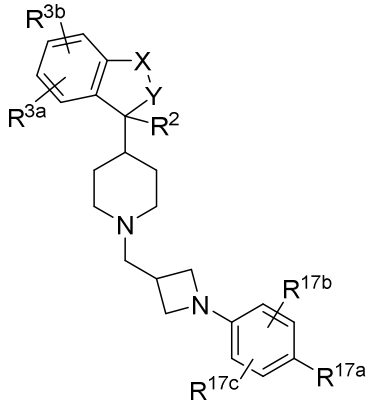
Med. Chem. 6:447-462 (2014); He *et al.*, *J. Med. Chem. 57*:1543−1556 (2014); and Borkin *et al.*, *Cancer Cell 27*:589–602 (2015).

[0008] Small molecules that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Nos. 9,212,180 and 9,216,993; and U.S. Patent Application Publication Nos. 2011/0065690; 2014/0275070; 2016/0045504; and 2016/0046647. Peptides that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Application Publication No. 2009/0298772.

[0009] There is an ongoing need for new agents, e.g., small molecules, for treating cancer and other diseases responsive to menin inhibition.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VIi**:



VIi,

wherein:

X-Y is selected from the group consisting of

-N(R^{1a})-C(=O)-;

-C(=O)-O-;

-C(=O)-N(R^{1b})-;

-CH_2N(R^{1c})-CH_2-;

-C(=O)N(R^{1d})-CH_2-;

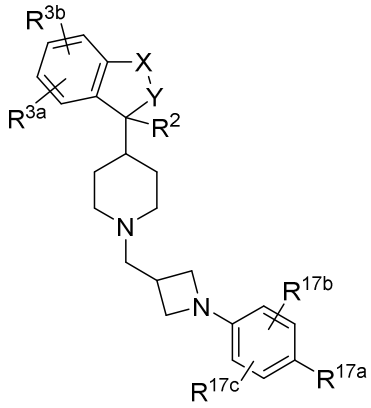
-CH_2CH_2-N(R^{1e})-;

-CH_2N(R^{1f})-C(=O)-; and

-CH_2O-CH_2-;

What is Claimed Is:

1. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **VIi**:



VIi,

wherein:

X-Y is selected from the group consisting of

-N(R^{1a})-C(=O)-;

-C(=O)-O-;

-C(=O)-N(R^{1b})-;

-CH_2N(R^{1c})-CH_2-;

-C(=O)N(R^{1d})-CH_2-;

-CH_2CH_2-N(R^{1e})-;

-CH_2N(R^{1f})-C(=O)-; and

-CH_2O-CH_2-;

R^{1a} is selected from the group consisting of hydrogen and alkyl;

R^{1b} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

R^{1c} is selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, (heteroaryl)alkyl, alkylcarbonyl, arylcarbonyl, and alkoxycarbonyl;

R^{1d} is selected from the group consisting of hydrogen, alkyl, and aralkyl;

R^{1e} is selected from the group consisting of hydrogen, alkyl, and (aryloxy)alkyl;

R^{1f} is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl;

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl; and

R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy.

2. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

R^{17a} is selected from the group consisting of alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl; and

R^{17b} and R^{17c} are hydrogen.

3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected from the group consisting of alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, optionally substituted heteroaryl, and aralkyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is unsubstituted cycloalkyl.

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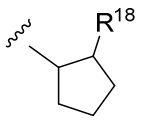
5. The compound of claim 3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is substituted cycloalkyl having Formula **VII**:



VII,

wherein:

R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, $-N(R^{19a})C(=O)-R^{19b}$, and $-N(R^{20a})SO_2-R^{20b}$;

R^{19a} is selected from the group consisting of hydrogen and alkyl;

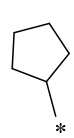
R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl;

R^{20a} is selected from the group consisting of hydrogen and alkyl; and

R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl.

6. The compound of claim 5, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{18} is selected from the group consisting of -OC(=O)-amino and $-NHC(=O)-R^{19b}$.

7. The compound of claim 3, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^2 is selected from the group consisting of:



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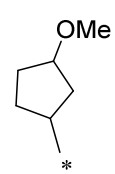

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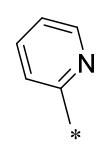

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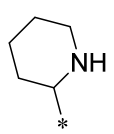
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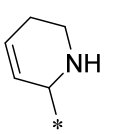
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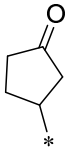
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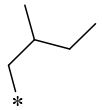
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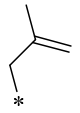
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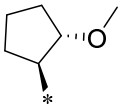
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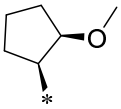
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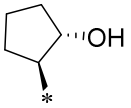
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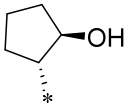
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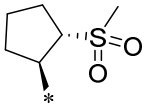
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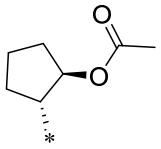
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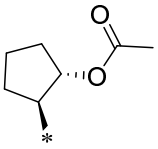
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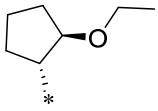
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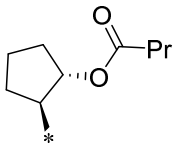
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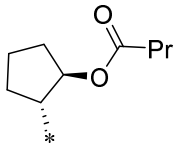
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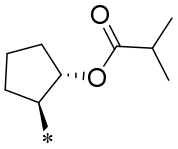
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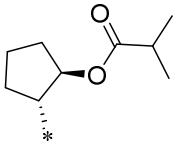
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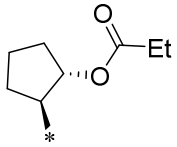
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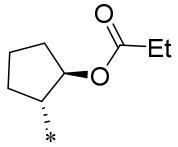
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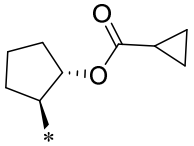
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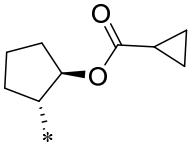
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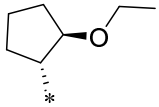
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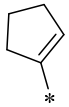
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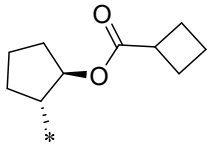
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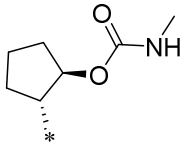
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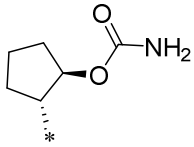
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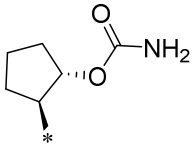
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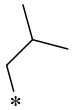
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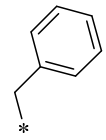
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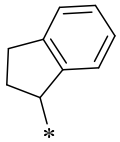
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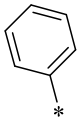
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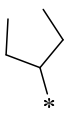
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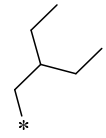
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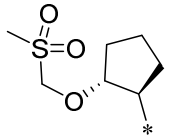
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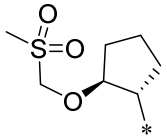
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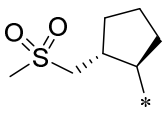
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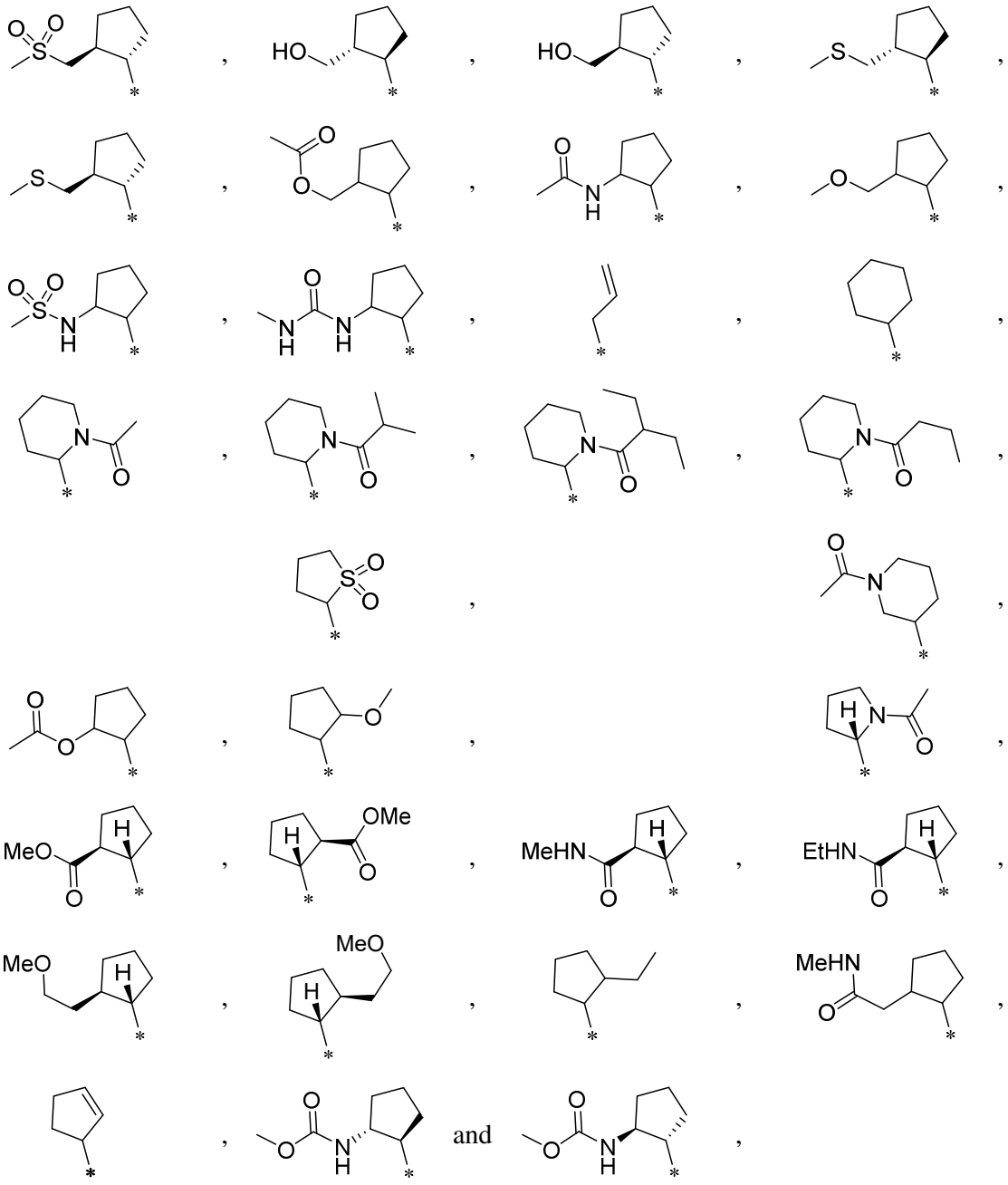


wherein " * " indicates the point of attachment to the remainder of the molecule.

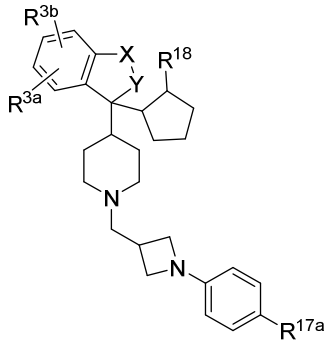
8. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is $-CH_2N(R^{1c})-CH_2-$.

9. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2CH_2-N(R^{1e})-.

10. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2N(R^{1f})-C(=O)-.

11. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein X-Y is -CH_2O-CH_2-.

12. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **IX**:



IX,

wherein:

X-Y is -CH_2N(R^{1c})-CH_2-,

R^{1c} is C_{1-3} alkyl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b}; and

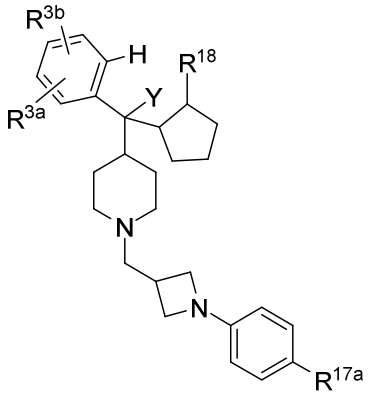
R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl.

13. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

X-Y is -CH_2N(R^{1c})-CH_2-; and

R^{1c} is selected from the group consisting of hydrogen and C_{1-6} alkyl.

14. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula X:



X,

wherein:

Y is selected from the group consisting of cyano, hydroxy, and -CH_2-R^{12};

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{12} is selected from the group consisting of hydroxy, amino, optionally substituted heteroaryl, optionally substituted heterocyclo, and -NHC(=O)-R^{16};

R^{16} is selected from the group consisting of alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl;

R^{17a} is selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, haloalkoxy, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, sulfonamido, optionally substituted heteroaryl, optionally substituted heterocyclo, carboxamido, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, carboxy, and carboxyalkyl;

R^{18} is selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, -N(R^{19a})C(=O)-R^{19b}, and N(R^{20a})SO_2-R^{20b};

R^{19a} is selected from the group consisting of hydrogen and alkyl;

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl;

R^{20a} is selected from the group consisting of hydrogen and alkyl; and

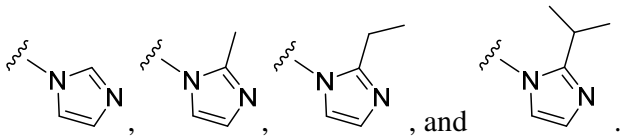
R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl.

15. The compound of claim 14, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein Y is $-CH_2-R^{12}$.

16. The compound of claim 15, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is a 5-membered heteroaryl.

17. The compound of claim 15, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is optionally substituted imidazol-1-yl.

18. The compound of claim 17, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is


, and .

19. The compound of claim 14, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

Y is selected from the group consisting of cyano and $-CH_2-R^{12}$;

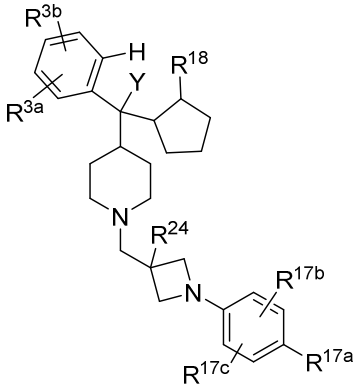
R^{12} is selected from the group consisting of amino and heteroaryl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

R^{18} is selected from the group consisting of -OC(=O)-amino and $-NHC(=O)-R^{19b}$; and

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl.

20. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **Xi**:



Xi,

wherein:

Y is selected from the group consisting of cyano and -CH_2-R^{12};

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{12} is selected from the group consisting of amino and heteroaryl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

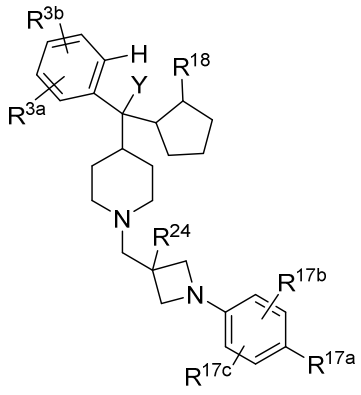
R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen and halo;

R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b};

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; and

R^{24} is selected from the group consisting of hydrogen and fluoro.

21. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having Formula **Xi**:



Xi,

wherein:

Y is selected from the group consisting of cyano and -CH_2-R^{12};

R^{3a} and R^{3b} are each independently selected from the group consisting of hydrogen, alkyl, halo, hydroxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkoxy, and haloalkoxy;

R^{12} is optionally substituted 5-membered heteroaryl;

R^{17a} is selected from the group consisting of chloro, cyano, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heteroarylsulfonyl;

R^{17b} and R^{17c} are independently selected from the group consisting of hydrogen and halo;

R^{18} is selected from the group consisting of -OC(=O)-amino and -NHC(=O)-R^{19b};

R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl; and

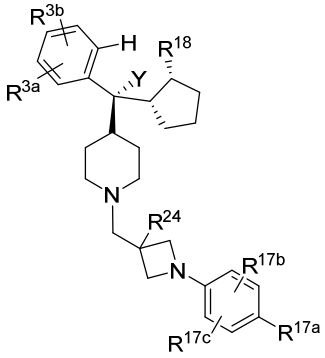
R^{24} is selected from the group consisting of hydrogen and fluoro.

22. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is optionally substituted imidazole-1-yl.

23. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is optionally substituted 1,3,4-triazole.

24. The compound of claim 21, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein R^{12} is optionally substituted 1,2,3-triazole.

25. The compound of any one of claims 20-24, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, having any one or more of the following formulae:



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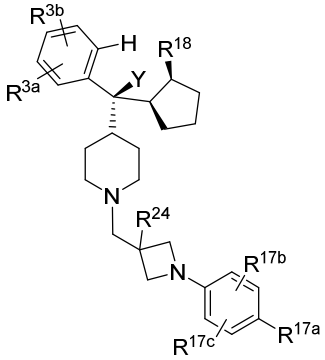
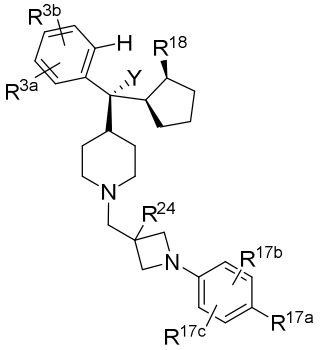


Formula **Xi-A** Formula **Xi-B**



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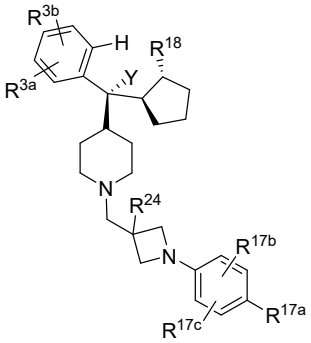
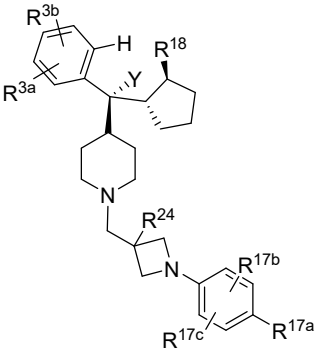


Formula **Xi-D** Formula **Xi-E**



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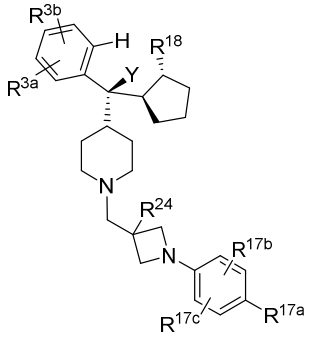
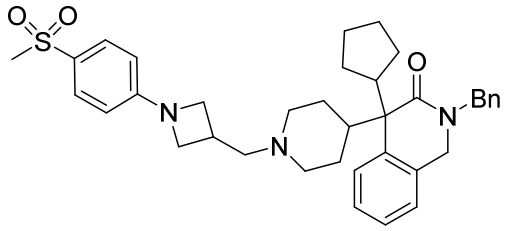


Formula **Xi-G** Formula **Xi-H**

26. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, selected from one or more of:

25 

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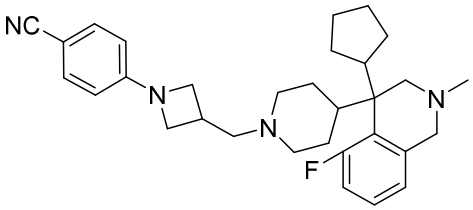
33 

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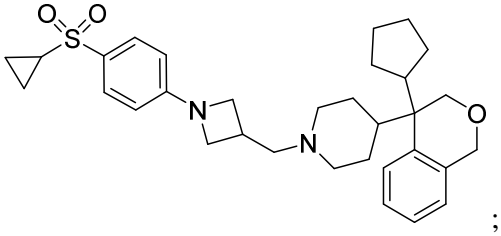
38 

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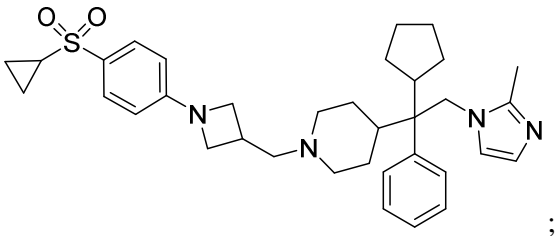
42 

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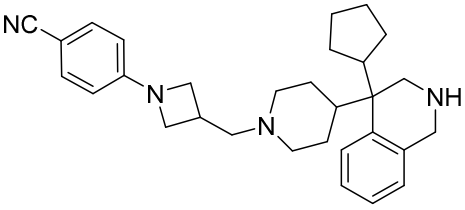
43 

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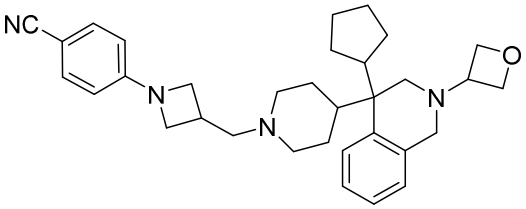
44 

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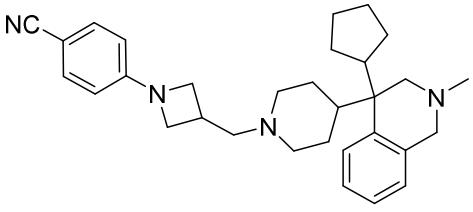
45 

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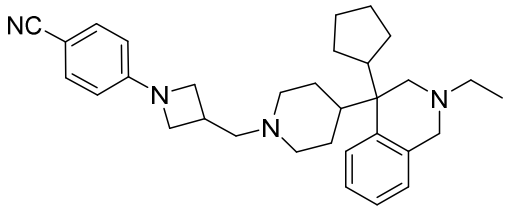
46 

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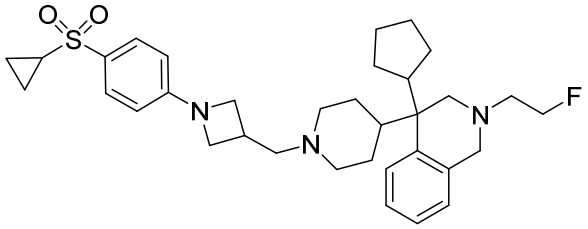
47 

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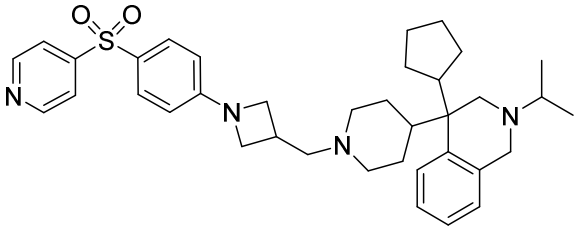
48 

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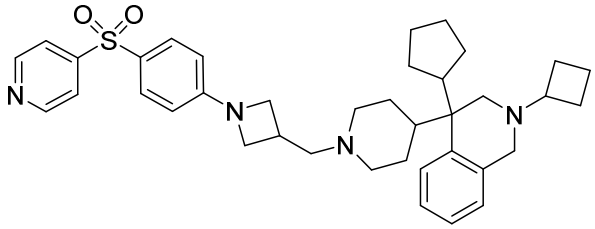
49 

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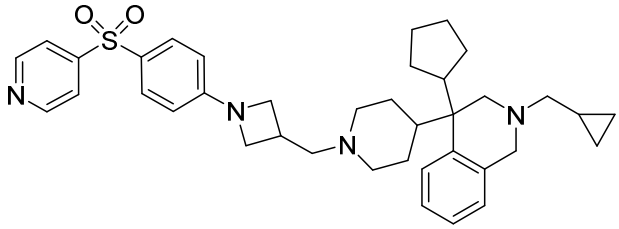
50 

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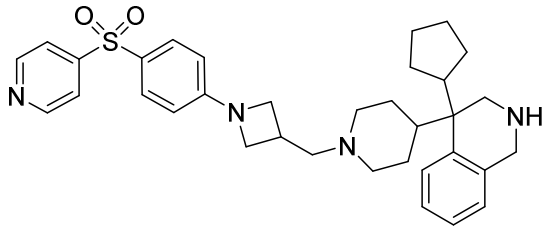
51 

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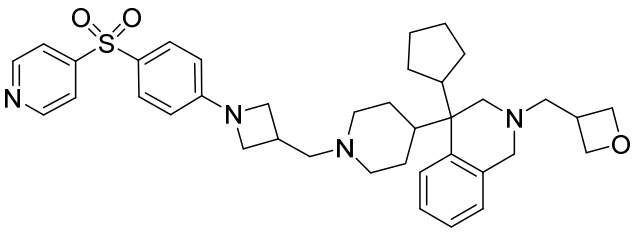
52 

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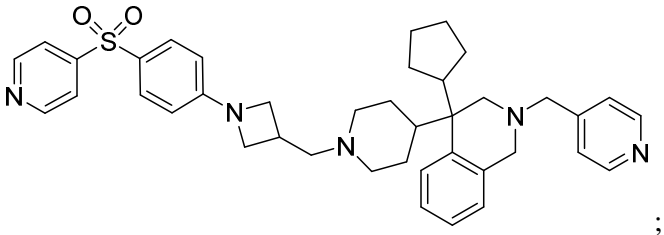
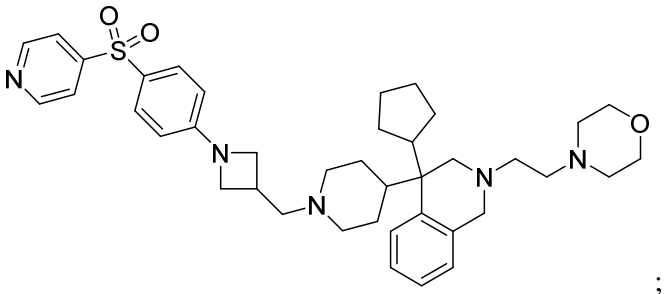
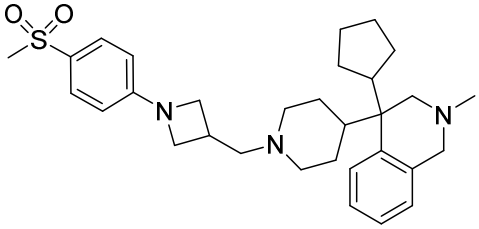
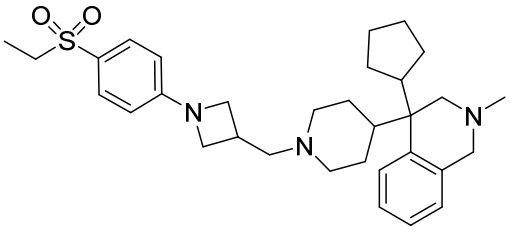
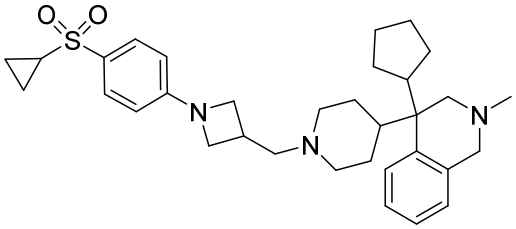
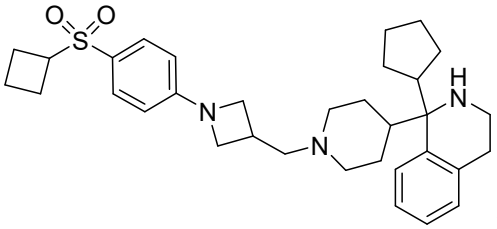
53  ;

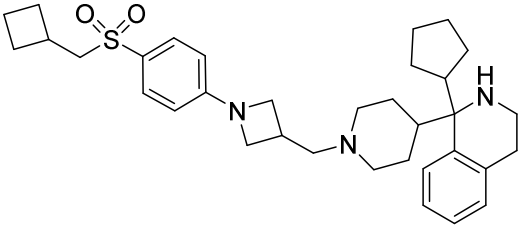
54  ;

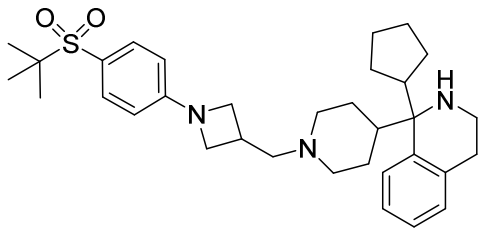
64  ;

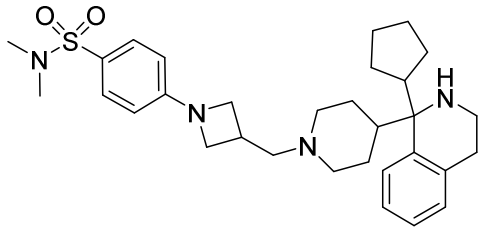
69  ;

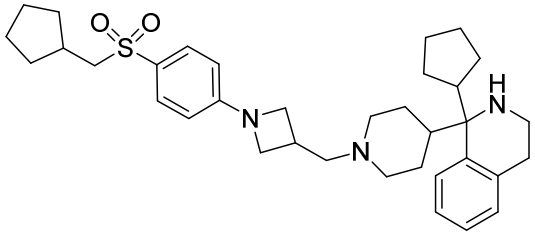
70  ;

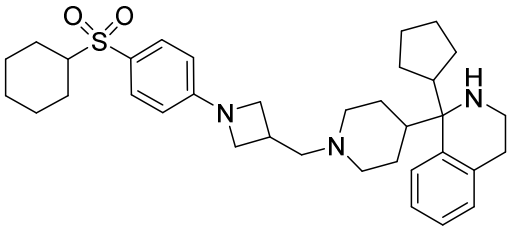
85  ;

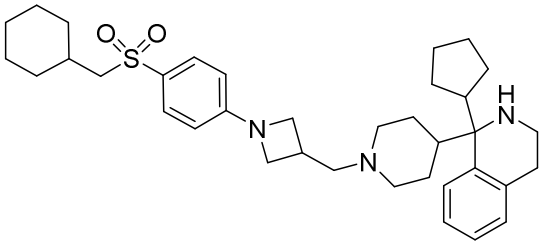
86  ;

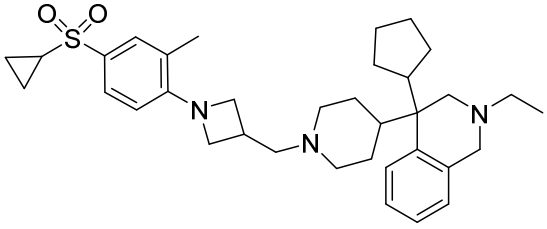
87  ;

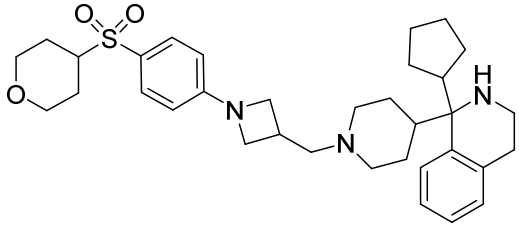
88  ;

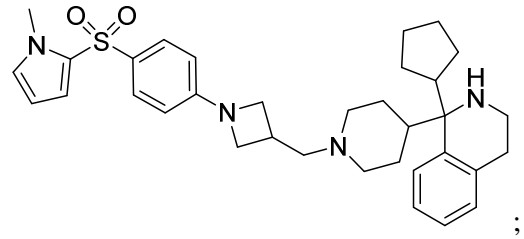
91  ;

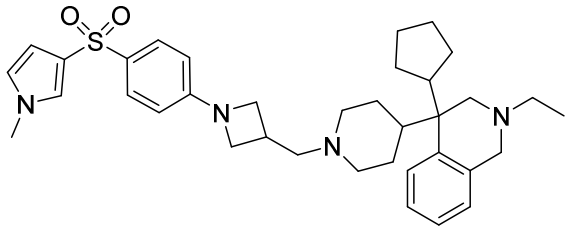
92  ;

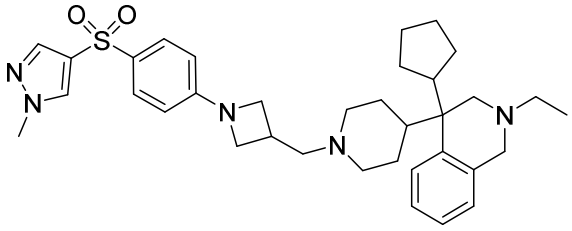
93  ;

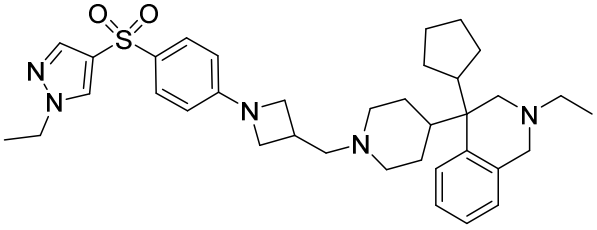
96  ;

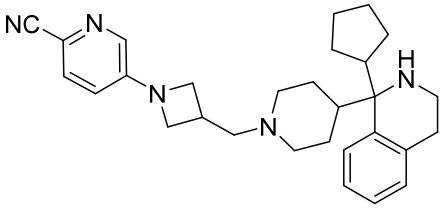
97  ;

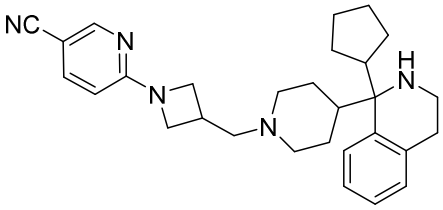
98  ;

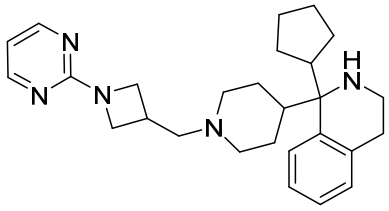
101  ;

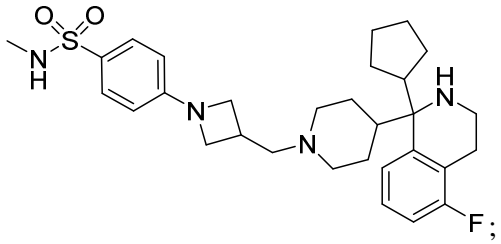
102  ;

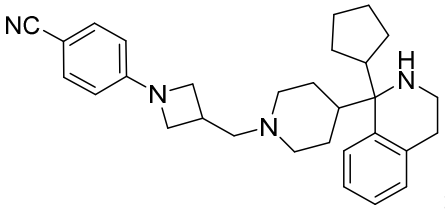
103  ;

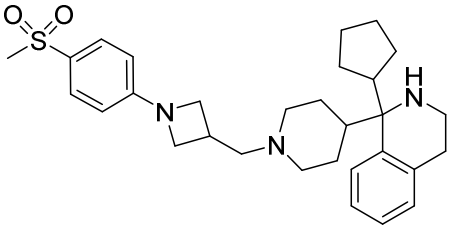
109  ;

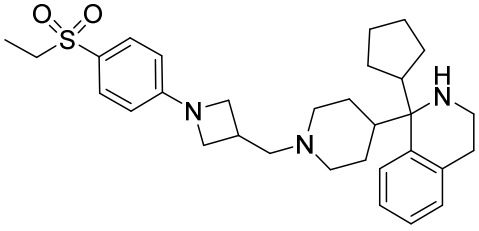
110  ;

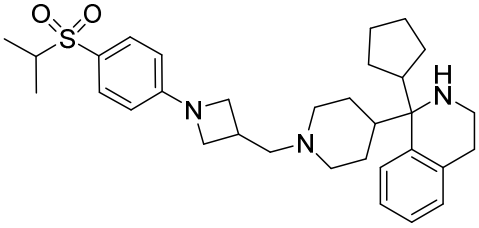
111  ;

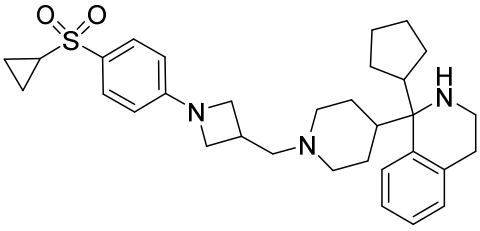
119  ;

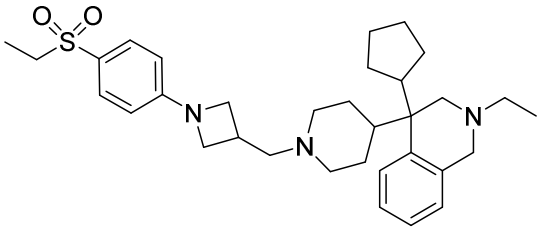
129  ;

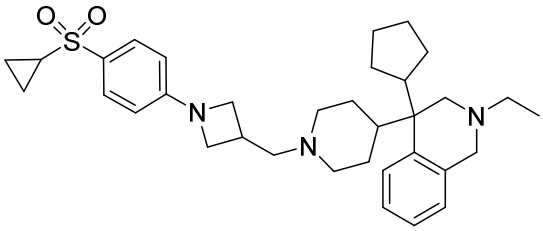
132  ;

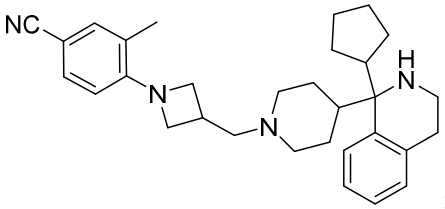
133  ;

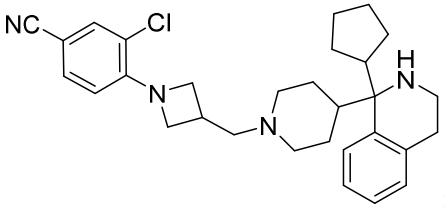
134  ;

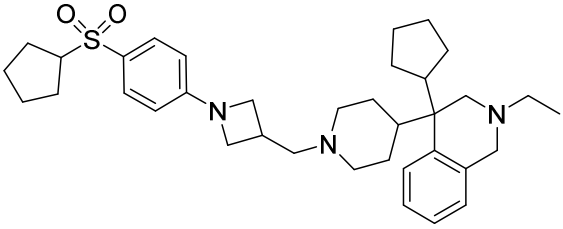
135  ;

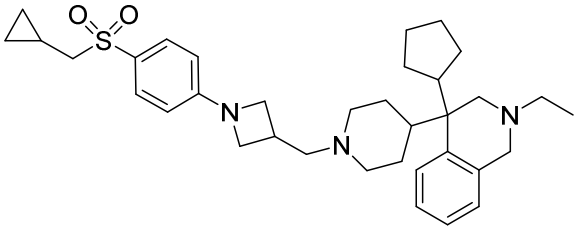
136  ;

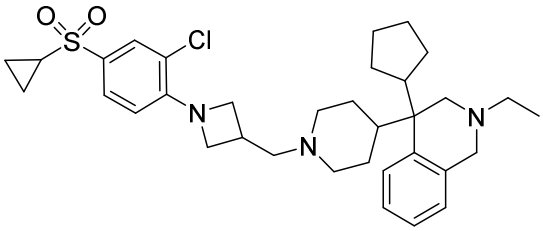
137  ;

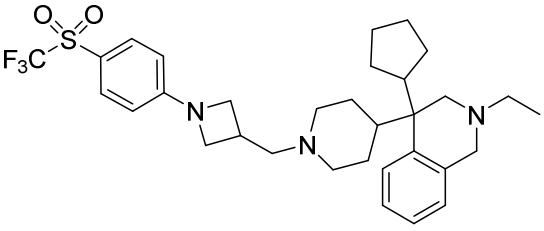
138  ;

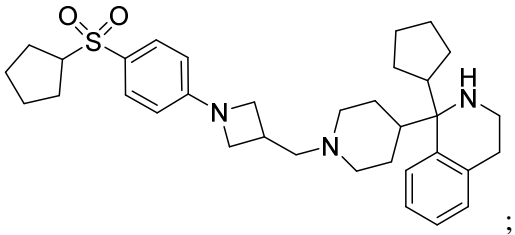
139  ;

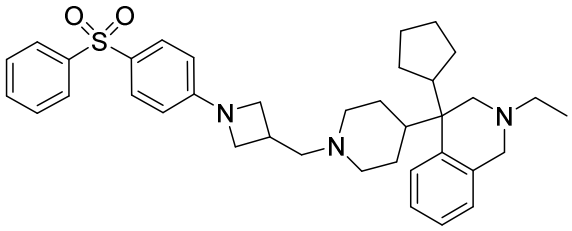
142  ;

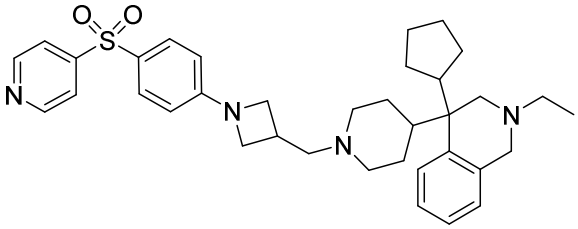
143  ;

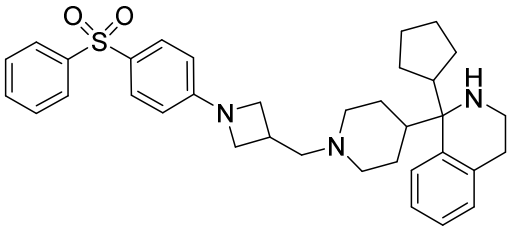
144  ;

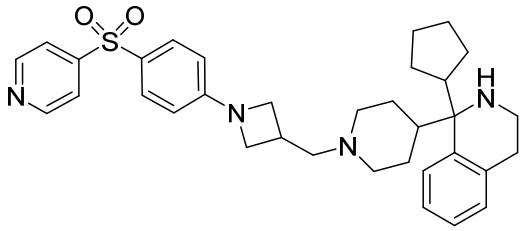
145  ;

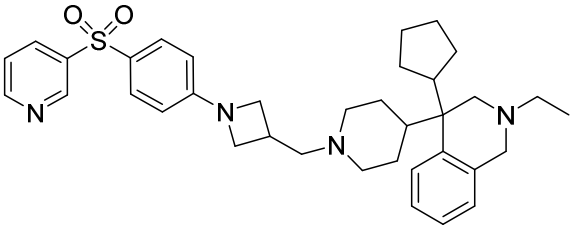
146  ;

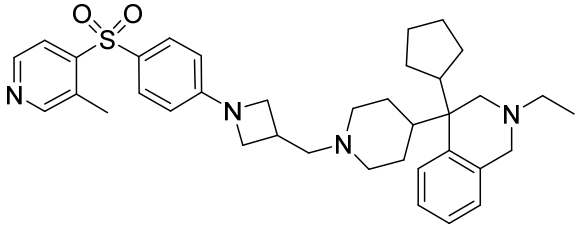
147  ;

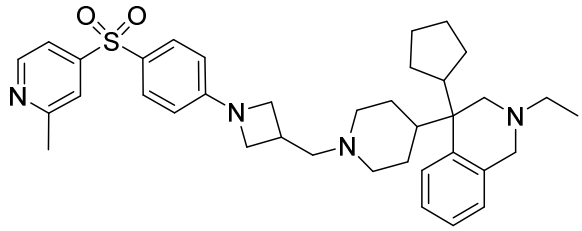
148  ;

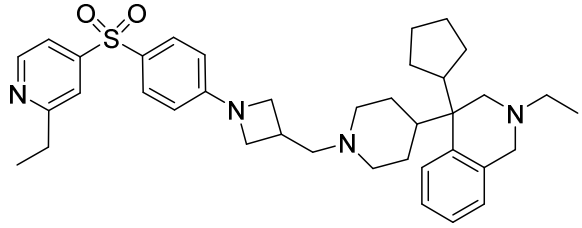
149  ;

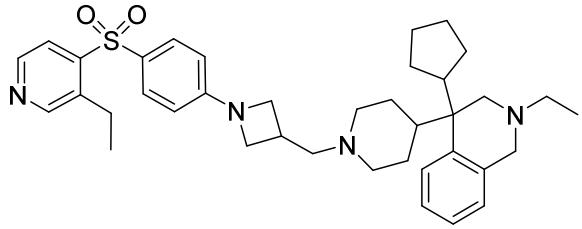
151  ;

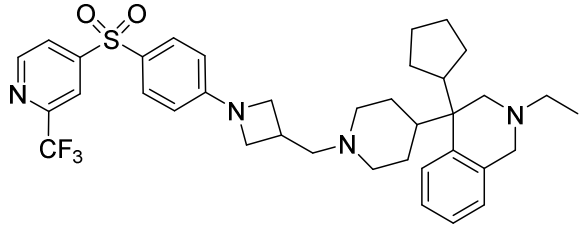
152  ;

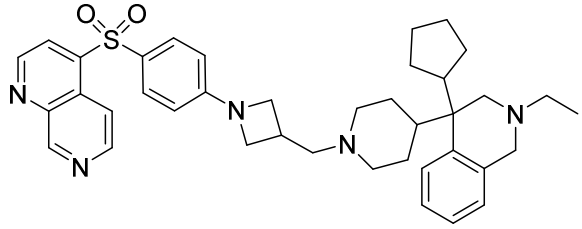
153  ;

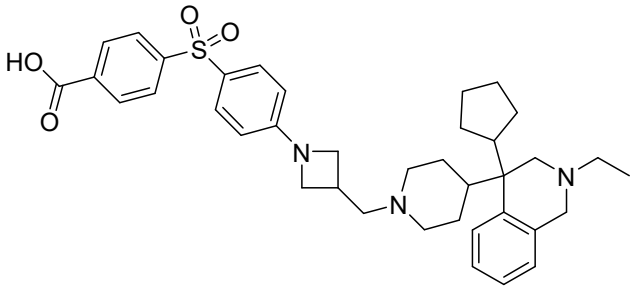
154  ;

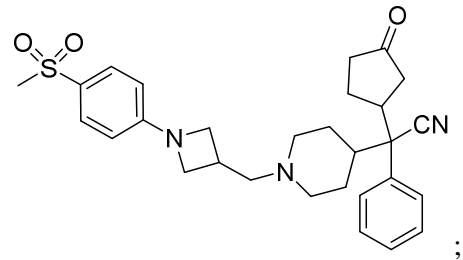
155  ;

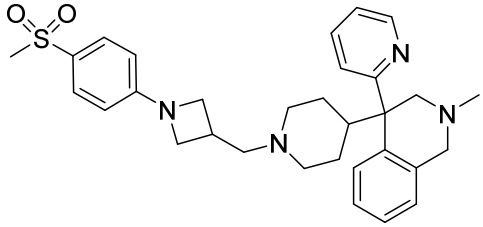
156  ;

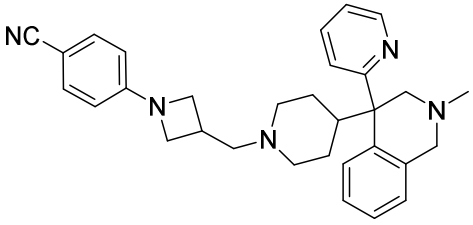
157  ;

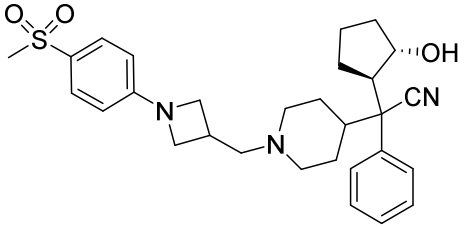
158  ;

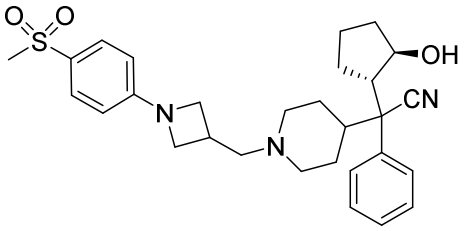
164  ;

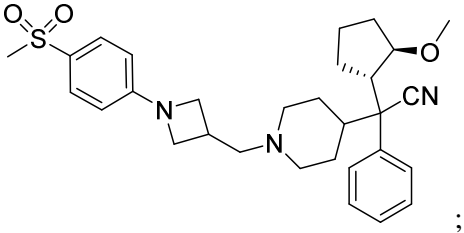
169  ;

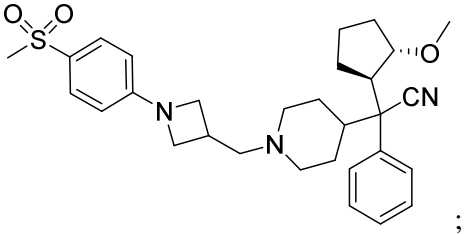
170  ;

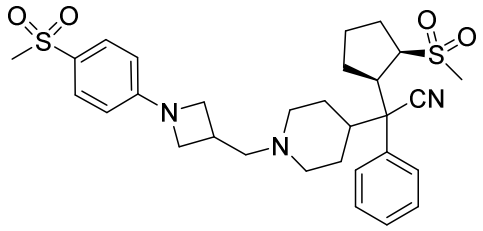
171  ;

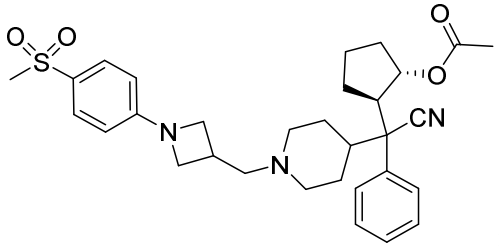
178  ;

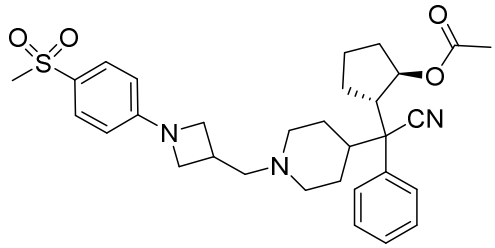
179  ;

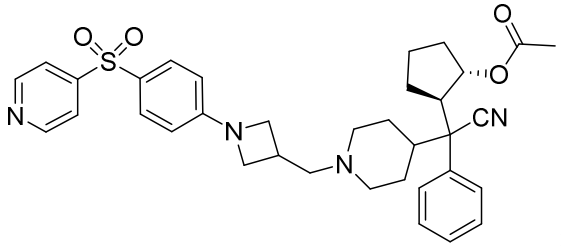
180  ;

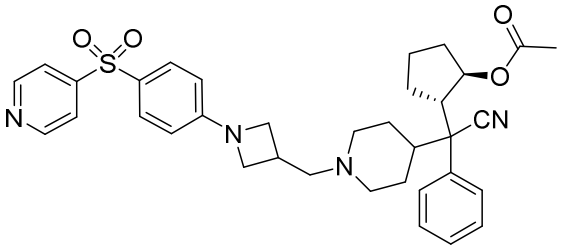
181  ;

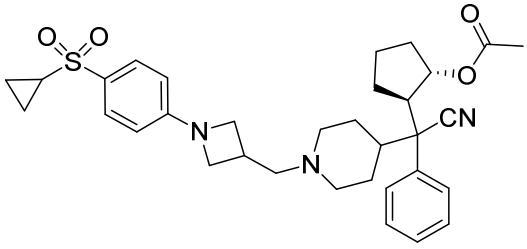
182  ;

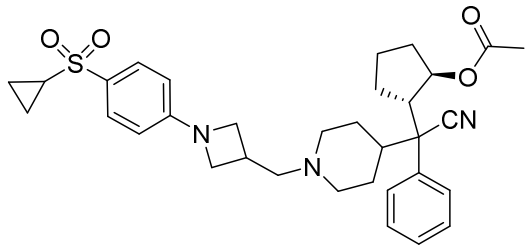
183  ;

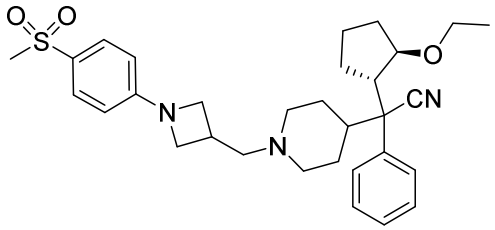
184  ;

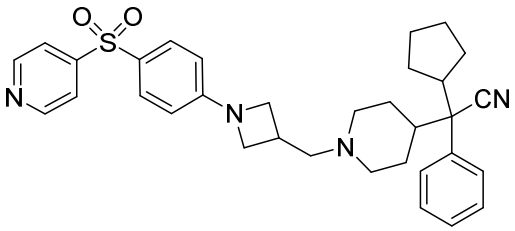
185  ;

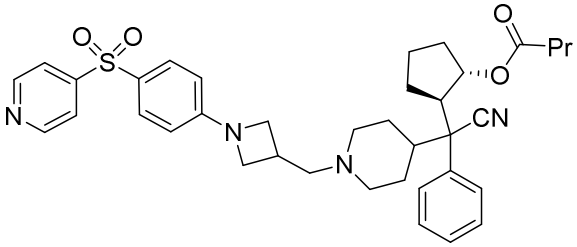
186  ;

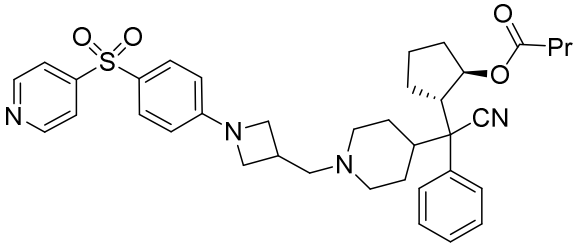
187  ;

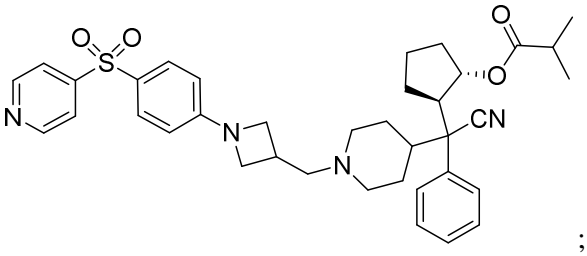
188  ;

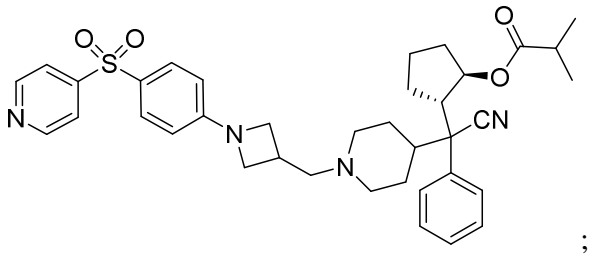
189  ;

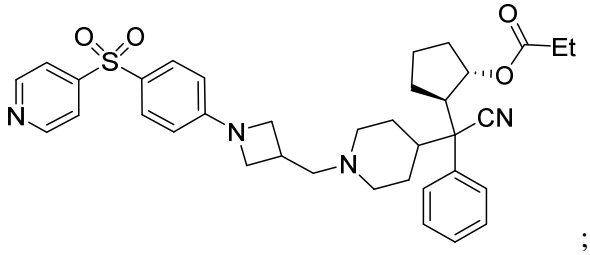
190  ;

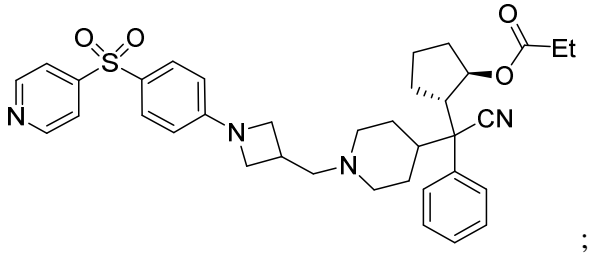
191  ;

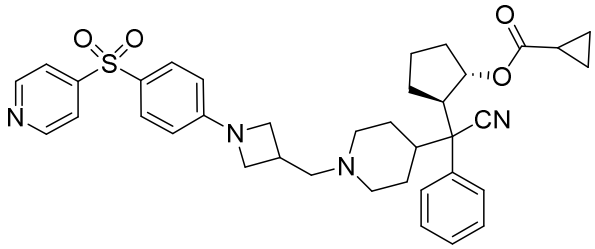
192  ;

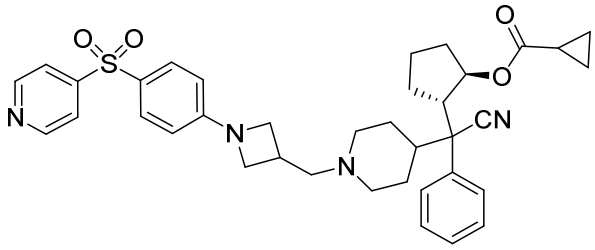
193  ;

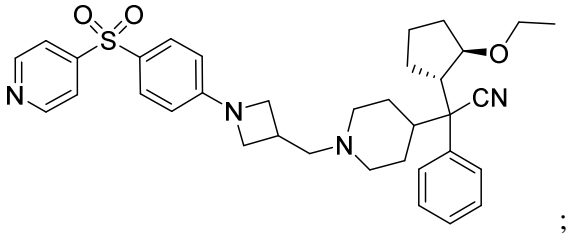
194  ;

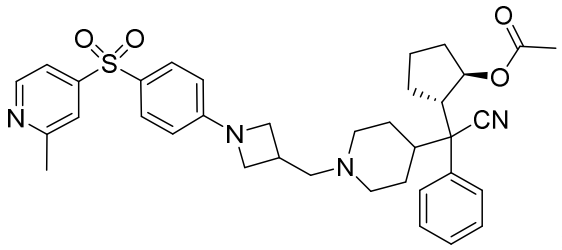
195  ;

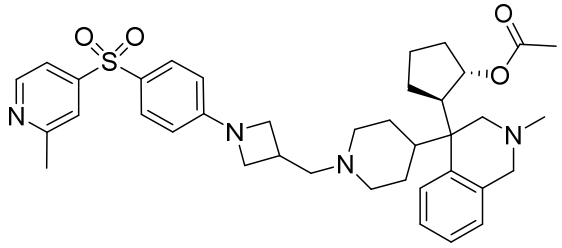
196  ;

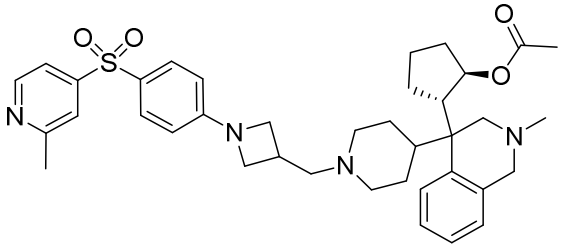
197  ;

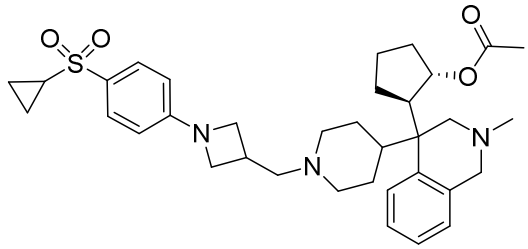
198  ;

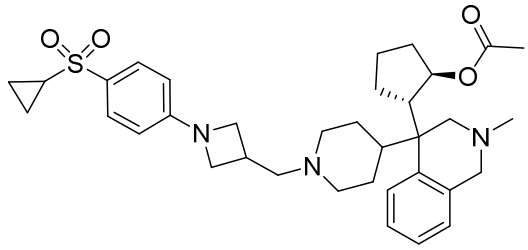
199  ;

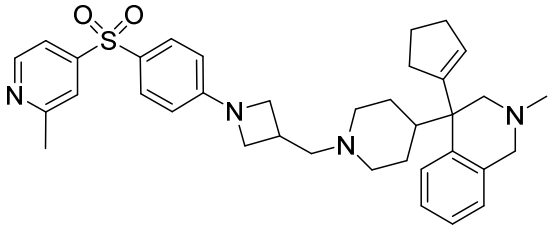
200  ;

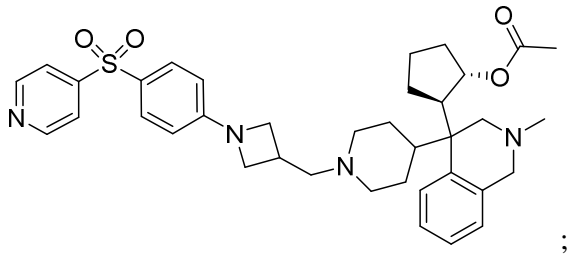
201  ;

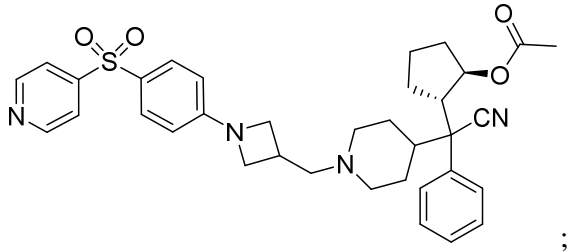
202  ;

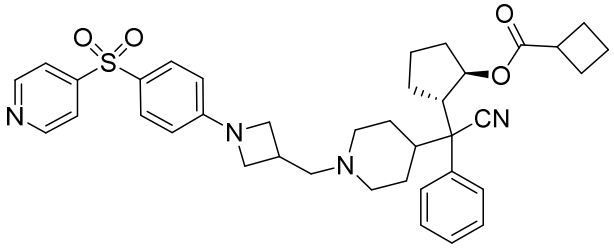
203  ;

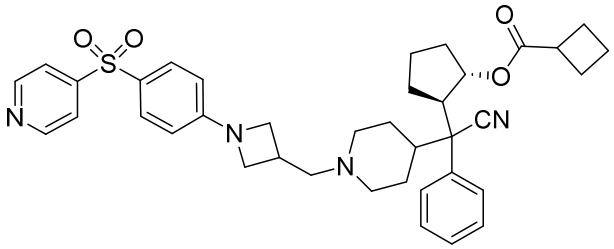
204  ;

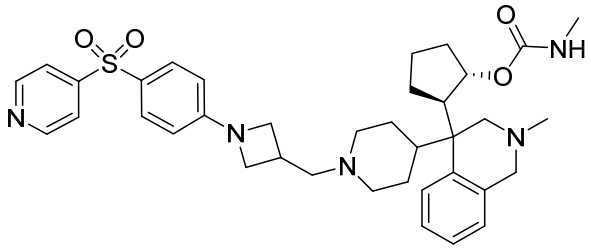
205  ;

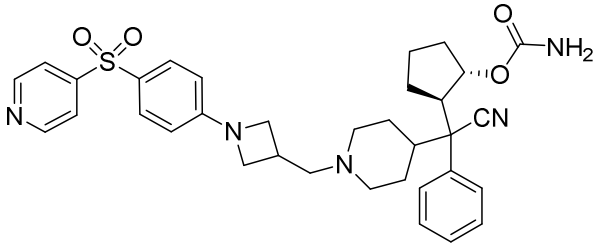
206  ;

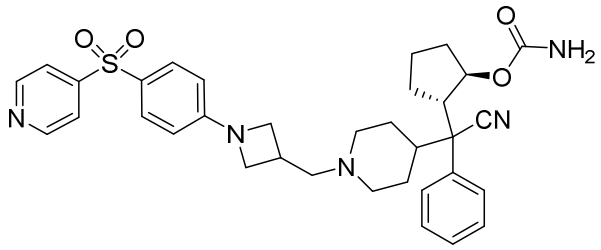
207  ;

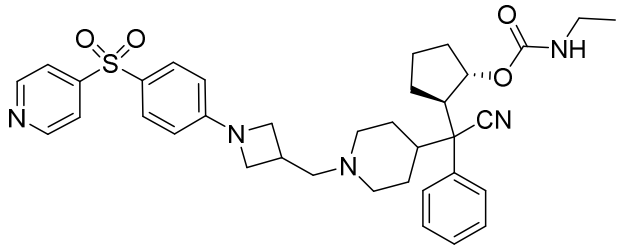
208  ;

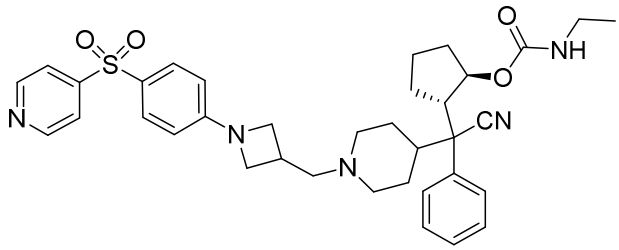
209  ;

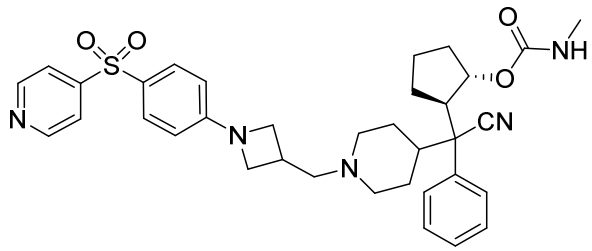
210  ;

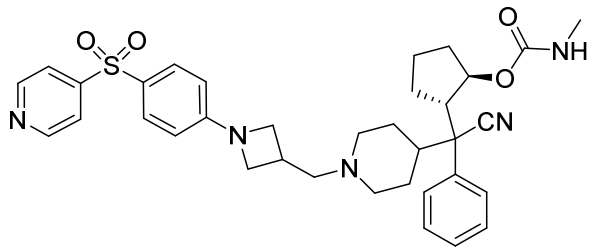
211  ;

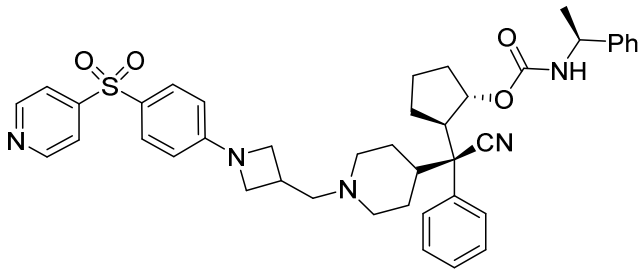
212  ;

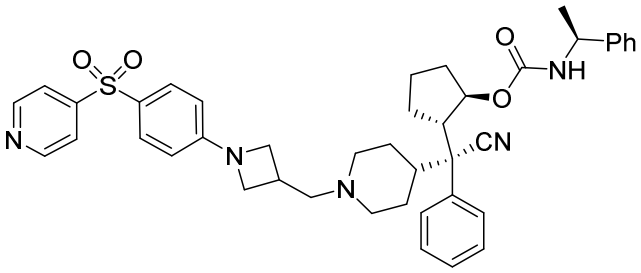
213  ;

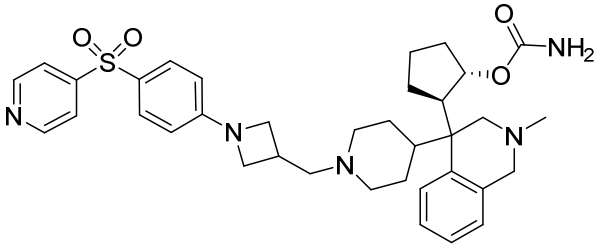
214  ;

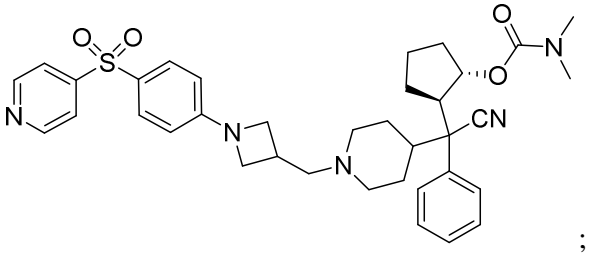
215  ;

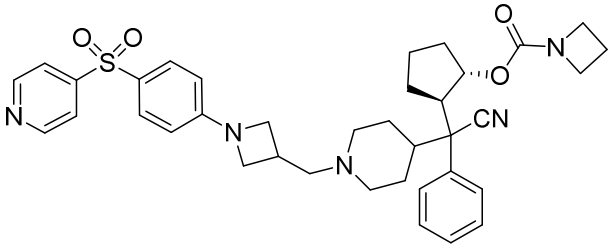
216  ;

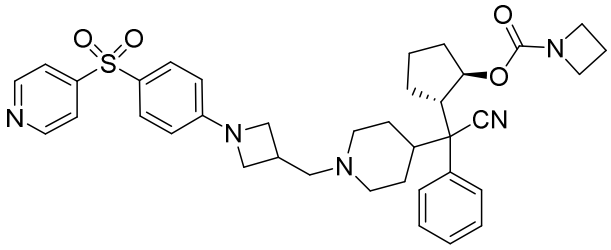
217  ;

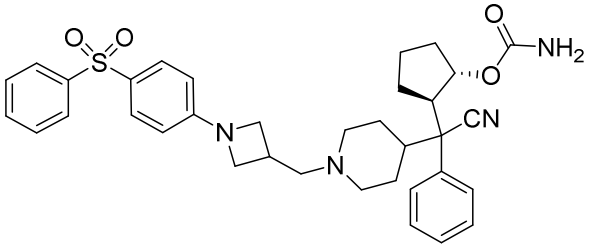
218  ;

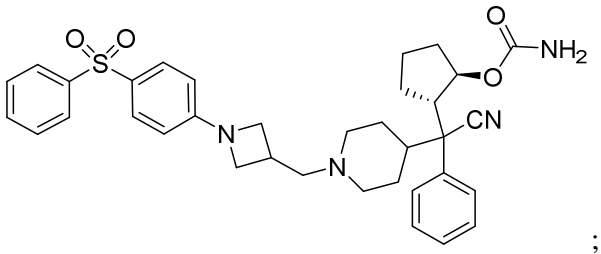
219  ;

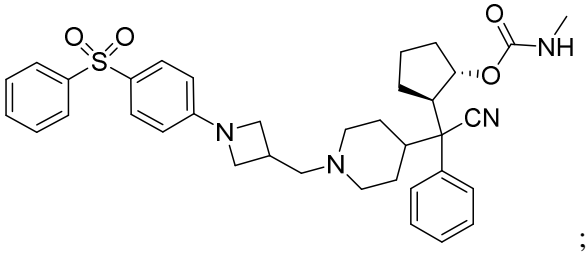
220  ;

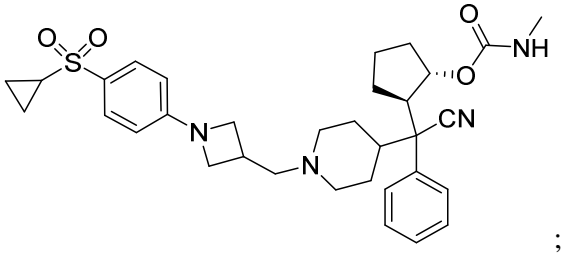
221  ;

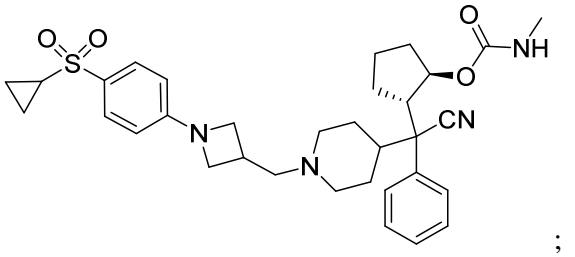
222  ;

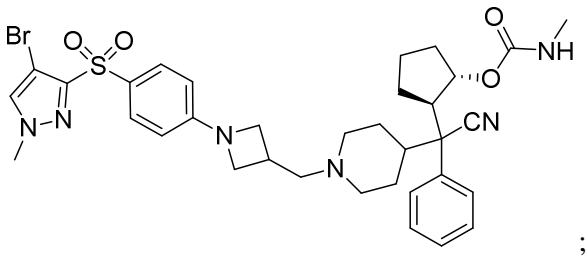
223  ;

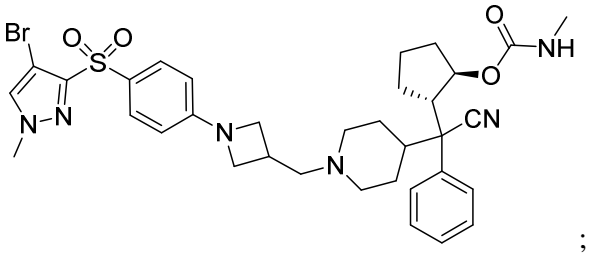
224  ;

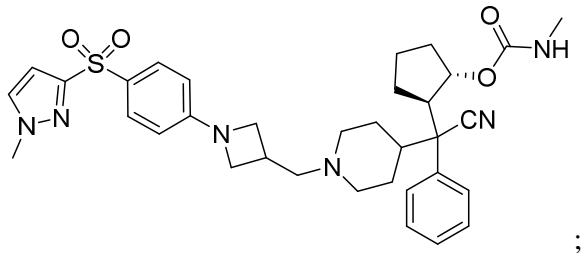
225  ;

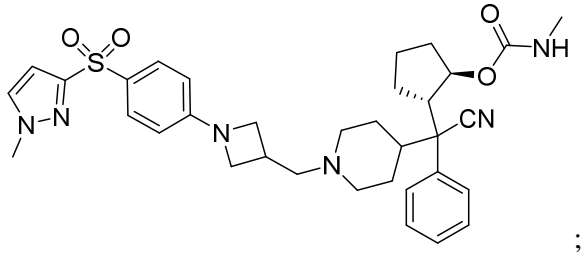
226  ;

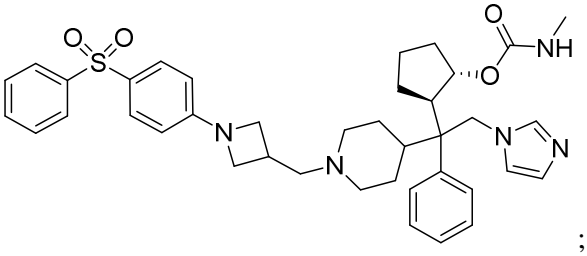
227  ;

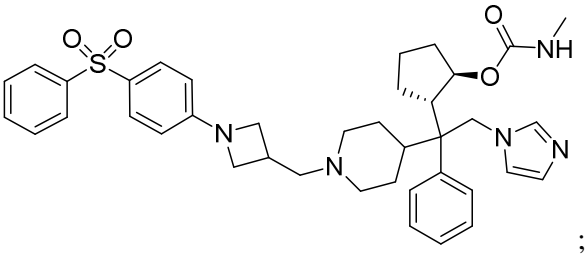
228  ;

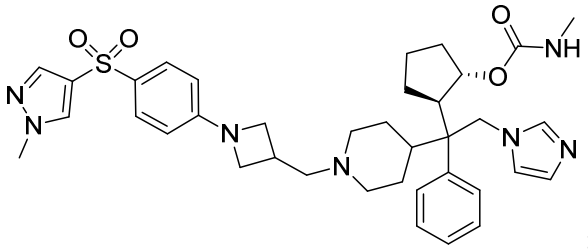
229  ;

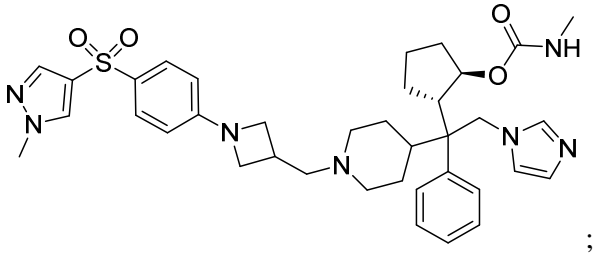
230  ;

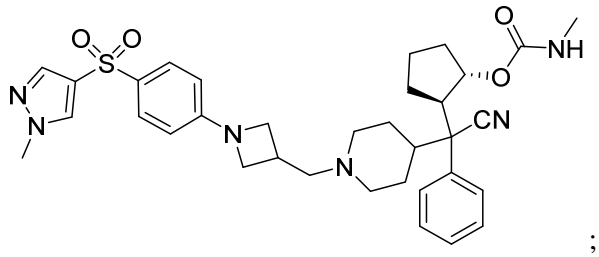
231  ;

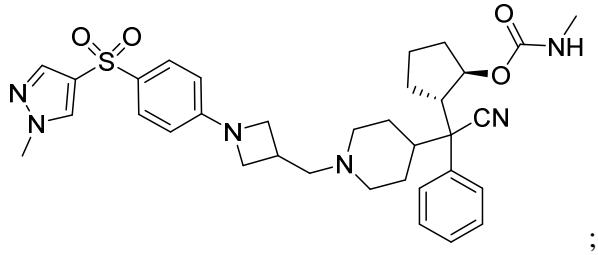
236  ;

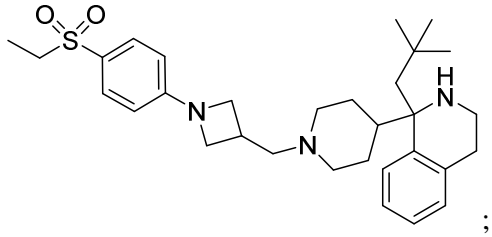
237  ;

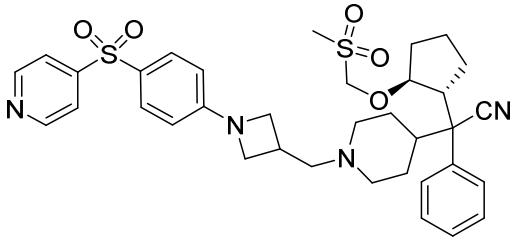
238  ;

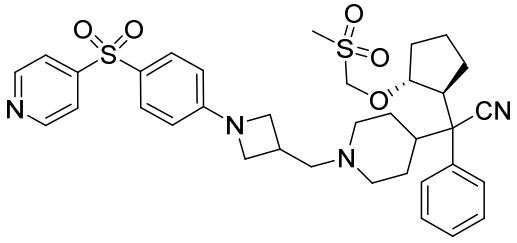
239  ;

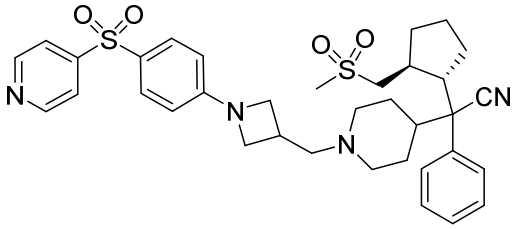
240  ;

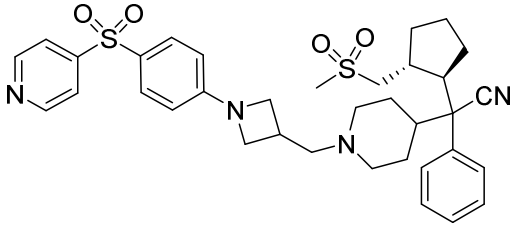
241  ;

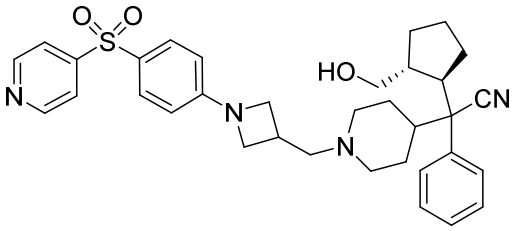
248  ;

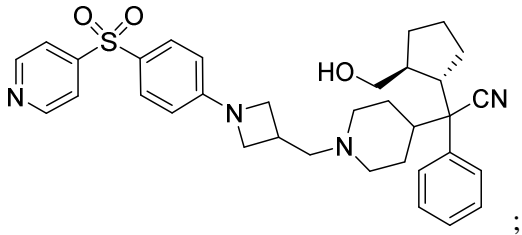
253  ;

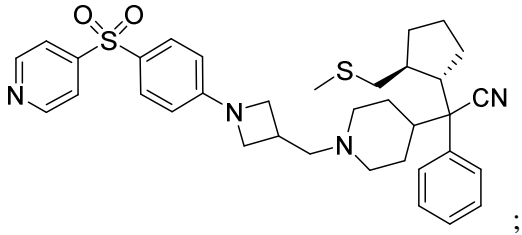
254  ;

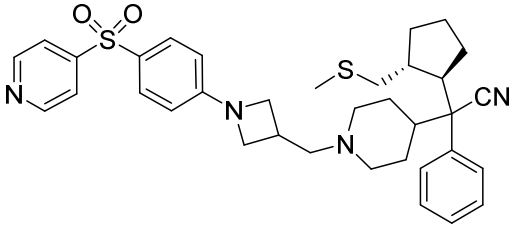
255  ;

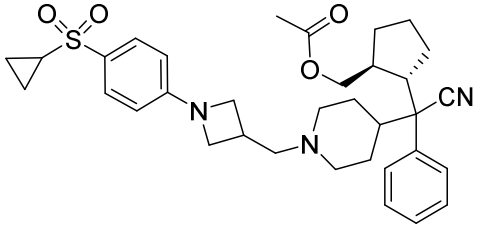
256  ;

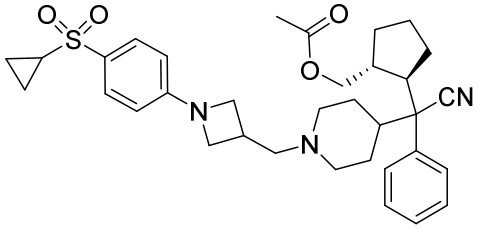
257  ;

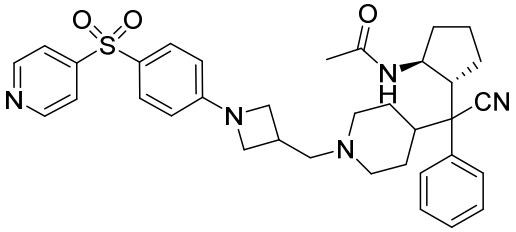
258  ;

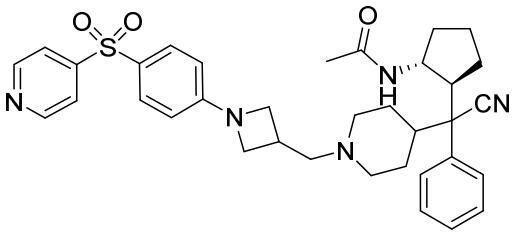
259  ;

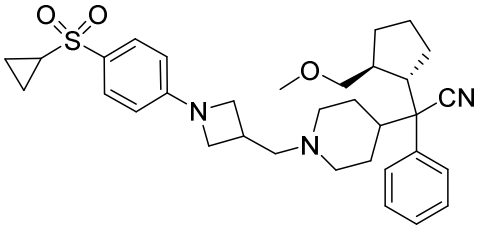
260  ;

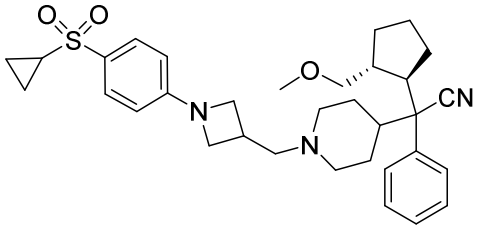
261  ;

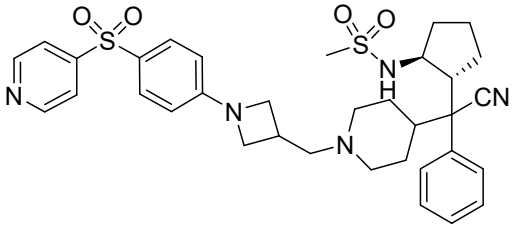
262  ;

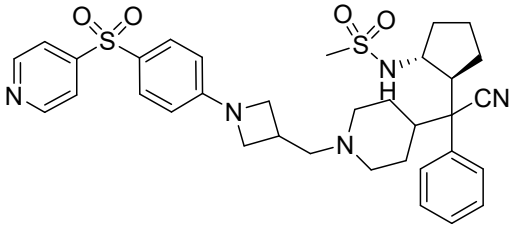
263  ;

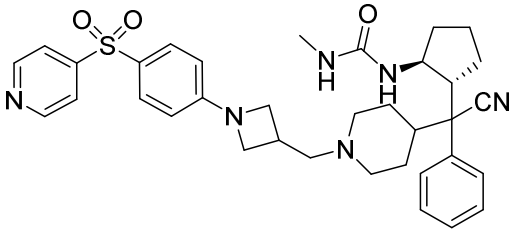
264  ;

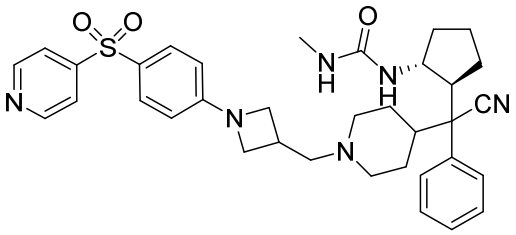
265  ;

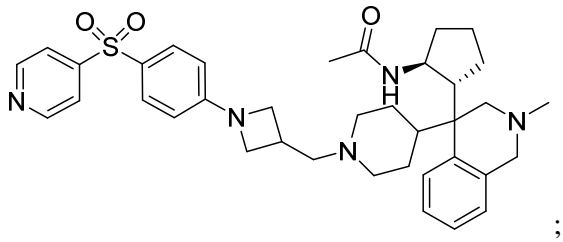
266  ;

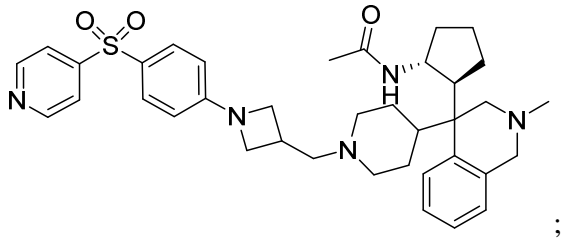
267  ;

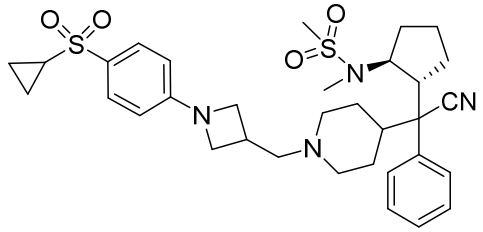
268  ;

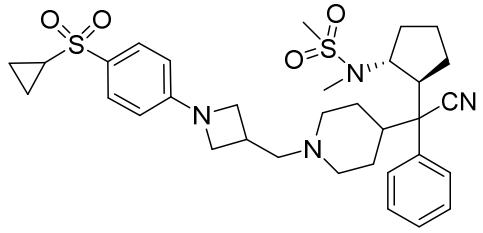
269  ;

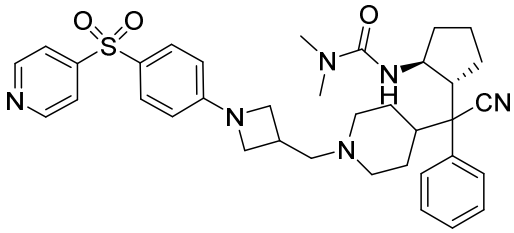
270  ;

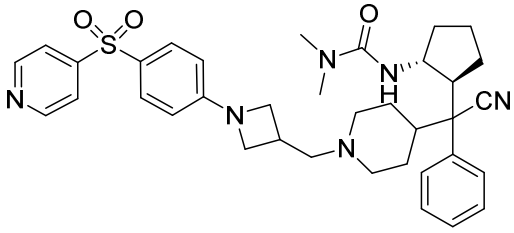
271  ;

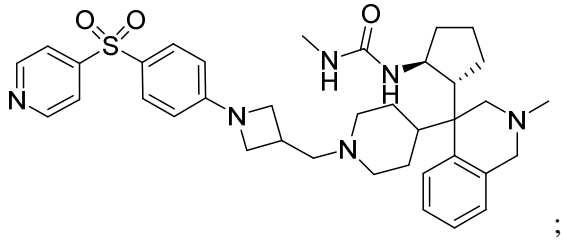
272  ;

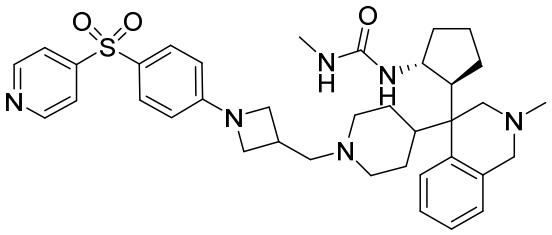
273  ;

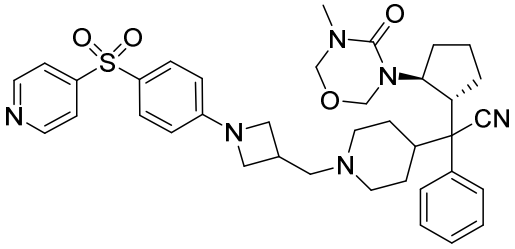
274  ;

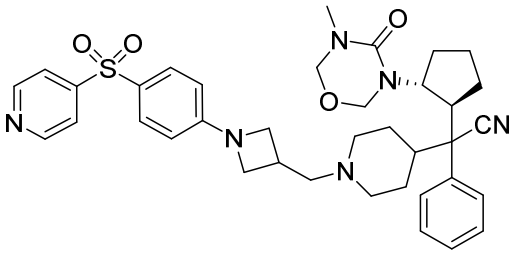
275  ;

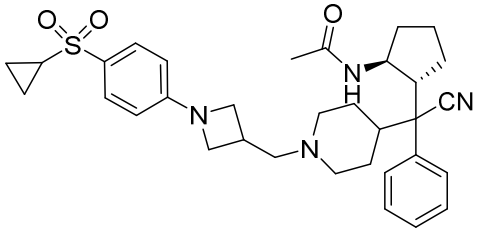
276  ;

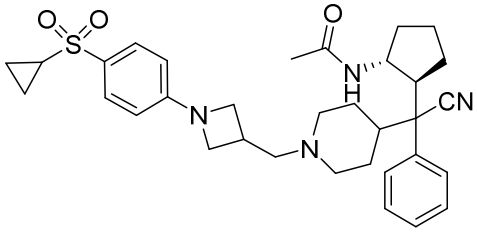
277  ;

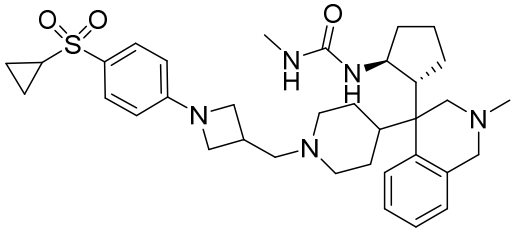
278  ;

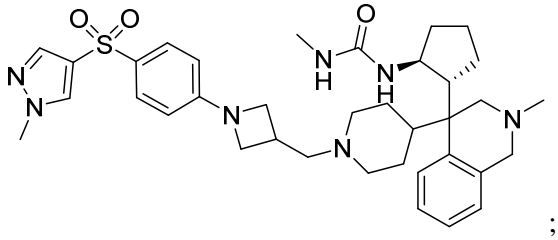
279  ;

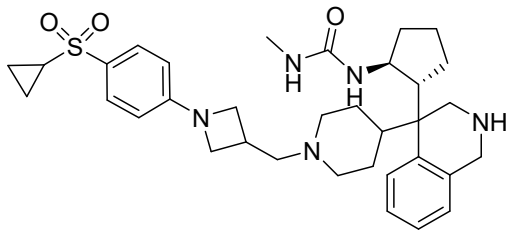
280  ;

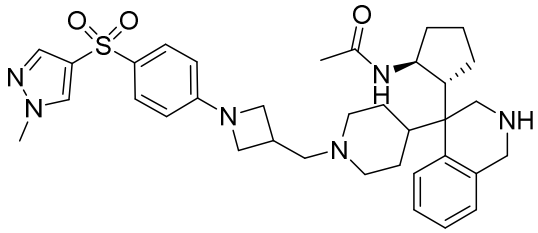
281  ;

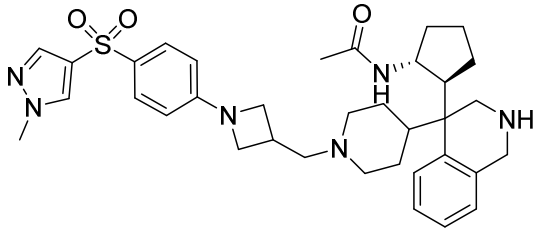
282  ;

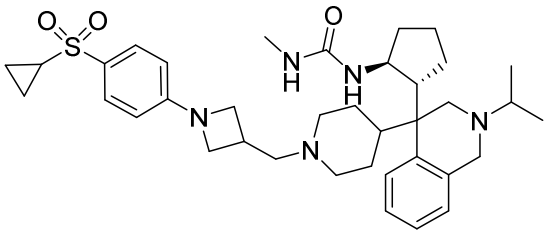
283  ;

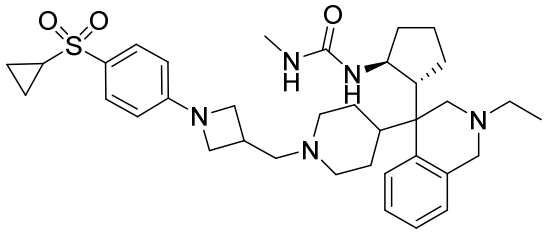
284  ;

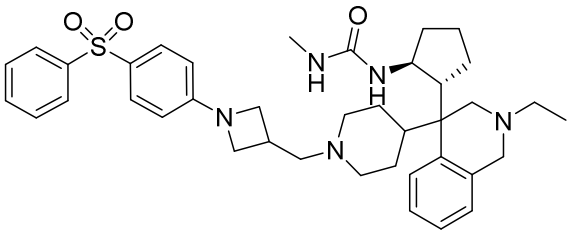
285  ;

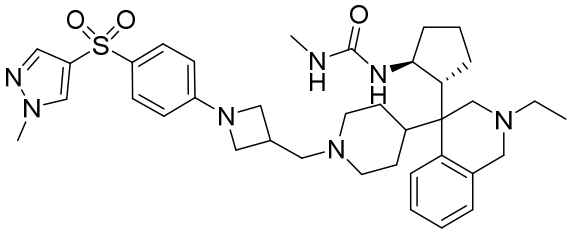
286  ;

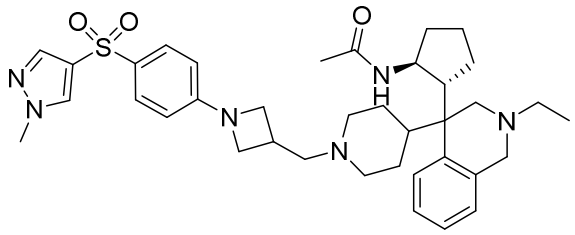
287  ;

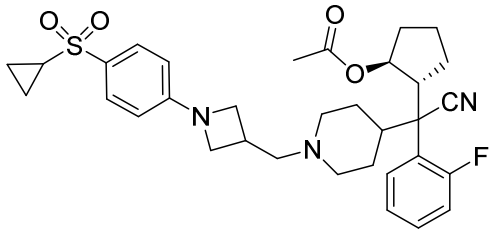
288  ;

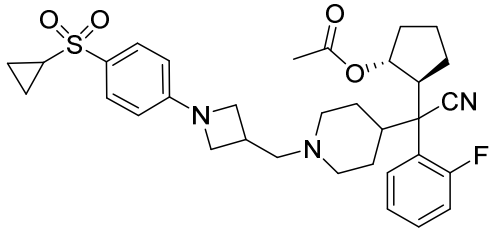
289  ;

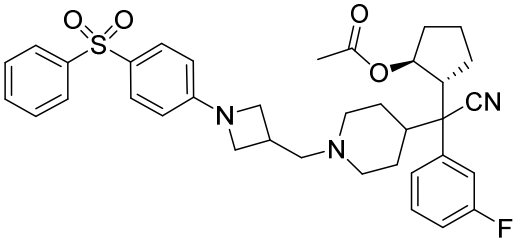
290  ;

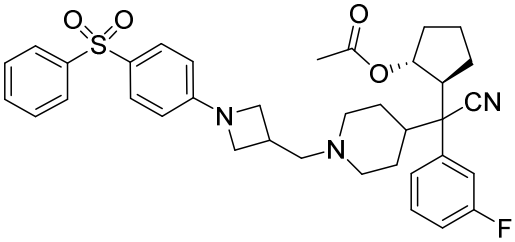
291  ;

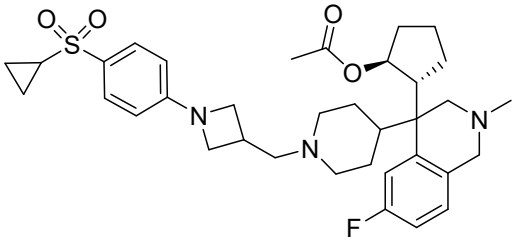
292  ;

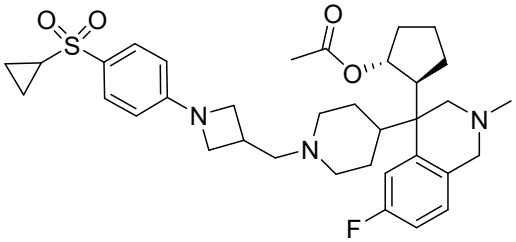
310  ;

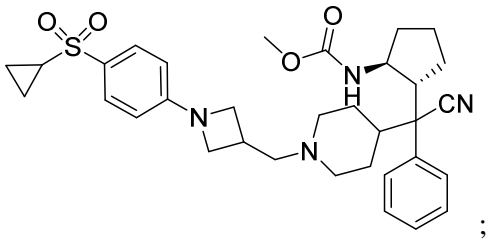
311  ;

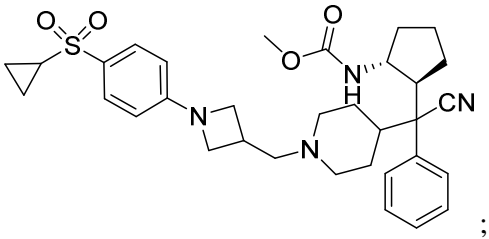
312  ;

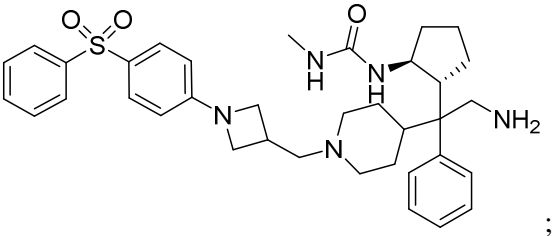
313  ;

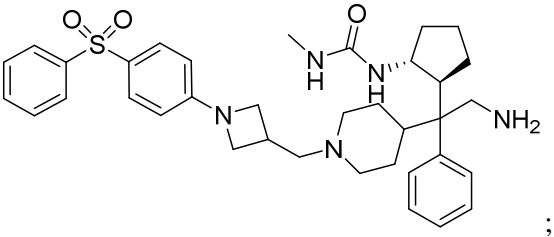
316  ;

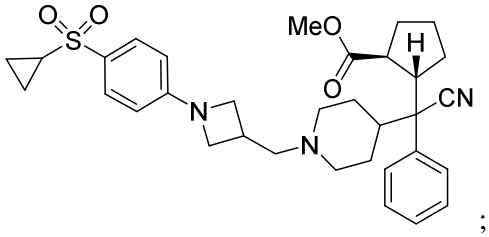
317  ;

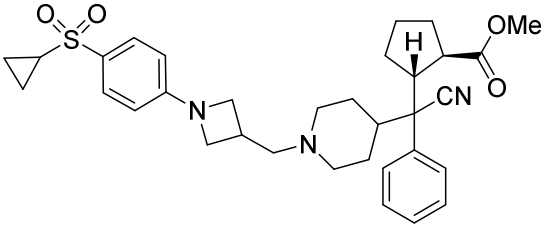
319  ;

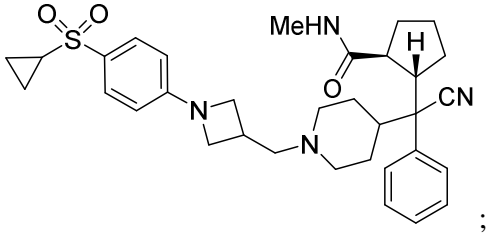
320  ;

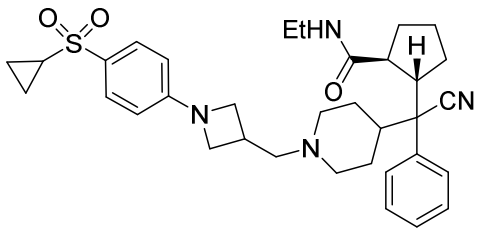
321  ;

322  ;

332  ;

333  ;

334  ;

335 

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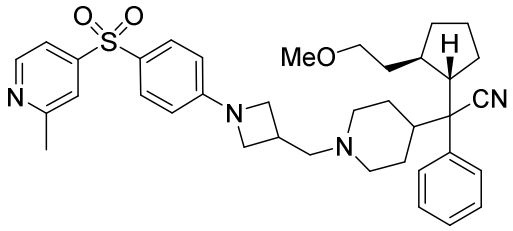
336 

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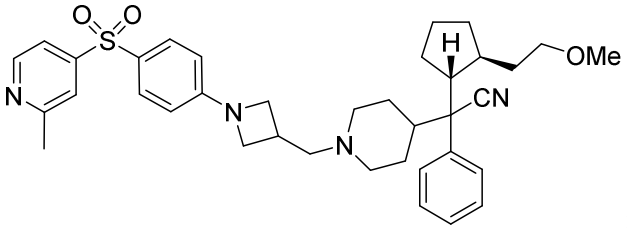
337 

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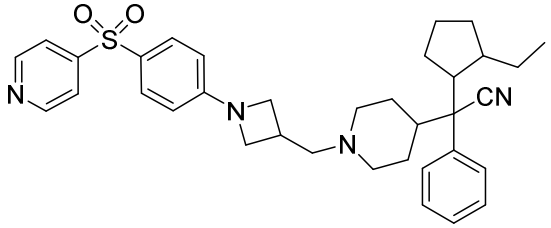
338 

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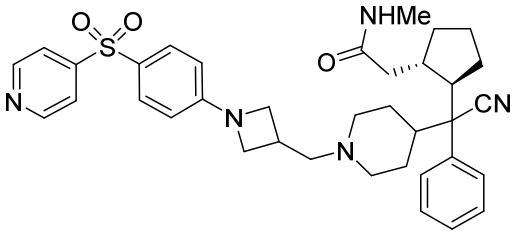
339 

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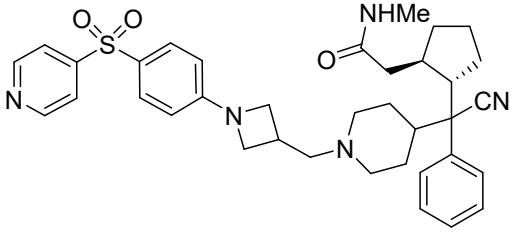
340 

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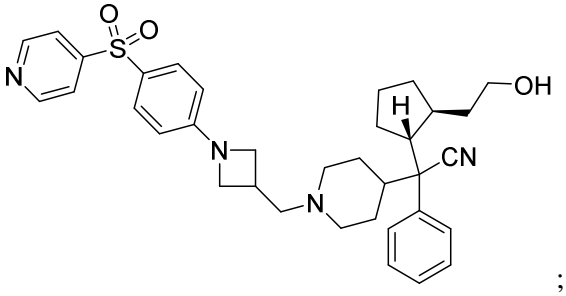
341 

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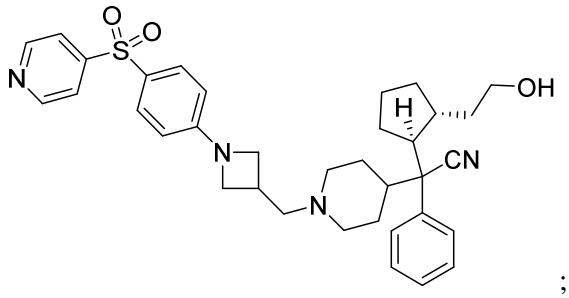
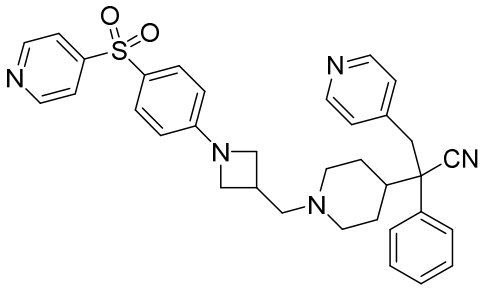
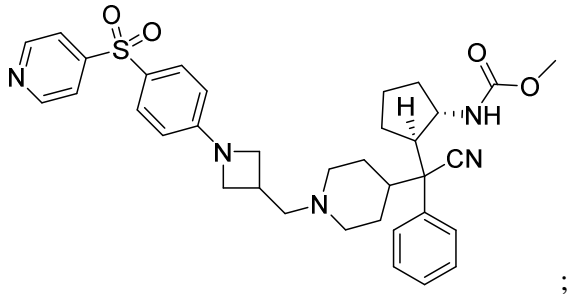
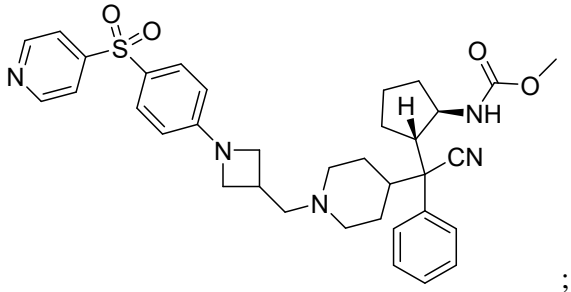
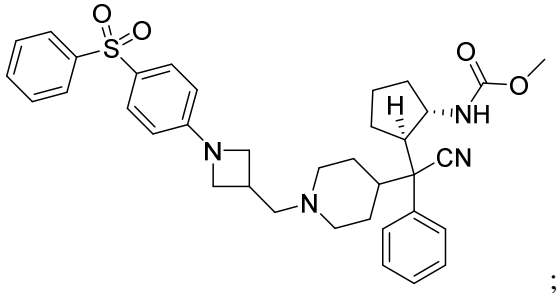
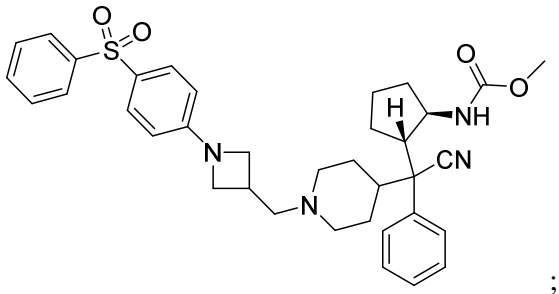
342  ;

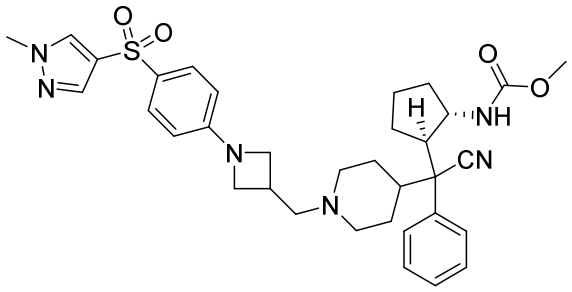
343  ;

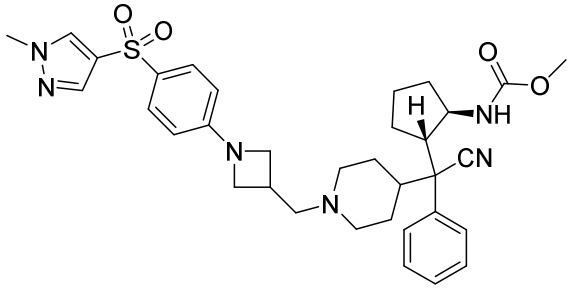
345  ;

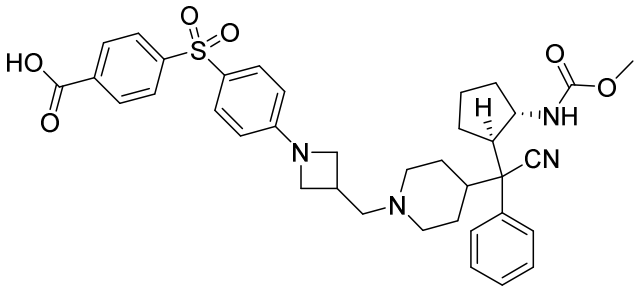
346  ;

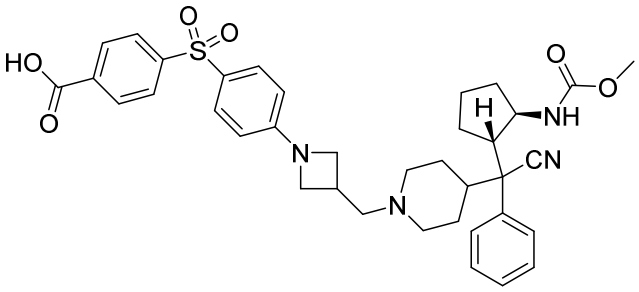
347  ;

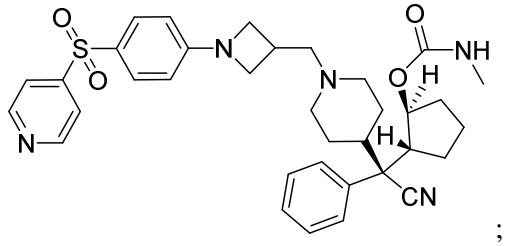
348  ;

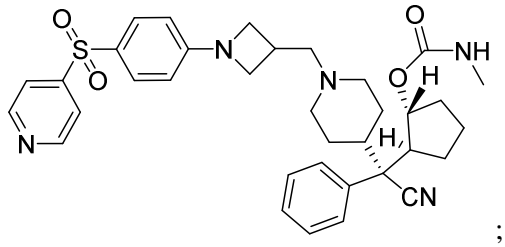
349  ;

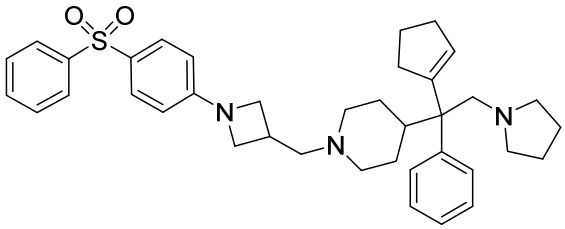
350  ;

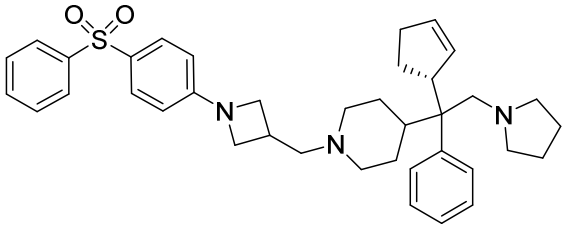
351  ;

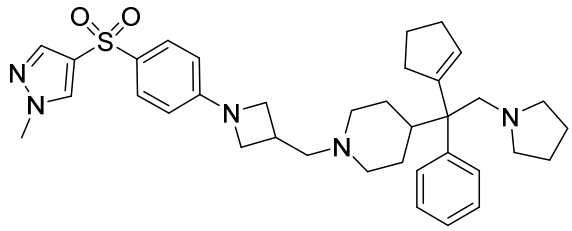
352  ;

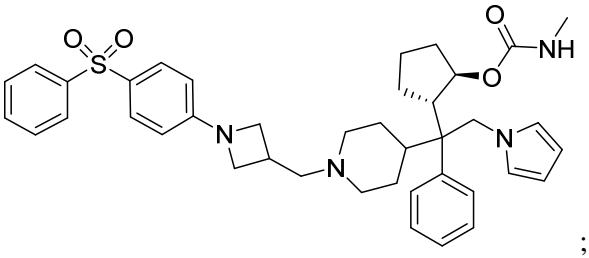
353  ;

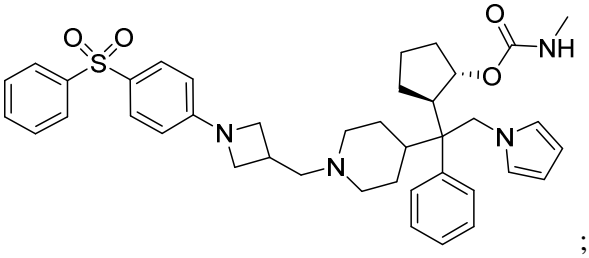
354  ;

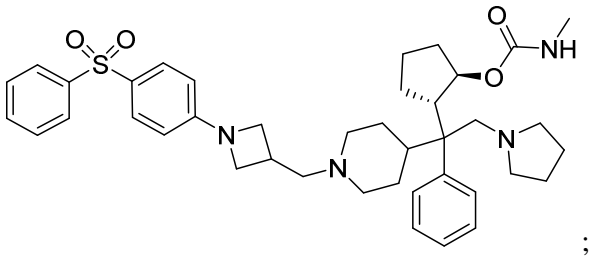
355  ;

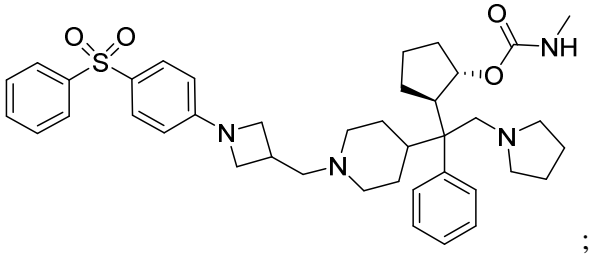
356  ;

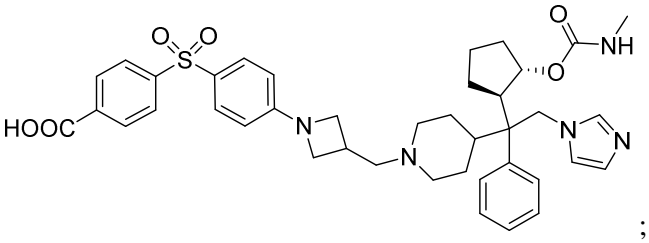
357  ;

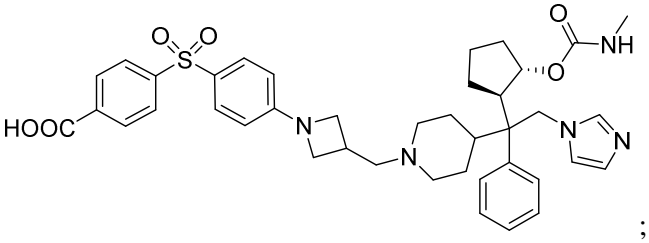
358  ;

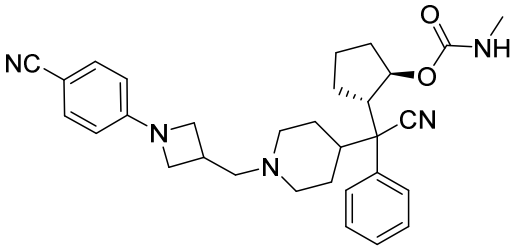
359  ;

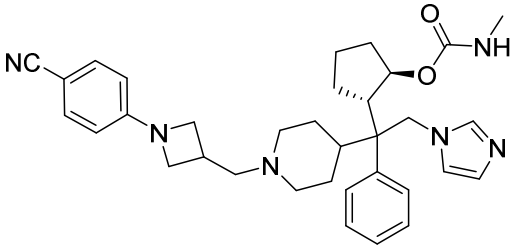
360  ;

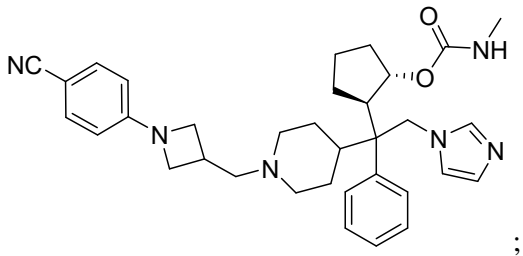
361  ;

362  ;

363  ;

364  ;

365  ;

366 

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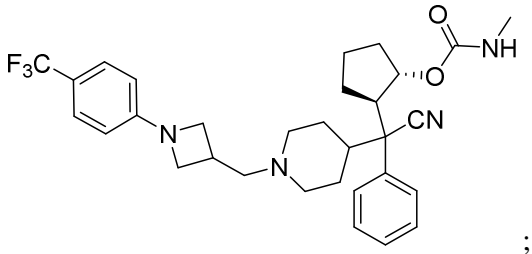
367 

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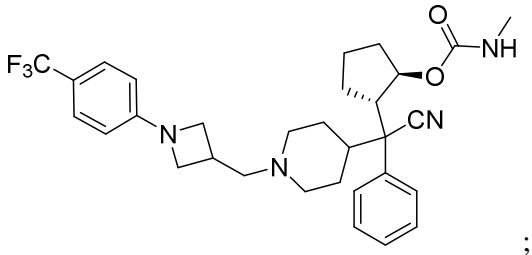
368 

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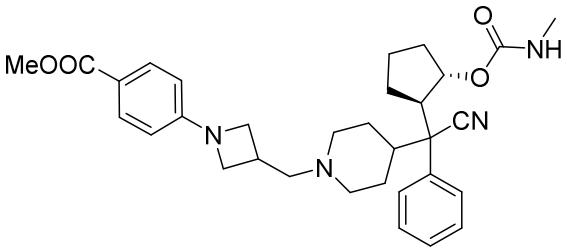
373 

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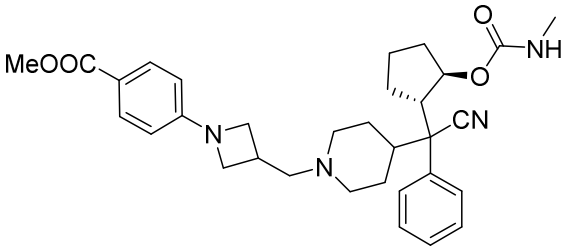
374 

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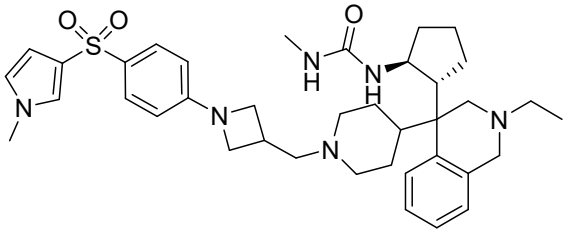
375 

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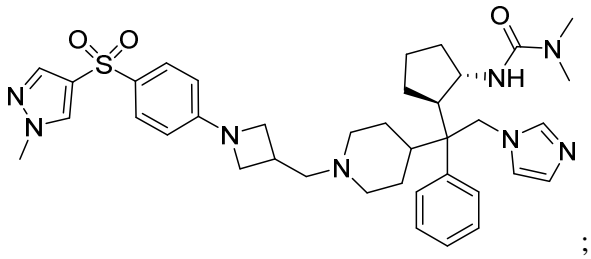
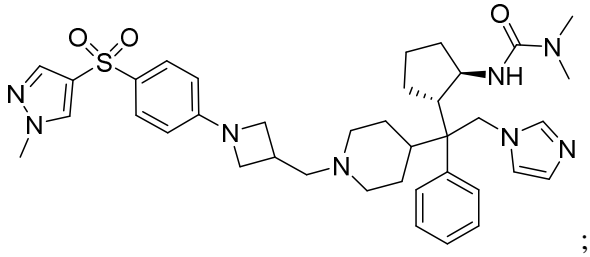
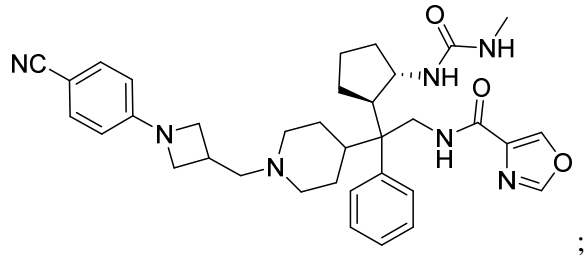
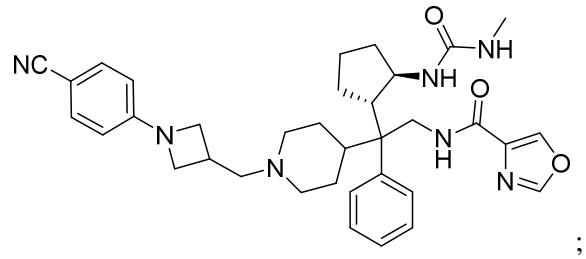
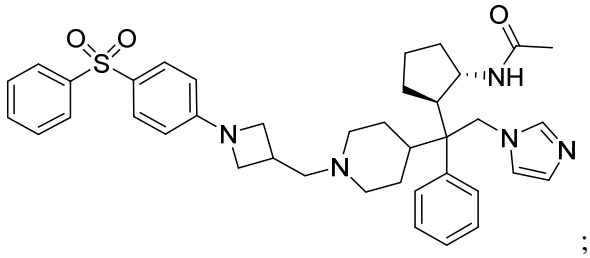
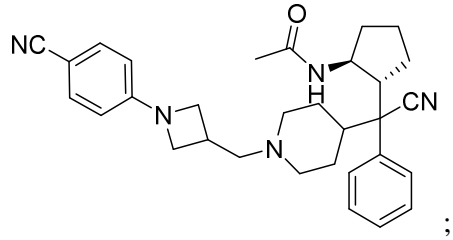
376  ;

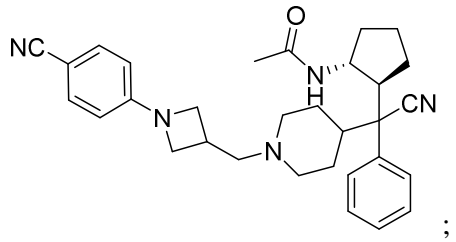
377  ;

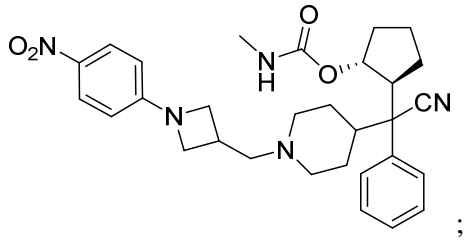
378  ;

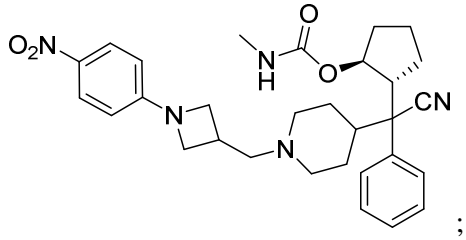
379  ;

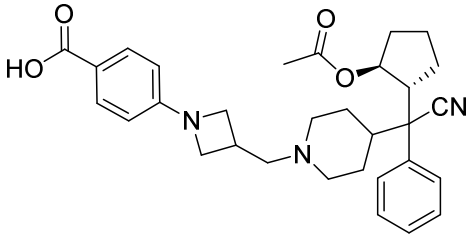
381  ;

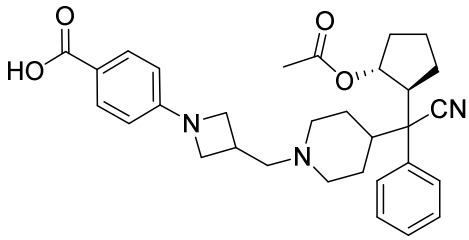
382  ;

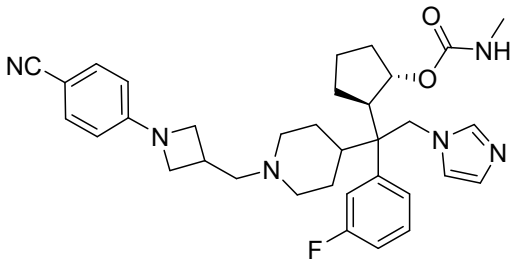
383  ;

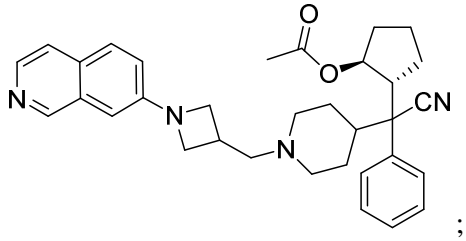
384  ;

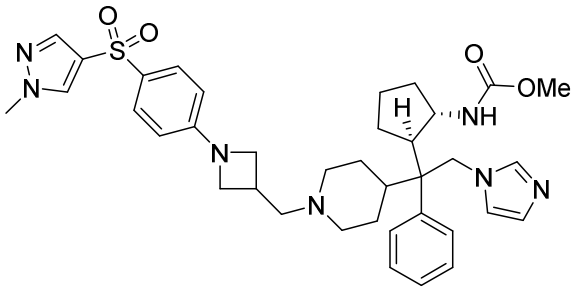
385  ;

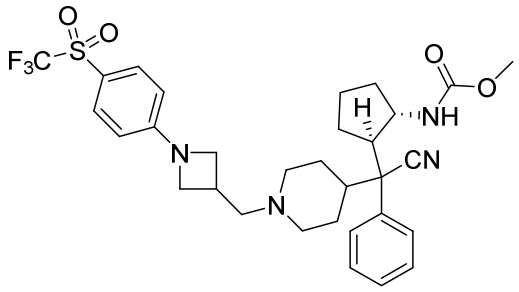
388  ;

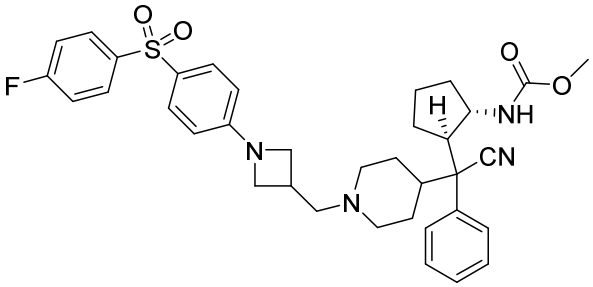
389  ;

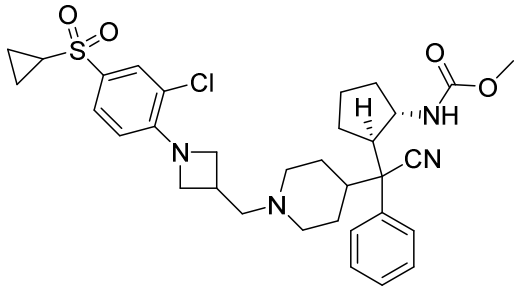
390  ;

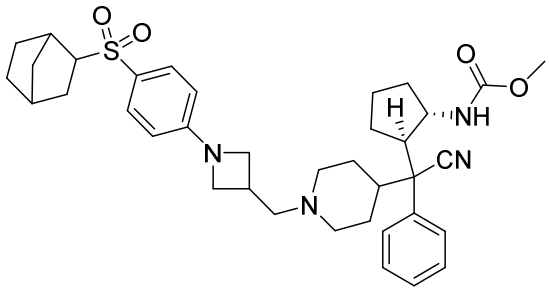
391  ;

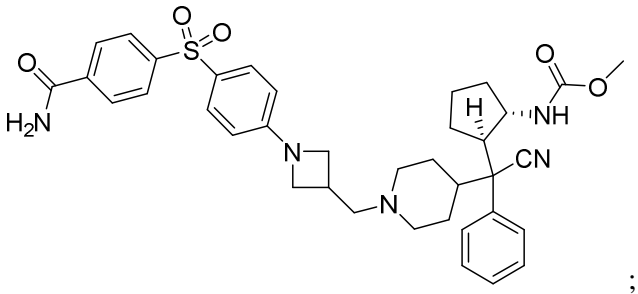
392  ;

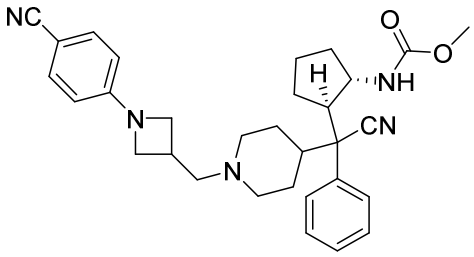
393  ;

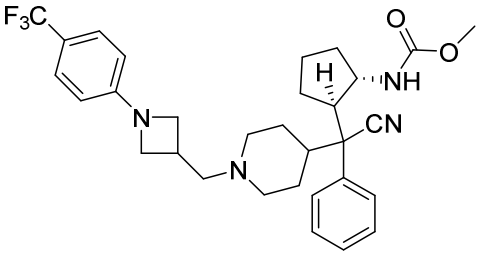
394  ;

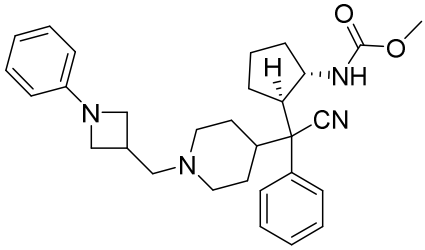
395  ;

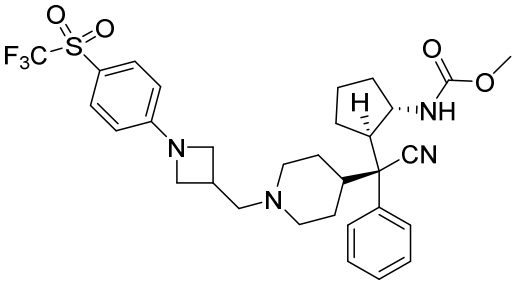
396  ;

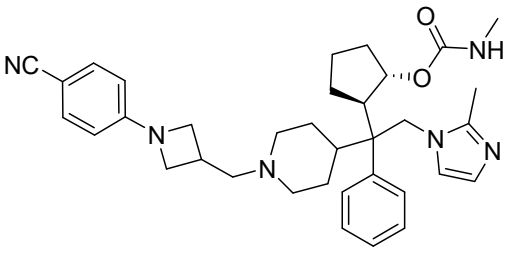
399  ;

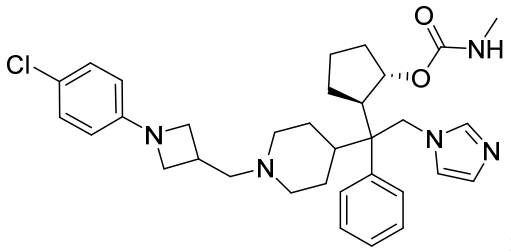
400  ;

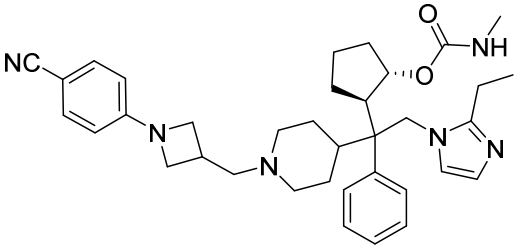
401  ;

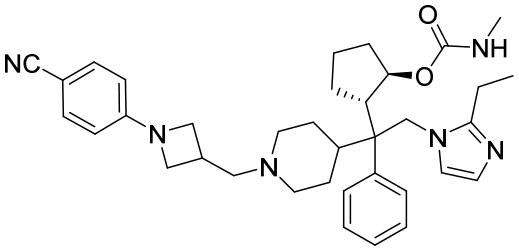
402  ;

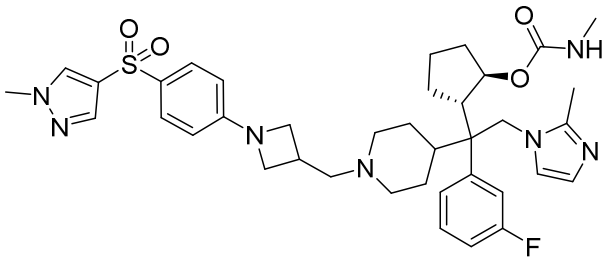
403  ;

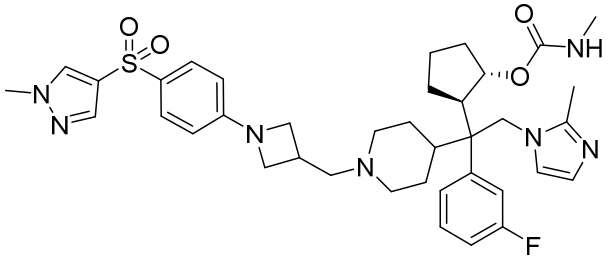
406  ;

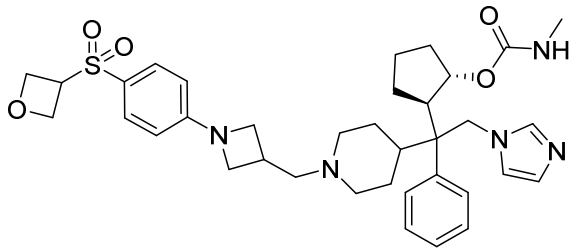
407  ;

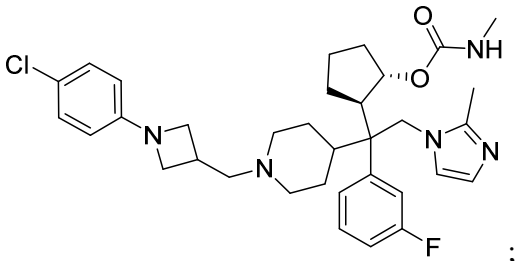
408  ;

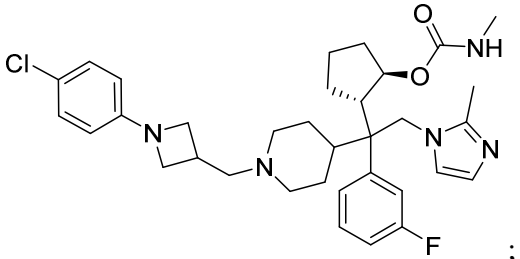
409  ;

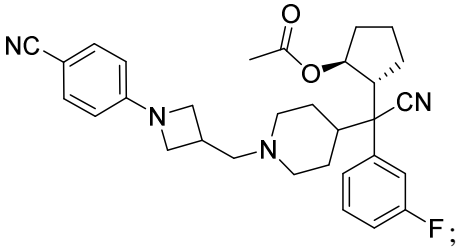
410  ;

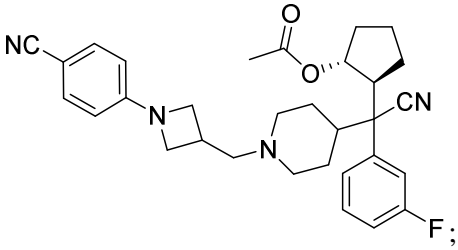
411  ;

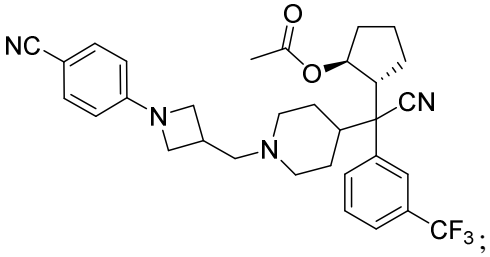
412  ;

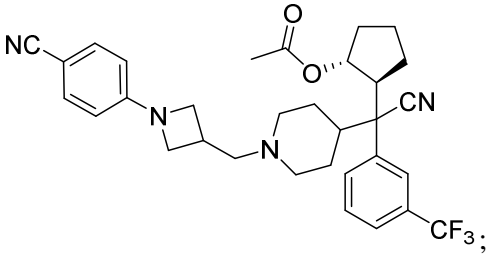
413  ;

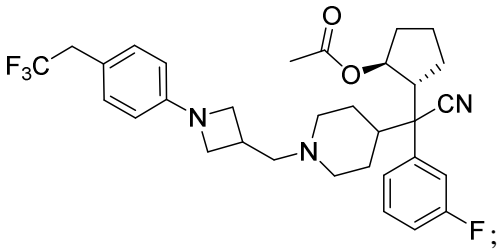
414  ;

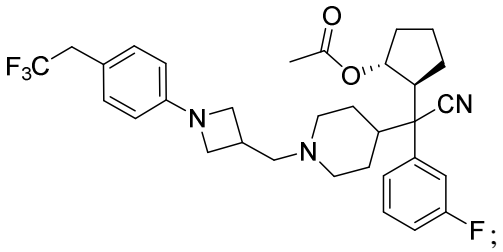
415  ;

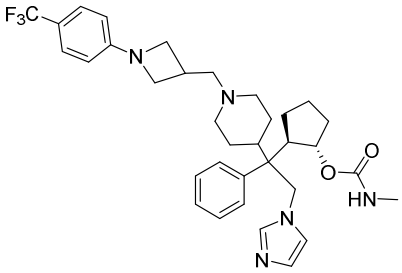
416  ;

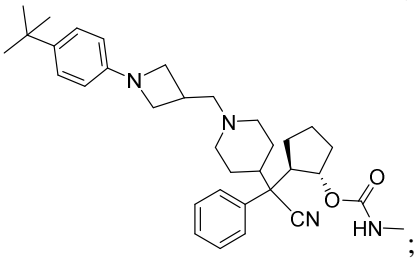
417  ;

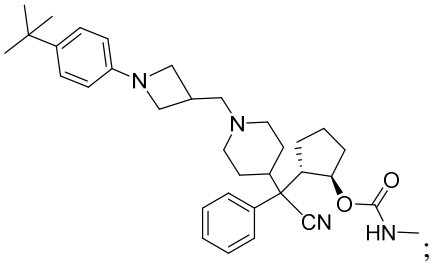
418  ;

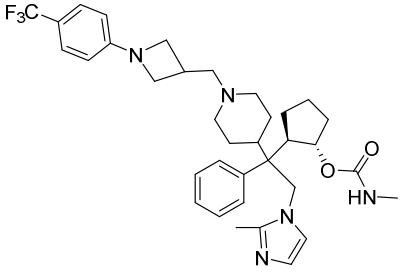
419  ;

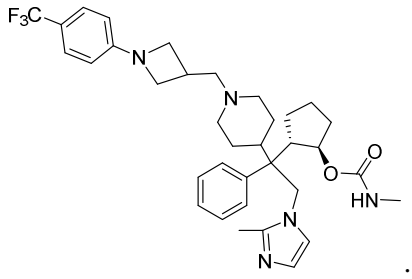
420  ;

421  ;

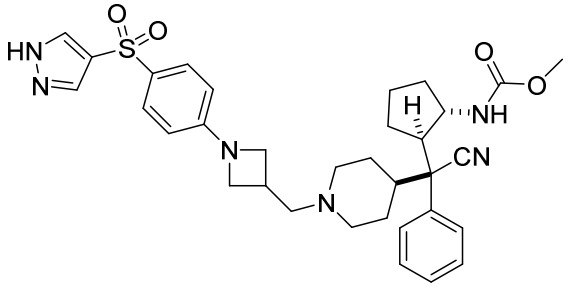
422  ;

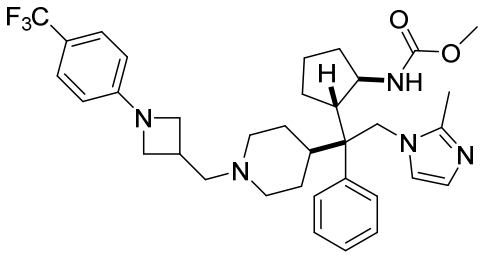
423  ;

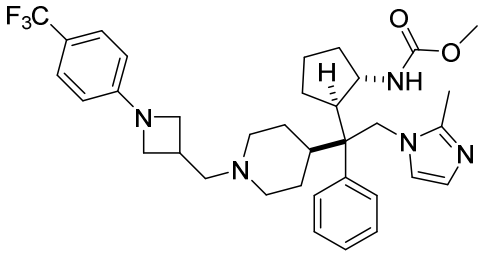
424  ; and

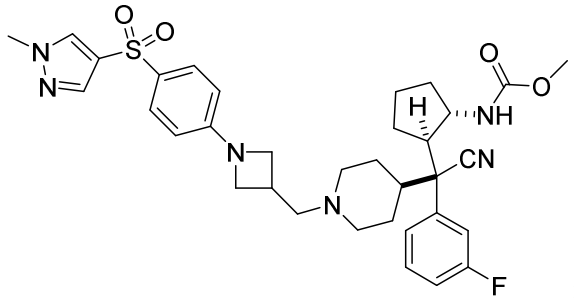
425  .

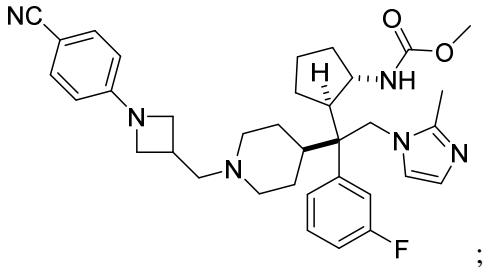
27. A compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, selected from one or more of:

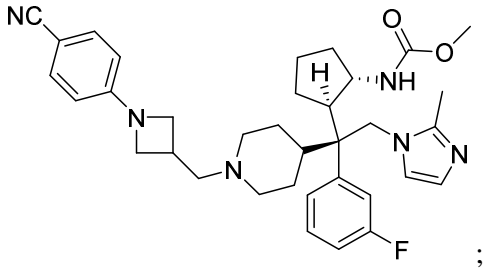
426  ;

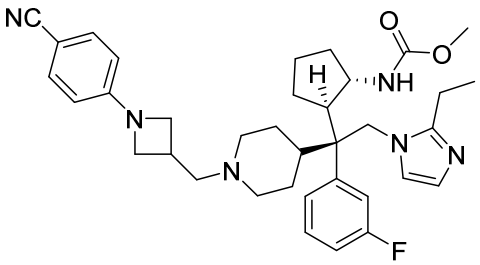
427  ;

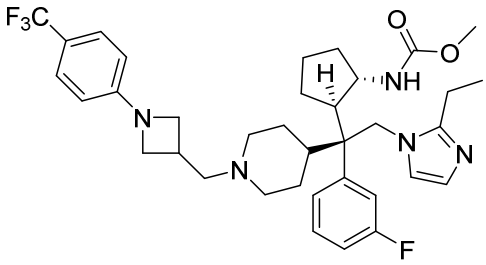
428  ;

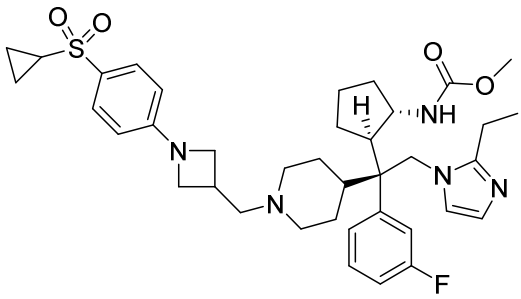
429  ;

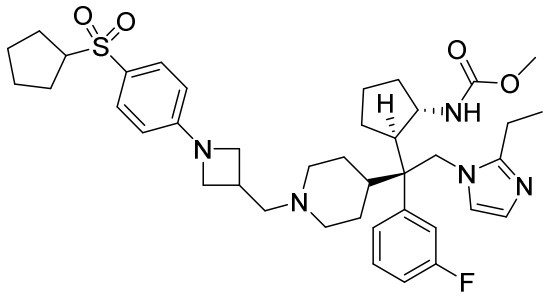
430  ;

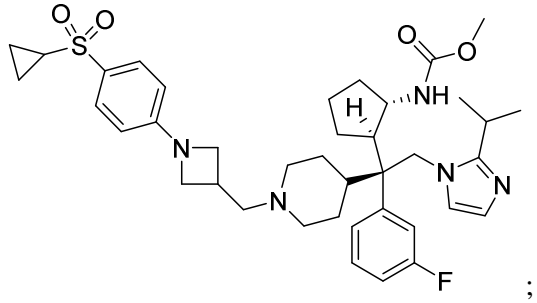
431  ;

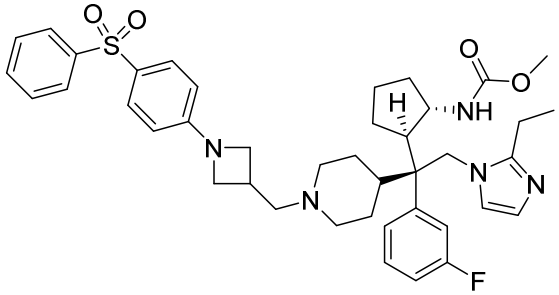
432  ;

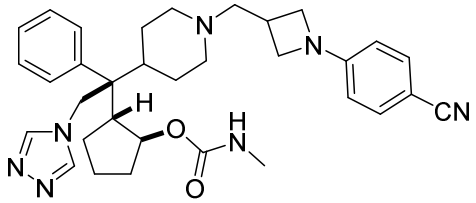
433  ;

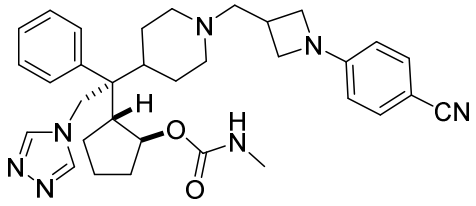
434  ;

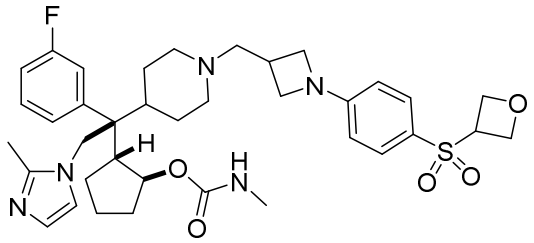
435  ;

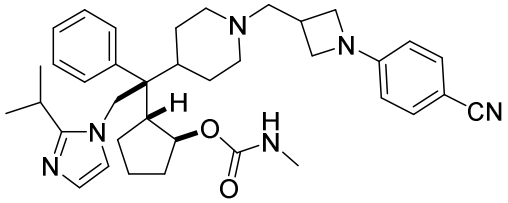
436  ;

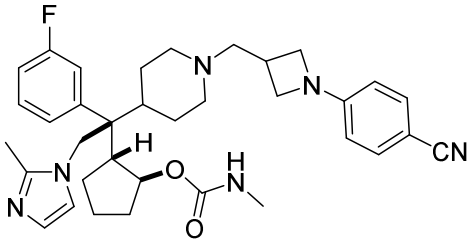
437  ;

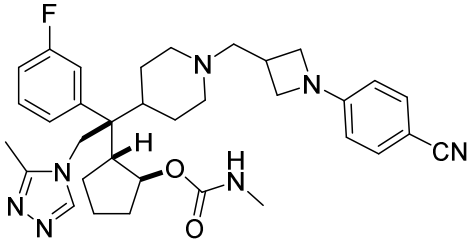
438  ;

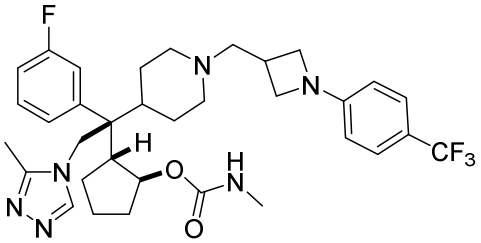
439  ;

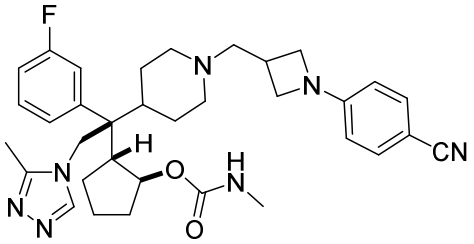
440  ;

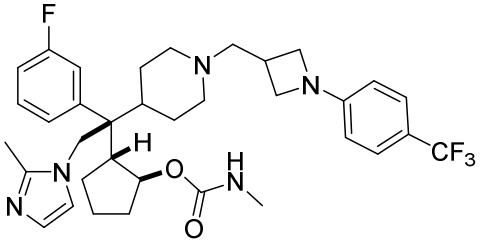
441  ;

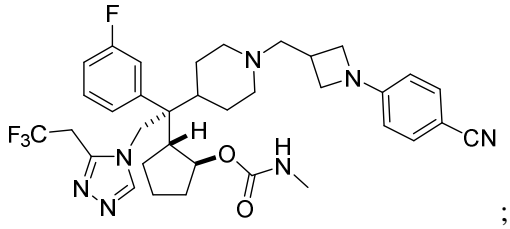
442  ;

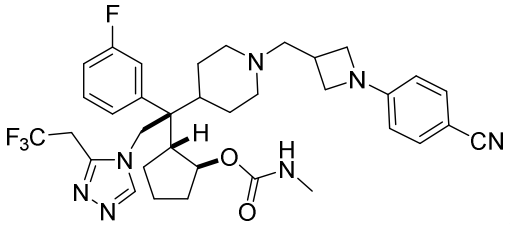
443  ;

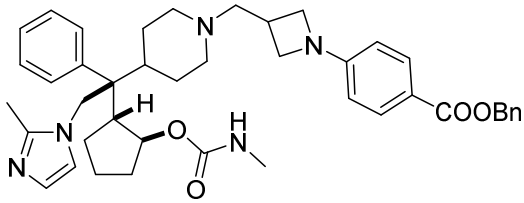
444  ;

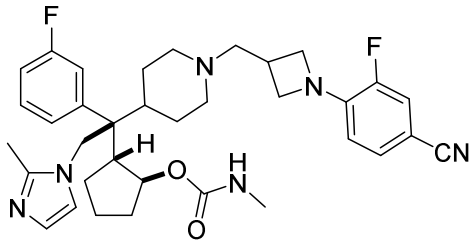
445  ;

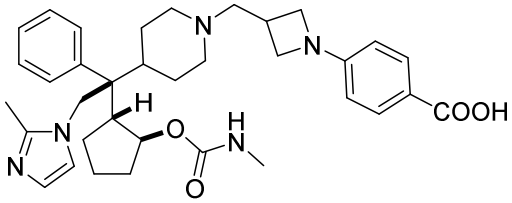
446  ;

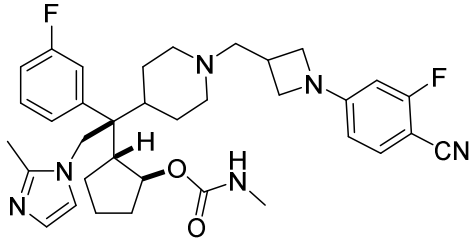
447  ;

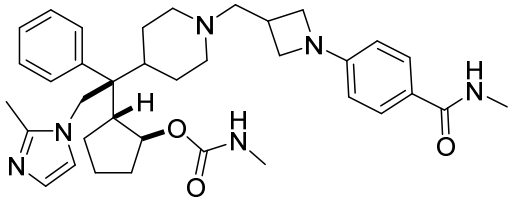
448  ;

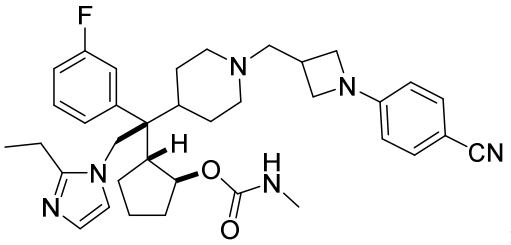
449  ;

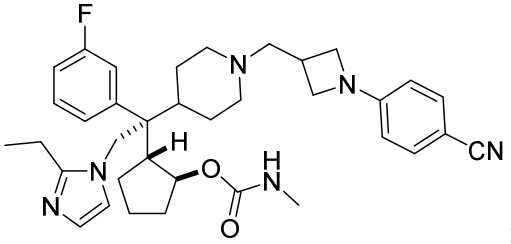
450  ;

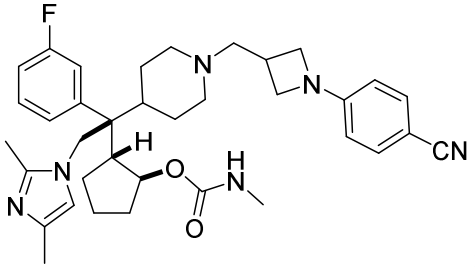
451  ;

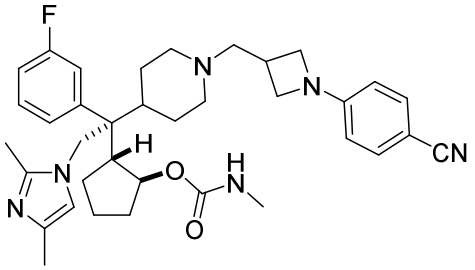
452  ;

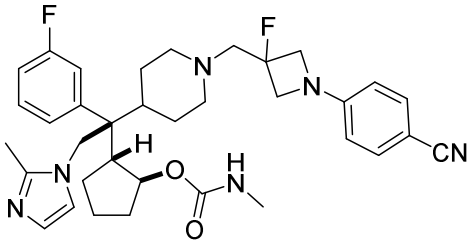
453  ;

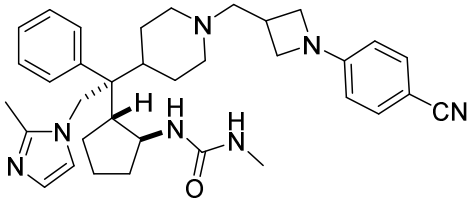
455  ;

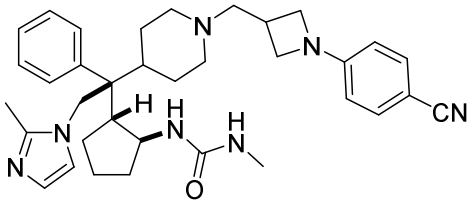
456  ;

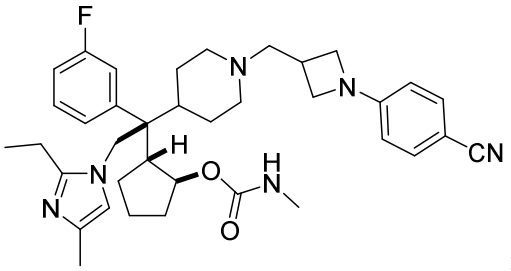
457  ;

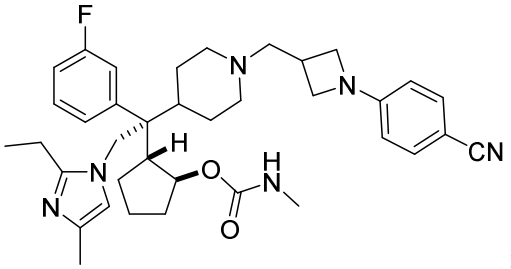
458  ;

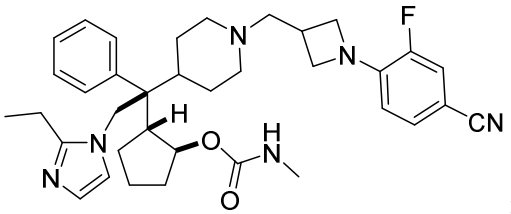
459  ;

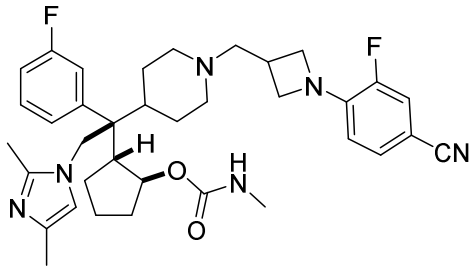
460  ;

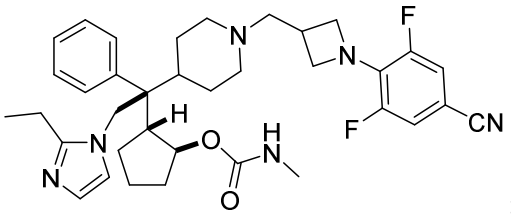
461  ;

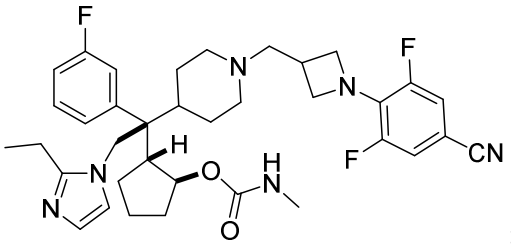
462  ;

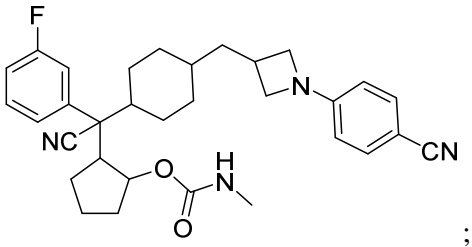
463  ;

464  ;

465  ;

466  ;

467  ;

468 
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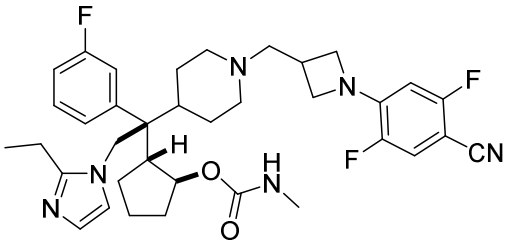
469 
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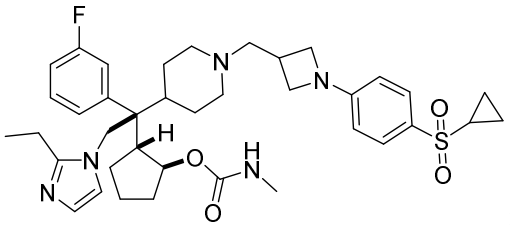
470 
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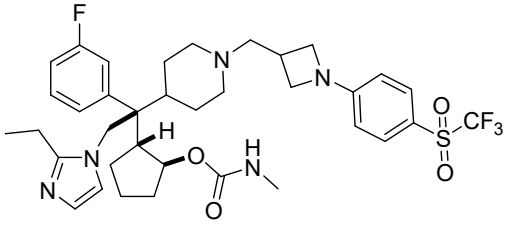
471 
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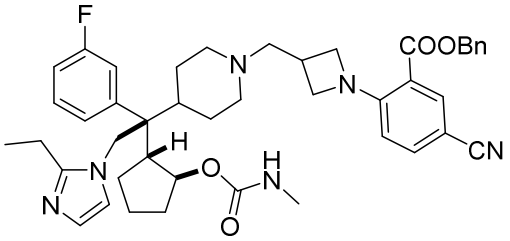
472 
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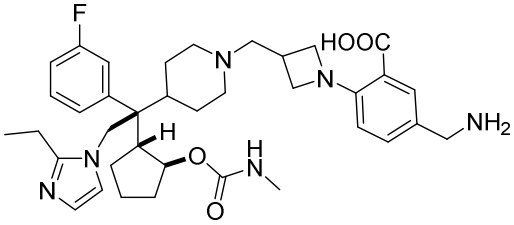
473 
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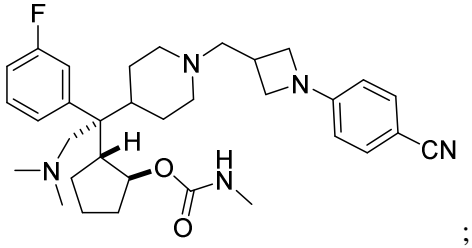
475 
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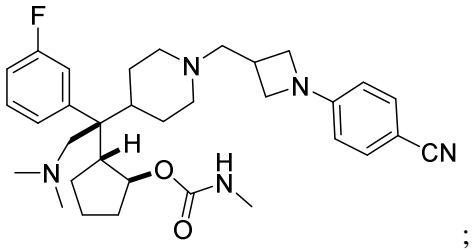
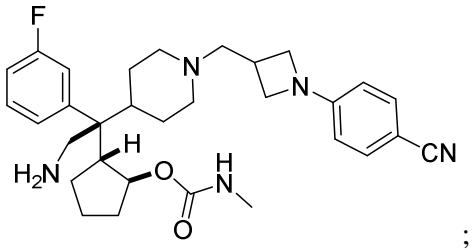
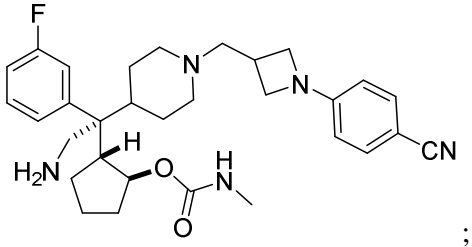
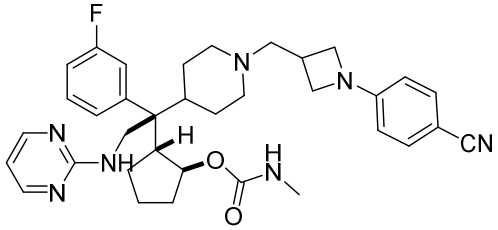
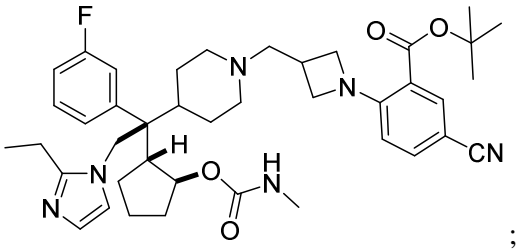
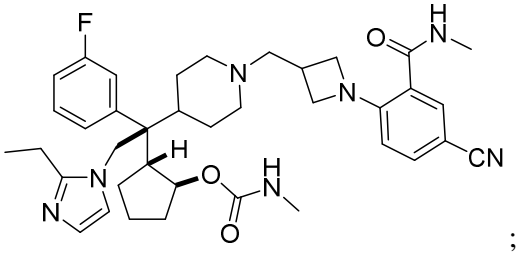
476  ;

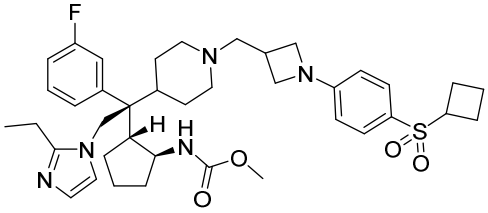
477  ;

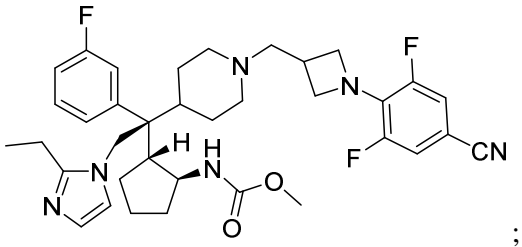
478  ;

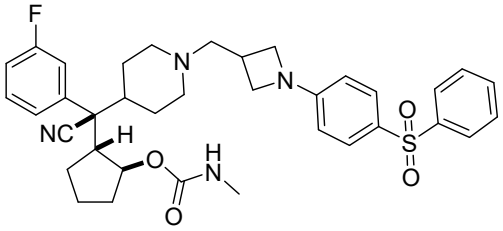
479  ;

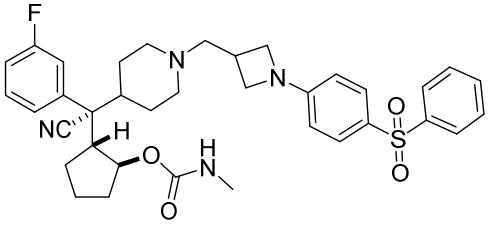
480  ;

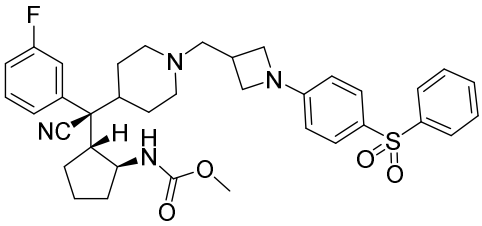
481  ;

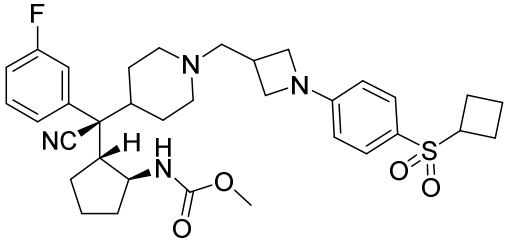
482  ;

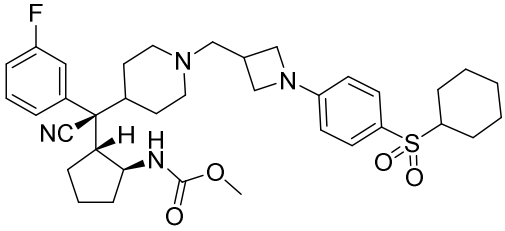
483  ;

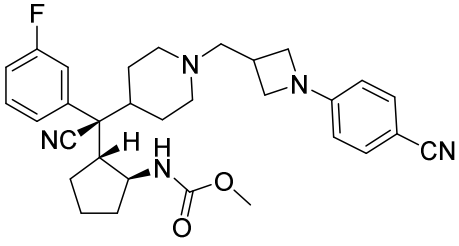
484  ;

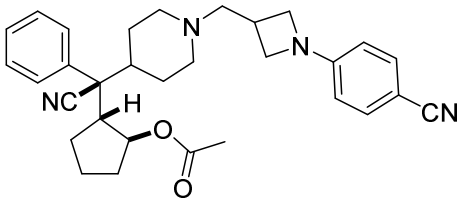
485  ;

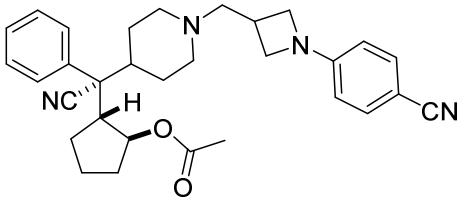
486  ;

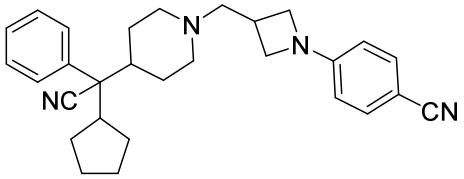
487  ;

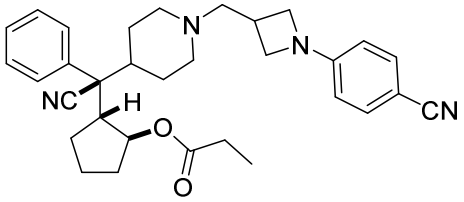
488  ;

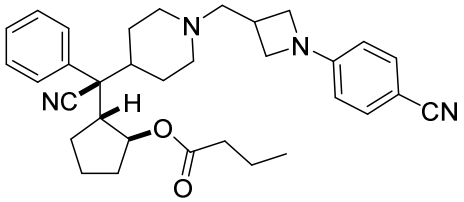
489  ;

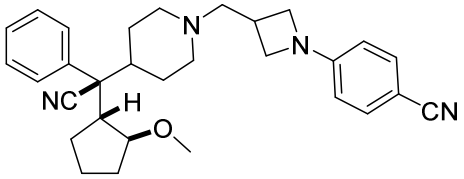
490  ;

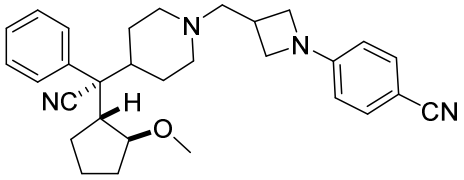
491  ;

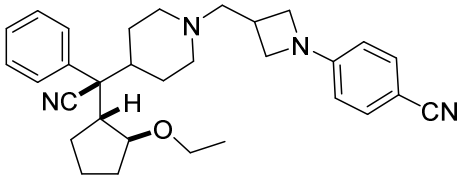
492  ;

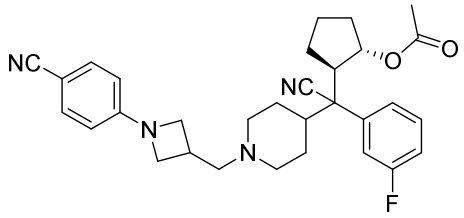
493  ;

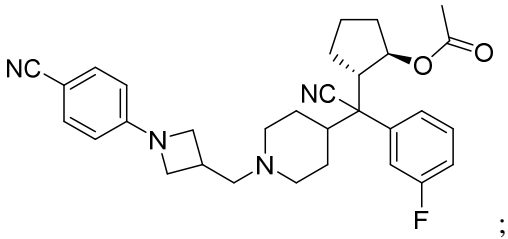
494  ;

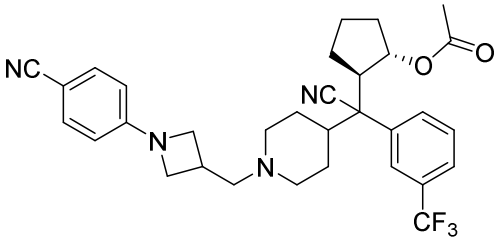
495  ;

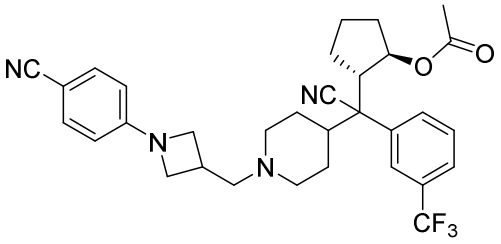
496  ;

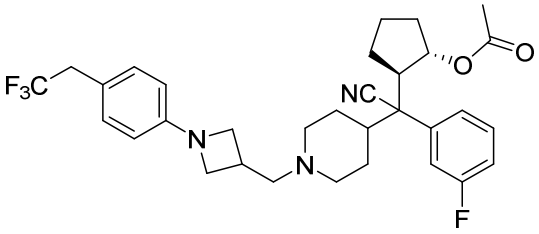
497  ;

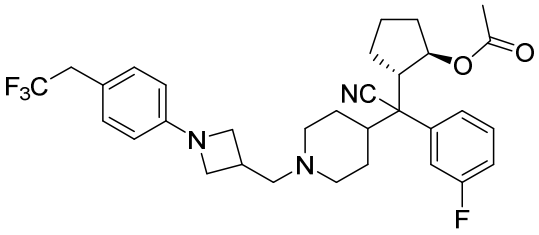
498  ;

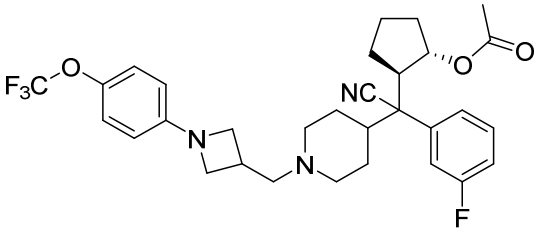
499  ;

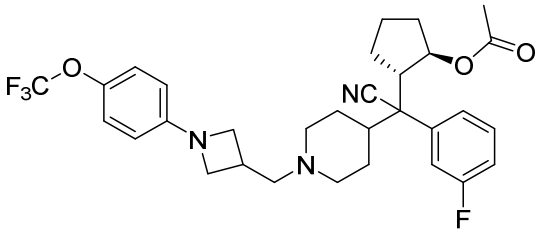
500  ;

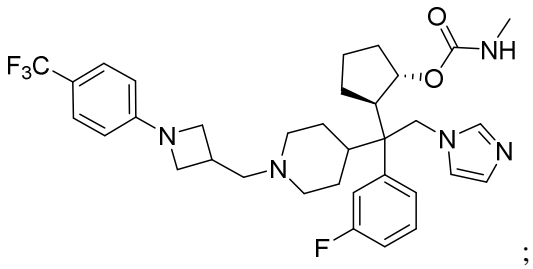
501  ;

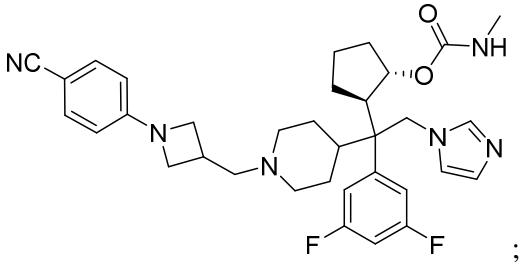
502  ;

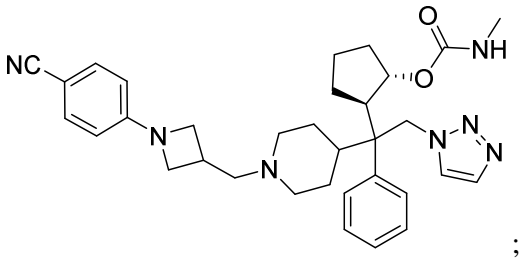
503  ;

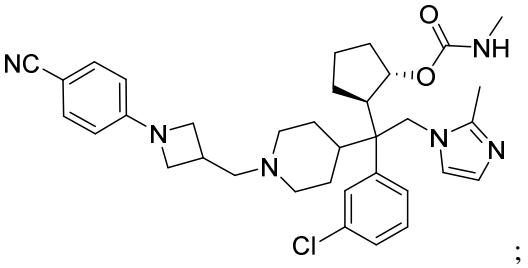
504  ;

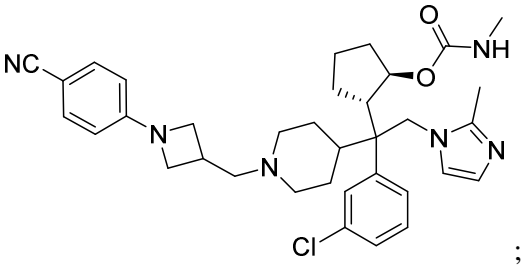
505  ;

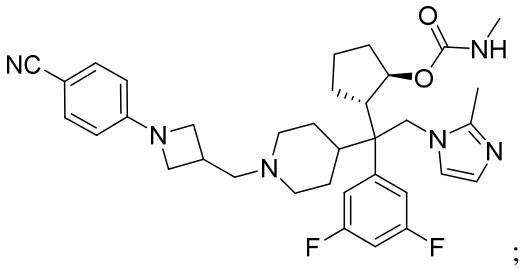
506  ;

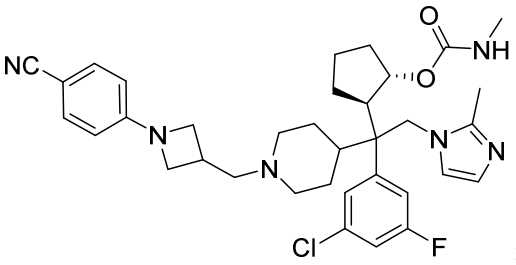
507  ;

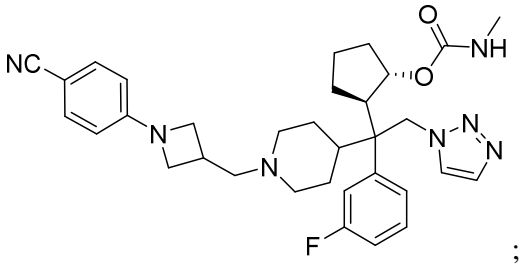
508  ;

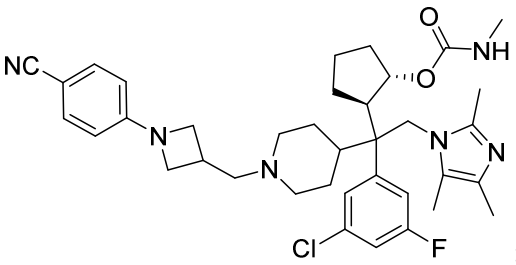
509  ;

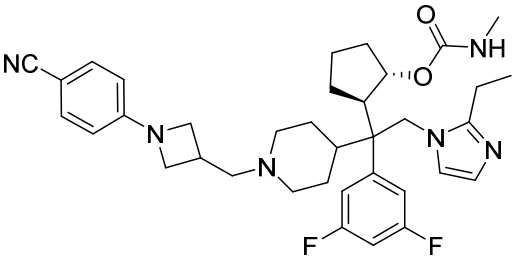
510  ;

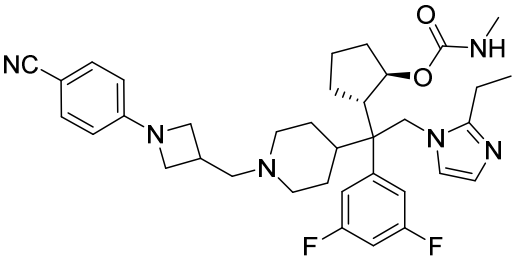
511  ;

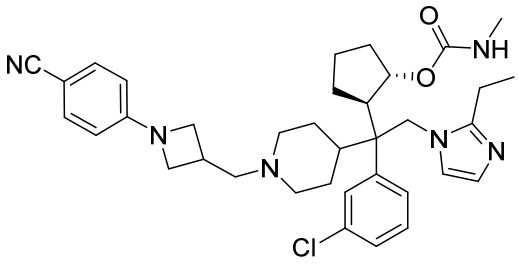
512  ;

513  ;

514  ;

517  ;

518  ;

519 

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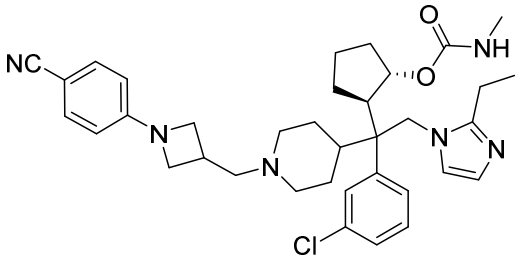
520 

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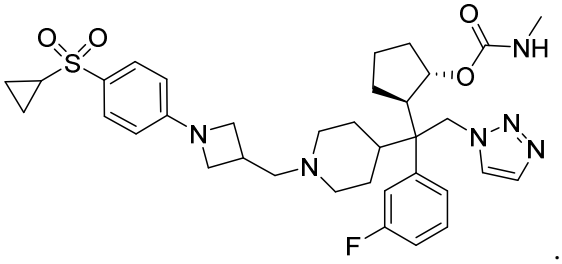
522 

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28. A pharmaceutical composition comprising the compound of any one of claims 1-27, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28 for use in therapy.

30. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for the manufacture of a medicament for treatment of cancer or a proliferative disorder.

31. The use of claim 30, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.