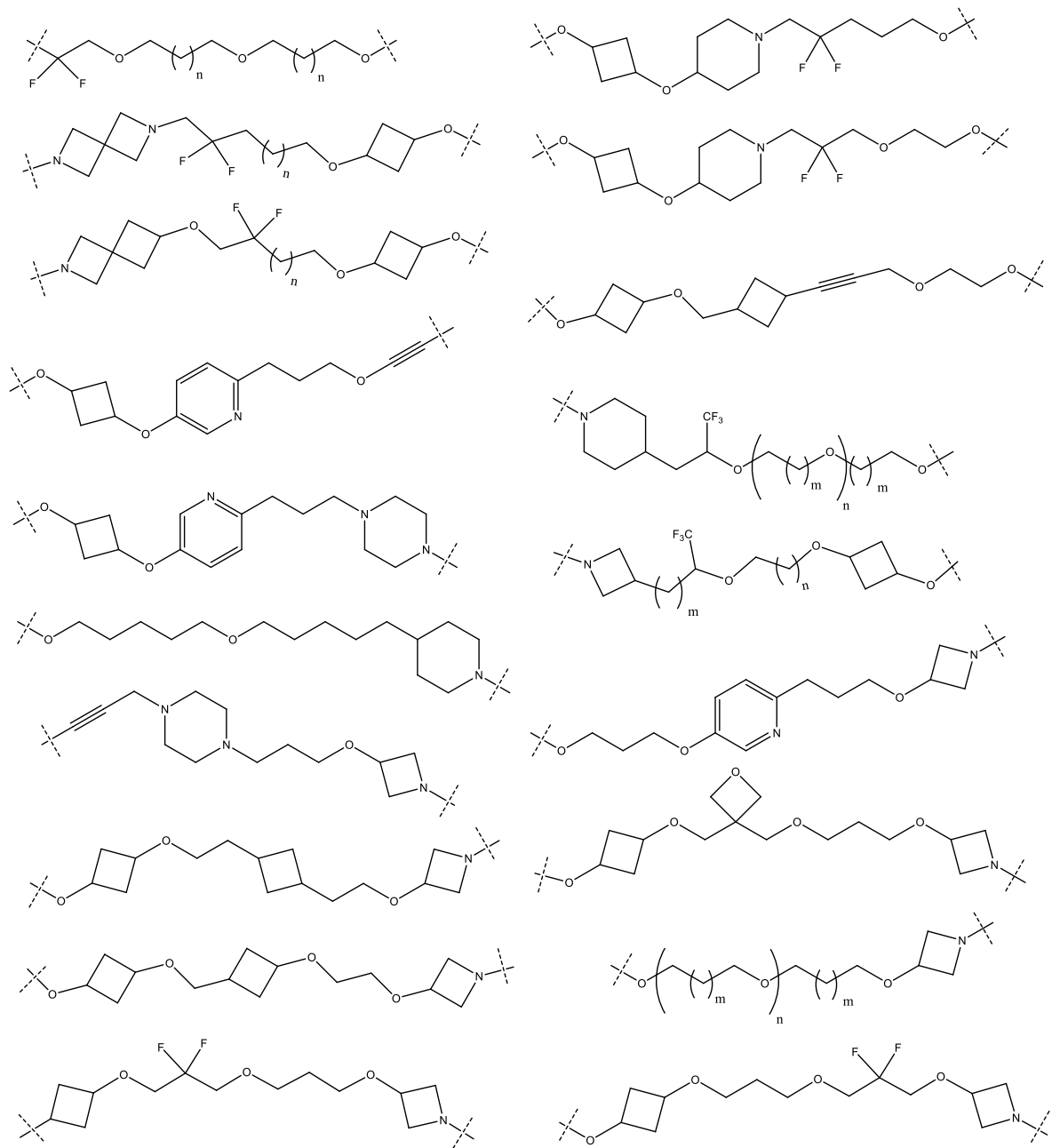


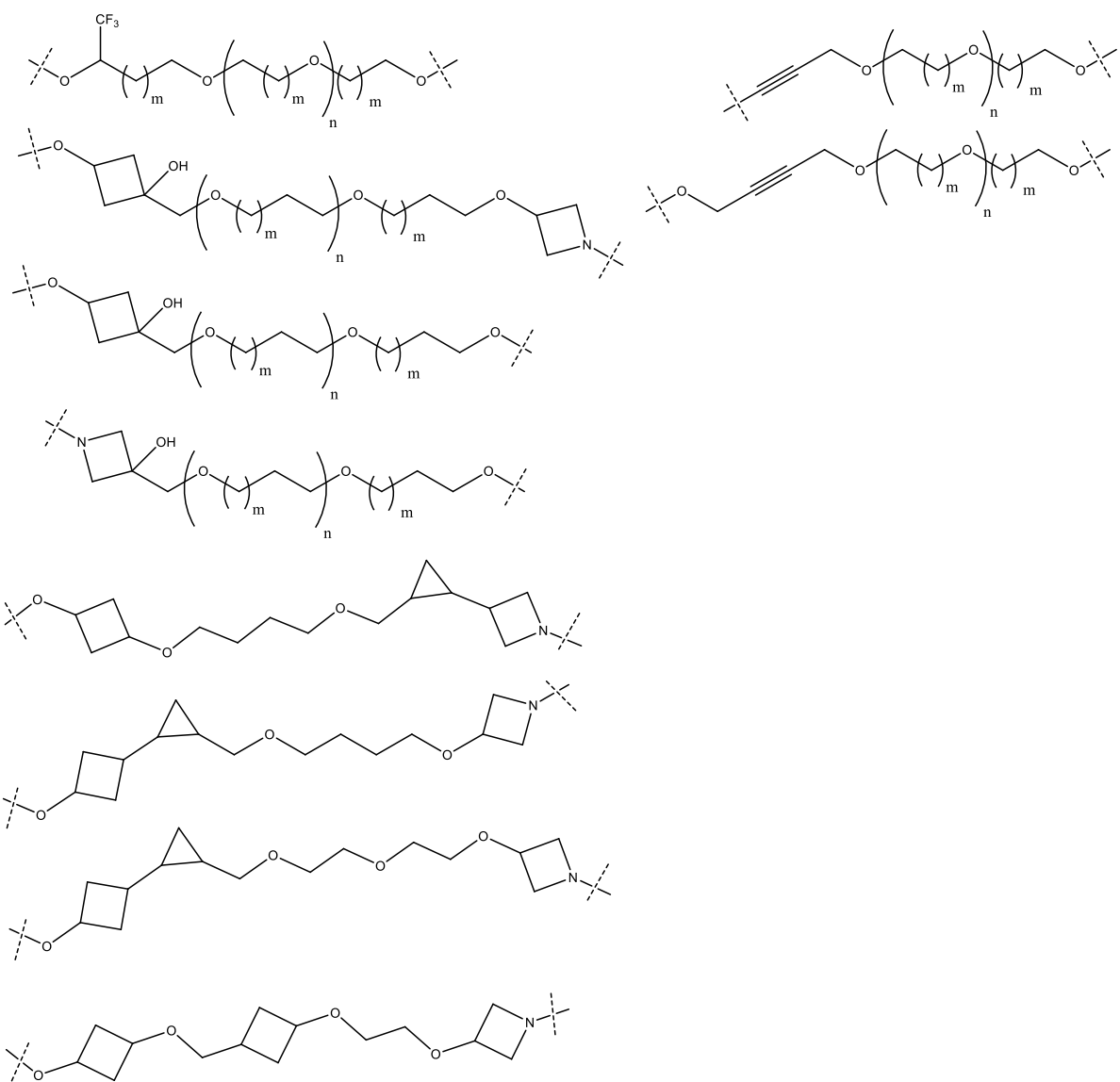


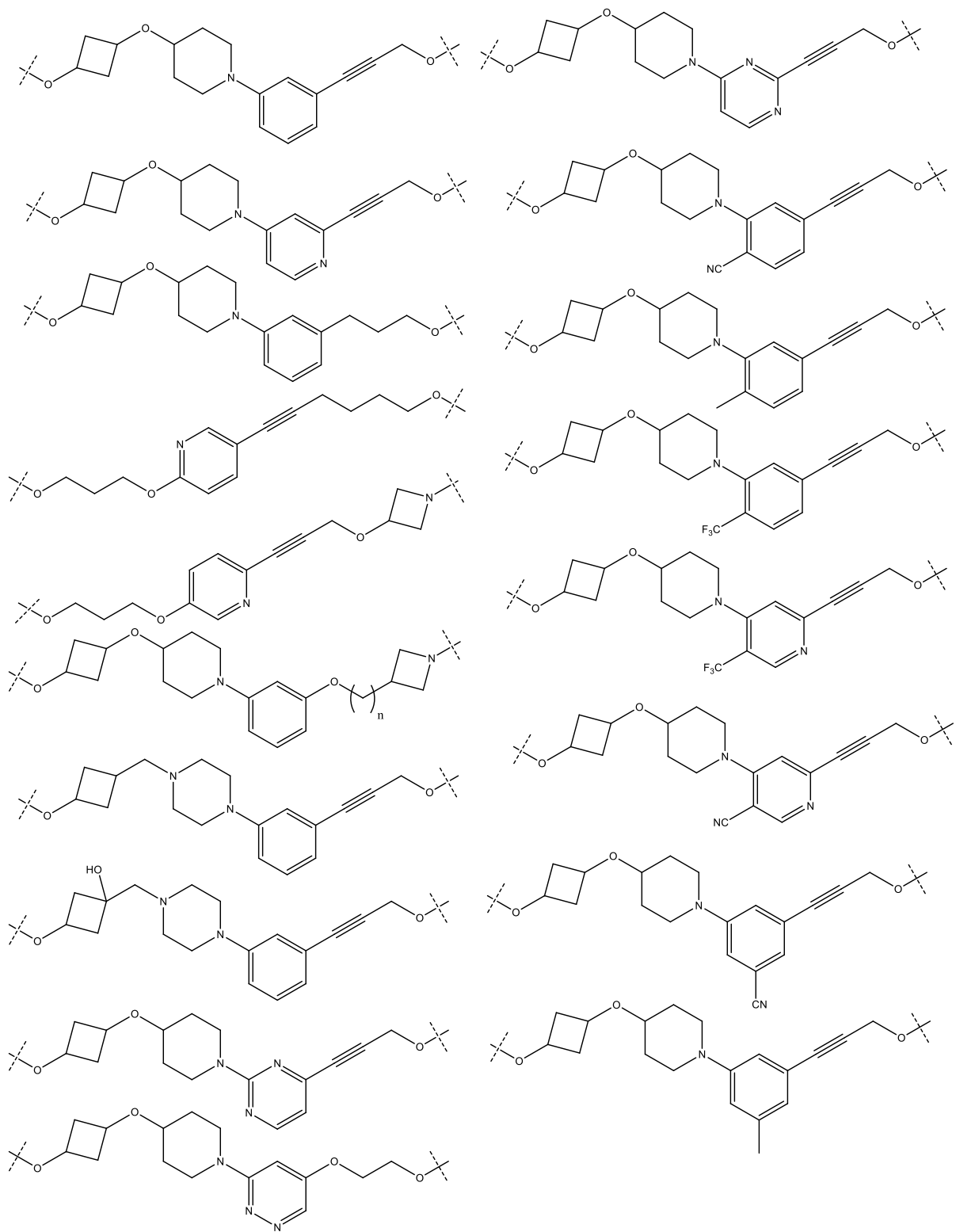


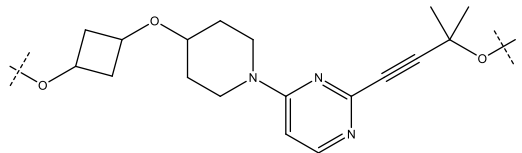
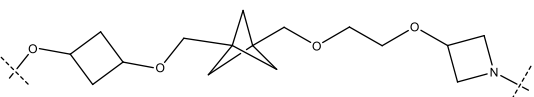
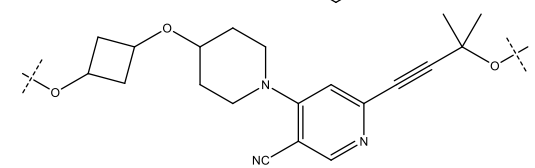
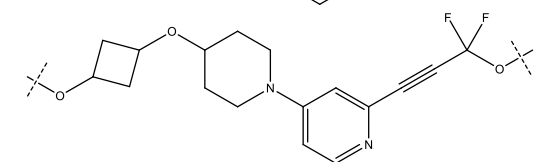
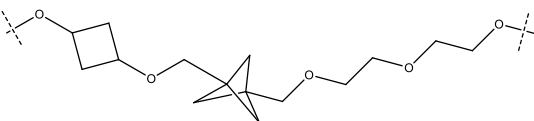
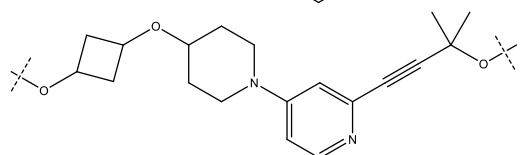
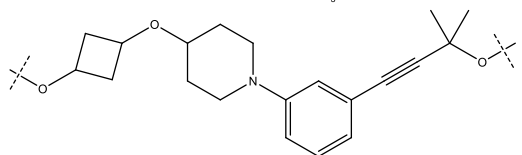
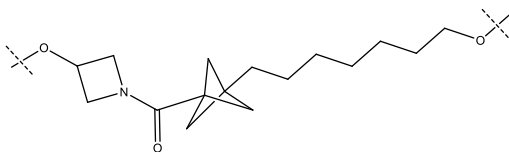
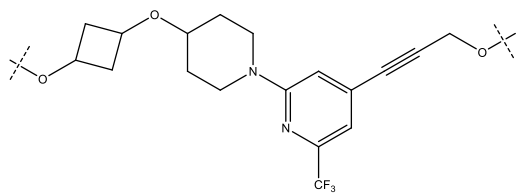
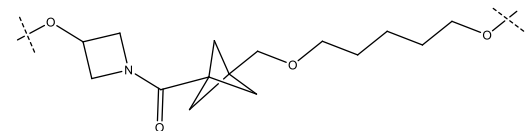
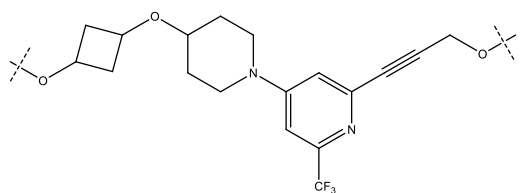
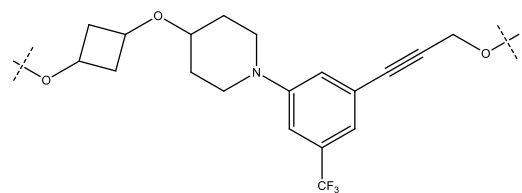


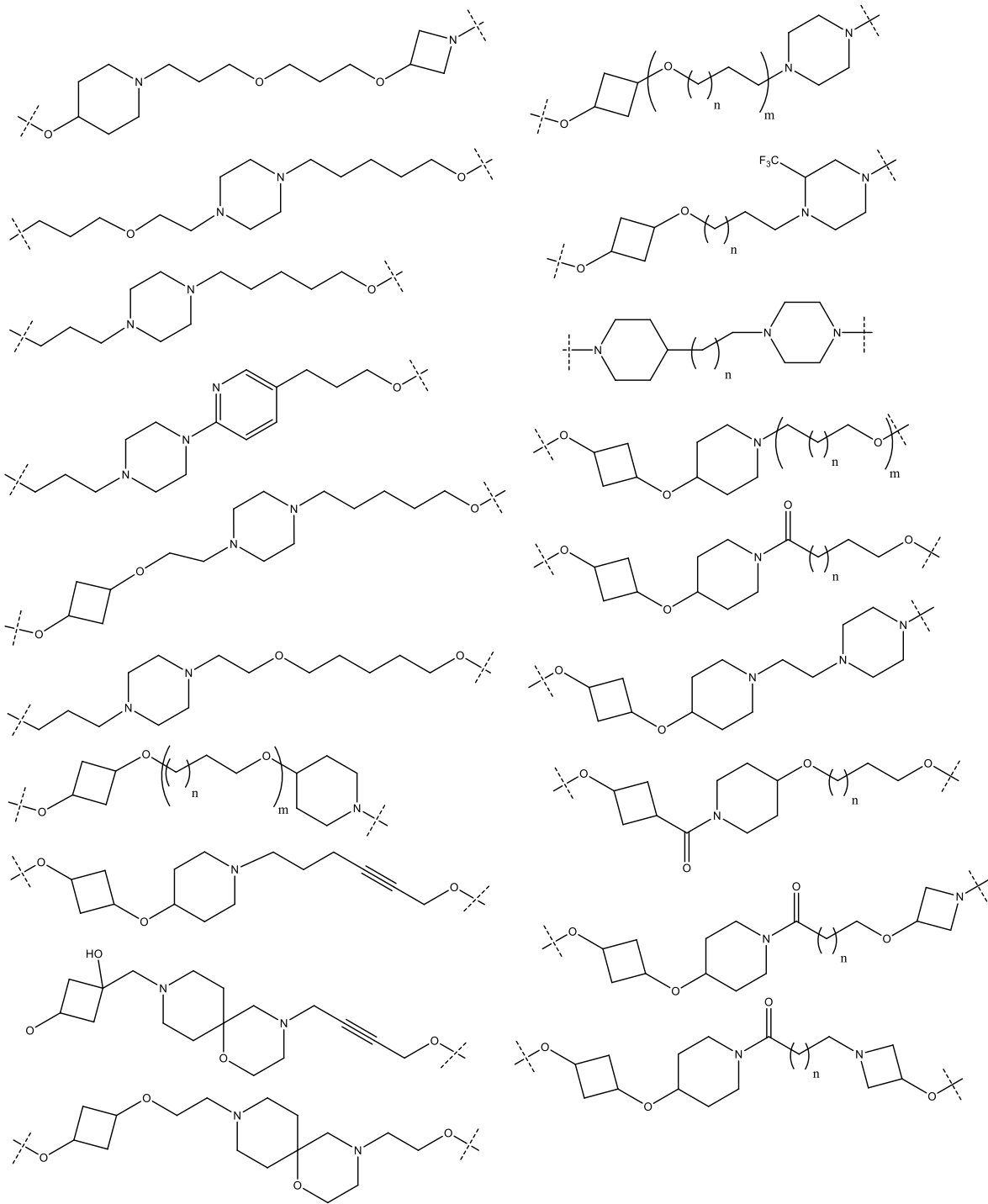


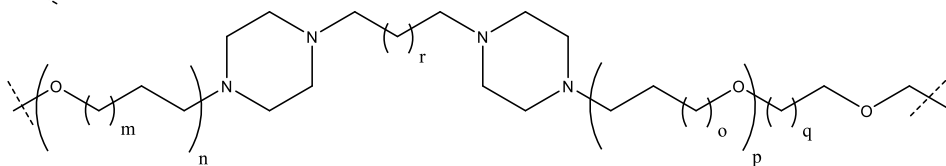
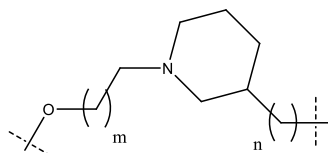
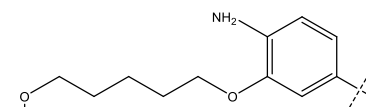
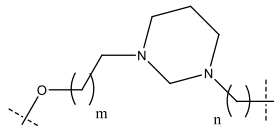
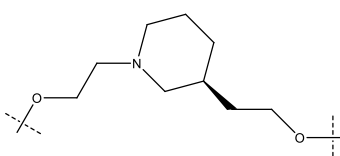
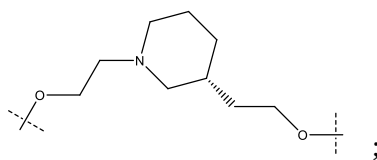
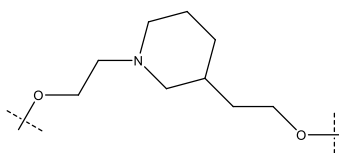
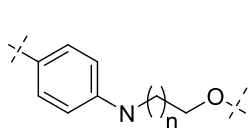
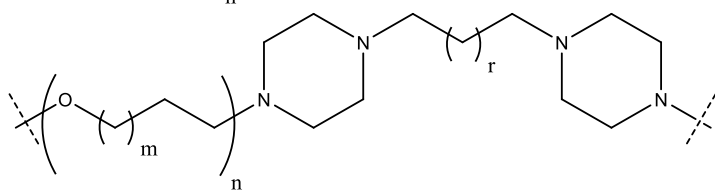
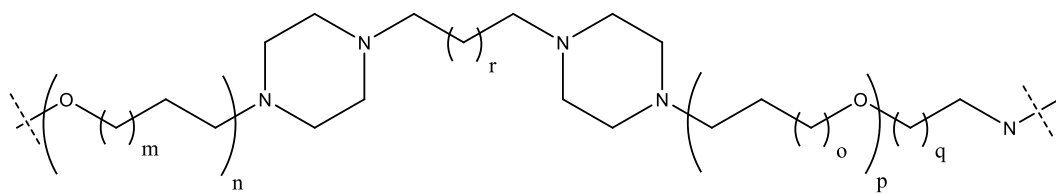
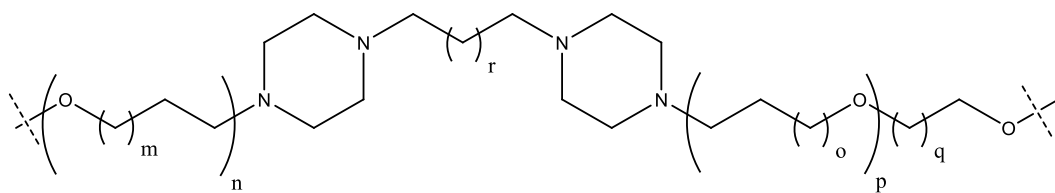


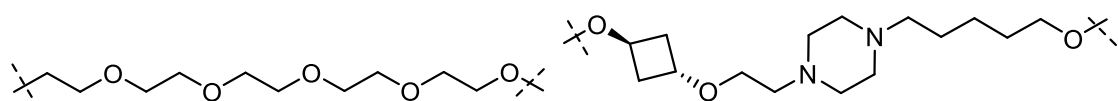


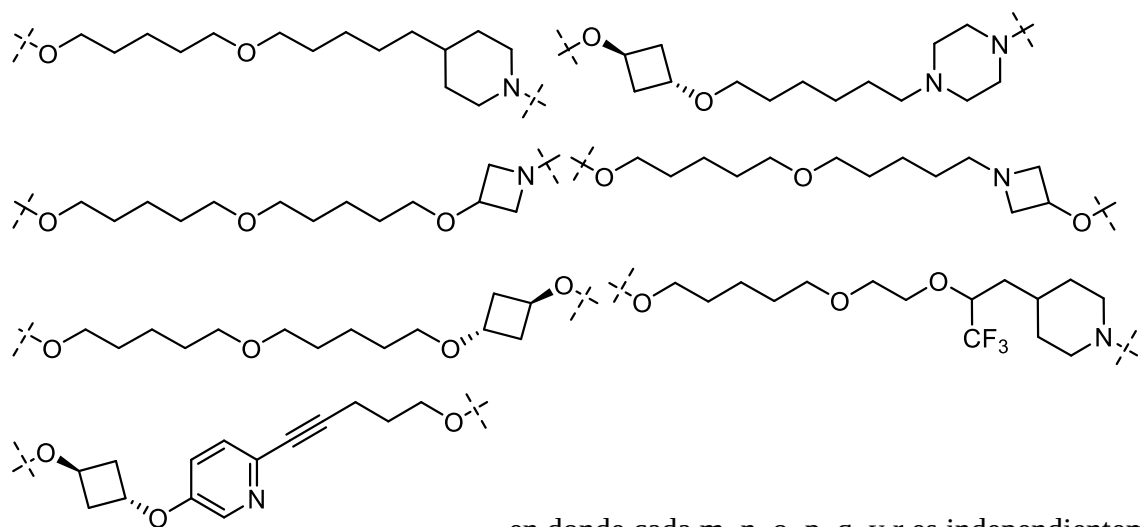






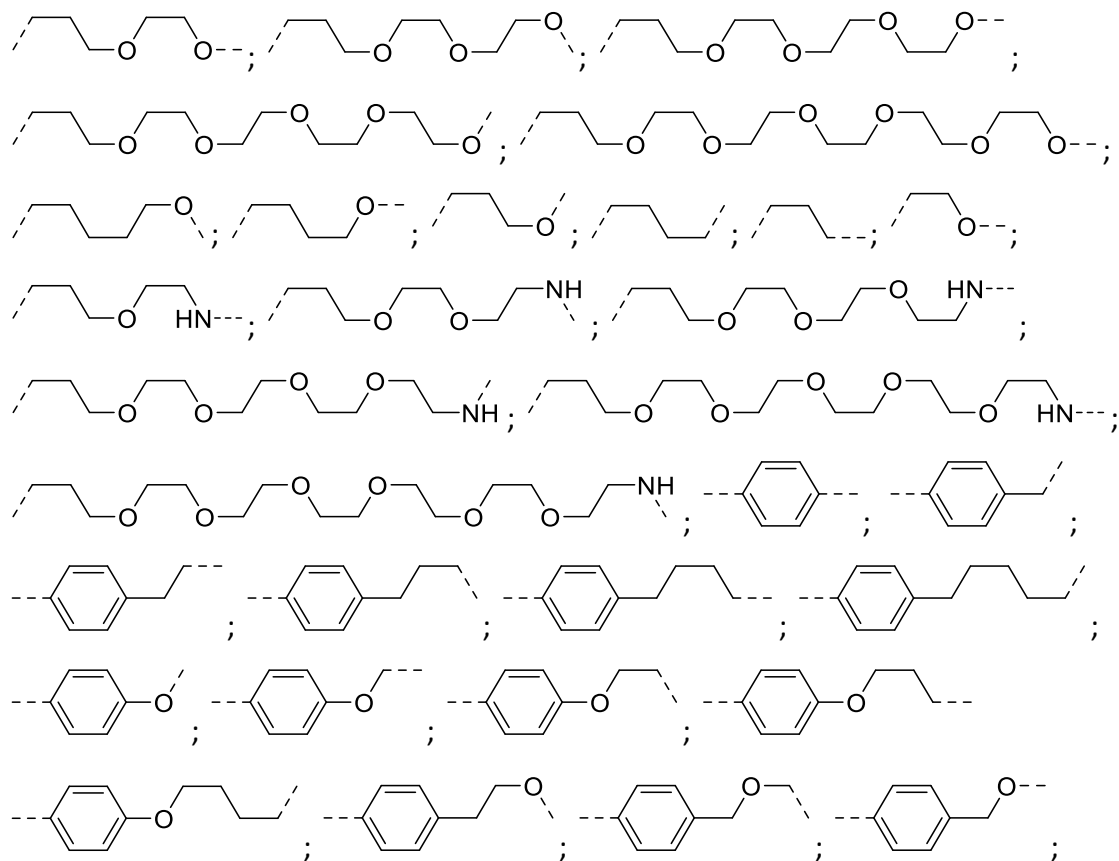


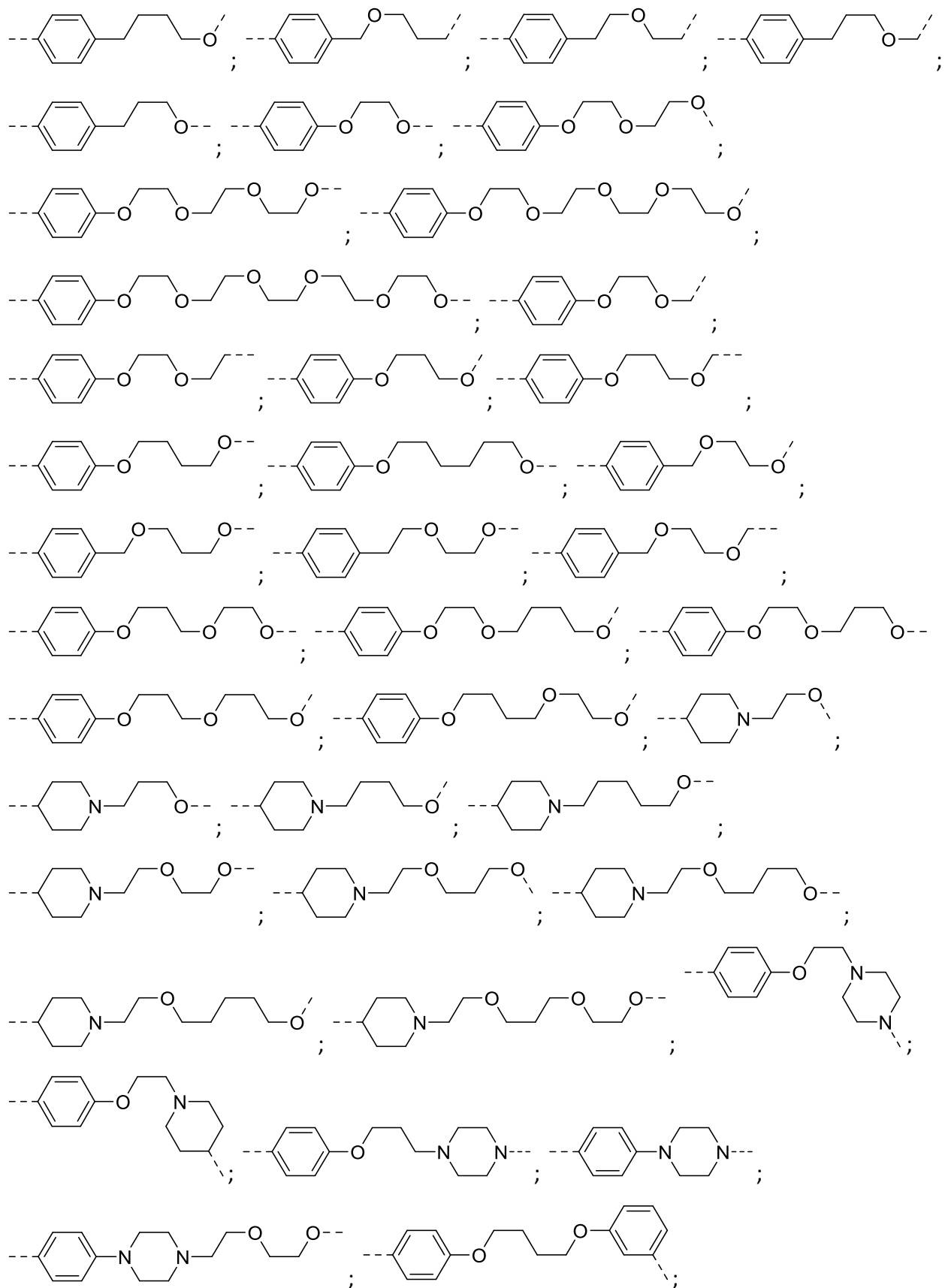


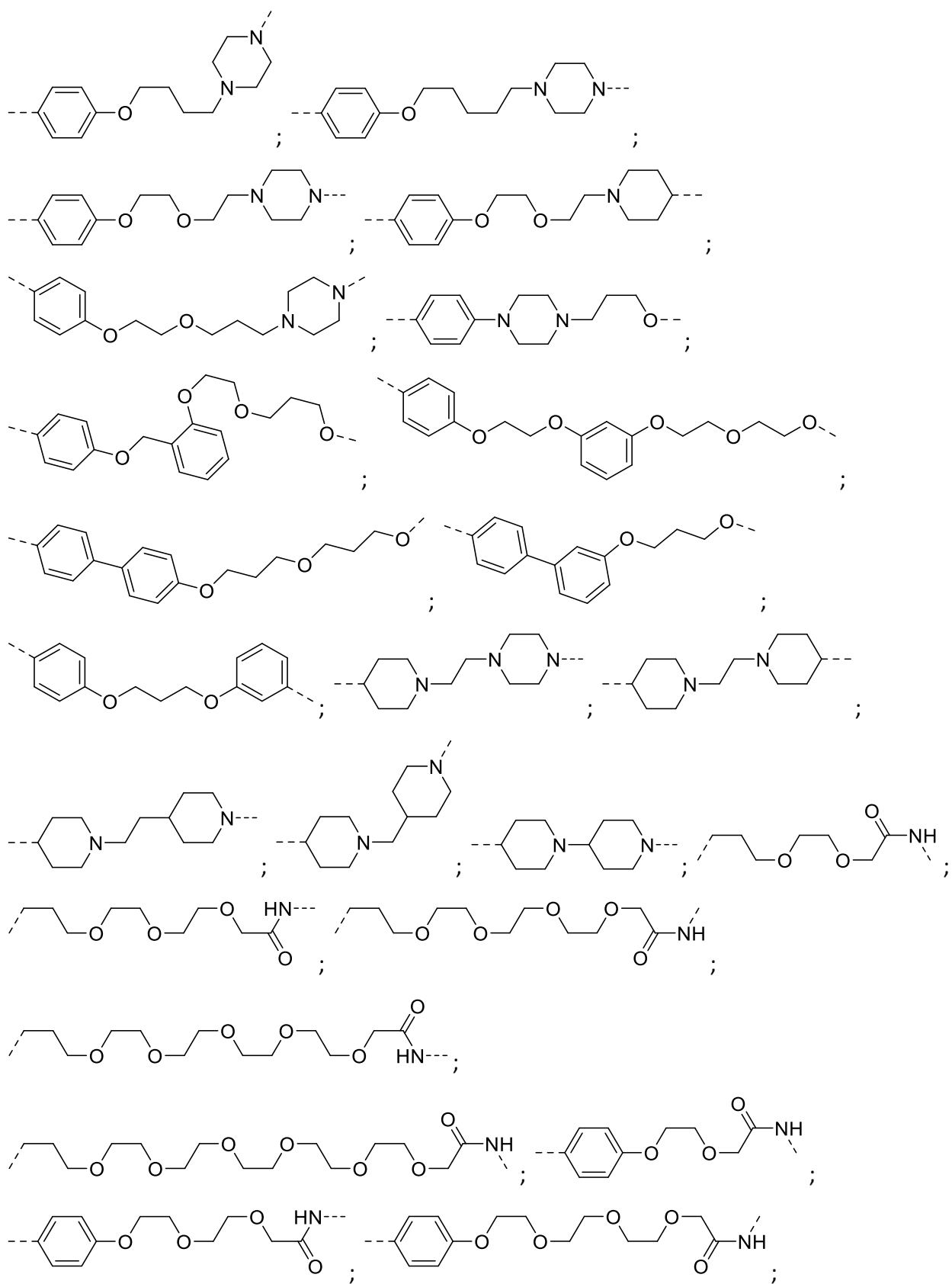


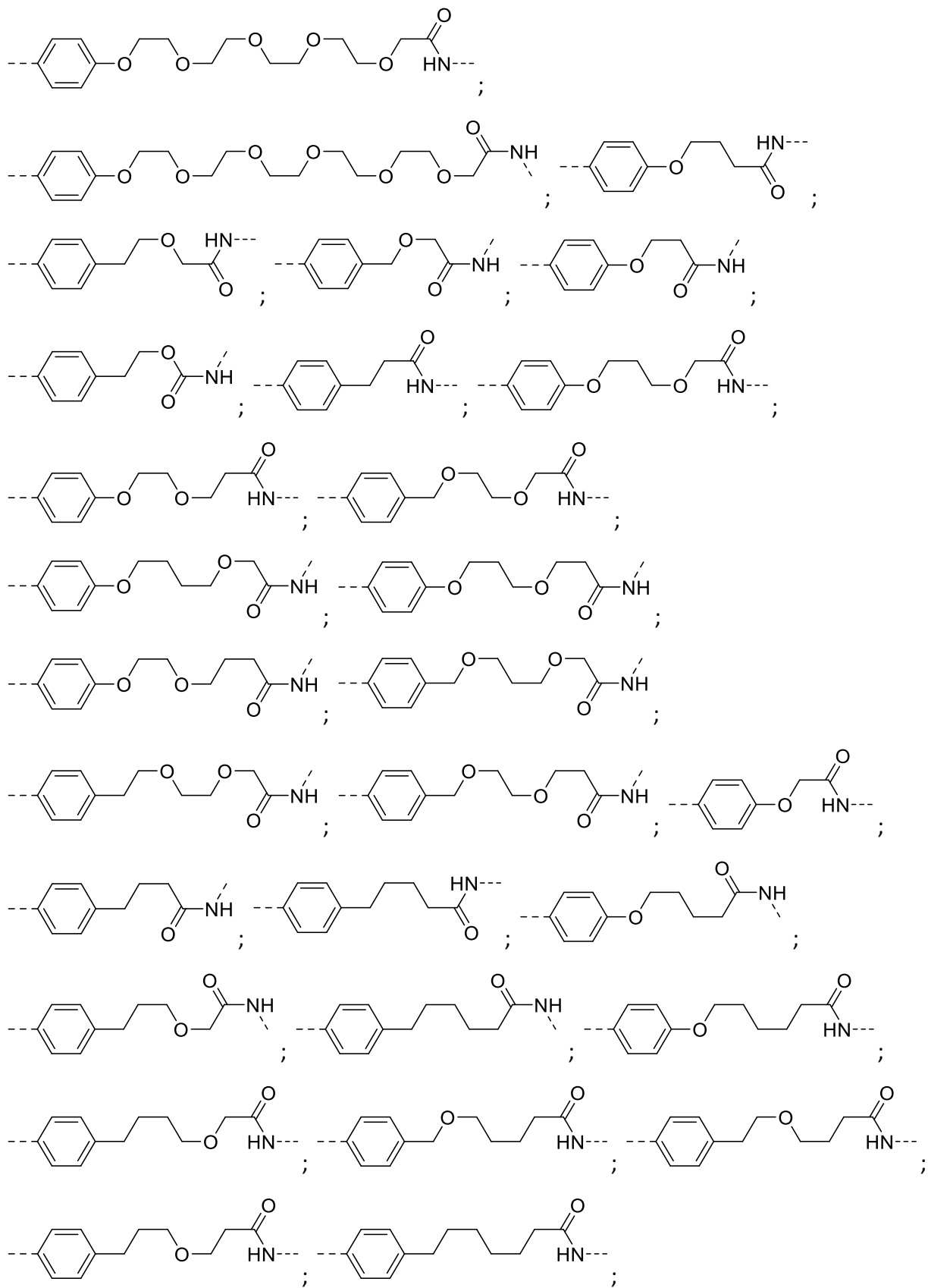
, en donde cada m, n, o, p, q, y r es independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, o 20.

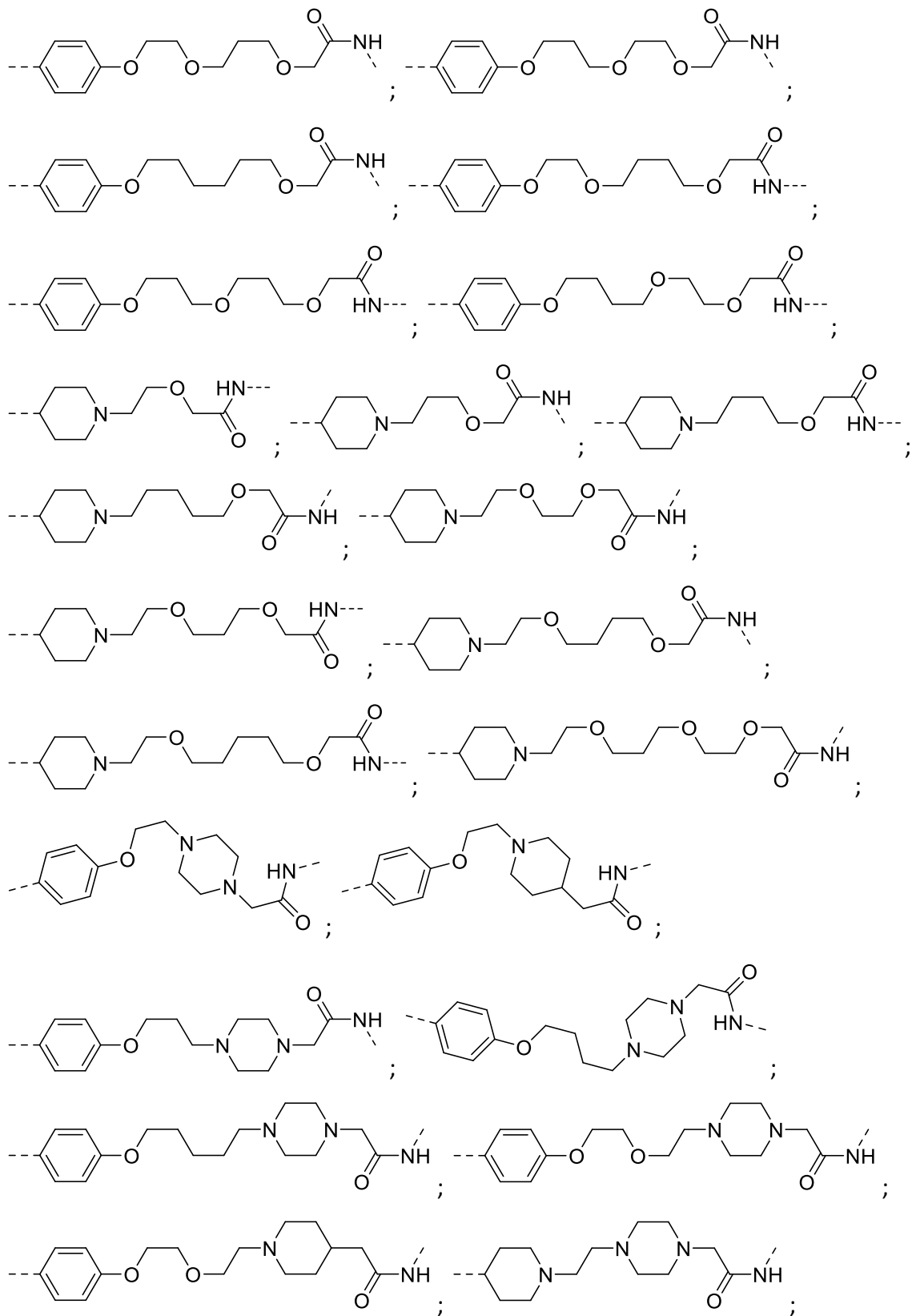
1312. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones **21-9**, en donde el enlazador (L) se selecciona del grupo que consiste en:

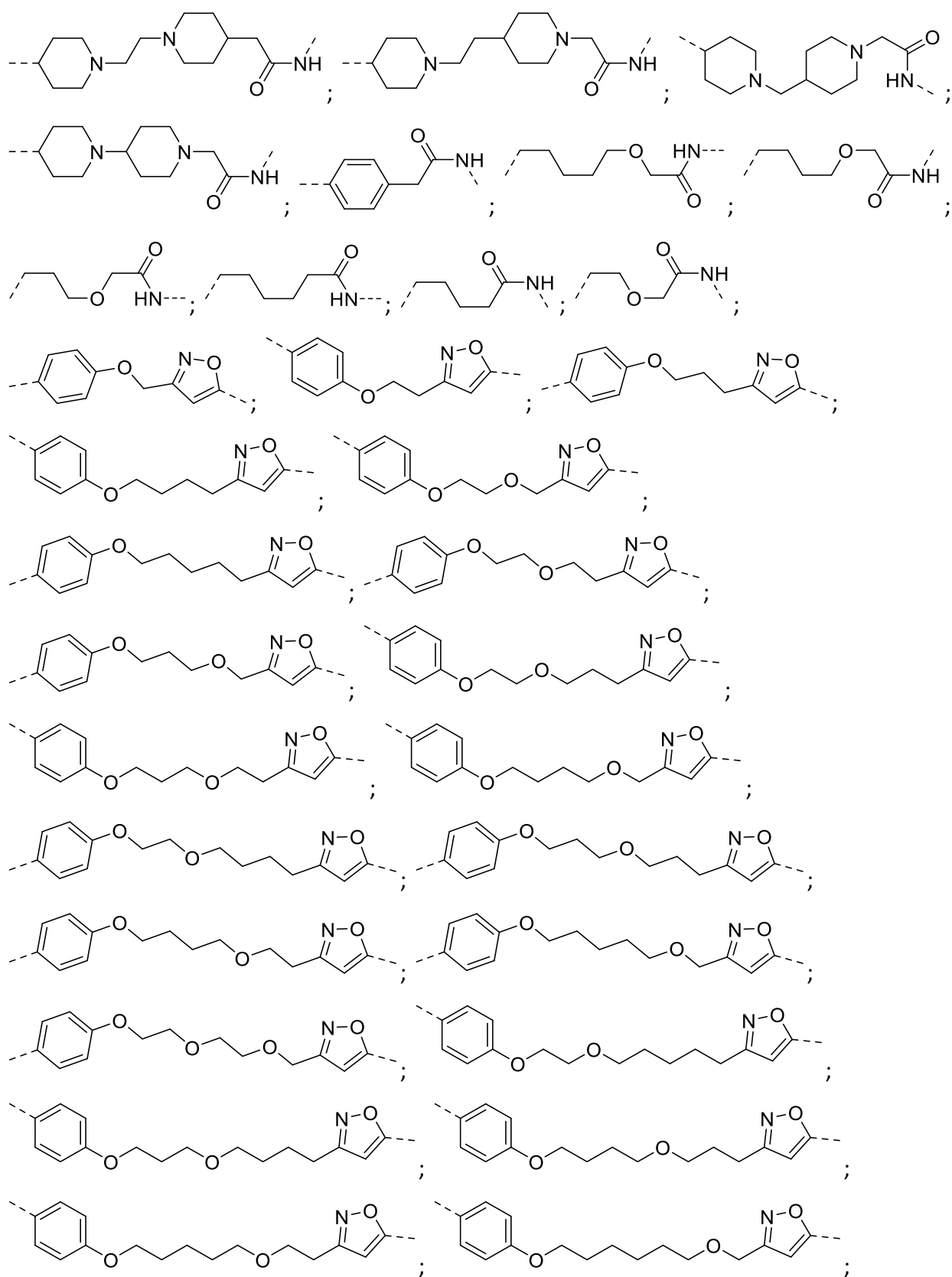


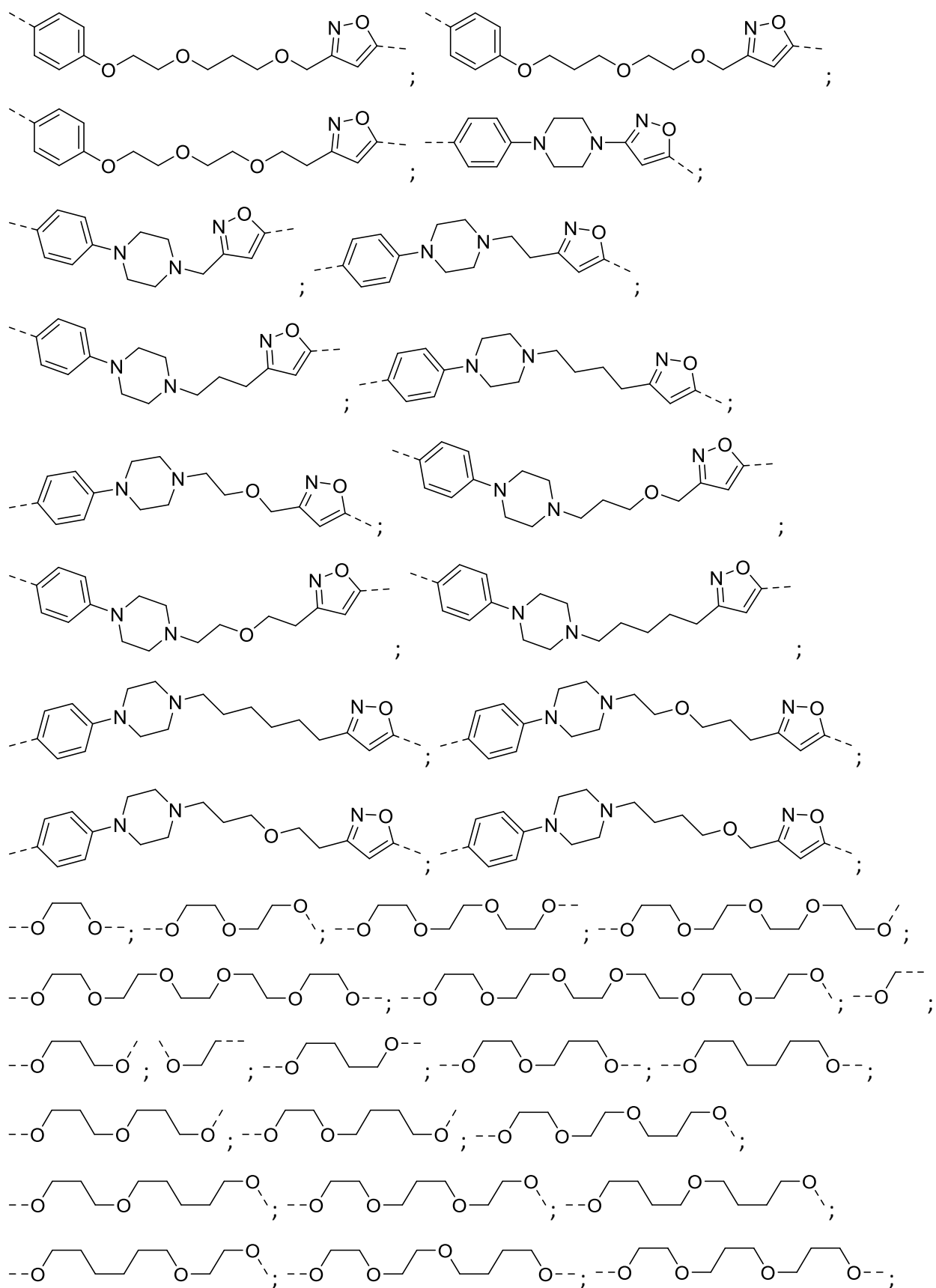


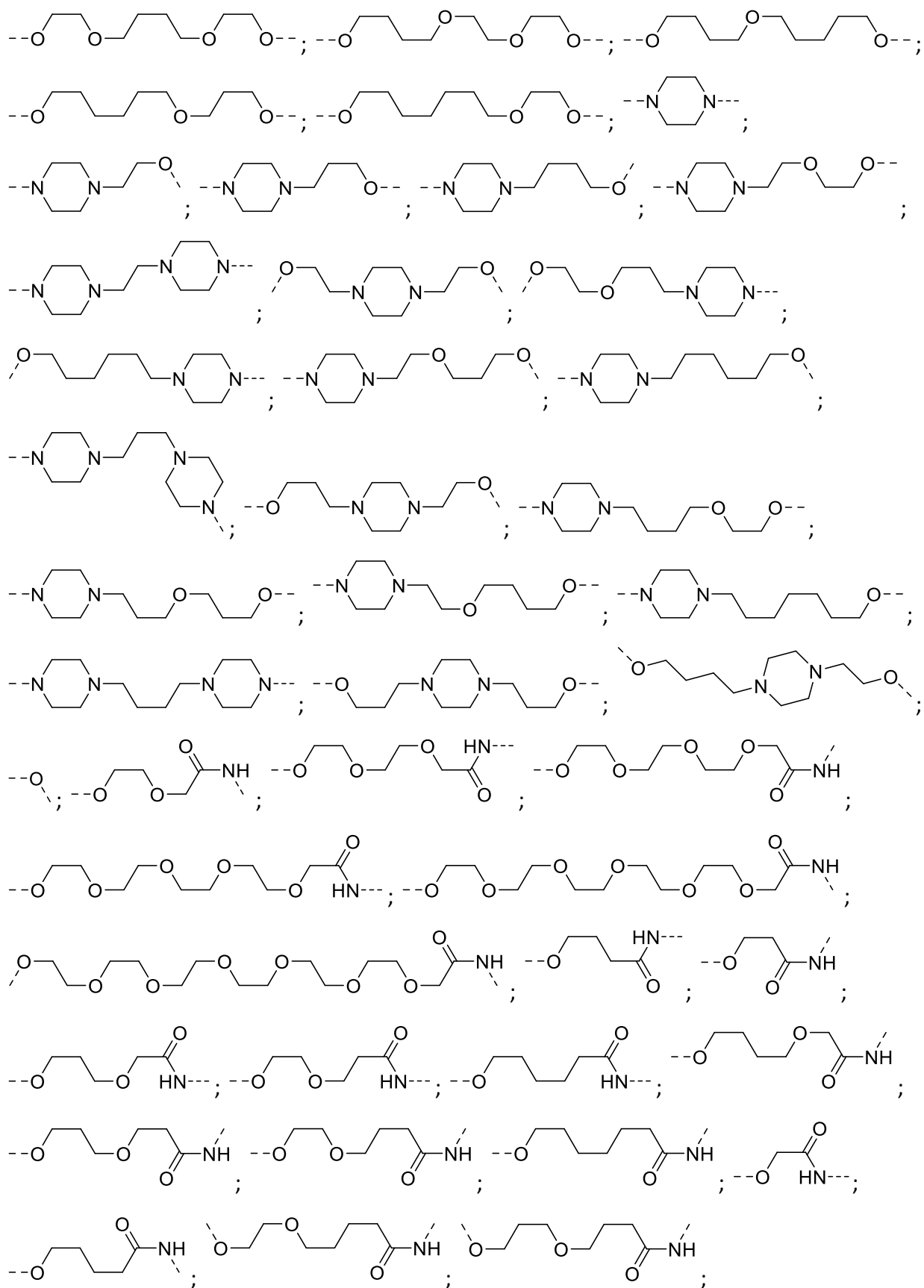


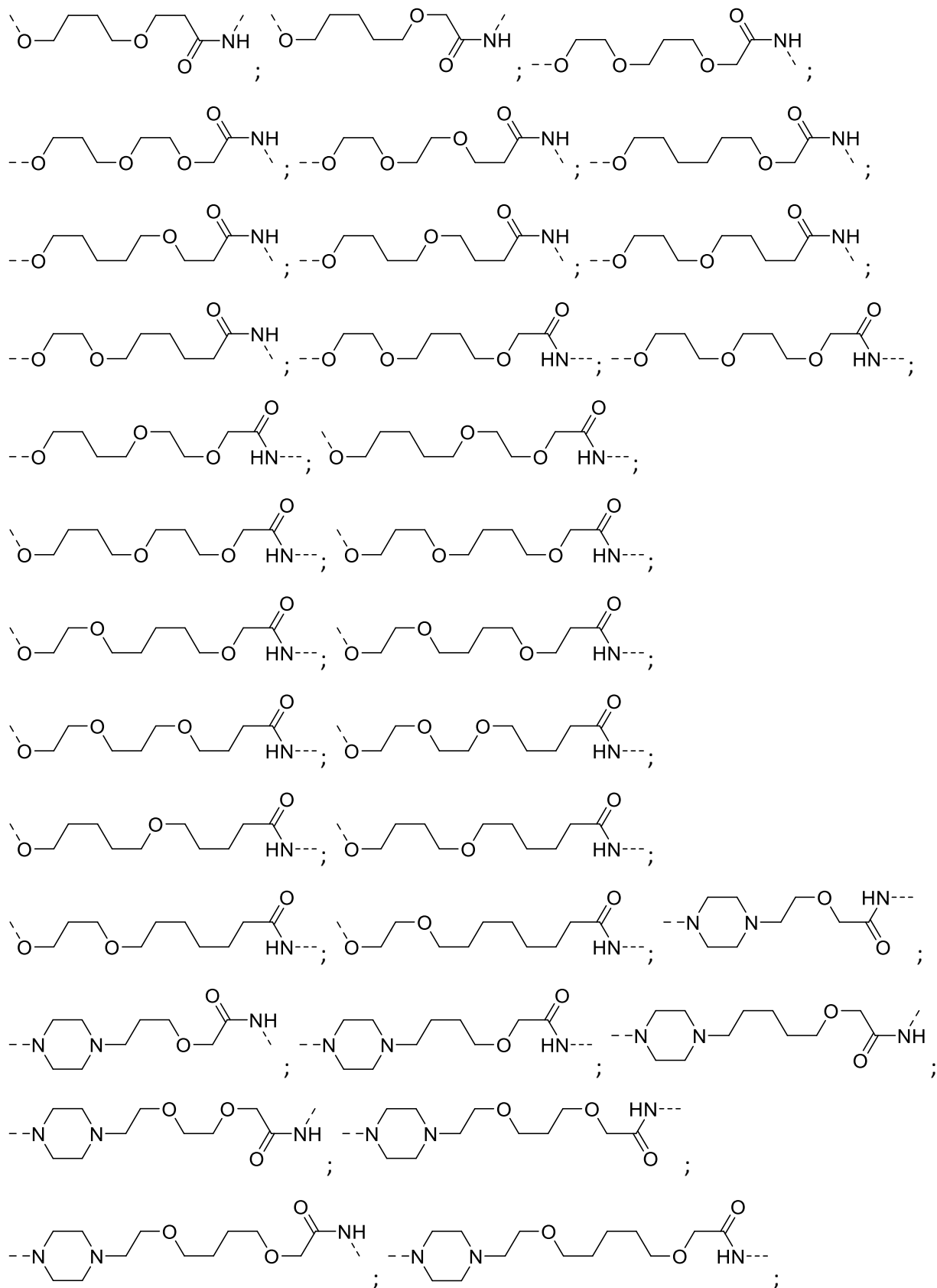


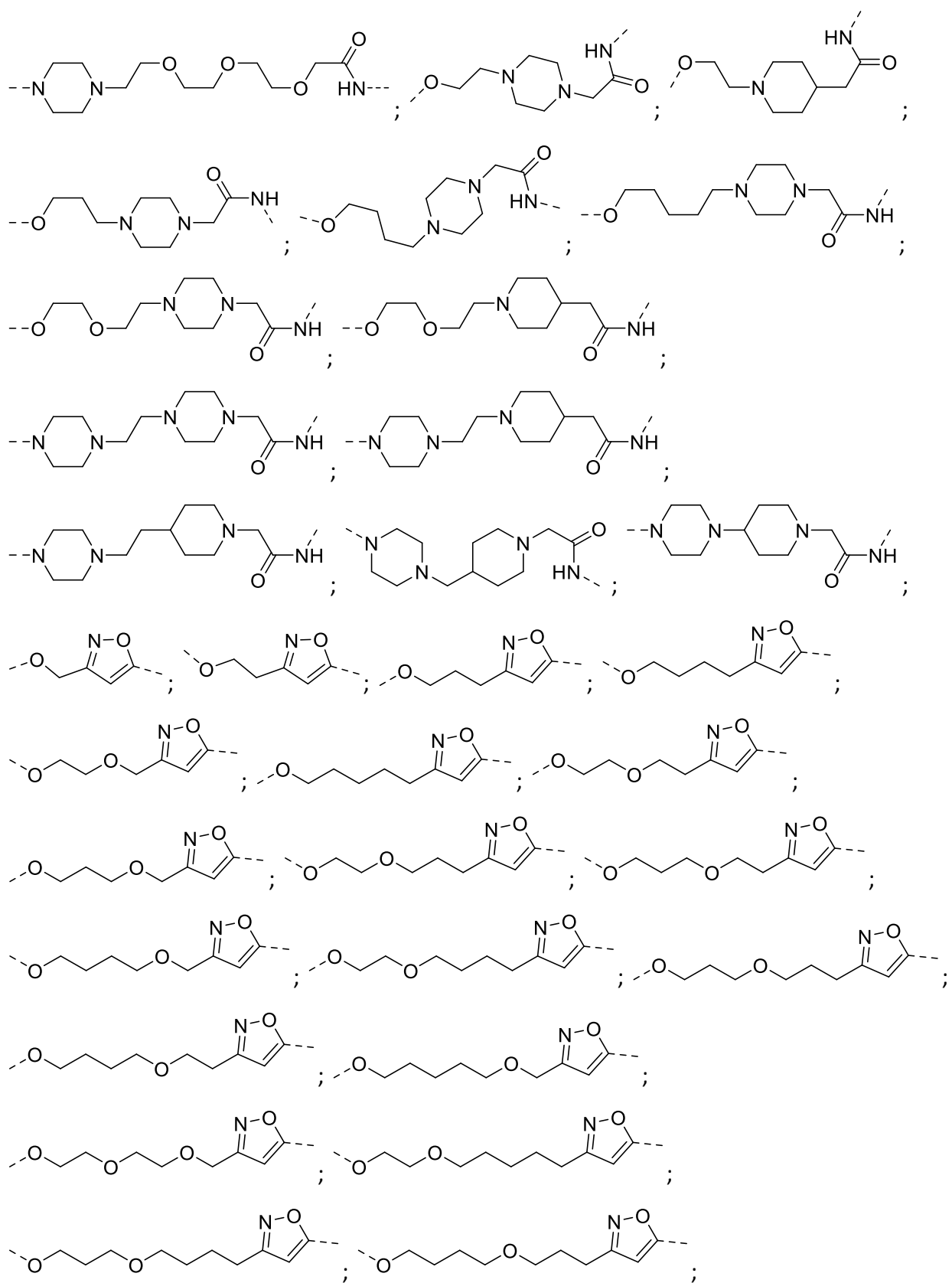


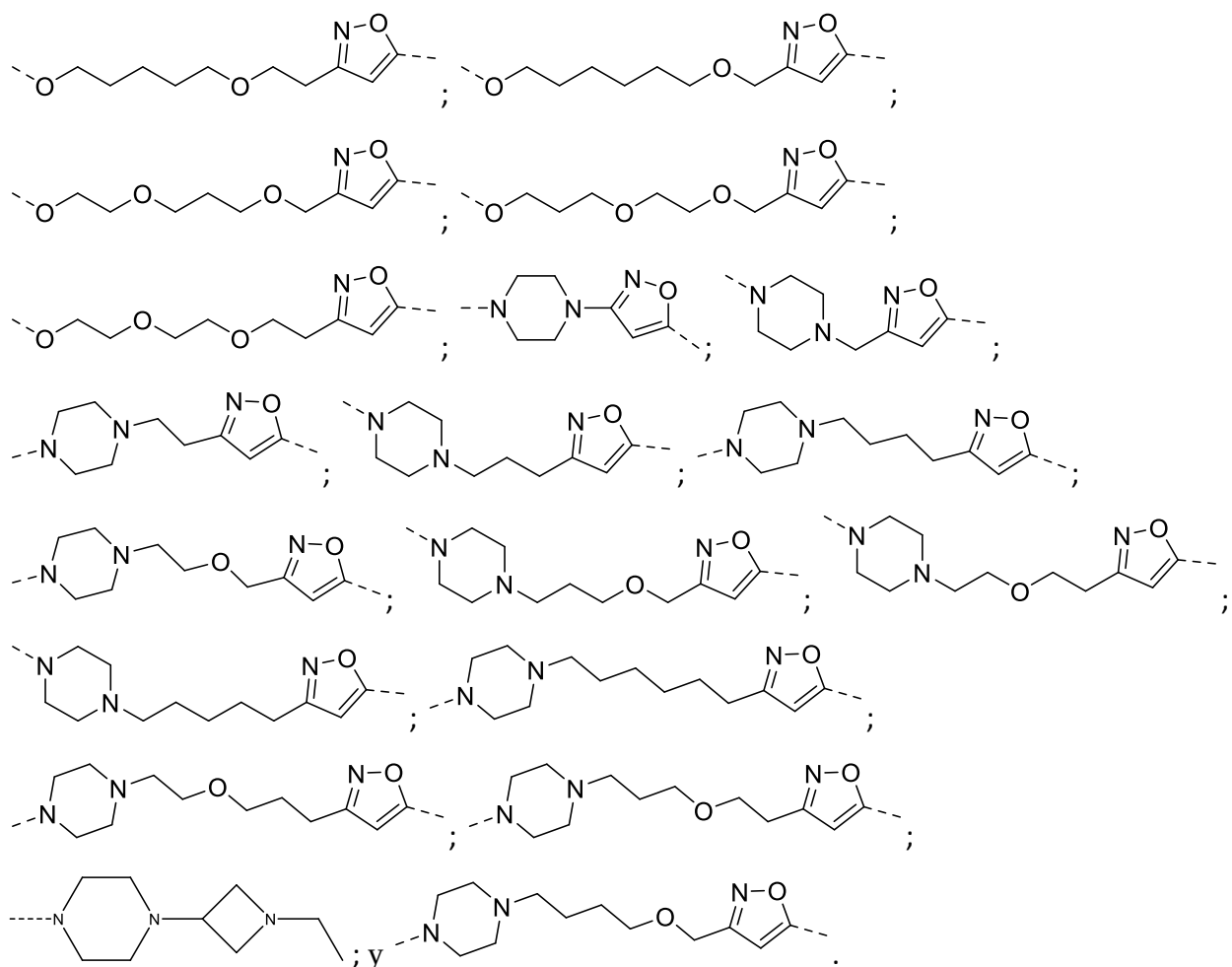




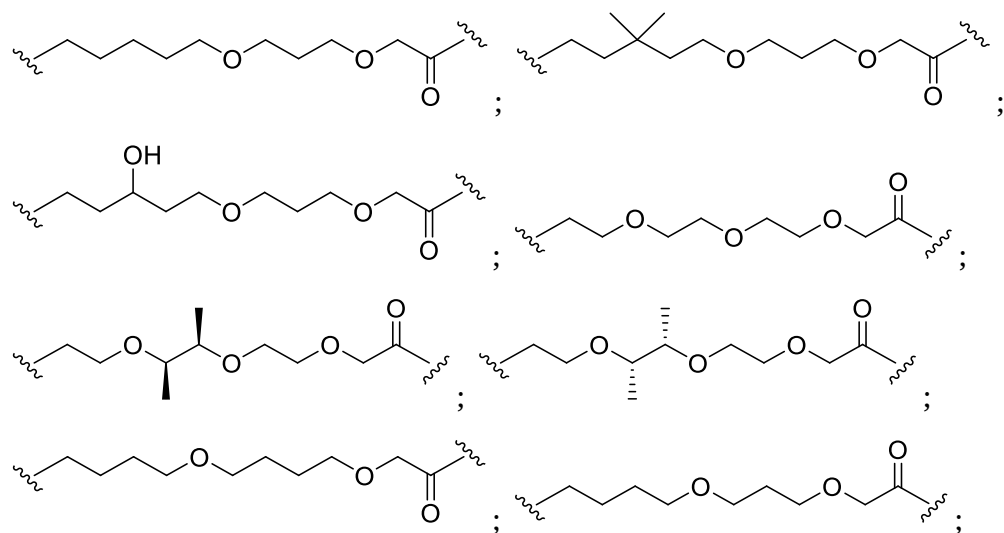


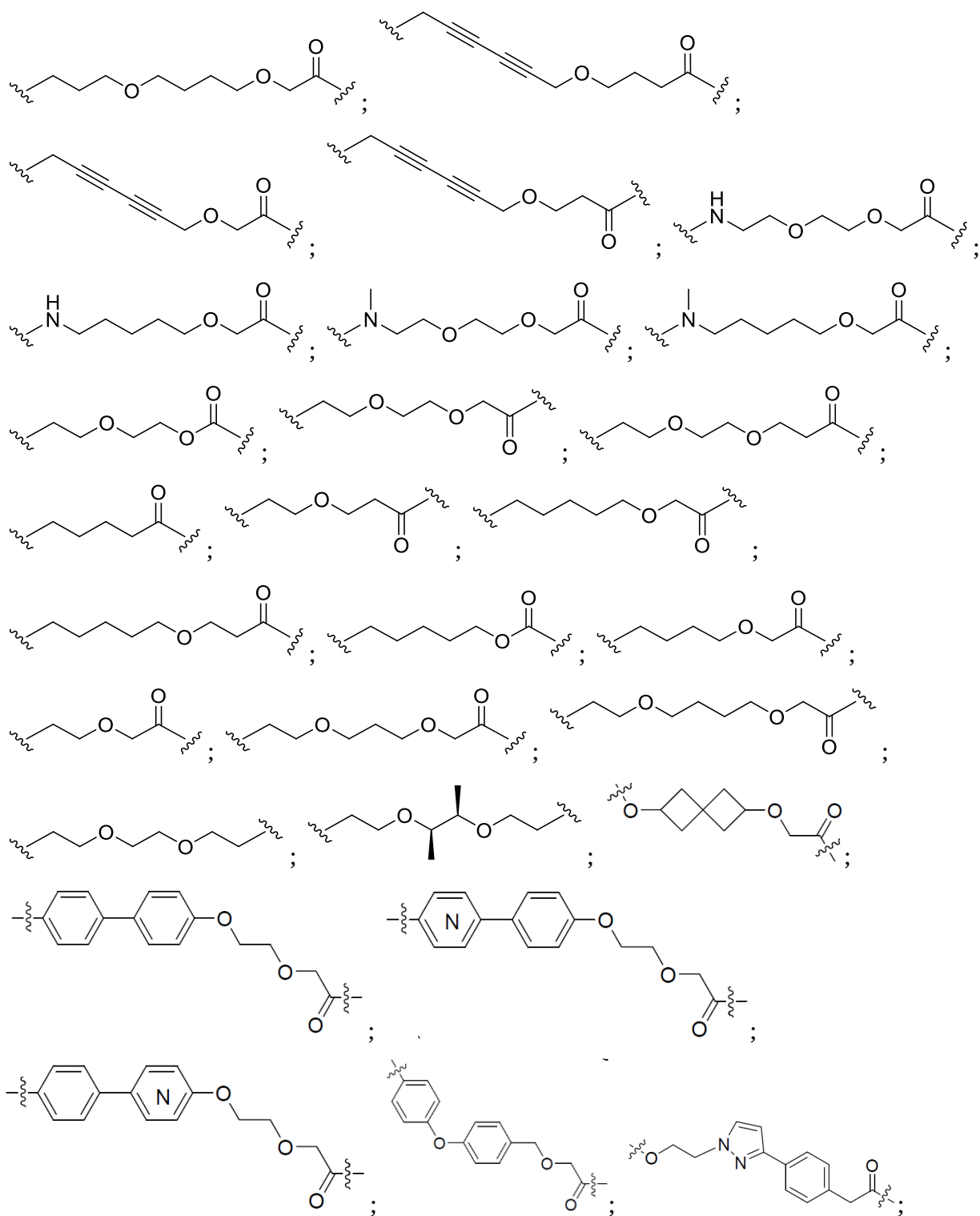


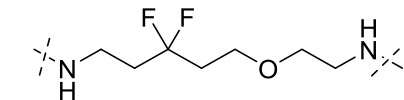
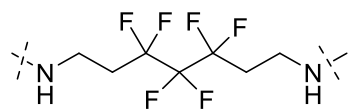
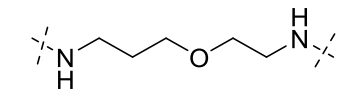
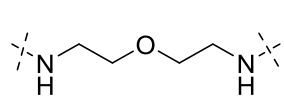
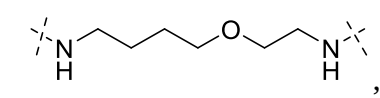
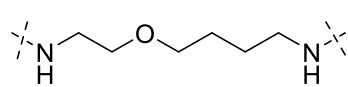
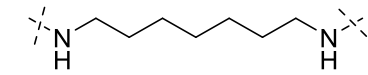
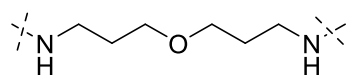
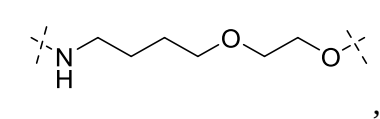
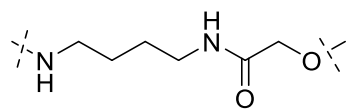
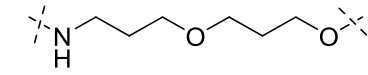
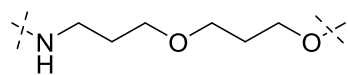
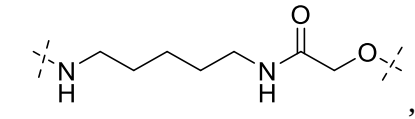
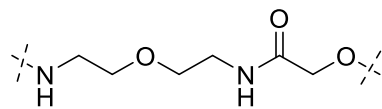
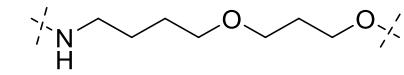
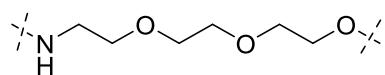
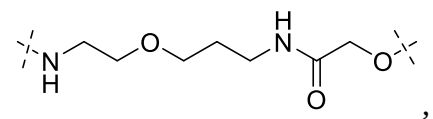
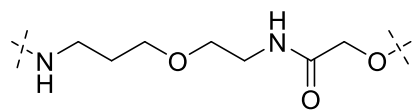
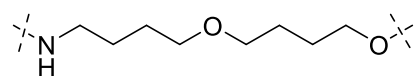
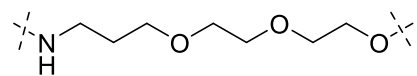
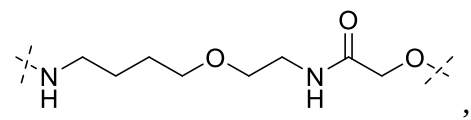
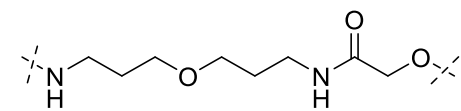
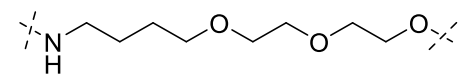
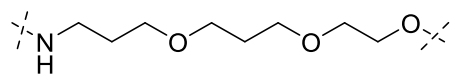
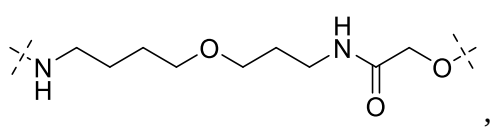
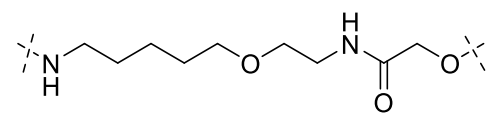
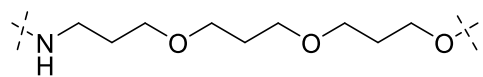
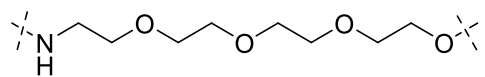


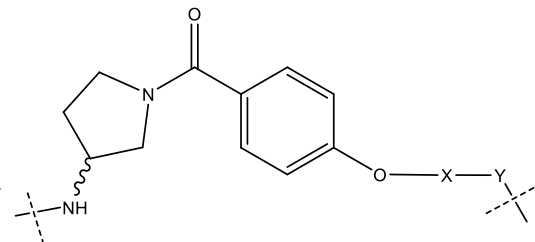
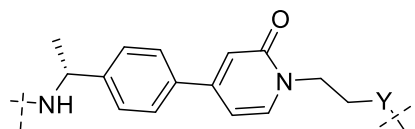
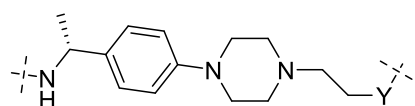
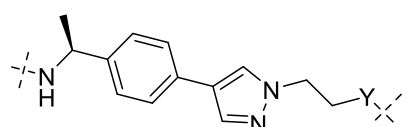
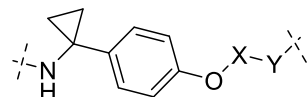
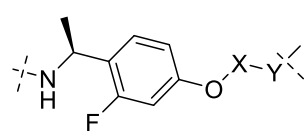
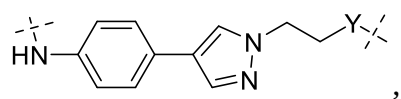
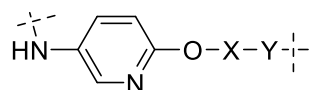
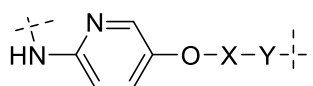
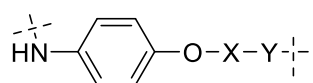


1413. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones **21-9**, en donde el enlazador (L) se selecciona de:





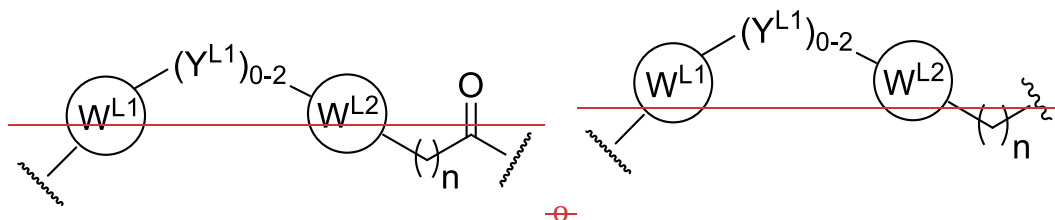




en donde:

"X" en las estructuras anteriores puede ser una cadena lineal con átomos que varían de 2 a 14,
y la cadena mencionada puede contener heteroátomos tales como oxígeno; y
"Y" en las estructuras anteriores puede ser O, N, S(O)_n (n = 0, 1, 2).

~~1514.~~ El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones
21-8, en donde el enlazador (L) ~~comprende una estructura seleccionada~~ selecciona de:



en donde:

~~W^{L1} y W^{L2} son cada uno independientemente un anillo de 4-8 miembros con 0-4~~
~~heteroátomos, opcionalmente sustituidos con R^Q, cada R^Q es independientemente un H,~~
~~halo, OH, CN, CF₃, C₁-C₆ alquilo (lineal, ramificado, opcionalmente sustituido), C₁-C₆~~
~~alcoxi (lineal, ramificado, opcionalmente sustituido), o 2 grupos R^Q tomados juntos con~~
~~el átomo al que se unen para formar un sistema de anillos de 4-8 miembros que contiene~~
~~0-4 heteroátomos;~~

~~Y^{L1} es cada uno independientemente un enlace, C₁-C₆ alquilo (lineal, ramificado,~~
~~opcionalmente sustituido) y opcionalmente uno o más átomos de C se reemplazan con O;~~
~~o C₁-C₆ alcoxi (lineal, ramificado, opcionalmente sustituido);~~

~~n es 0-10; y~~

~~una línea discontinua indica el punto de unión a las porciones PTM o CLM~~

en donde:

W^{L1} y W^{L2} son cada uno independientemente arilo, heteroarilo, cíclico, heterocíclico, C_{1-6} alquilo, bicíclico, biarilo, biheteroarilo, o biheterocíclico, cada uno opcionalmente sustituido con R^Q , cada R^Q es independientemente un H, halo, OH, CN, CF_3 , hidroxilo, nitro, $C\equiv CH$, C_{2-6} alqueno, C_{2-6} alquino, C_1-C_6 alquilo (lineal, ramificado, opcionalmente sustituido), C_1-C_6 alcoxi (lineal, ramificado, opcionalmente sustituido), OC_{1-3} alquilo (opcionalmente sustituido por 1 o más F), OH, NH_2 , $NR^{Y1}R^{Y2}$, CN, o 2 grupos R^Q tomados juntos con el átomo al que se unen para formar un sistema de anillos de 4-8 miembros que contiene 0-4 heteroátomos;

Y^{L1} es cada uno independientemente un enlace, NR^{YL1} , O, S, NR^{YL2} , $CR^{YL1}R^{YL2}$, $C=O$, $C=S$, SO, SO_2 , C_1-C_6 alquilo (lineal, ramificado, opcionalmente sustituido) y opcionalmente uno o más átomos de C se sustituyen con O; C_1-C_6 alcoxi (lineal, ramificado, opcionalmente sustituido);

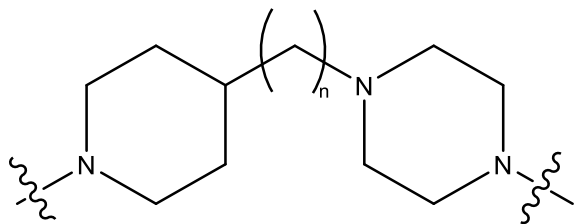
Q^L es un anillo alicíclico o aromático de 3-6 miembros con 0-4 heteroátomos, que opcionalmente establecen puentes, opcionalmente sustituido con 0-6 R^Q , cada R^Q es independientemente H, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido por 1 o más halo, C_{1-6}) alcoxi, o 2 grupos R^Q tomados juntos con el átomo al que se unen para formar un sistema de anillos de 3-8 miembros que contiene 0-2 heteroátomos);

R^{YL1} , R^{YL2} son cada uno independientemente H, OH, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido por 1 o más halo, C_{1-6} alcoxi), o R^1 , R^2 junto con el átomo al que se unen para formar un sistema de anillos de 3-8 miembros que contiene 0-2 heteroátomos);

n es 0-10; y

una línea discontinua indica el punto de unión a las porciones PTM o CLM.

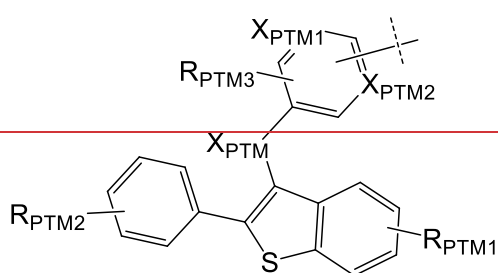
1716. El compuesto bifuncional de conformidad con ~~cualquiera de las reivindicaciones~~ reivindicaciones 2-915, en donde el enlazador (L) es ~~un grupo polietileno~~ opcionalmente sustituido con arilo o fenilo que comprende de 1 a 10 unidades de etilenglicol



, preferiblemente en donde n es 1.

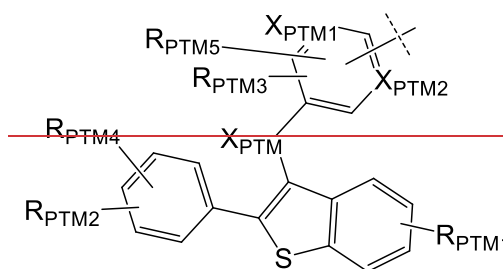
~~18. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 2-17, en donde la PTM es una estructura química que incluye al menos uno de (A), (B), (C), (D), (E), o una combinación de estos:~~

~~(A) una porción de unión al receptor de estrógeno (EBM) que comprende PTM I o PTM II:~~



~~PTM-I~~

~~y~~



~~PTM-II~~

~~en donde:~~

~~X_{PTM} es O o C=O;~~

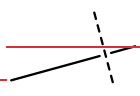
~~cada uno de X_{PTM1} y X_{PTM2} se seleccionan independientemente de N o CH;~~

~~R_{PTM1} se selecciona independientemente de OH, O(CO)R_{PTM}, O alquilo inferior, en donde R_{PTM} es un grupo alquilo o arilo en el éster;~~

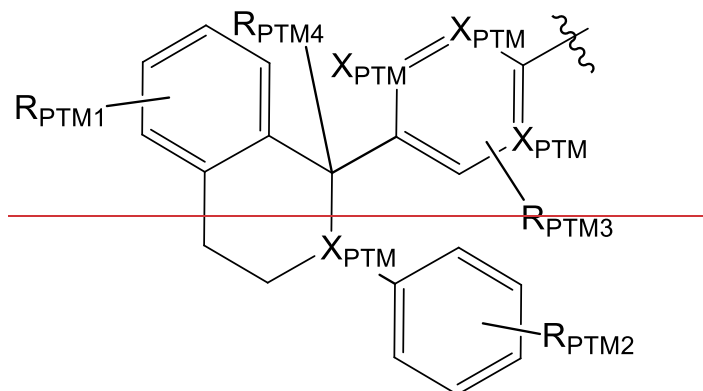
~~R_{PTM2} y R_{PTM4} se seleccionan independientemente de H, OH, halógeno, CN, CF₃, SO₂-alquilo, O-alquilo inferior;~~

~~R_{PTM3} y R_{PTM5} se seleccionan independientemente de H, halógeno;~~

~~PTM I tiene al menos una R_{PTM2} y al menos una R_{PTM3} en cada uno de los anillos~~

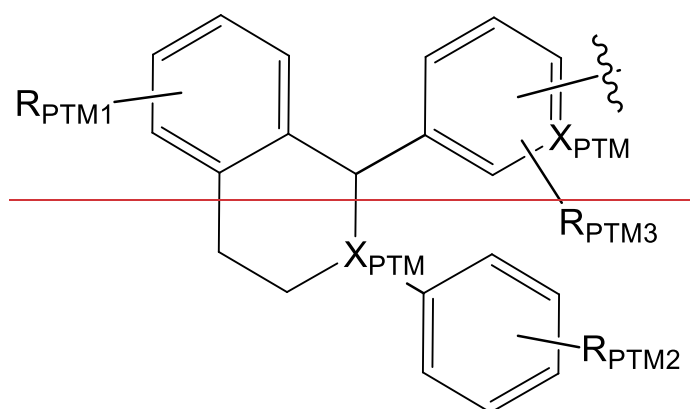
~~respectivos; y el  indica el sitio de unión de al menos uno del enlazador, la CLM, una CLM', o una combinación de estos;~~

~~(B) una porción de direccionamiento a la proteína del receptor de estrógeno representado por la estructura química:~~



-θ

Fórmula (I_{PTM})



5

Fórmula (H_{PTM})

en donde:

cada X_{PTM} es independientemente CH, N;



indica el sitio de unión de al menos uno de enlazador, la CLM, una CLM', o una combinación de estos;

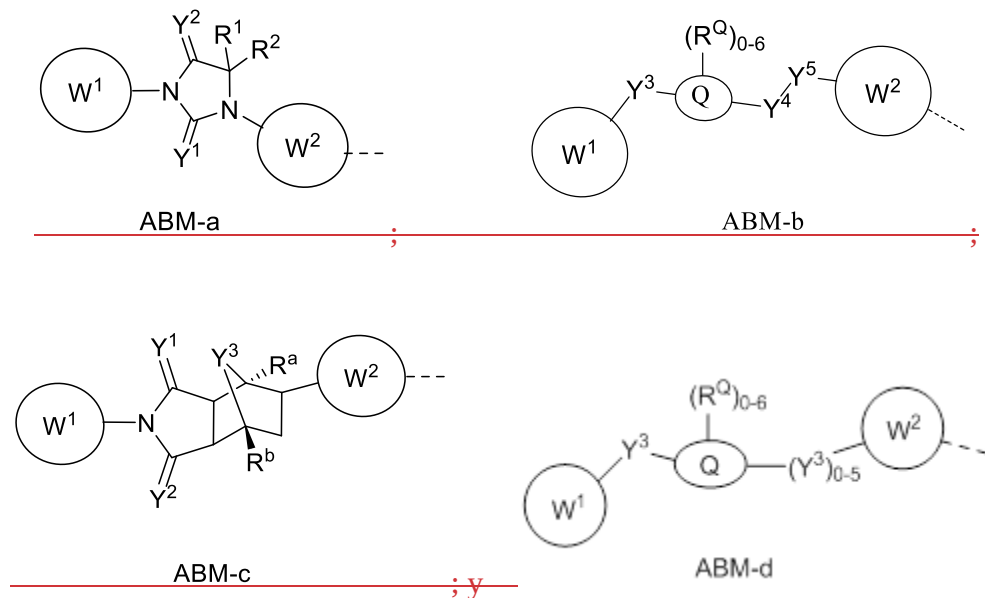
cada R_{PTM1} es independientemente OH, halógeno, alcoxi, metoxi, etoxi, $O(CO)R_{PTM5}$, en donde la sustitución puede ser una sustitución mono, di o tri y el R_{PTM} es un grupo alquilo o cicloalquilo con 1 a 6 carbonos o grupos arilos;

cada R_{PTM2} es independientemente H, halógeno, CN, CF_3 , alquilo lineal o ramificado, alcoxi, metoxi, etoxi, en donde la sustitución puede ser una sustitución mono o di;

cada R_{PTM3} es independientemente H, halógeno, en donde la sustitución puede ser una sustitución mono o di; y

R_{PTM4} es un H, alquilo, metilo, etilo.

(C) una porción de unión (ABM) al receptor de andrógenos (AR) comprende una estructura seleccionada del grupo que consiste en:



en donde:

W^1 es arilo, heteroarilo, bicíclico, o biheterocíclico, cada uno independientemente sustituido con 1 o más H, halo, hidroxilo, nitro, CN, $C\equiv CH$, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo), C_{1-6} alcoxilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo), C_{2-6} alquenilo, C_{2-6} alquinilo, o CF_3 ;

Y^1, Y^2 son cada uno independientemente NR^{Y1} , O, S, SO_2 , heteroarilo o arilo;

Y^3, Y^4, Y^5 son cada uno independientemente un enlace, O, NR^{Y2} , $CR^{Y1}R^{Y2}$, $C=O$, $C=S$, SO, SO_2 , heteroarilo o arilo;

Q es un anillo de 3-6 miembros con 0-4 heteroátomos, opcionalmente sustituido con 0-6 R^Q , cada R^Q es independientemente H, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido, por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo), halógeno, C_{1-6} alcoxi, 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);

$R^1, R^2, R^a, R^b, R^{Y1}, R^{Y2}$ son cada uno independientemente H, C_{1-6} -alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} -alcóxido), halógeno, C_{1-6} -alcóxido, cíclico, heterocíclico o R^1, R^2 junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos);

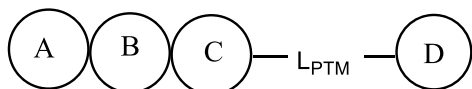
W^2 es un enlace, C_{1-6} -alquilo, C_{1-6} -heteroalquilo, O, arilo, heteroarilo, alicíclico, heterocíclico, biheterocíclico, biarilo, o biheteroarilo, cada uno opcionalmente sustituido con 1-10 R^{W2} ;

cada R^{W2} es independientemente H, halo, C_{1-6} -alquilo (lineal o ramificado opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más F), OR^{W2A} , C_{3-6} -cicloalquilo, C_{4-6} -cicloheteroalquilo, C_{1-6} -alquilo (opcionalmente sustituido), heterocíclico (opcionalmente sustituido), arilo (opcionalmente sustituido), o heteroarilo (opcionalmente sustituido), heteroarilo o arilo bicíclico, OC_{1-3} -alquilo (opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más F), OH, NH_2 , $NR^{Y1}R^{Y2}CN$;

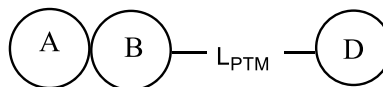
R^{W2A} es H, C_{1-6} -alquilo (lineal, ramificado), o C_{1-6} -heteroalquilo (lineal, ramificado), cada uno opcionalmente sustituido con un cicloalquilo, cicloheteroalquilo, arilo, heterocíclico, heteroarilo, halo, u OC_{1-3} -alquilo; y

la línea discontinua indica el sitio de unión de al menos uno del enlazador, la CLM, una CLM' o una combinación de estos;

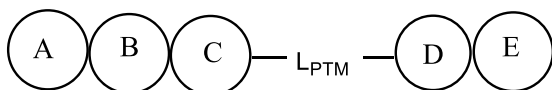
(D) una porción de direccionamiento a la proteína Tau que se representa por al menos uno de la Fórmula I-XI:



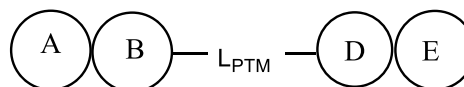
I



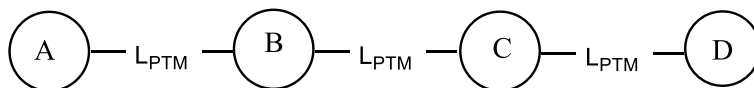
II



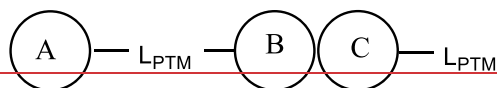
III



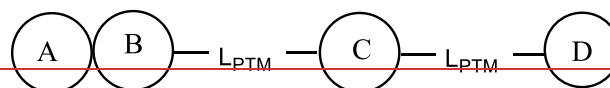
IV



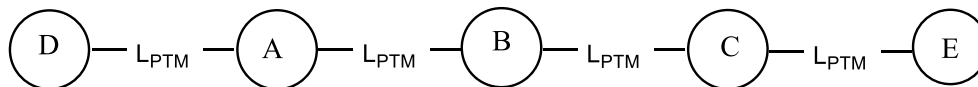
V



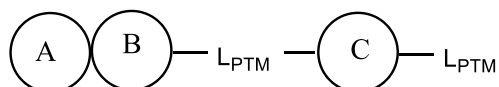
VI



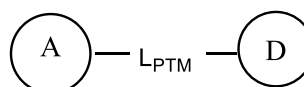
VII



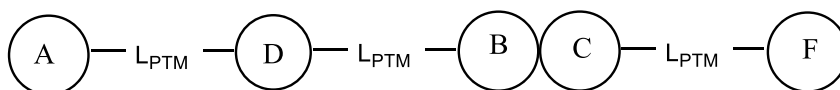
VIII



IX



X



XI

en donde:

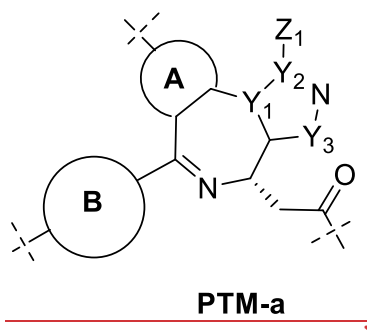
A, B, C, D, E, y F se seleccionan independientemente de un anillo arilo o heteroarilo de 5 o 6 miembros opcionalmente sustituidos, un cicloalquilo de 4 a 7 miembros

opcionalmente sustituido o un heterocicloalquilo, donde el contacto entre los círculos indican la fusión de los anillos;

L_{PTM} se selecciona de un enlace, un alquilo, un alquenilo o un alquinilo, opcionalmente interrumpidos por uno o más anillos (es decir, cicloalquilo, heterocicloalquilo, arilo o heteroarilo), o uno o más grupos funcionales seleccionados de los grupos O , S , NR^1_{PTM} , $N=N$, $S(O)$, SO_2 , $C(O)$, $NHC(O)$, $C(O)NH$, $NHSO_2$, $NHC(O)NH$, $NHC(O)O$, o $OC(O)NH$, en donde el dicho grupo funcional se localiza opcionalmente en ambos extremos del enlazador; y

R^1_{PTM} se selecciona de H o alquilo.

(E) un ligando de unión a diazepina o azepina tricíclicas BET/BRD4 que comprende un grupo de acuerdo con la estructura química PTM-a:



en donde:

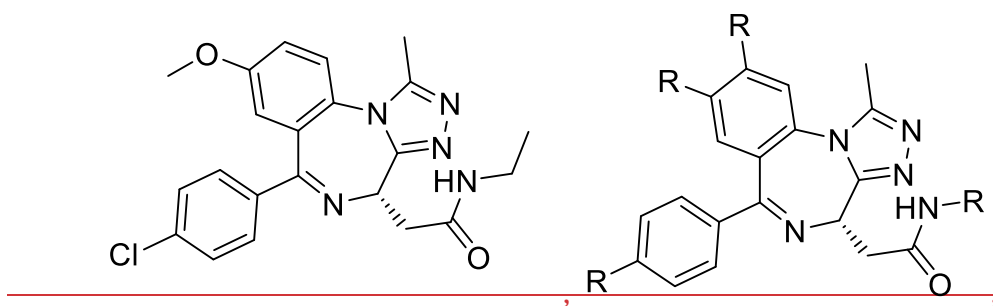
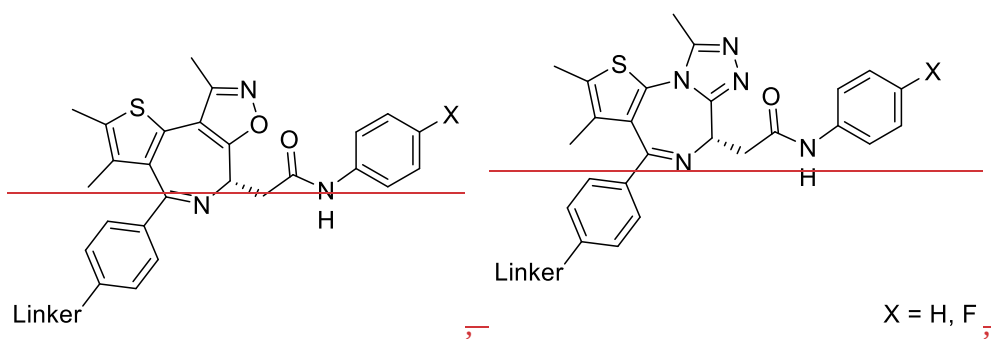
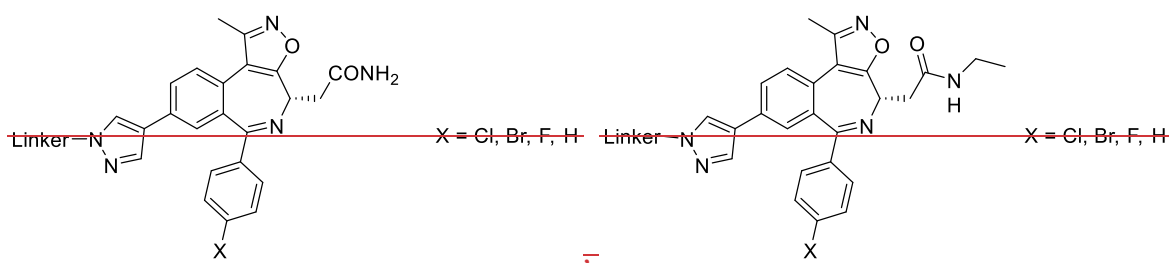
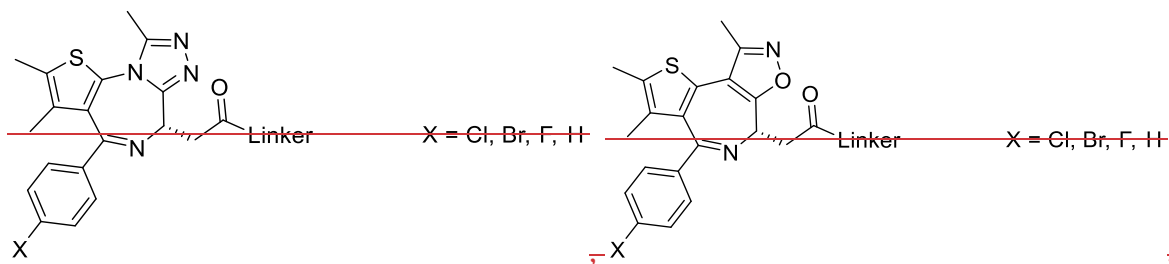
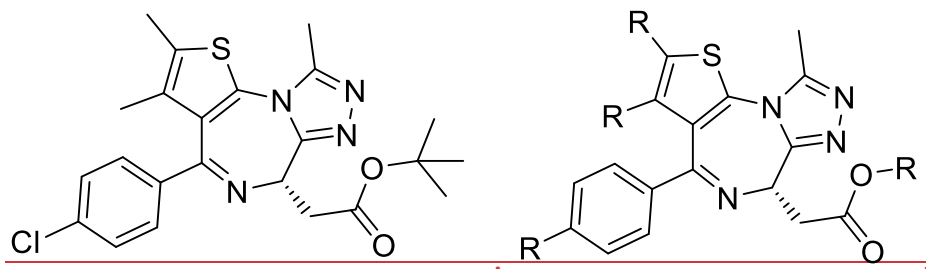
Y_1 , Y_2 y Y_3 se seleccionan independientemente del grupo de carbono, nitrógeno u oxígeno y junto con los átomos para formar un anillo aromático fusionado.

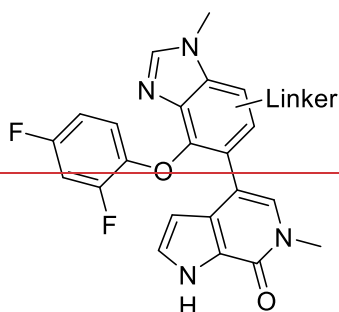
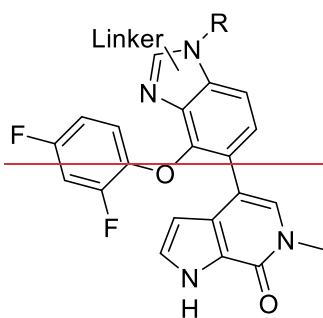
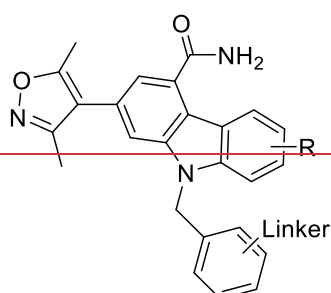
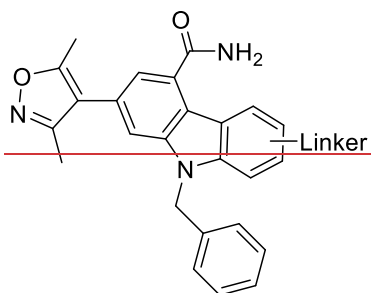
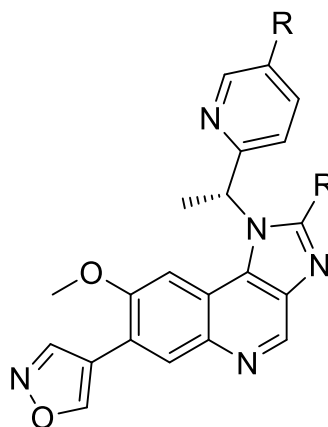
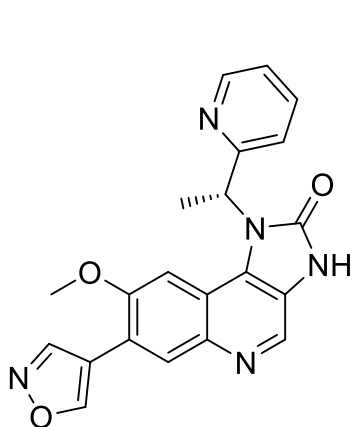
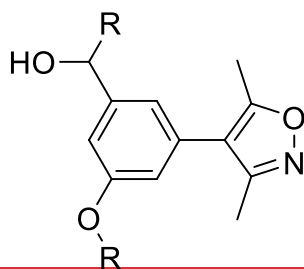
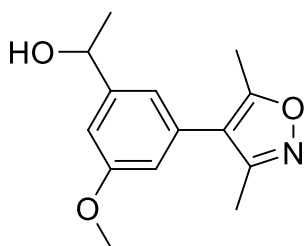
A y B se seleccionan independientemente del grupo de un anillo aromático de 5 miembros, un anillo aromático de 6 miembros, un anillo heteroaromático, un carbocíclico, un tiofeno, un anillo de pirrol, una piridina, una pirimidina, una pirazina, un anillo de pirazol cada uno opcionalmente sustituido con alquilo, alcoxi, halógeno, un anillo aromático y heteroaromático; en donde el anillo A se fusiona con la porción central de azepina ($Y_1=C$) o diazepina ($Y_1=N$); y

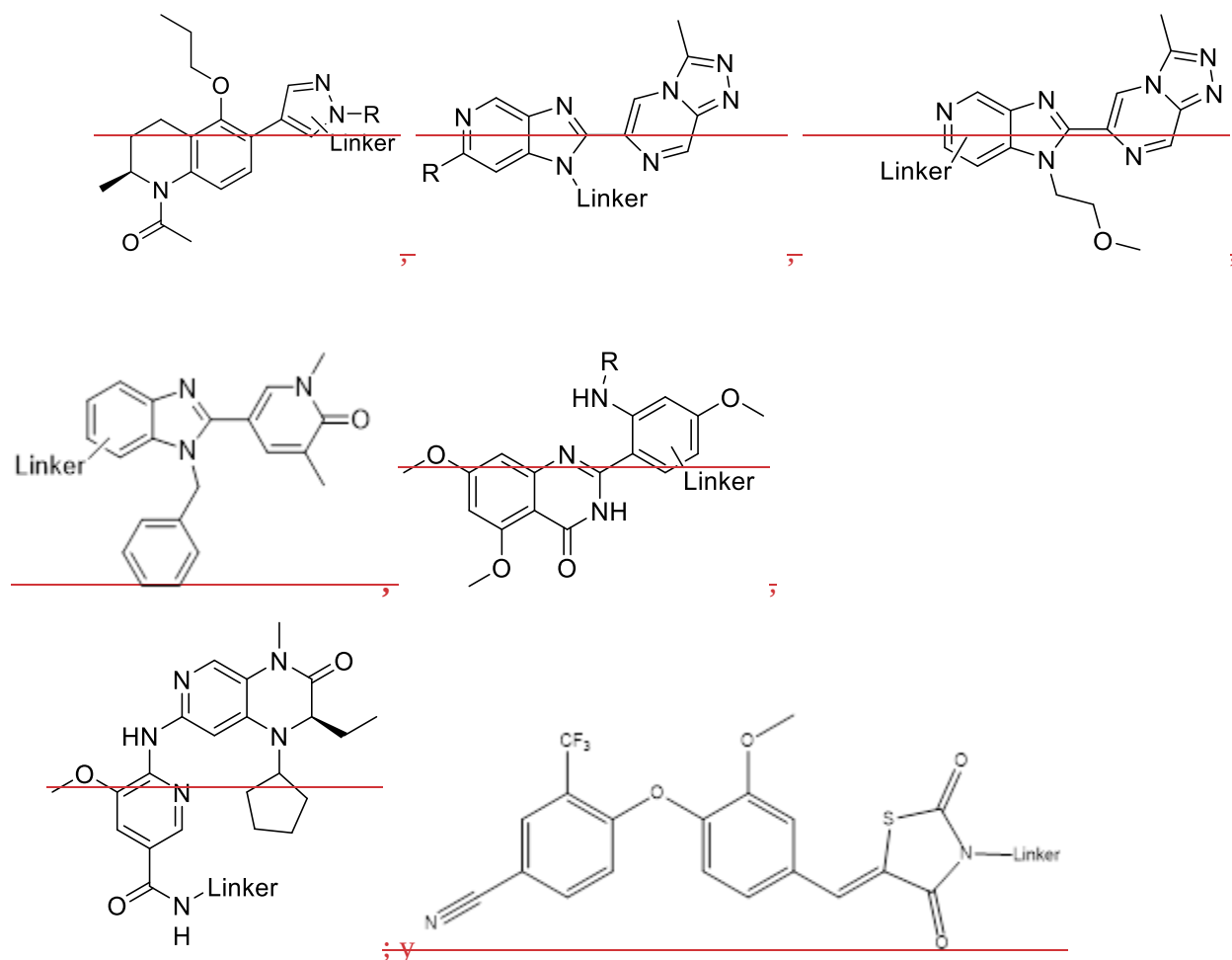
Z_1 se selecciona del grupo de grupos metilo o analquilo, y

en donde la línea discontinua indica el sitio de unión de al menos uno del enlazador, la CLM, una CLM' o una combinación de estos.

~~19. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 2-19, en donde la PTM tiene una estructura seleccionada del grupo que consiste en:~~



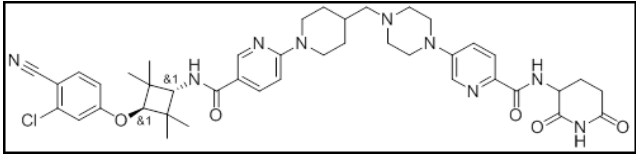
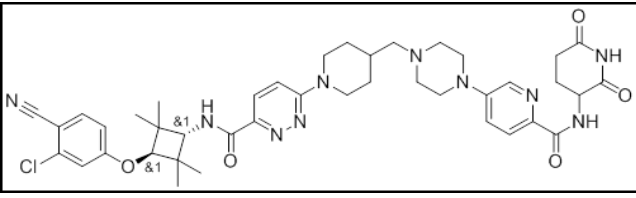
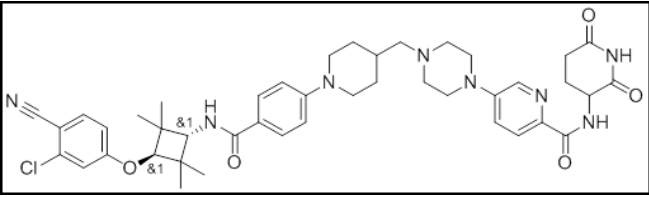
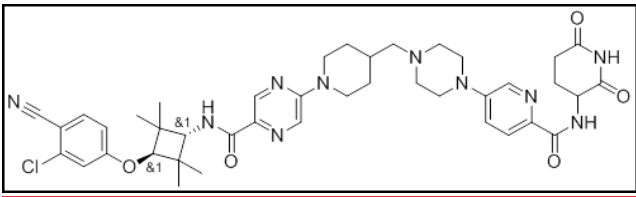
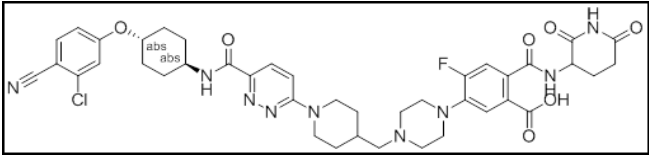
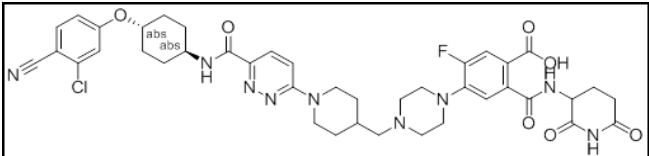
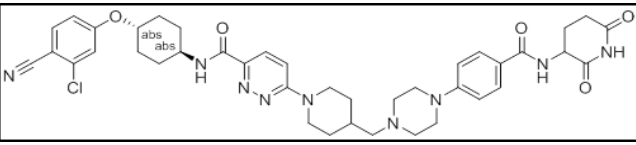


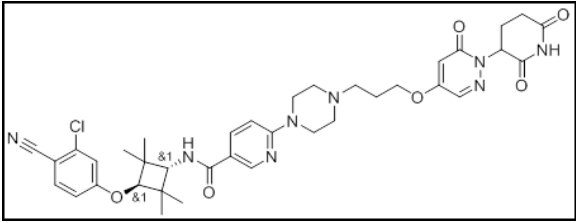
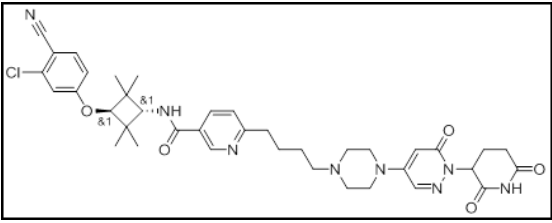
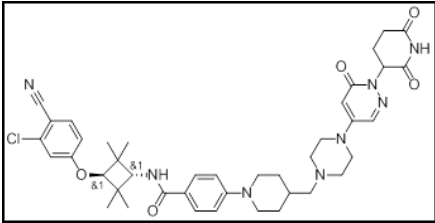
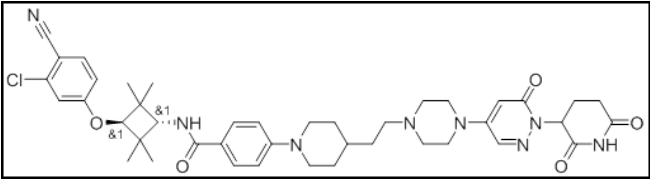
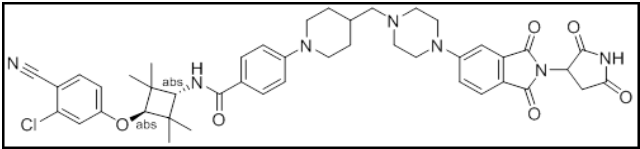
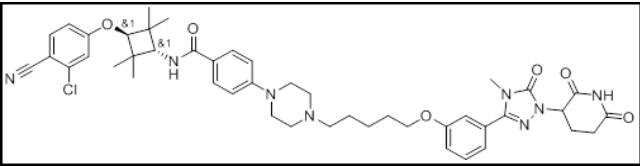
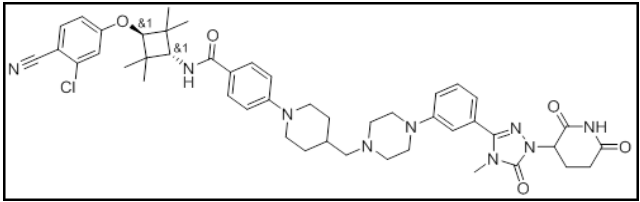


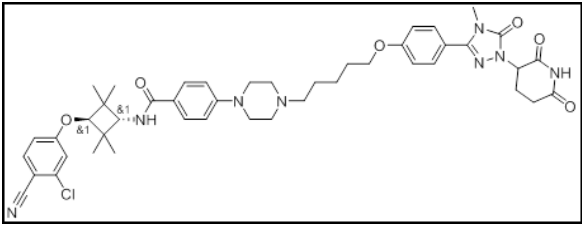
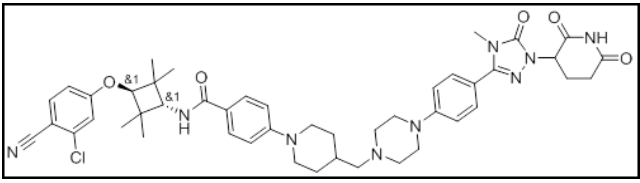
en donde R o enlazador es un enlace o una porción de enlazador químico que une la CLM a la PTM, que incluye sus formas de sal aceptables farmacéuticamente.

2017. El compuesto bifuncional de conformidad con la reivindicación 21, en donde el compuesto se selecciona del grupo que consiste en el PROTAC-1-27 hasta el PROTAC-41229, el PROTAC-48 hasta el PROTAC-63, y el PROTAC-66 hasta el PROTAC-70:

<u>PROTAC-27</u>			
-------------------------	--	--	--

<u>PROTAC-53</u>	 Chemical structure of PROTAC-53, featuring a 4-chloro-3-cyanophenyl group linked via an ether to a spirocyclic system, which is connected to a pyridine ring. This pyridine is linked via a piperidine and a piperazine to another pyridine, which is finally linked to a cyclic urea moiety.
<u>PROTAC-54</u>	 Chemical structure of PROTAC-54, similar to PROTAC-53 but with a different cyclic urea moiety at the end of the linker.
<u>PROTAC-55</u>	 Chemical structure of PROTAC-55, featuring a 4-chloro-3-cyanophenyl group linked via an ether to a spirocyclic system, which is connected to a pyridine ring. This pyridine is linked via a piperidine and a piperazine to another pyridine, which is finally linked to a cyclic urea moiety.
<u>PROTAC-56</u>	 Chemical structure of PROTAC-56, similar to PROTAC-55 but with a different cyclic urea moiety at the end of the linker.
<u>PROTAC-57</u>	 Chemical structure of PROTAC-57, featuring a 4-chloro-3-cyanophenyl group linked via an ether to a spirocyclic system, which is connected to a pyridine ring. This pyridine is linked via a piperidine and a piperazine to another pyridine, which is finally linked to a cyclic urea moiety.
<u>PROTAC-58</u>	 Chemical structure of PROTAC-58, similar to PROTAC-57 but with a different cyclic urea moiety at the end of the linker.
<u>PROTAC-59</u>	 Chemical structure of PROTAC-59, featuring a 4-chloro-3-cyanophenyl group linked via an ether to a spirocyclic system, which is connected to a pyridine ring. This pyridine is linked via a piperidine and a piperazine to another pyridine, which is finally linked to a cyclic urea moiety.

<u>PROTAC-60</u>	 Chemical structure of PROTAC-60, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-61</u>	 Chemical structure of PROTAC-61, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-62</u>	 Chemical structure of PROTAC-62, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-63</u>	 Chemical structure of PROTAC-63, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-66</u>	 Chemical structure of PROTAC-66, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-67</u>	 Chemical structure of PROTAC-67, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.
<u>PROTAC-68</u>	 Chemical structure of PROTAC-68, featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core, which is linked via an amide bond to a pyridine ring. This pyridine ring is connected through a piperazine linker to a 2,6-pyridinedicarboxamide moiety.

<u>PROTAC-69</u>	
<u>PROTAC-70</u>	

18. Un compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1- 17, para uso en un método de tratamiento de un estado de enfermedad o de mejoramiento de los síntomas de una enfermedad o afección en un sujeto que lo necesite, el método comprende administrar a dicho sujeto una cantidad del compuesto.

19. El compuesto bifuncional para uso de la reivindicación 18, en donde el compuesto es administrado en combinación con un agente bioactivo adicional.

20. El compuesto bifuncional para uso de la reivindicación 18 o 19, en donde la enfermedad o afección es cáncer.

21. Una composición que comprende una cantidad ~~eficaz~~ de un compuesto bifuncional de conformidad con cualquiera de las reivindicaciones ~~21-2017~~, y un portador aceptable farmacéuticamente.

22. La composición de conformidad con la reivindicación 21, en donde la composición comprende, además, al menos uno de un agente bioactivo adicional u otro compuesto bifuncional de conformidad con cualquiera de las reivindicaciones ~~21-2017~~.

23. La composición de conformidad con la reivindicación 22, en donde el agente bioactivo adicional es un agente anticancerígeno, ~~un agente antineurodegenerativo, un agente antimicrobiano, un agente antiviral, un agente anti-VIH, o un agente antifúngico.~~

24. Una composición para tratar o mejorar al menos un síntoma de una enfermedad o trastorno, caracterizado por que comprende una cantidad ~~eficaz~~ de al menos un compuesto de conformidad con cualquiera de las reivindicaciones ~~21-20~~ 17 y un portador, aditivo y/o excipiente aceptable farmacéuticamente ~~para tratar una enfermedad o trastorno en un sujeto, el método comprende administrar la composición a un sujeto que lo necesite, en donde el compuesto es eficaz para tratar o mejorar al menos un síntoma de la enfermedad o trastorno.~~

25. La composición para uso de conformidad con la reivindicación 24, en donde la enfermedad o trastorno se asocia con la acumulación y/o agregación de la proteína diana.

~~26. — La composición de conformidad con la reivindicación 24 o 25, en donde la enfermedad o trastorno se selecciona del grupo que consiste en asma, enfermedades autoinmunitarias tales como esclerosis múltiple, diversos cánceres, ciliopatías, paladar hendido, diabetes, enfermedad cardíaca, hipertensión, enfermedad inflamatoria intestinal, retraso mental, trastorno del ánimo, obesidad, error de refracción, infertilidad, síndrome de Angelman, enfermedad de Canavan, enfermedad Celiaca, enfermedad de Charcot Marie Tooth, Fibrosis quística, distrofia muscular de Duchenne, Hemocromatosis, Hemofilia, síndrome de Klinefelter, Neurofibromatosis, Fenilcetonuria, enfermedad renal poliquística, (PKD1) o 4 (PKD2), síndrome de Prader Willi, Sicklemia, enfermedad de Tay Sachs, y síndrome de Turner.~~

~~27. — La composición de conformidad con la reivindicación 24 o 25, en donde la enfermedad o trastorno se selecciona del grupo que consiste en enfermedad de Alzheimer, Esclerosis lateral amiotrófica (enfermedad de Lou Gehrig), Anorexia nerviosa, Trastorno de ansiedad, Aterosclerosis, Trastorno por déficit de atención con hiperactividad, Autismo, Trastorno bipolar, Síndrome de fatiga crónica, Enfermedad pulmonar obstructiva crónica, Enfermedad de Crohn, Enfermedad coronaria, Demencia, Depresión, Diabetes mellitus tipo 1, Diabetes mellitus tipo 2, Epilepsia, Síndrome de Guillain Barré, Síndrome del intestino irritable, Lupus, Síndrome~~

metabólico, Esclerosis múltiple, Infarto del miocardio, Obesidad, Trastorno obsesivo-compulsivo, Trastorno de pánico, Enfermedad de Parkinson, Psoriasis, Artritis reumatoide, Sarcoidosis, Esquizofrenia, Accidente cerebrovascular, Tromboangiitis obliterante, Síndrome de Tourette, Vasculitis.

2826. La composición para uso de conformidad con la reivindicación 24 o 25, en donde la enfermedad o trastorno es selecciona del grupo que consiste en aceruloplasminemia, acondrogénesis tipo II, acondroplasia, acrocefalia, enfermedad de Gaucher tipo 2, porfiria intermitente aguda, enfermedad de Canavan, poliposis coli adenomatosa, deficiencia de deshidratasa ALA, deficiencia de adenilosuccinato liasa, síndrome adrenogenital, adrenoleucodistrofia, porfiria ALA-D, deficiencia de ALA deshidratasa, alcaptonuria, enfermedad de Alexander, ocronosis alcaptonúrica, deficiencia de alfa 1-antitripsina, inhibidor de alfa-1-proteinasa, enfisema, esclerosis lateral amiotrófica Síndrome de Alström, enfermedad de Alexander, amelogénesis imperfecta, deficiencia de ALA deshidratasa, enfermedad de Anderson-Fabry, síndrome de insensibilidad a los andrógenos, Anemia Angioqueratoma corpóreo difuso, angiomatosis retina (enfermedad de von Hippel-Lindau), síndrome de Apert, aracnodactilia (síndrome de Marfan), Síndrome de Stickler, Artrochalasis múltiple congénita (síndrome de Ehlers-Danlos #tipo artrochalasia) ataxia telangiectásica, síndrome de Rett, hipertensión pulmonar primaria, enfermedad de Sandhoff, neurofibromatosis tipo II, síndrome de Beare-Stevenson-cutis gyrata, fiebre Mediterránea familiar, síndrome de Benjamin, beta-talasemia, Neurofibromatosis Bilateral Acústica (neurofibromatosis tipo II), trombofilia factor V de Leiden, síndrome de Bloch-Sulzberger (incontinencia pigmenti), síndrome de Bloom, anemia sideroblástica ligada al X, síndrome de Bonnevie-Ullrich (síndrome de Turner), enfermedad de Bourneville (esclerosis tuberosa), enfermedad de priones, síndrome de Birt-Hogg-Dubé, enfermedad de los huesos de Brittle (osteogénesis imperfecta), síndrome de Broad-Thumb-Hallux (síndrome de Rubinstein-Taybi), Diabetes de Bronce/Cirrosis de Bronce (hemocromatosis), atrofia Bulbospinal muscular (enfermedad de Kennedy), síndrome de Burger-Grutz (deficiencia de lipasa de lipoproteína), trastorno granulomatoso crónico CGD, displasia Campomélica, deficiencia de biotinidasa, Cardiomiopatía (síndrome de Noonan), Cri-du-chat, CAVD (ausencia congénita de los vasos deferentes), síndrome cardiofacial de Caylor (CBAVD), CEP (porfiria eritropoyética congénita), fibrosis quística, hipotiroidismo congénito, síndrome de Condrodistrofia (acondroplasia), displasia

otospondilomegaepifiseal, síndrome de Lesch-Nyhan, galactosemia, síndrome de Ehlers-Danlos, displasia Tanatofórica, síndrome de Coffin-Lowry, síndrome de Cockayne, (poliposis familiar adenomatosa), porfiria eritropoyética congénita, enfermedad cardíaca Congénita, Metahemoglobinemia/Metahemoglobinemia Congénita, acondroplasia, anemia sideroblástica ligada al X, enfermedad del tejido conectivo, síndrome de anomalía conotruncal facial, anemia de Cooley (beta-talasemia), enfermedad de almacenamiento de cobre (enfermedad de Wilson), enfermedad de transporte de cobre (enfermedad de Menkes), coproporfiria hereditaria, síndrome de Cowden, disartrosis Craniofacial (síndrome de Crouzon), enfermedad de Creutzfeldt-Jakob (enfermedad de priones), síndrome de Cockayne, síndrome de Cowden, síndrome de Curschmann-Batten-Steinert (distrofia miotónica), síndrome de Beare-Stevenson-cutis-gyrata, hiperoxaluria primaria, displasia espondiloepimetáfiseal (tipo Strudwick), distrofia muscular, tipos Duchenne y Becker (DBMD), síndrome de Usher, enfermedad degenerativa nerviosa que incluye síndrome de Grouchy y síndrome de Dejerine-Sottas, discapacidades del desarrollo, atrofia muscular espinal distal, tipo V, síndrome de insensibilidad a los andrógenos, Esclerosis difusa de cuerpos globoides (enfermedad de Krabbe), síndrome de Di-George, deficiencia del receptor de Dihidrotestosterona, síndrome de insensibilidad a los andrógenos, síndrome de Down, enanismo, protoporfiria eritropoyética-eritroide, deficiencia de 5-aminolevulinato-sintetasa, porfiria eritropoyética, protoporfiria eritropoyética, uroporfiria eritropoyética, ataxia de Friedreich, poliserositis paroxismal familiar, porfiria cutánea tarda, neuropatía sensible al a presión familiar, hipertensión pulmonar primaria (PPH), enfermedad fibroquística del páncreas, síndrome frágil X, galactosemia, trastornos genéticos del cerebro, hepatitis de células gigantes (hemocromatosis neonatal), síndrome de Gronblad-Strandberg (pseudoxantoma elasticum), enfermedad de Gunther (porfiria eritropoyética congénita), hemocromatosis, síndrome de Hallgren, anemia drepanocítica, hemofilia, porfiria hepatoeritropoyética (HEP), enfermedad de Hippel-Lindau (enfermedad de von Hippel-Lindau), enfermedad de Huntington, síndrome de progeria de Hutchinson-Gilford (progeria), Hiperandrogenismo, Hipocondroplasia, anemia Hipocrómica, trastornos del sistema inmunitario, que incluye la inmunodeficiencia severa combinada ligada al X, síndrome de Insley-Astley, síndrome de Kennedy, síndrome de Jackson-Weiss, síndrome de Joubert, síndrome de Lesch-Nyhan, síndrome de Jackson-Weiss, enfermedades de los riñones, que incluye hiperoxaluria, síndrome de Klinefelter, displasia de Kniest, demencia Lacunar, acondrogenésis de Langer-Saldino, ataxia-telangiectásica, síndrome de Lynch, deficiencia de Lisil-hidroxilasa,

~~enfermedad de Machado-Joseph, trastornos Metabólicos, que incluyen la displasia de Kniest, síndrome de Marfan, trastornos del movimiento, síndrome de Mowat-Wilson, fibrosis quística, síndrome de Muenke, neurofibromatosis Múltiple, síndrome de Nance-Insley, condrodisplasia de Nance-Sweeney, enfermedad de Niemann-Pick, síndrome de Noack (síndrome de Pfeiffer), enfermedad de Osler-Weber-Rendu, síndrome de Peutz-Jeghers, enfermedad de riñón poliquístico, displasia polioestótica fibrosa (síndrome de McCune-Albright), síndrome de Peutz-Jeghers, síndrome de Prader-Labhart-Willi, hemocromatosis, síndrome de hiperuricemia primaria (síndrome de Lesch-Nyhan), hipertensión pulmonar primaria, demencia primaria senil degenerativa, enfermedad de priones, progeria (síndrome de Progeria de Hutchinson-Gilford), corea progresiva, crónica hereditaria (Huntington) (enfermedad de Huntington), atrofia muscular progresiva, atrofia muscular espinal, acidemia propiónica, protoporfiria, distrofia miotónica proximal, hipertensión arterial pulmonar, PXE (pseudoxantoma elasticum), Rb (retinoblastoma), enfermedad de Recklinghausen (neurofibromatosis tipo I), poliserositis recurrente, trastornos de la Retina, Retinoblastoma, síndrome de Rett, RFALS tipo 3, síndrome de Ricker, síndrome de Riley-Day, síndrome de Roussy-Levy, acondroplasia severa con retardo del desarrollo y acantosis nigricans (SADDAN), síndrome de Li-Fraumeni, sarcoma, síndrome de mama, leucemia, y glándula adrenal (SBLA), esclerosis tuberosa (esclerosis tuberosa), SDAT, SED congénita (displasia congénita espondiloepifiseal), SED Strudwick (displasia espondiloepimetafiseal, tipo Strudwick), SEDe (displasia congénita espondiloepifiseal) SEMD, tipo Strudwick (displasia espondiloepimetafiseal, tipo Strudwick), síndrome de Shprintzen, trastornos de pigmentación de la piel, síndrome de Smith-Lemli-Opitz, porfiria genética de Sudáfrica (porfiria variegada), parálisis espástica de comienzo infantil ascendente hereditaria, trastornos del lenguaje y la comunicación, esfingolipidosis, enfermedad de Tay-Sachs, ataxia espino-cerebelar, síndrome de Stickler, infarto cerebral, síndrome de insensibilidad a los andrógenos, deficiencia de tetrahidrobiopterina, beta-talasemia, enfermedad de la Tiroides, neuropatía Tomaculous (neuropatía hereditaria con riesgo de parálisis por presión), síndrome de Treacher-Collins, síndrome de Triplo X (síndrome de triple X), trisomía 21 (síndrome de Down), trisomía X, síndrome de VHL (enfermedad de von Hippel-Lindau), discapacidad visual y ceguera (síndrome de Alström), enfermedad de Vrolik, síndrome de Waardenburg, síndrome de Warburg-Sjo-Fledelius, síndrome de Weissenbacher-Zweymüller, síndrome de Wolf-Hirschhorn, enfermedad periódica de Wolff, síndrome de Weissenbacher-Zweymüller y Xeroderma pigmentoso.~~

2927. La composición de conformidad con cualquiera de las reivindicaciones 24-~~2826~~, que comprende, además, un agente bioactivo adicional.

3028. La composición de conformidad con la reivindicación 2927, en donde el agente bioactivo adicional es ~~al menos uno de un agente anticancerígeno, un agente antineurodegenerativo, un agente antimicrobiano, un agente antiviral, un agente anti-VIH, un agente antifúngico o una combinación de estos.~~

3129. La composición para uso de conformidad con la reivindicación 3028, en donde dicho agente anticancerígeno se selecciona del grupo que consiste en everolimus, trabectedin, abraxano, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, un inhibidor de FLT-3, un inhibidor de VEGFR, un inhibidor de EGFR TK, un inhibidor de aurora quinasa, un modulador de PIK-1, un inhibidor de Bcl-2, un inhibidor de HDAC, un inhibidor de c-MET, un inhibidor de PARP, un inhibidor de Cdk, ~~un inhibidor de EGFR TK~~, un inhibidor de IGFR-TK, un anticuerpo anti-HGF, un inhibidor de PI3 quinasa, un inhibidor de AKT, un inhibidor de mTORC1/2, un inhibidor de JAK/STAT, un inhibidor del punto de control-1 o 2, un inhibidor de la quinasa de adhesión focal, un inhibidor de Map quinasa quinasa (mek), un anticuerpo atrapador de VEGF, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitida, gimatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposido, gemcitabina, doxorubicina, doxorubicina liposomal, 5'-deoxy-5-fluorouridina, vincristina, temozolomida, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabina, ácido L-Glutámico, N-[4-[2-(2-amino-4,7-dihidro-4-oxo-1H-pirrol[2,3-d]pirimidin-5-il)etil]benzoil]-, sal disódica, heptahidrato, camptothecin, irinotecan marcado con PEG, tamoxifeno, citrato de toremifeno, anastrozol, exemestano, letrozol, DES(dietilstilbestrol), estradiol, estrógeno, estrógeno conjugado,

bevacizumab, IMC-1C11, CHIR-258); 3-[5-(metilsulfonilpiperadinametil)- indolil-quinolona, vatalanib, AG-013736, AVE-0005, ~~la sal de acetato de [D-Ser(Bu t)-6, Azgly 10] (piro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro-Azgly NH₂-acetato [C₅₉H₈₄N₁₈O₁₄-(C₂H₄O₂)_x donde x = 1 a 2.4]~~, acetato de goserelina, acetato de leuprolido, pamoato de triptorelina, acetato de medroxiprogesterona, caproato de hidroxiprogesterona, acetato de megestrol, raloxifeno, bicalutamida, flutamida, nilutamida, ~~acetato de megestrol~~, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, anticuerpo ABX-EGF, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostina, NVP-LAQ824, ácido hidroxámico suberoil analida, ácido valproico, tricostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutetimida, arnsacrina, anagrelida, L-asparaginasa, vacuna del Bacillus Calmette-Guerin (BCG), adriamicina, bleomicina, buserelina, busulfán, carboplatino, carmustina, clorambucil, cisplatino, cladribina, clodronato, ciproterona, citarabina, dacarbazina, dactinomicina, daunorubicina, ~~diestilbestrol~~, epirubicina, fludarabina, fludrocortisona, fluoximesterona, ~~flutamida~~, gleevec, ~~gemcitabina~~, hidroxiurea, idarubicina, ifosfamida, imatinib, leuprolida, levamisol, lomustina, mecloretamina, melfalán, 6-mercaptopurina, mesna, metotrexato, mitomicina, mitotano, mitoxantrona, nilutamida, octreotido, oxaliplatino, pamidronato, pentostatina, plicamicina, porfimer, procarbazona, raltitrexed, rituximab, estreptozotocina, teniposido, testosterona, talidomida, tioguanina, tiotepa, tretinoin, vindesina, ácido 13-cis-retinoico, mostaza fenilalanina, mostaza uracilo, estramustina, altretaminae, floxuridinae, 5-deoxiuridina, citosina arabinosido, 6-mercaptopurina, deoxicoformicina, calcitriol, valrubicina, mitramicina, vinblastina, vinorelbina, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamina, endostatina, SU5416, SU6668, EMD121974, interleucina-12, IM862, angiostatina, vitaxin, droloxifeno, idoxifeno, espironolactona, finasterida, cimetidina, trastuzumab, denileukin diftitox, gefitinib, bortezomib, paclitaxel, paclitaxel libre de cremóforo, docetaxel, epitolona B, BMS- 247550, BMS-310705, droloxifeno, 4-hidroxitamoxifeno, pipendoxifeno, ERA-923, arzoxifeno, fulvestrant, acolbifeno, lasofoxifeno, idoxifeno, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamicina, 40-O-(2-hidroxi-etil)-rapamicina, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, eritropoietina, factor estimulador de colonia de granulocitos, zolendronato, prednisona, cetuximab, factor estimulador de colonias de granulocitos macrófagos, histrelin, interferón alfa-2a pegilado, interferón alfa-2a,

interferón alfa-2b pegilado, interferón alfa-2b, azacitidina, PEG-L-asparaginasa, lenalidomida, gemtuzumab, hidrocortisona, interleucina-11, dexrazoxano, alemtuzumab, ácido retinoico todo-trans, ketoconazol, interleucina-2, megestrol, inmuno globulina, mostaza nitrógeno, metilprednisolona, ibritumomab tiuxetan, andrógenos, decitabina, hexametilmelamina, bexaroteno, tositumomab, trióxido de arsénico, cortisona, editronato, mitotano, ciclosporina, daunorubicina liposomal, Edwina-asparaginasa, estroncio 89, casopitant, netupitant, un antagonista del receptor NK-1, palonosetron, aprepitant, difenhidramina, hidroxizina, metoclopramida, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexametasona, ~~metilprednisolona,~~—proclorperazina, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, eritropoietina, epoetin alfa, darbepoetin alfa y mezclas de estos.

3230. Un ~~compuestométodo~~ para inducir la degradación de una proteína diana en una célula, caracterizada porque es de conformidad con la reivindicación 1~~comprende administrar una cantidad eficaz de un compuesto de conformidad con cualquiera de las reivindicaciones 1-20 a la célula, en donde el compuesto efectúa la degradación de la proteína diana.~~

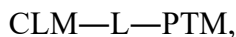
3331. Una composición para tratar cáncer caracterizada porque comprende una cantidad eficaz ~~de un~~ compuesto de conformidad con ~~cualquiera de las reivindicaciones 2-20 para usar en un método para tratar el cáncer, dicho método comprende administrar la composición a un paciente que lo necesite, en donde la composición es eficaz para el tratamiento o alivio de al menos un síntoma de cáncer en el paciente~~la reivindicación 1.

3432. La composición para uso de conformidad con la reivindicación 3331, en donde el cáncer es ~~carcinoma de células escamosas, carcinoma de células basales, adenocarcinoma, carcinomas hepatocelulares, y carcinomas de células renales, cáncer de vejiga, intestino, mama, cuello uterino, colon, esófago, cabeza, riñón, hígado, pulmón, cuello, ovario, páncreas, próstata y estómago; leucemias, linfomas benignos y malignos, particularmente linfoma de Burkitt y linfoma no-Hodgkin; melanomas benignos y malignos; enfermedades mieloproliferativas; mieloma múltiple, sarcomas, que incluye el sarcoma de Ewing, hemangiosarcoma, sarcoma de Kaposi, liposarcoma, miosarcomas, neuroepitelioma periférico, sarcoma sinovial, gliomas, astrocitomas, oligodendrogliomas, —ependimomas, —glioblastomas, —neuroblastomas, —ganglioneuromas,~~

~~gangliomas, meduloblastoma, tumores de la célula pineal, meningiomas, sarcomas meníngicos, neurofibromas, y schwannomas; cáncer de intestino, cáncer de mama, cáncer de próstata, cáncer de cuello uterino, cáncer uterino, cáncer de pulmón, o cáncer de ovario, cáncer testicular, cáncer de tiroides, astrocitoma, cáncer de esófago, cáncer de páncreas, cáncer de estómago, cáncer de hígado, cáncer de colon, melanoma; carcinosarcoma, enfermedad de Hodgkin, tumor de Wilms o teratocarcinomas, leucemia linfoblástica aguda de linaje T (T-ALL), linfoma linfoblástico de linaje T (T-LL), linfoma de células T periférico, leucemia de células T adultas, ALL pre-B, Linfomas Pre-B, Linfoma de células B grandes, Linfoma de Burkitts, ALL de células B, ALL cromosoma Filadelfia positiva y CML cromosoma Filadelfia positiva.~~

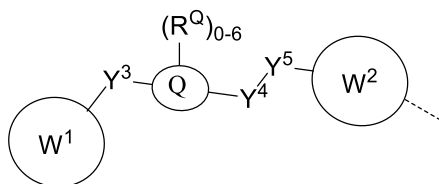
REIVINDICACIONES

1. Un compuesto bifuncional que tiene la estructura química:



o una de sus sales, enantiómeros, o estereoisómeros aceptables farmacéuticamente,
en donde:

- (a) la PTM es una porción de unión (ABM) al receptor de andrógenos (AR) que comprende



la estructura

ABM-b

;

en donde:

W^1 es arilo, heteroarilo, bicíclico, o biheterocíclico, cada uno independientemente sustituido con 1 o más H, halo, hidroxilo, nitro, CN, $C\equiv CH$, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo), C_{1-6} alcoxilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo), C_{2-6} alquenilo, C_{2-6} alquinilo, o CF_3 ;

Y^3 , Y^4 , Y^5 son cada uno independientemente un enlace, O, NR^{Y2} , $CR^{Y1}R^{Y2}$, $C=O$, $C=S$, SO, SO_2 , heteroarilo o arilo;

Q es un anillo de 3-6 miembros con 0-4 heteroátomos, opcionalmente sustituido con 0-6 R^Q , en donde cada R^Q , es independientemente H, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido, por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo), halógeno, o C_{1-6} alcoxi, o 2 grupos R^Q tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos);

R^{Y1} , R^{Y2} son cada uno independientemente H, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo), halógeno, C_{1-6} alcoxi, cíclico, o heterocíclico;

W^2 es un enlace, C_{1-6} alquilo, C_{1-6} heteroalquilo, O, arilo, heteroarilo, alicíclico, heterocíclico, biheterocíclico, biarilo, o biheteroarilo, cada uno opcionalmente sustituido con 1-10 R^{W2} ;

cada R^{W2} es independientemente H, halo, C_{1-6} alquilo (lineal o ramificado opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más F), - OR^{W2A} , C_{3-6} cicloalquilo, C_{4-6} cicloheteroalquilo, C_{1-6} alquilo (opcionalmente sustituido), heterocíclico (opcionalmente sustituido), arilo (opcionalmente sustituido), o heteroarilo (opcionalmente sustituido), heteroarilo bicíclico, o arilo OC_{1-3} alquilo (opcionalmente sustituido; por ejemplo, opcionalmente sustituido con 1 o más -F), OH, NH_2 , $NR^{Y1}R^{Y2}CN$;

R^{W2A} es H, C_{1-6} alquilo (lineal, ramificado), o C_{1-6} heteroalquilo (lineal, ramificado), cada uno opcionalmente sustituido con un cicloalquilo, cicloheteroalquilo, arilo, heterocíclico, heteroarilo, halo, u OC_{1-3} alquilo; y

la línea discontinua indica el sitio de unión del enlazador;

(b) el L es una porción de enlace químico que une covalentemente la CLM y la PTM, y comprende una unidad estructural química representada por la Fórmula $-(A^L)_q$ - en donde:

$(A^L)_q$ se conecta a la CLM y la PTM;

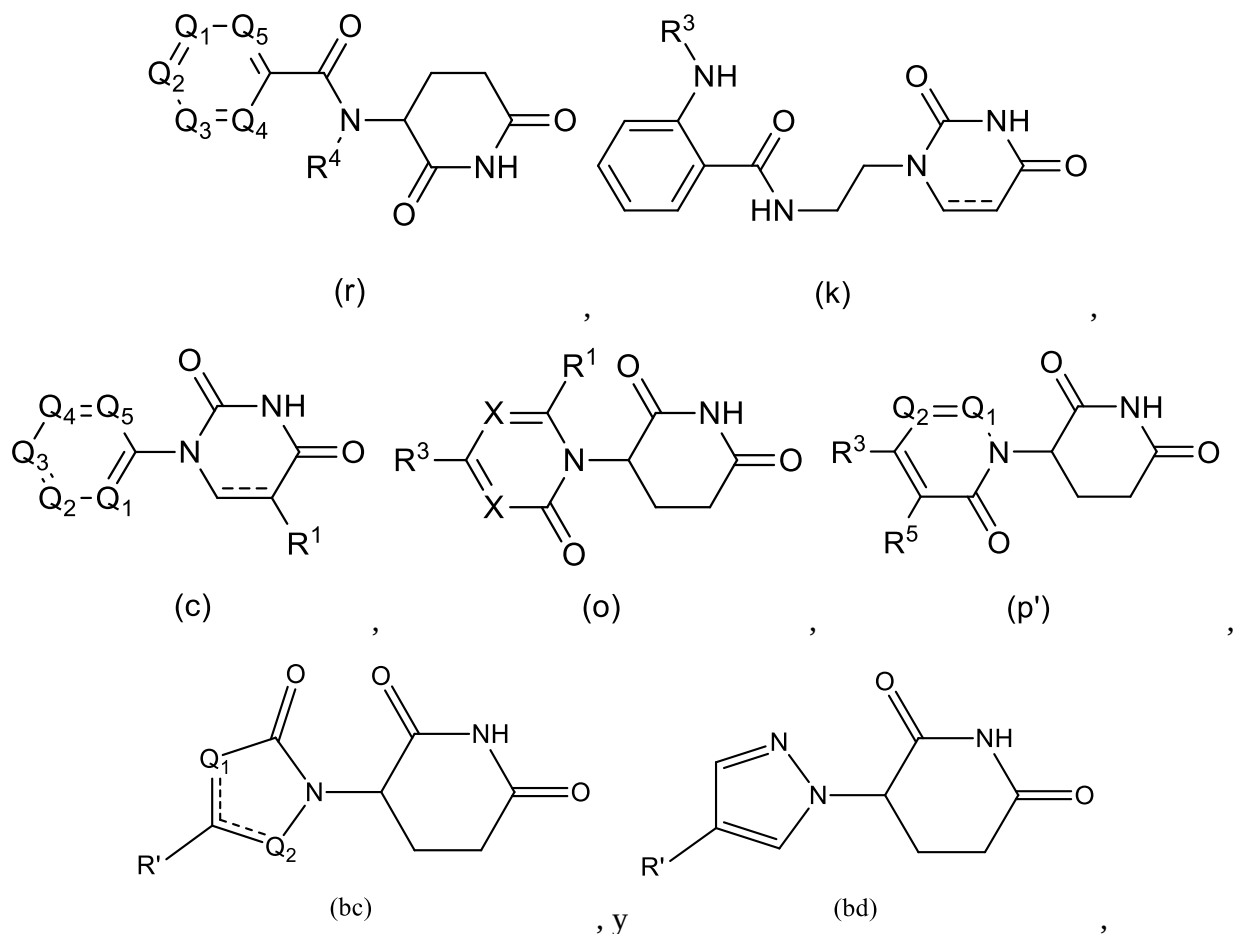
q es un número mayor que o igual a 1;

cada A^L se selecciona independientemente del grupo que consiste en, 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, $CR^{L1}=CR^{L2}$, $C\equiv C$, $SiR^{L1}R^{L2}$, $P(O)R^{L1}$, $P(O)OR^{L1}$, $NR^{L3}C(=NCN)NR^{L4}$, $NR^{L3}C(=NCN)$, $NR^{L3}C(=CNO_2)NR^{L4}$, C_{3-11} cicloalquilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2} , C_{3-11} heterociclilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2} , arilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2} , heteroarilo opcionalmente sustituido con 0-6 R^{L1} y/o grupos R^{L2} , donde R^{L1} o R^{L2} , cada uno independientemente se unen opcionalmente a otros grupos para formar porciones 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 independientemente, H, halo, C_{1-8} alquilo, OC_{1-8} alquilo, SC_{1-8} alquilo, NHC_{1-8} alquilo, $N(C_{1-8}alquilo)_2$, C_{3-11} cicloalquilo, arilo, heteroarilo, C_{3-11} heterociclilo, OC_{1-8} cicloalquilo, SC_{1-8} cicloalquilo, NHC_{1-8} cicloalquilo, $N(C_{1-8}$

8cicloalquilo)₂, N(C₁₋₈cicloalquilo)(C₁₋₈alquilo), OH, NH₂, SH, SO₂C₁₋₈alquilo, P(O)(OC₁₋₈alquilo)(C₁₋₈alquilo), P(O)(OC₁₋₈alquilo)₂, CC-C₁₋₈alquilo, CCH, CH=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=CH(C₁₋₈alquilo), C(C₁₋₈alquilo)=C(C₁₋₈alquilo)₂, Si(OH)₃, Si(C₁₋₈alquilo)₃, Si(OH)(C₁₋₈alquilo)₂, COC₁₋₈alquilo, CO₂H, halógeno, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO₂NHC₁₋₈alquilo, SO₂N(C₁₋₈alquilo)₂, SONHC₁₋₈alquilo, SON(C₁₋₈alquilo)₂, CONHC₁₋₈alquilo, CON(C₁₋₈alquilo)₂, N(C₁₋₈alquilo)CONH(C₁₋₈alquilo), N(C₁₋₈alquilo)CON(C₁₋₈alquilo)₂, NHCONH(C₁₋₈alquilo), NHCON(C₁₋₈alquilo)₂, NHCONH₂, N(C₁₋₈alquilo)SO₂NH(C₁₋₈alquilo), N(C₁₋₈alquilo) SO₂N(C₁₋₈alquilo)₂, NH SO₂NH(C₁₋₈alquilo), NH SO₂N(C₁₋₈alquilo)₂, NH SO₂NH₂ y

(c) la CLM es una porción de unión a la ligasa de ubiquitinaE3 cereblon de molécula pequeña que se une o se dirige a una ligasa de ubiquitina E3 cereblon y tiene una estructura química seleccionada del grupo que consiste en:



en donde:

Q₁, Q₂, Q₃, Q₄, Q₅ representan cada uno independientemente un C o N sustituido con un grupo seleccionado independientemente de R', N o N-óxido;

R¹ es ausente, H, OH, CN, C₁-C₃ alquilo, o C=O;

R² es ausente, H, OH, CN, C₁-C₃ alquilo, CHF₂, CF₃, CHO, C(=O)NH₂;

R³ es ausente, H, alquilo (preferiblemente un C₁-C₆ o C₁-C₃ alquilo), alquilo sustituido (preferiblemente C₁-C₆ o C₁-C₃ alquilo sustituido), alcoxi (preferiblemente un C₁-C₆ o C₁-C₃ alcoxilo), alcoxi sustituido (por ejemplo, C₁-C₆ o C₁-C₃ alcoxilo sustituido);

R⁴ se selecciona de H, alquilo, alquilo sustituido;

R⁵ es H, halógeno, C(=O)R'; CN, OH, o CF₃ ;

X es C, CH, C=O, o N; R' se selecciona de H, halógeno, amina, alquilo (preferiblemente C₁-C₃ alquilo), alquilo sustituido (preferiblemente un C₁-C₃ alquilo sustituido), alcoxi (preferiblemente un C₁-C₃ alcoxilo), alcoxi sustituido (preferiblemente un C₁-C₃ alcoxilo sustituido), NR²R³, C(=O)OR², fenilo opcionalmente sustituido; y

// es un enlace simple o doble.

2. El compuesto bifuncional de conformidad con la reivindicación 1, en donde la CLM se une al grupo enlazador químico (L) a través de X, R¹, R², R³, R⁴, R', Q₁, Q₂, Q₃, Q₄, o Q₅.

3. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1 o 2, en donde:

W¹ es arilo, o heteroarilo, cada uno independientemente sustituido con 1 o más H, halo, hidroxilo, nitro, CN, C≡CH, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), C₁₋₆ alcoxilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo), C₂₋₆ alquenilo, C₂₋₆ alquinilo, o CF₃;

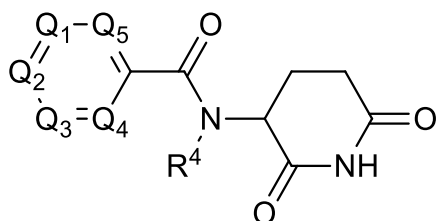
Q es un anillo alicíclico de 4 miembros con 0-2 heteroátomos, opcionalmente sustituido con 0-6 R^Q, cada R^Q es independientemente H, C₁₋₆ alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C₁₋₆ alcoxilo), o 2 grupos R^Q tomados junto con el átomo al que se unen, forman un sistema de anillo de 3-8 miembros que contiene 0-2 heteroátomos);

R^{Y1} , R^{Y2} son cada uno independientemente H, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más halo, C_{1-6} alcoxilo);

W^2 es un enlace, C_{1-6} alquilo, C_{1-6} heteroalquilo, O, C_{1-6} alicíclico, heterocíclico, arilo, biheterocíclico, biarilo, o biheteroarilo, o heteroarilo, cada uno opcionalmente sustituido con 1, 2 o 3 R^{W2} ; y

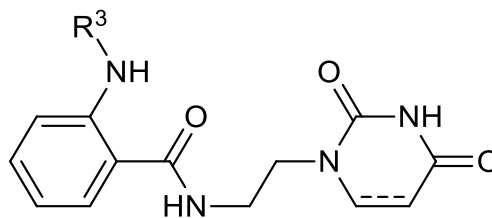
cada R^{W2} es independientemente H, halo, C_{1-6} alquilo (lineal, ramificado, opcionalmente sustituido con 1 o más F), C_{1-6} heteroalquilo (lineal, ramificado, opcionalmente sustituido), -OR^{W2A} OC₁₋₃alquilo (opcionalmente sustituido con 1 o más -F), C_{3-6} cicloalquilo, C_{4-6} cicloheteroalquilo (opcionalmente sustituido), heterocíclico (opcionalmente sustituido), arilo (opcionalmente sustituido), heteroarilo (opcionalmente sustituido), heteroarilo bicíclico (opcionalmente sustituido), arilo bicíclico, OH, NH₂, NR^{Y1}R^{Y2}, o CN.

4. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-3, en donde el CLM tiene la estructura



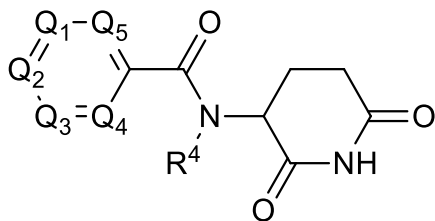
(r)

o



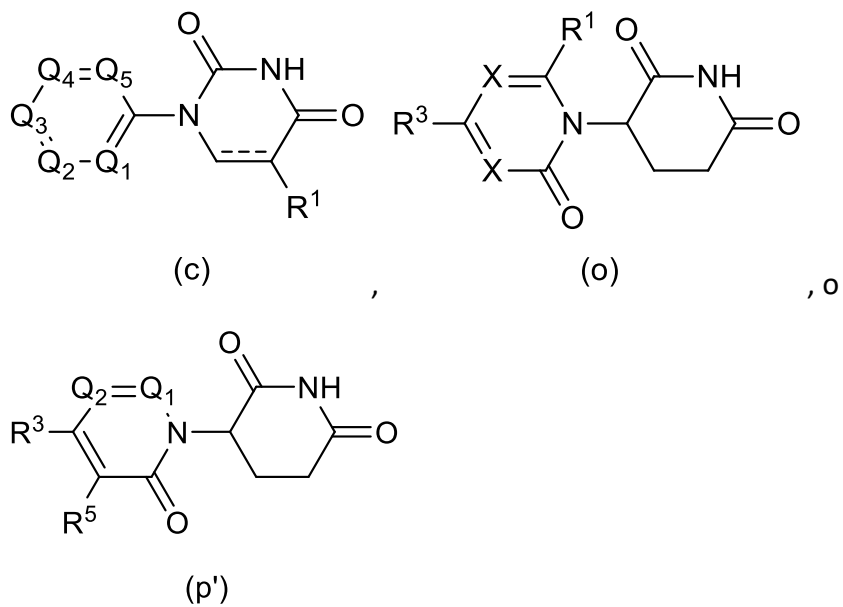
(k)

5. El compuesto bifuncional de conformidad con la reivindicación 4, en donde la CLM tiene la estructura

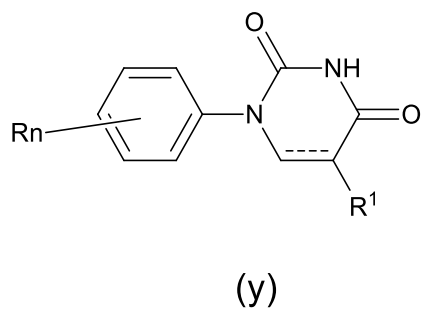


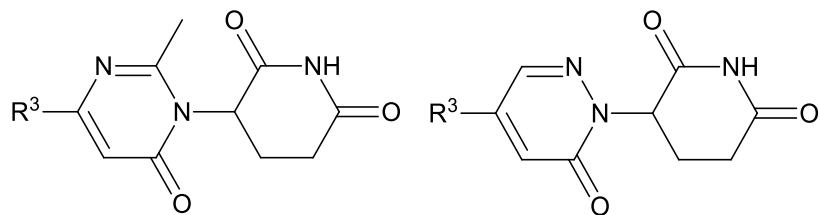
(r)

6. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-3, en donde la CLM tiene la estructura



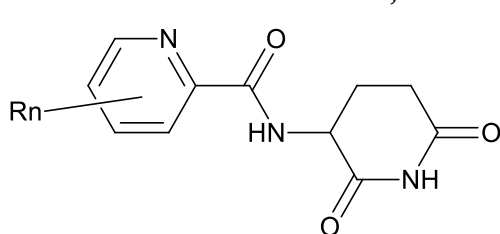
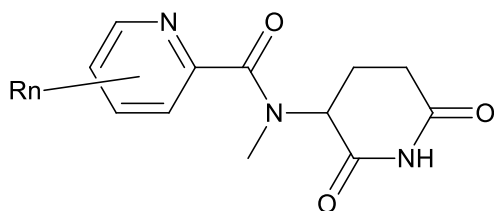
7. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-6, en donde la CLM se representa por una estructura química seleccionada del grupo que consiste en:





(ad)

(ae)

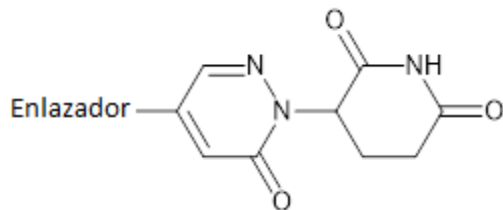
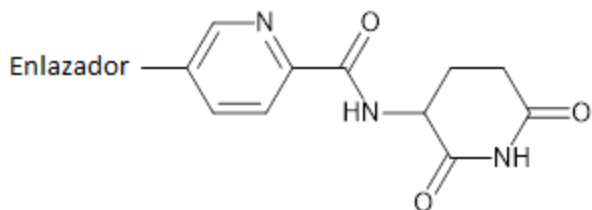
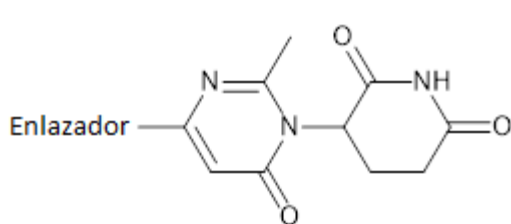


(af)

(ag)

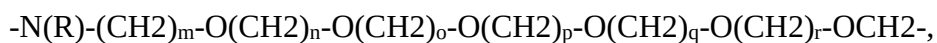
, y
en donde Rn comprende un grupo funcional o un átomo.

8. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-7, en donde la CLM se representa por una estructura química seleccionada por:



y

9. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-8, en donde L se selecciona del grupo que consiste en:



-O-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-OCH₂-;

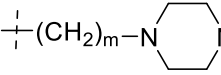
-O-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

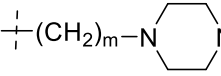
-N(R)-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

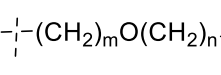
-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

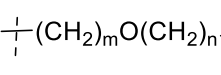
-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-OCH₂-;

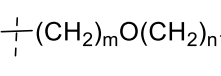
-(CH₂)_mO (CH₂)_r-  N-(CH₂)_oO (CH₂)_p- ;

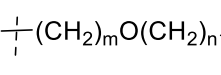
 N-(CH₂)_n-NH  ;

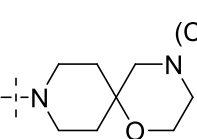
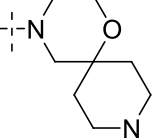
 N-(CH₂)_n-O  ;

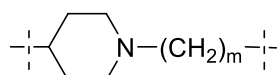
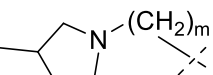
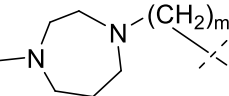
 N-(CH₂)_o-NH  ;

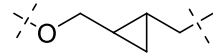
 N-(CH₂)_o-O  ;

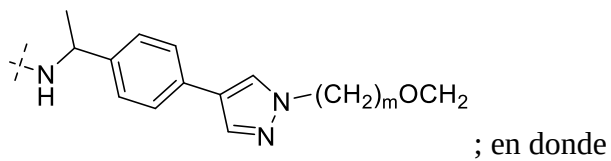
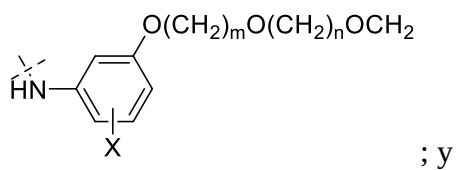
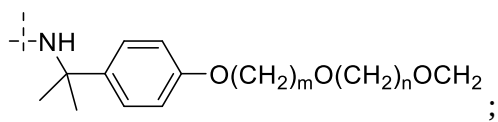
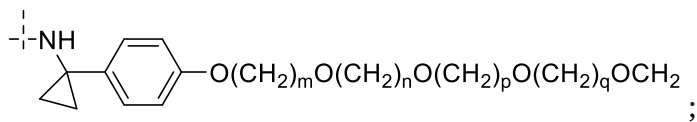
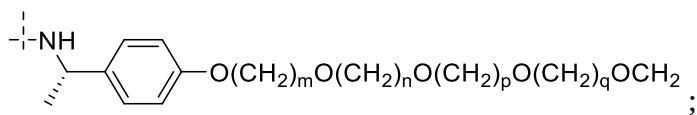
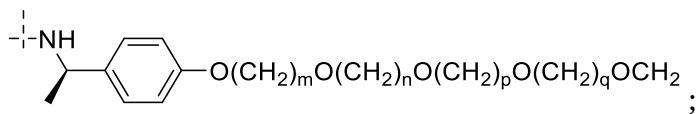
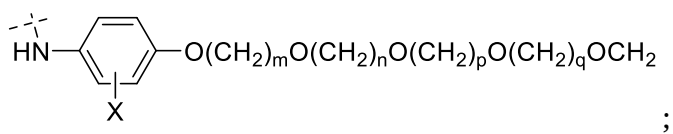
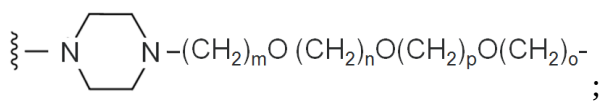
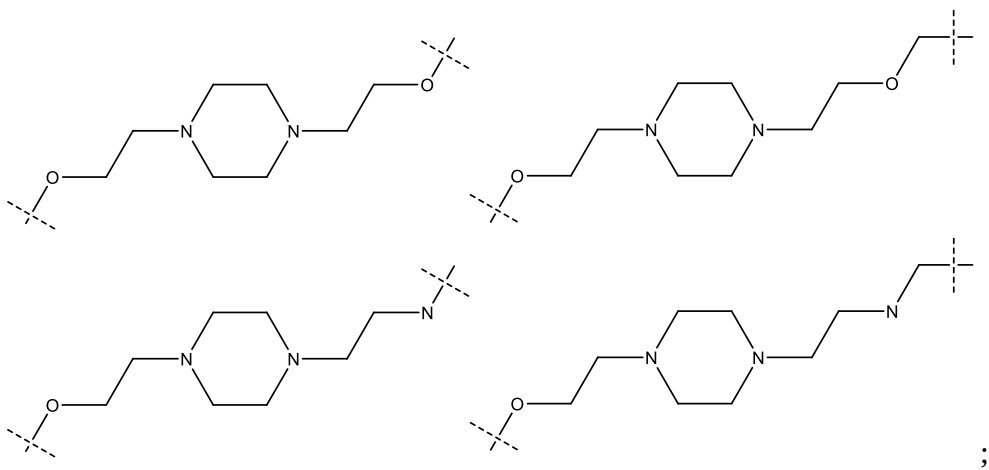
 N-(CH₂)_o-NH  ;

 N-(CH₂)_o-O  ;

 (CH₂)_m  ;  (CH₂)_m  ;

 N-(CH₂)_m  ;  N-(CH₂)_m  ;  N-(CH₂)_m  ;

 O  ;  (CH₂)_m  ;

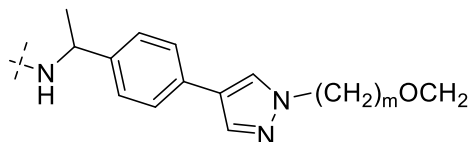


m, n, o, p, q, y r del enlazador son independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20;

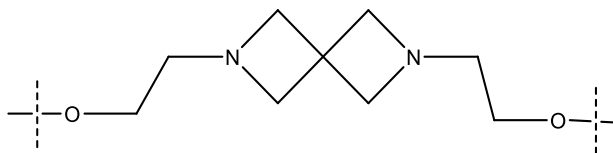
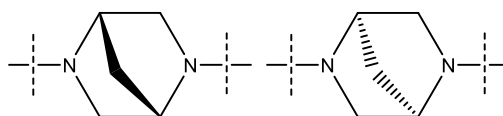
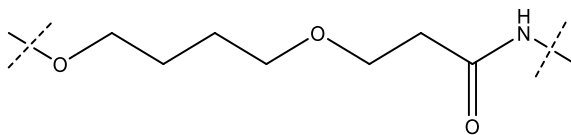
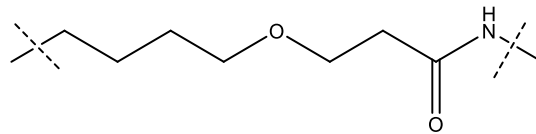
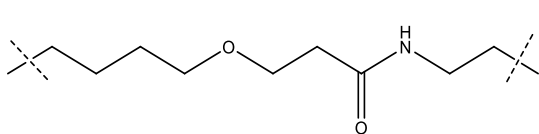
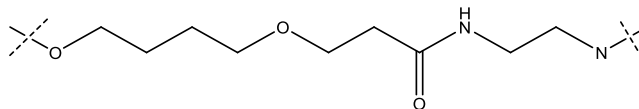
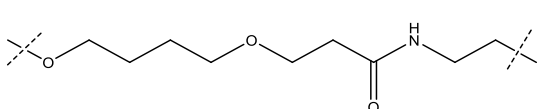
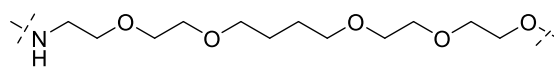
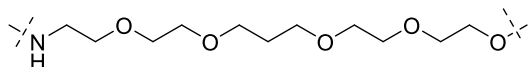
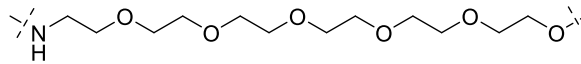
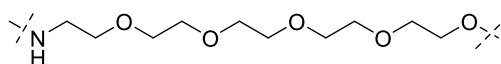
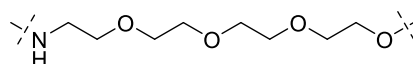
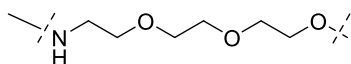
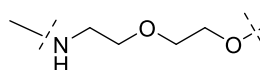
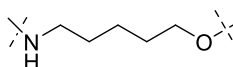
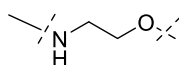
cuando el número es cero, no hay enlace N-O u O-O

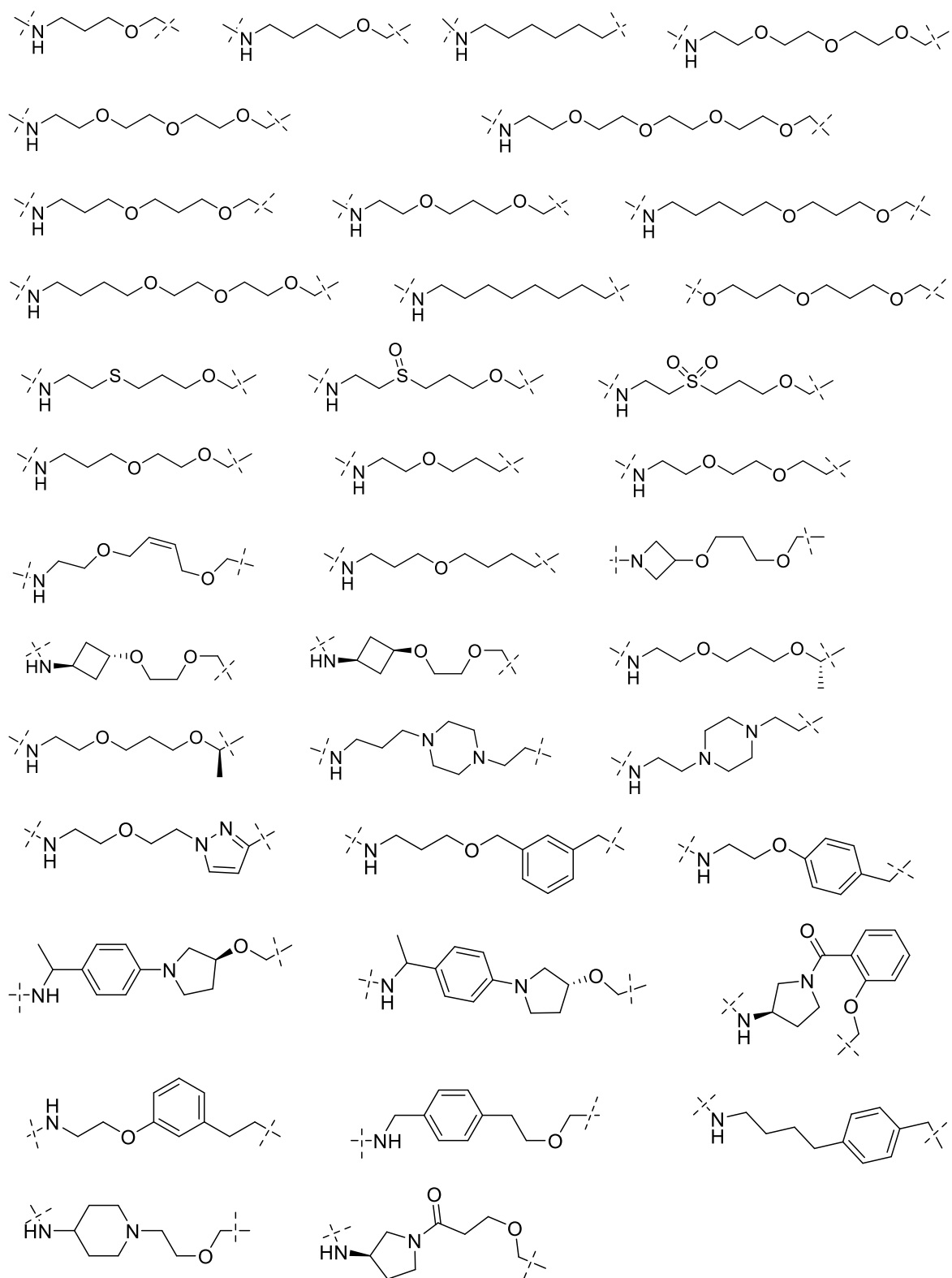
R del enlazador es H, metilo y etilo;

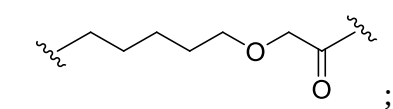
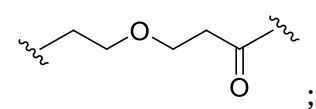
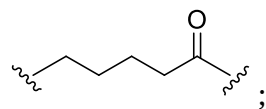
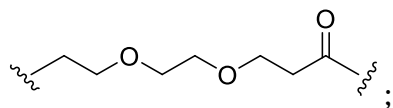
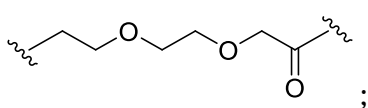
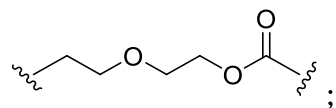
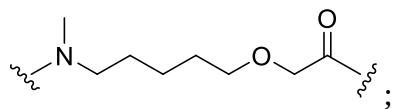
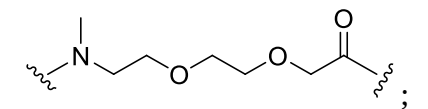
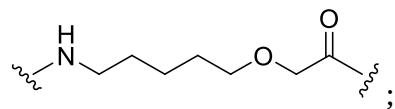
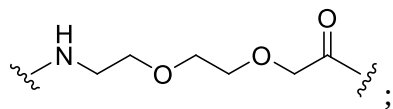
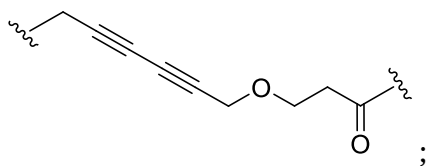
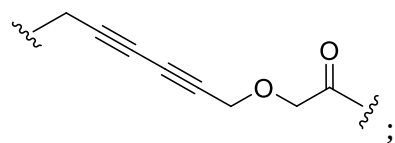
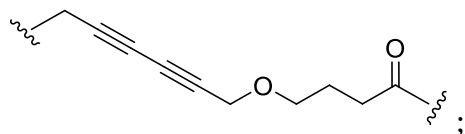
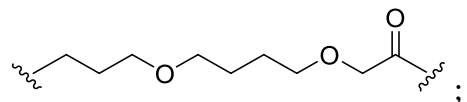
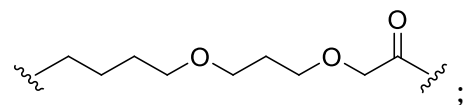
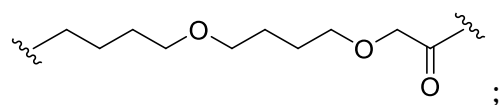
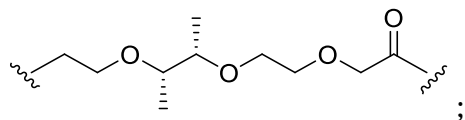
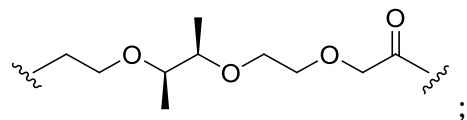
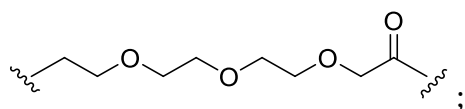
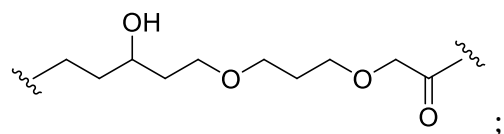
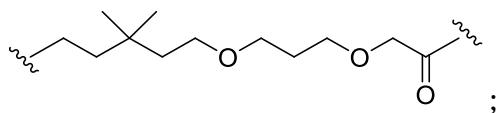
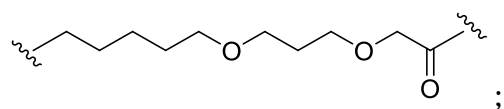
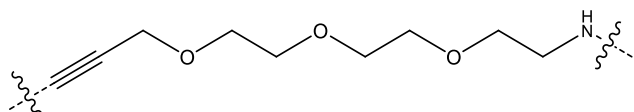
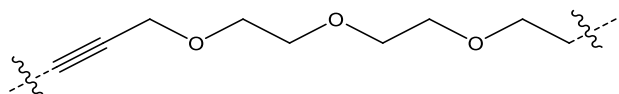
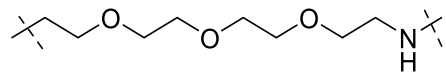
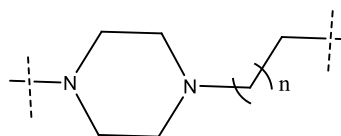
X del enlazador es H y F

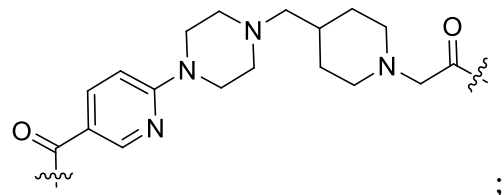
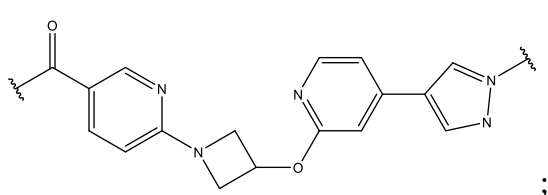
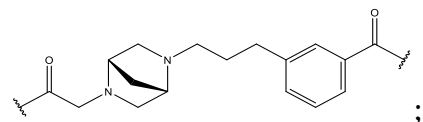
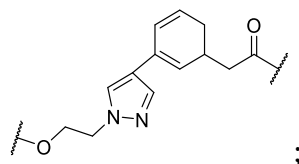
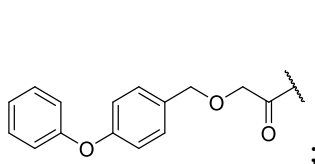
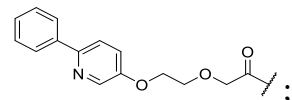
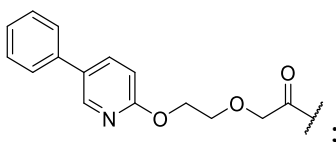
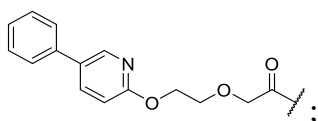
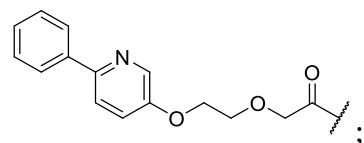
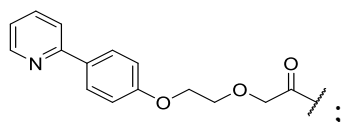
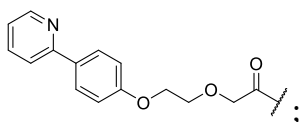
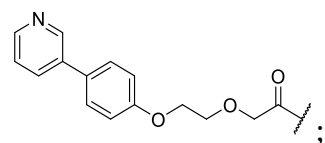
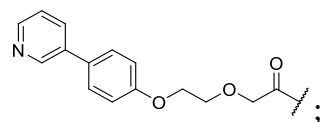
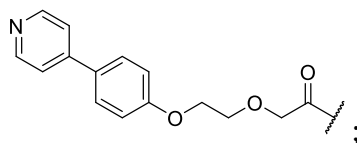
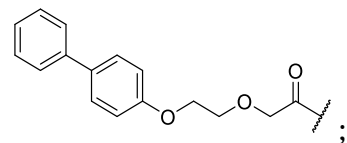
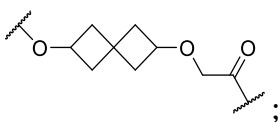
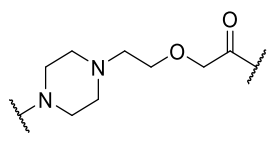
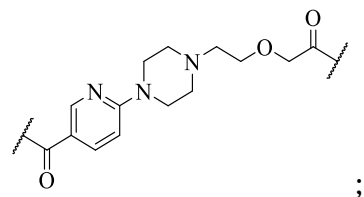
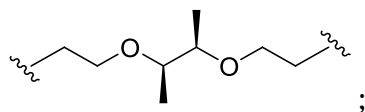
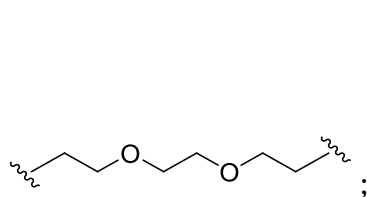
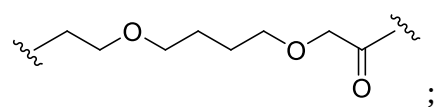
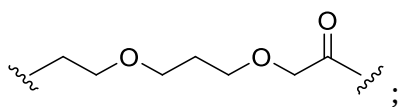
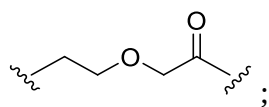
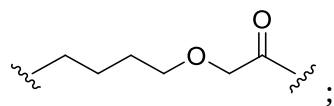
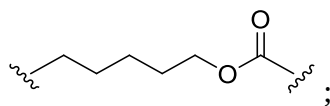
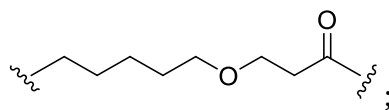


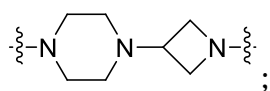
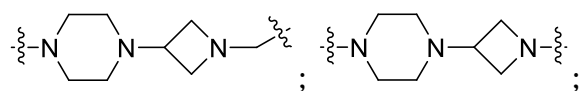
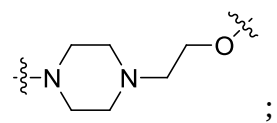
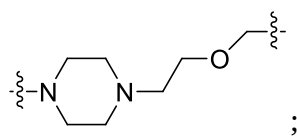
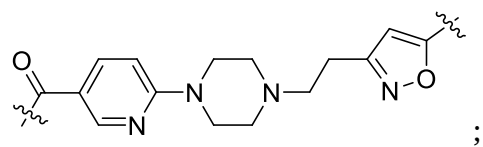
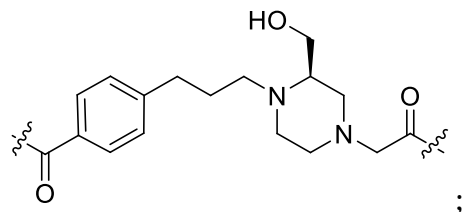
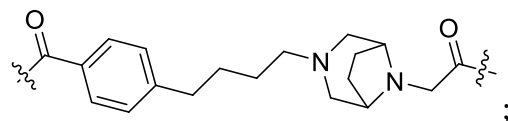
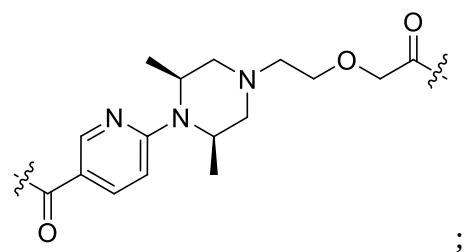
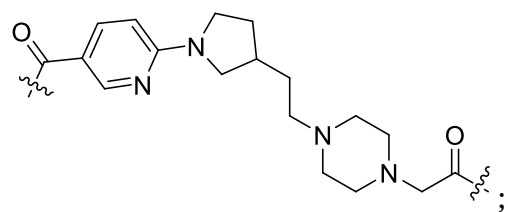
donde m del enlazador puede ser 2, 3, 4, 5

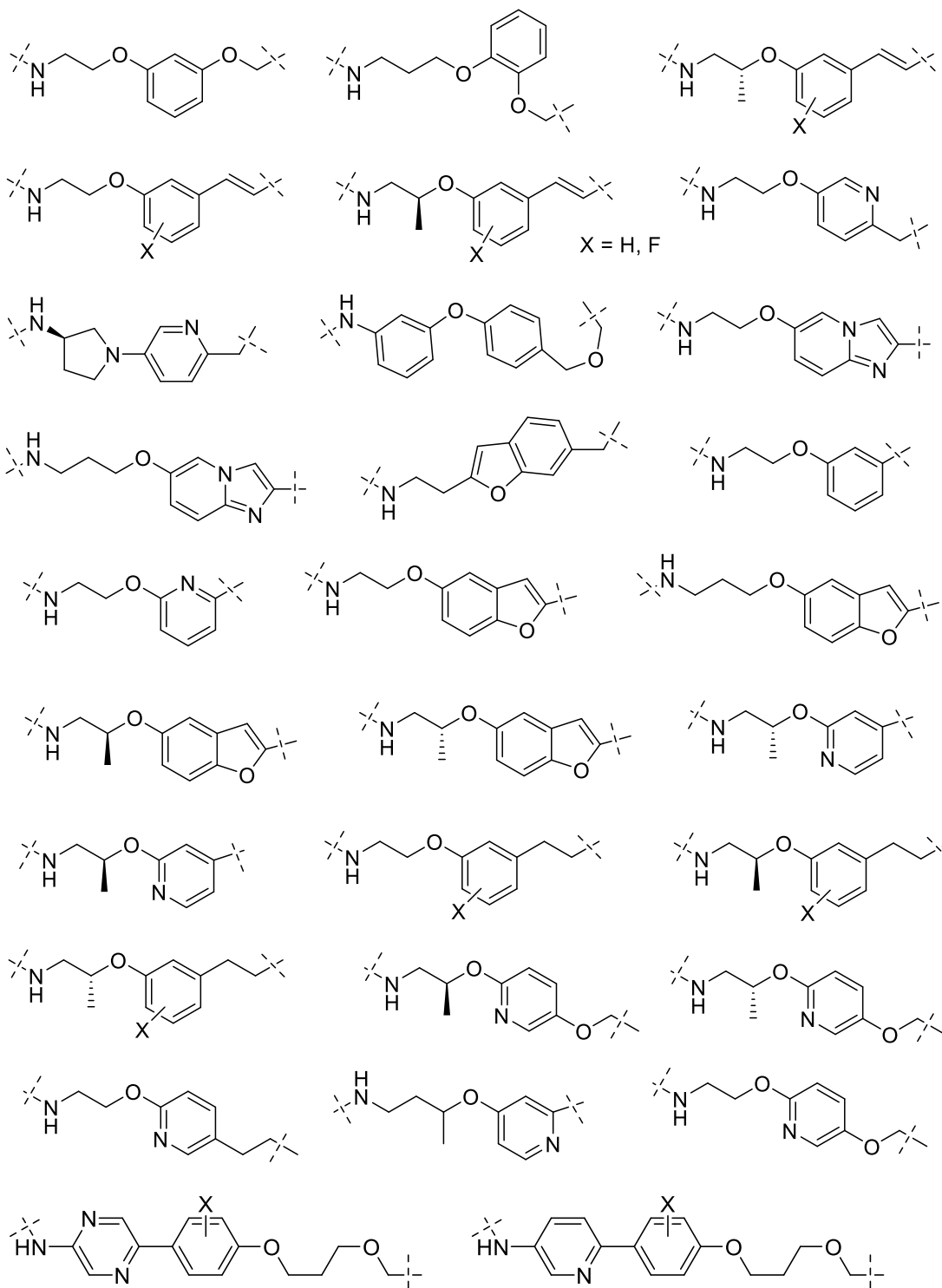


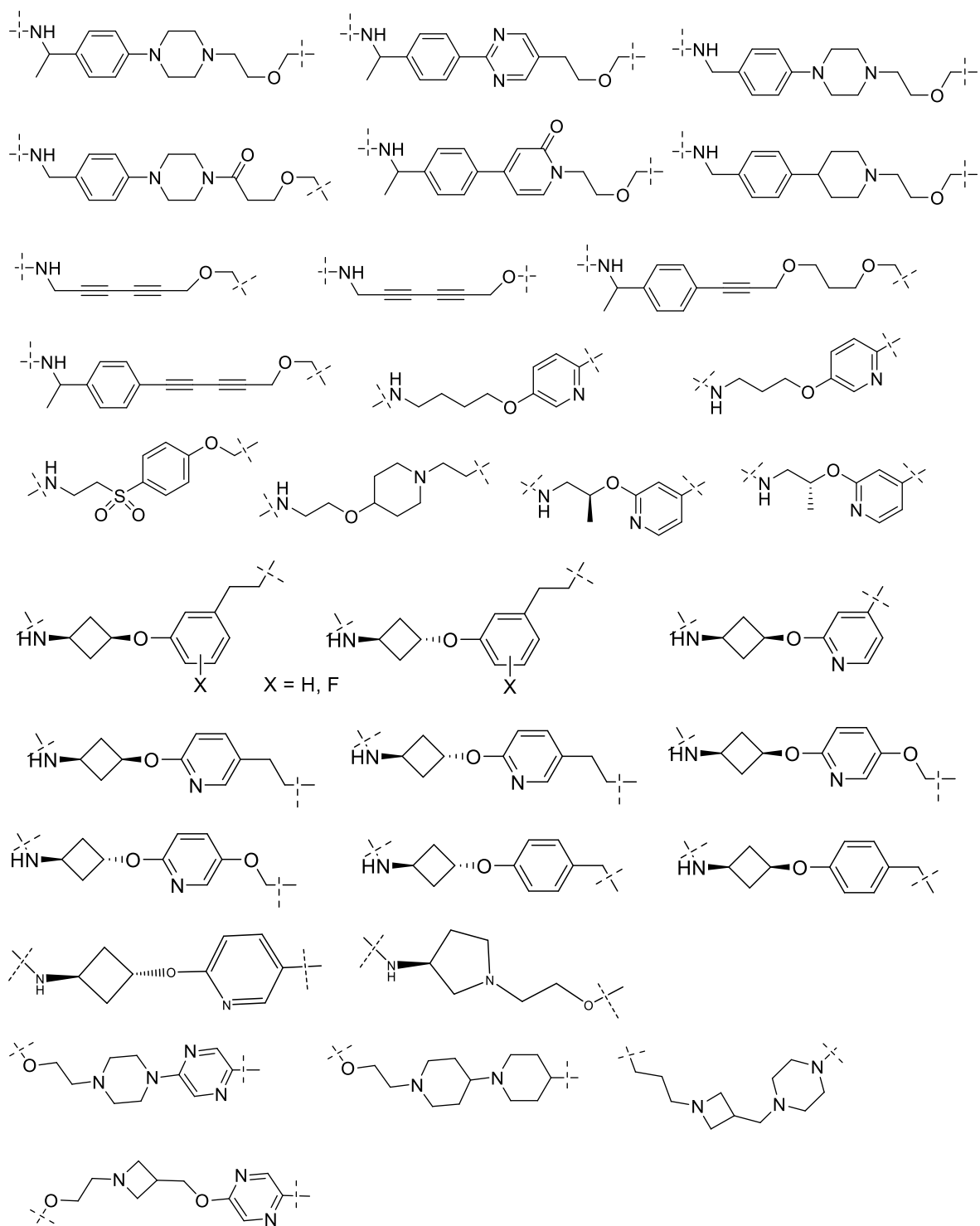


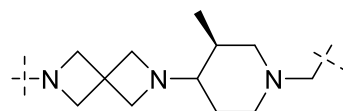
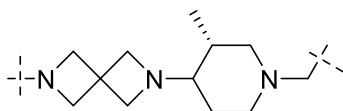
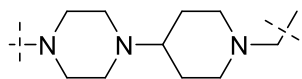
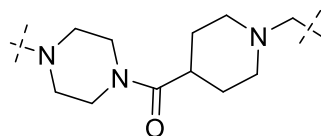
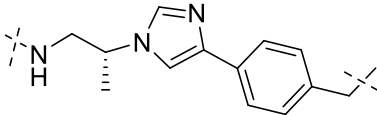
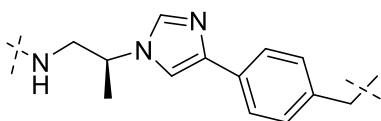
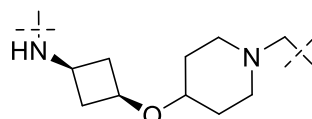
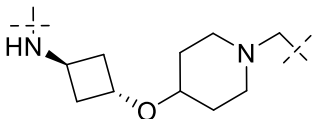
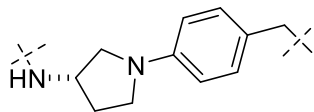
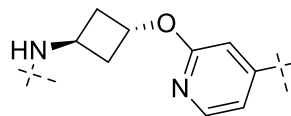
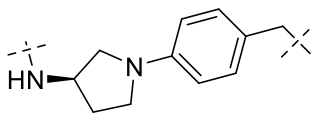
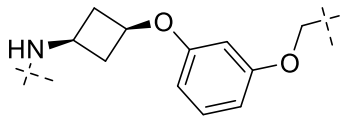
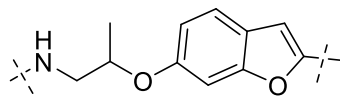
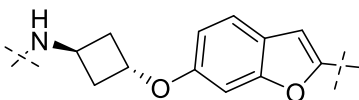
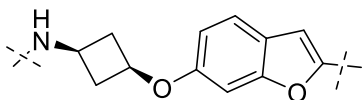
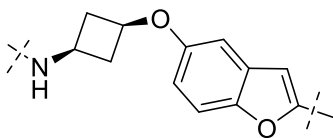
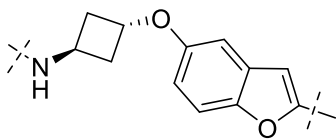
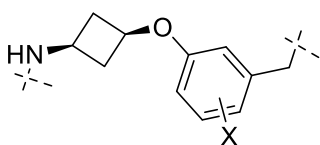
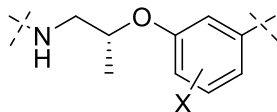
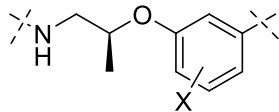
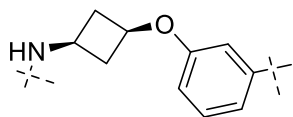
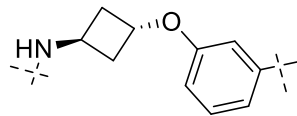
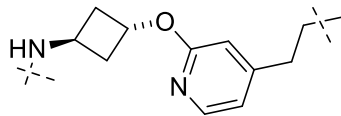
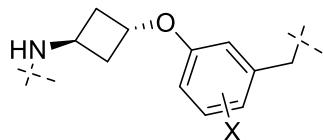
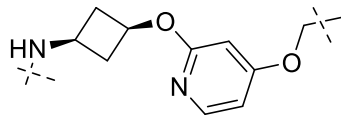
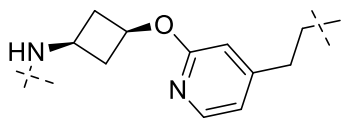
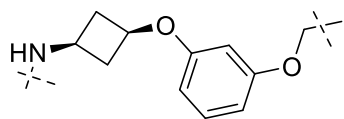


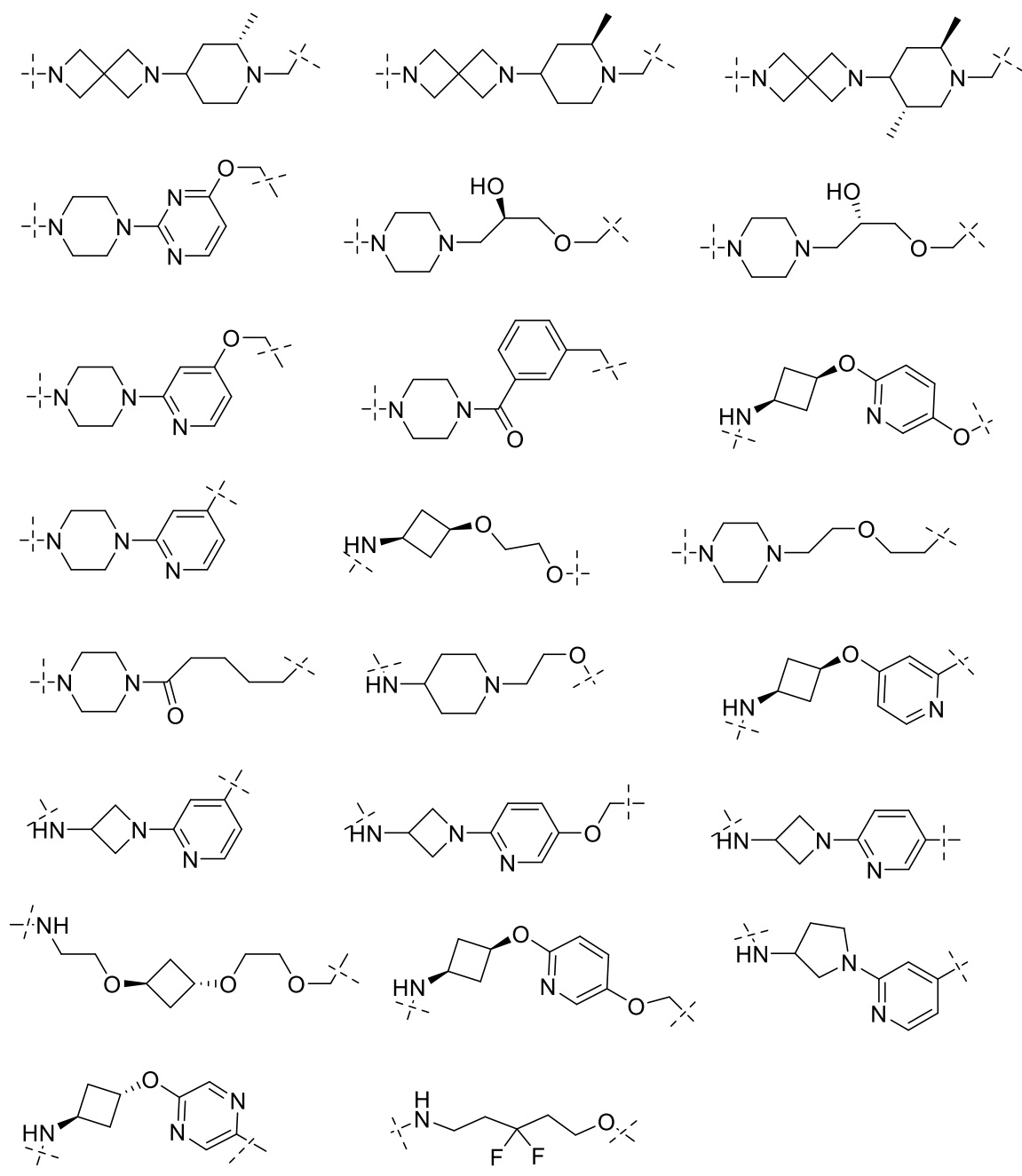






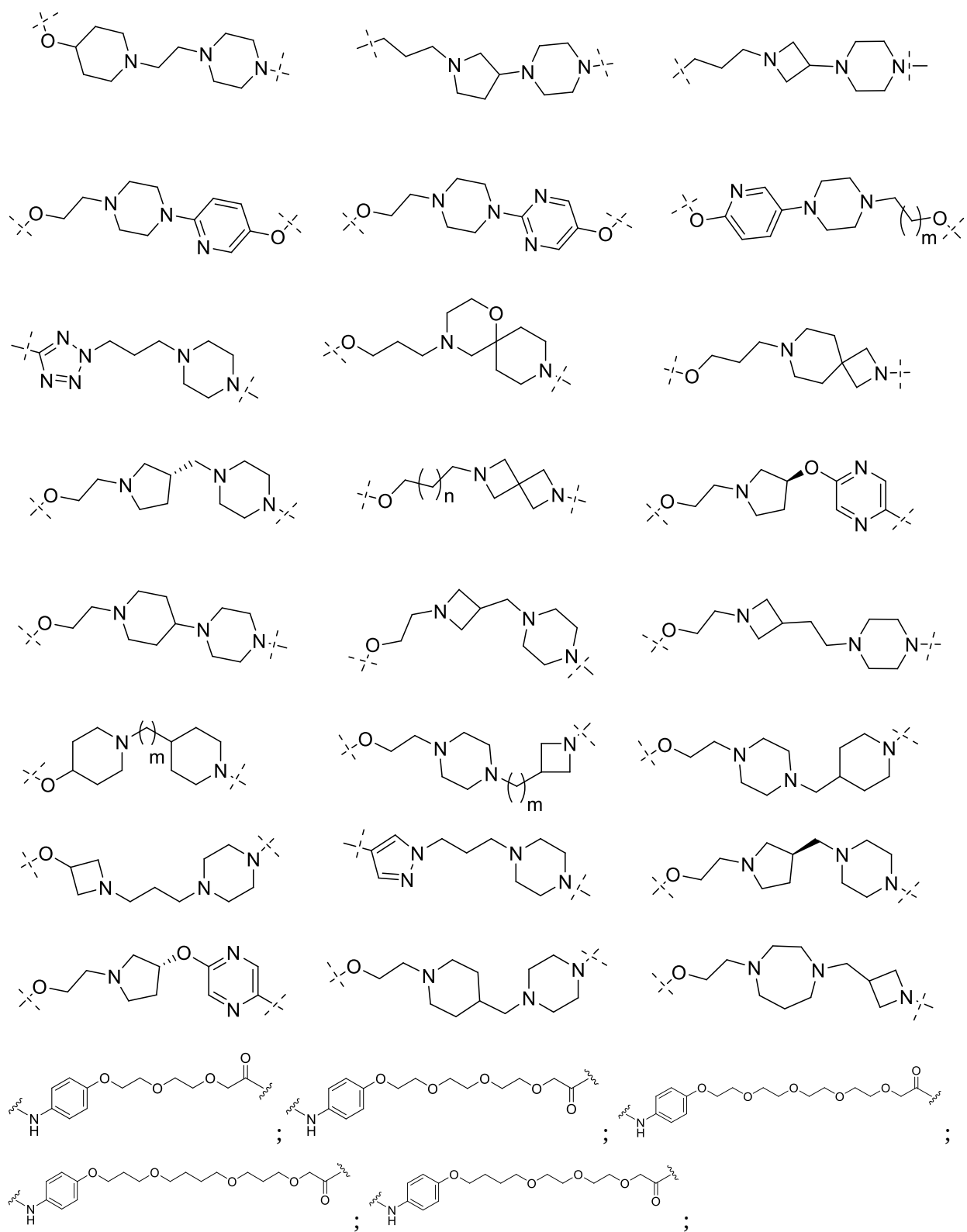


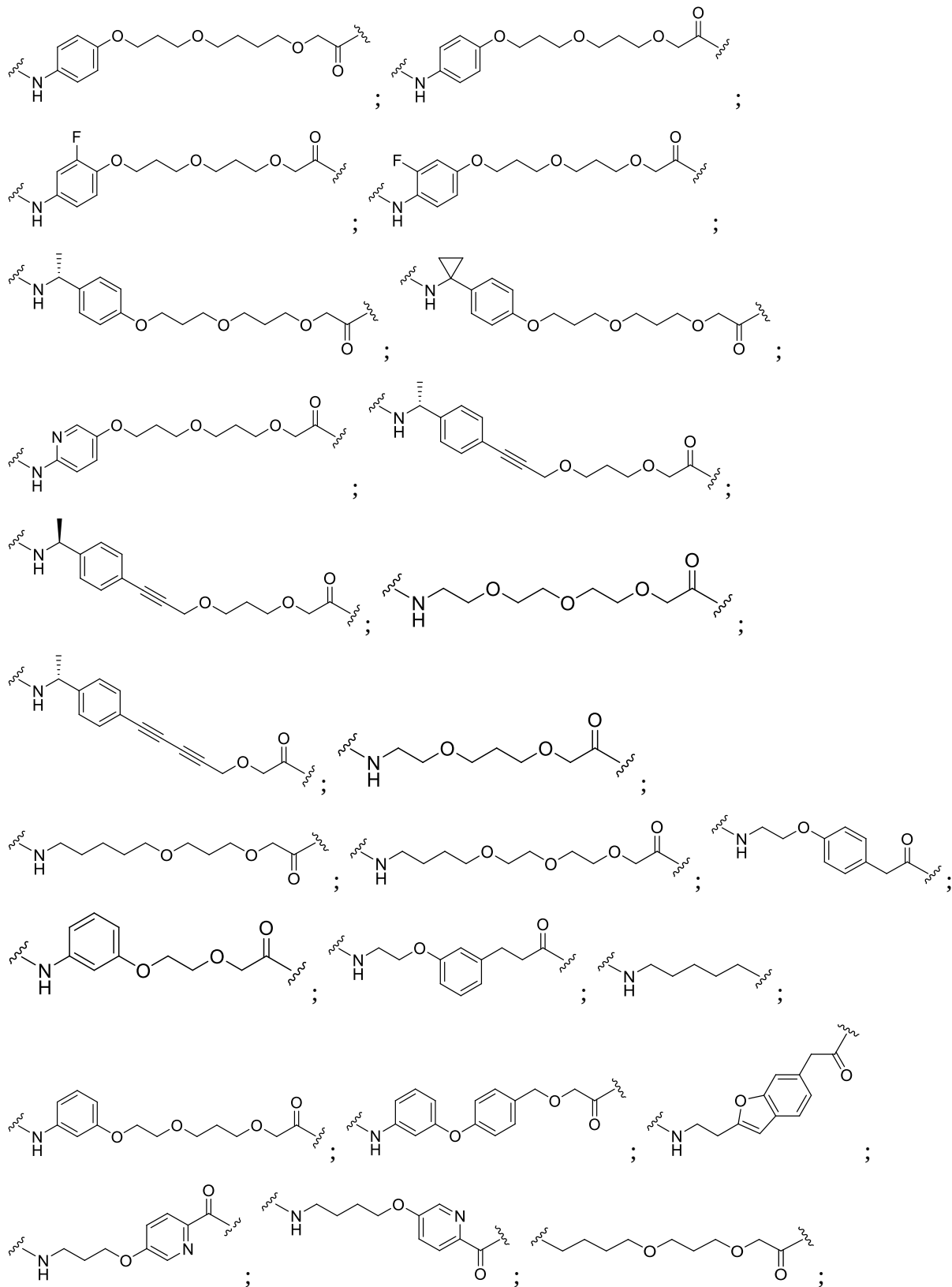


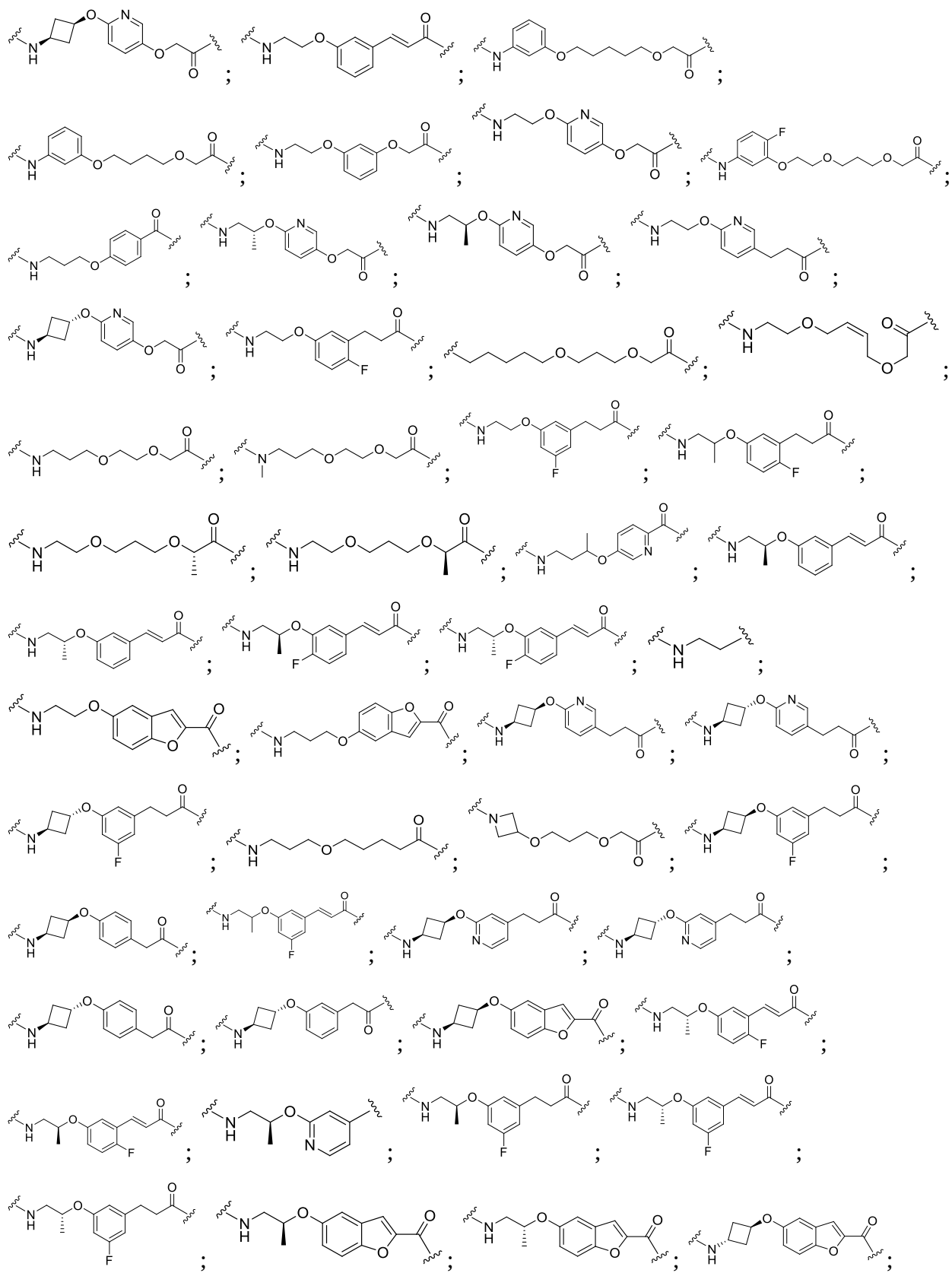


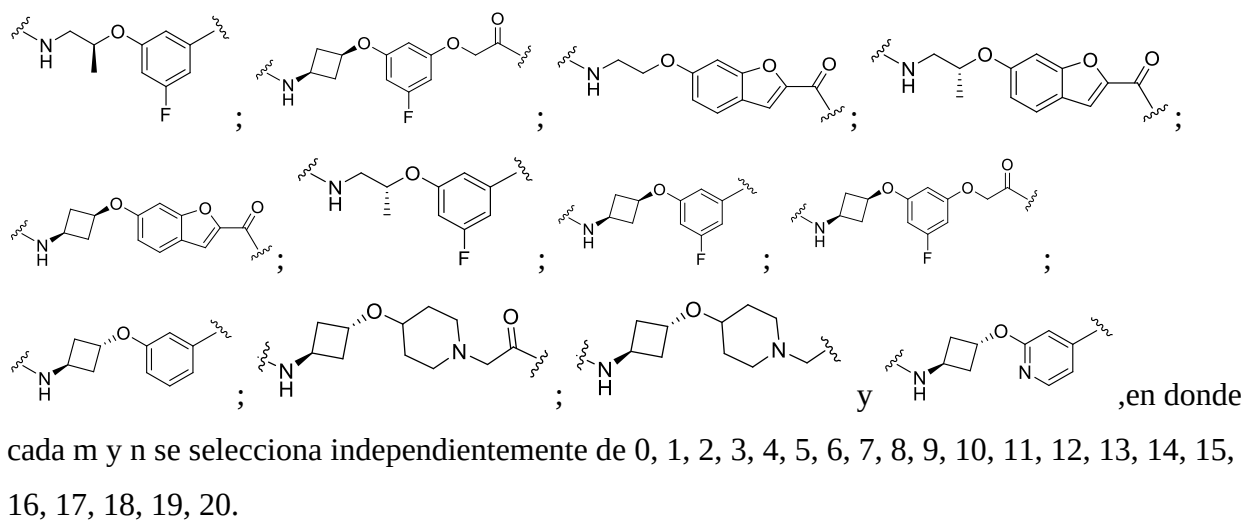
donde cada n y m del enlazador puede ser independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 20. 1.

10. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-9, en donde L se selecciona del grupo que consiste en:

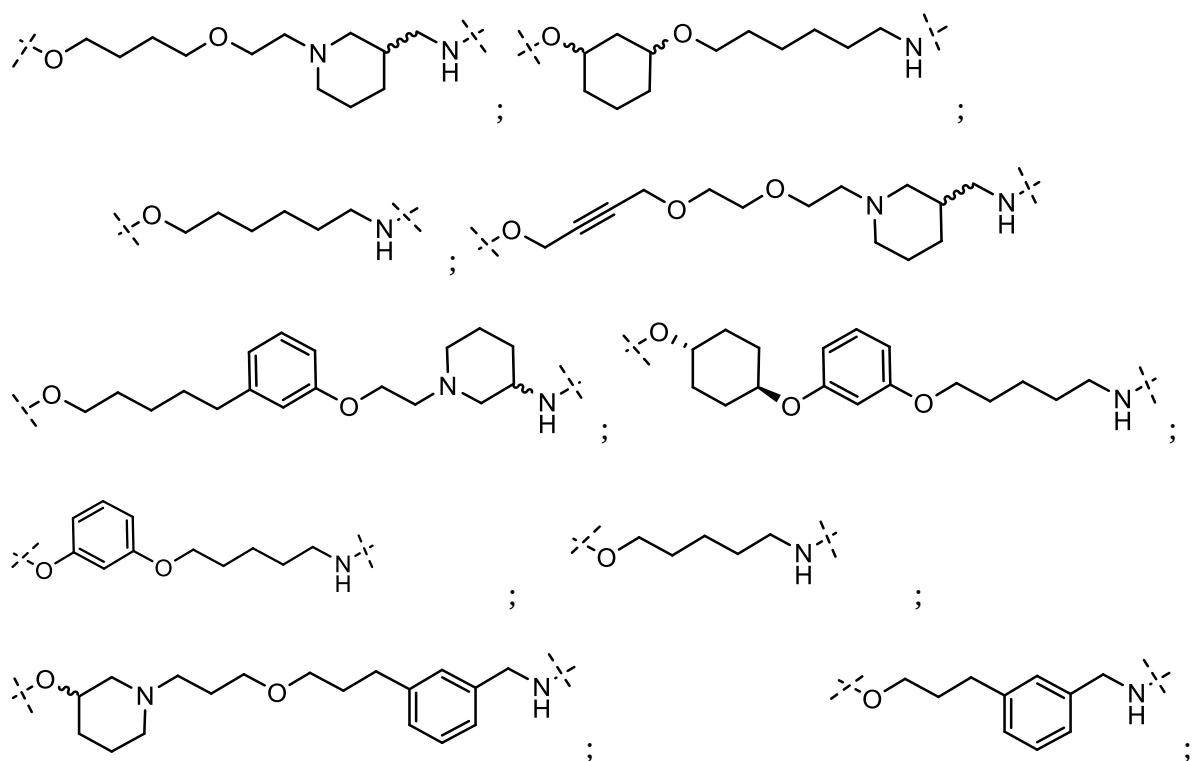


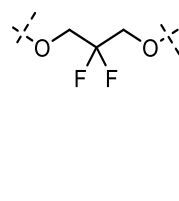
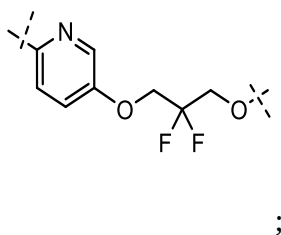
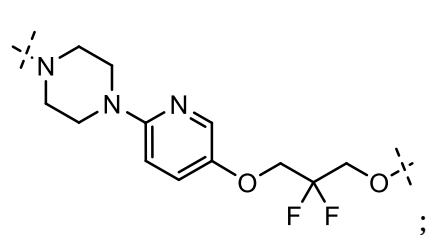
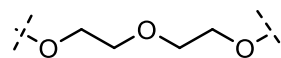
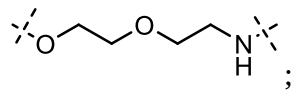
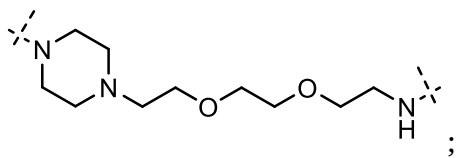
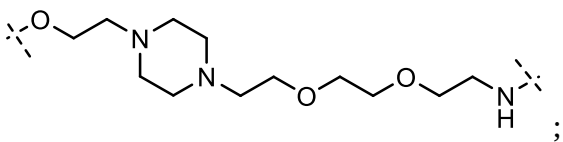
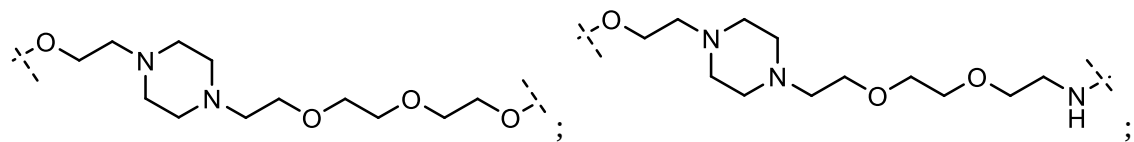
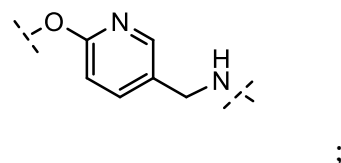
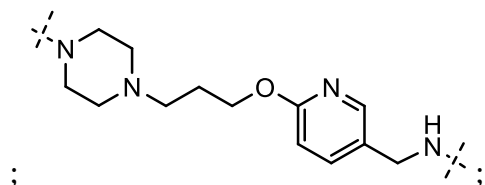
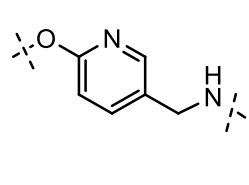
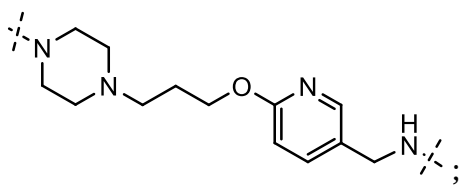
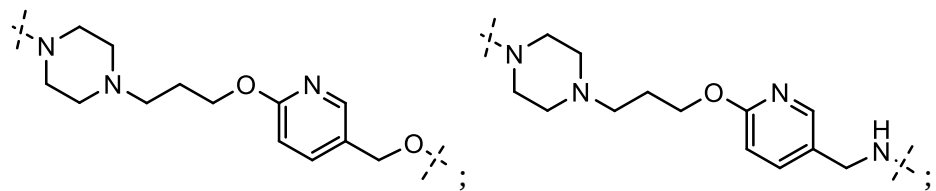
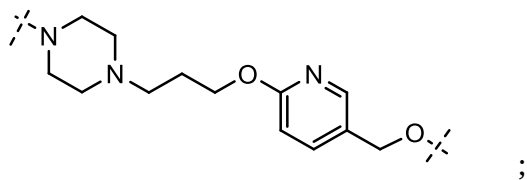
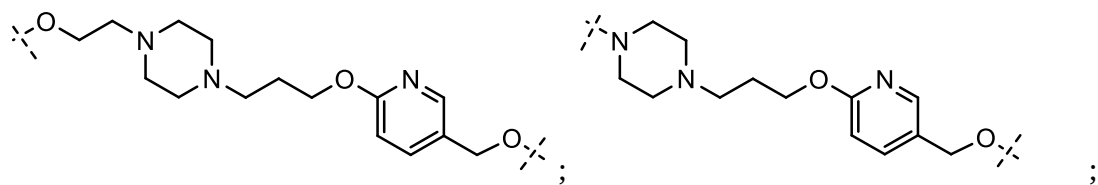
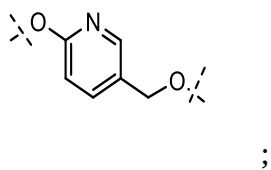
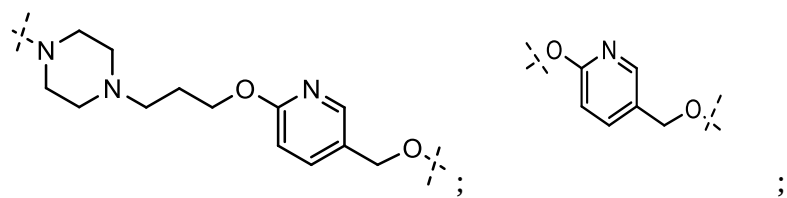


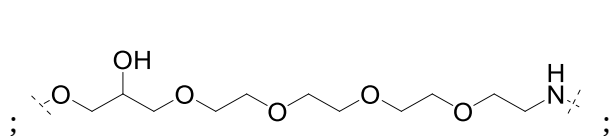
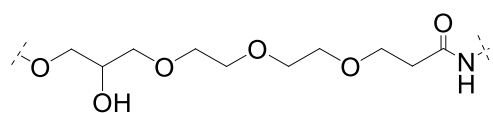
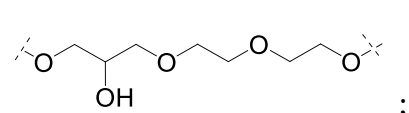
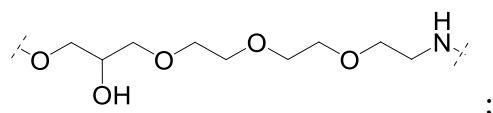
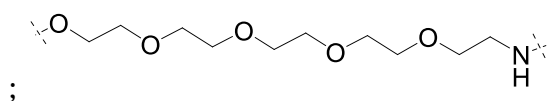
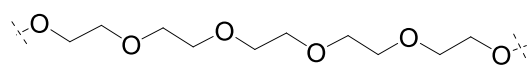
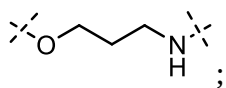
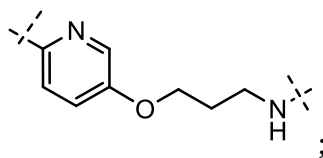
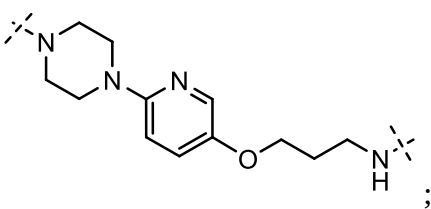
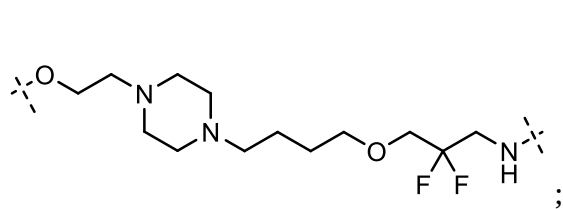
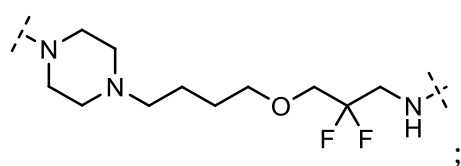
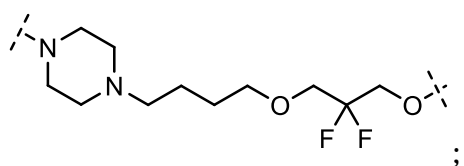
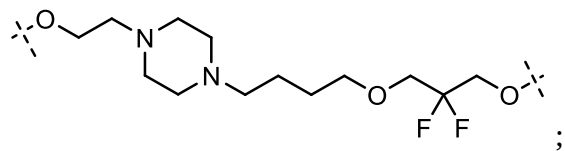
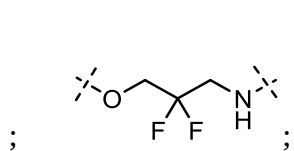
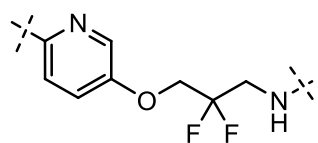
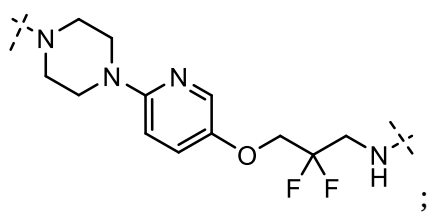
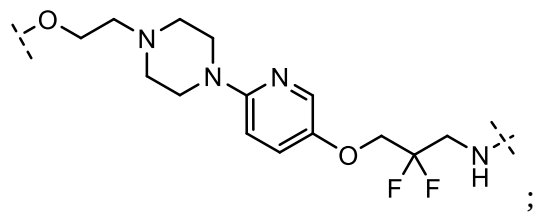


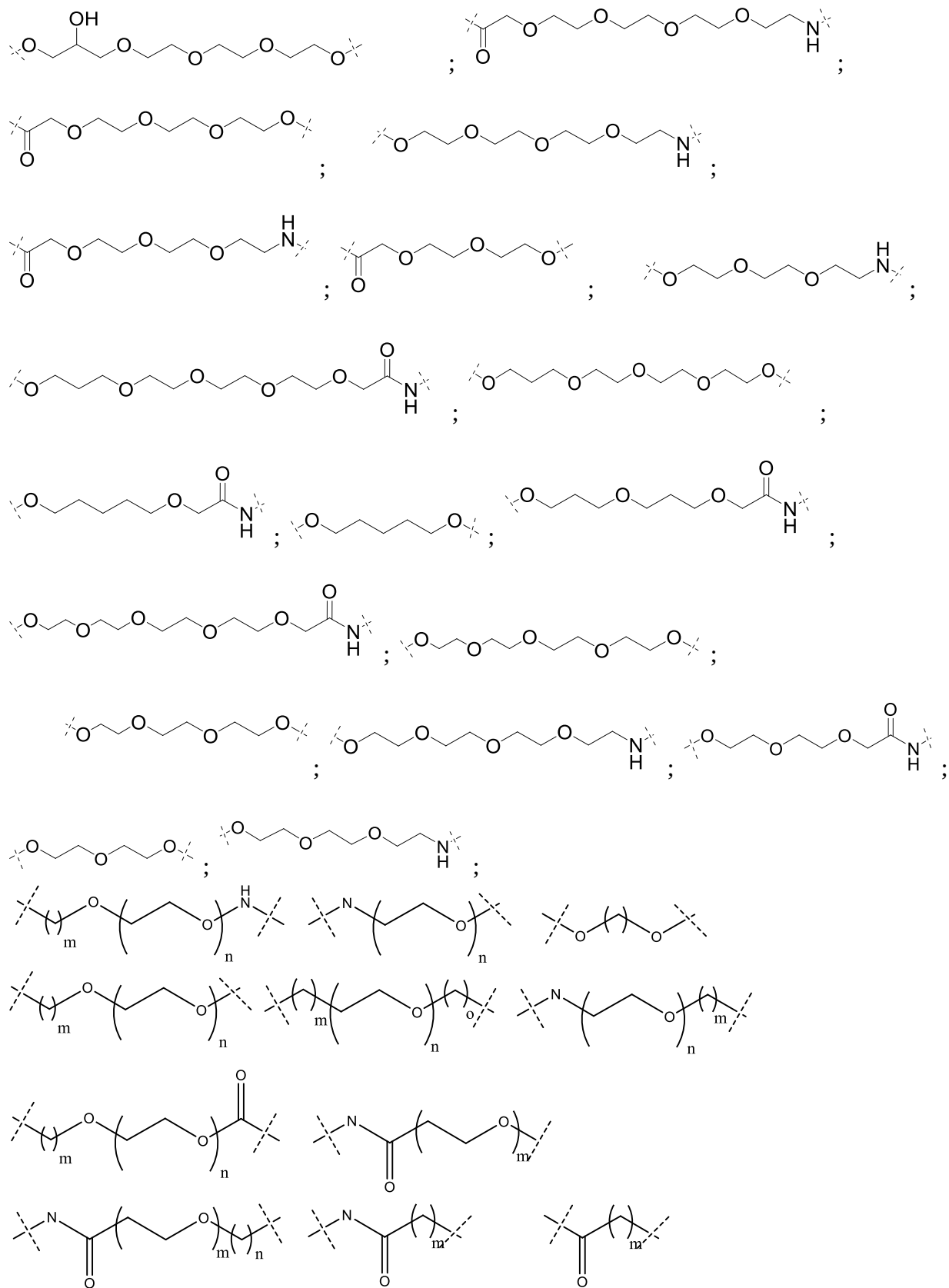


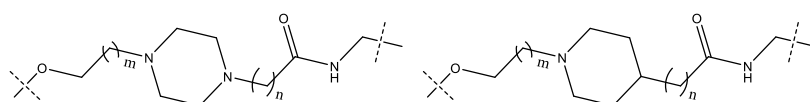
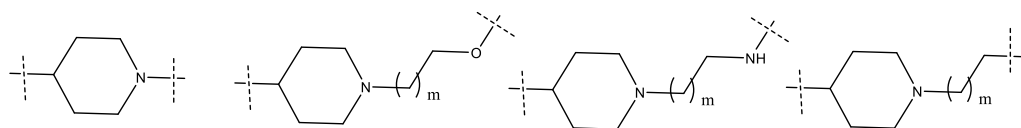
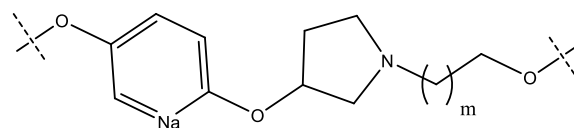
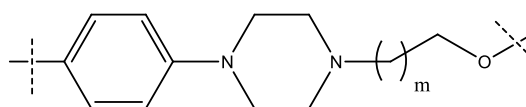
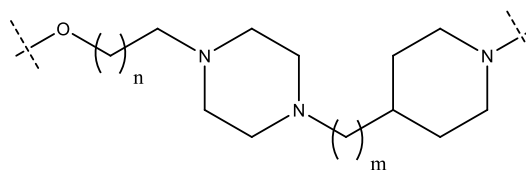
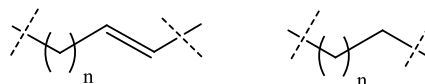
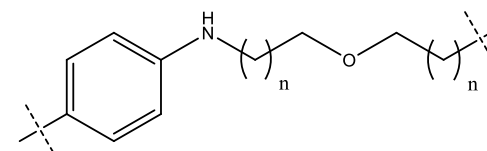
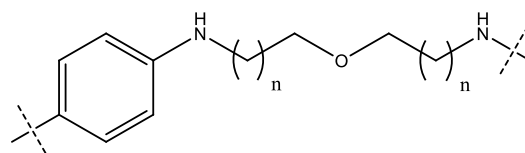
11. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-9, en donde el enlazador (L) se selecciona del grupo que consiste en:

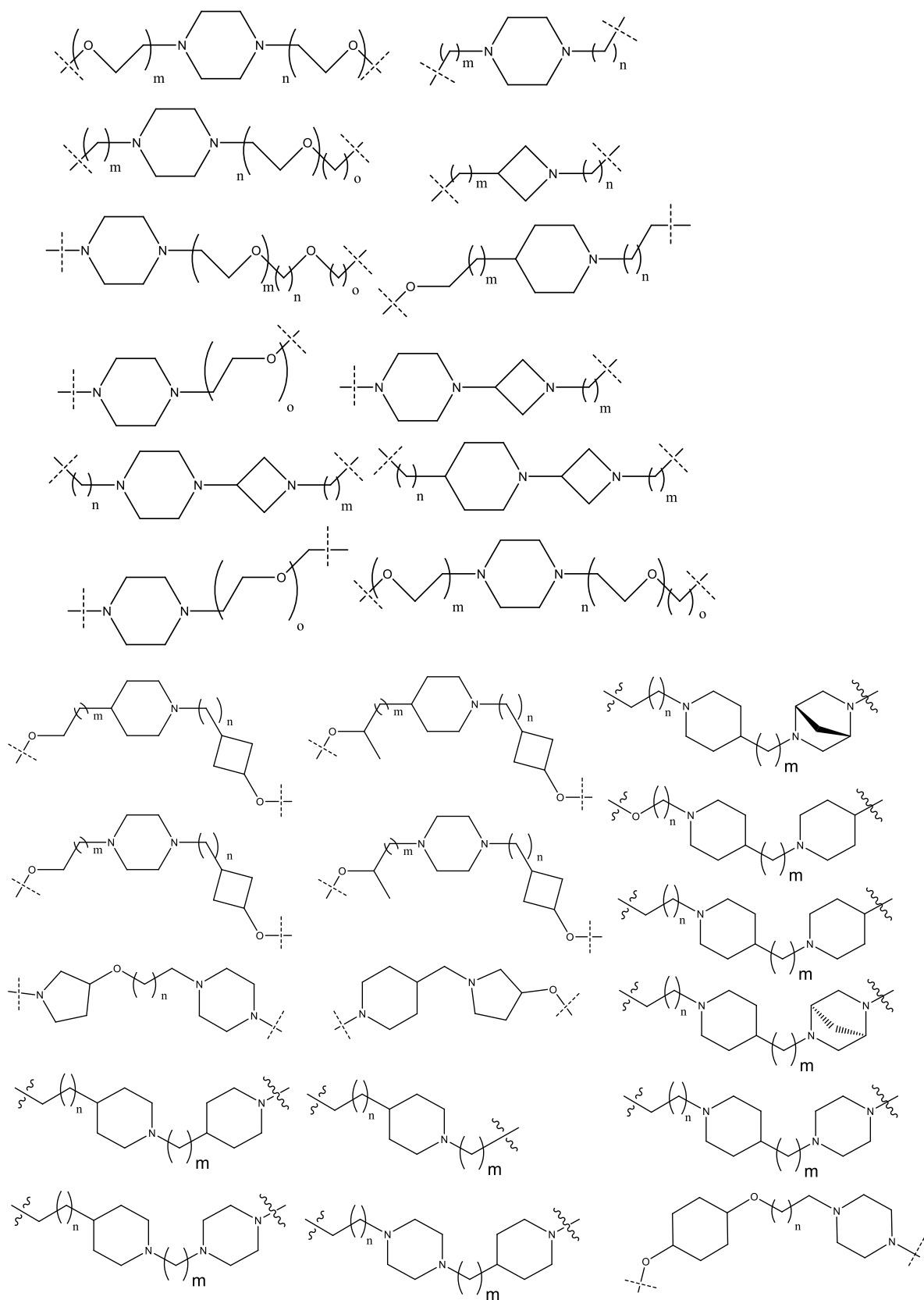


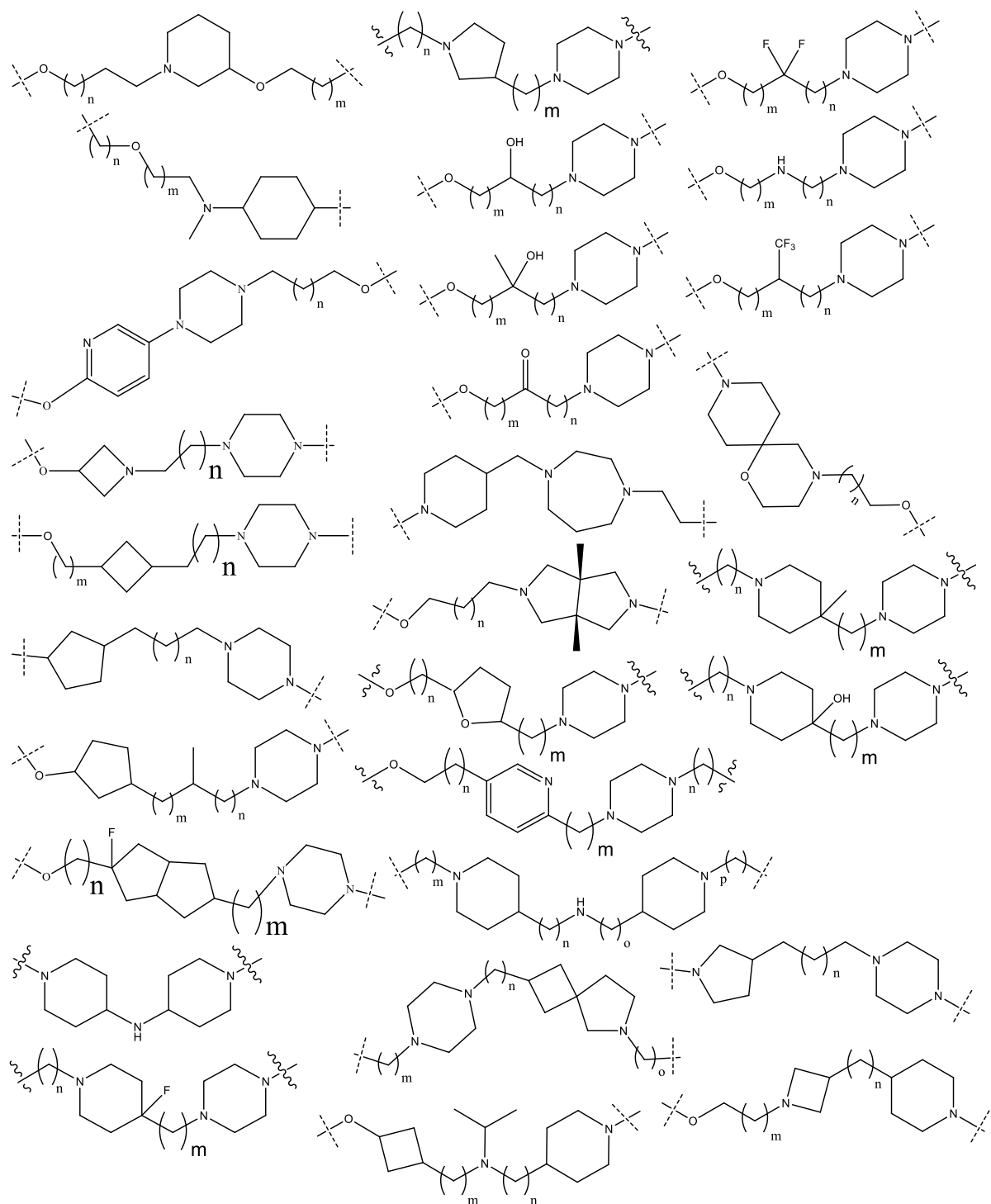


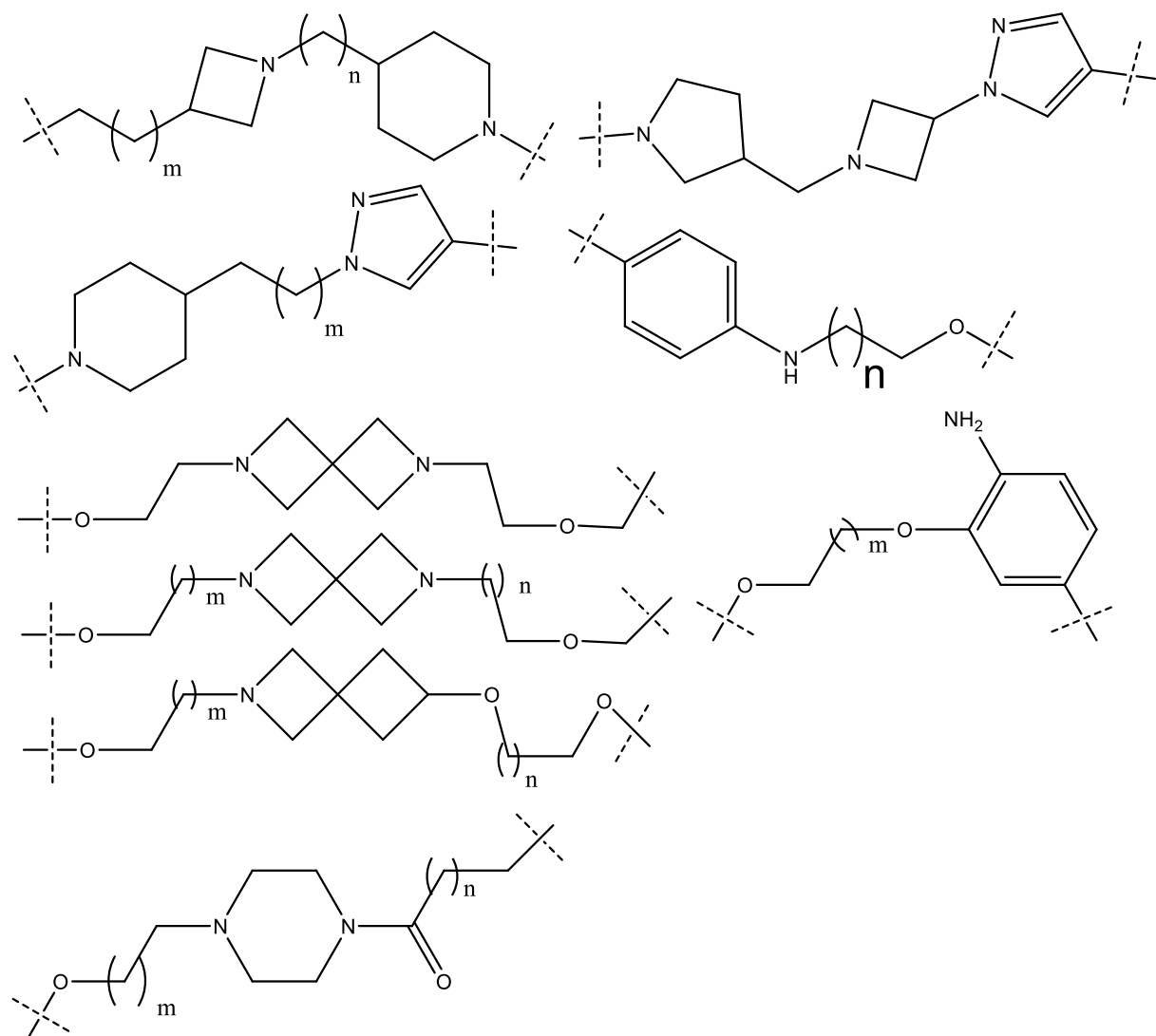


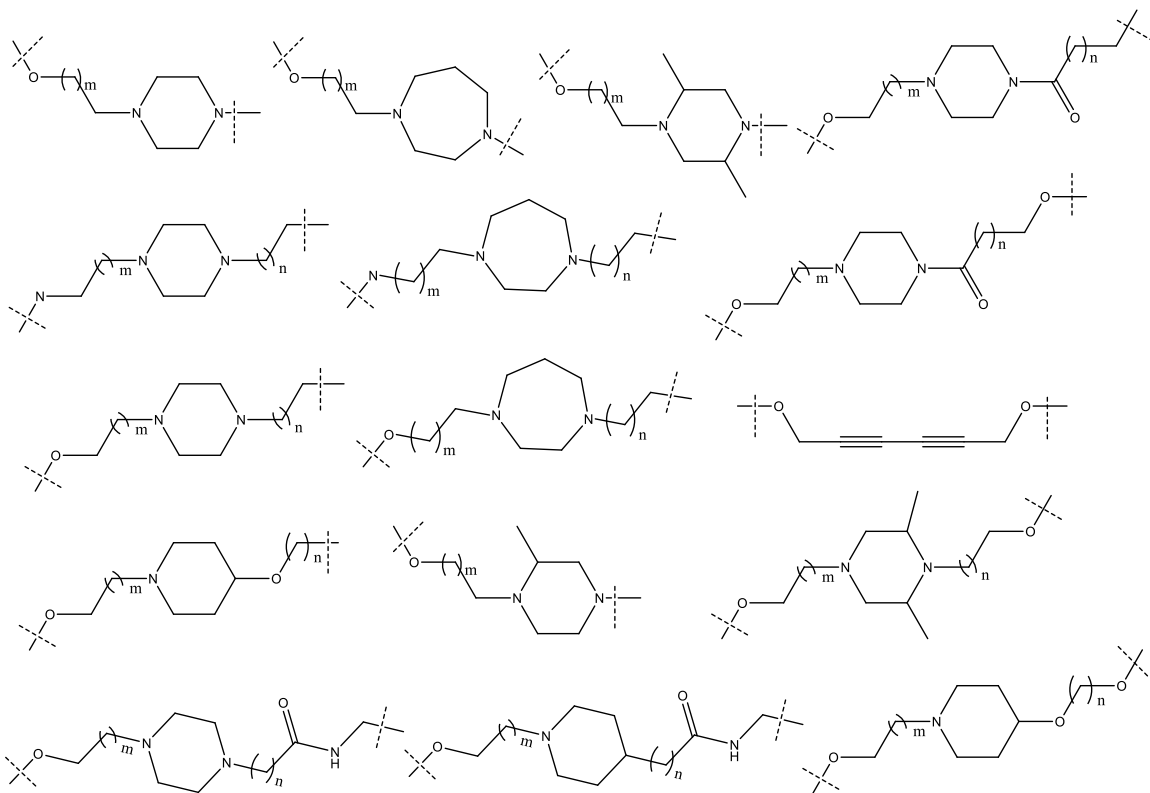
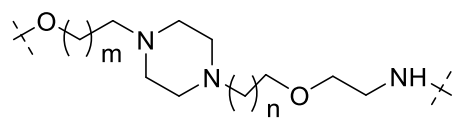
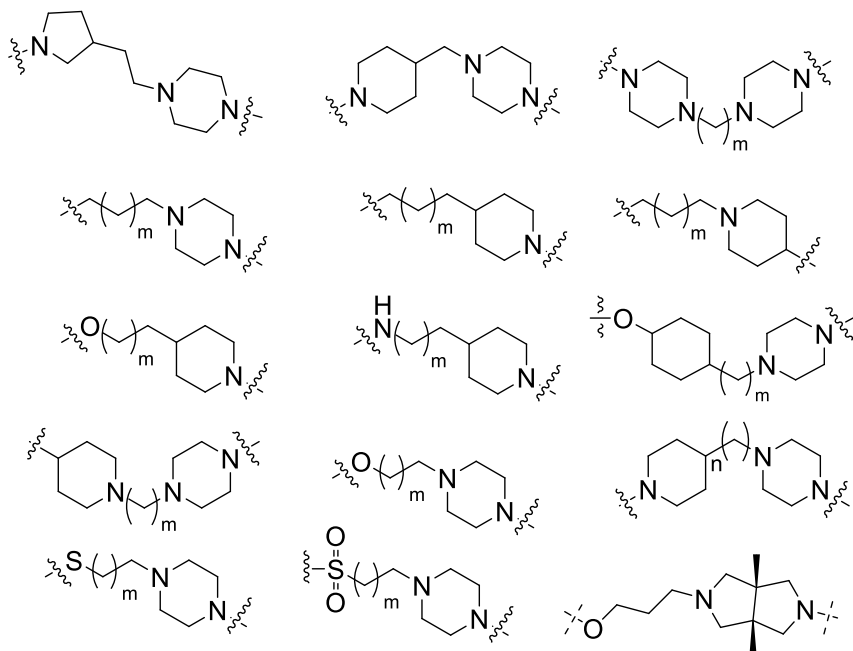


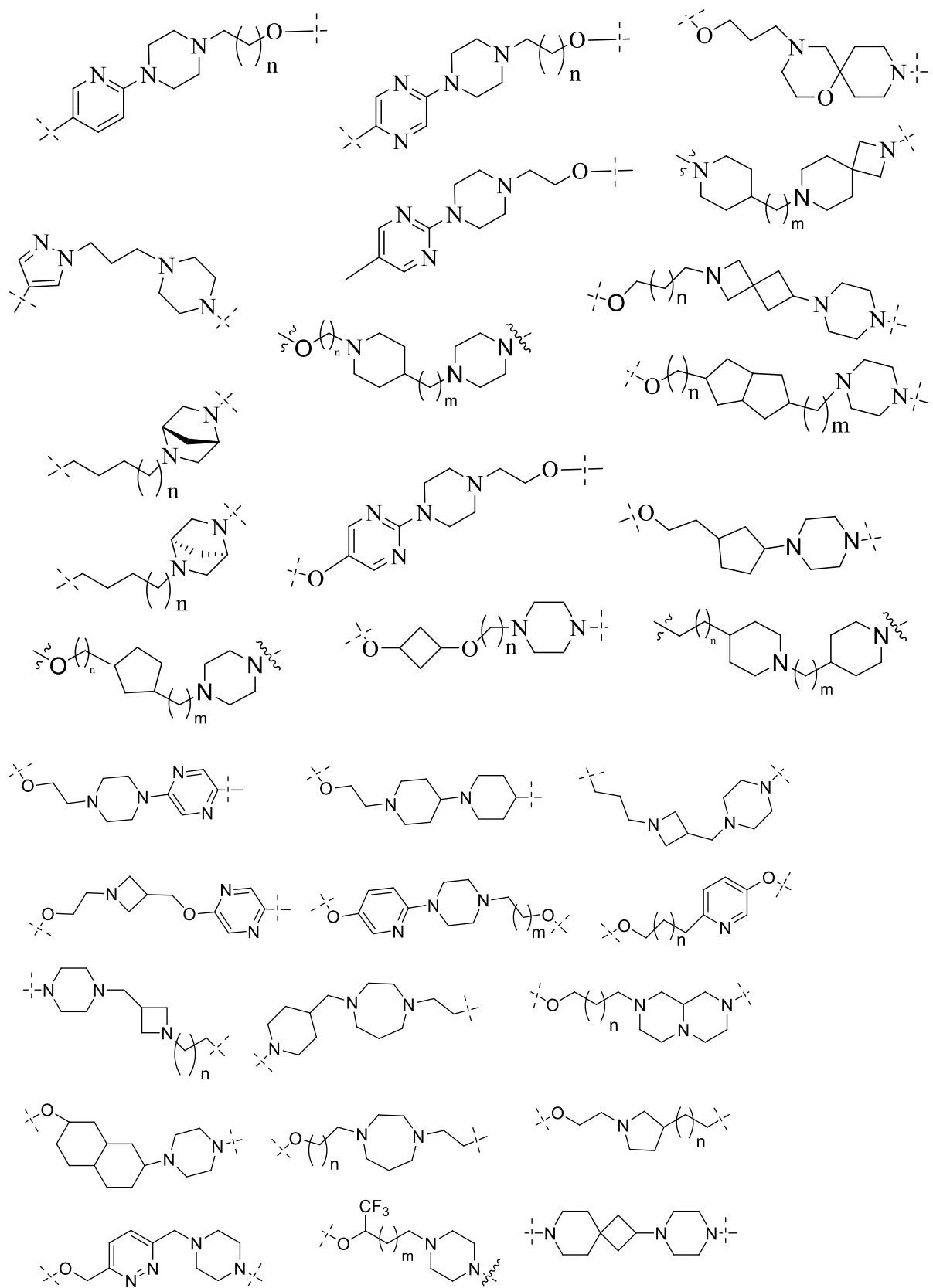


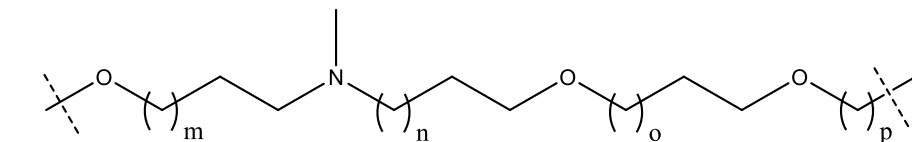


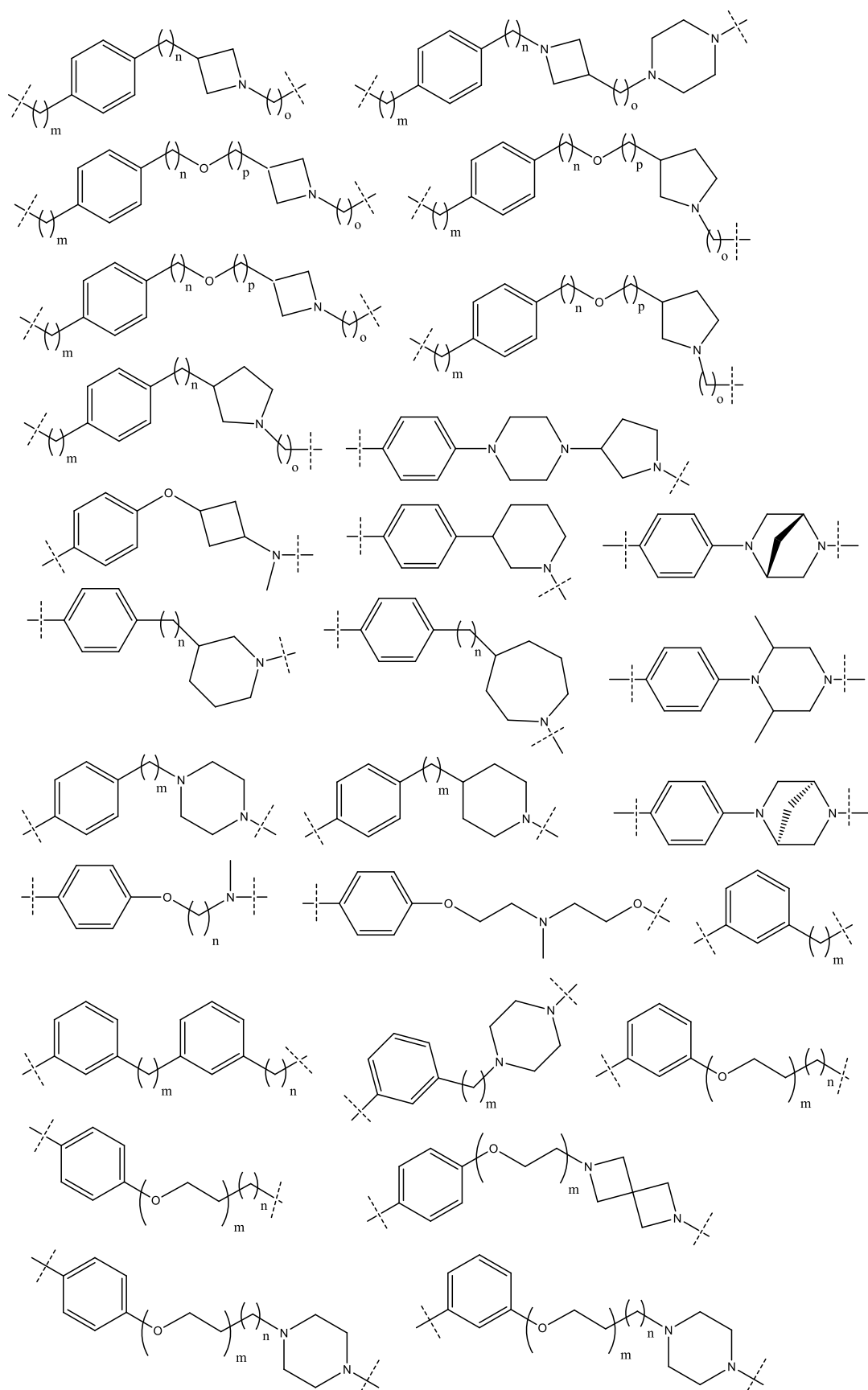


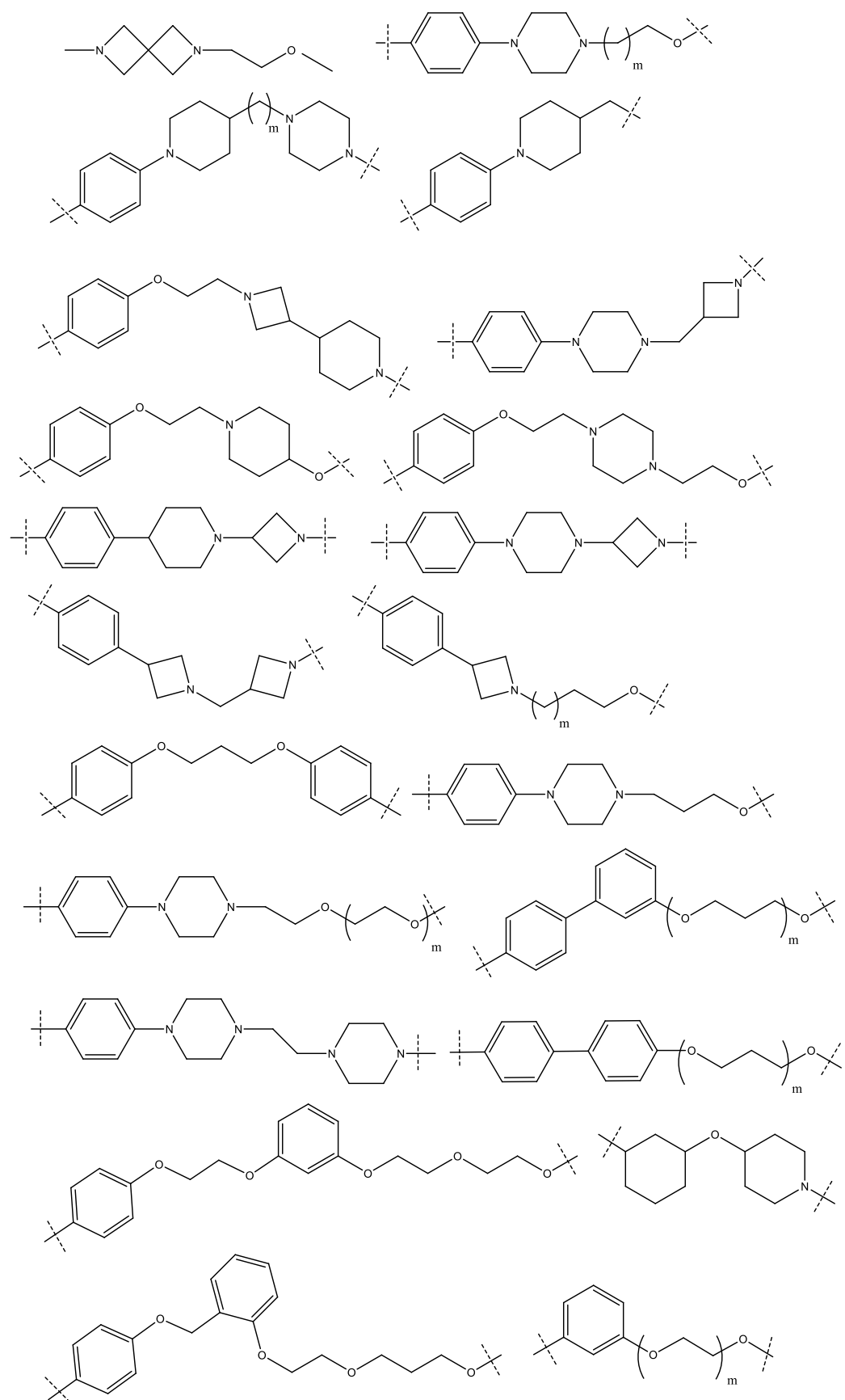


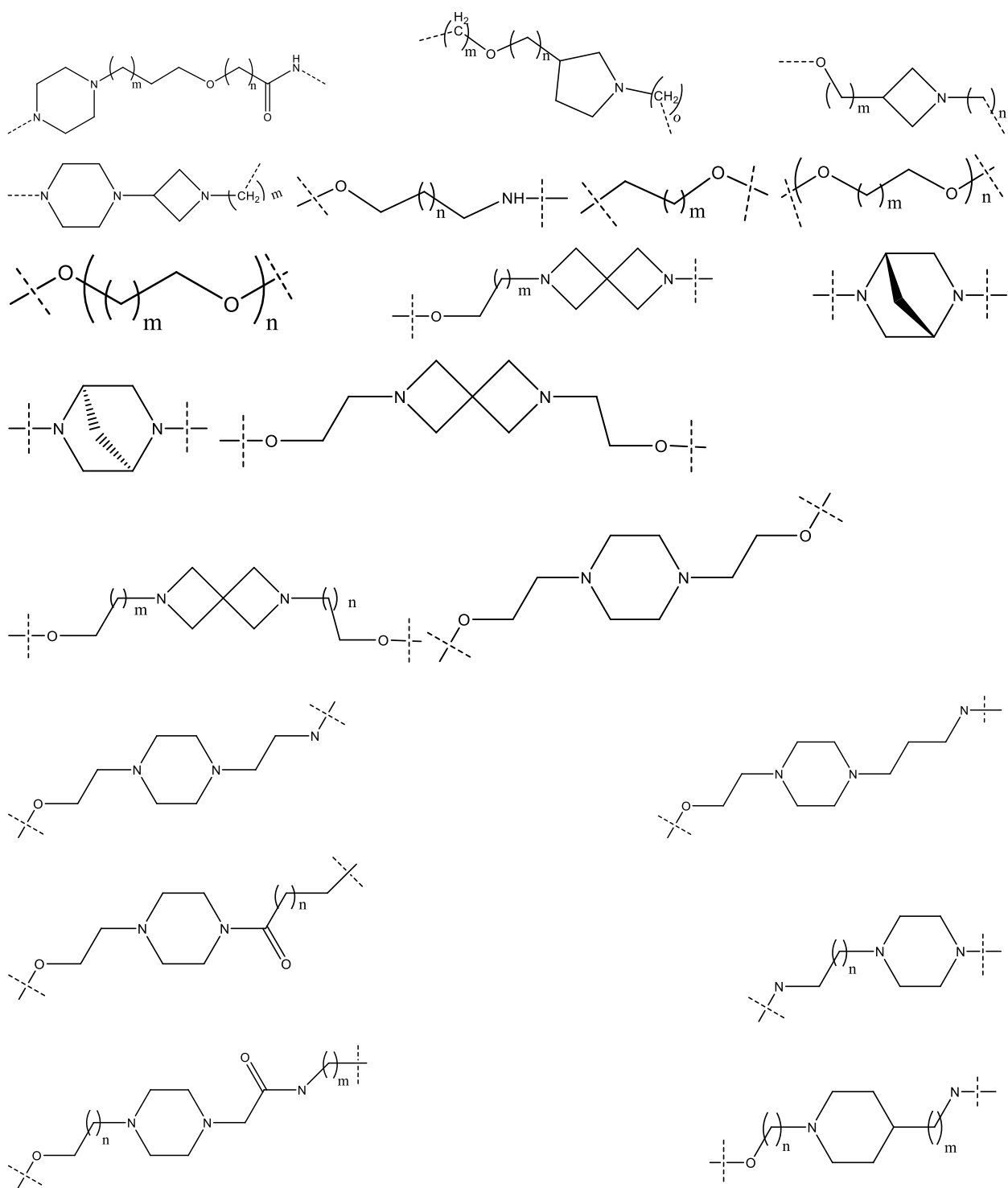


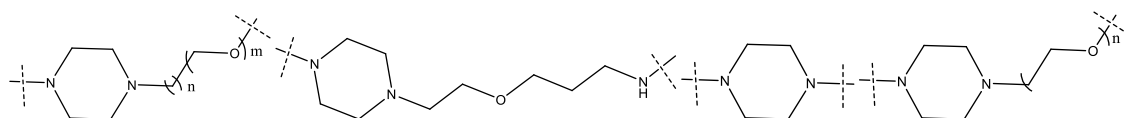
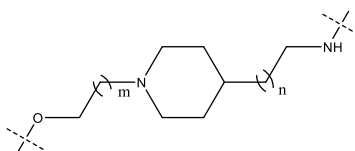
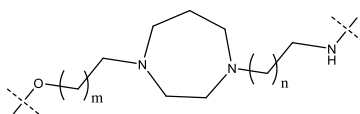
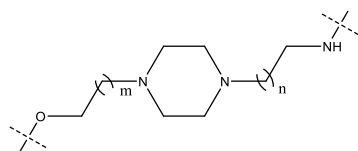
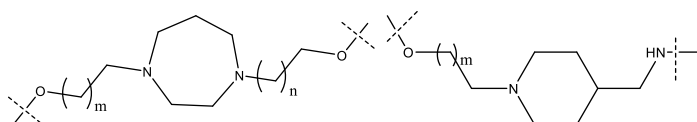
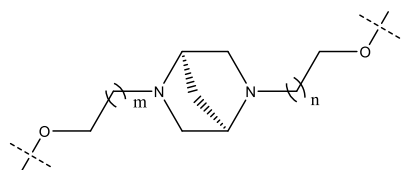
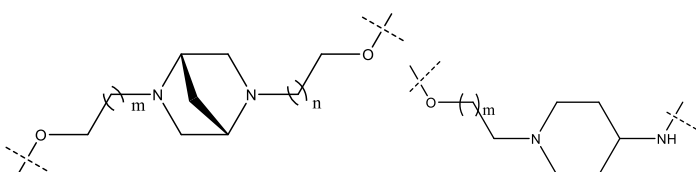
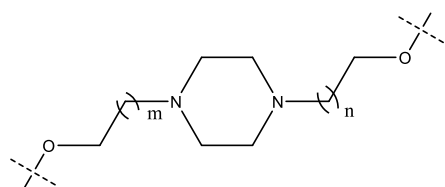
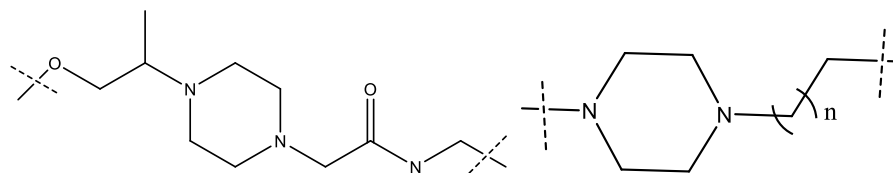
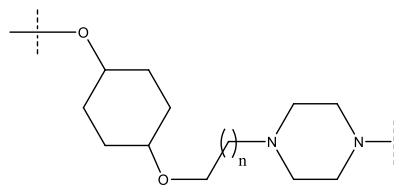
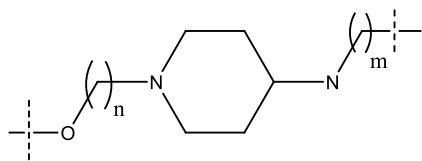


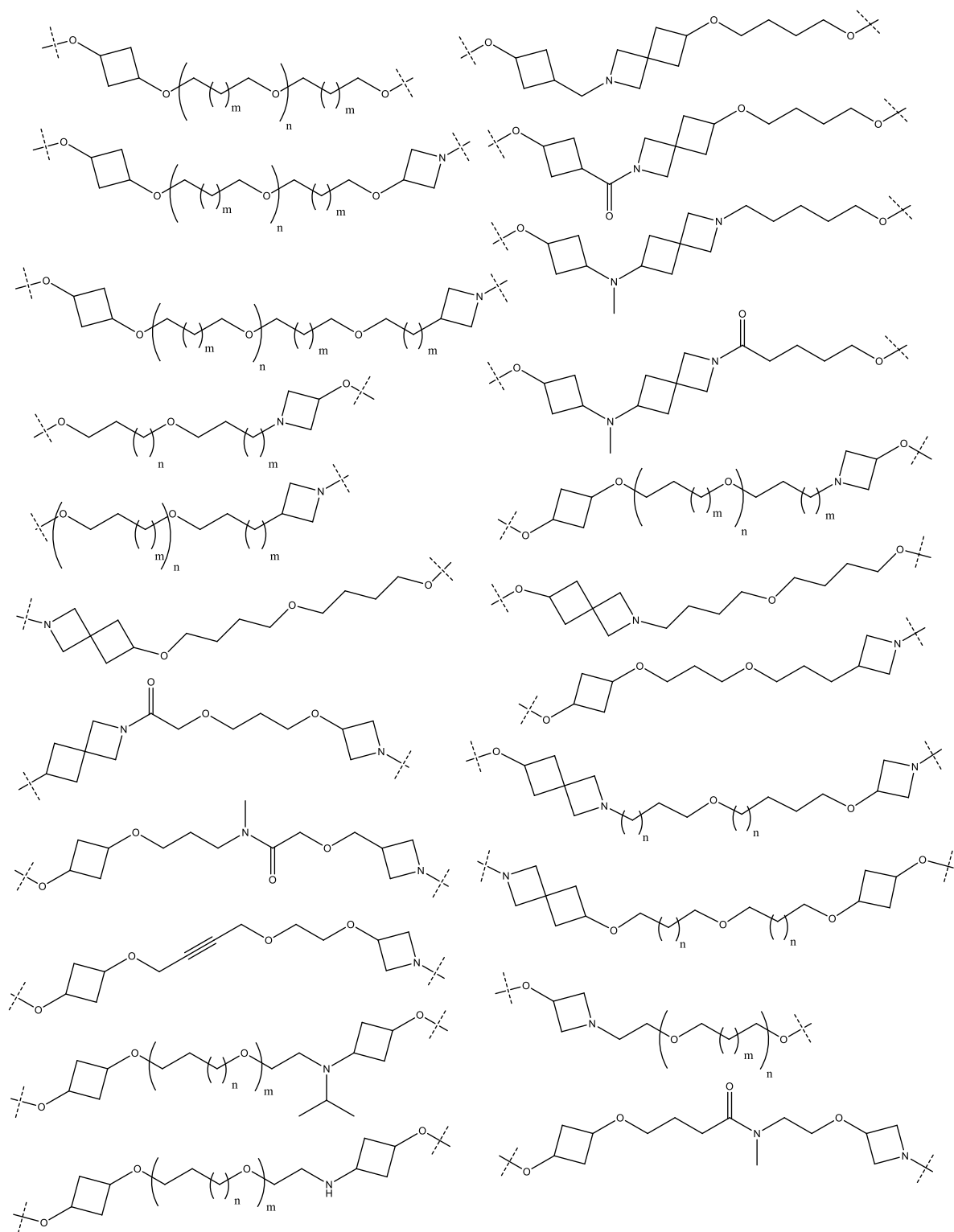


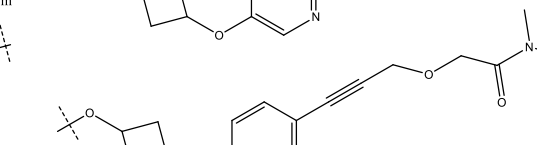
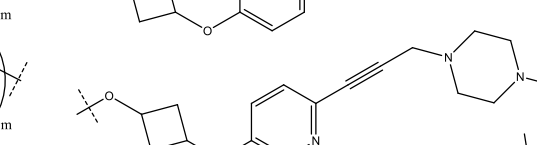
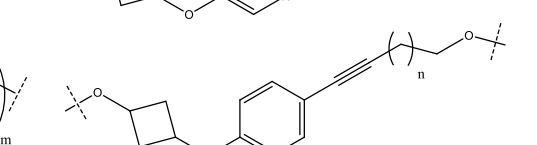
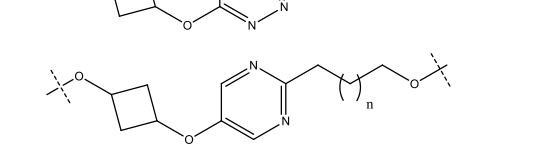
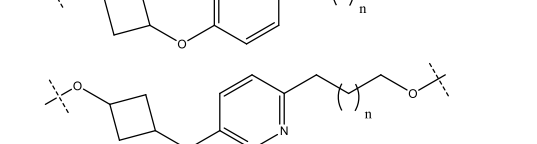
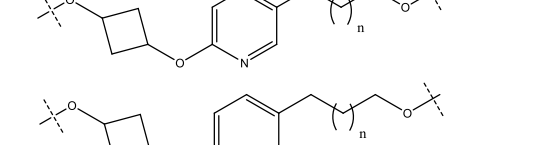
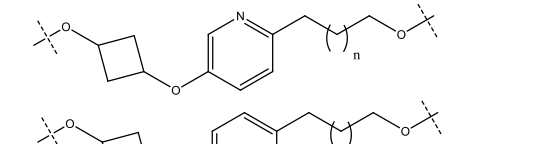
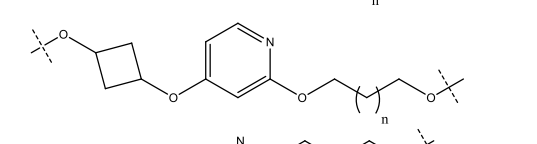
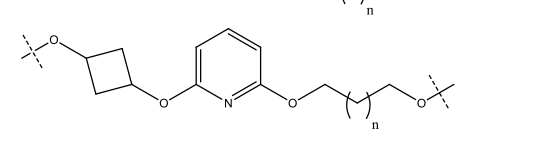
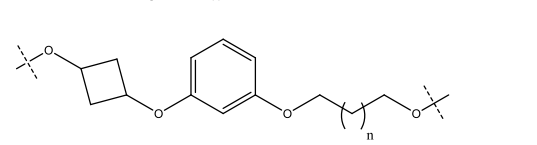
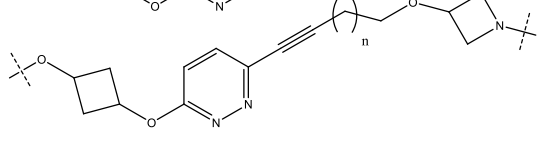
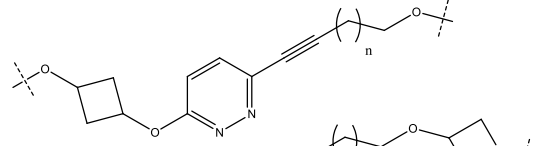
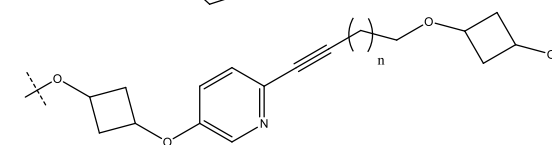
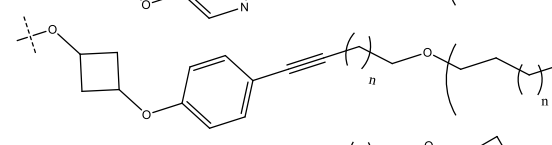
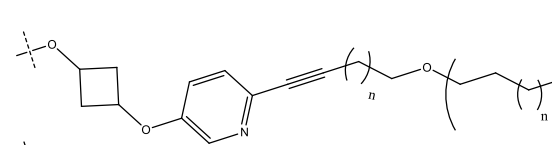
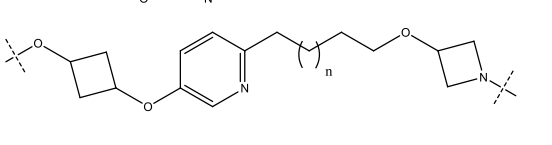
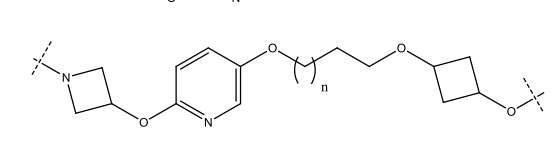
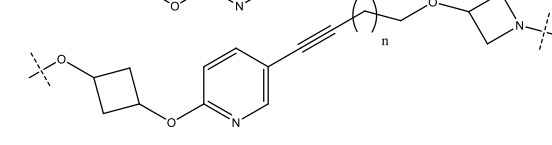
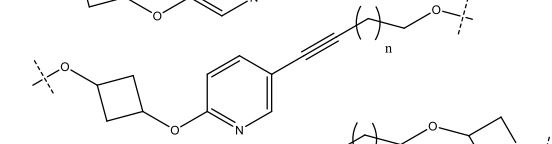
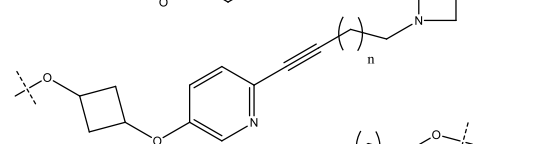
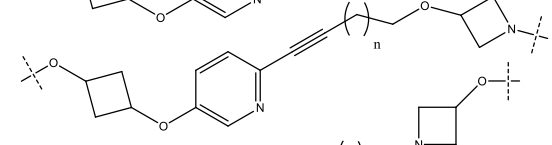
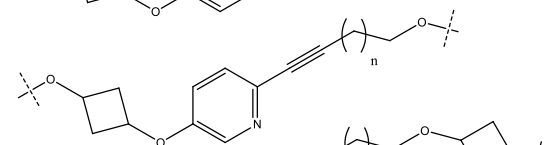
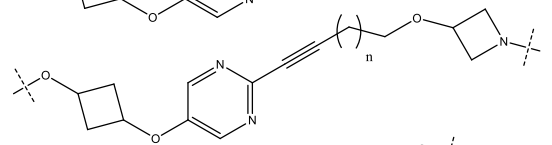
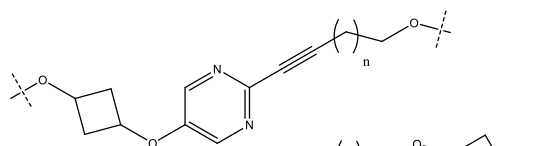


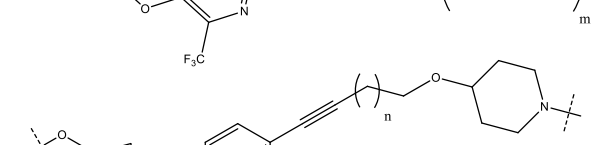
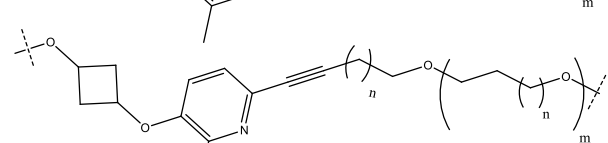
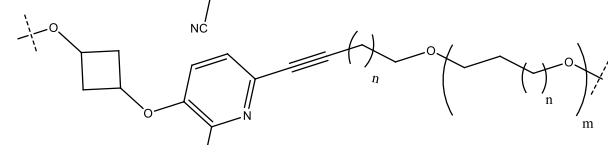
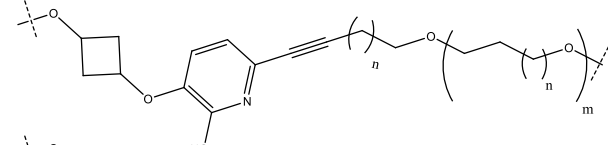
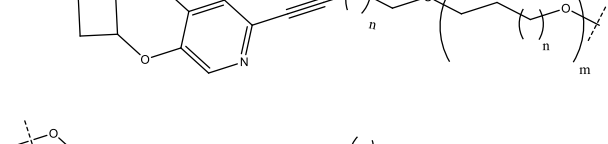
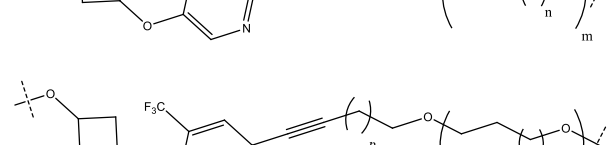
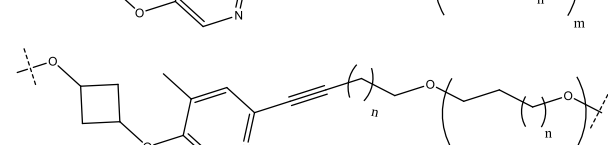
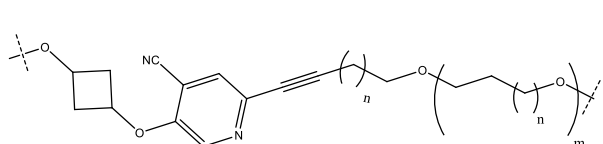
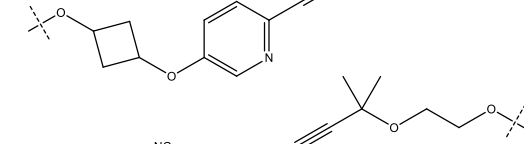
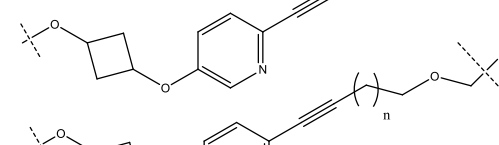
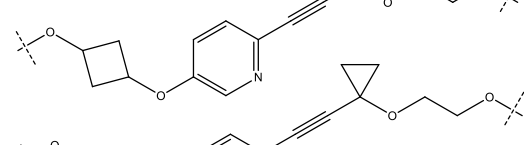
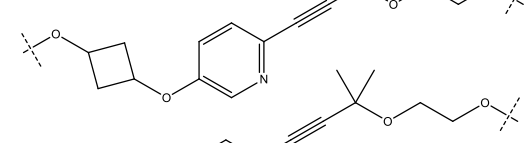
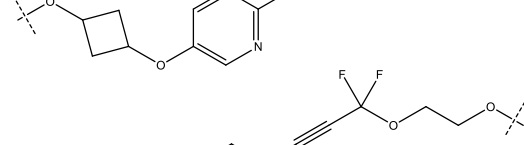
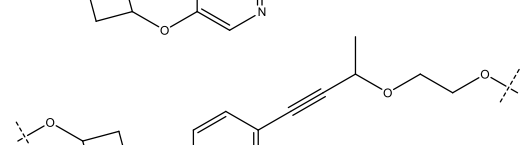
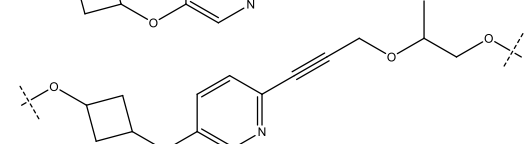
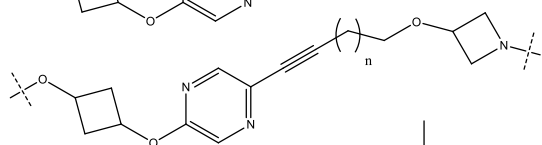
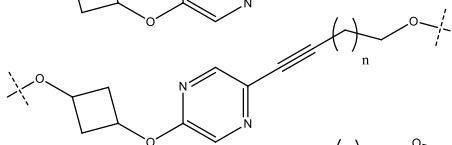
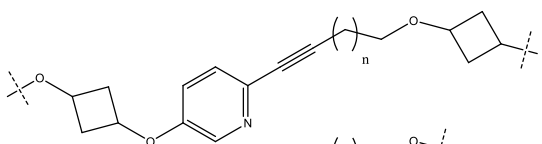


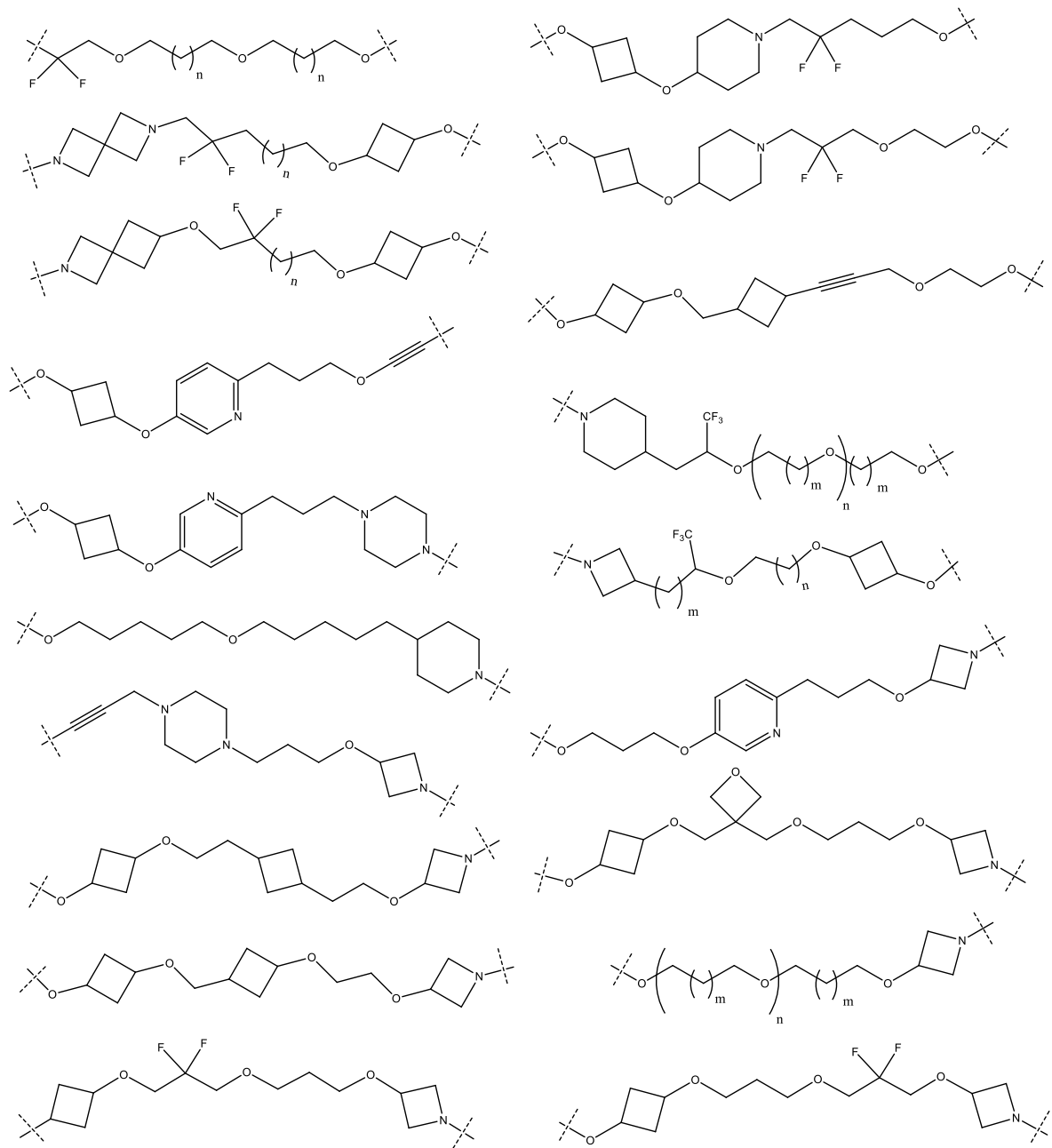


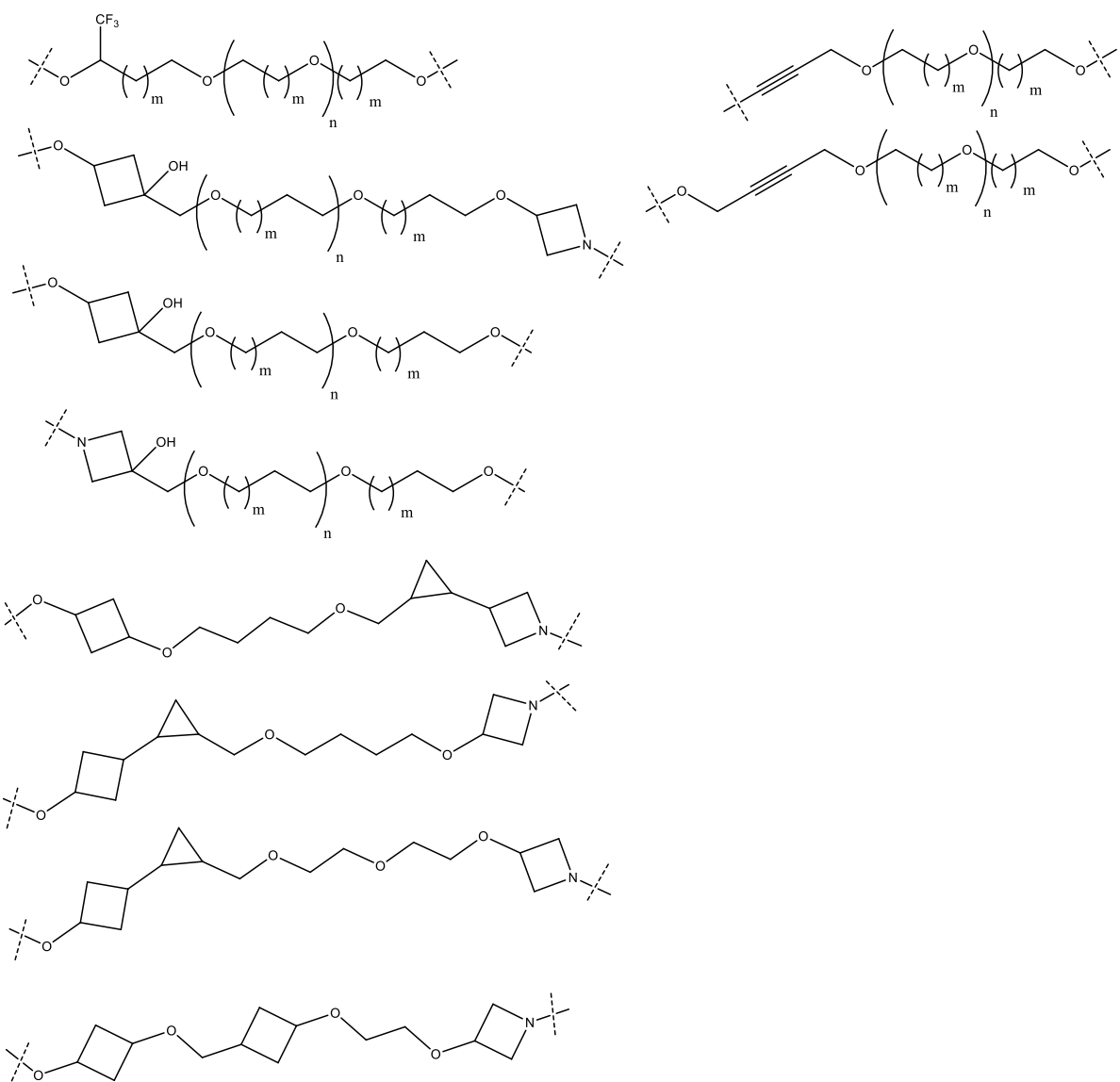


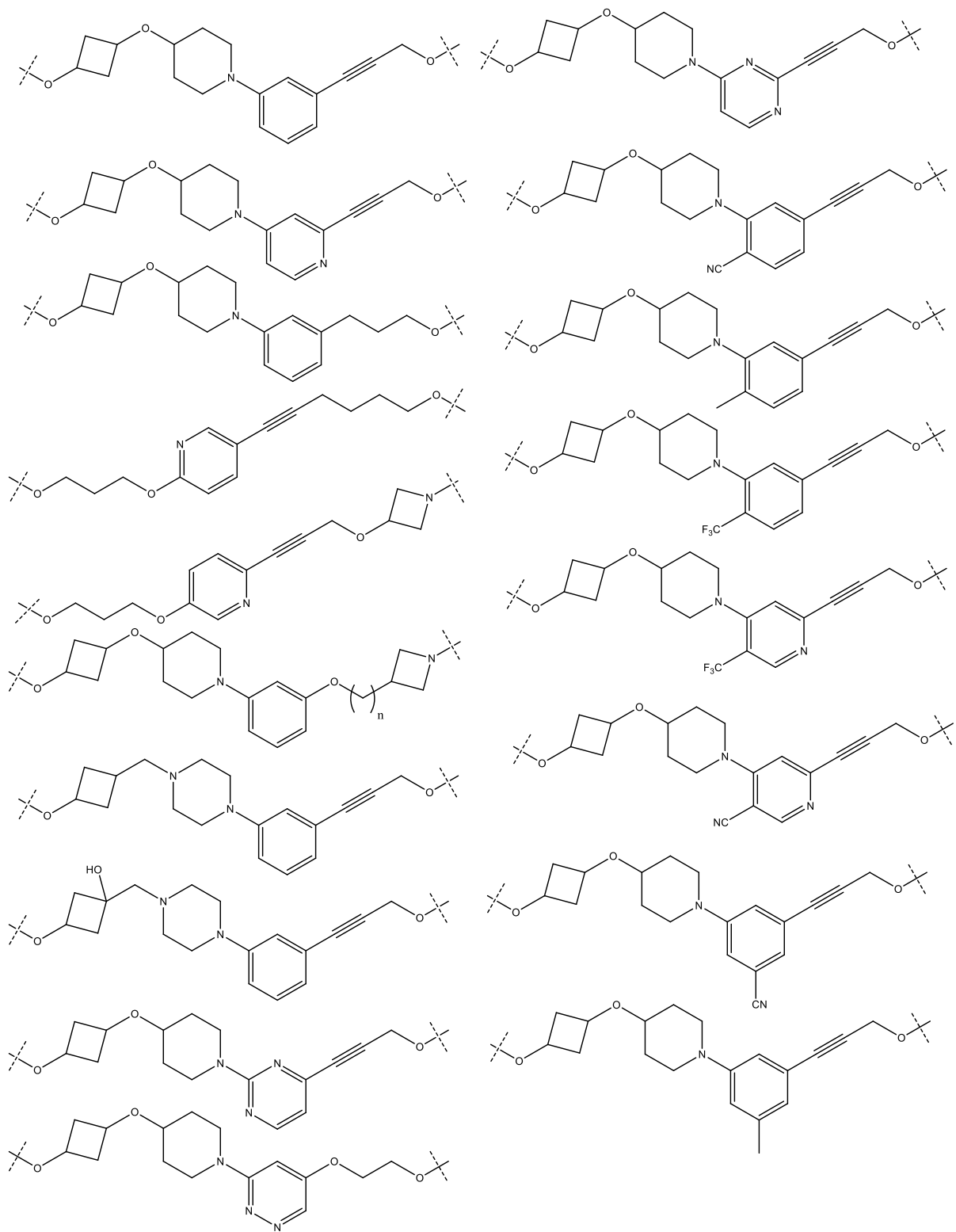


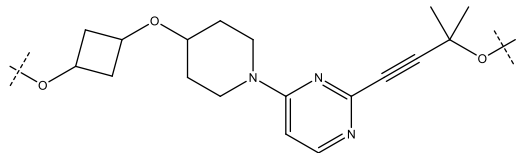
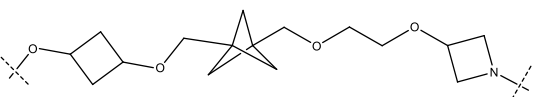
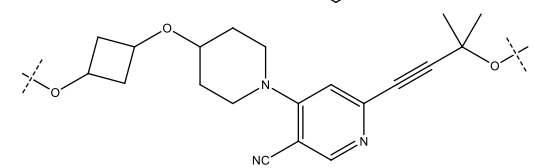
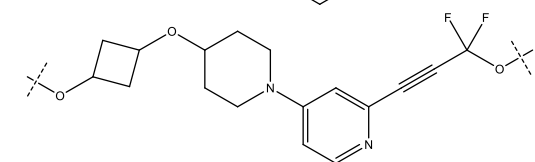
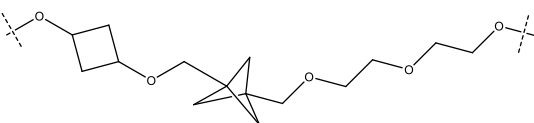
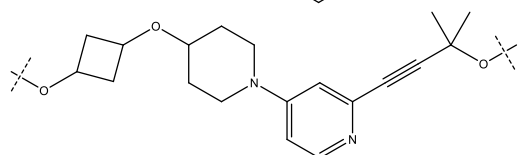
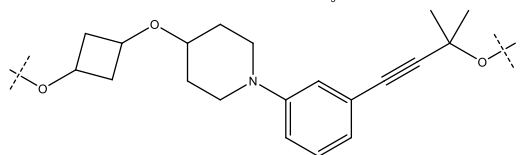
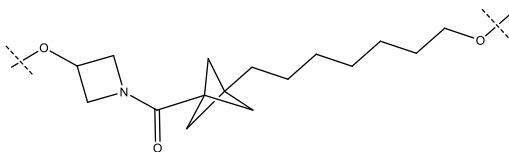
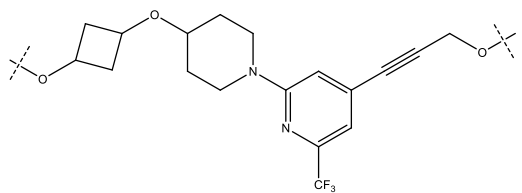
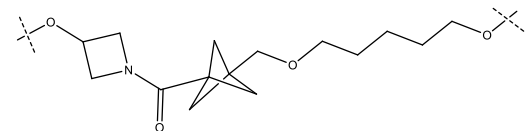
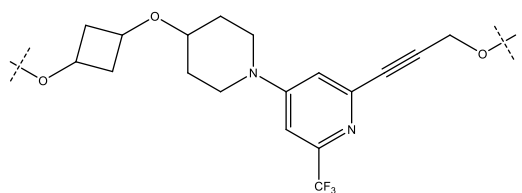
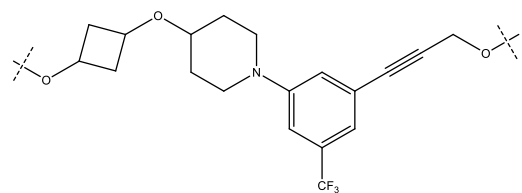


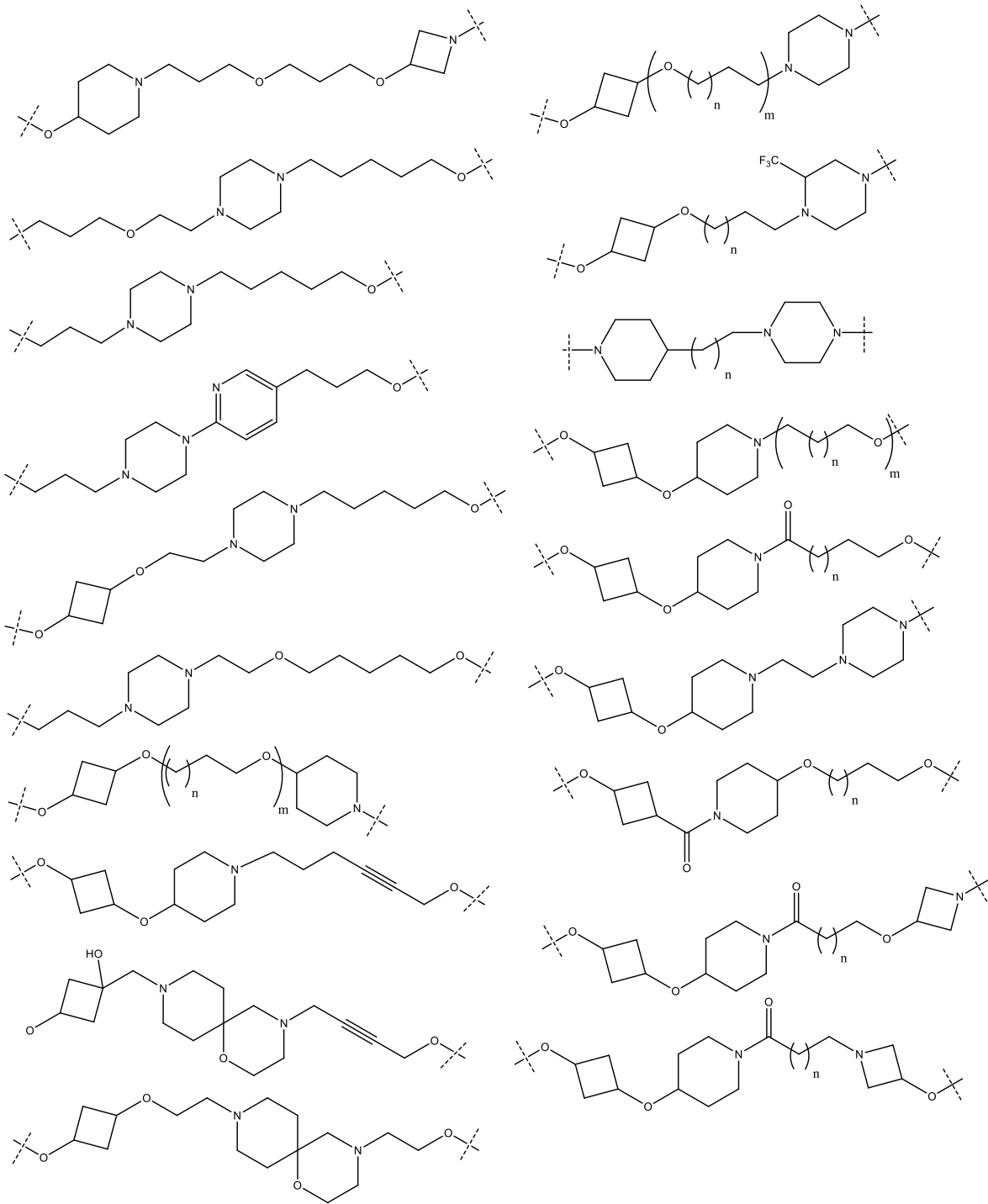


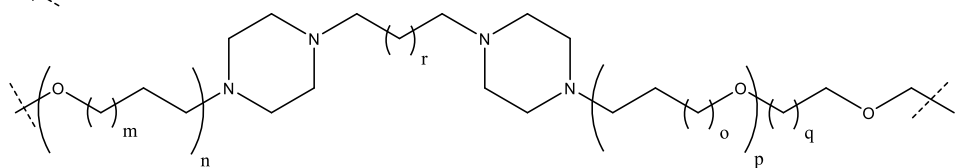
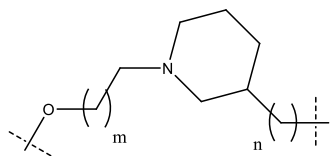
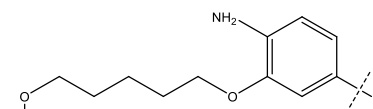
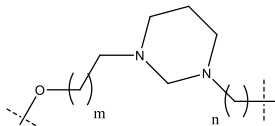
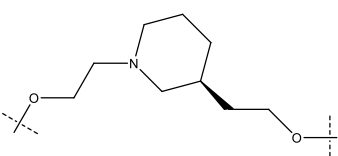
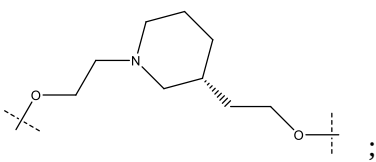
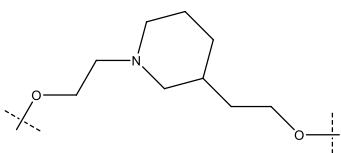
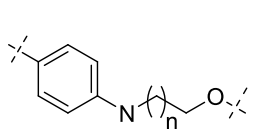
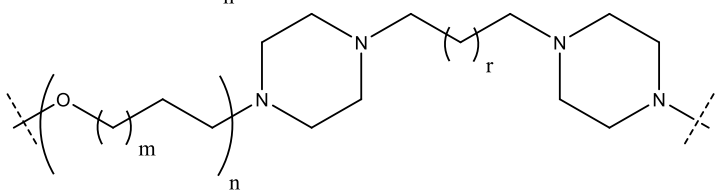


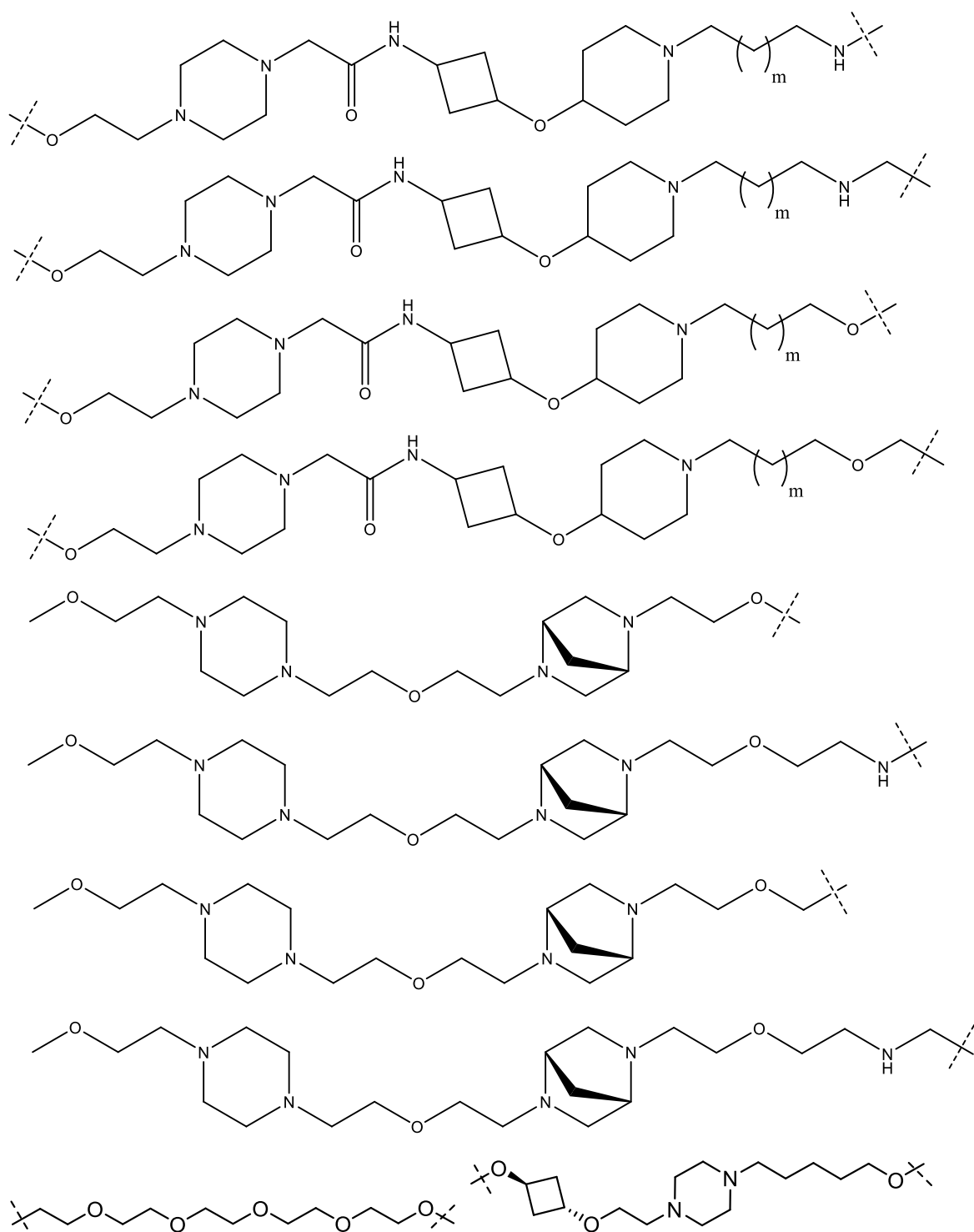


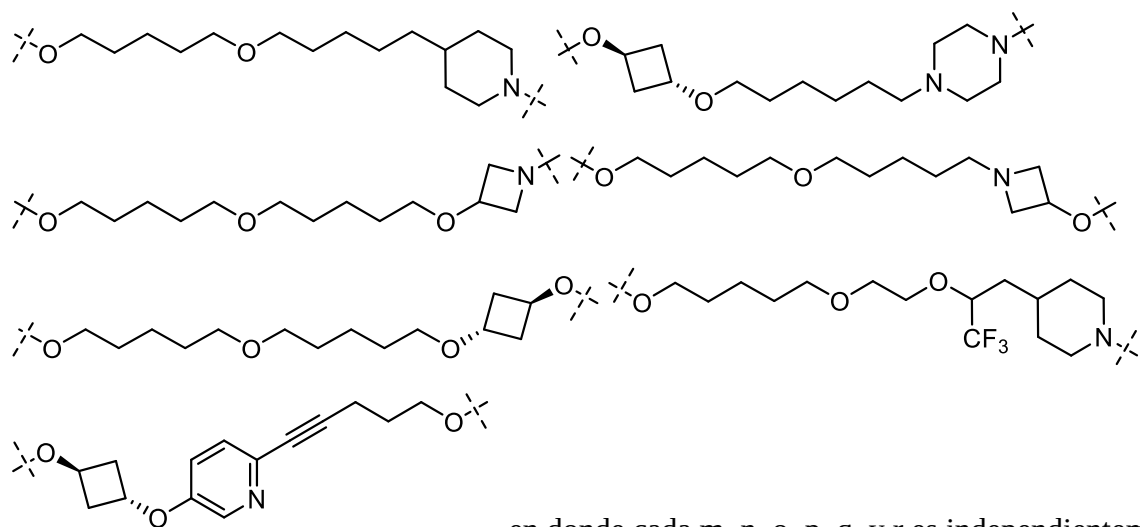






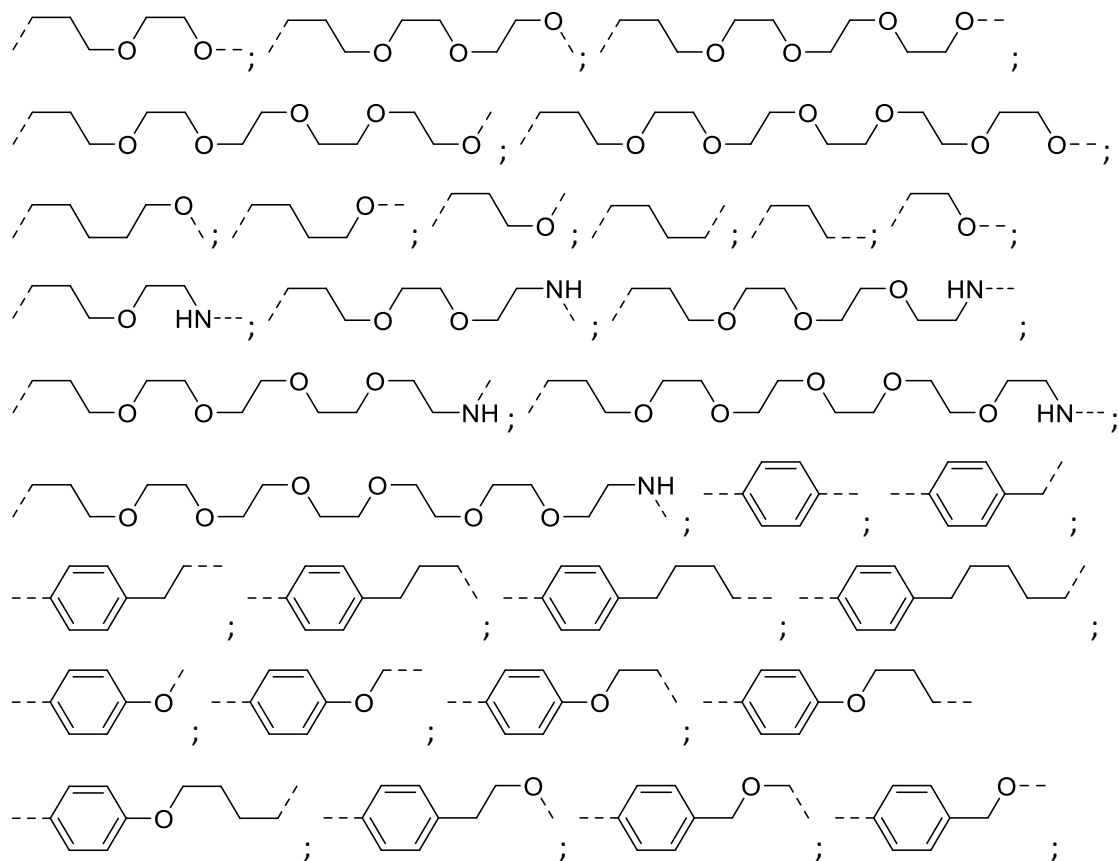


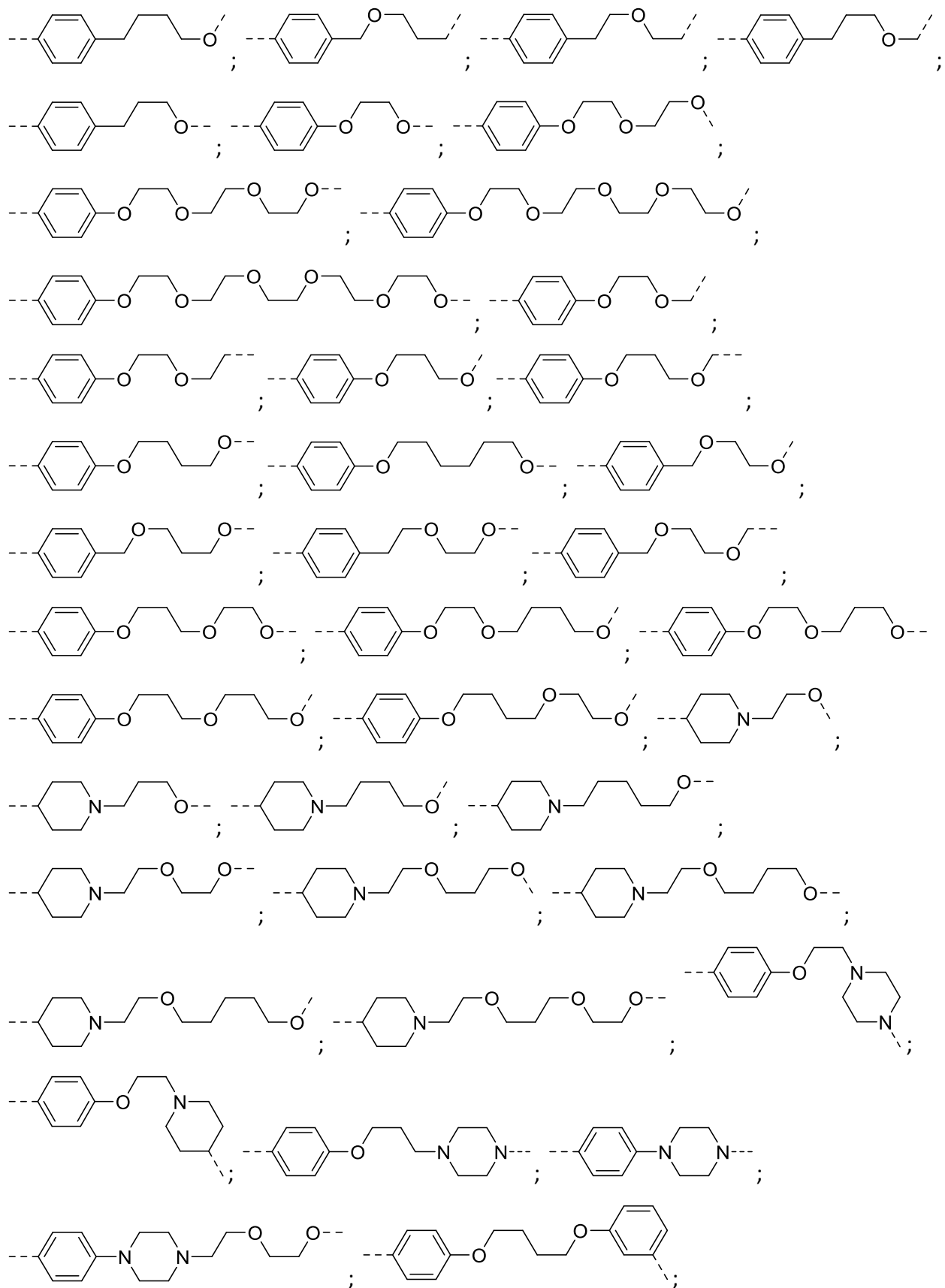


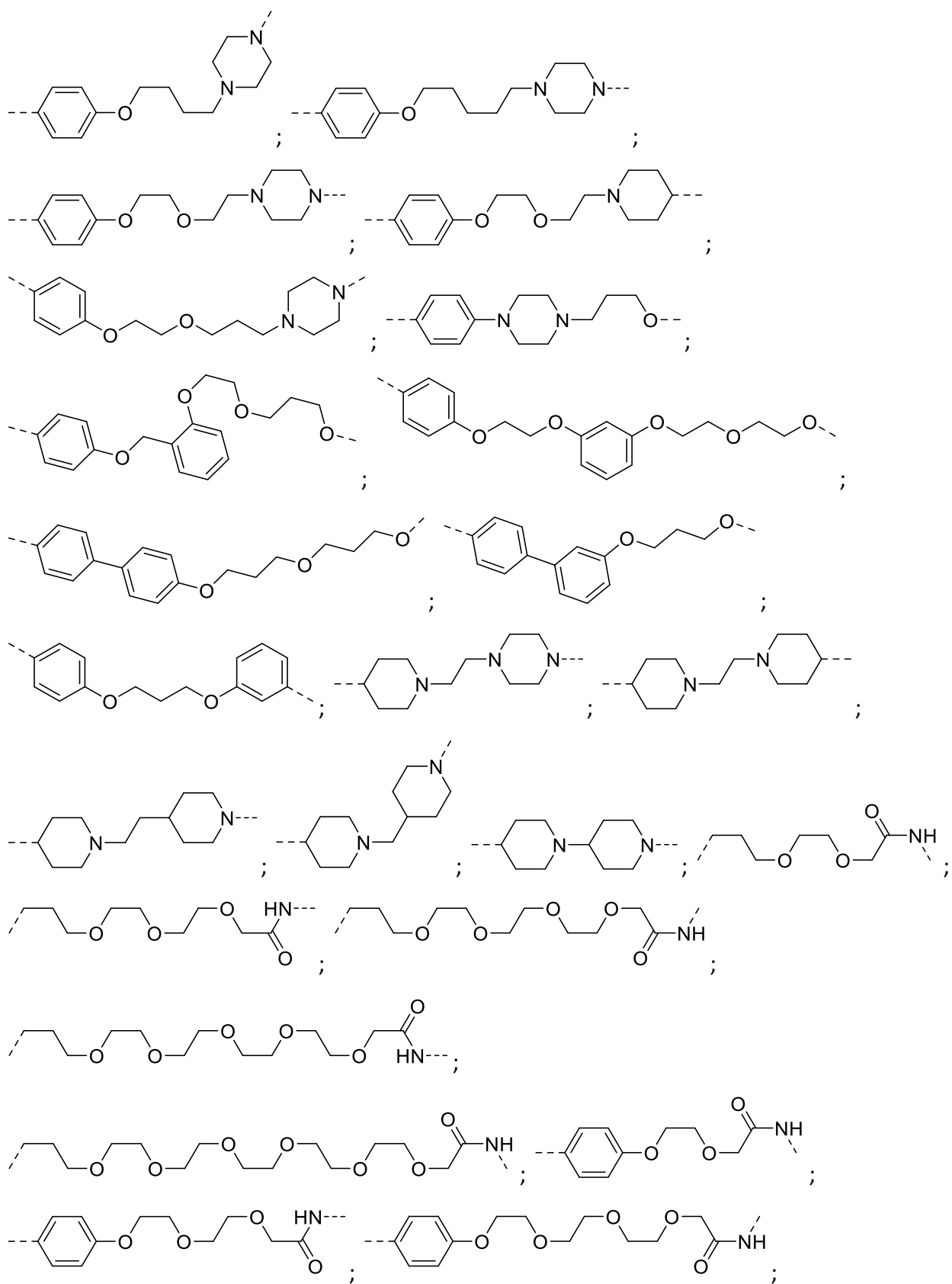


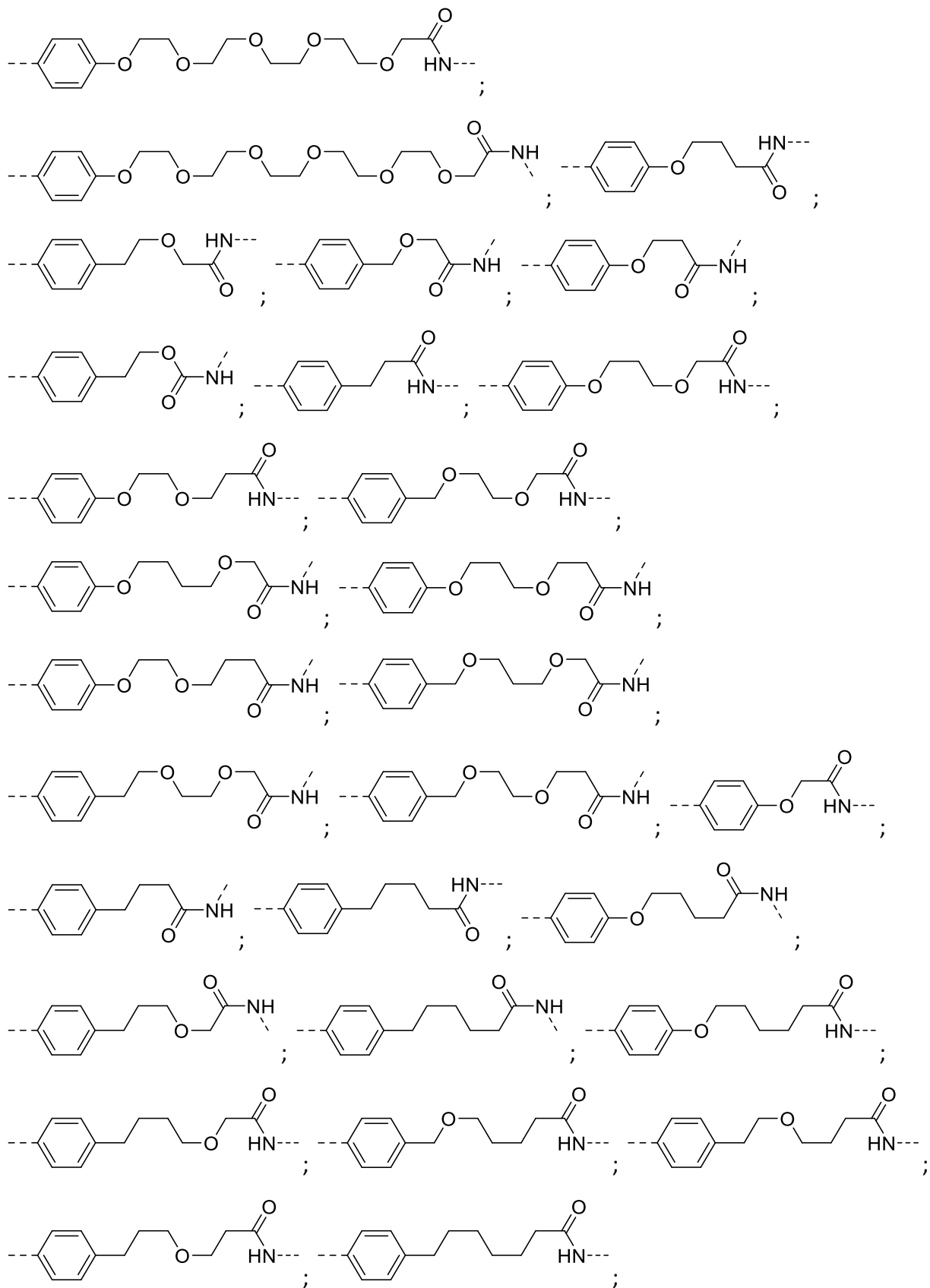
, en donde cada m, n, o, p, q, y r es independientemente 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, o 20.

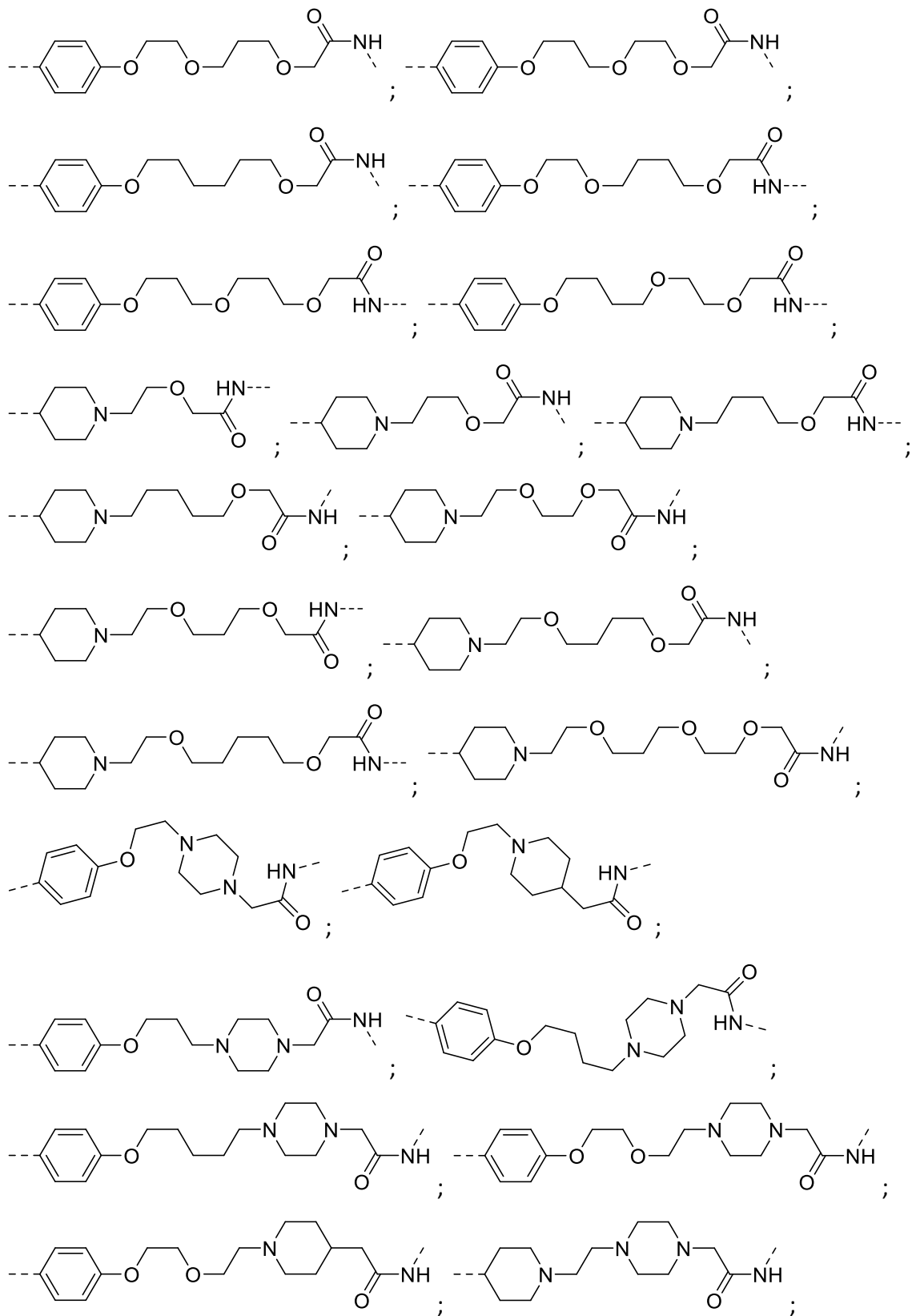
12. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-9, en donde el enlazador (L) se selecciona del grupo que consiste en:

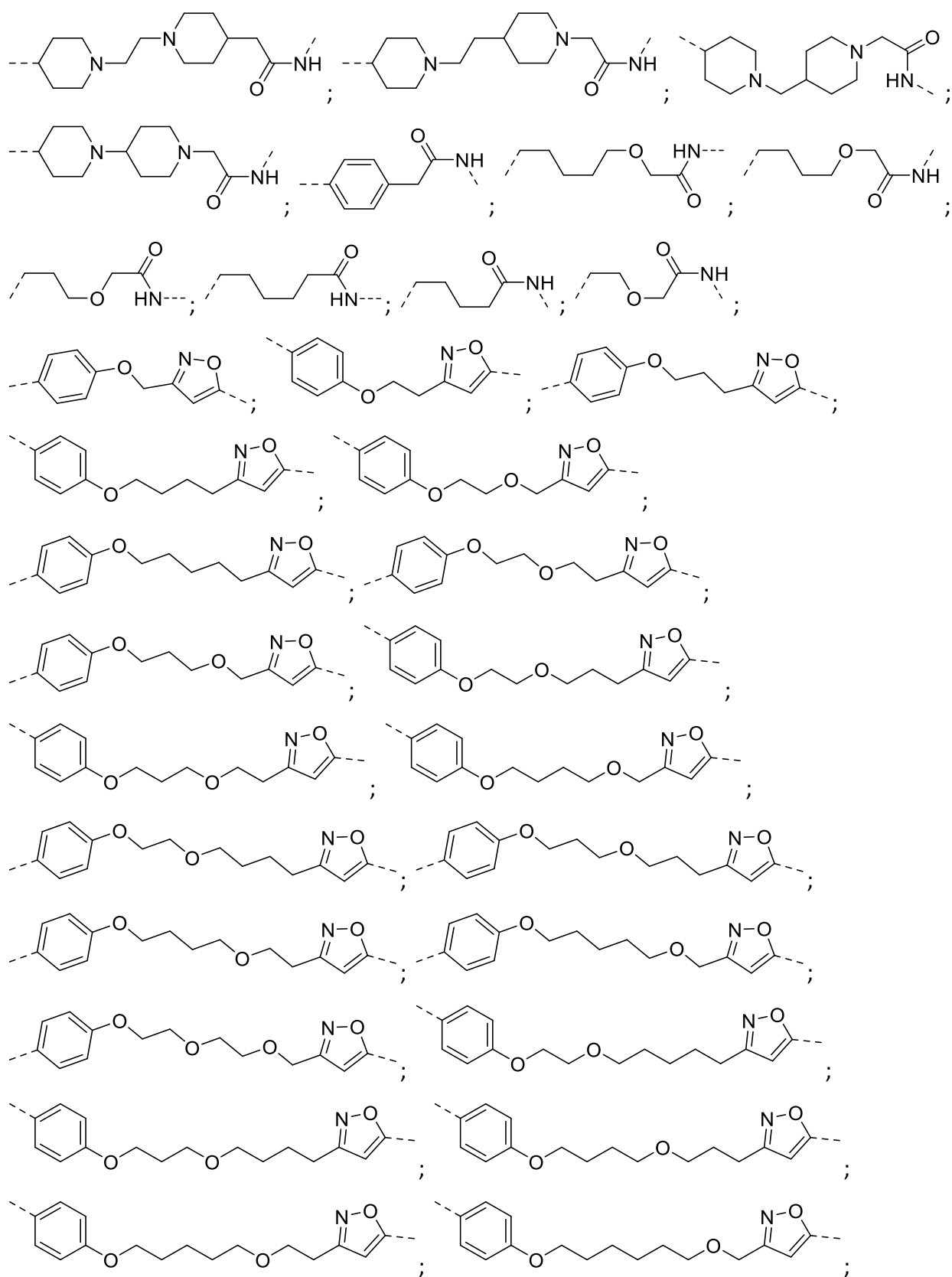


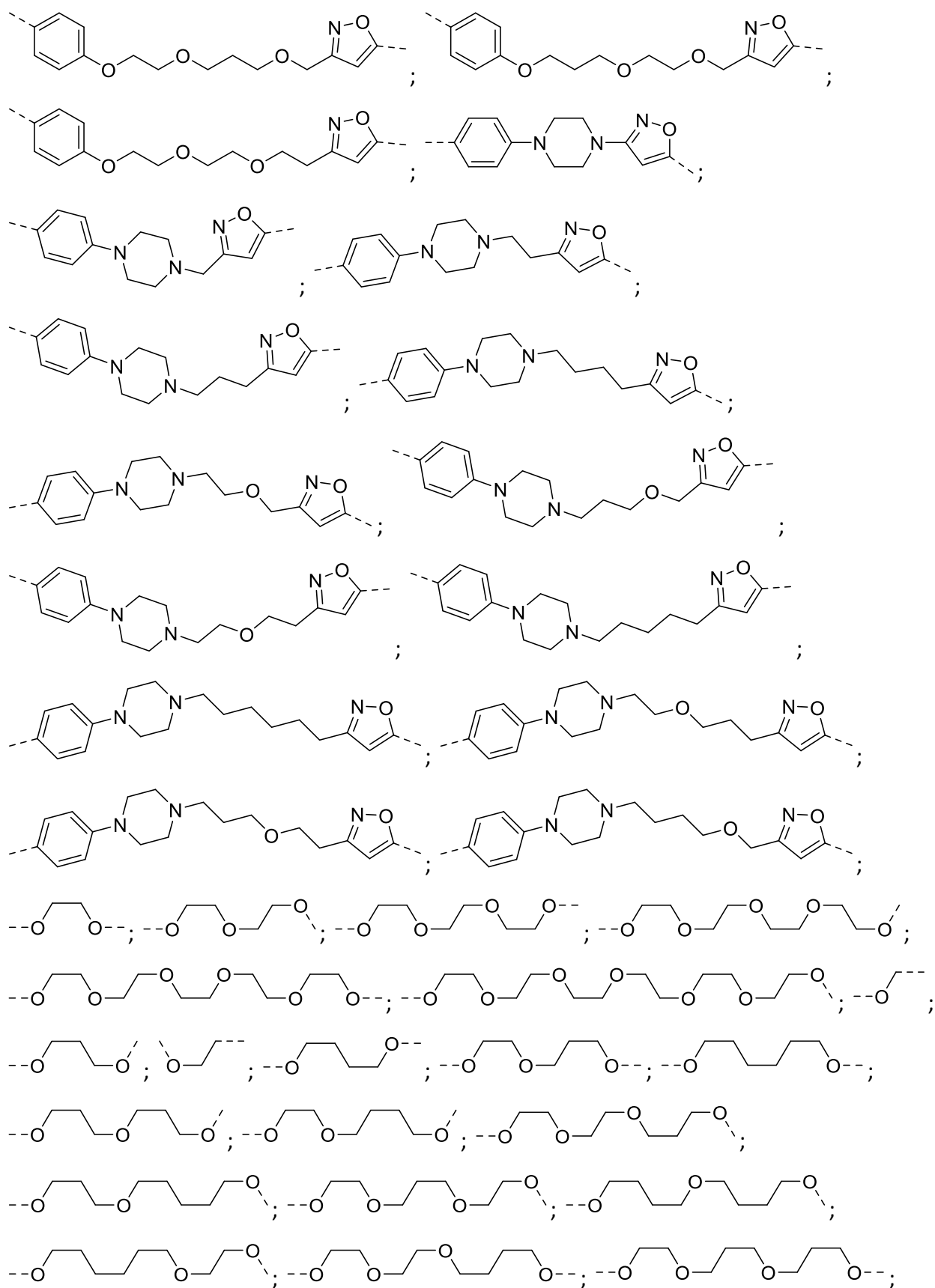


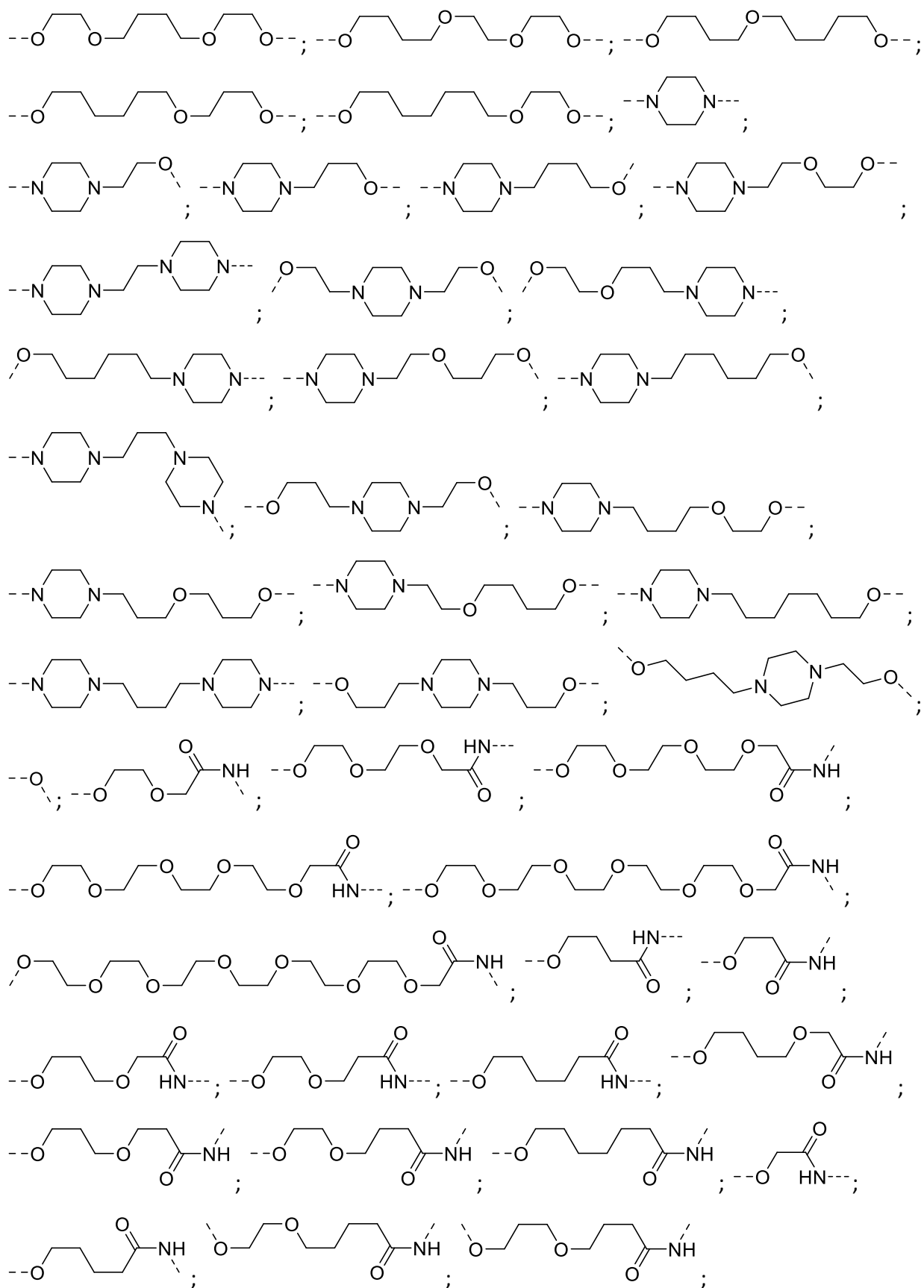


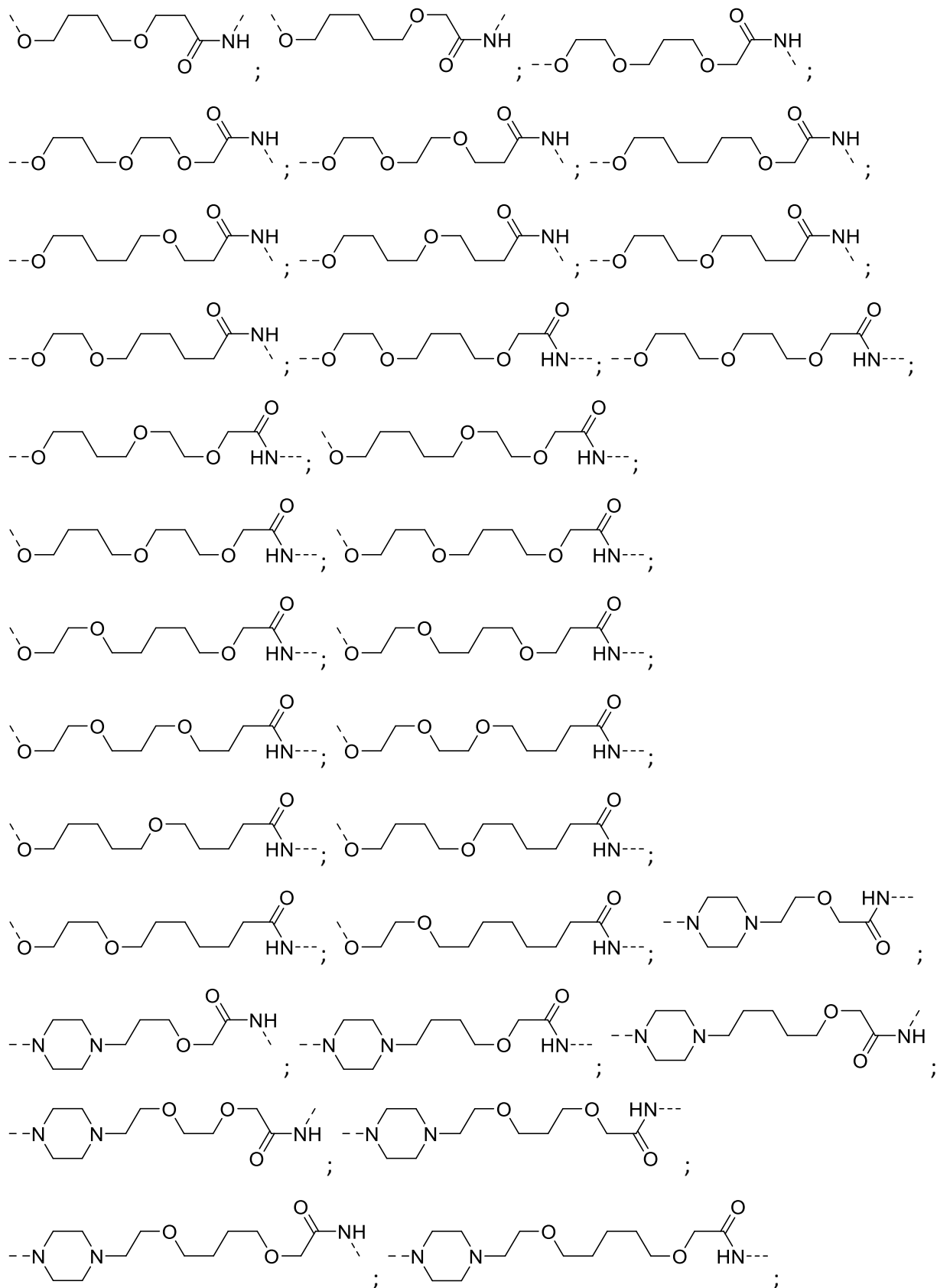


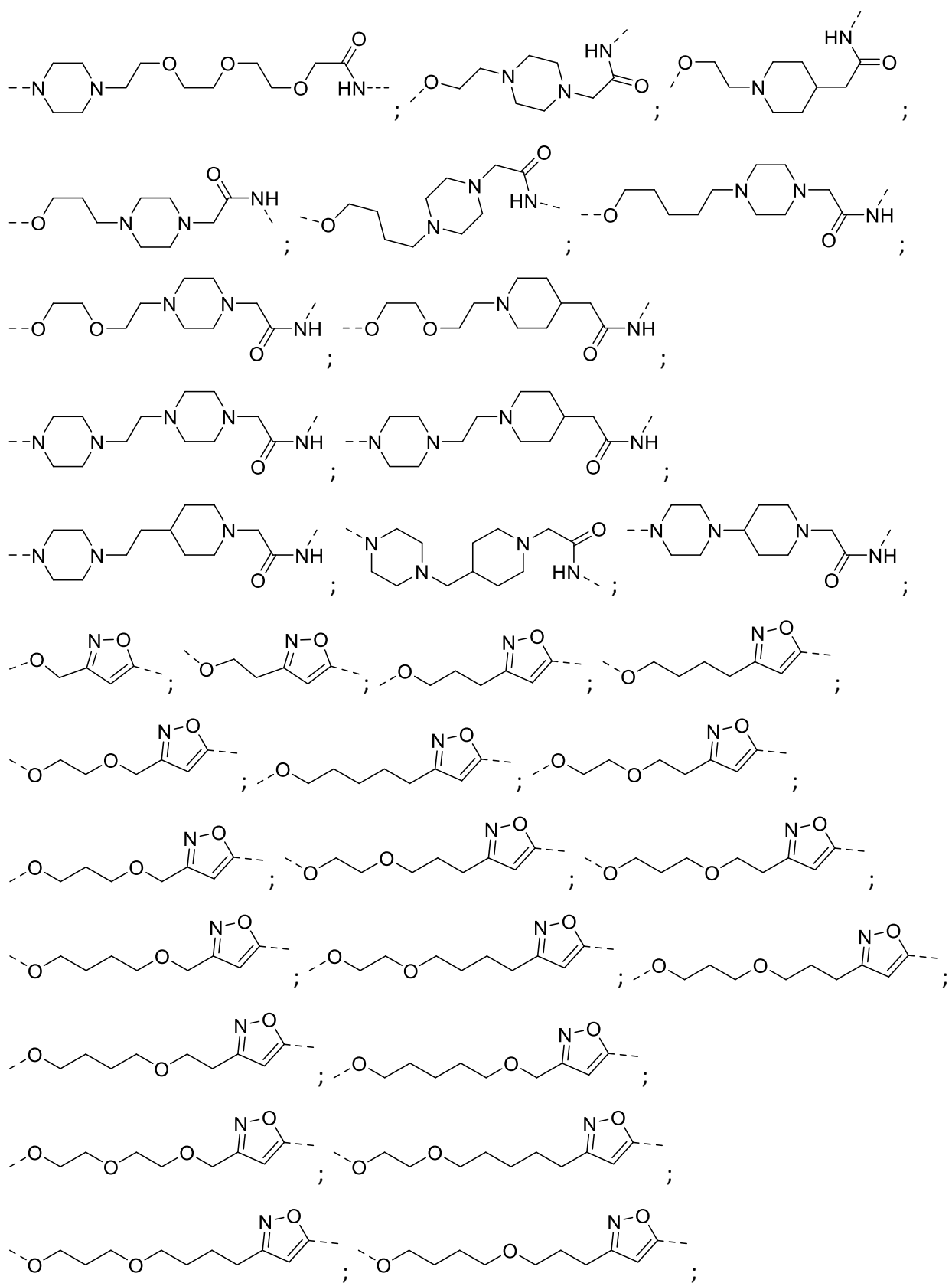


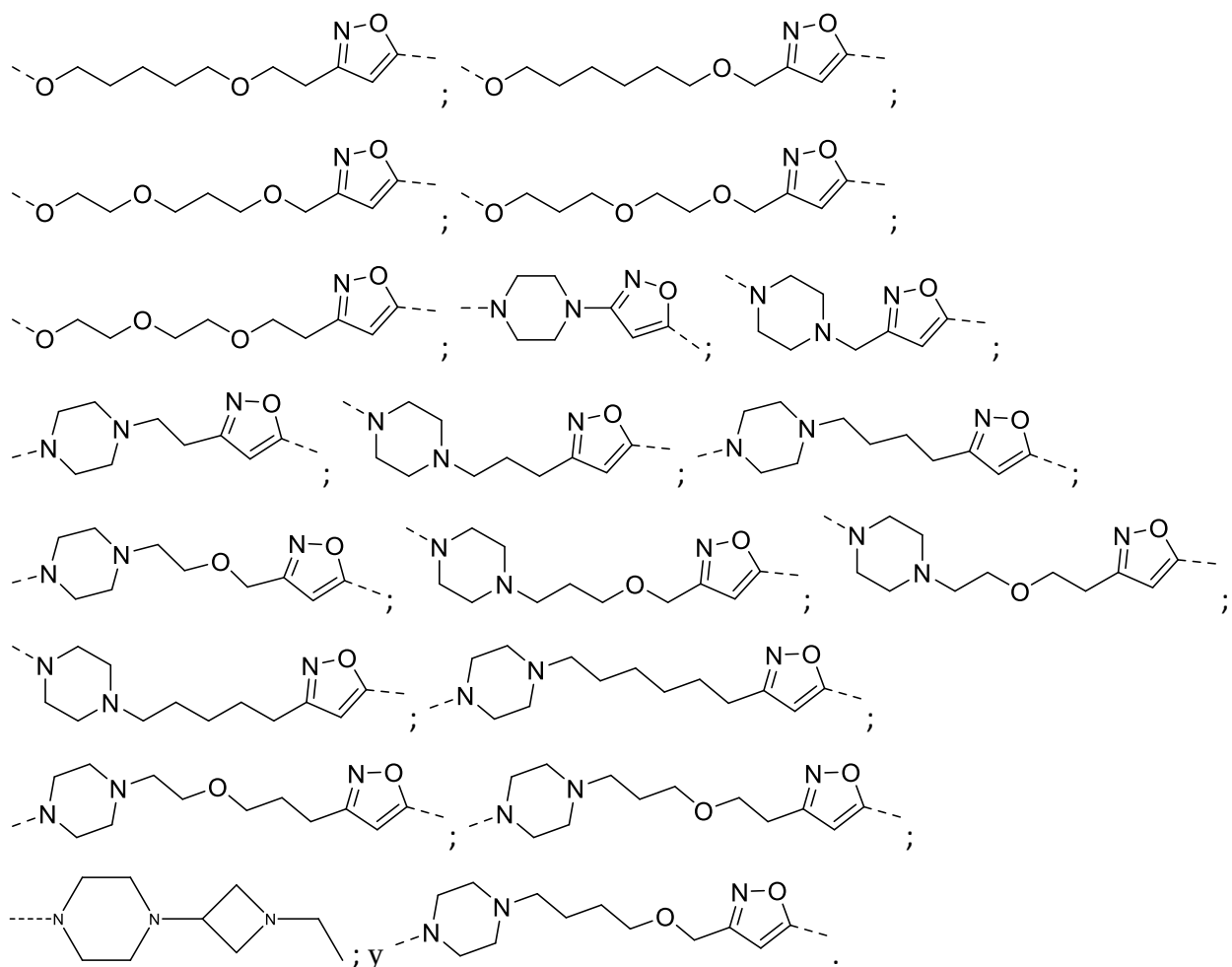




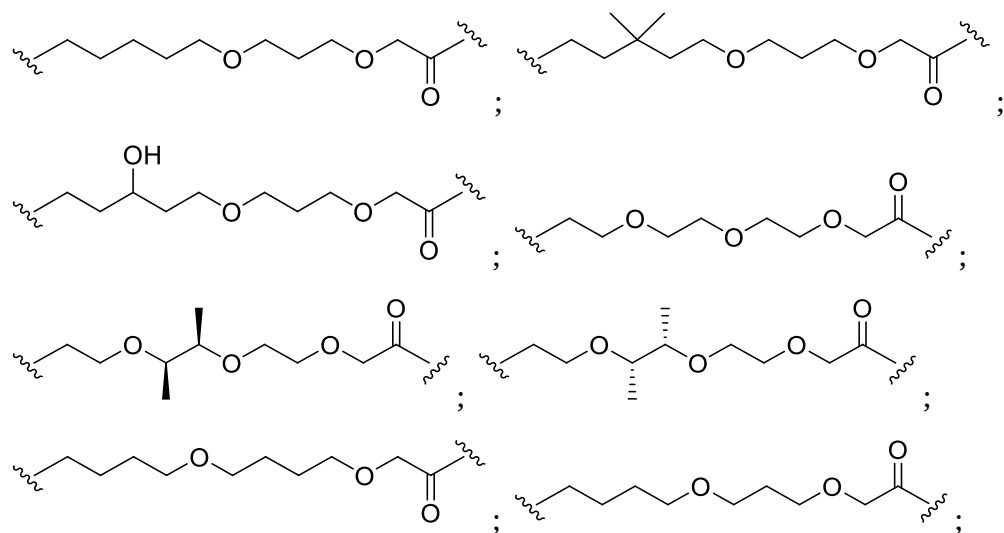


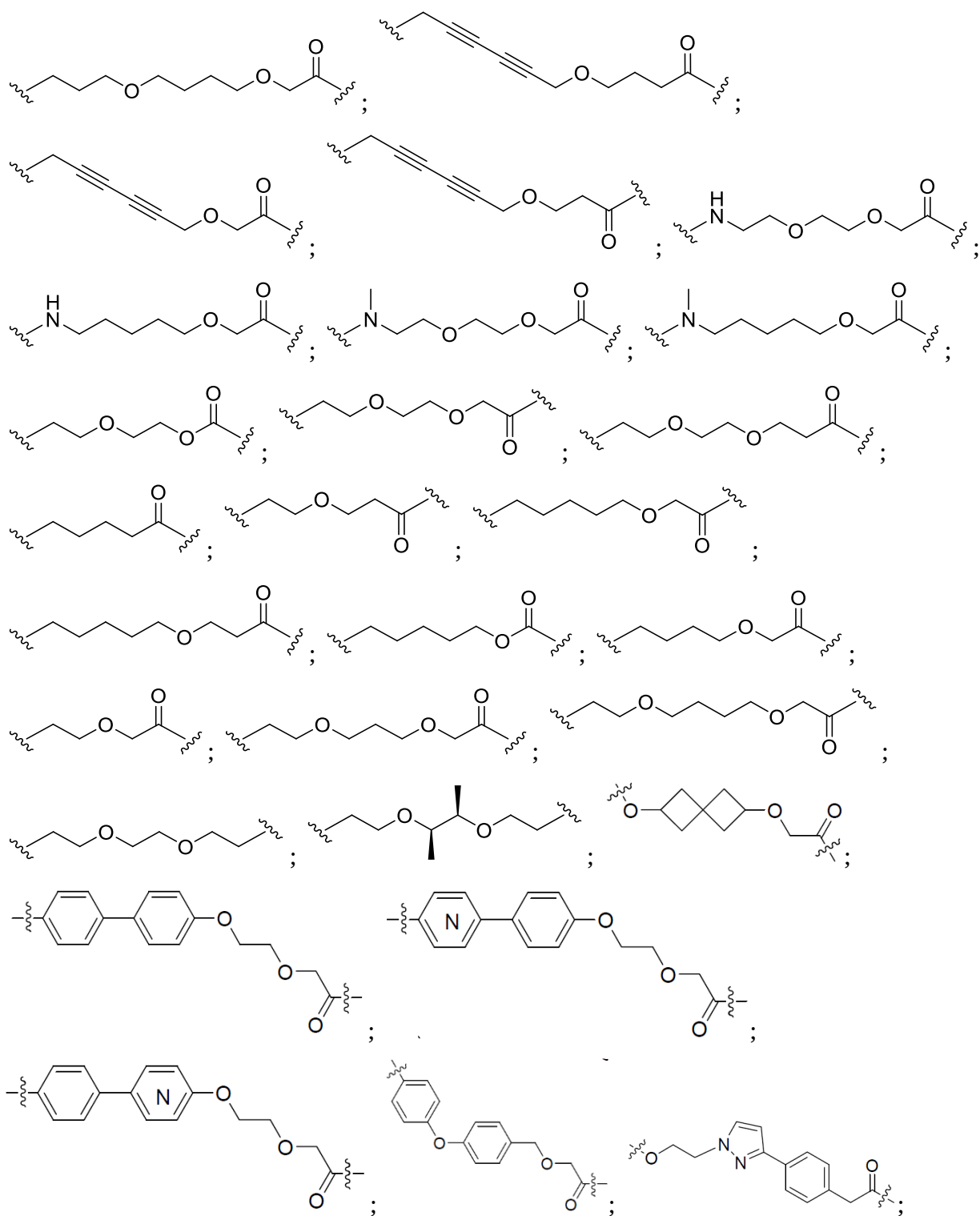


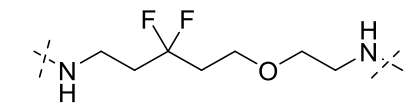
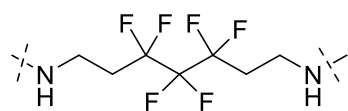
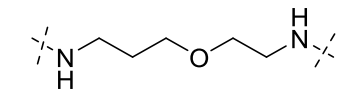
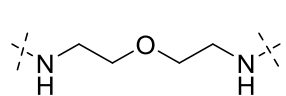
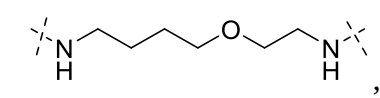
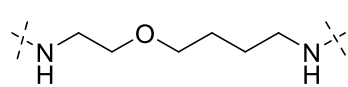
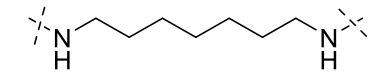
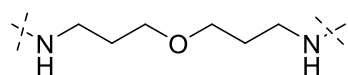
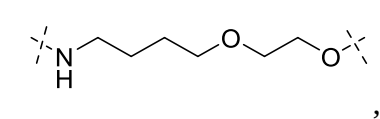
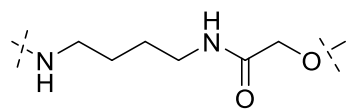
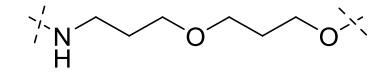
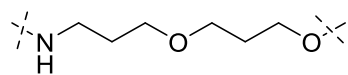
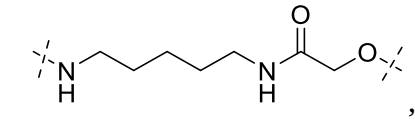
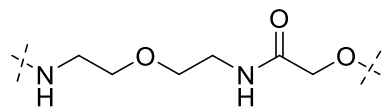
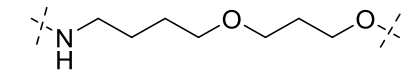
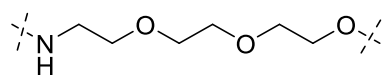
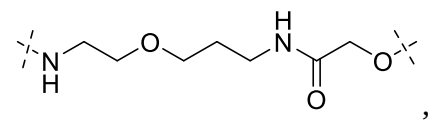
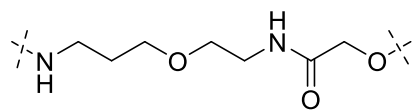
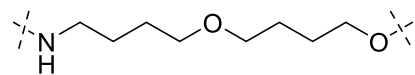
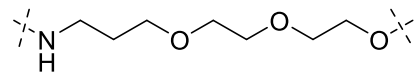
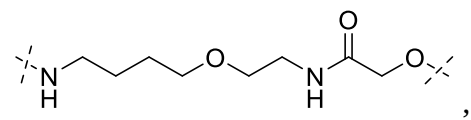
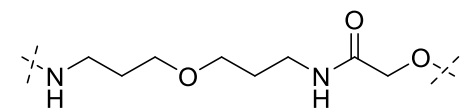
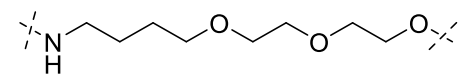
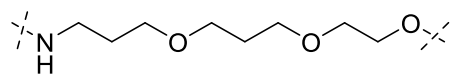
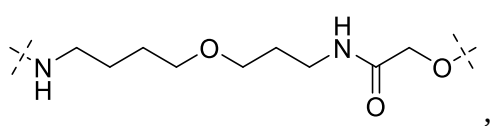
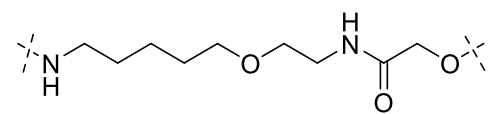
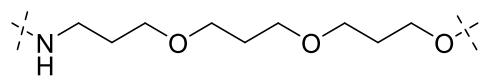
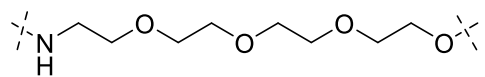


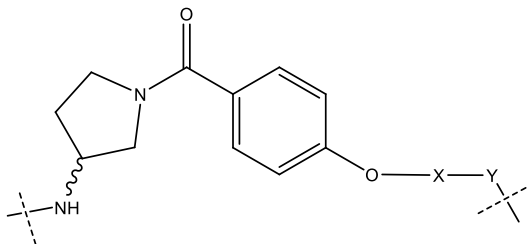
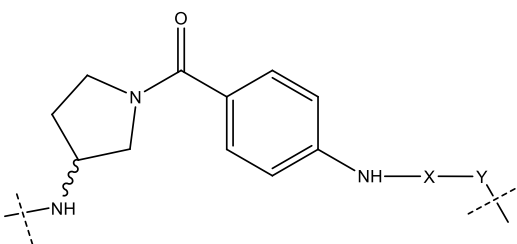
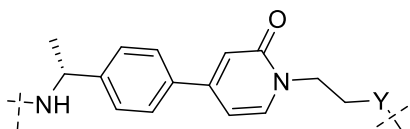
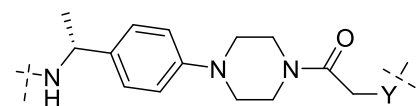
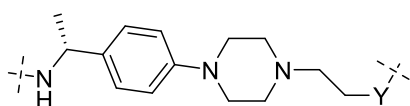
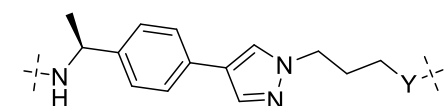
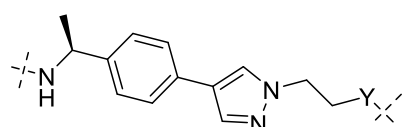
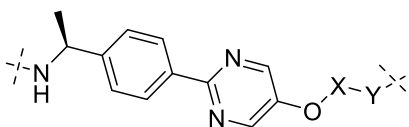
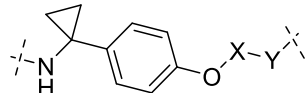
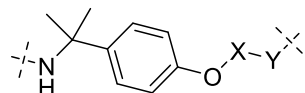
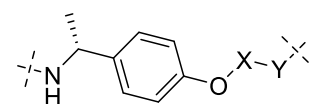
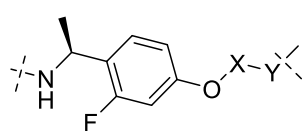
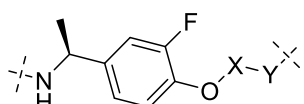
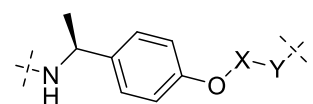
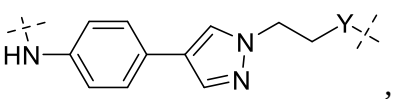
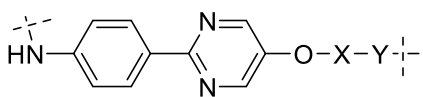
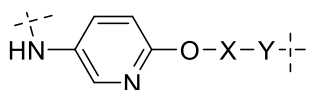
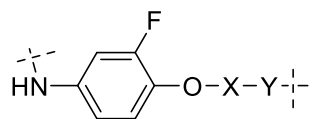
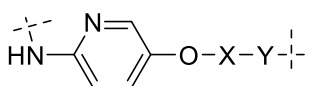
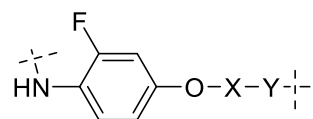
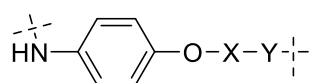
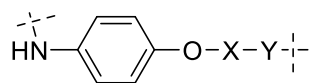


13. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-9, en donde el enlazador (L) se selecciona de:





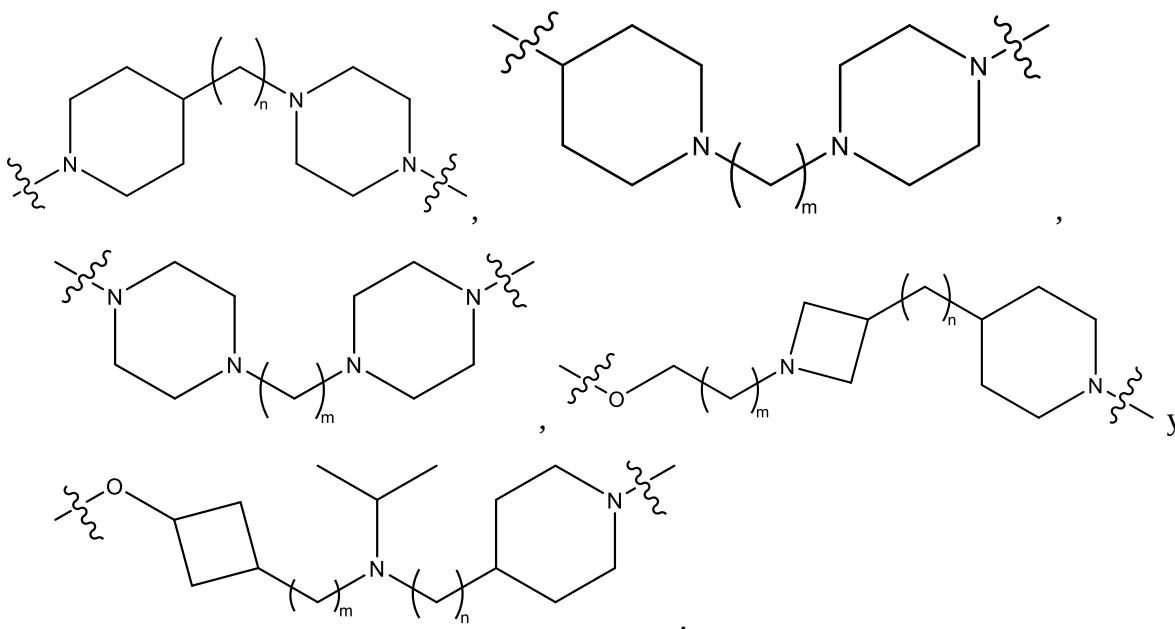




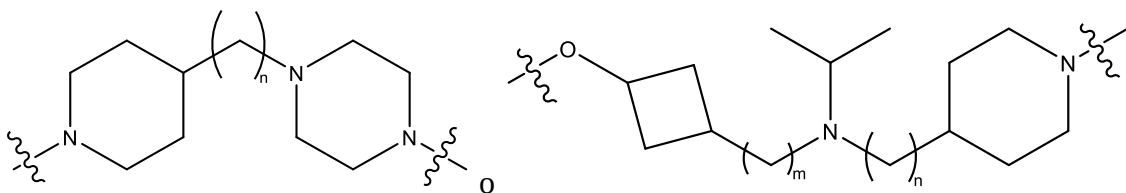
en donde:

"X" en las estructuras anteriores puede ser una cadena lineal con átomos que varían de 2 a 14, y la cadena mencionada puede contener heteroátomos tales como oxígeno; y "Y" en las estructuras anteriores puede ser O, N, S(O)_n (n = 0, 1, 2).

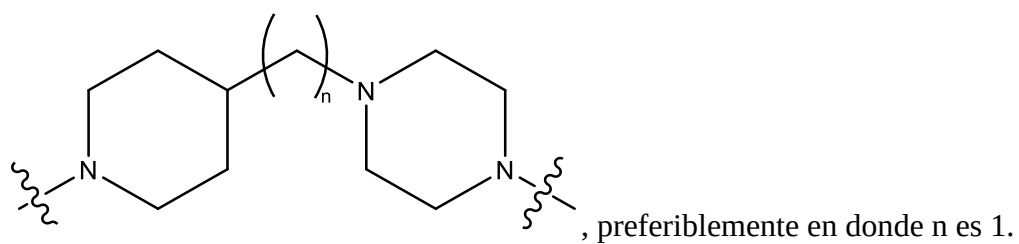
14. El compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-8, en donde el enlazador (L) se selecciona de



15. El compuesto bifuncional de conformidad con la reivindicación 14, en donde el enlazador (L) es

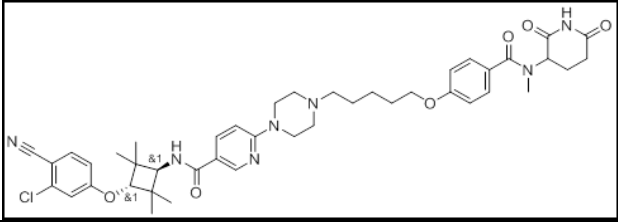
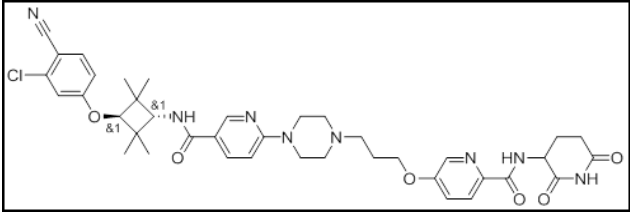
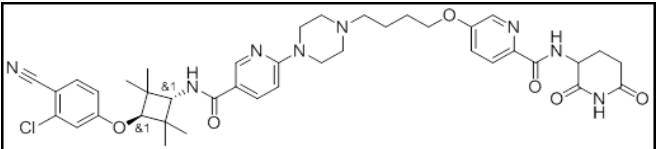
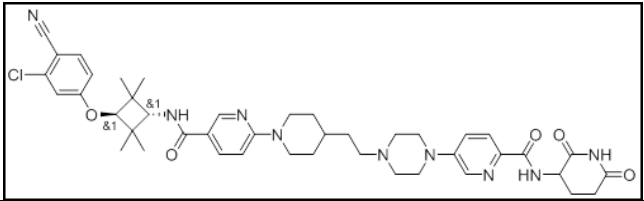
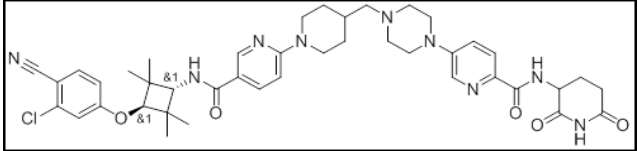
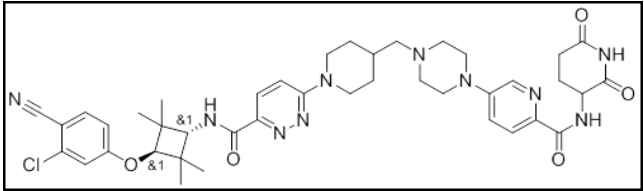
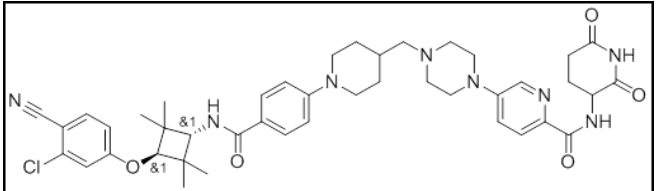


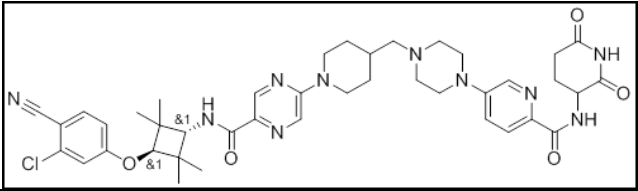
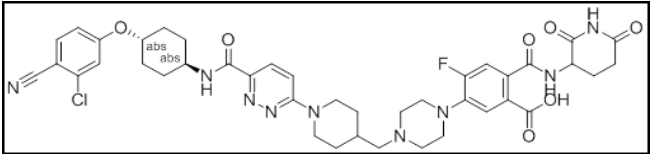
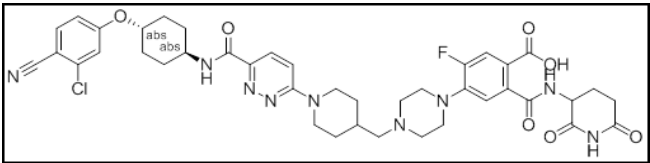
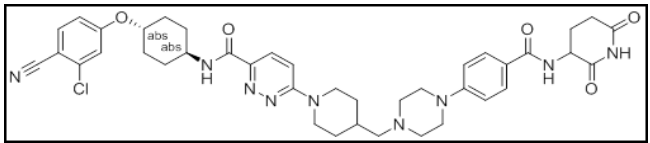
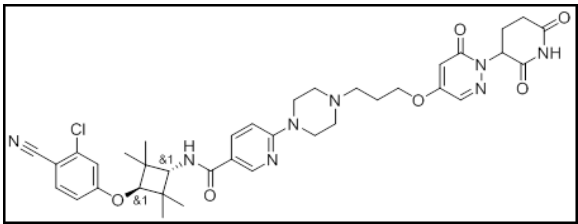
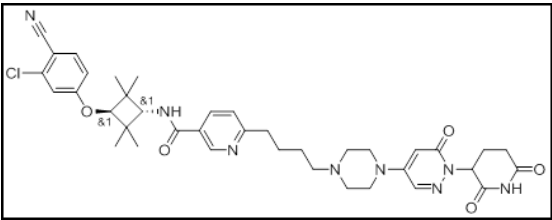
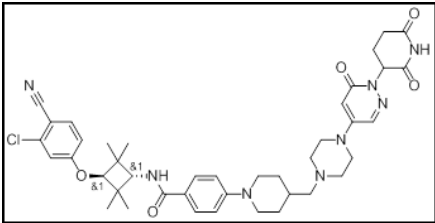
16. El compuesto bifuncional de conformidad con la reivindicación 15, en donde el enlazador (L) es

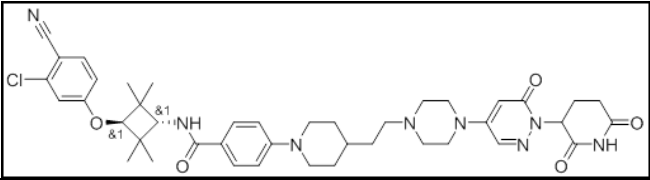
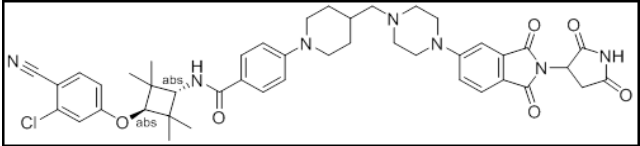
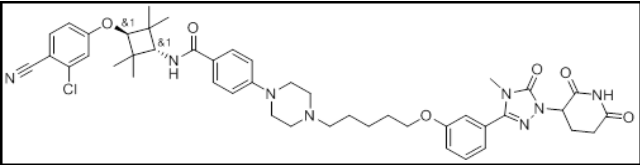
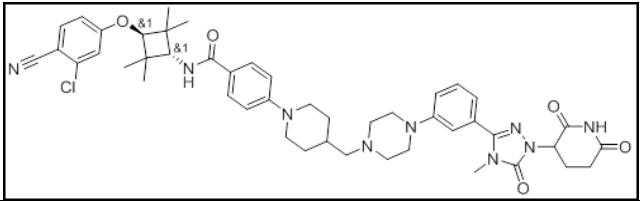
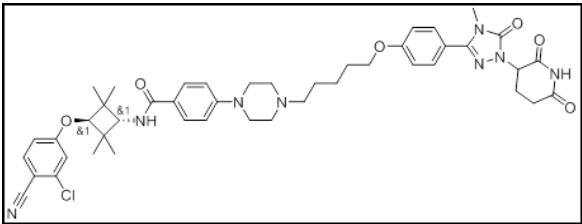
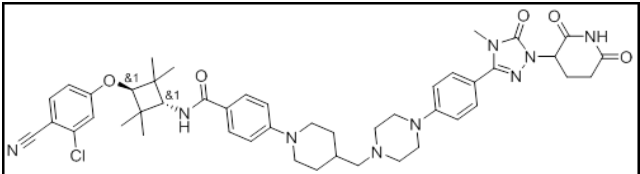


17. El compuesto bifuncional de conformidad con la reivindicación 1, en donde el compuesto se selecciona del grupo que consiste en el PROTAC-27 hasta el PROTAC-29, el PROTAC-48 hasta el PROTAC-63, y el PROTAC-66 hasta el PROTAC-70:

PROTAC-27	
PROTAC-28	
PROTAC-29	
PROTAC-48	

PROTAC-49	 Chemical structure of PROTAC-49: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-50	 Chemical structure of PROTAC-50: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-51	 Chemical structure of PROTAC-51: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-52	 Chemical structure of PROTAC-52: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-53	 Chemical structure of PROTAC-53: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-54	 Chemical structure of PROTAC-54: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.
PROTAC-55	 Chemical structure of PROTAC-55: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a spirocyclic core. The core is linked via an amide bond to a pyridine ring, which is further connected through a piperazine ring to a 4-(4-methoxyphenyl)pyridine moiety. The methoxy group is part of a 4-methoxy-2-methyl-5-oxo-1,2,3,4-tetrahydropyridine-6-carboxamide derivative.

PROTAC-56	 Chemical structure of PROTAC-56: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a quaternary carbon (C1) via an ether linkage. This carbon is also bonded to two methyl groups and a hydrogen atom. The quaternary carbon is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-57	 Chemical structure of PROTAC-57: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a cyclohexane ring via an ether linkage. The cyclohexane ring is also bonded to two hydrogen atoms and a hydrogen atom. The cyclohexane ring is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-58	 Chemical structure of PROTAC-58: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a cyclohexane ring via an ether linkage. The cyclohexane ring is also bonded to two hydrogen atoms and a hydrogen atom. The cyclohexane ring is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-59	 Chemical structure of PROTAC-59: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a cyclohexane ring via an ether linkage. The cyclohexane ring is also bonded to two hydrogen atoms and a hydrogen atom. The cyclohexane ring is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-60	 Chemical structure of PROTAC-60: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a quaternary carbon (C1) via an ether linkage. This carbon is also bonded to two methyl groups and a hydrogen atom. The quaternary carbon is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-61	 Chemical structure of PROTAC-61: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a quaternary carbon (C1) via an ether linkage. This carbon is also bonded to two methyl groups and a hydrogen atom. The quaternary carbon is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.
PROTAC-62	 Chemical structure of PROTAC-62: A molecule featuring a 4-chloro-3-cyanophenoxy group attached to a quaternary carbon (C1) via an ether linkage. This carbon is also bonded to two methyl groups and a hydrogen atom. The quaternary carbon is connected to a pyridine ring via an amide bond. The pyridine ring is linked to a piperidine ring, which is further connected to a piperazine ring. The piperazine ring is linked to a pyridine ring, which is finally connected to a 2,6-pyridinedione moiety.

PROTAC-63	
PROTAC-66	
PROTAC-67	
PROTAC-68	
PROTAC-69	
PROTAC-70	

18. Un compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1- 17, para uso en un método de tratamiento de un estado de enfermedad o de mejoramiento de los

síntomas de una enfermedad o afección en un sujeto que lo necesite, el método comprende administrar a dicho sujeto una cantidad del compuesto.

19. El compuesto bifuncional para uso de la reivindicación 18, en donde el compuesto es administrado en combinación con un agente bioactivo adicional.

20. El compuesto bifuncional para uso de la reivindicación 18 o 19, en donde la enfermedad o afección es cáncer.

21. Una composición que comprende una cantidad de un compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-17, y un portador aceptable farmacéuticamente.

22. La composición de conformidad con la reivindicación 21, en donde la composición comprende, además, al menos uno de un agente bioactivo adicional u otro compuesto bifuncional de conformidad con cualquiera de las reivindicaciones 1-17.

23. La composición de conformidad con la reivindicación 22, en donde el agente bioactivo adicional es un agente anticancerígeno.

24. Una composición para tratar o mejorar al menos un síntoma de una enfermedad o trastorno, caracterizado porque comprende una cantidad de al menos un compuesto de conformidad con cualquiera de las reivindicaciones 1-17 y un portador, aditivo y/o excipiente aceptable farmacéuticamente.

25. La composición para uso de conformidad con la reivindicación 24, en donde la enfermedad o trastorno se asocia con la acumulación y/o agregación de la proteína diana.

26. La composición para uso de conformidad con la reivindicación 24 o 25, en donde la enfermedad o trastorno es atrofia Bulbospinal muscular (enfermedad de Kennedy).

27. La composición de conformidad con cualquiera de las reivindicaciones 24-26, que comprende, además, un agente bioactivo adicional.

28. La composición de conformidad con la reivindicación 27, en donde el agente bioactivo adicional es un agente anticancerígeno.

29. La composición para uso de conformidad con la reivindicación 28, en donde dicho agente anticancerígeno se selecciona del grupo que consiste en everolimus, trabectedin, abraxano, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, un inhibidor de FLT-3, un inhibidor de VEGFR, un inhibidor de EGFR TK, un inhibidor de aurora quinasa, un modulador de PIK-1, un inhibidor de Bcl-2, un inhibidor de HDAC, un inhibidor de c-MET, un inhibidor de PARP, un inhibidor de Cdk, un inhibidor de IGFR-TK, un anticuerpo anti-HGF, un inhibidor de PI3 quinasa, un inhibidor de AKT, un inhibidor de mTORC1/2, un inhibidor de JAK/STAT, un inhibidor del punto de control-1 o 2, un inhibidor de la quinasa de adhesión focal, un inhibidor de Map quinasa quinasa (mek), un anticuerpo atrapador de VEGF, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitida, gimatecan, IL13-PE38QQR, INO 1001, IPdR₁ KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposido, gemcitabina, doxorubicina, doxorubicina liposomal, 5'-deoxi-5-fluorouridina, vincristina, temozolomida, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabina, ácido L-Glutámico, N-[4-[2-(2-amino-4,7-dihidro-4-oxo-1H-pirrol[2,3-d]pirimidin-5-il)etil]benzoil]-, sal disódica, heptahidrato, camptothecin, irinotecan marcado con PEG, tamoxifeno, citrato de toremifeno, anastrozol, exemestano, letrozol, DES(dietilstilbestrol), estradiol, estrógeno, estrógeno conjugado, bevacizumab, IMC-1C11, CHIR-258); 3-[5-(metilsulfonilpiperadinametil)-indolil-quinolona, vatalanib, AG-013736, AVE-0005, acetato de goserelina, acetato de leuprolido, pamoato de triptorelina, acetato de medroxiprogesterona, caproato de hidroxiprogesterona, acetato de megestrol, raloxifeno, bicalutamida, flutamida,

nilutamida, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, anticuerpo ABX-EGF, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostina, NVP-LAQ824, ácido hidroxámico suberoil analida, ácido valproico, tricostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutetimida, arnsacrina, anagrelida, L-asparaginasa, vacuna del Bacillus Calmette-Guerin (BCG), adriamicina, bleomicina, buserelina, busulfán, carboplatino, carmustina, clorambucil, cisplatino, cladribina, clodronato, ciproterona, citarabina, dacarbazina, dactinomicina, daunorubicina, epirubicina, fludarabina, fludrocortisona, fluoximesterona, gleevec, hidroxiurea, idarubicina, ifosfamida, imatinib, leuprolida, levamisol, lomustina, mecloretamina, melfalán, 6-mercaptopurina, mesna, metotrexato, mitomicina, mitotano, mitoxantrona, nilutamida, octreotido, oxaliplatino, pamidronato, pentostatina, plicamicina, porfimer, procarbazona, raltitrexed, rituximab, estreptozotocina, teniposido, testosterona, talidomida, tioguanina, tiotepa, tretinoin, vindesina, ácido 13-cis-retinoico, mostaza fenilalanina, mostaza uracilo, estramustina, altretaminae, floxuridinae, 5-deoxiuridina, citosina arabinosido, 6-mercaptopurina, deoxicoformicina, calcitriol, valrubicina, mitramicina, vinblastina, vinorelbina, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamina, endostatina, SU5416, SU6668, EMD121974, interleucina-12, IM862, angiostatina, vitaxin, droloxifeno, idoxifeno, espironolactona, finasterida, cimetidina, trastuzumab, denileukin diftotox, gefitinib, bortezomib, paclitaxel, paclitaxel libre de cremóforo, docetaxel, epitolona B, BMS- 247550, BMS-310705, droloxifeno, 4-hidroxitamoxifeno, pipendoxifeno, ERA-923, arzoxifeno, fulvestrant, acolbifeno, lasofoxifeno, idoxifeno, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamicina, 40-O-(2-hidroxi-etil)-rapamicina, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, eritropoietina, factor estimulador de colonia de granulocitos, zolendronato, prednisona, cetuximab, factor estimulador de colonias de granulocitos macrófagos, histrelin, interferón alfa-2a pegilado, interferón alfa-2a, interferón alfa-2b pegilado, interferón alfa-2b, azacitidina, PEG-L-asparaginasa, lenalidomida, gemtuzumab, hidrocortisona, interleucina-11, dexrazoxano, alemtuzumab, ácido retinoico todo-trans, ketoconazol, interleucina-2, megestrol, inmuno globulina, mostaza nitrógeno, metilprednisolona, ibritumomab tiuxetan, andrógenos, decitabina, hexametilmelamina, bexaroteno, tositumomab, trióxido de arsénico, cortisona, editronato, mitotano, ciclosporina, daunorubicina liposomal, Edwina-asparaginasa, estroncio 89, casopitant, netupitant, un

antagonista del receptor NK-1, palonosetron, aprepitant, difenhidramina, hidroxizina, metoclopramida, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexametasona, proclorperazina, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, eritropoietina, epoetin alfa, darbepoetin alfa y mezclas de estos.

30. Un compuesto para inducir la degradación de una proteína diana en una célula caracterizada porque es de conformidad con la reivindicación 1.

31. Una composición para tratar cáncer caracterizada porque comprende una cantidad del compuesto de conformidad con la reivindicación 1.

32. La composición para uso de conformidad con la reivindicación 31, en donde el cáncer es carcinomas hepatocelulares, carcinomas de células renales, cáncer de mama, cáncer de próstata, cáncer de cuello uterino, cáncer uterino, o cáncer de ovario.