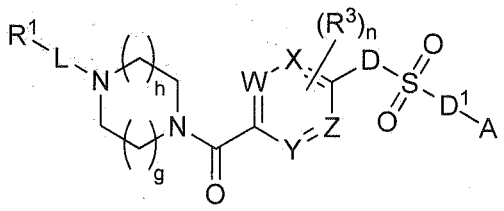
CLAIMS

What is claimed is:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

W, X, Y and Z are each independently selected from CH or N;

D and D^1 are independently selected from a bond or NR^b;

A is optionally substituted quinolinyl;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$-;

R^1 is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$ or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted cyclyl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2; and

g is 0, 1 or 2.

2. The compound of claim 1, wherein h is 1 and g is 1.

3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein W, X, Y and Z are CH.

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof , wherein D is NR^b and D^1 is a bond.

5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein R^b is H, methyl or ethyl.

6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein L is a bond and R^1 is alkyl, aryl or heteroaryl substituted with 0-5 occurrences of R^d.

7. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein L is $-(CR^cR^c)_m-$ and R^1 is cycloalkyl, aryl, heteroaryl or heterocyclyl substituted with 0-5 occurrences of R^d.

8. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein L is $-NR^bC(O)-$, R^b is hydrogen, and R^1 is aryl substituted with 0-5 occurrences of R^d.

9. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof , wherein L is $-(CR^cR^c)_m-C(O)-$ and R^1 is cycloalkyl, aryl or heteroaryl substituted with 0-5 occurrences of R^d.

10. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof , wherein L is -C(O)- and R^1 is aryl, alkyl, or heteroaryl substituted with 0-5 occurrences of R^d.

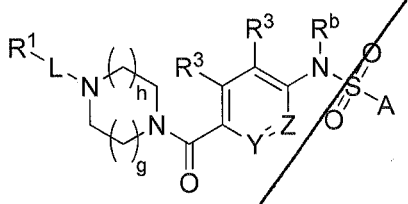
11. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof , wherein L is –OC(O)- and R^1 is alkyl, aryl or heterocyclyl substituted with 0-5 occurrences of R^d.

12. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein L is $-(CR^cR^c)_m$-OC(O)- and R^1 is heterocyclyl or cycloalkyl substituted with 0-5 occurrences of R^d.

13. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein n is 0.

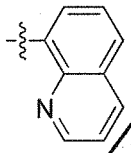
14. The compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^3 is CH_3, CH_2CH_3, OCH_3, OCH_2CH_3, OH, F, Cl, or CF_3.

15. The compound of any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (Id):

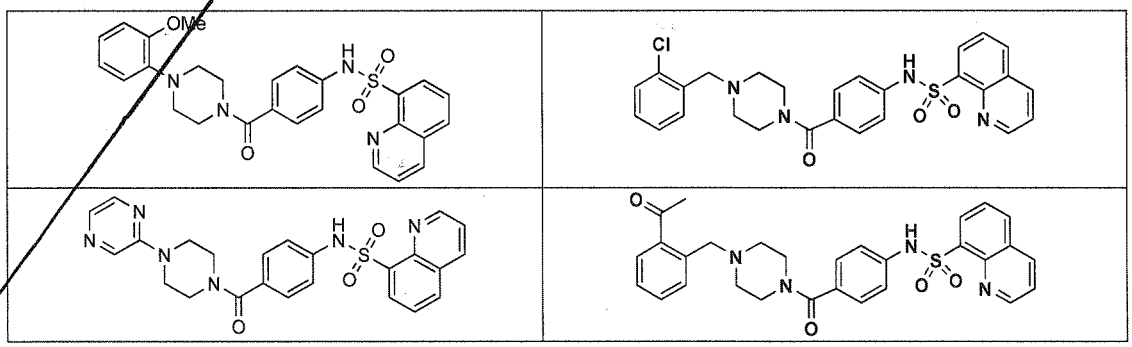


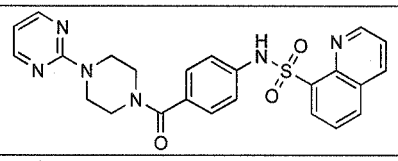
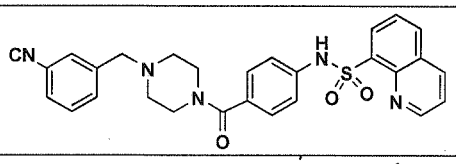
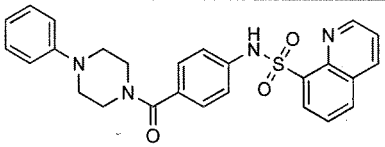
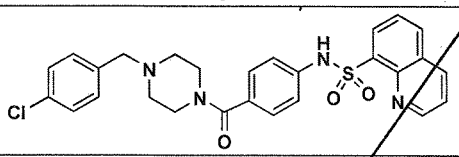
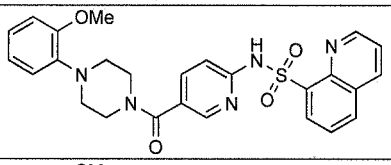
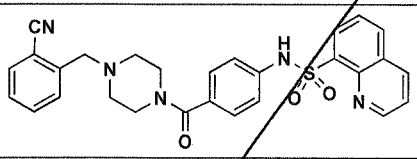
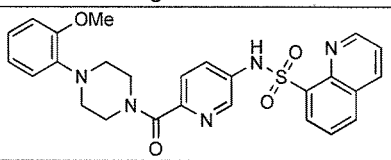
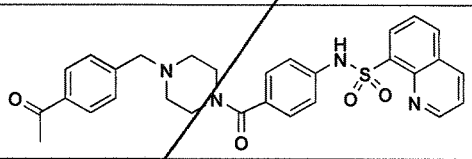
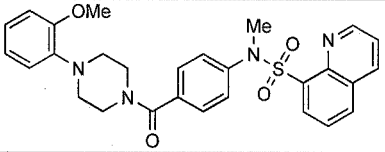
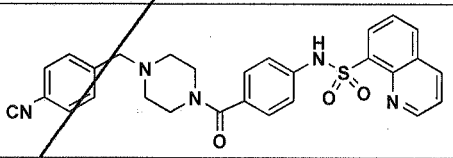
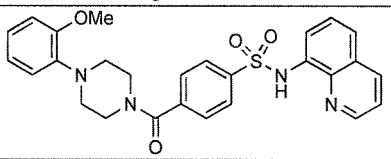
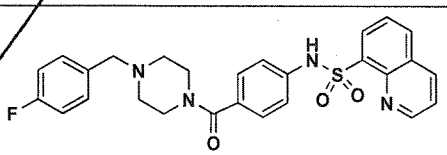
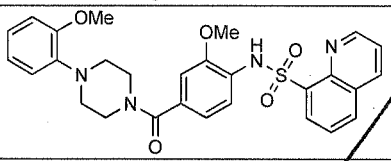
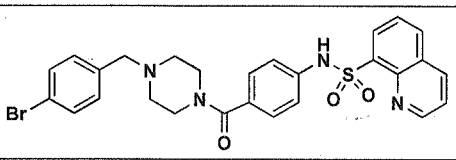
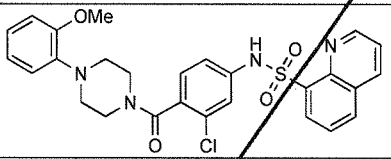
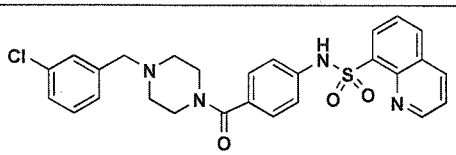
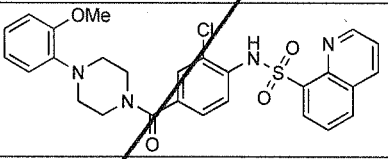
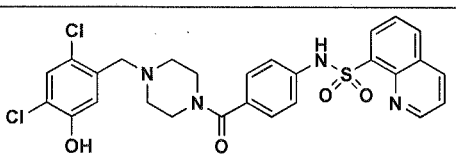
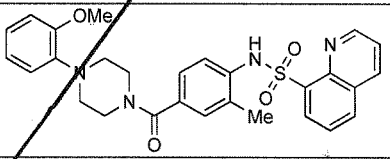
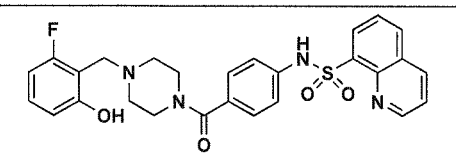
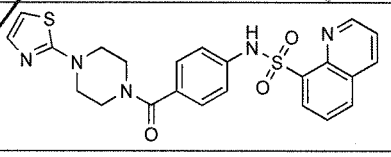
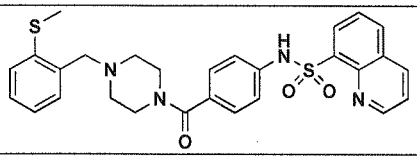
(Id)

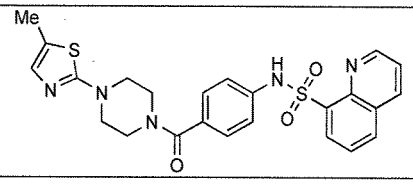
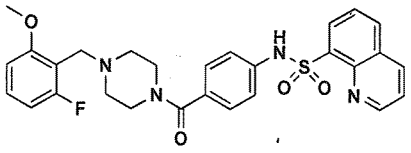
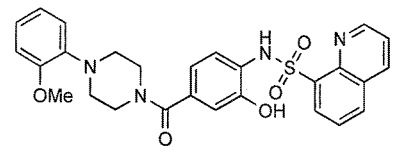
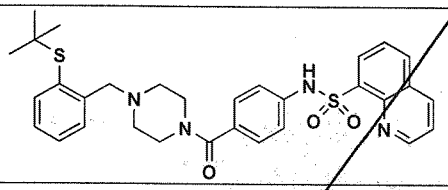
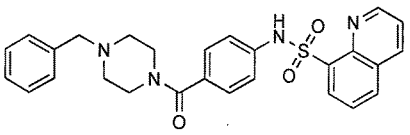
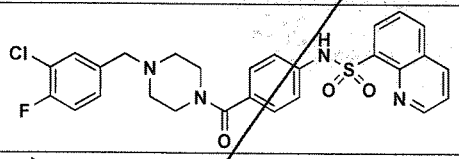
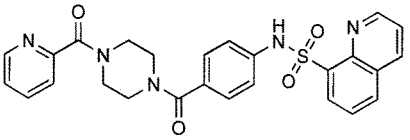
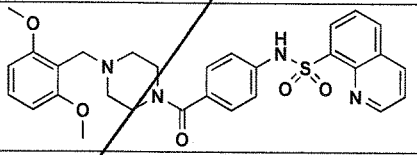
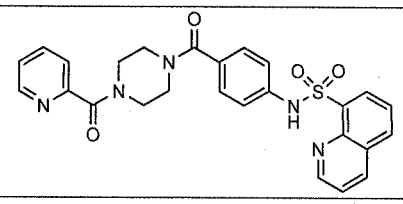
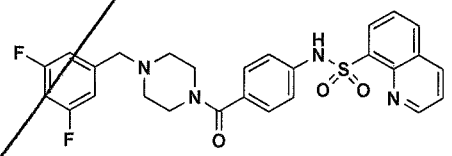
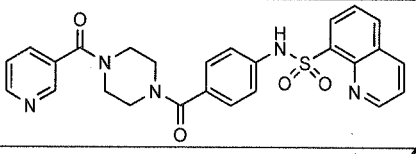
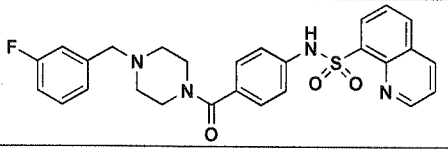
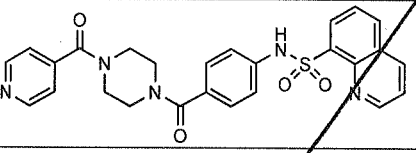
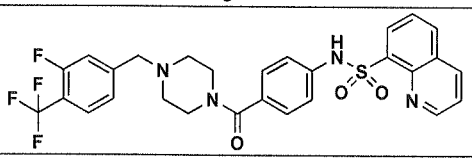
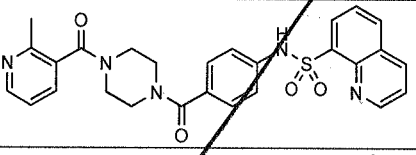
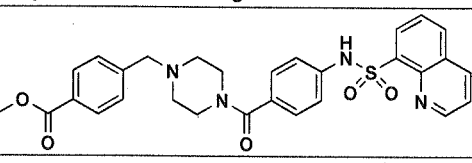
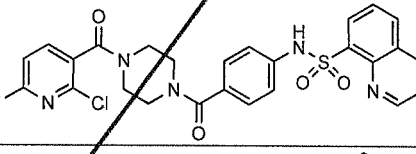
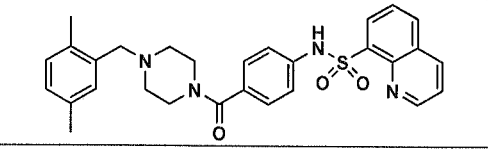
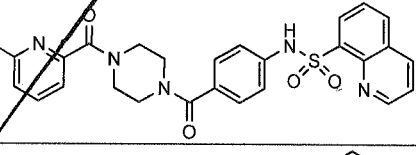
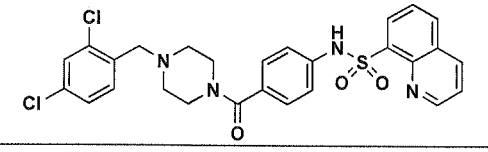
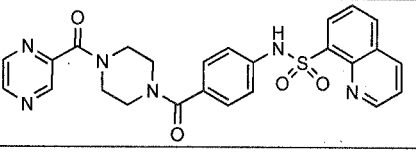
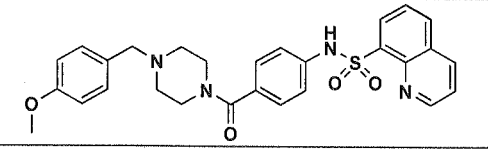
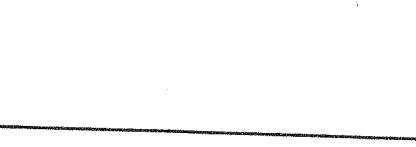
wherein A is optionally substituted quinolinyl.

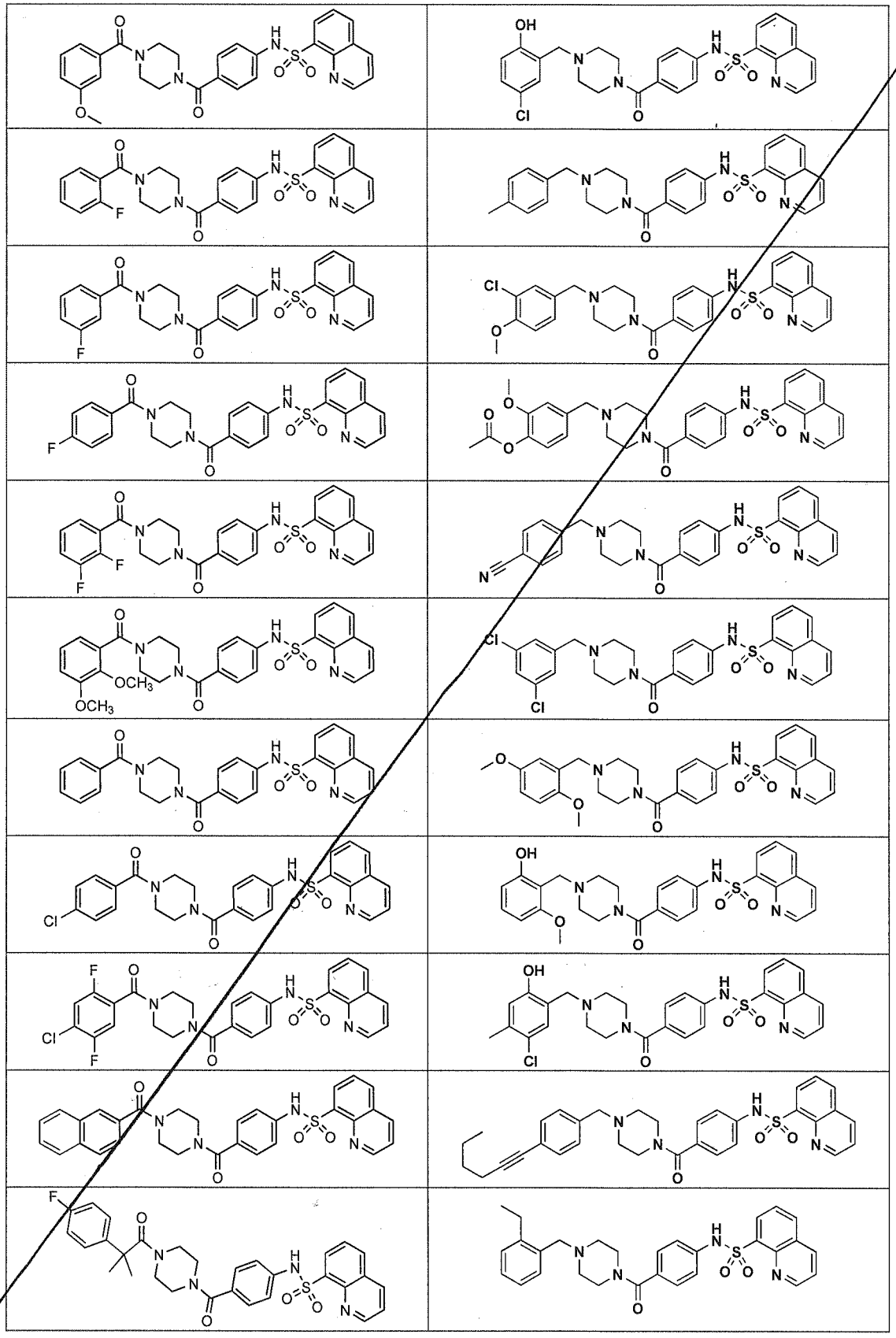
16. The compound of any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, wherein A is .

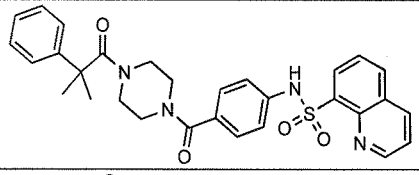
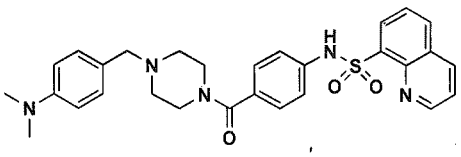
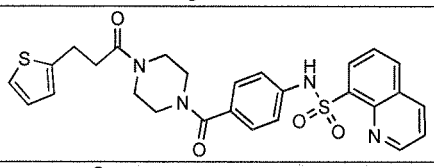
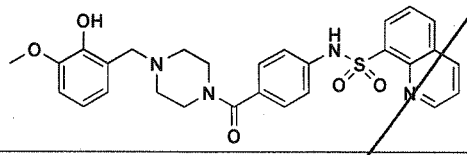
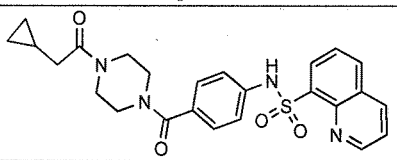
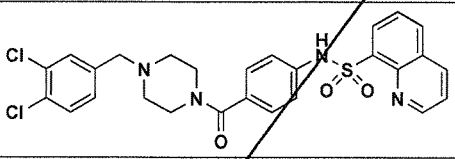
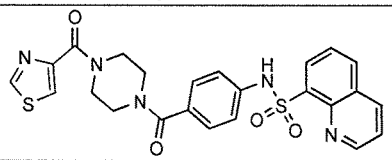
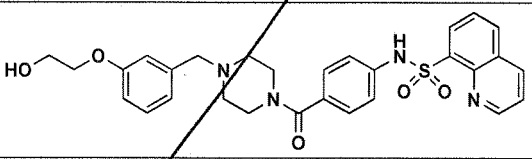
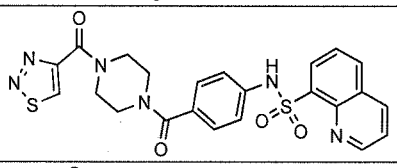
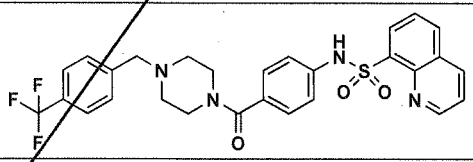
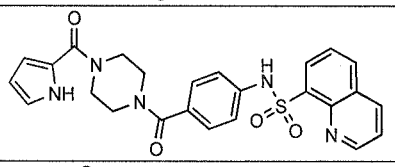
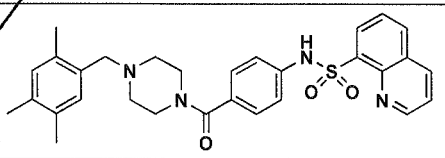
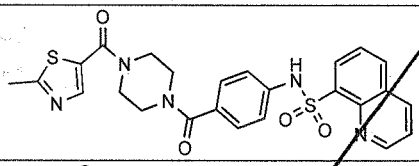
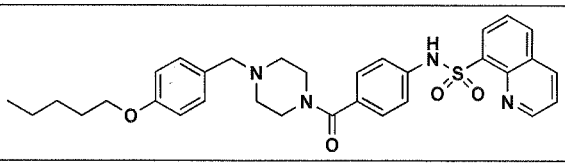
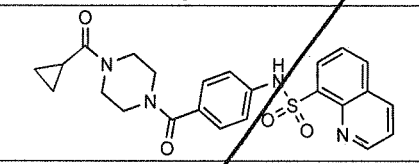
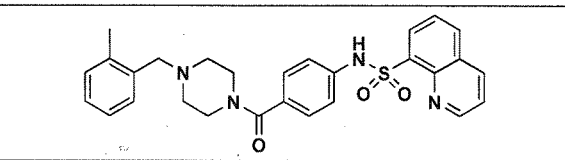
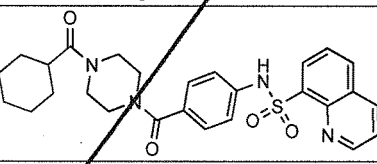
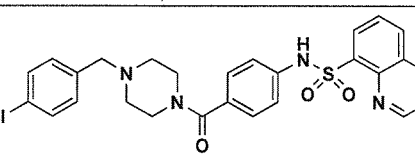
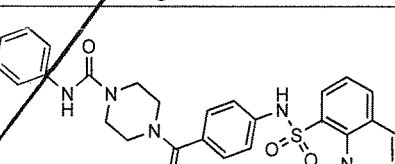
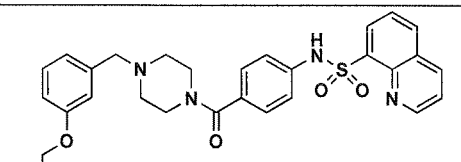
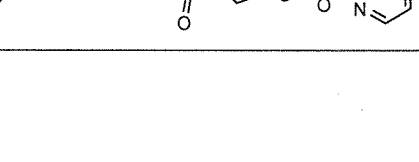
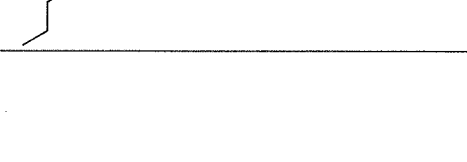
17. The compound of claim 1, wherein the compound is selected from the group consisting of:

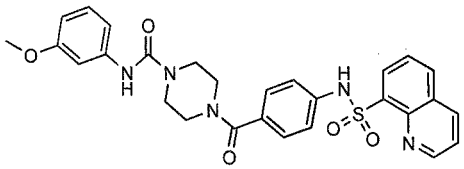
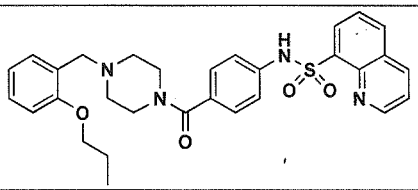
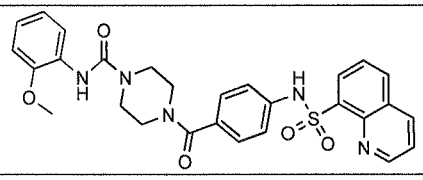
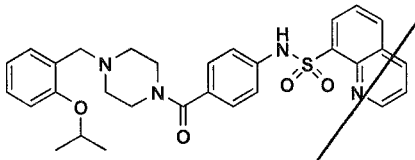
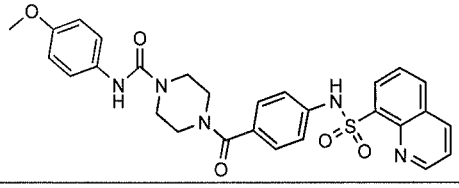
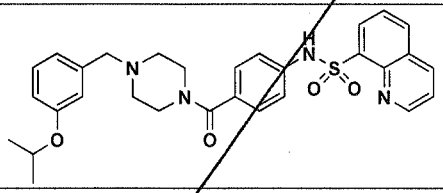
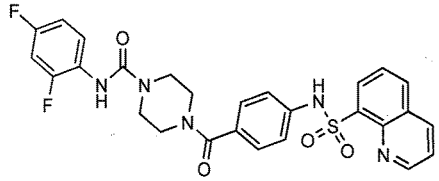
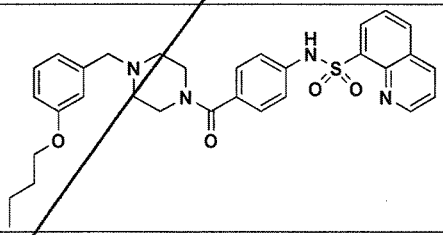
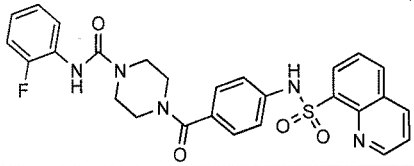
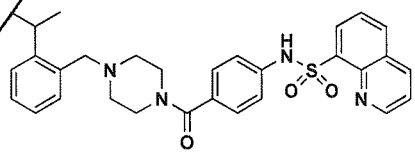
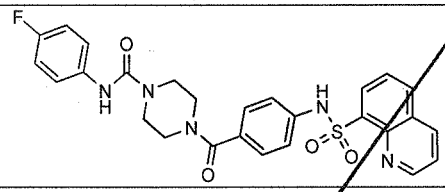
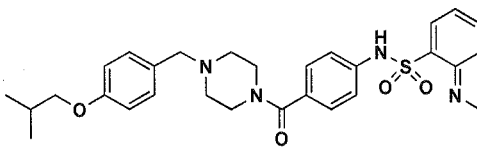
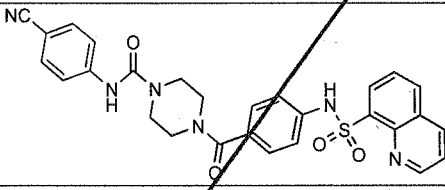
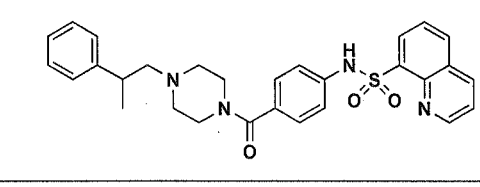
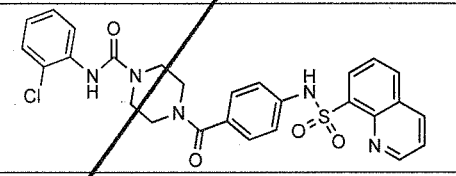
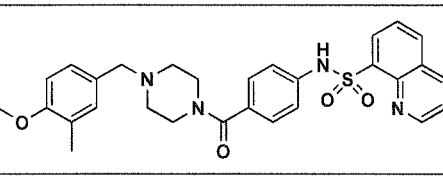
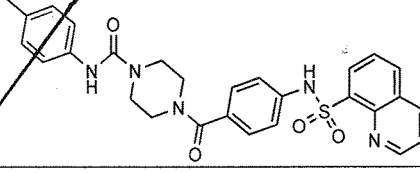
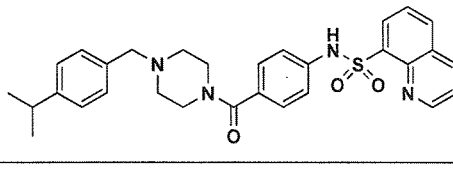


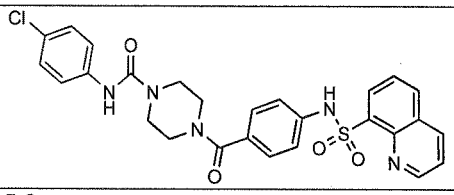
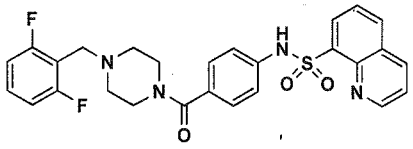
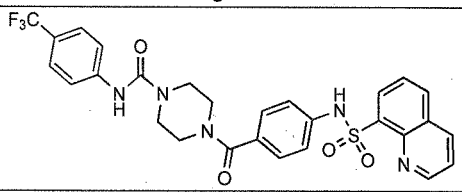
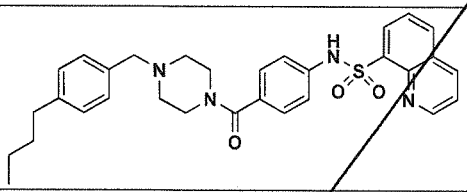
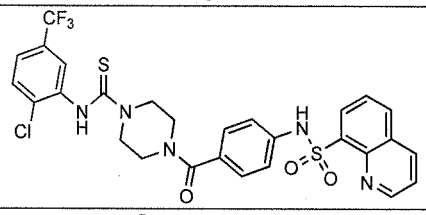
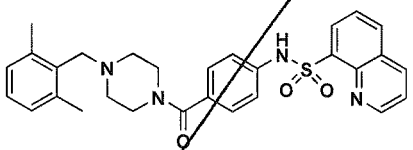
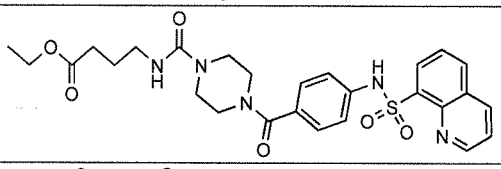
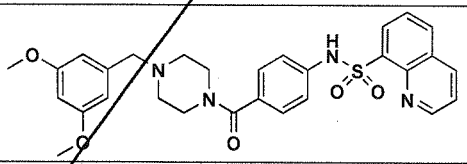
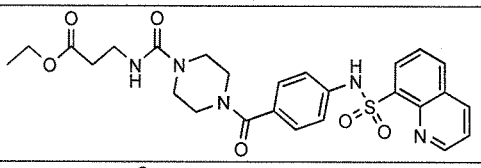
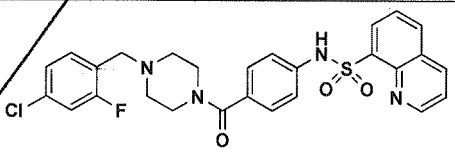
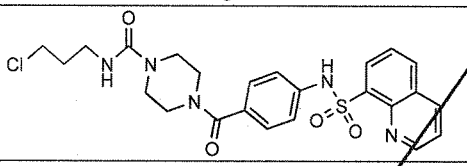
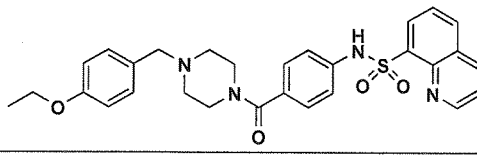
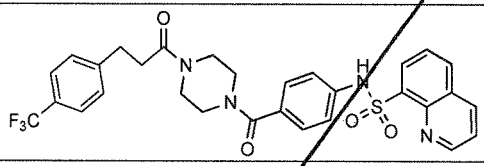
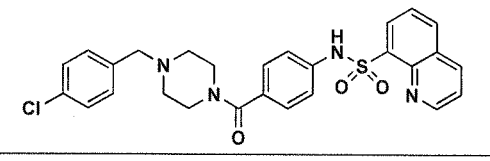
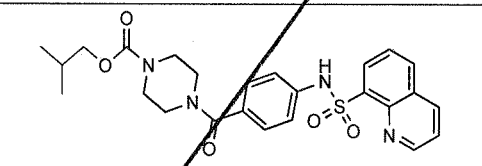
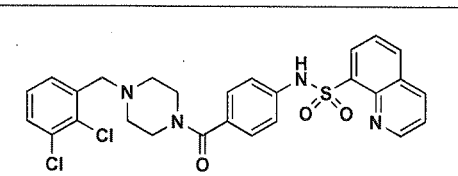
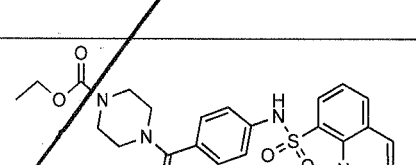
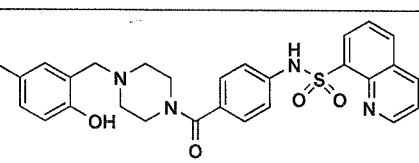
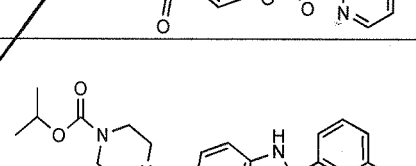
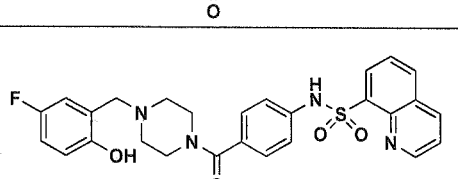
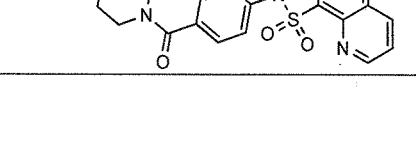
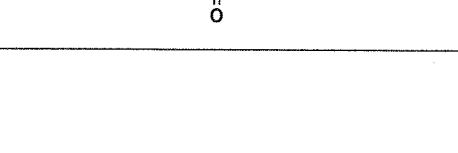
	
	
	
	
	
	
	
	
	
	
	

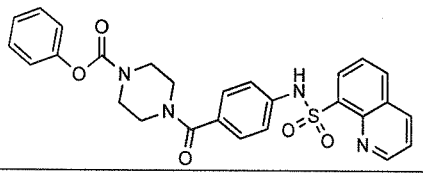
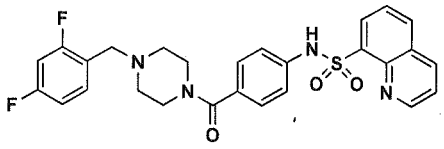
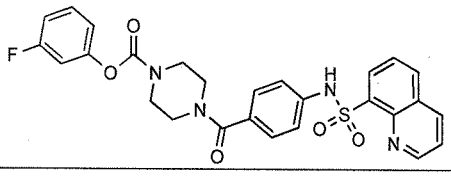
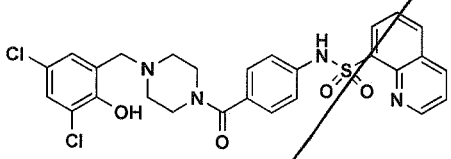
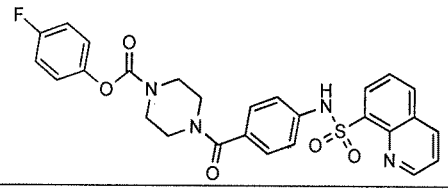
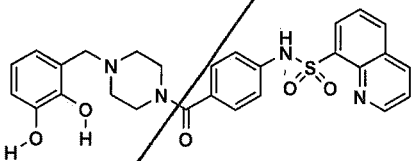
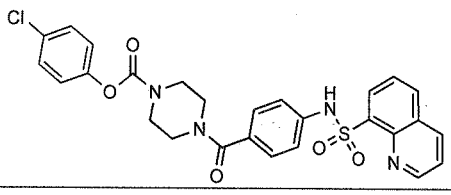
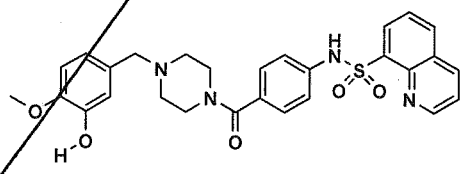
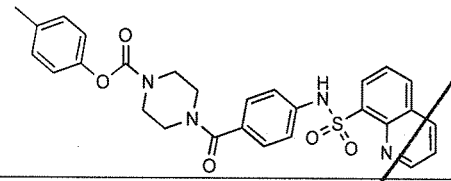
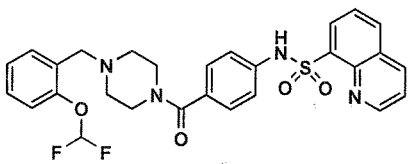
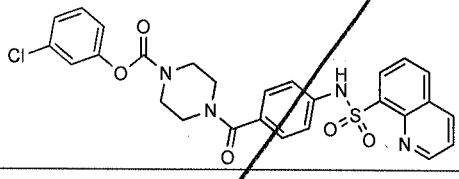
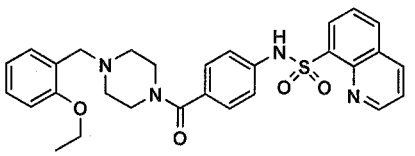
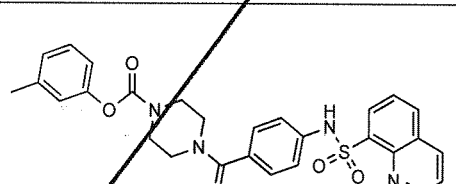
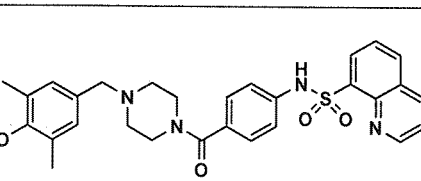
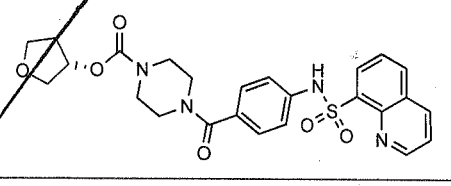
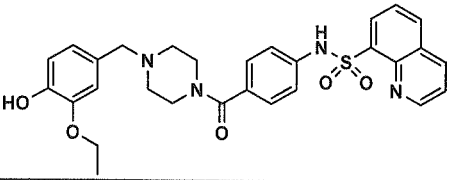
	
	
	
	
	
	
	
	
	
	
	
	
	

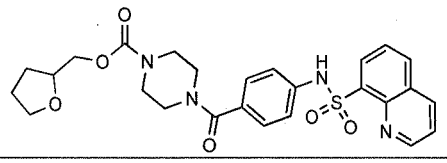
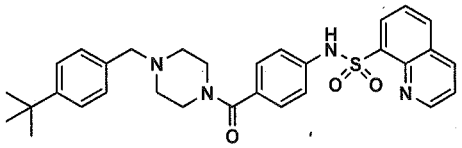
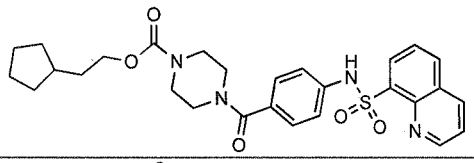
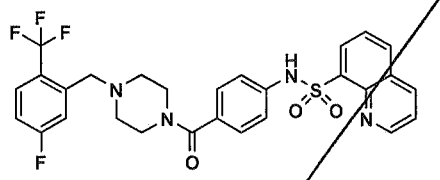
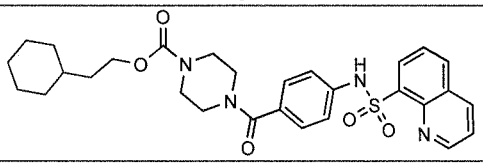
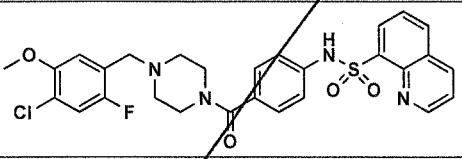
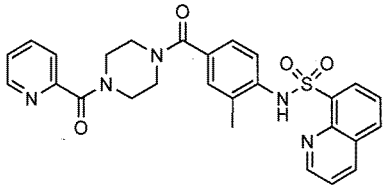
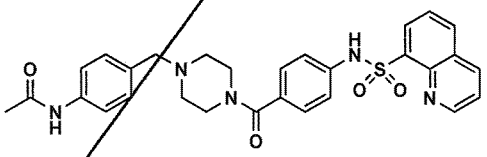
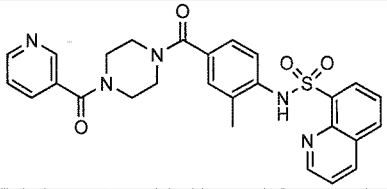
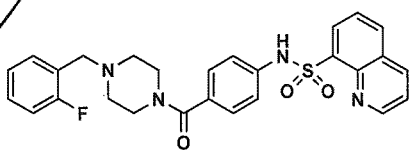
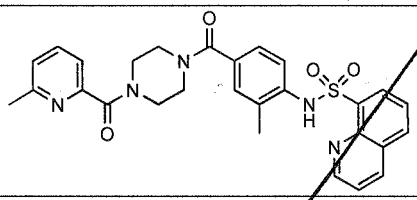
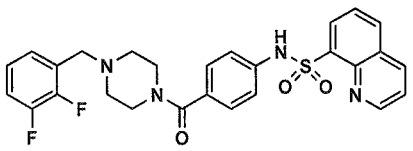
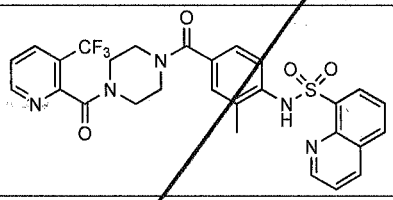
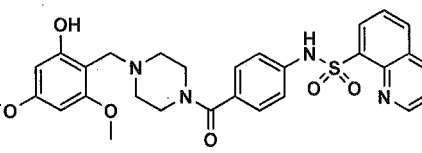
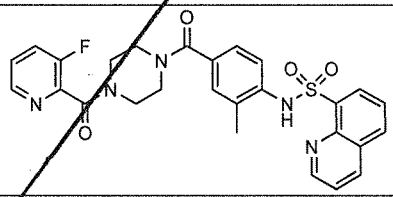
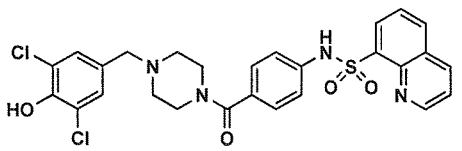
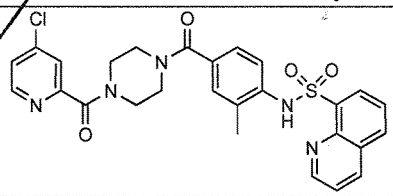
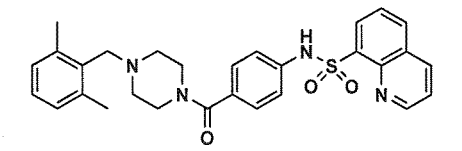
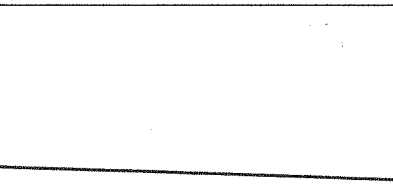


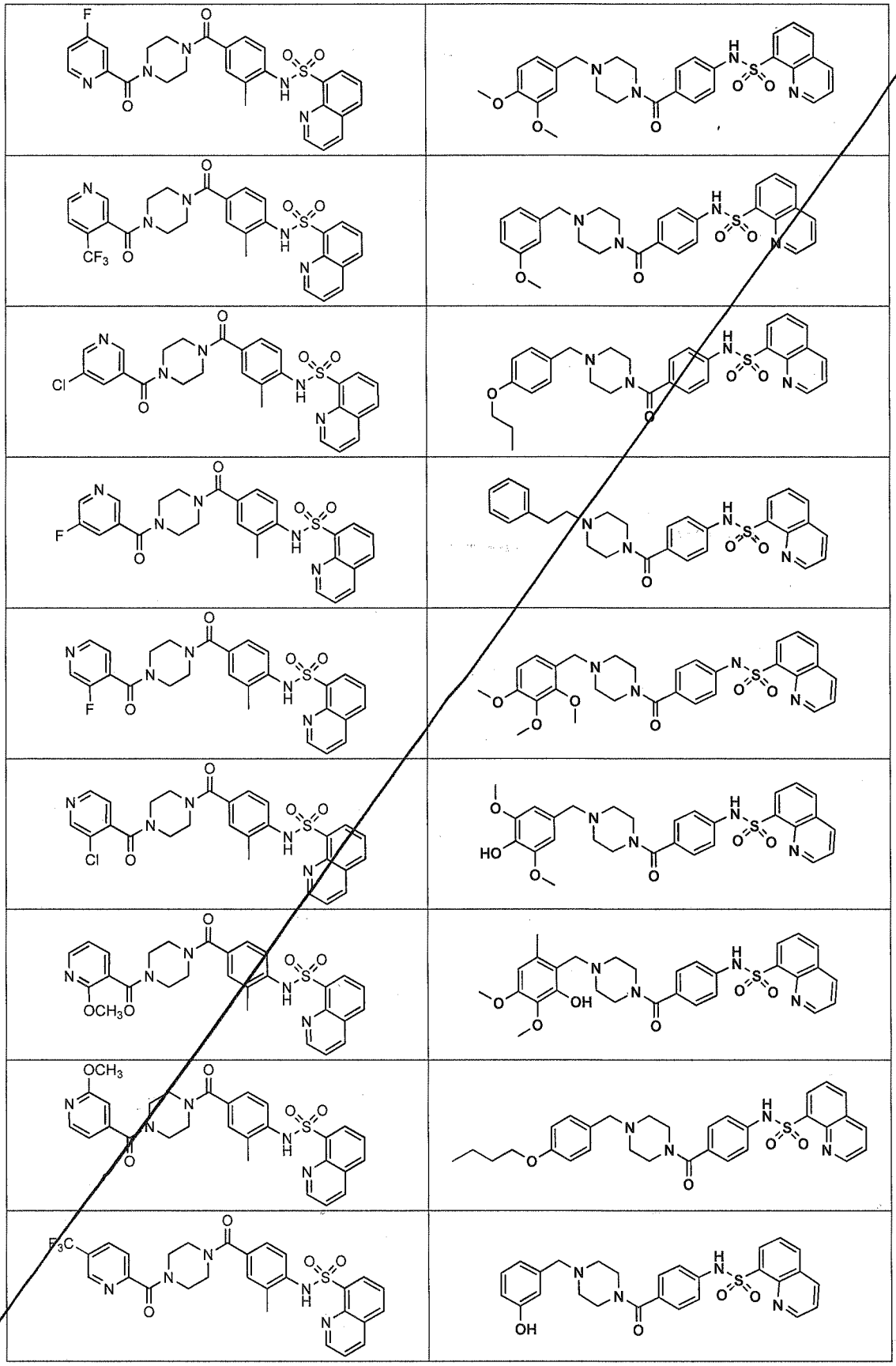
	
	
	
	
	
	
	
	
	
	
	

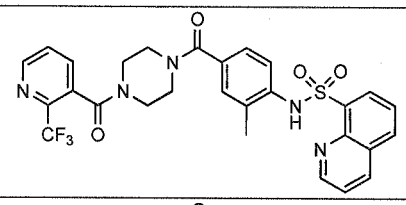
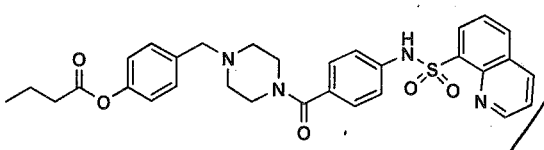
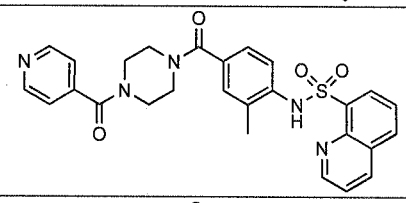
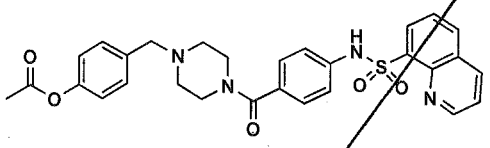
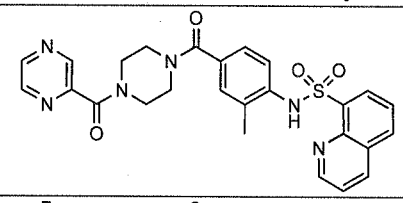
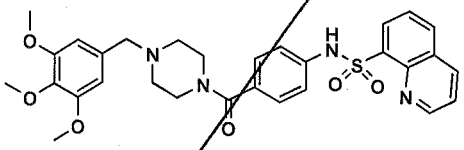
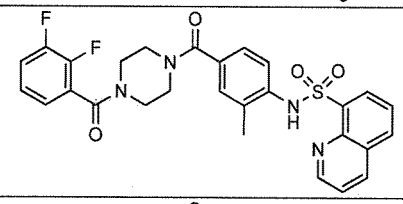
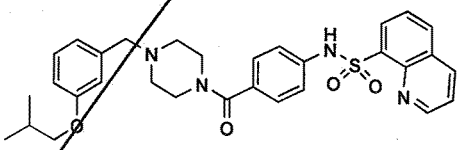
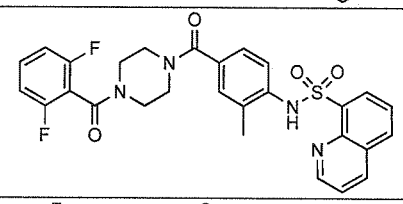
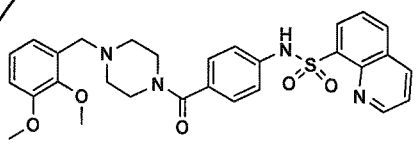
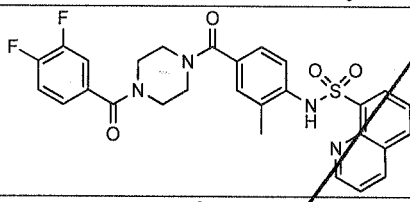
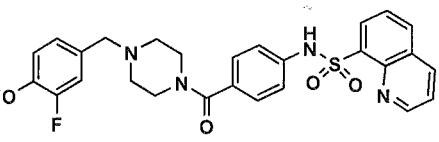
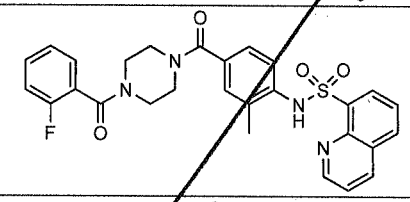
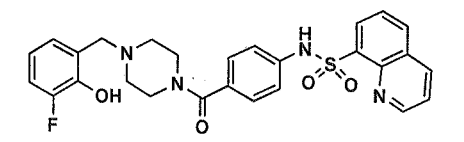
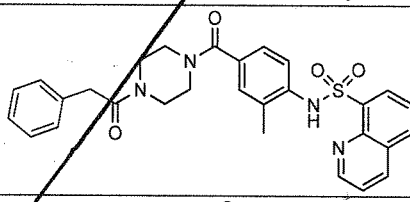
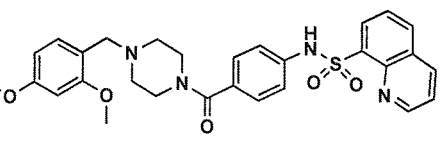
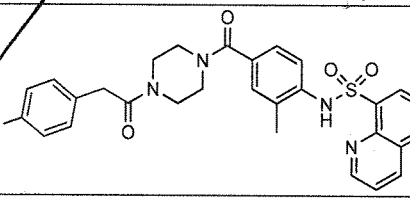
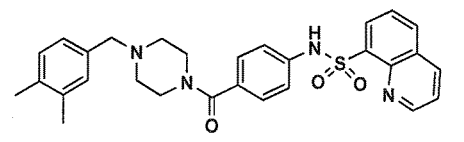
	
	
	
	
	
	
	
	
	
	

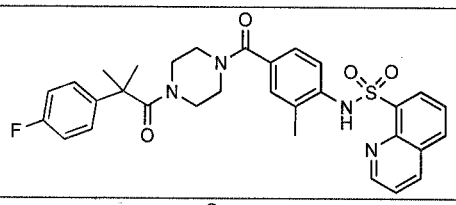
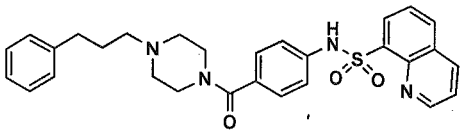
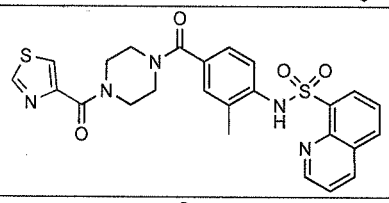
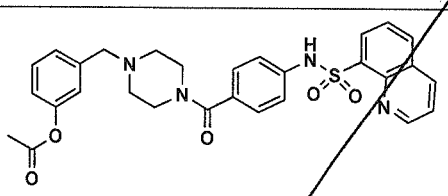
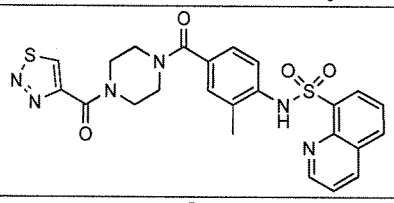
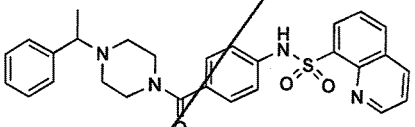
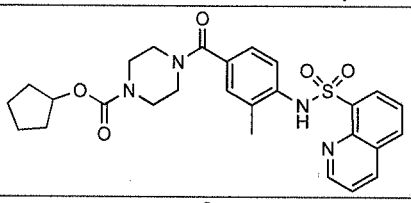
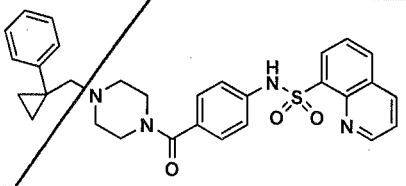
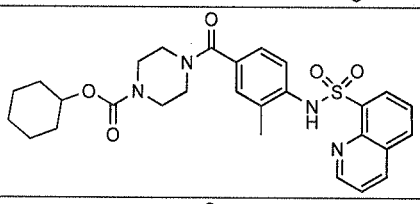
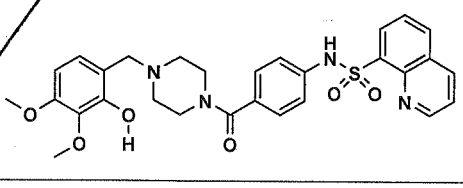
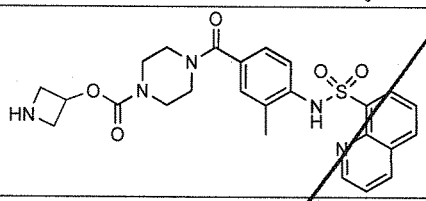
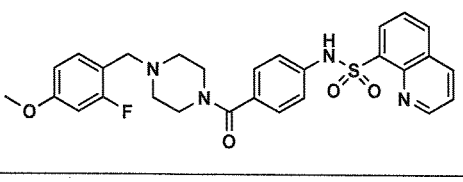
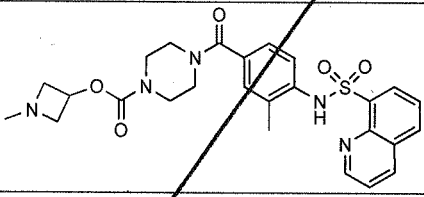
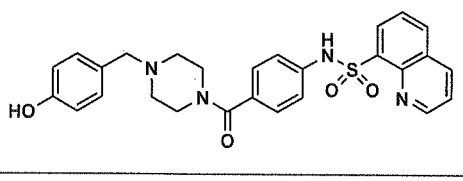
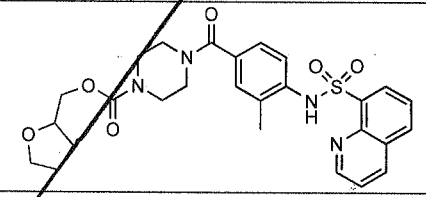
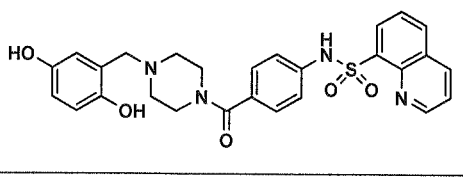
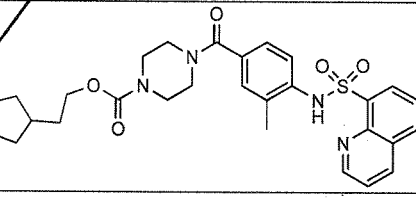
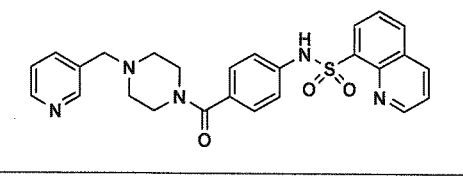
	
	
	
	
	
	
	
	
	
	
	

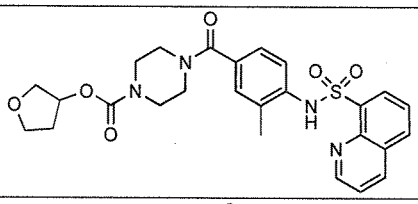
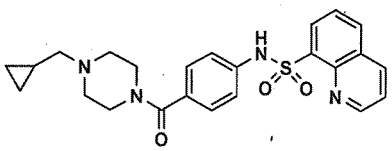
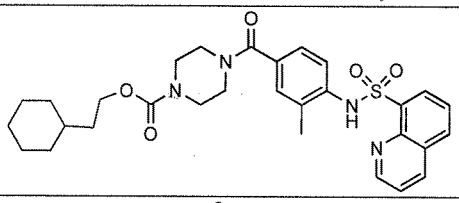
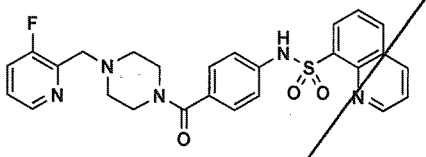
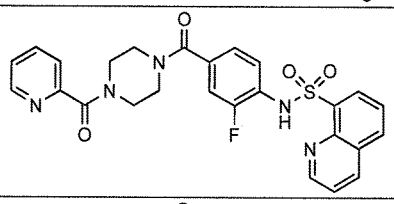
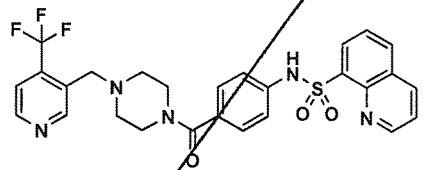
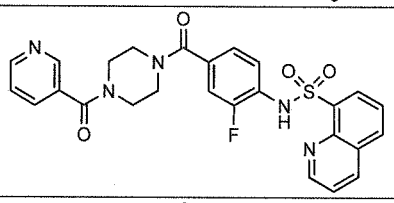
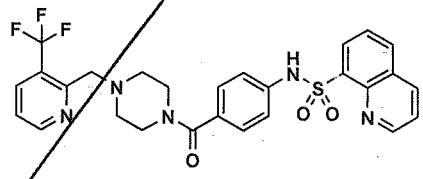
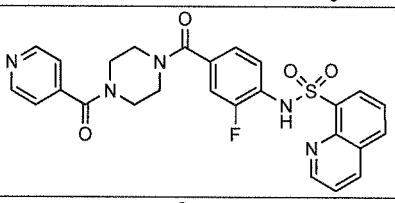
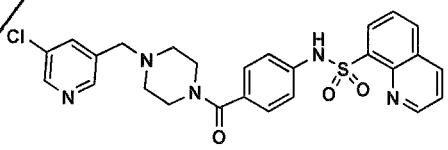
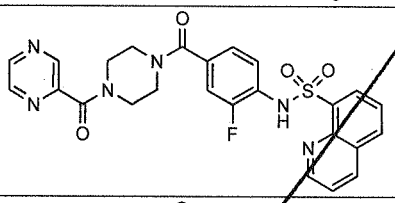
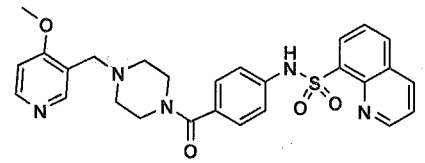
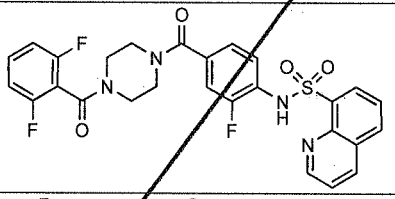
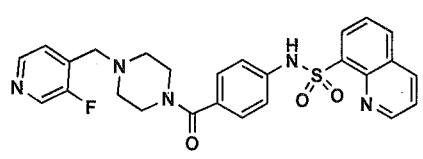
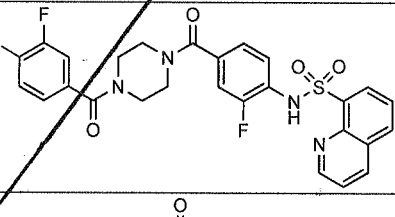
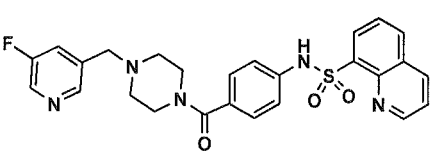
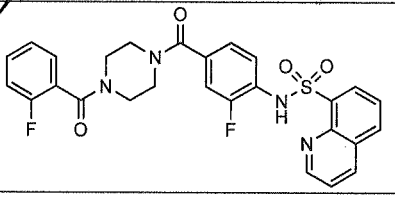
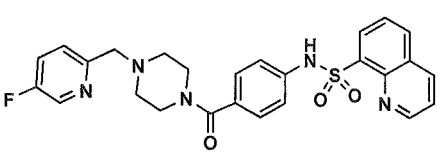
	
	
	
	
	
	
	
	

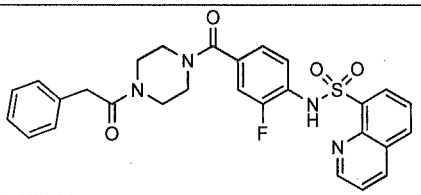
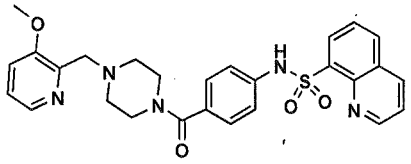
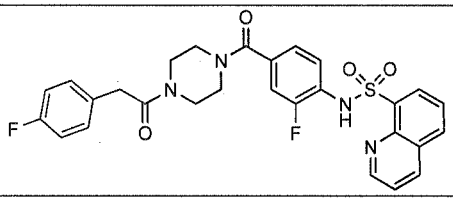
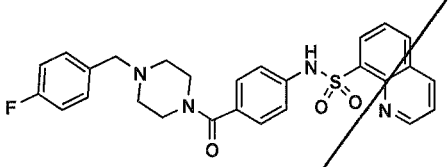
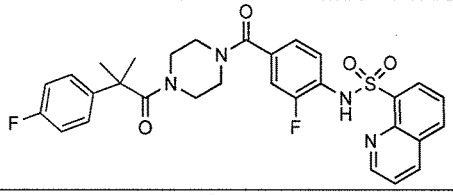
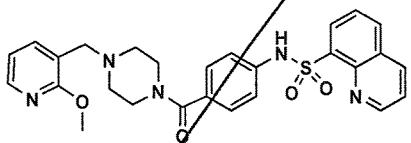
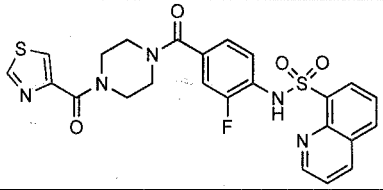
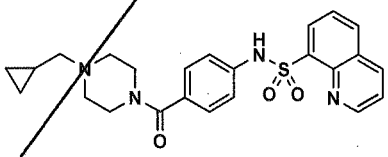
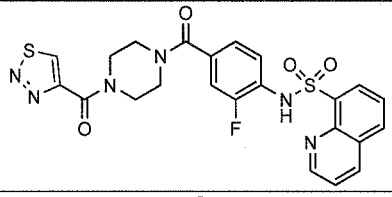
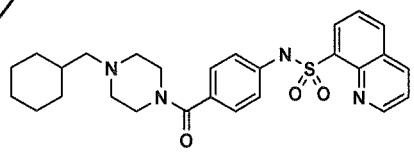
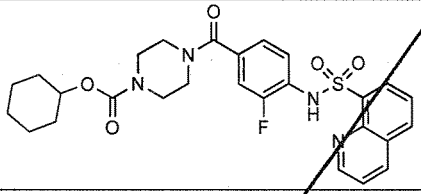
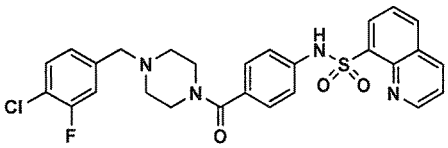
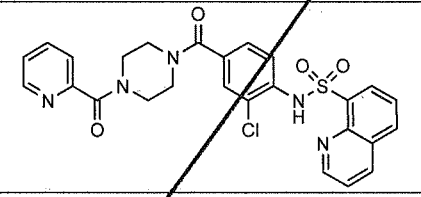
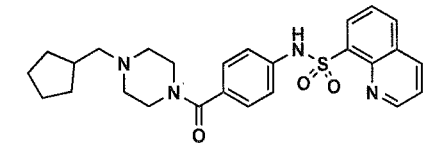
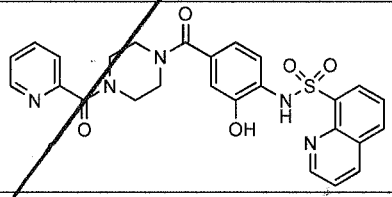
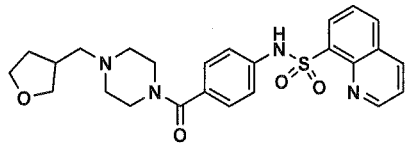
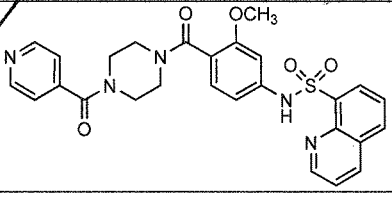
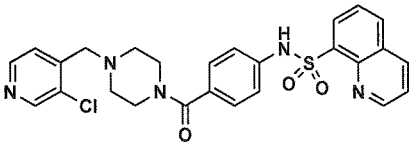
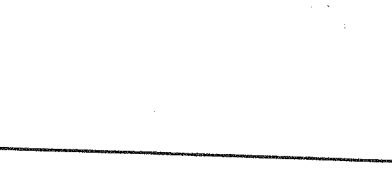
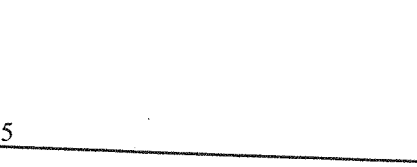
	
	
	
	
	
	
	
	
	
	

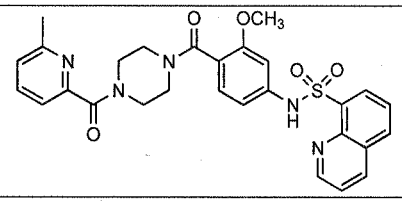
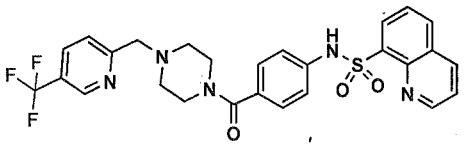
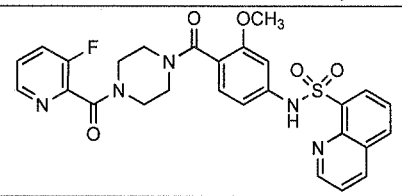
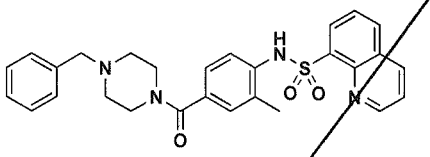
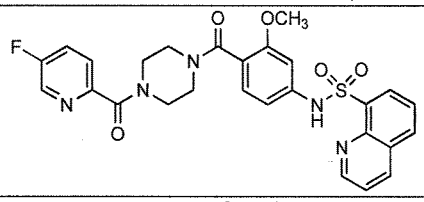
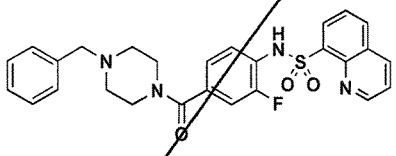
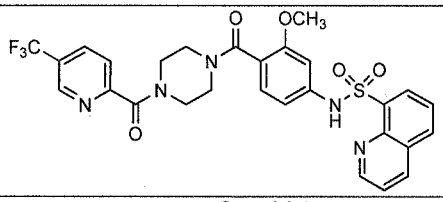
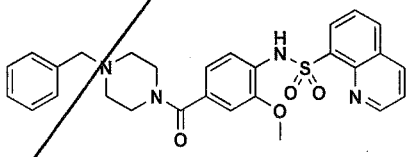
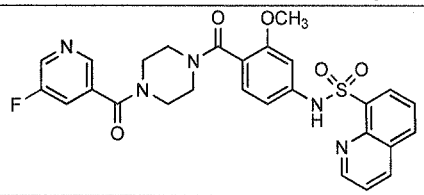
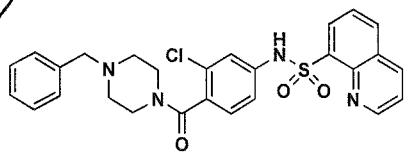
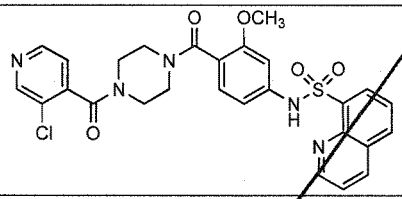
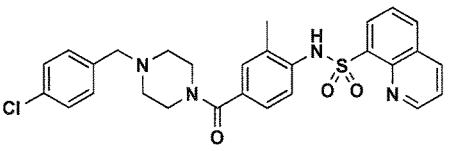
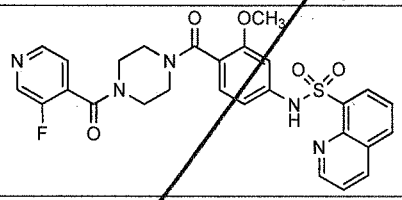
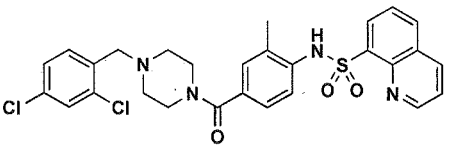
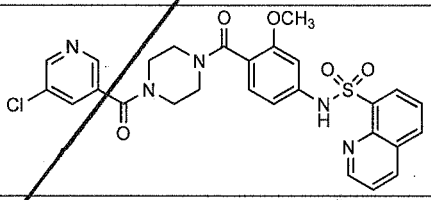
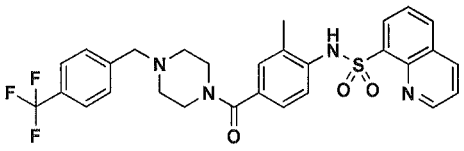
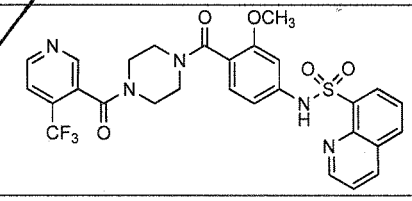
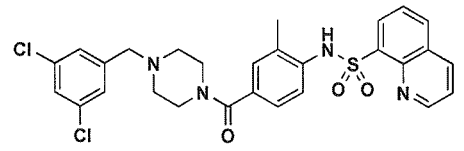


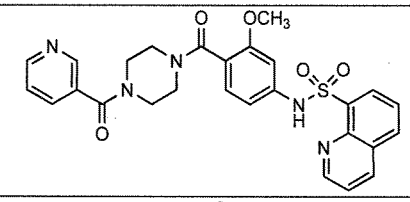
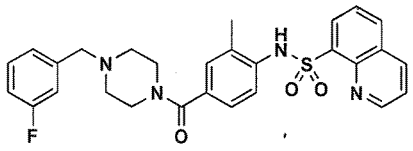
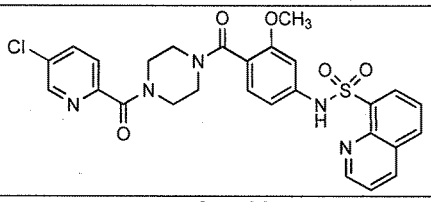
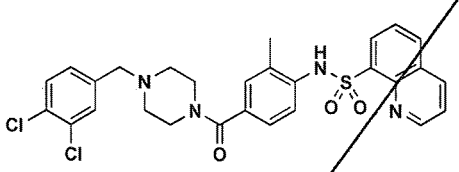
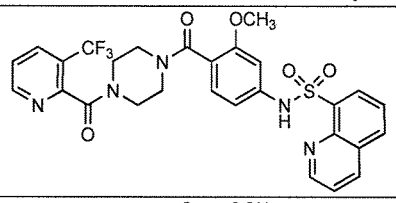
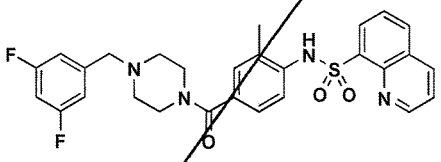
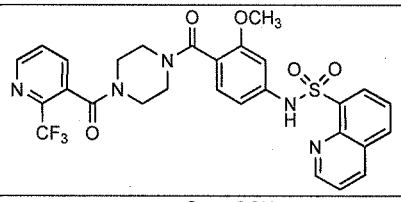
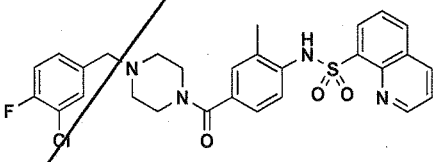
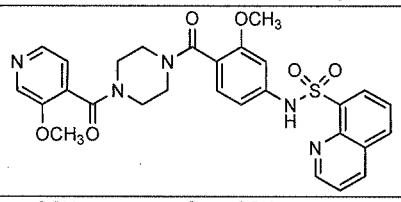
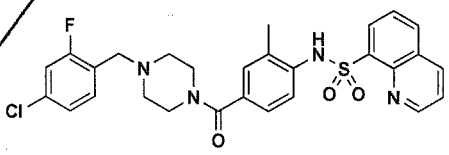
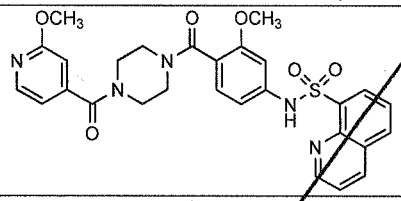
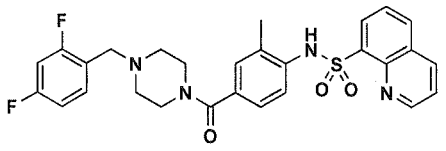
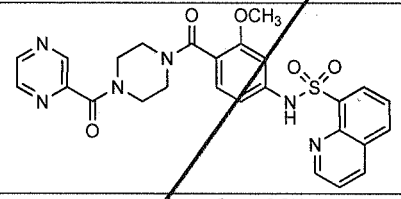
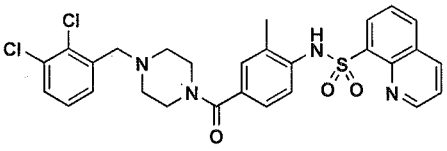
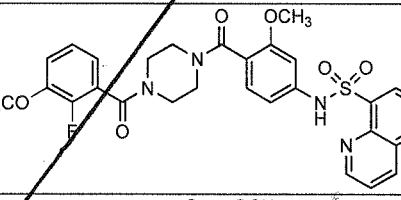
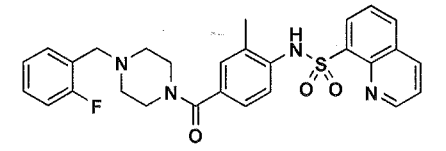
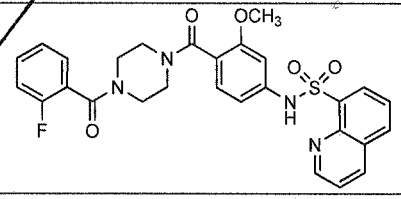
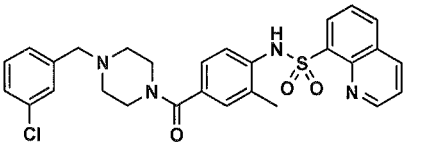
	
	
	
	
	
	
	
	
	

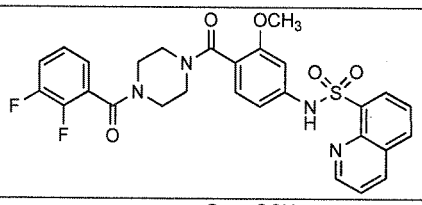
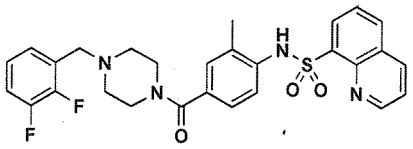
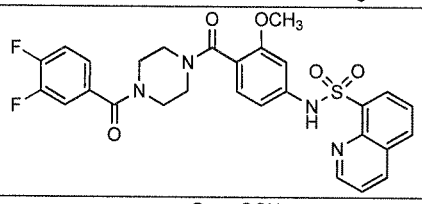
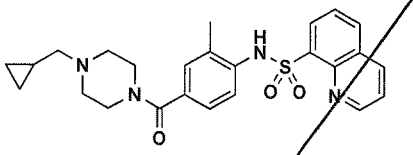
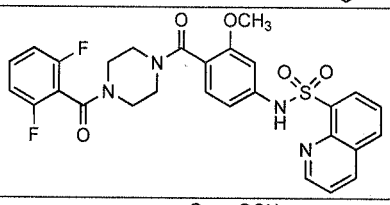
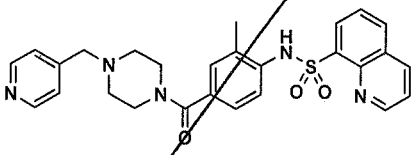
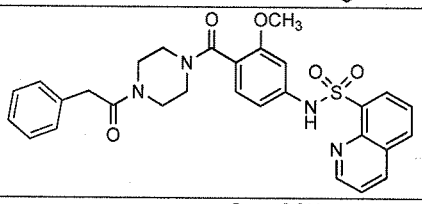
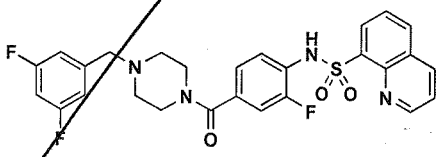
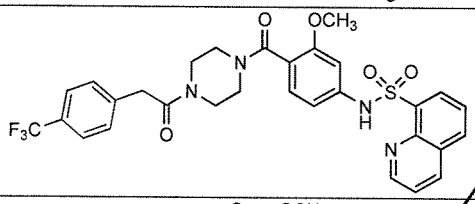
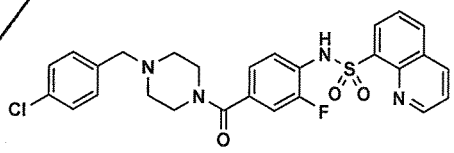
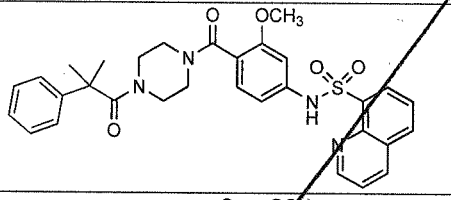
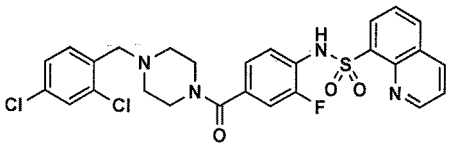
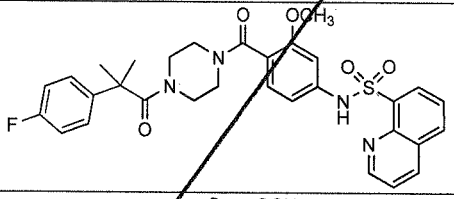
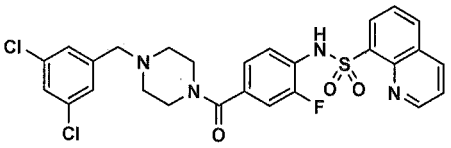
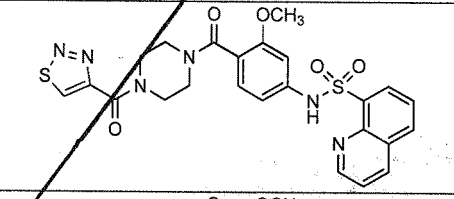
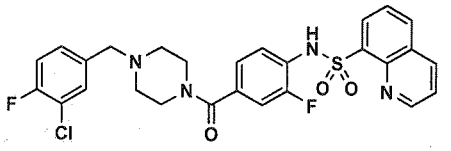
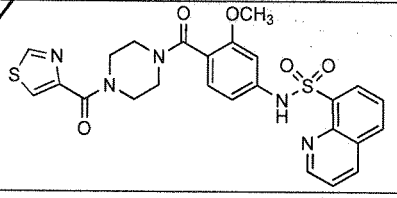
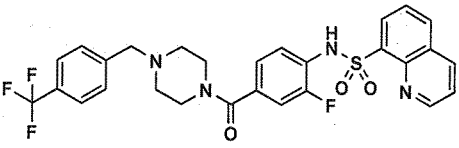
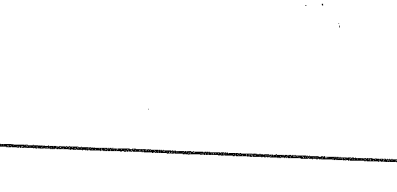
	
	
	
	
	
	
	
	
	

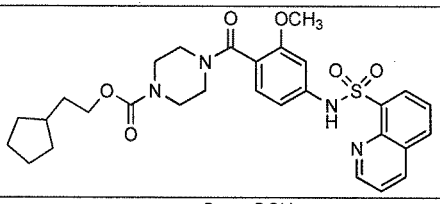
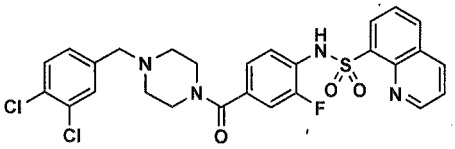
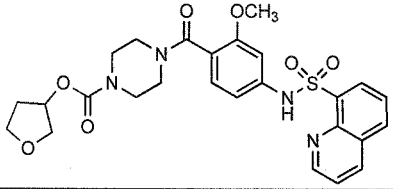
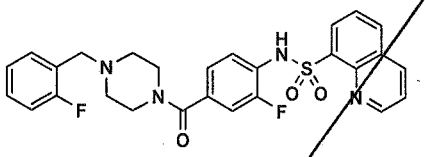
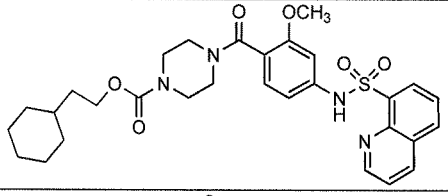
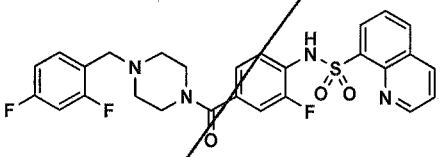
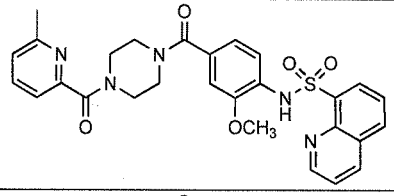
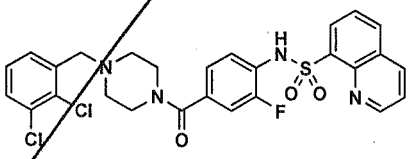
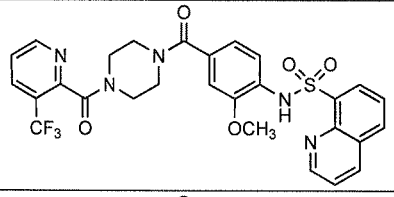
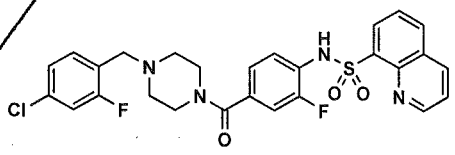
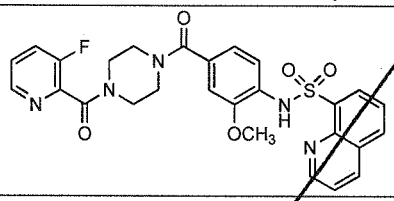
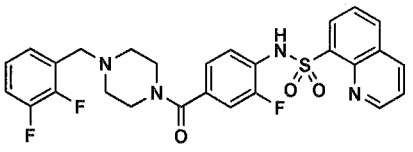
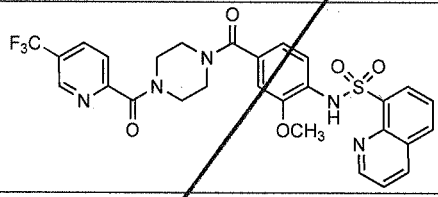
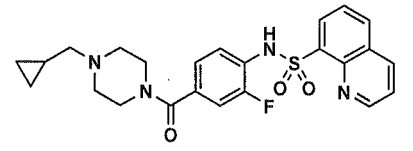
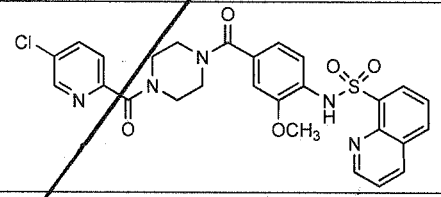
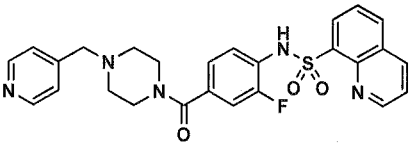
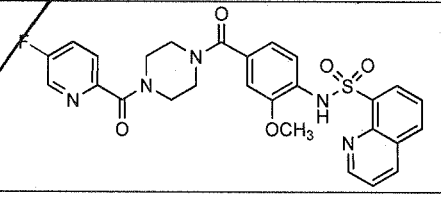
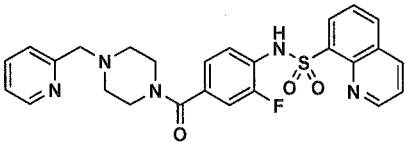
	
	
	
	
	
	
	
	
	

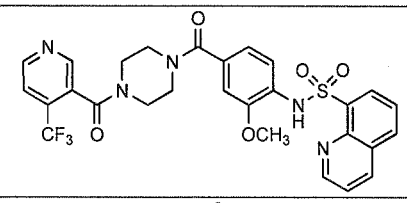
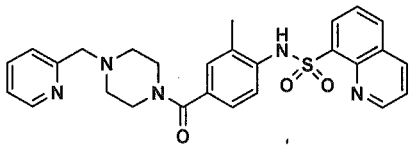
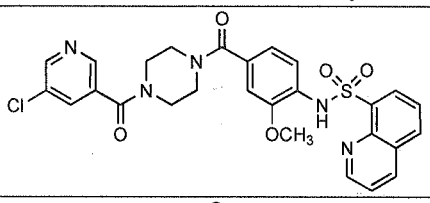
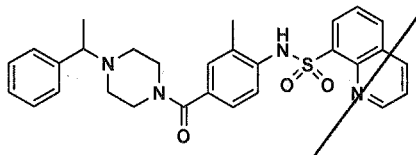
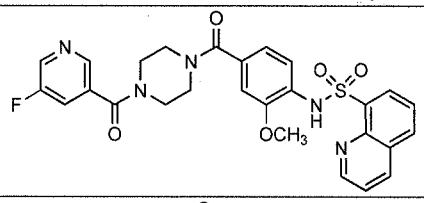
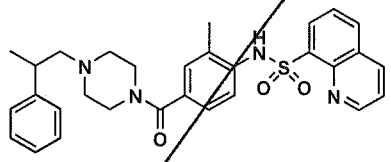
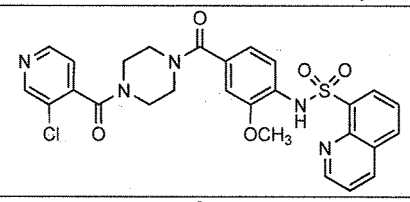
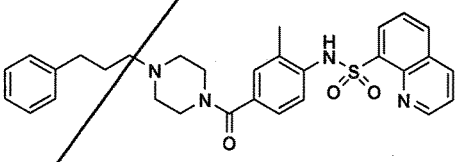
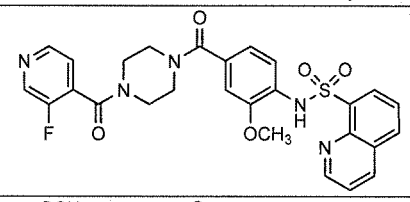
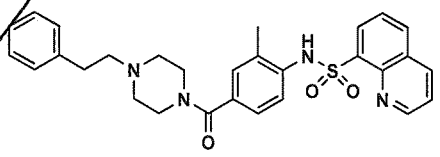
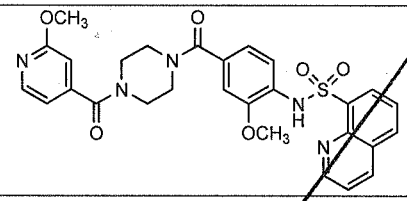
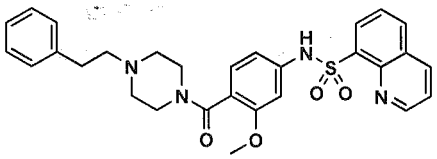
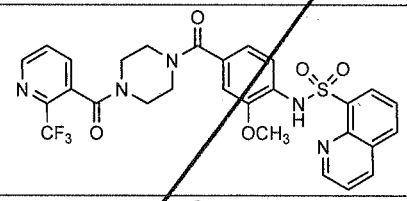
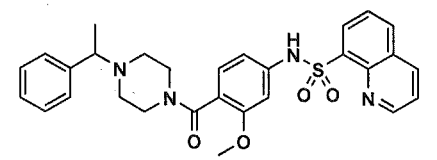
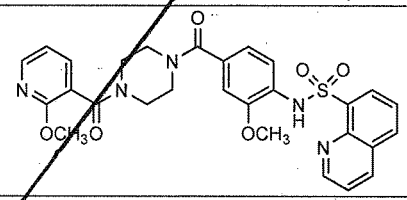
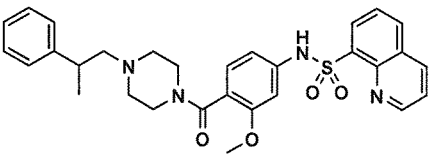
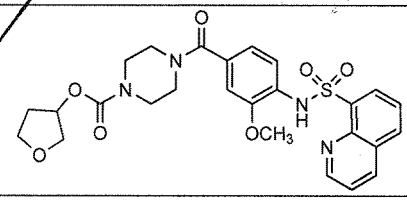
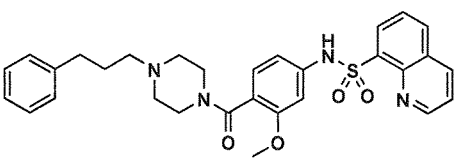
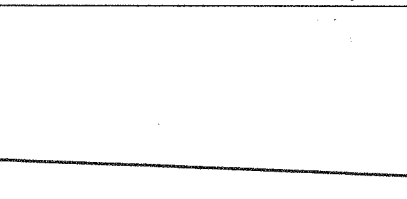
	
	
	
	
	
	
	
	
	
	

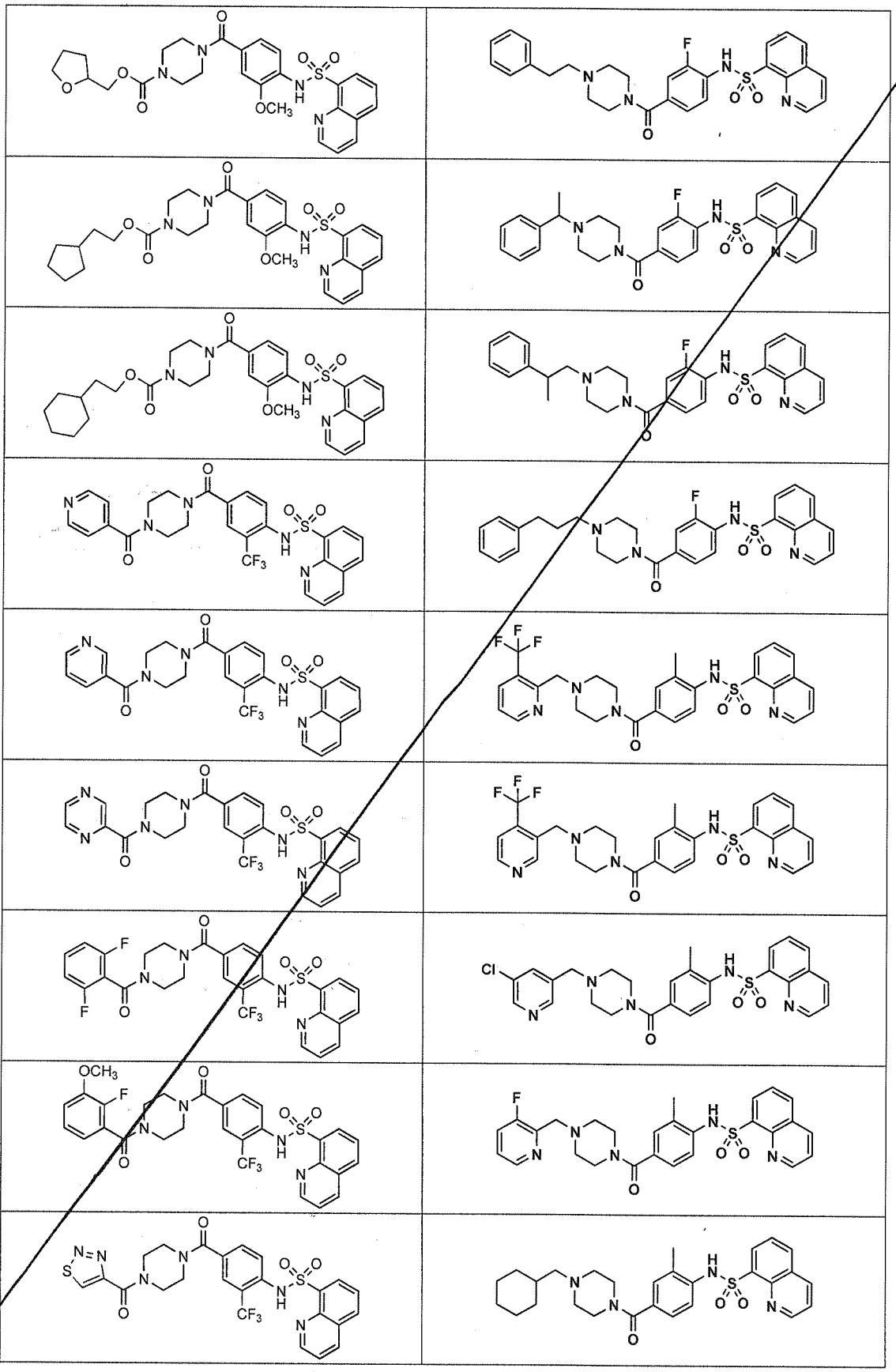
	
	
	
	
	
	
	
	
	

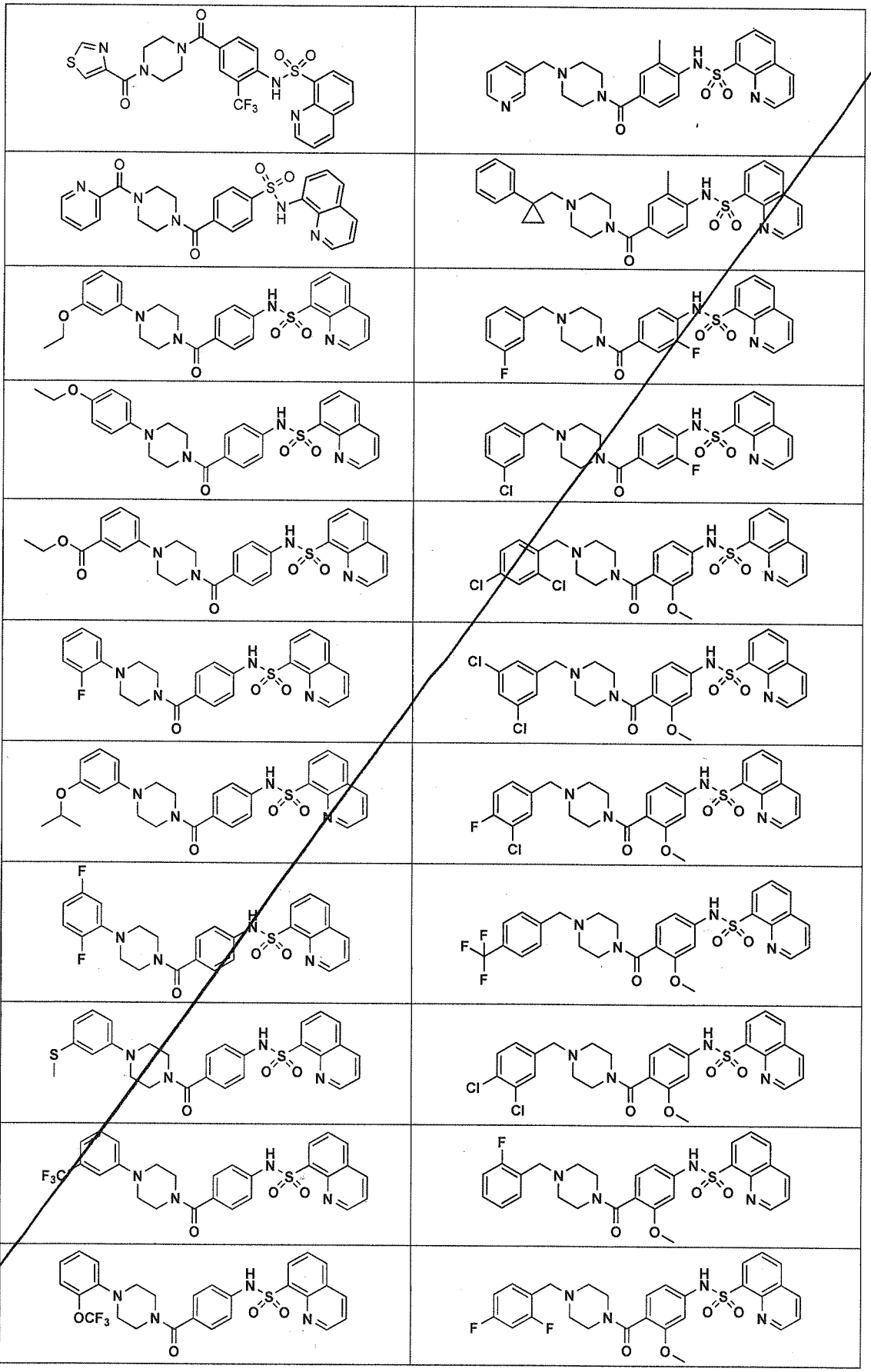
	
	
	
	
	
	
	
	
	

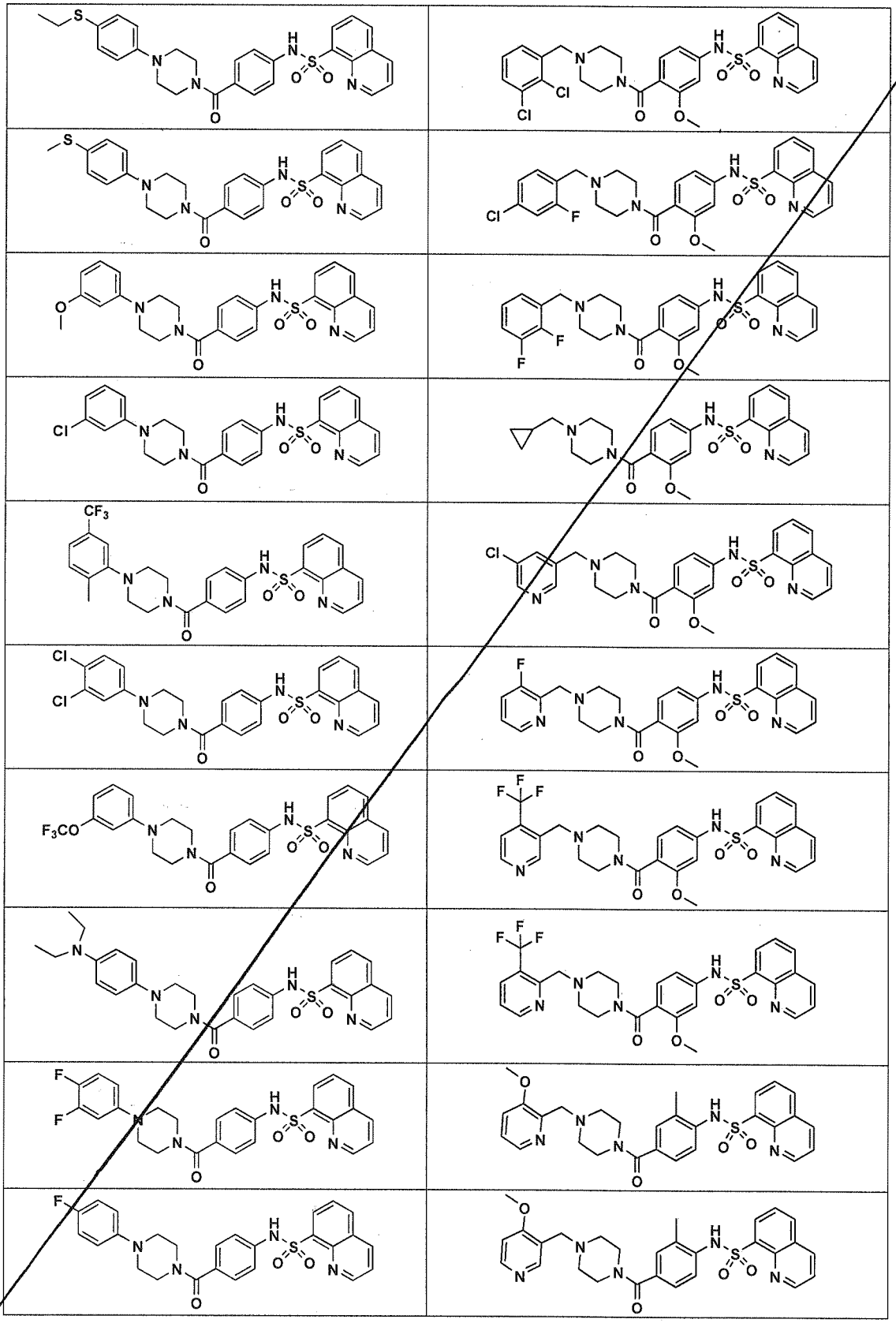
	
	
	
	
	
	
	
	
	
	

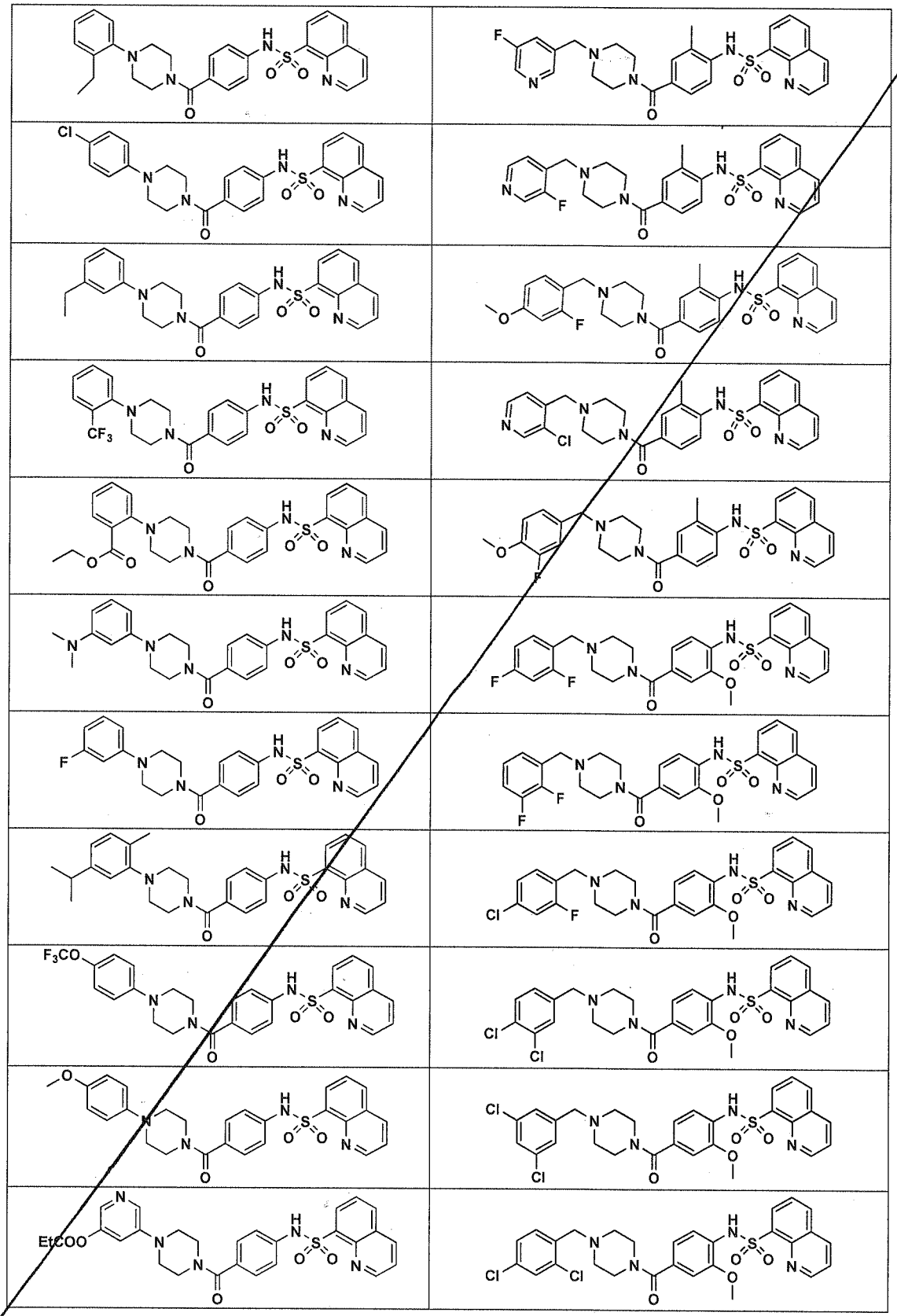
	
	
	
	
	
	
	
	
	

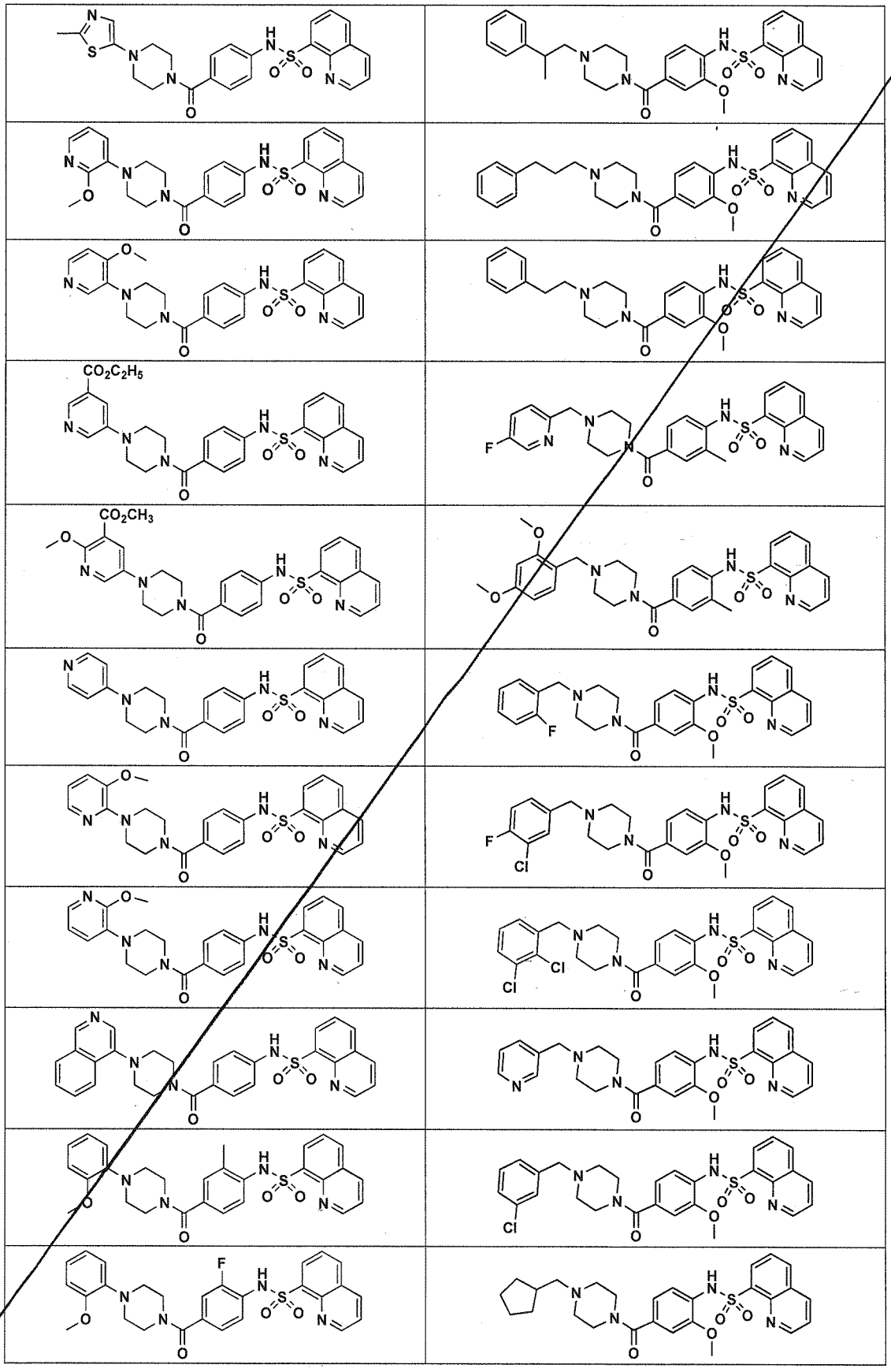
	
	
	
	
	
	
	
	
	
	

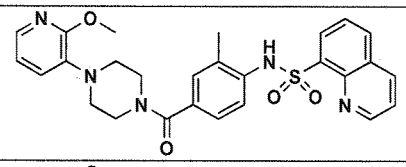
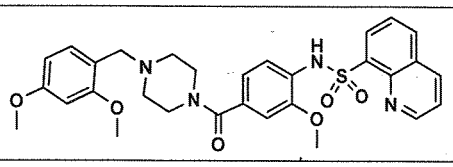
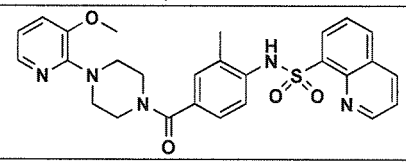
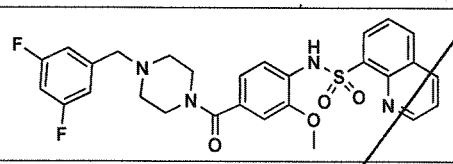
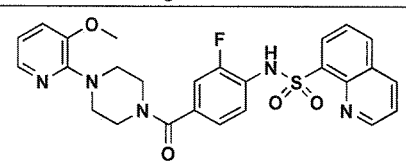
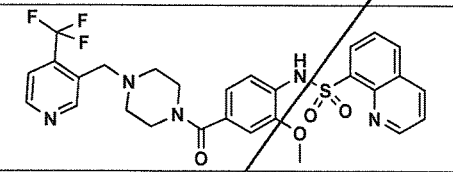
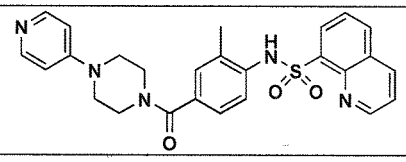
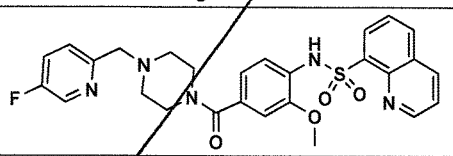
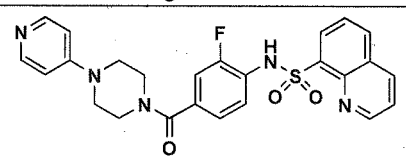
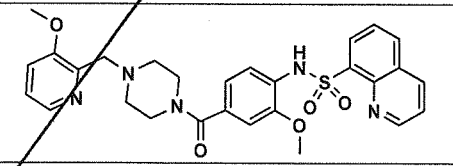
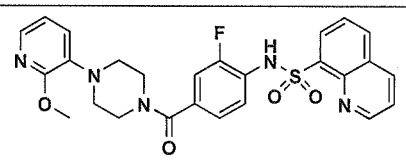
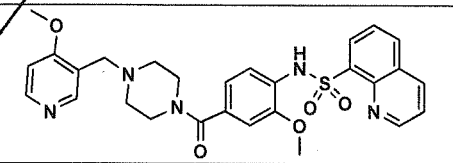
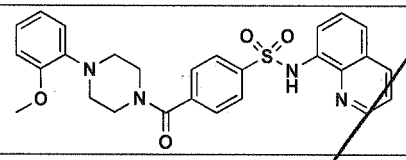
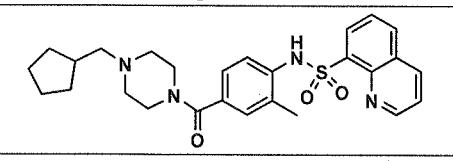
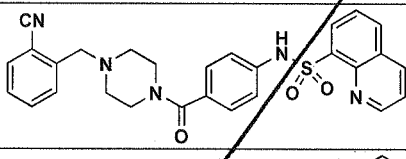
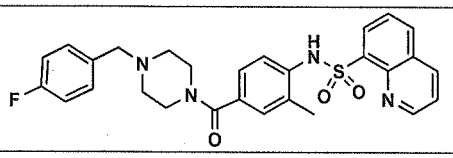
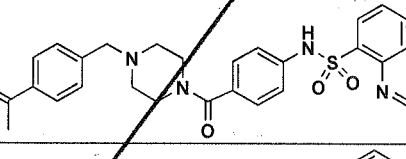
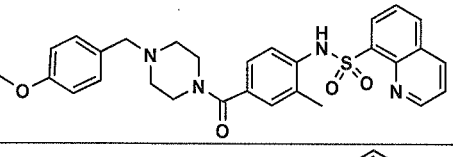
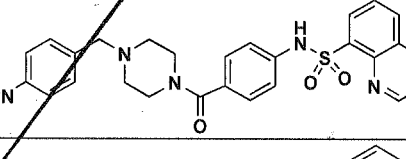
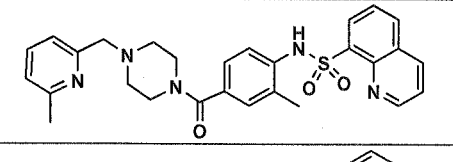
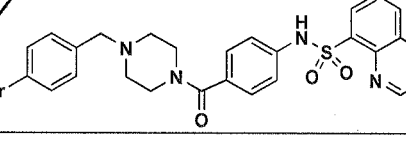
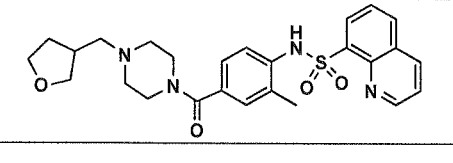


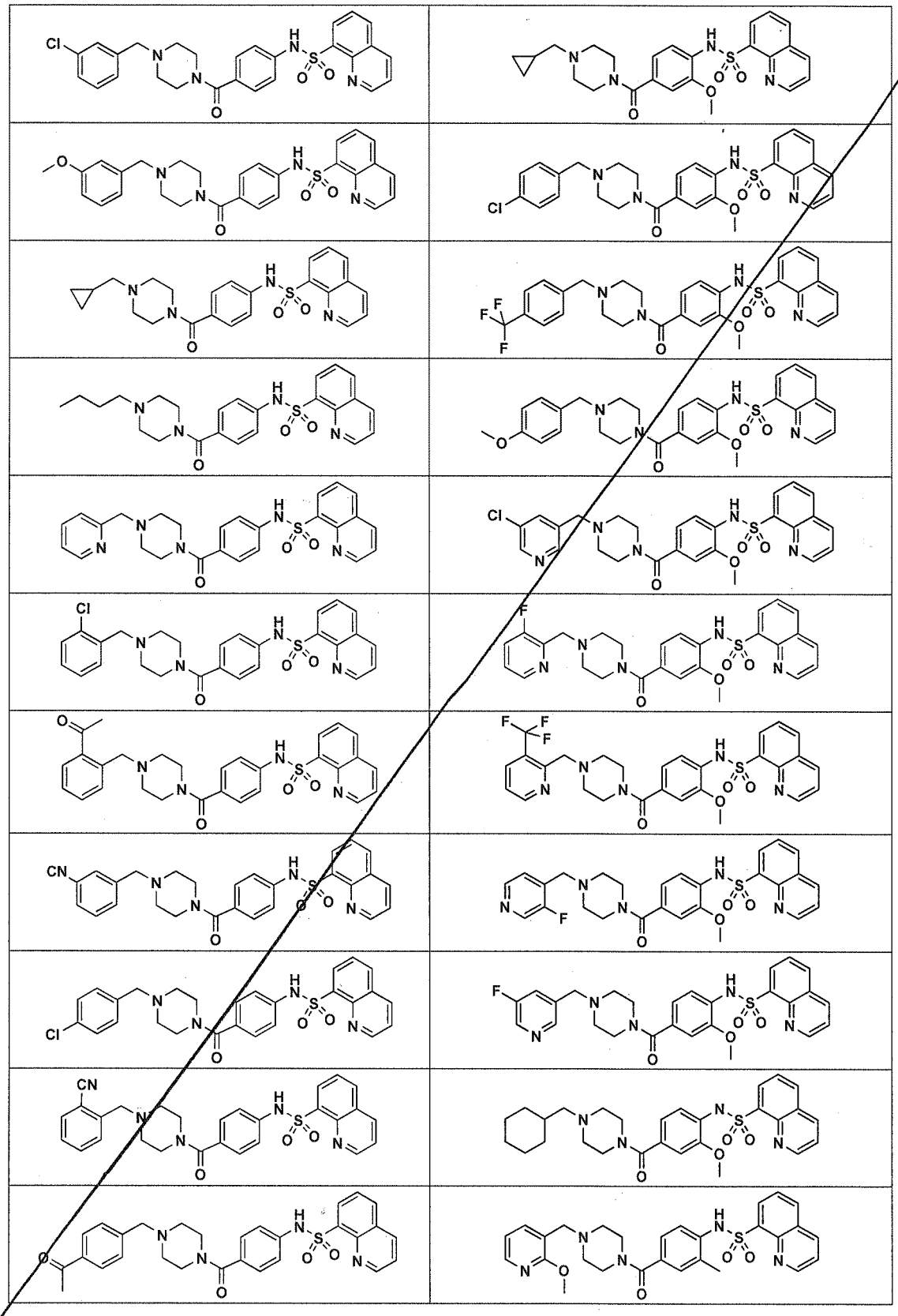


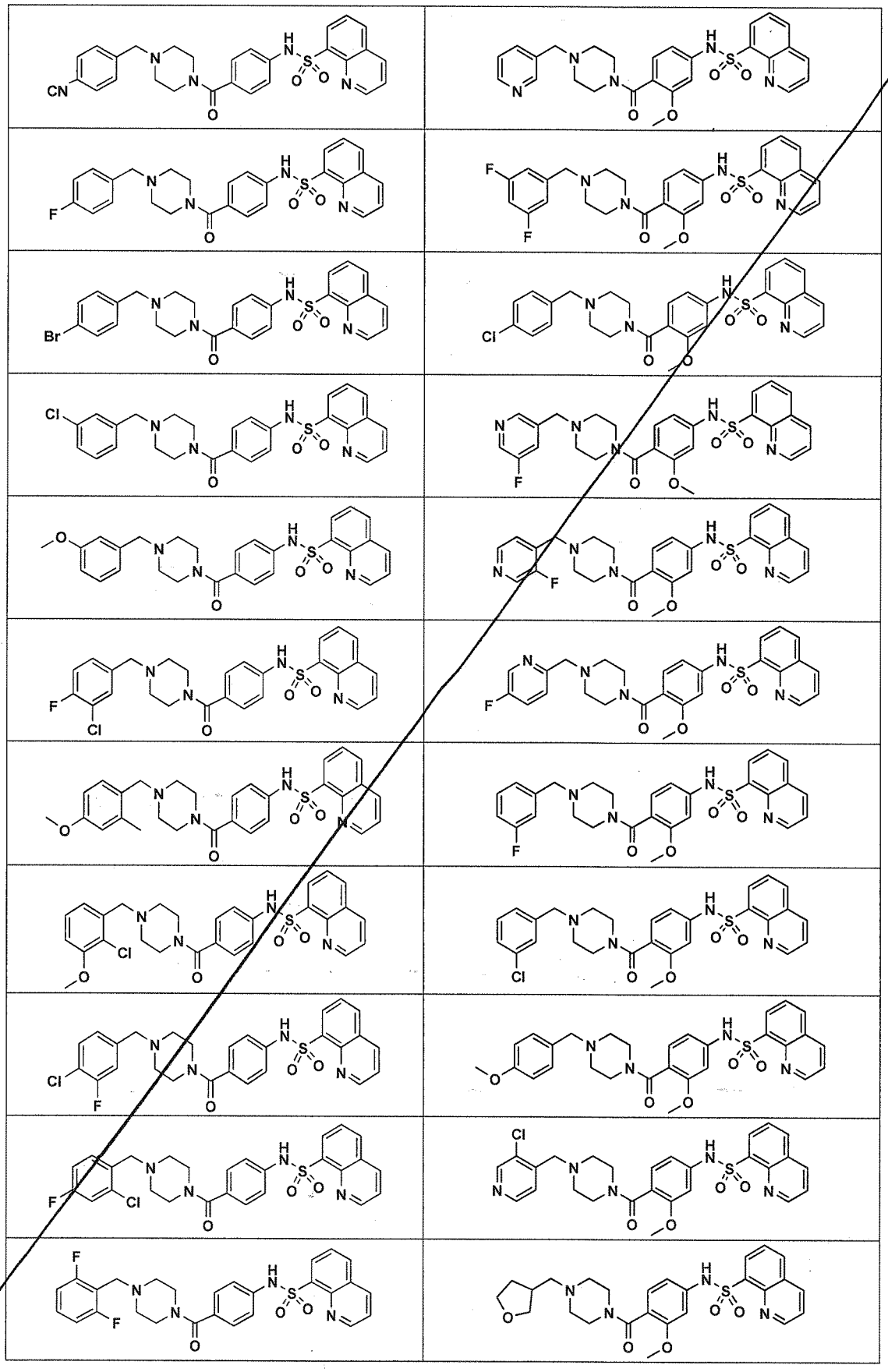


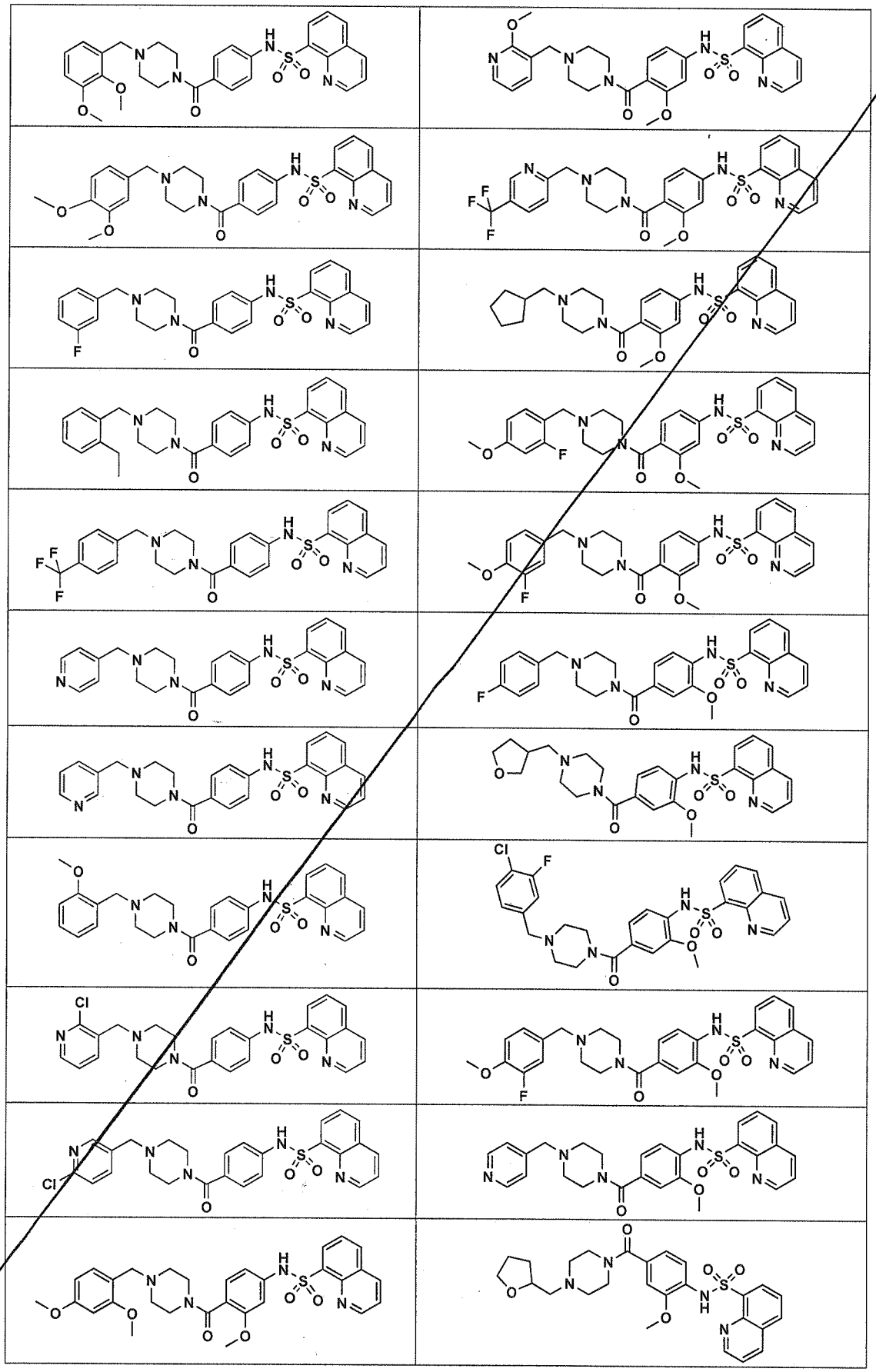


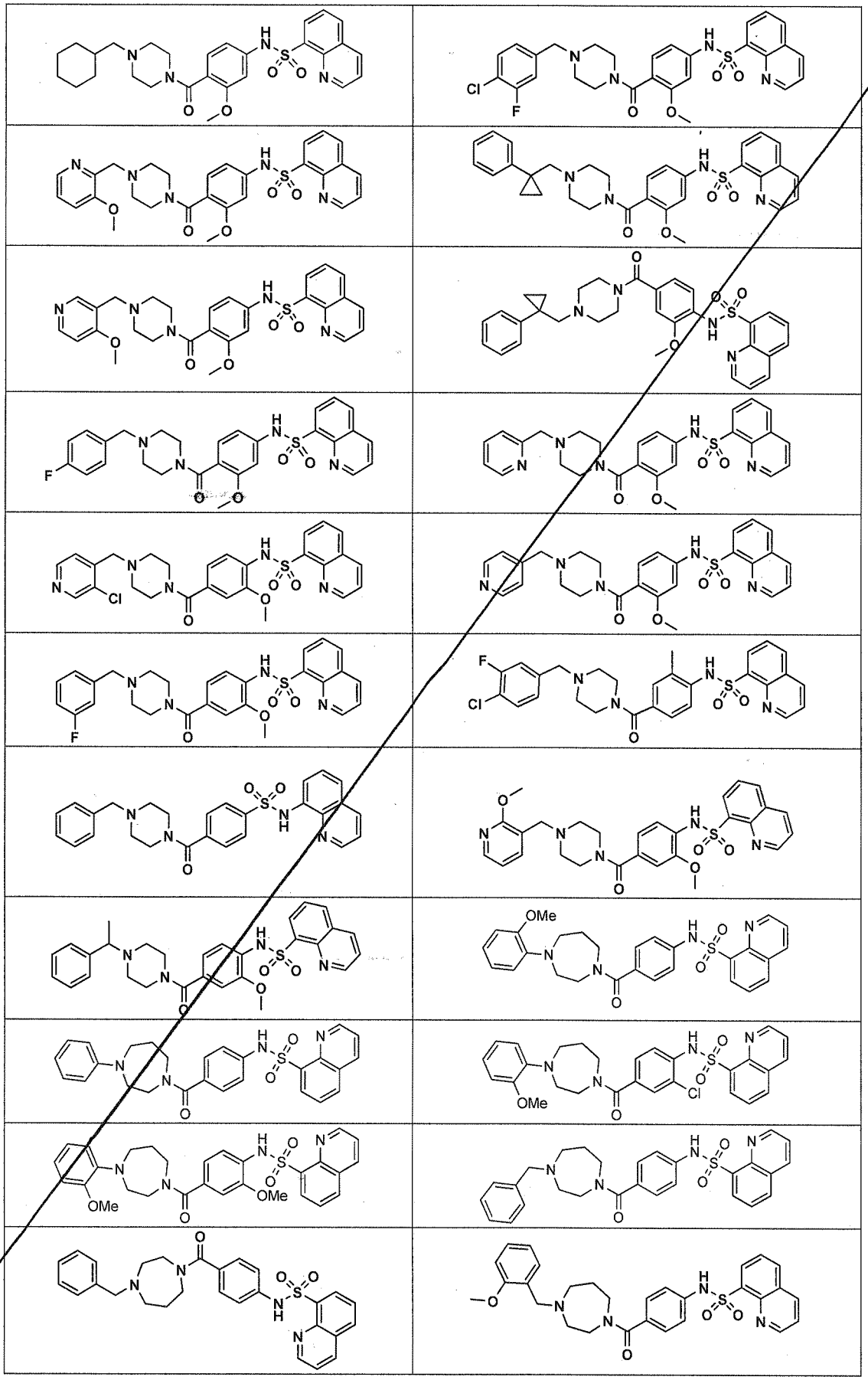


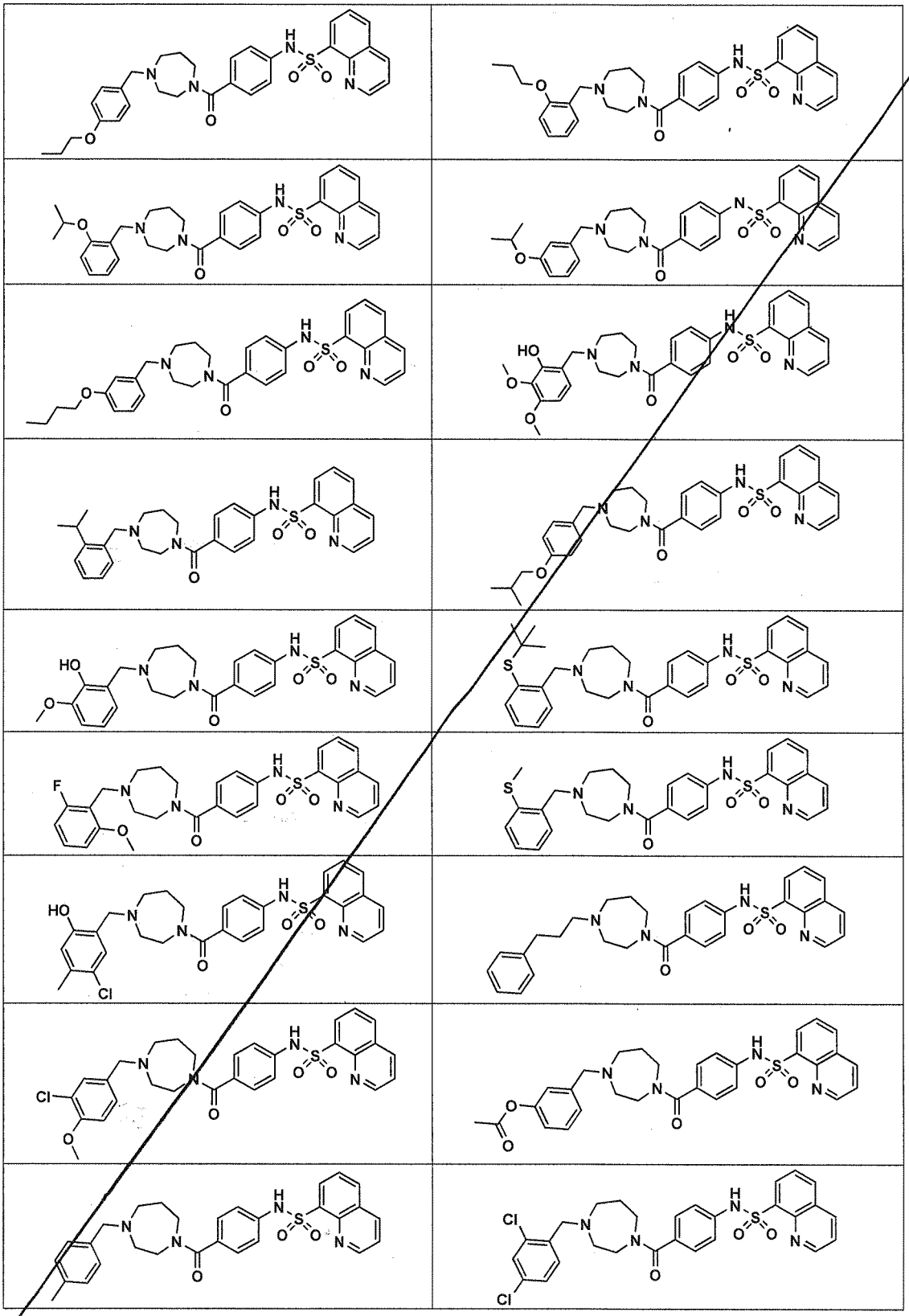
	
	
	
	
	
	
	
	
	
	
	
	

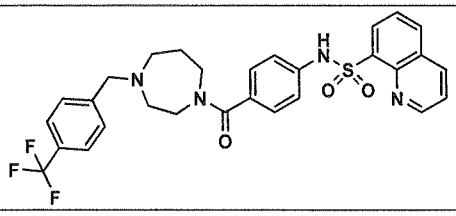
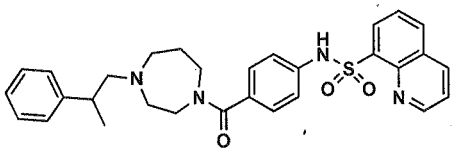
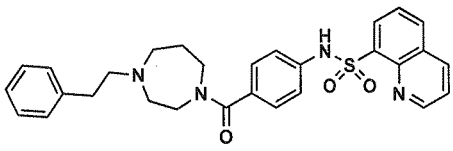
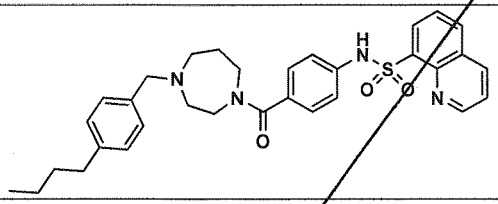
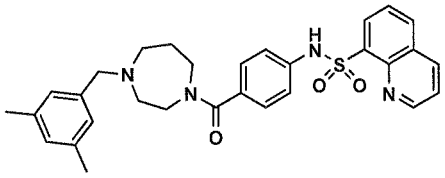
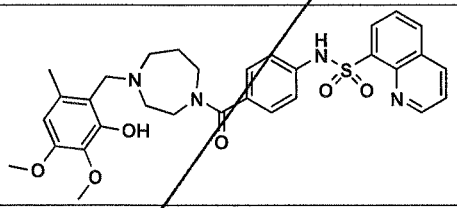
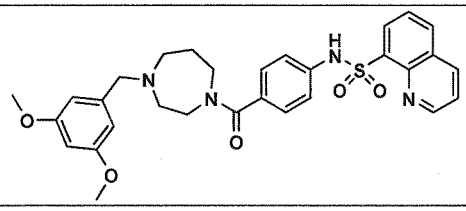
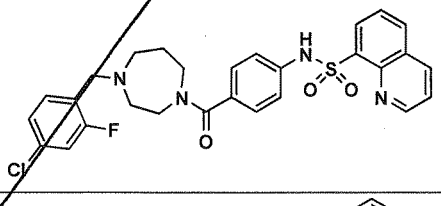
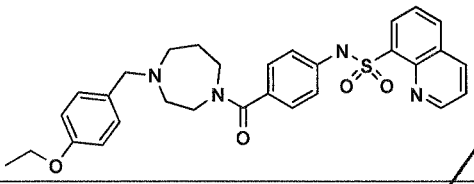
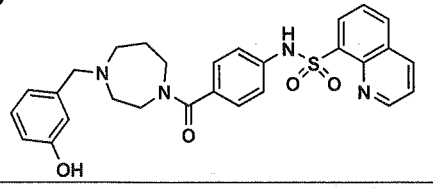
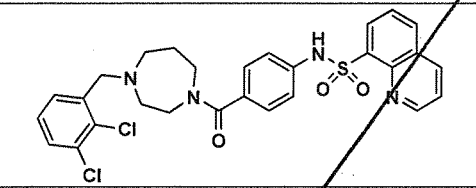
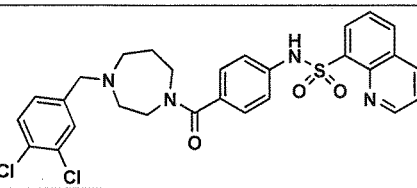
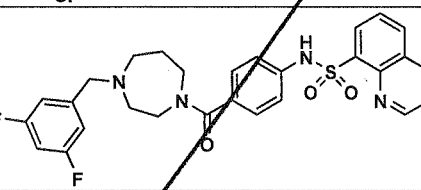
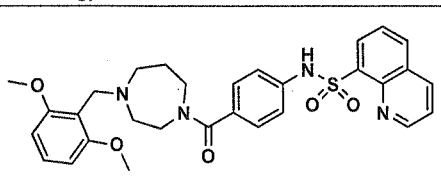
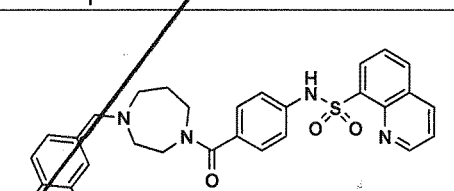
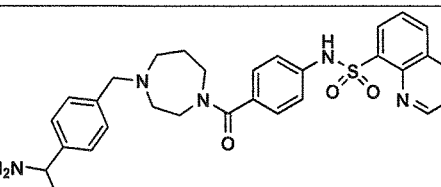


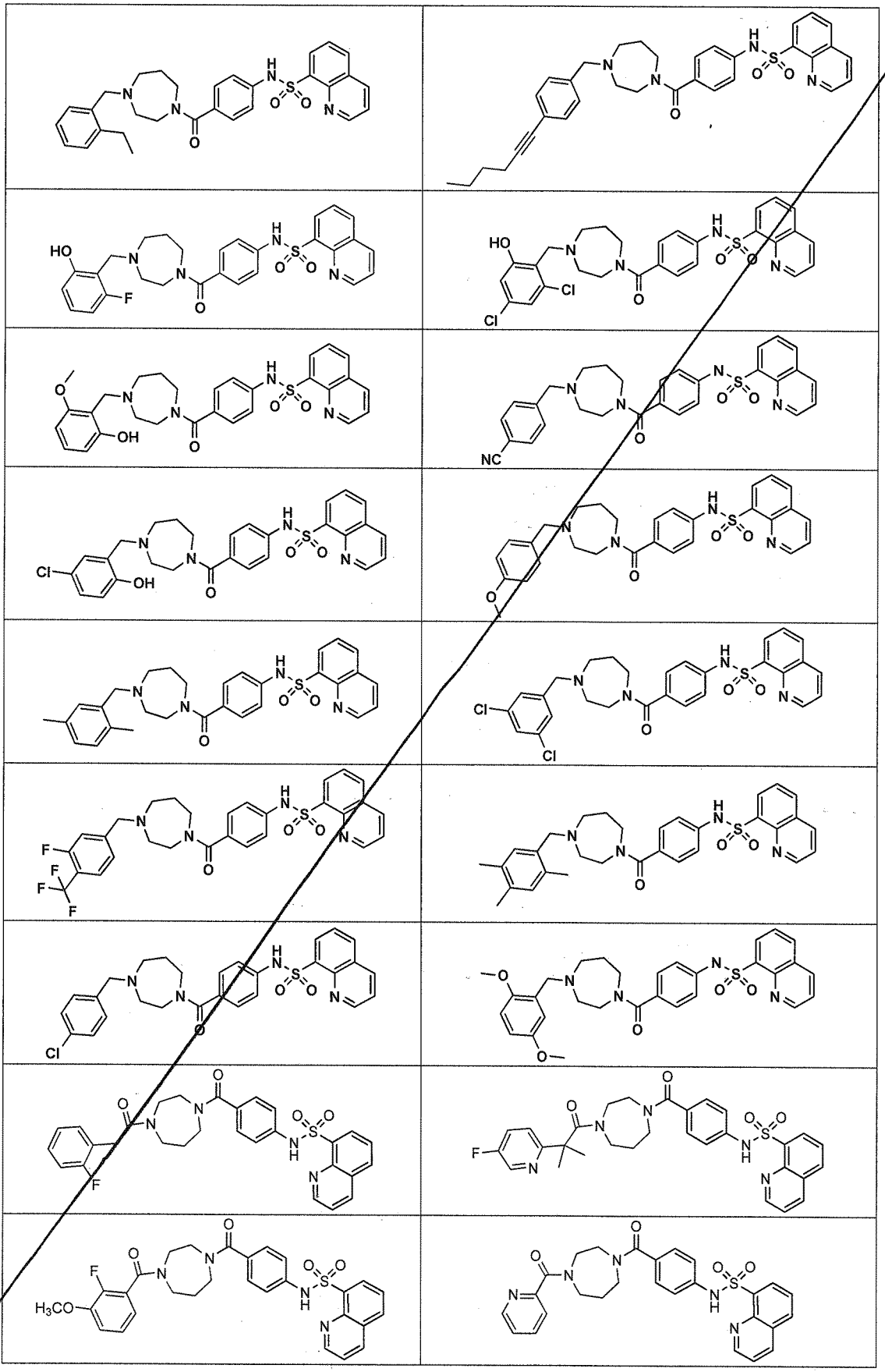


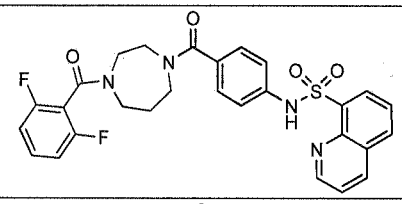
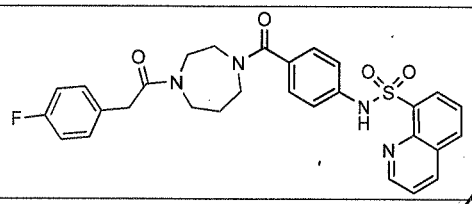
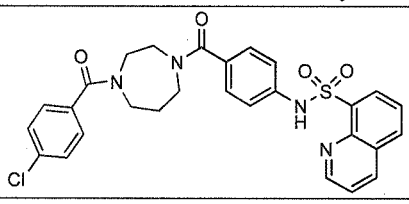
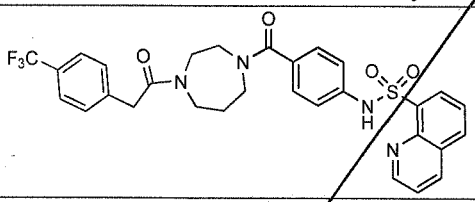
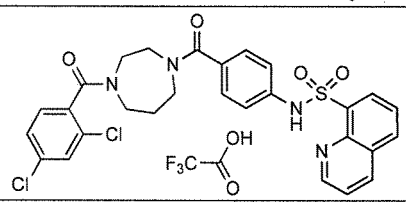
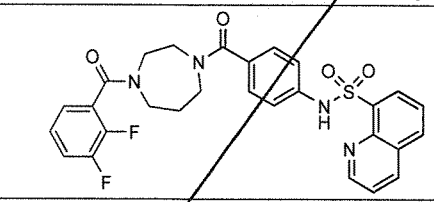
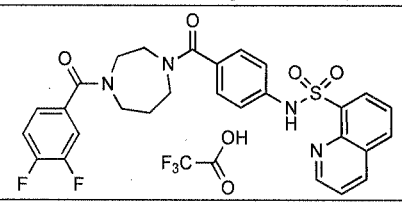
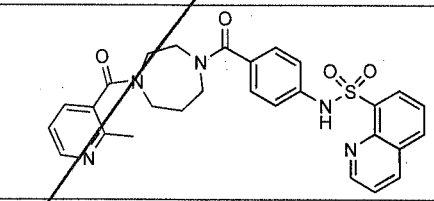
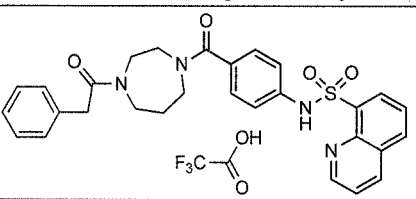
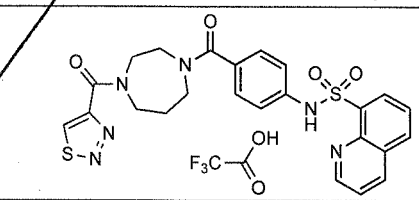
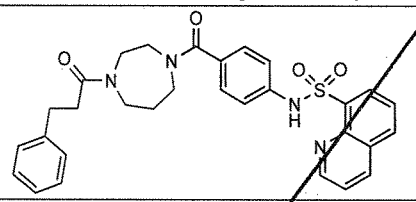
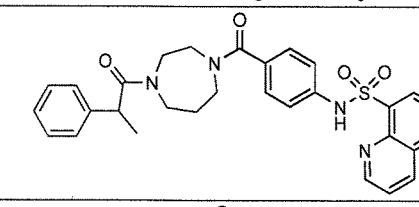
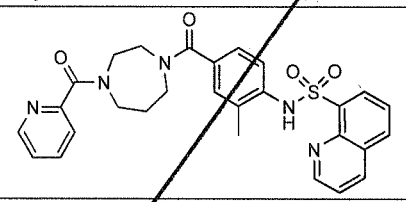
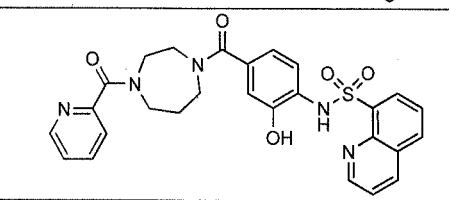
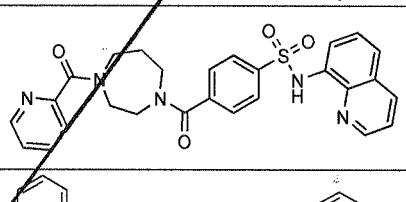
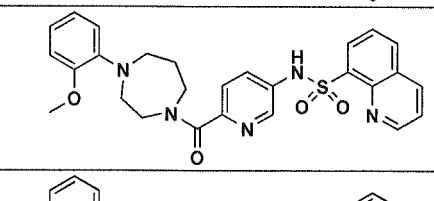
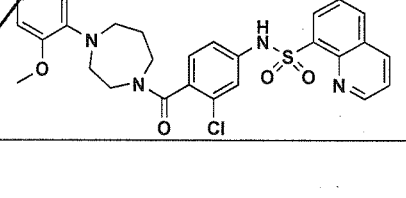
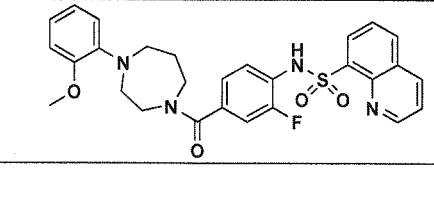
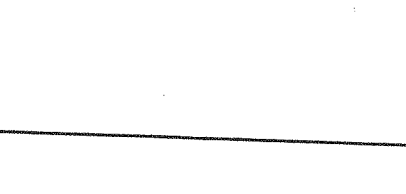
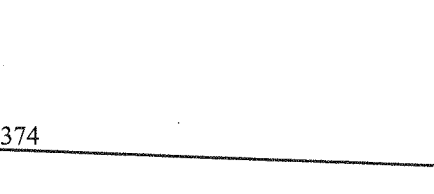


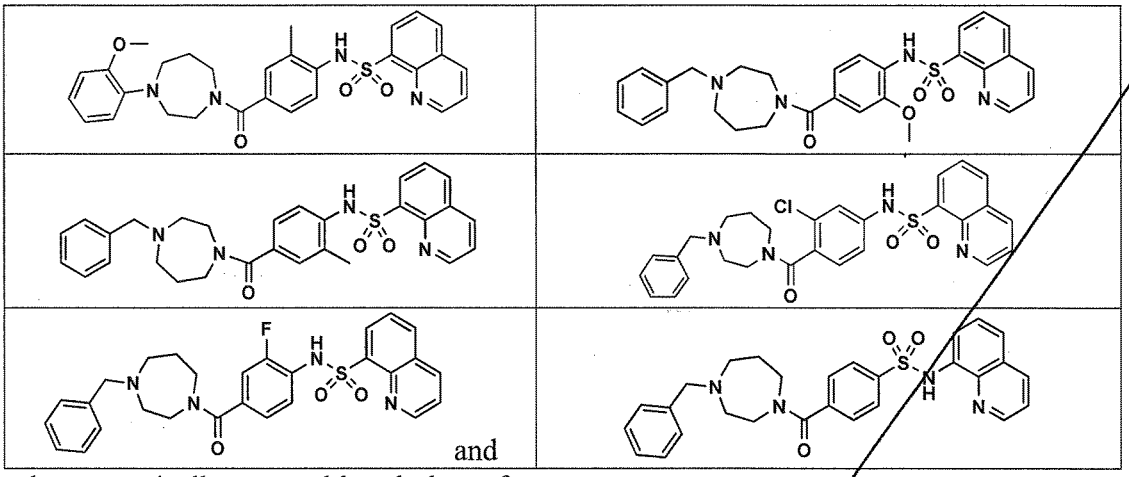




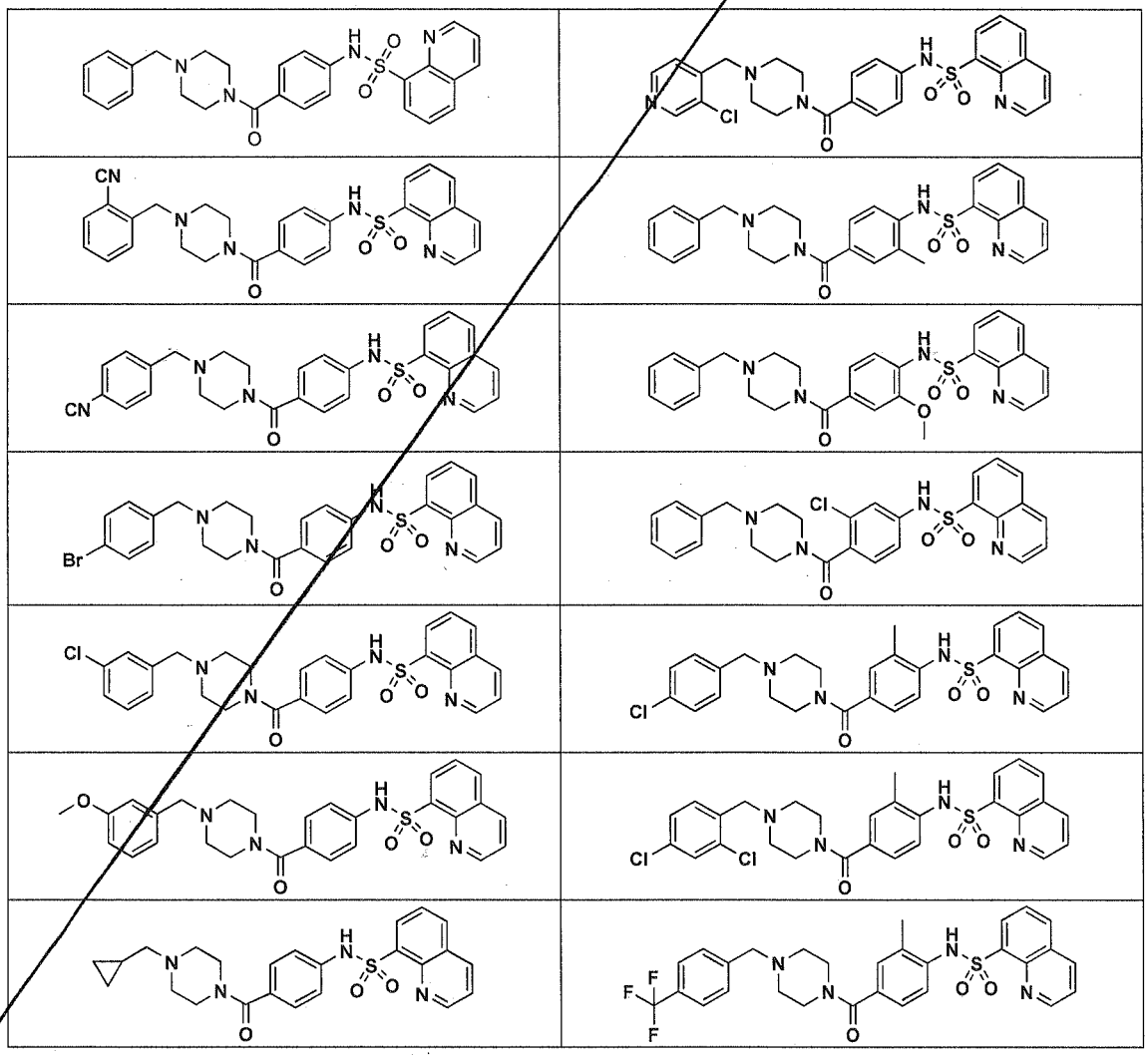


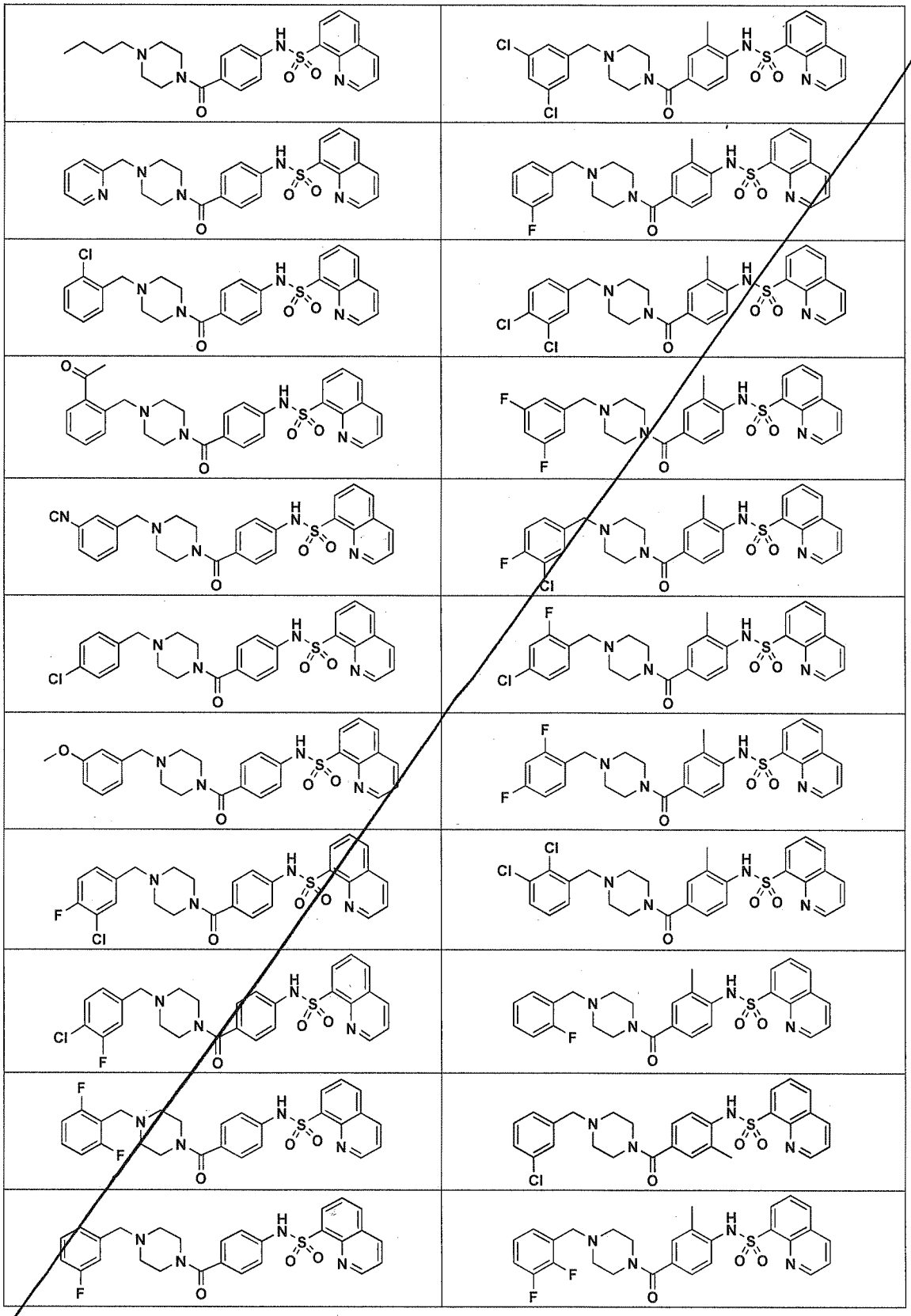
	
	
	
	
	
	
	
	
	
	

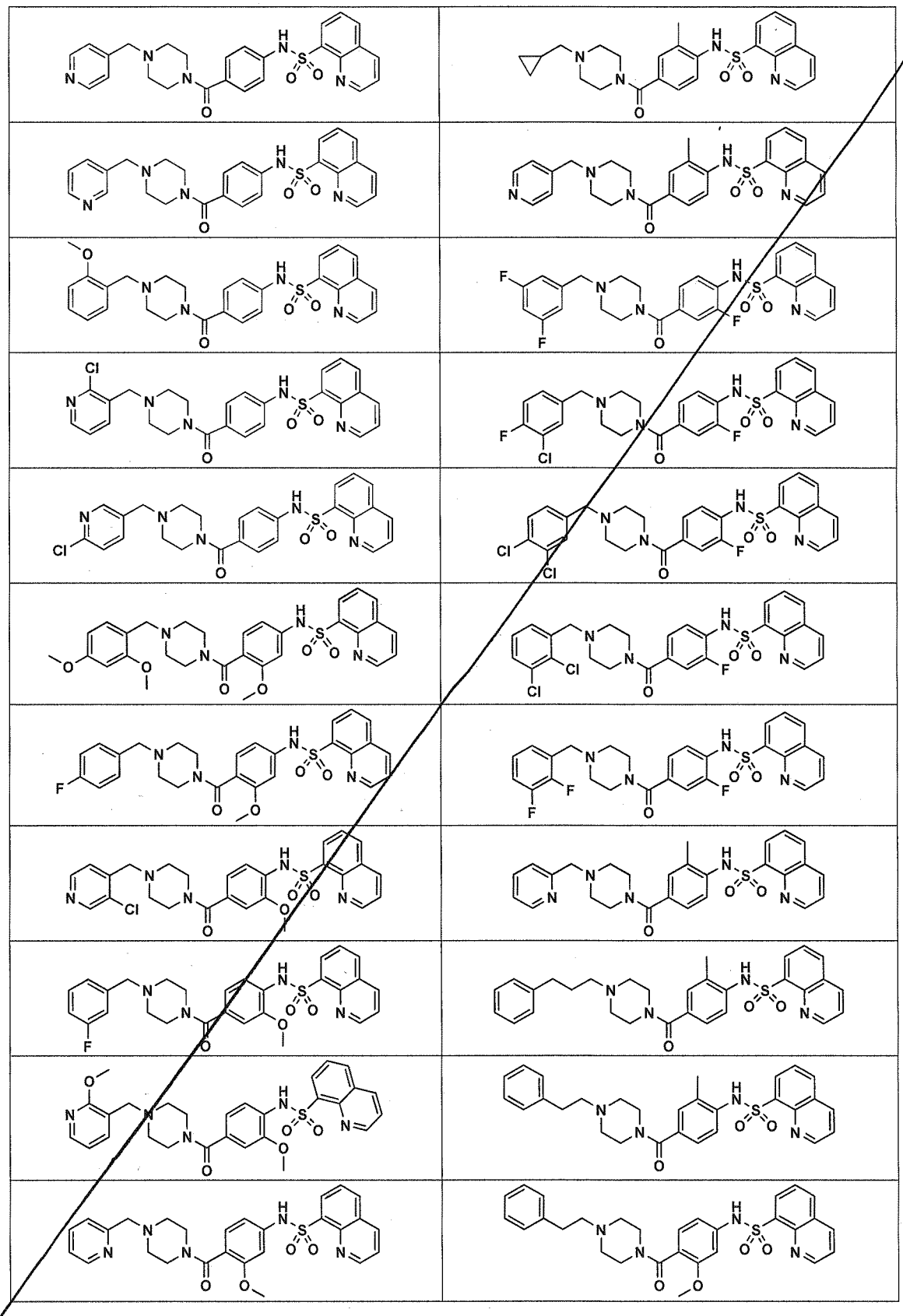


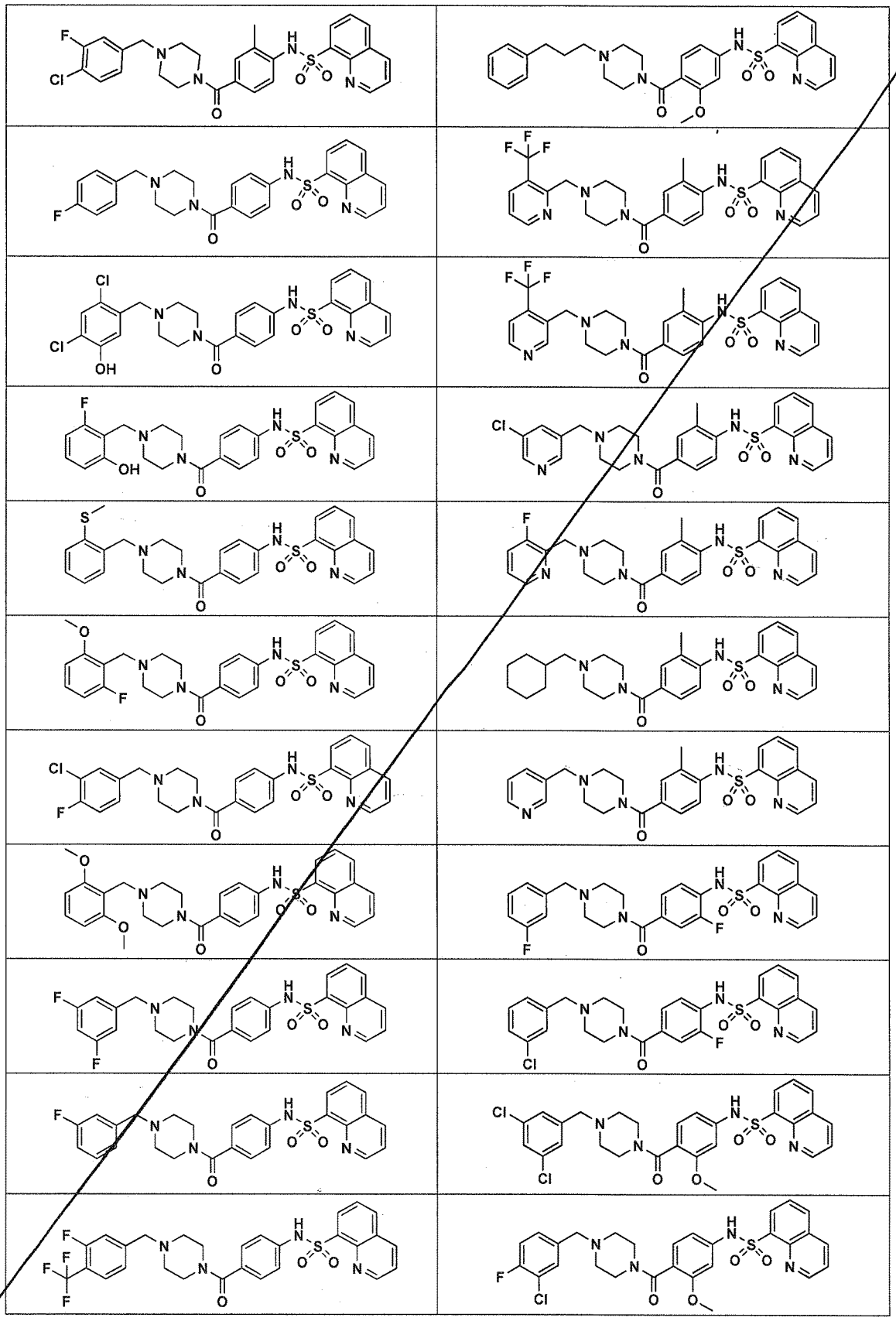
and or pharmaceutically acceptable salt thereof.

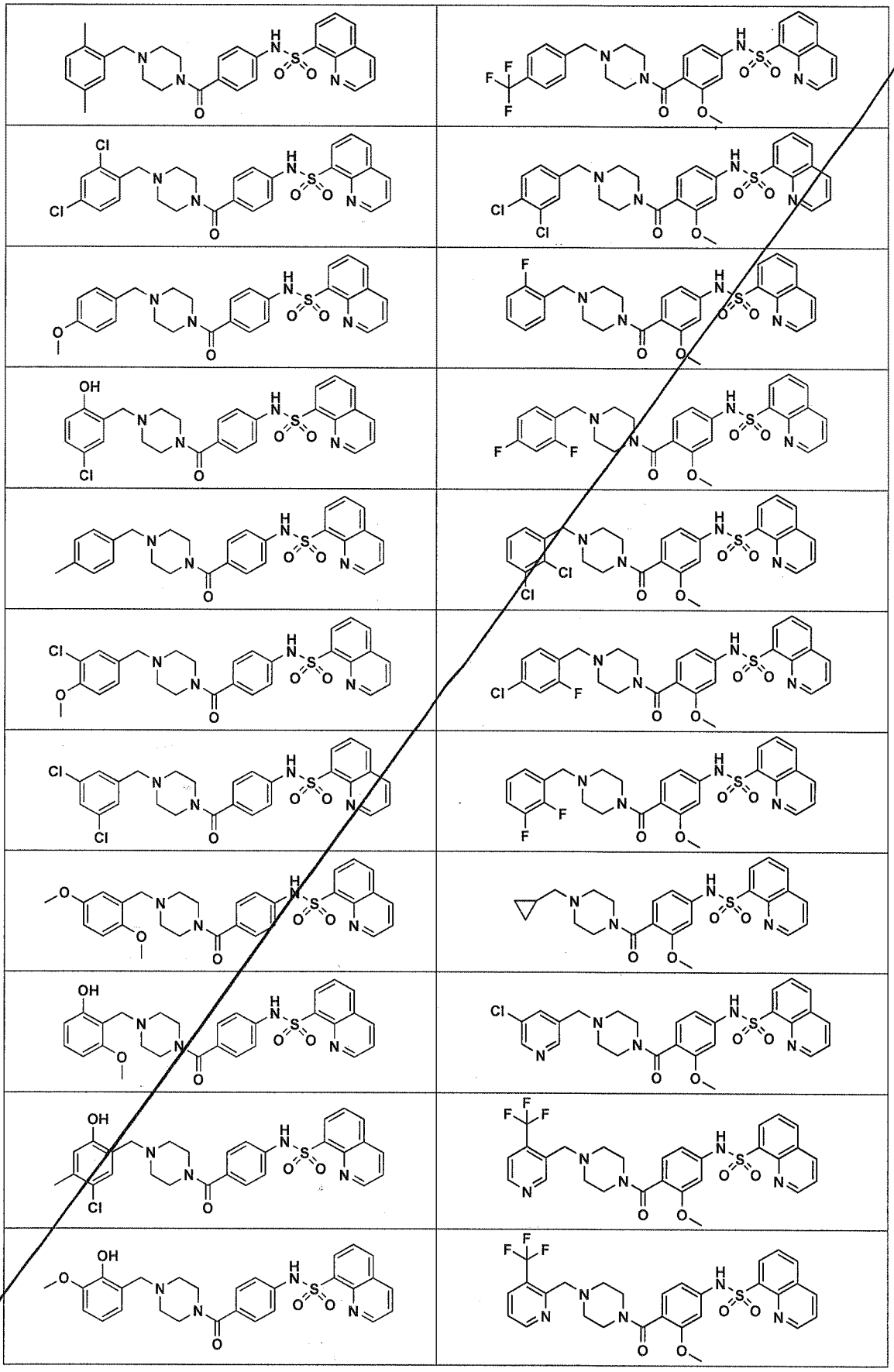
18. The compound of claim 1, wherein the compound is selected from the group consisting of:

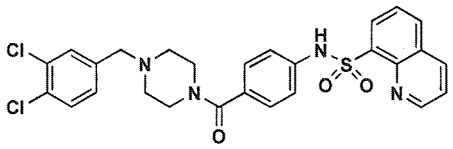
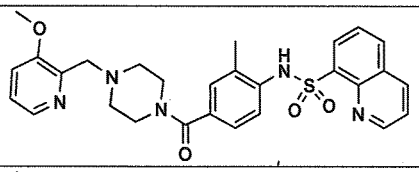
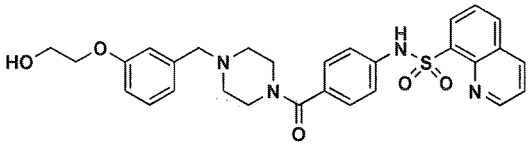
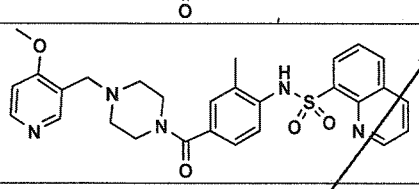
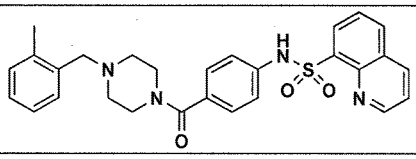
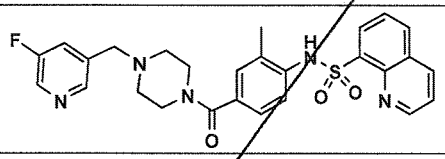
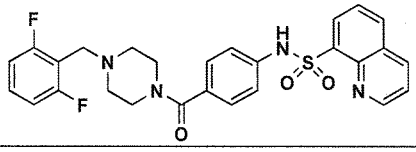
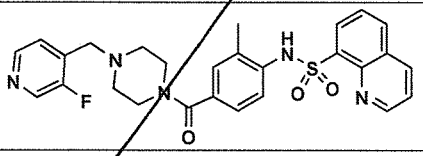
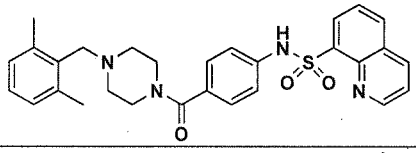
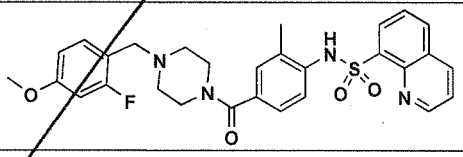
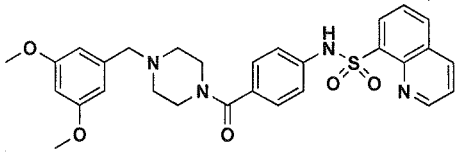
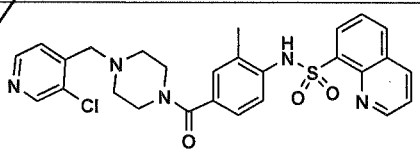
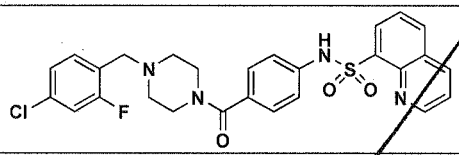
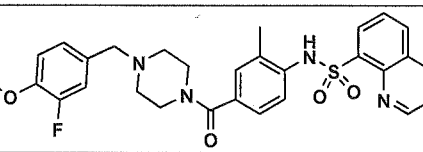
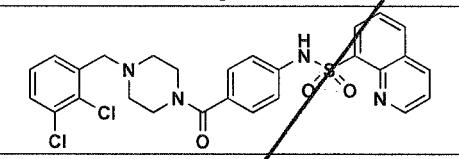
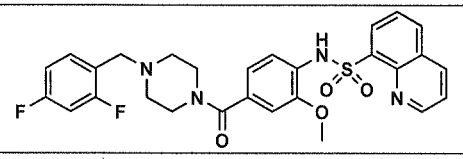
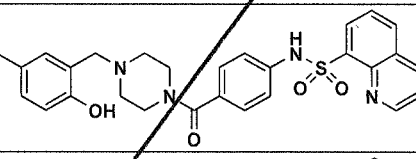
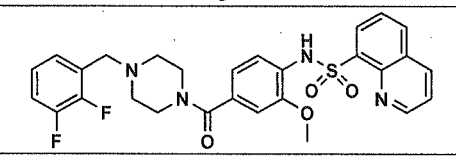
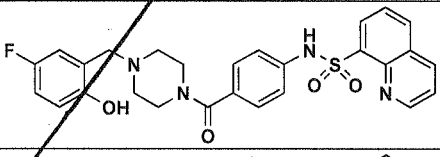
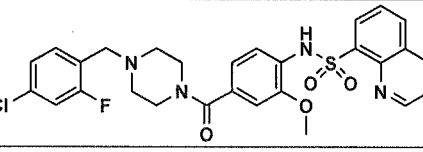
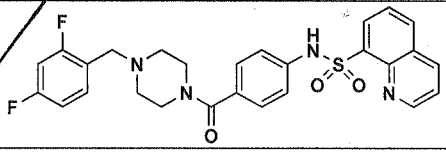
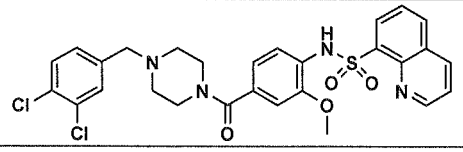


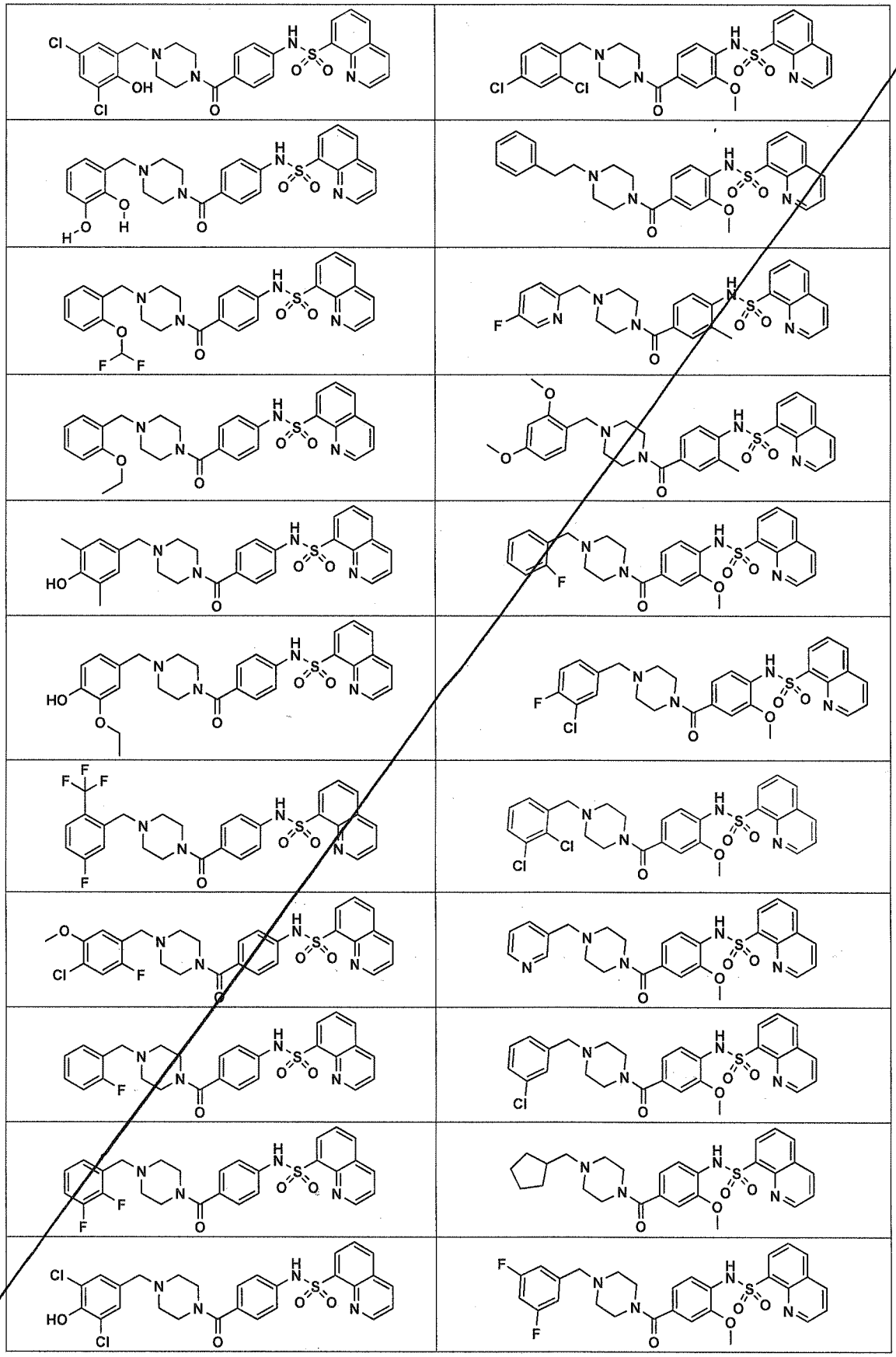


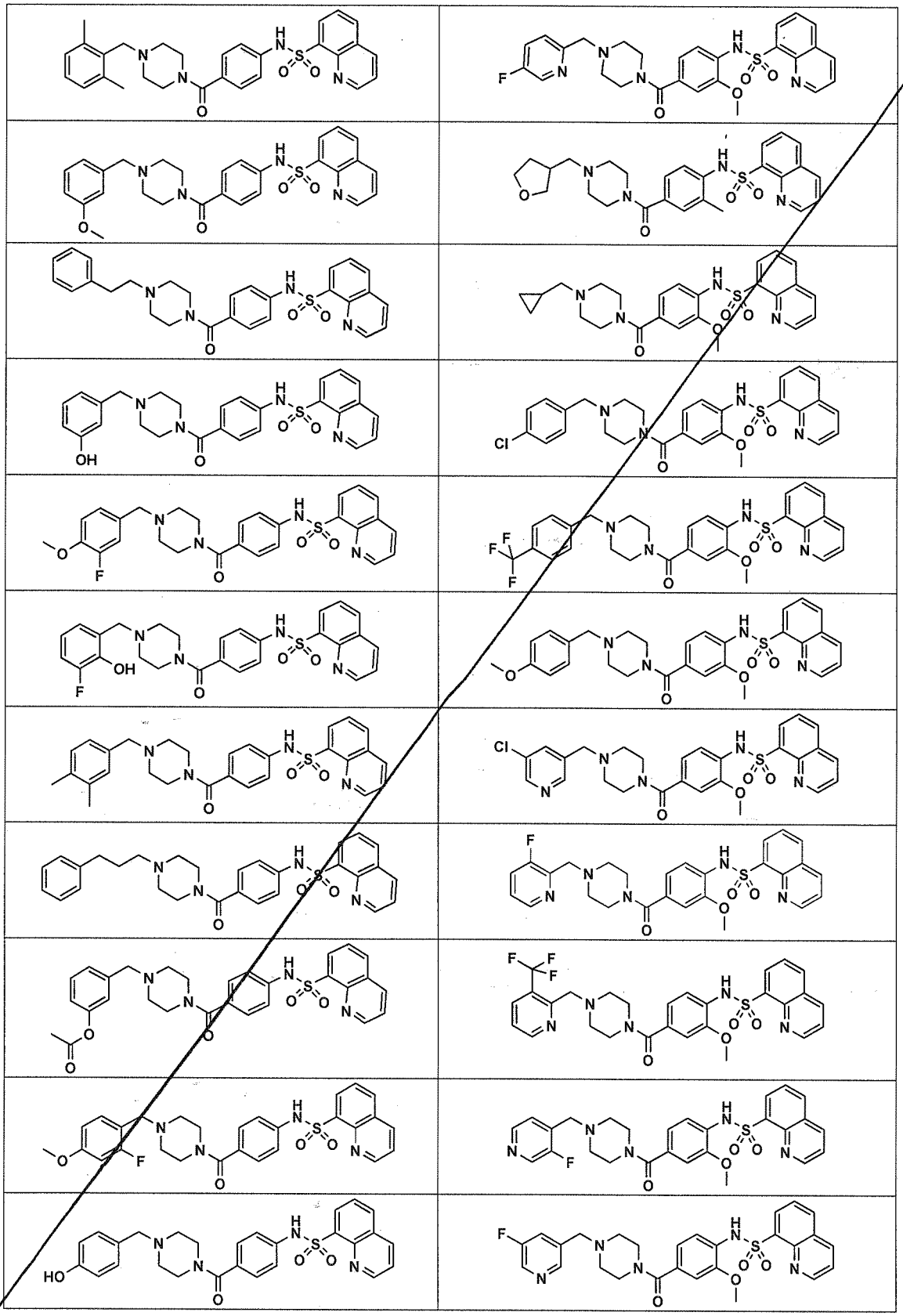


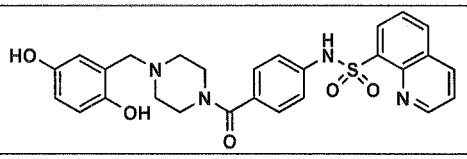
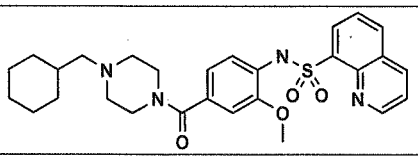
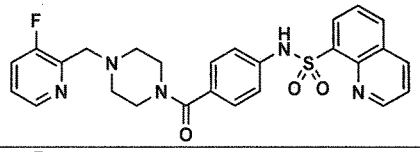
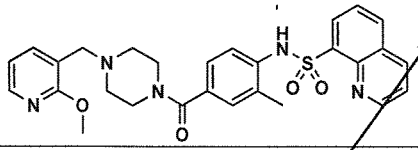
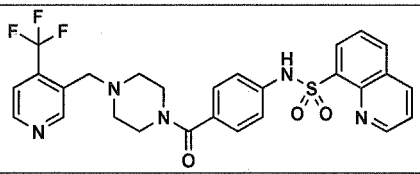
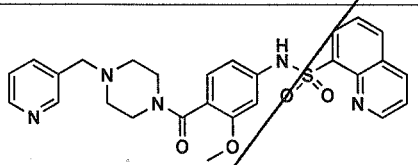
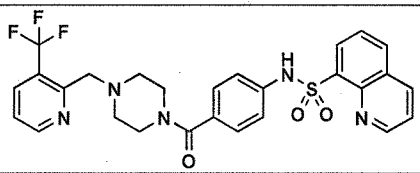
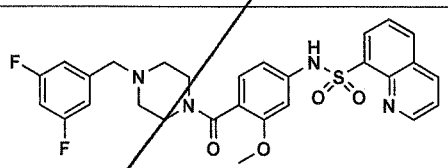
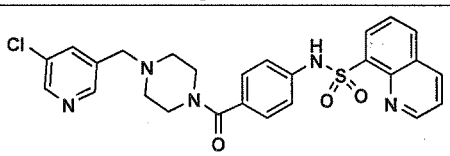
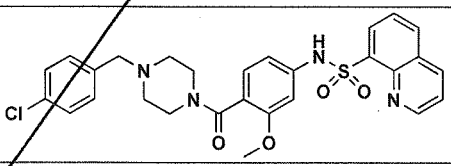
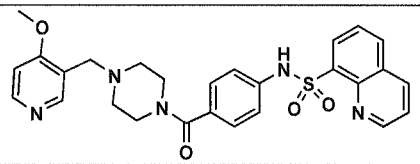
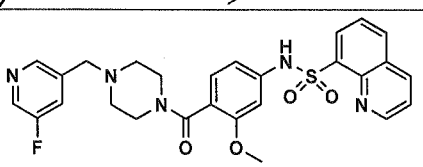
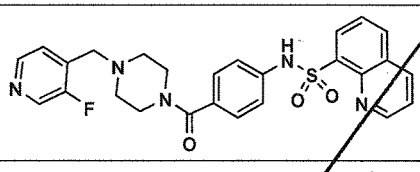
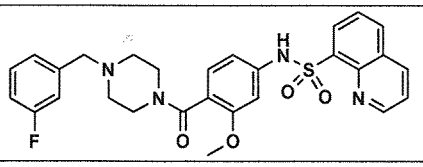
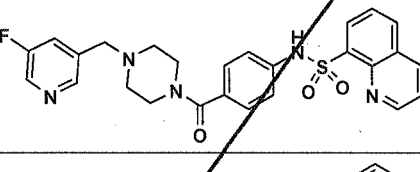
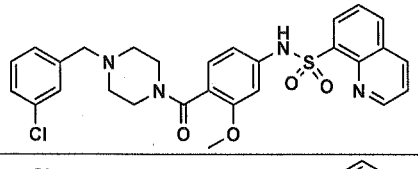
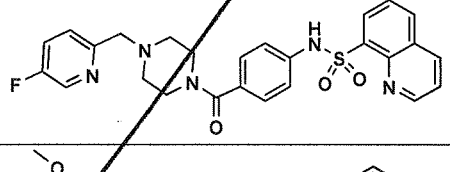
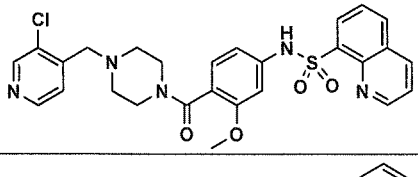
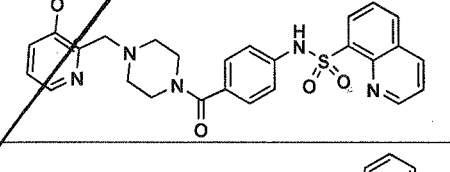
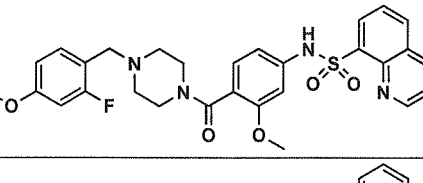
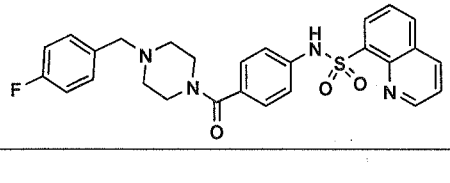
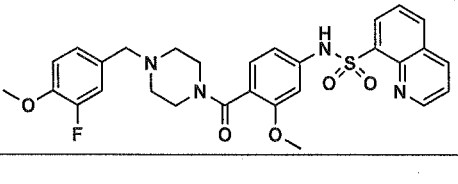
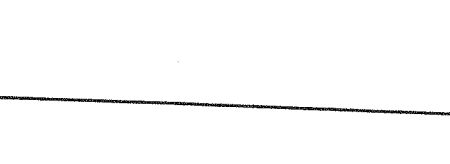
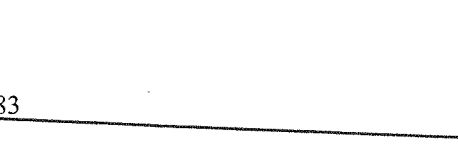


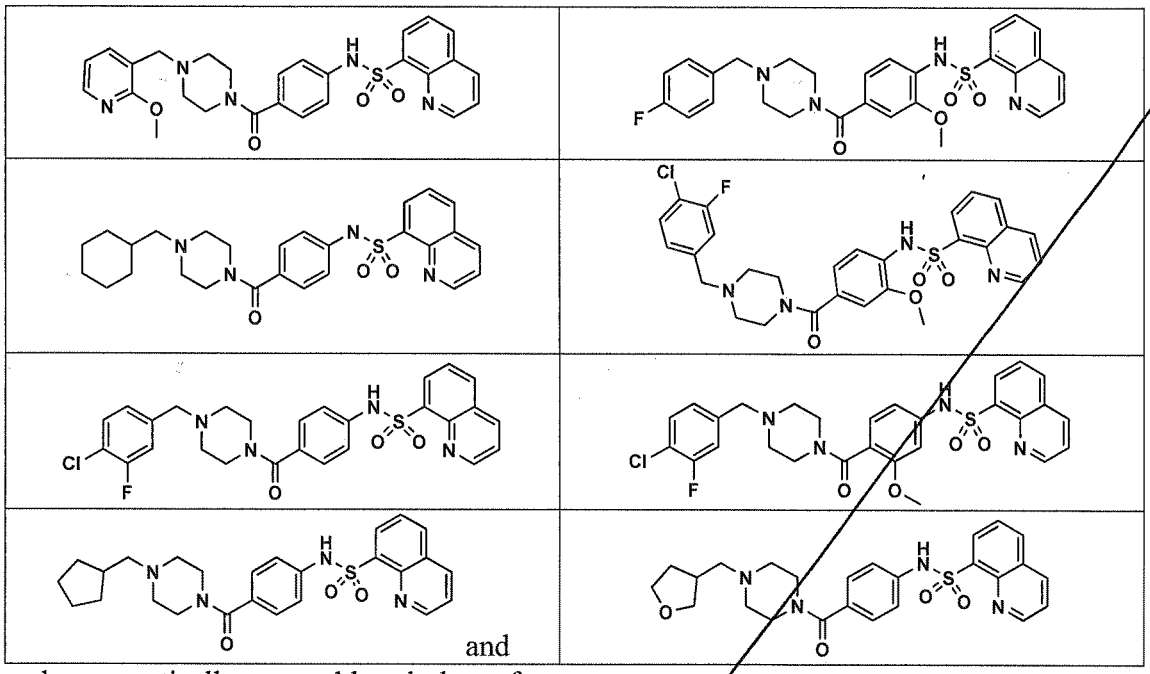




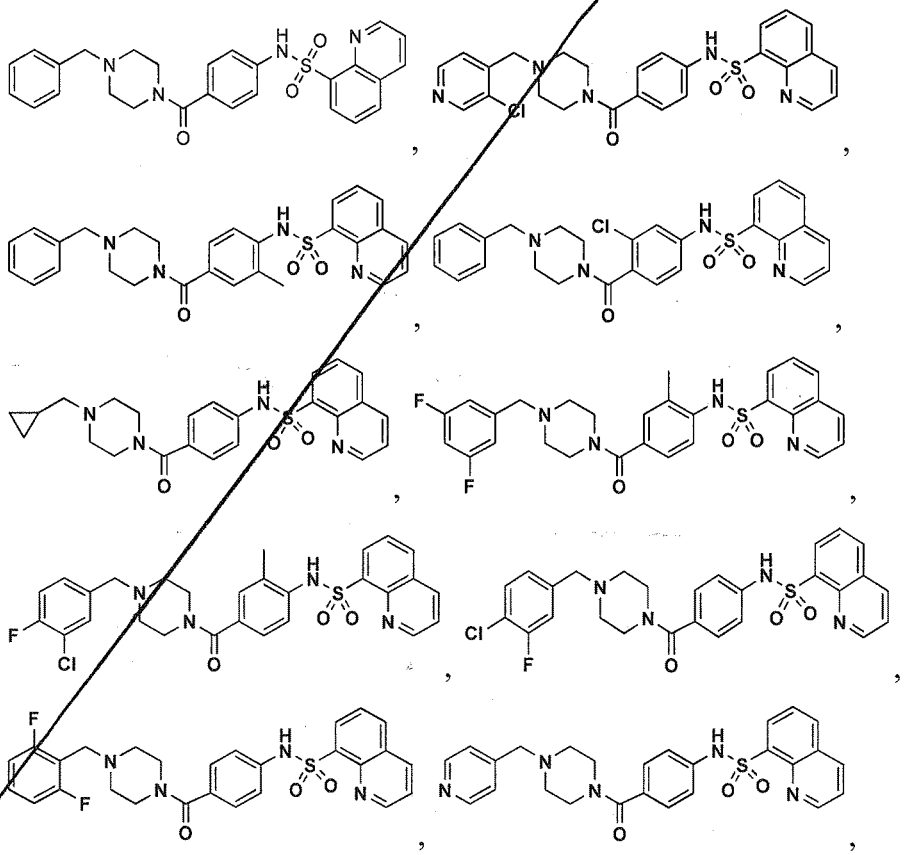


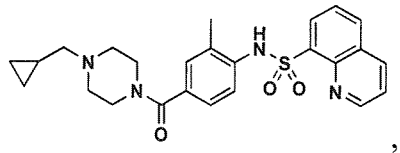
	
	
	
	
	
	
	
	
	
	
	
	



and or pharmaceutically acceptable salt thereof.

19. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

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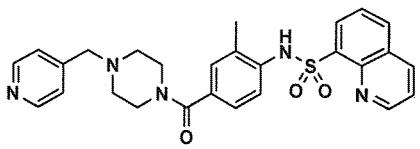
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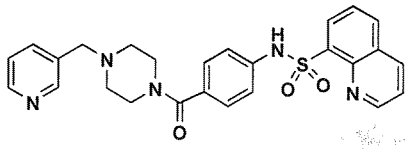
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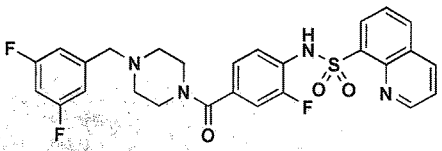
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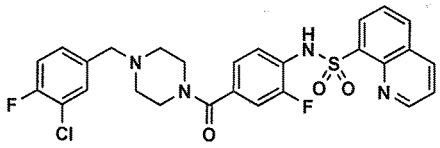
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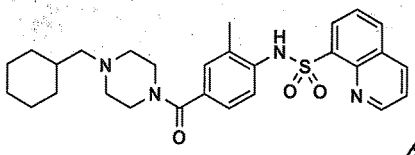
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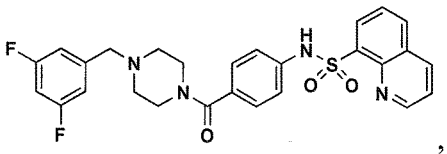
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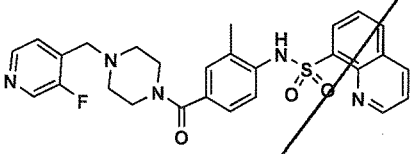
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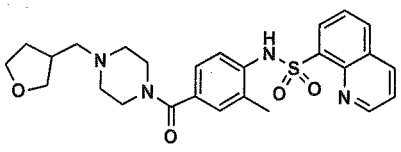
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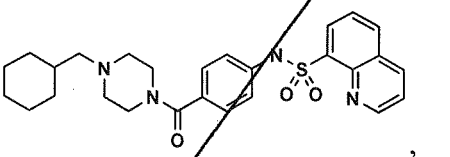
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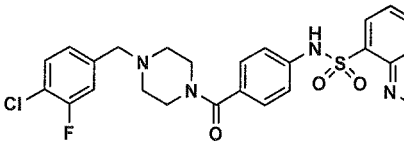
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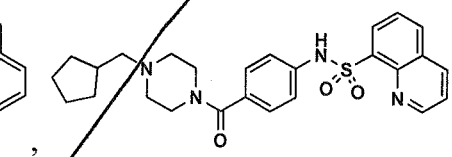
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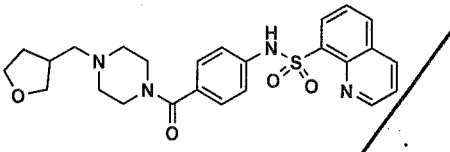
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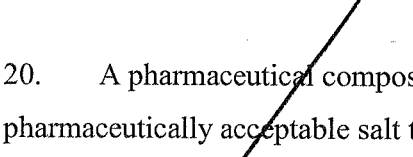
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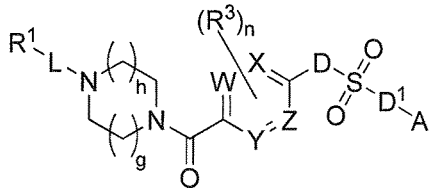
20. A pharmaceutical composition comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition of any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof for use in modulating PKM2 activity in a subject in need thereof.

22. A pharmaceutical composition of any one of claims 1 to 19 or a pharmaceutically acceptable salt thereof for use in treating a cancer associated with PKM2 activity in a subject in need thereof.

23. A compound of formula (I) for use as a medicament or a pharmaceutically acceptable salt thereof:



(I)

wherein:

W, X, Y and Z are each independently selected from CH or N;

D and D^1 are independently selected from a bond or NR^b;

A is optionally substituted quinolinyl;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$-;

R^1 is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$ or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted cyclyl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

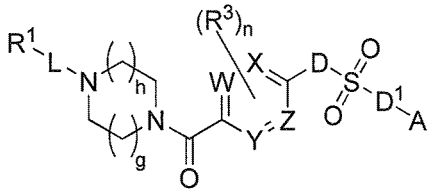
n is 0, 1, or 2;

m is 1, 2 or 3;

h is 0, 1, 2; and

g is 0, 1 or 2.

24. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

W, X, Y and Z are each independently selected from CH or N;

D and D^1 are independently selected from a bond or NR^b;

A is optionally substituted quinolinyl;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$-;

R^1 is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$ or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted cyclyl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

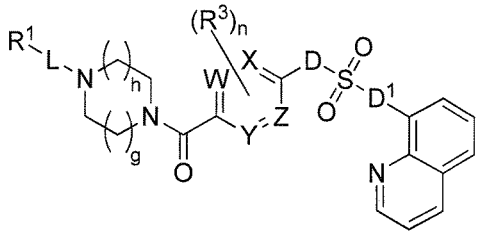
h is 0, 1, 2; and

g is 0, 1 or 2;

in the manufacture of a medicament for for treating a disease or disorder related to PKM2 function selected from the group consisting of cancer, obesity, diabetes, atherosclerosis, restenosis, and autoimmune diseases.

CLAIMS

1. A compound of formula II or a pharmaceutically acceptable salt thereof, wherein:



(II)

W, X, Y and Z are each independently selected from CH or N;

D and D^1 are independently selected from a bond or NR^b;

L is a bond, -C(O)-, $-(CR^cR^c)_m$-, -OC(O)-, $-(CR^cR^c)_m$-OC(O)-, $-(CR^cR^c)_m$-C(O)-, $-NR^bC(S)$-, or $-NR^bC(O)$- (wherein the point of the attachment to R^1 is on the left-hand side);

R^1 is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and $-OR^a$ or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, $-C(O)R^a$, $-OC(O)R^a$, $-C(O)OR^a$, $-SR^a$, $-NR^aR^b$ and $-OR^a$, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

n is 0, 1, or 2;

m is 1, 2 or 3;

h is 1; and

g is 1.

2. The compound of claim 1, wherein W, X, Y and Z are CH.

3. The compound of claim 1, wherein D is NR^b and D^1 is a bond.

4. The compound of claim 3, wherein R^b is H, methyl or ethyl.

5. The compound of claim 1, wherein L is a bond, $-(CR^cR^c)_m-$, $-NR^bC(O)-$, $-(CR^cR^c)_m-C(O)-$, -C(O)-, or -O(CO)-.

6. The compound of claim 5, wherein L is a bond.

7. The compound of claim 6, wherein R^1 is alkyl, aryl or heteroaryl, each substituted with 0-5 occurrences of R^d.

8. The compound of claim 5, wherein L is $-(CR^cR^c)_m-$.

9. The compound of claim 8, wherein R^1 is cycloalkyl, aryl, heteroaryl or heterocyclyl, each substituted with 0-5 occurrences of R^d.

10. The compound of claim 5, wherein L is $-NR^bC(O)-$ and R^b is hydrogen.

11. The compound of claim 10, wherein R^1 is aryl substituted with 0-5 occurrences of R^d.

12. The compound of claim 5, wherein L is $-(CR^cR^c)_m-C(O)-$.

13. The compound of claim 12, wherein R^1 is cycloalkyl, aryl or heteroaryl, each substituted with 0-5 occurrences of R^d.

14. The compound of claim 5, wherein L is -C(O)-.

15. The compound of claim 14, wherein R^1 is aryl, alkyl, or heteroaryl, each substituted with 0-5 occurrences of R^d.

16. The compound of claim 5, wherein L is –OC(O)-.

17. The compound of claim 16, wherein R^1 is alkyl, aryl or heterocyclyl, each substituted with 0-5 occurrences of R^d.

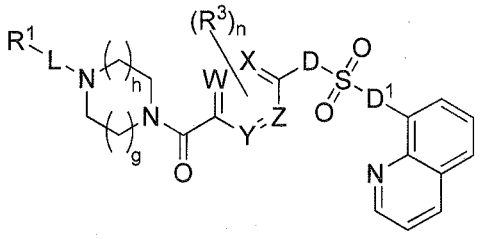
18. The compound of claim 1, wherein L is $-(CR^cR^c)_m$-OC(O)-.

19. The compound of claim 19, wherein R^1 is heterocyclyl or cycloalkyl, each substituted with 0-5 occurrences of R^d.

20. The compound of claim 5, wherein n is 0.

21. The compound of claim 5, wherein n is 1 and R^3 is CH_3, CH_2CH_3, OCH_3, OCH_2CH_3, OH, F, Cl, or CF_3.

22. A pharmaceutical composition comprising a compound formula II or a pharmaceutically acceptable salt thereof, wherein:



(II)

W, X, Y and Z are each independently selected from CH or N;

D and D^1 are independently selected from a bond or NR^b;

L is a bond, -C(O)-, -$(CR^cR^c)_m$-, -OC(O)-, -$(CR^cR^c)_m$-OC(O)-, -$(CR^cR^c)_m$-C(O)-, -$NR^bC(S)$-, or -$NR^bC(O)$- (wherein the point of the attachment to R^1 is on the left-hand side);

R^1 is selected from alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; each of which is substituted with 0-5 occurrences of R^d;

each R^3 is independently selected from halo, haloalkyl, alkyl, hydroxyl and -OR^a, or two adjacent R^3 taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

each R^a is independently selected from alkyl, acyl, hydroxyalkyl and haloalkyl;

each R^b is independently selected from hydrogen and alkyl;

each R^c is independently selected from hydrogen, halo, alkyl, alkoxy and halo alkoxy or two R^c taken together with the carbon atoms to which they are attached form an optionally substituted cycloalkyl;

each R^d is independently selected from halo, haloalkyl, haloalkoxy, alkyl, alkynyl, nitro, cyano, hydroxyl, -$C(O)R^a$, -$OC(O)R^a$, -$C(O)OR^a$, -SR^a, -NR^aR^b and –OR^a, or two R^d taken together with the carbon atoms to which they are attached form an optionally substituted heterocyclyl;

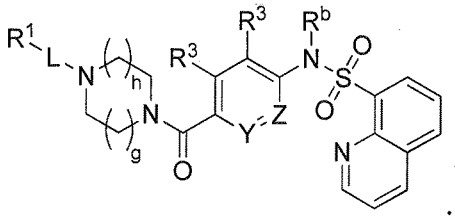
n is 0, 1, or 2;

m is 1, 2 or 3;

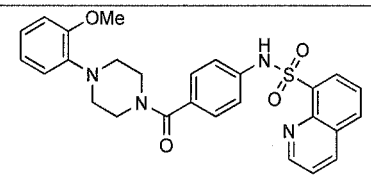
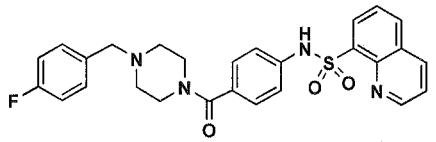
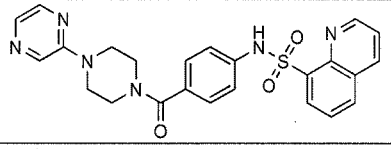
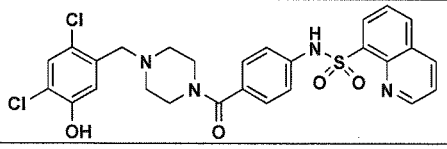
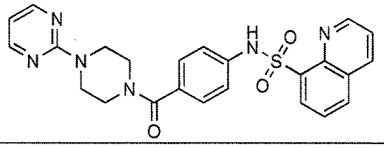
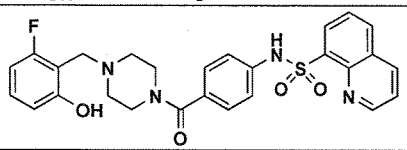
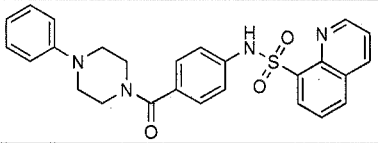
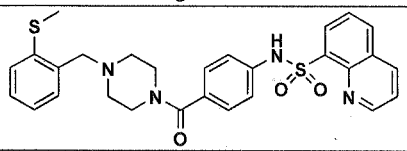
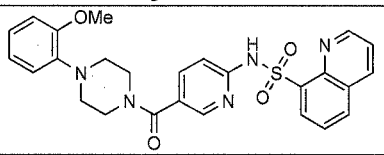
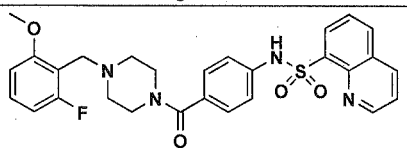
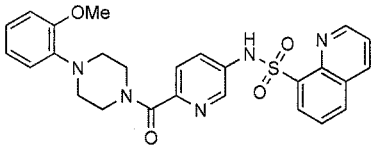
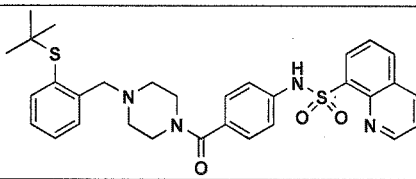
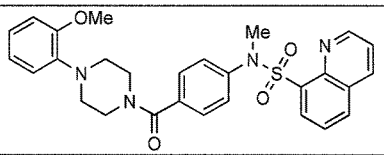
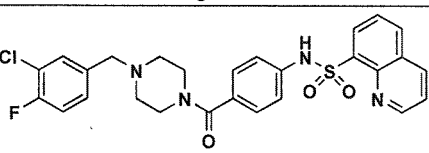
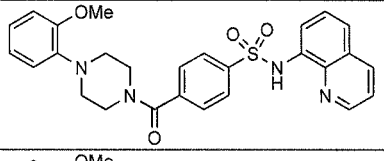
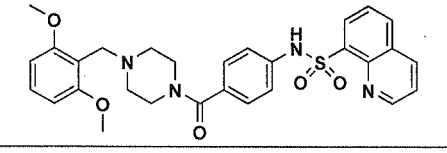
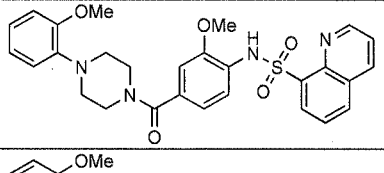
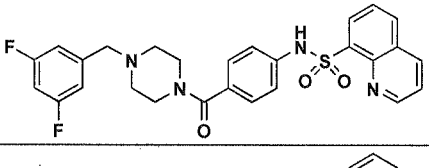
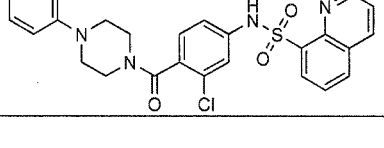
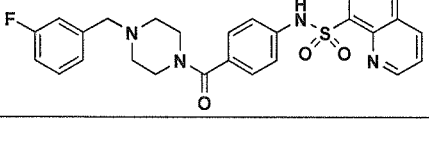
h is 1; and

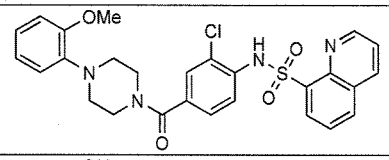
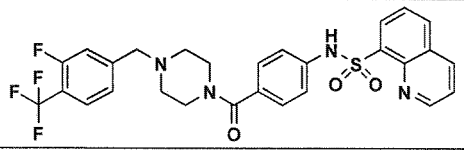
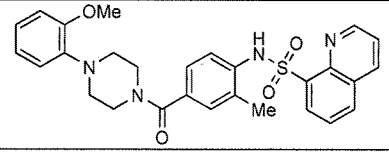
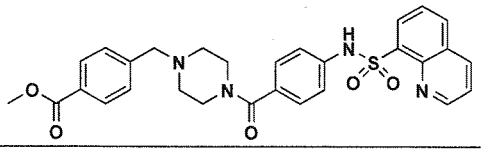
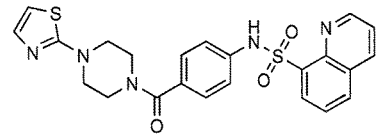
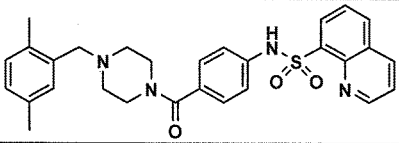
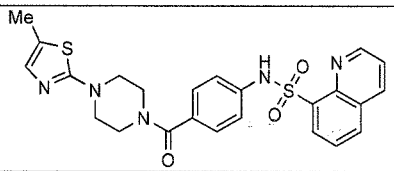
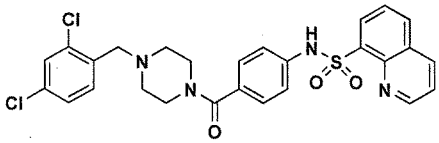
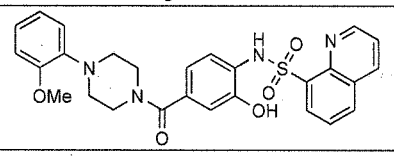
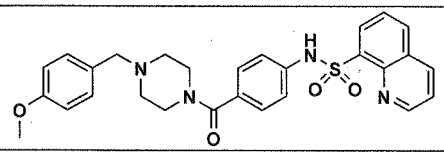
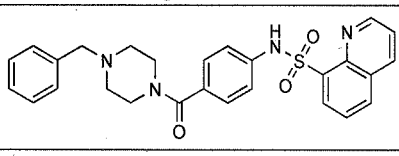
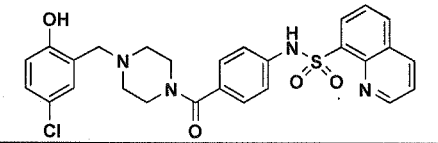
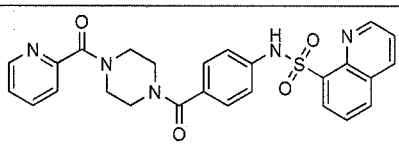
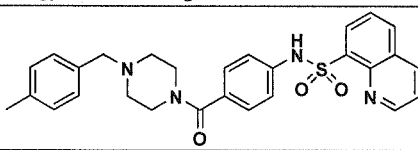
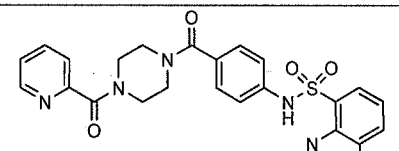
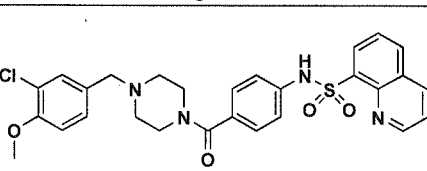
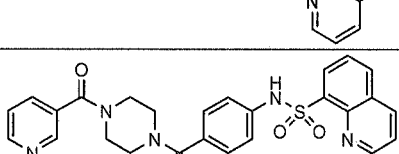
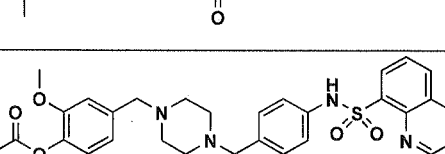
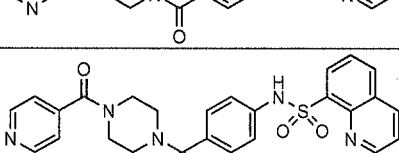
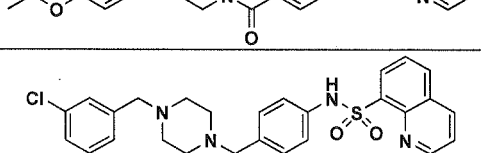
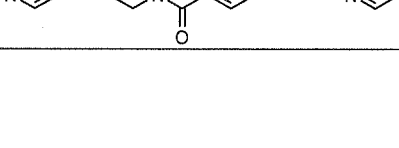
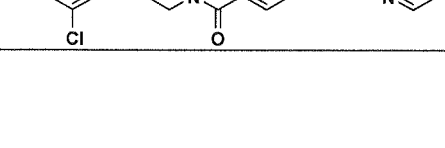
g is 1.

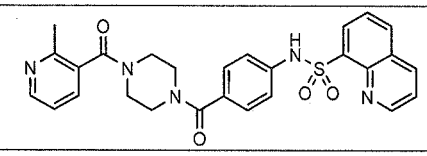
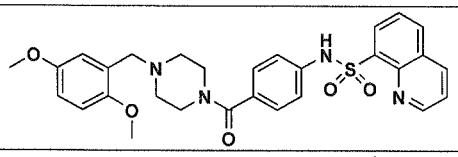
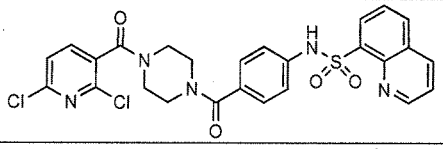
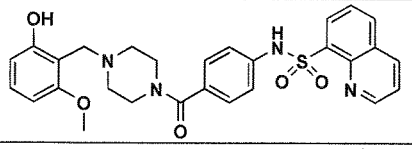
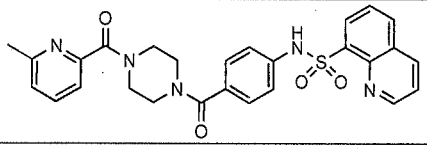
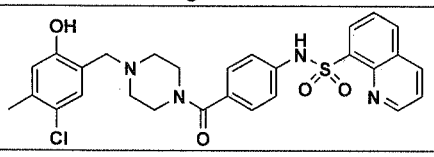
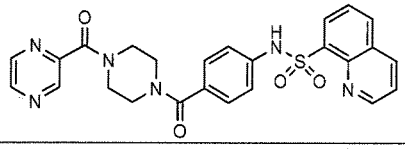
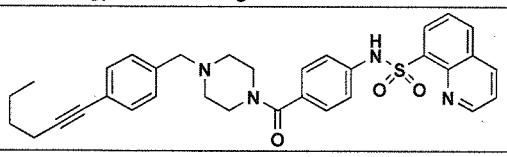
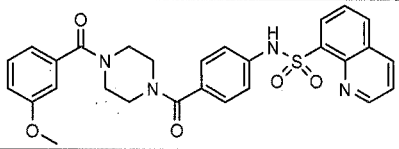
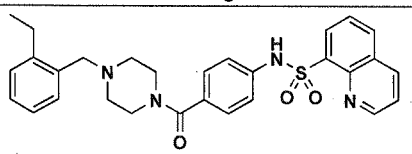
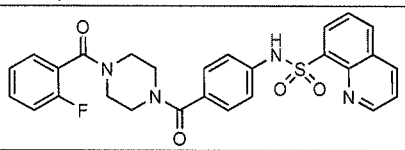
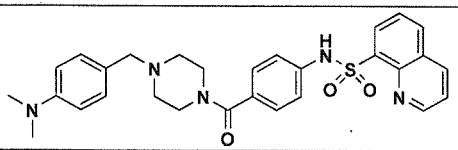
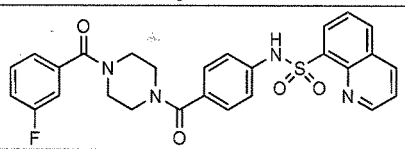
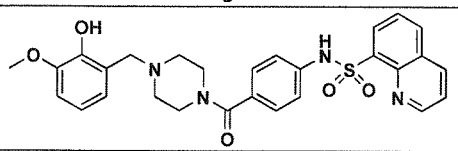
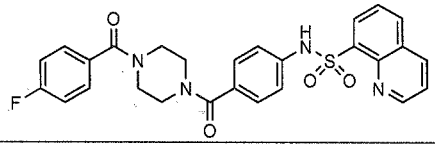
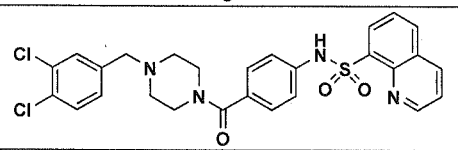
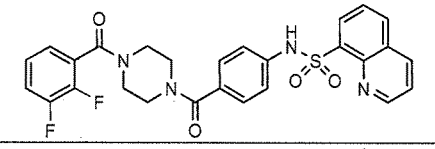
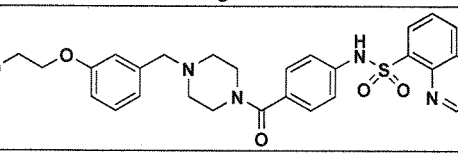
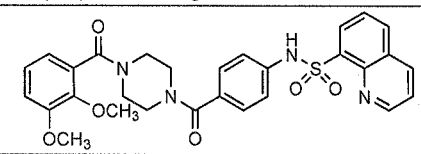
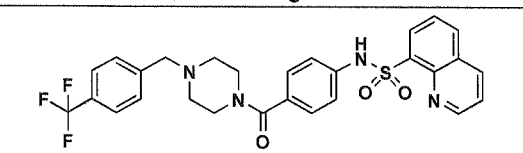
23. The pharmaceutical composition of claim 22, wherein the compound is a compound of formula:

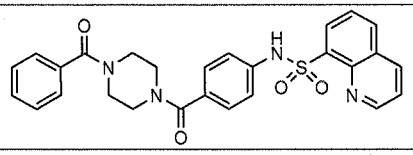
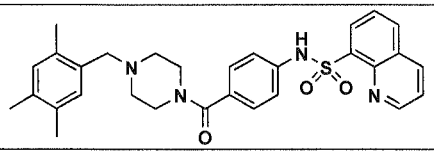
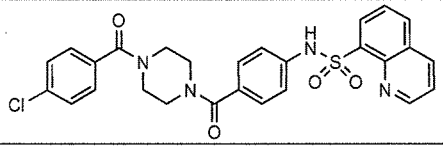
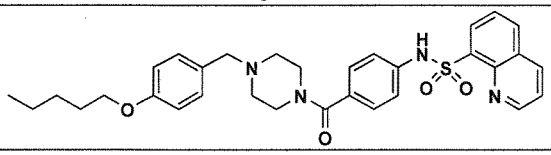
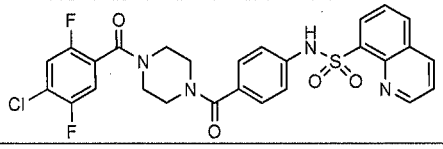
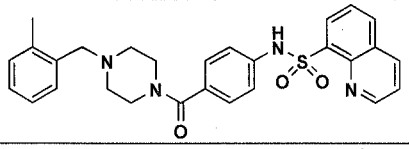
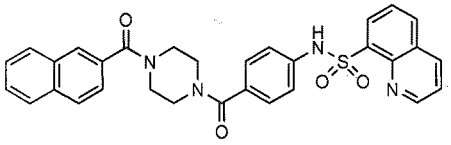
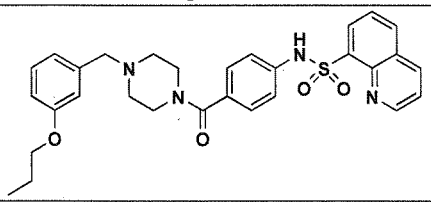
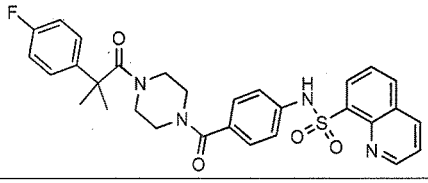
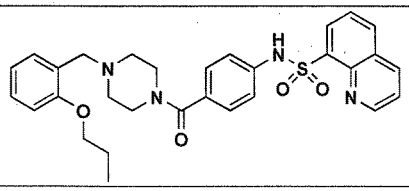
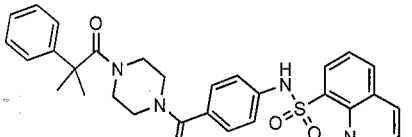
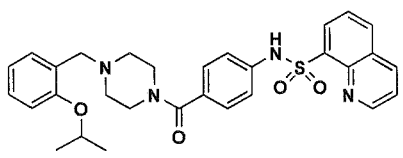
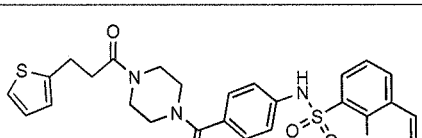
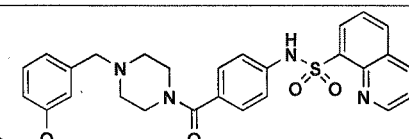
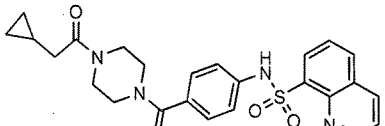
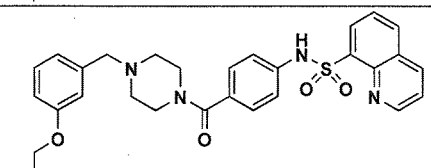
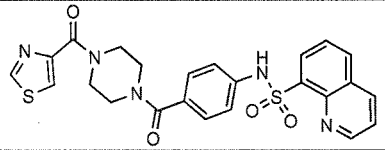
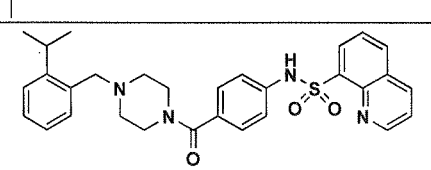


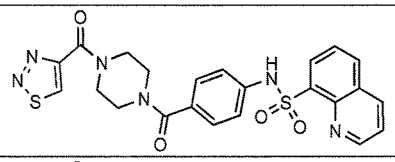
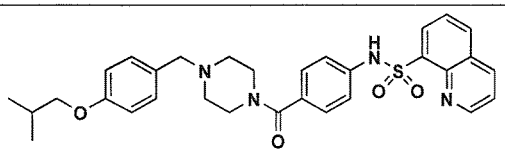
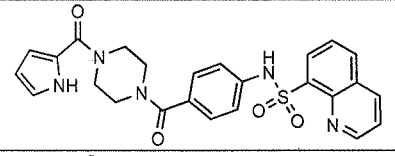
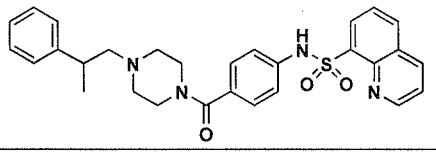
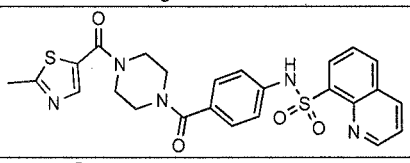
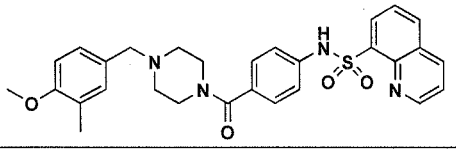
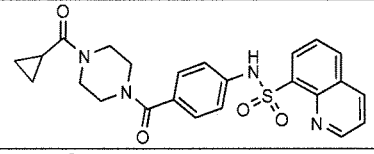
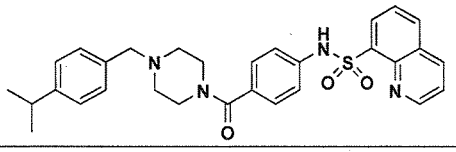
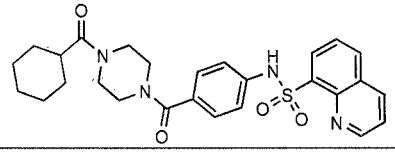
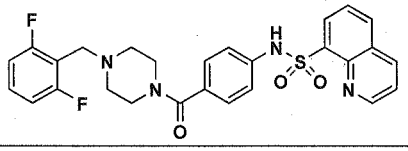
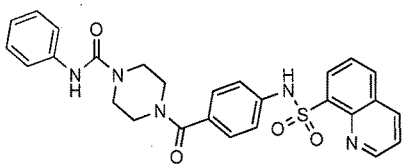
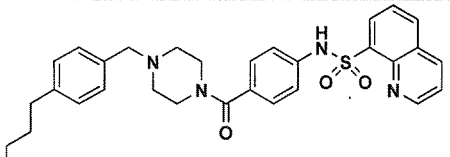
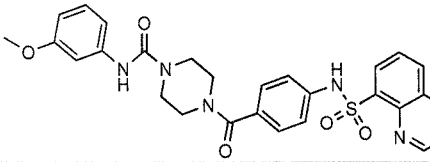
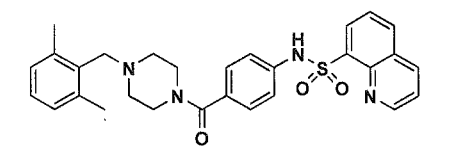
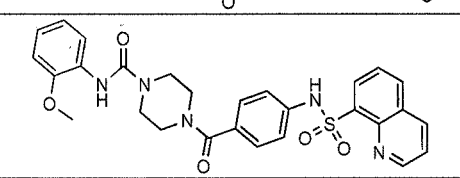
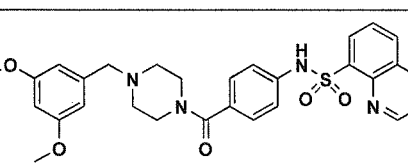
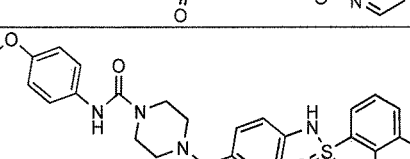
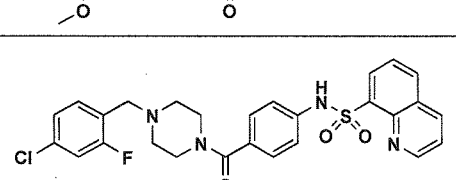
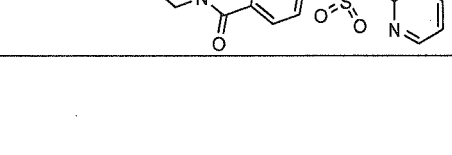
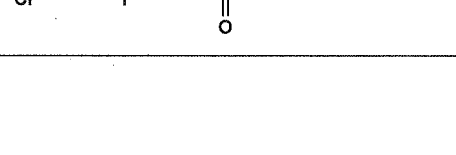
24. The compound of claim 1, wherein the compound is selected from the following:

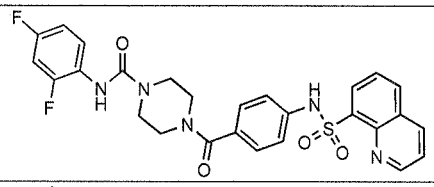
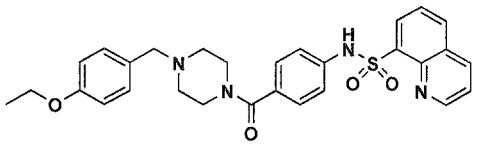
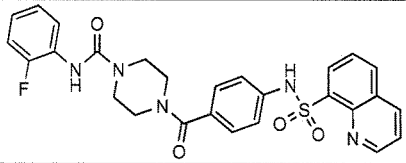
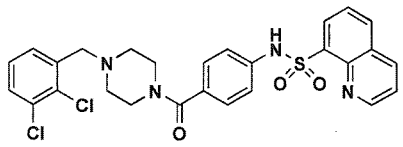
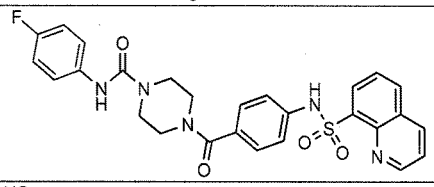
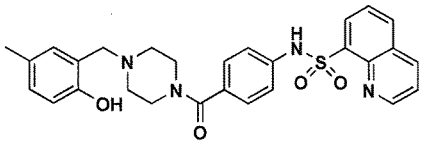
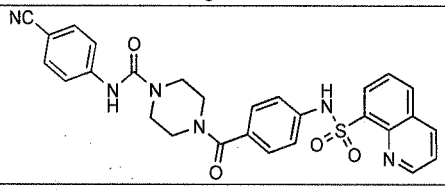
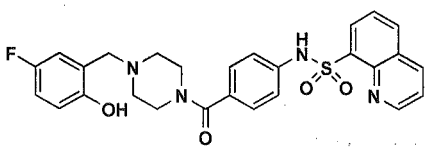
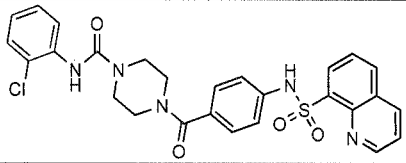
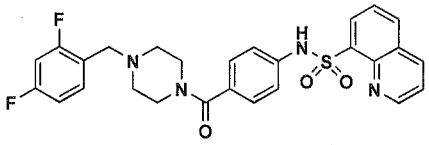
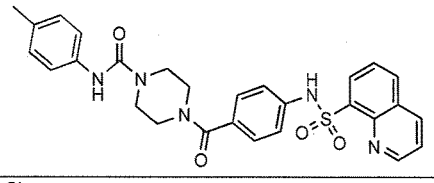
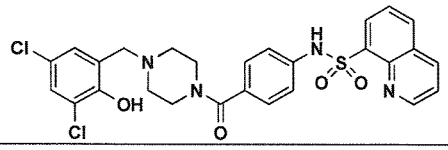
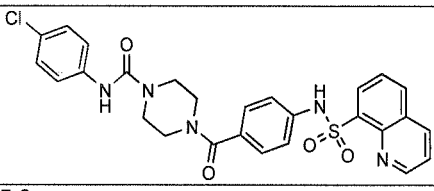
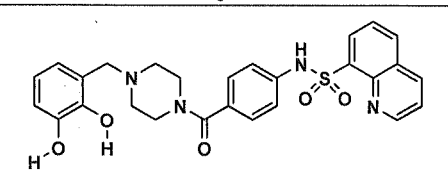
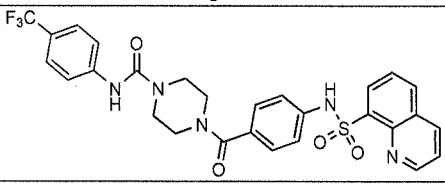
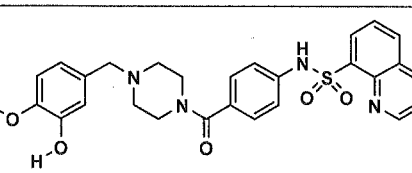
	
	
	
	
	
	
	
	
	
	

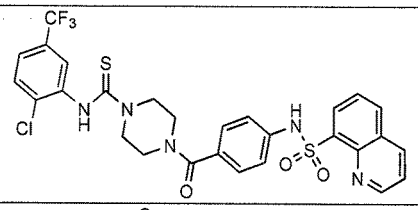
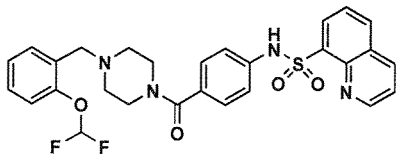
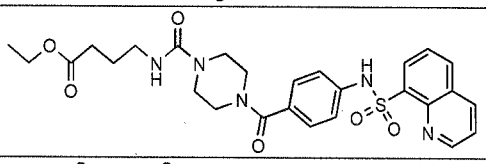
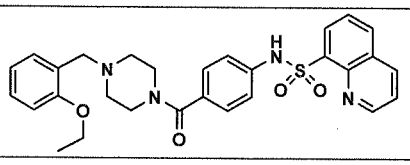
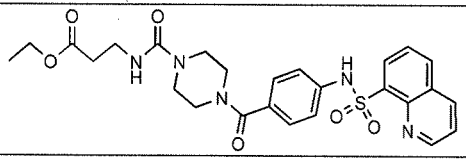
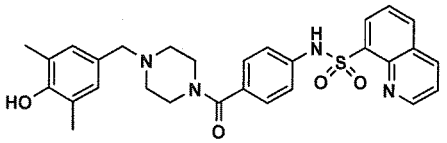
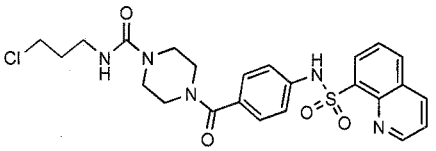
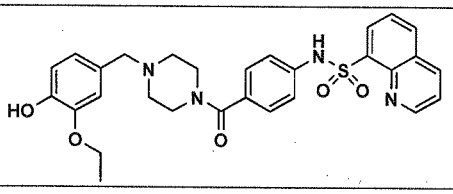
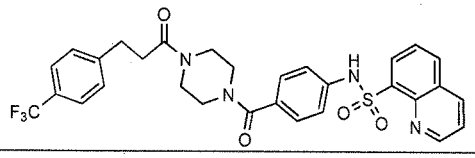
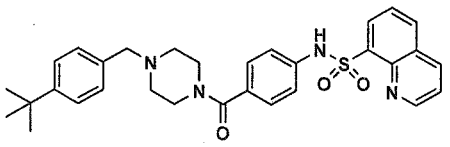
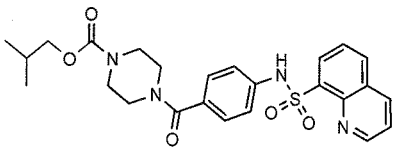
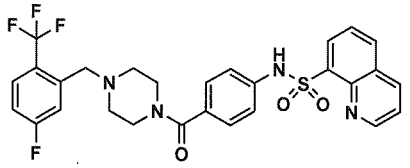
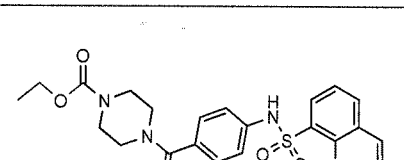
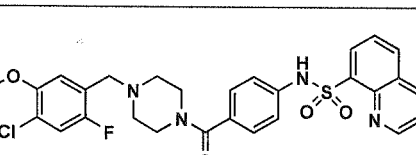
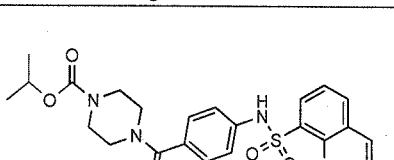
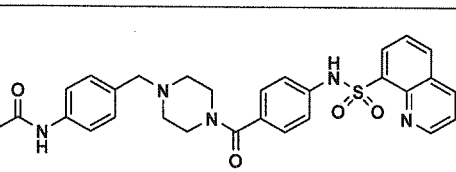
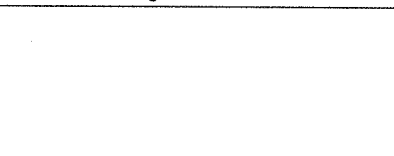
	
	
	
	
	
	
	
	
	
	
	

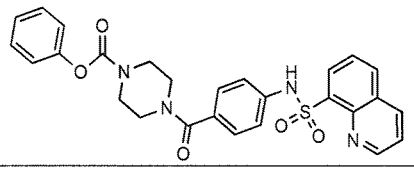
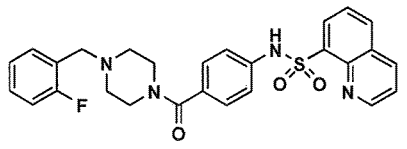
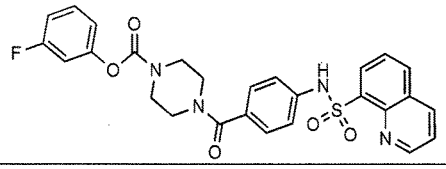
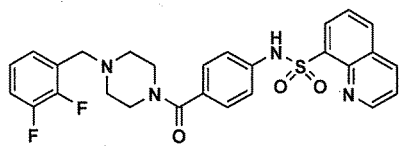
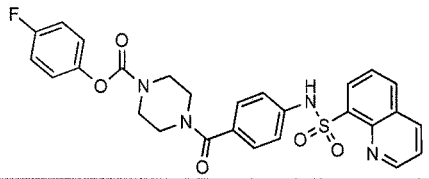
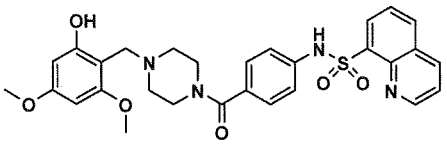
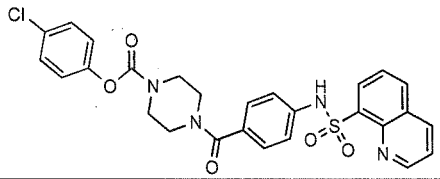
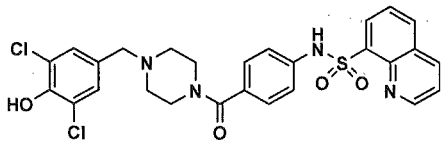
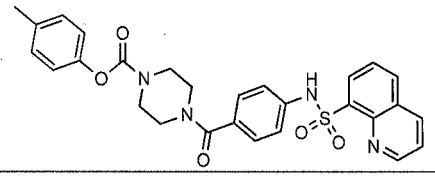
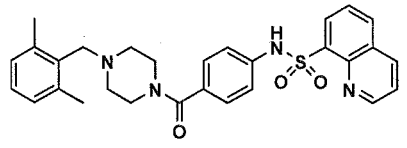
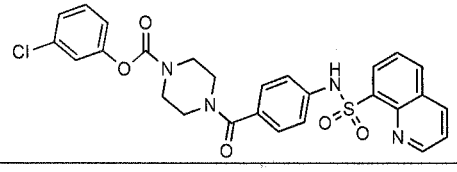
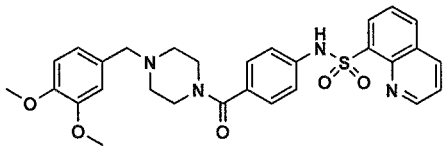
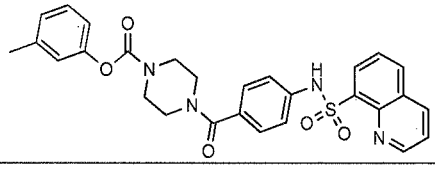
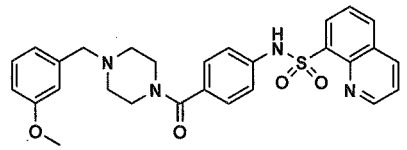
	
	
	
	
	
	
	
	
	
	

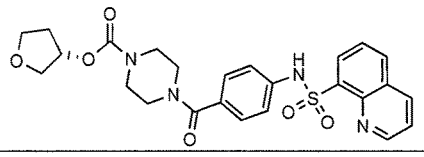
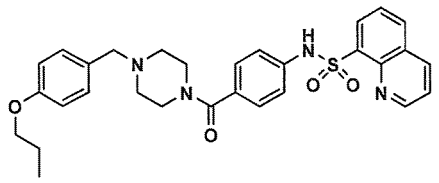
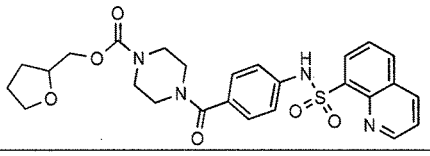
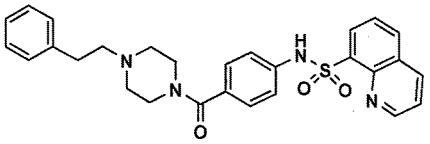
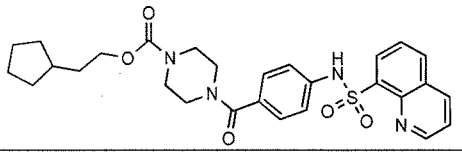
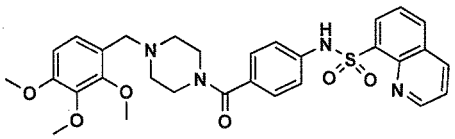
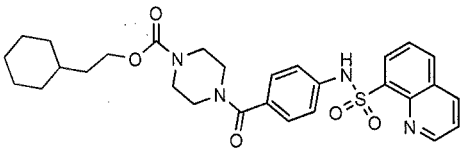
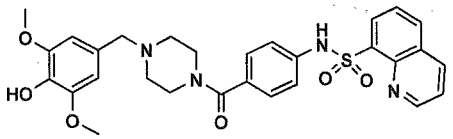
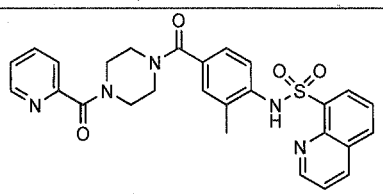
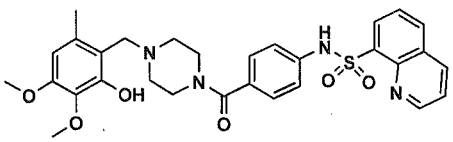
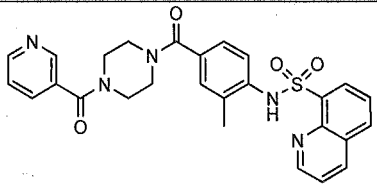
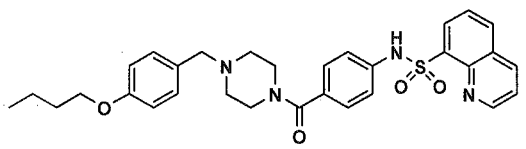
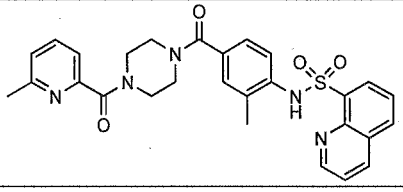
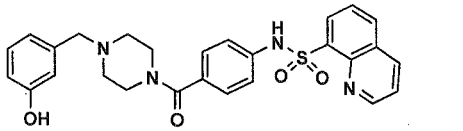
	
	
	
	
	
	
	
	
	

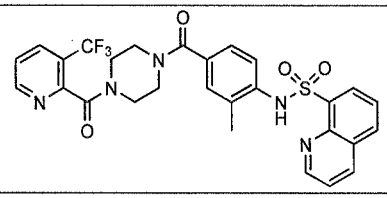
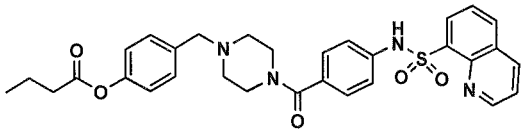
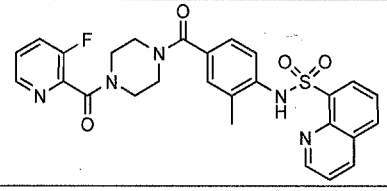
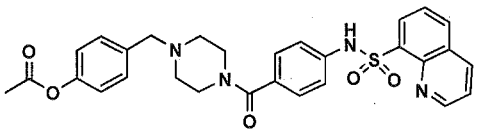
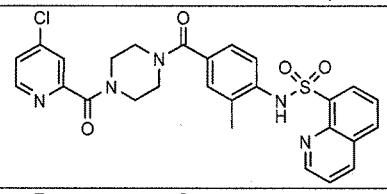
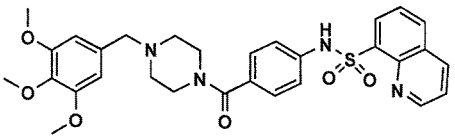
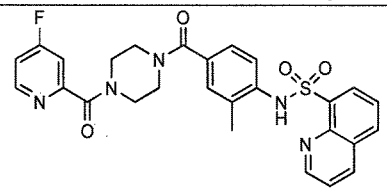
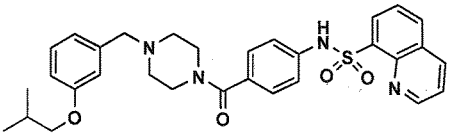
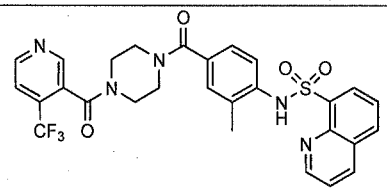
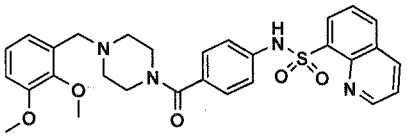
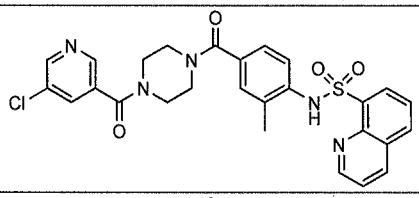
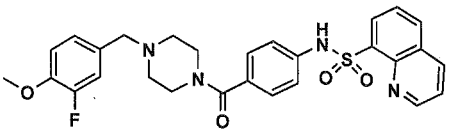
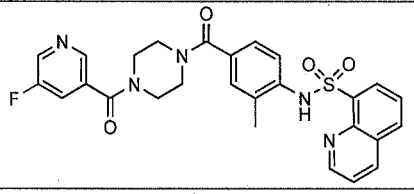
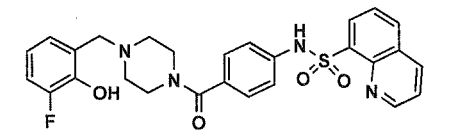
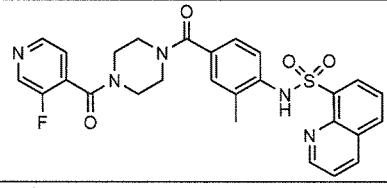
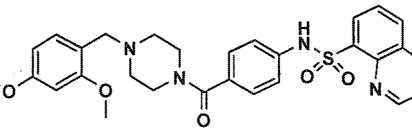
	
	
	
	
	
	
	
	
	
	

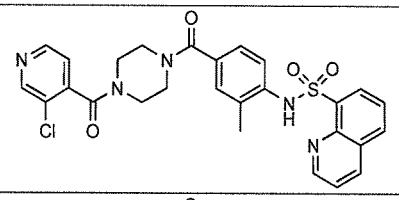
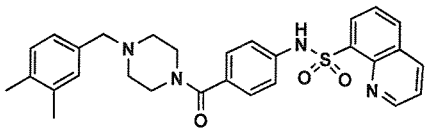
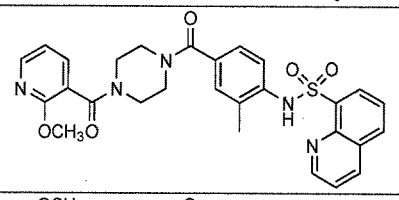
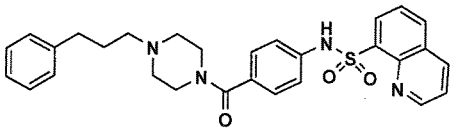
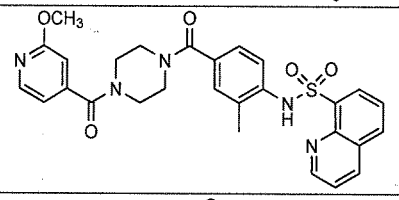
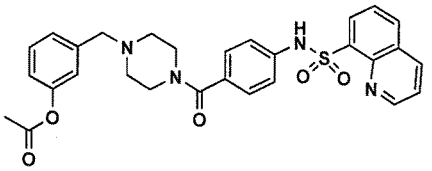
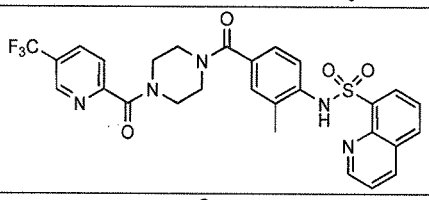
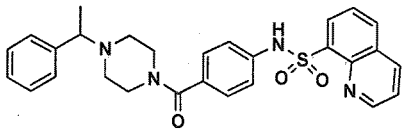
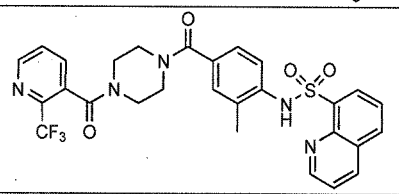
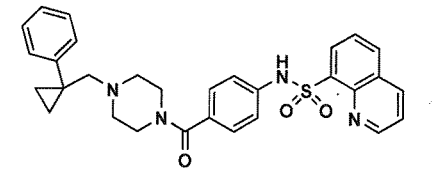
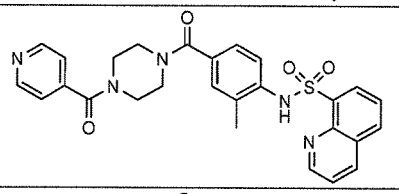
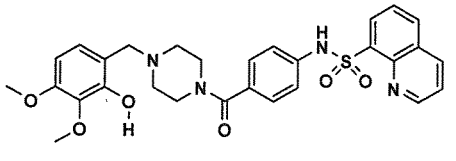
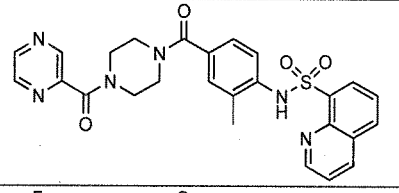
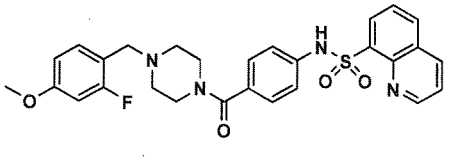
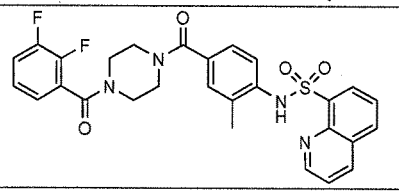
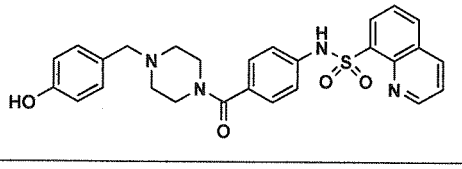
	
	
	
	
	
	
	
	

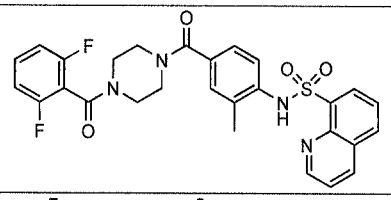
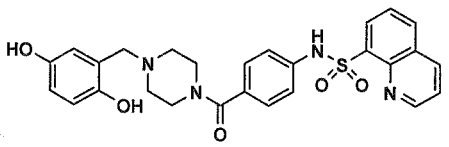
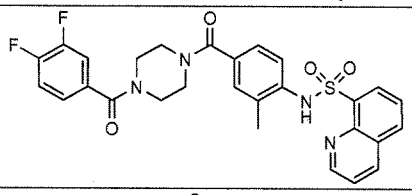
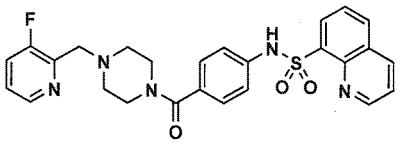
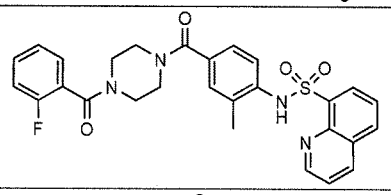
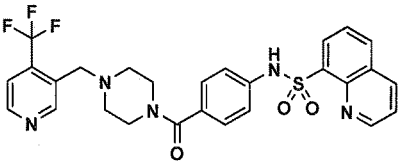
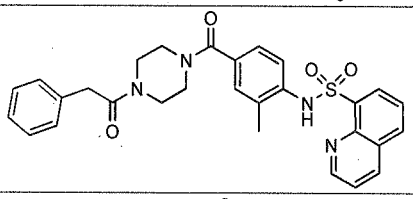
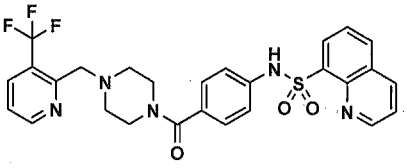
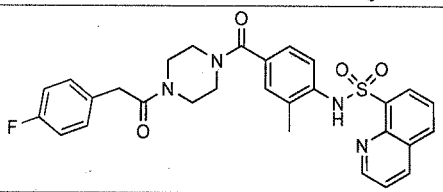
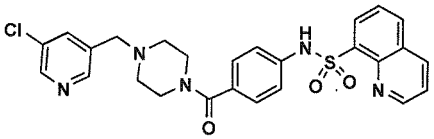
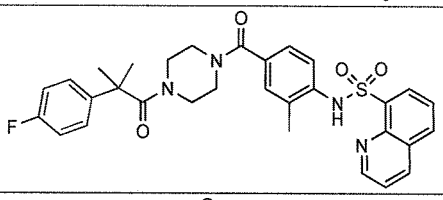
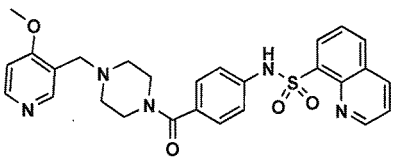
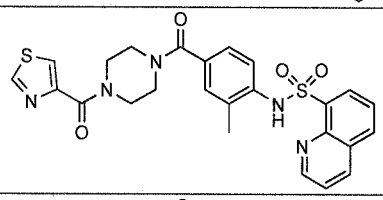
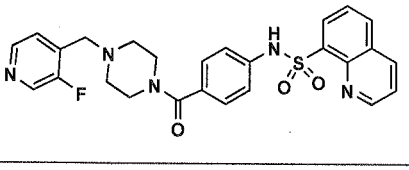
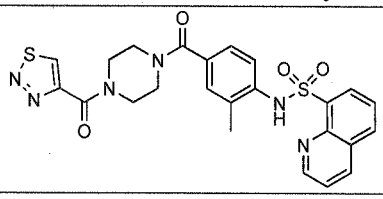
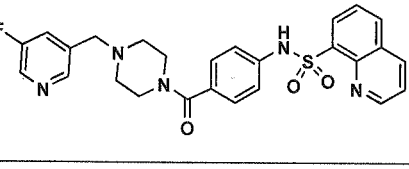
	
	
	
	
	
	
	
	
	

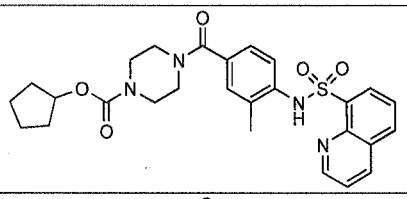
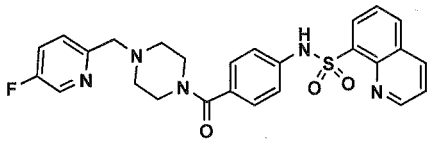
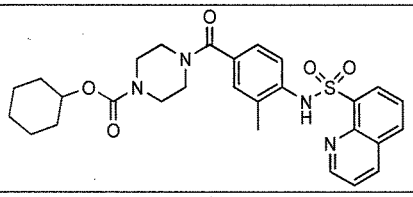
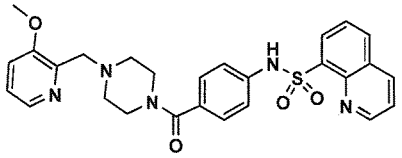
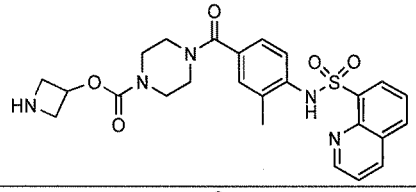
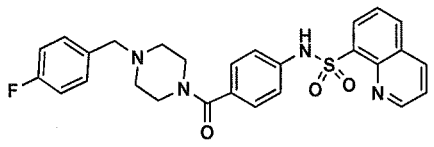
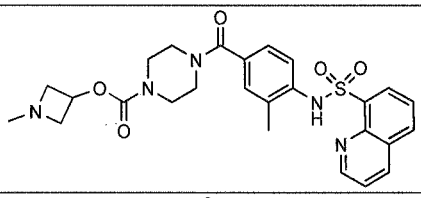
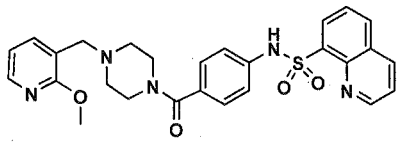
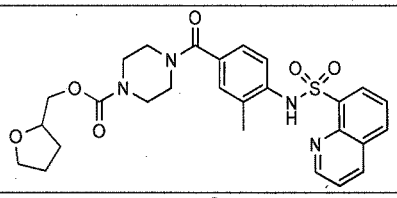
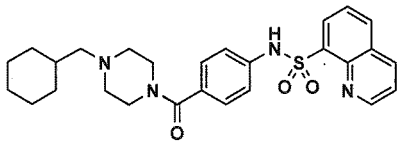
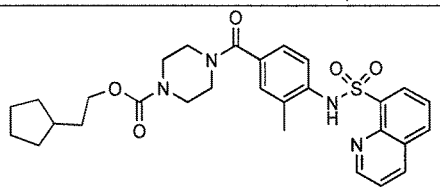
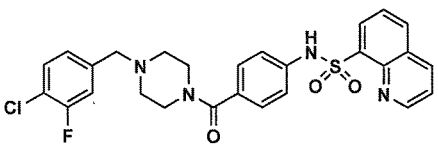
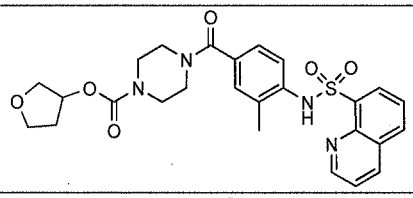
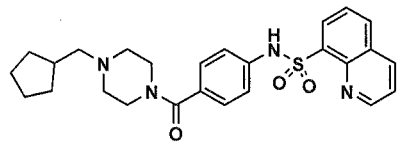
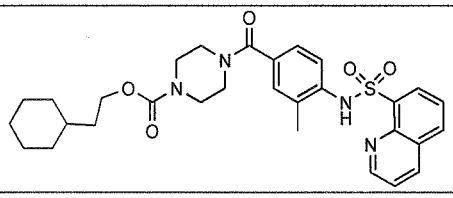
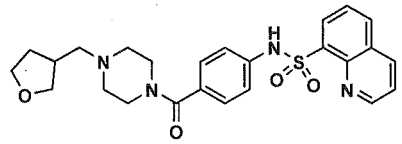
	
	
	
	
	
	
	

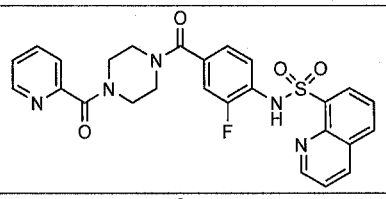
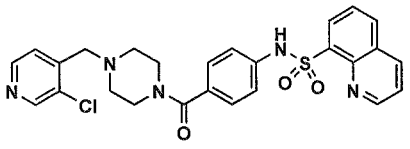
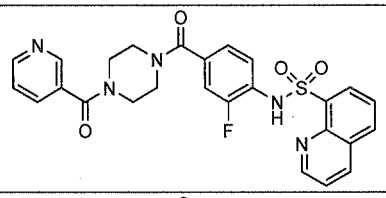
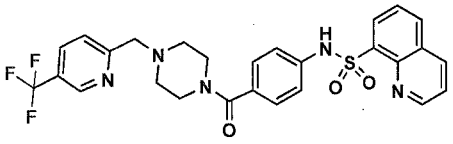
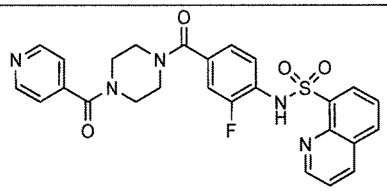
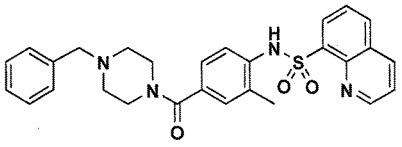
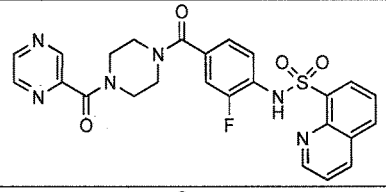
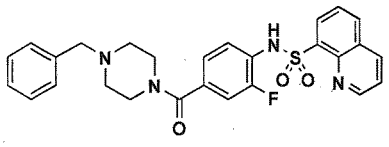
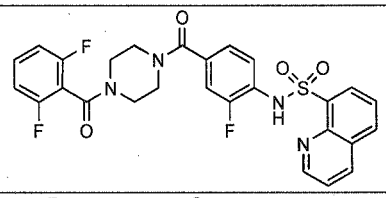
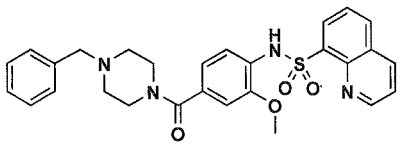
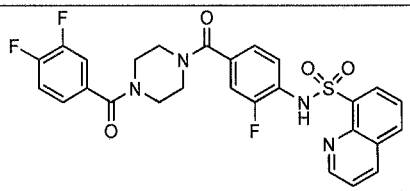
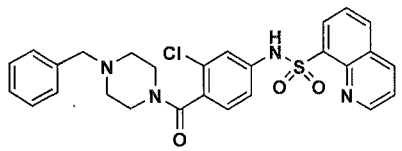
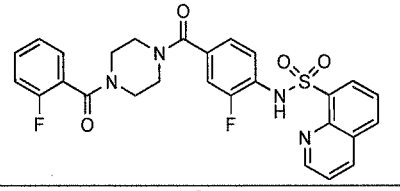
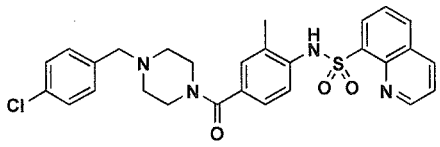
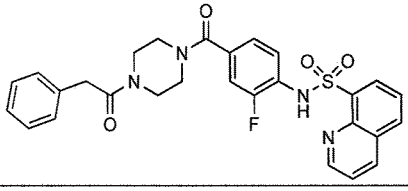
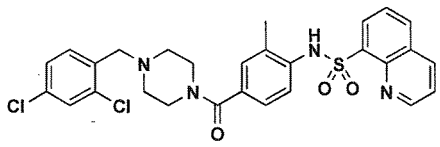
	
	
	
	
	
	
	

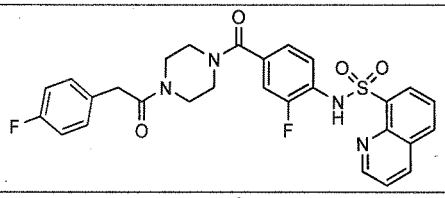
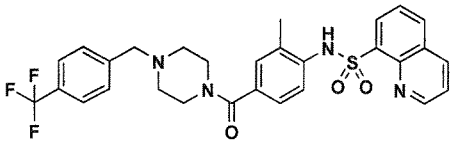
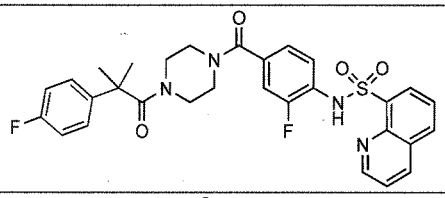
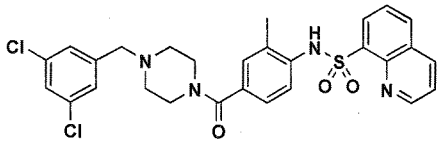
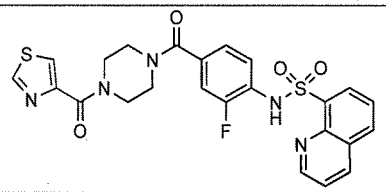
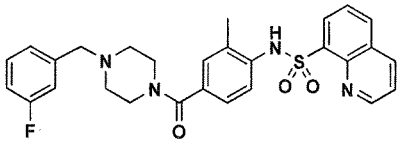
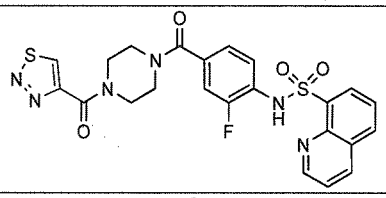
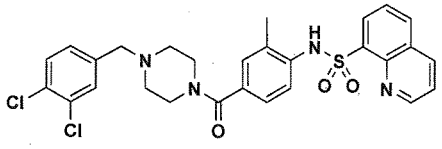
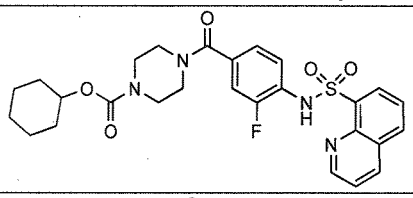
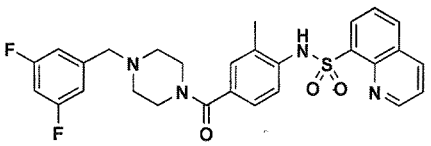
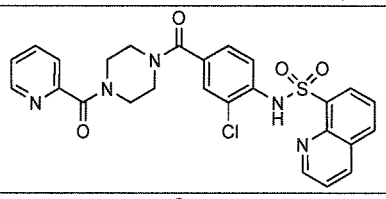
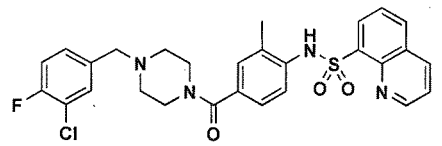
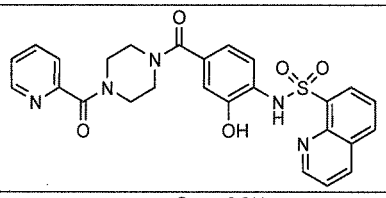
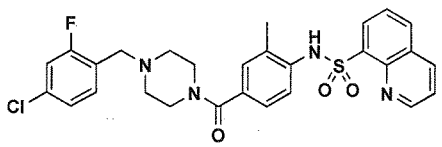
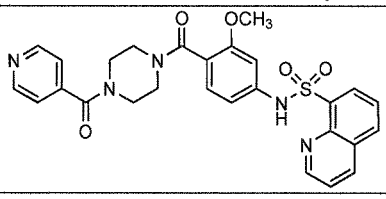
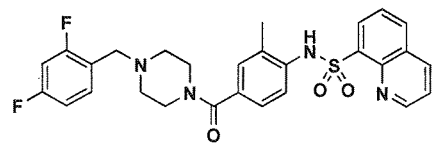
	
	
	
	
	
	
	
	

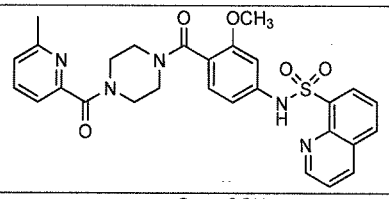
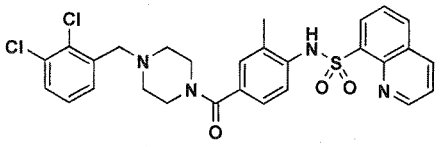
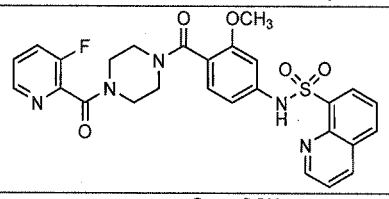
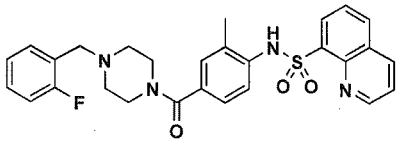
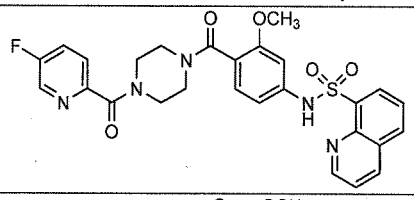
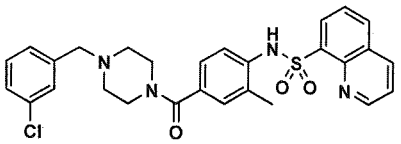
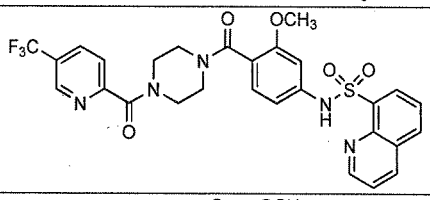
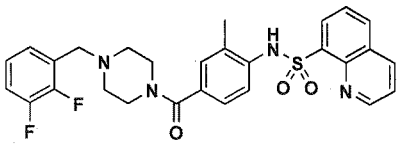
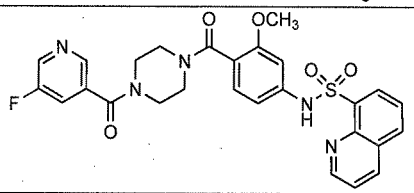
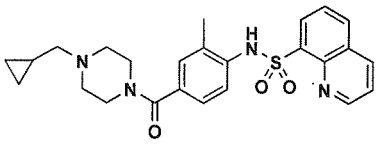
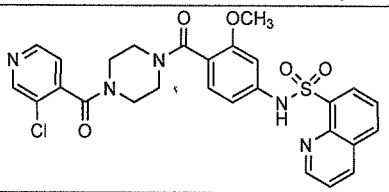
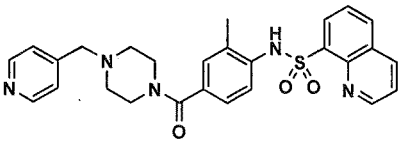
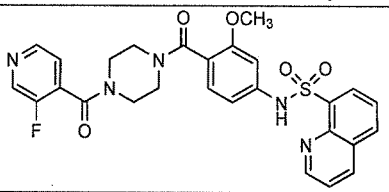
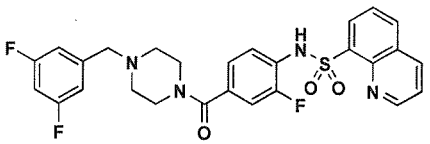
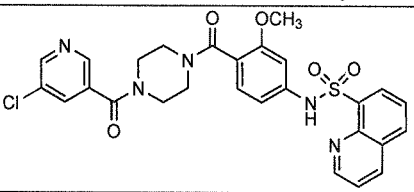
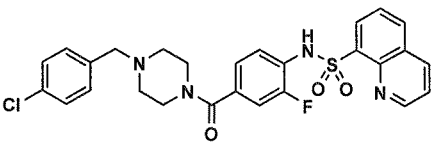
	
	
	
	
	
	
	
	

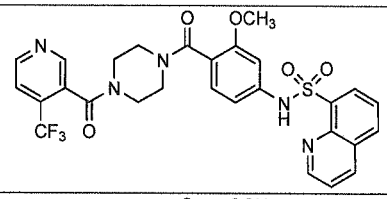
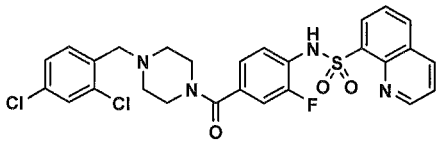
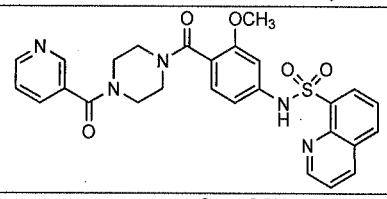
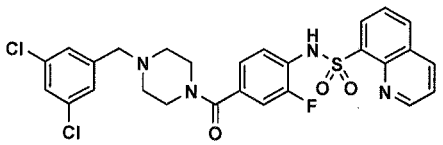
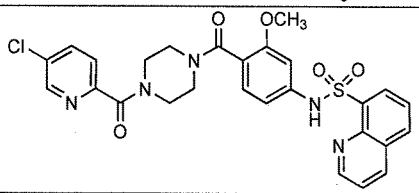
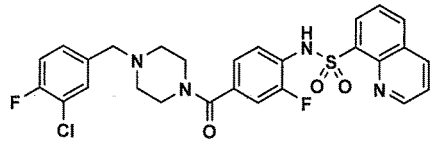
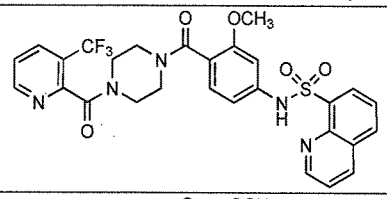
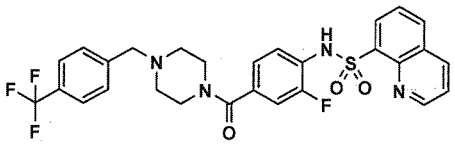
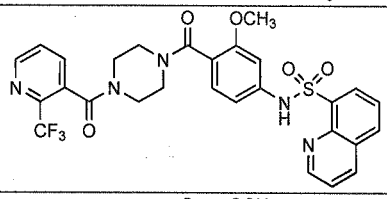
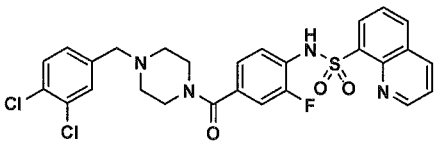
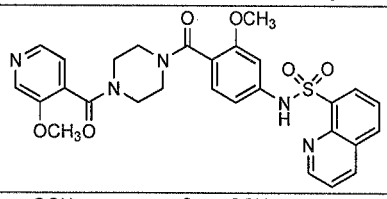
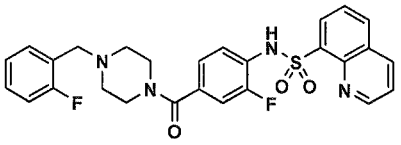
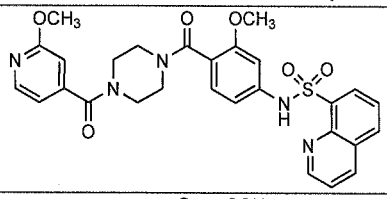
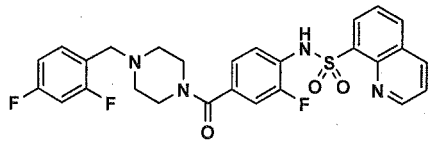
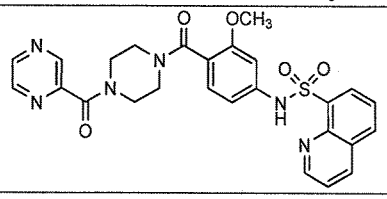
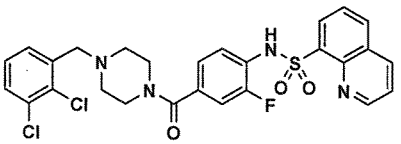
	
	
	
	
	
	
	
	

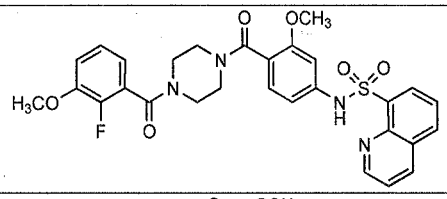
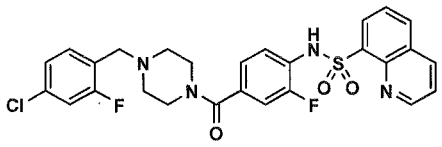
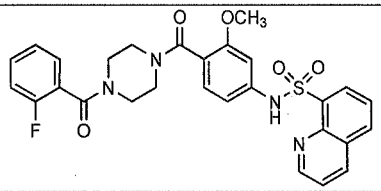
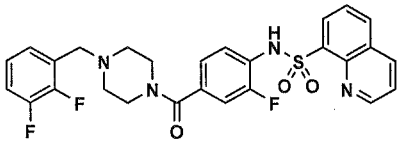
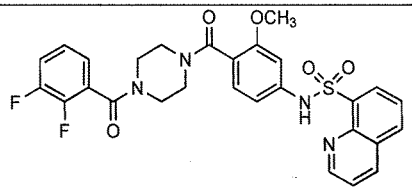
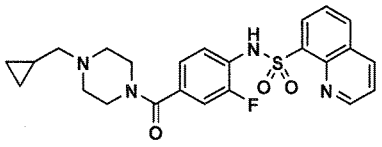
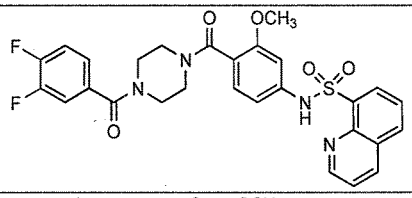
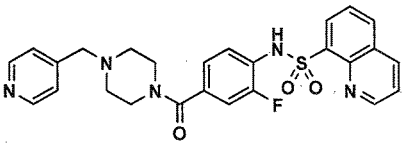
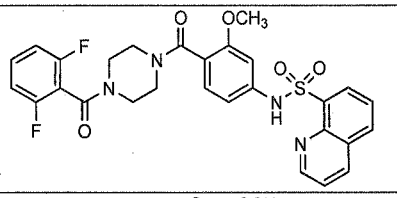
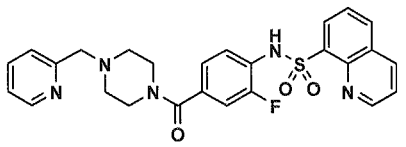
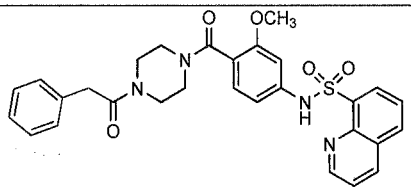
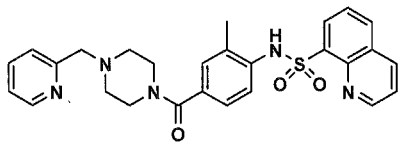
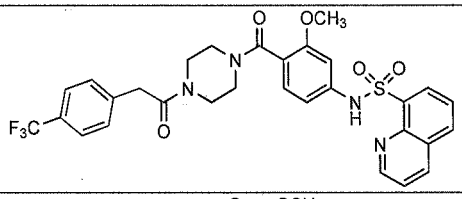
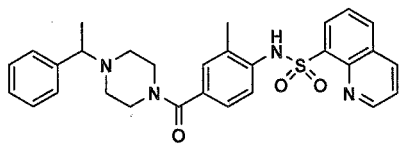
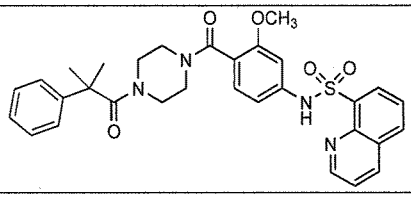
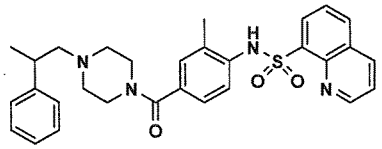
	
	
	
	
	
	
	
	

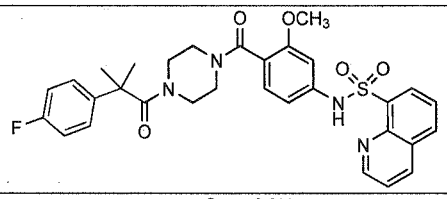
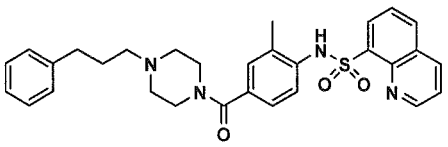
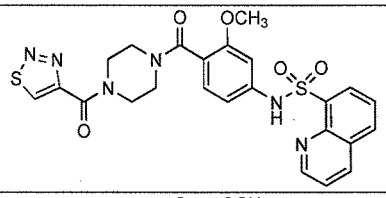
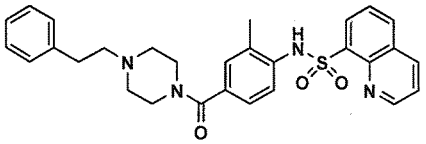
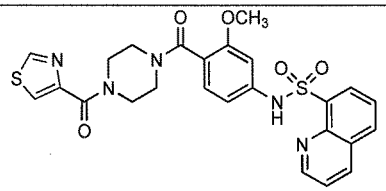
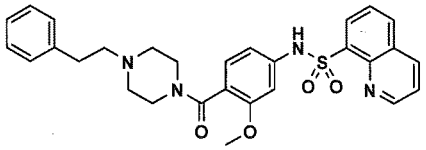
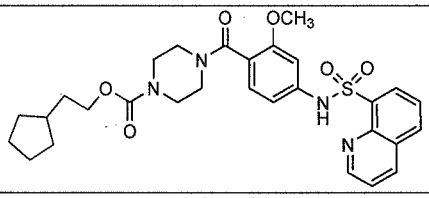
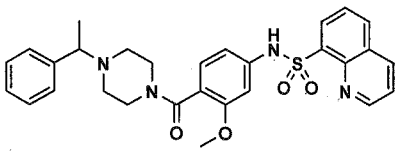
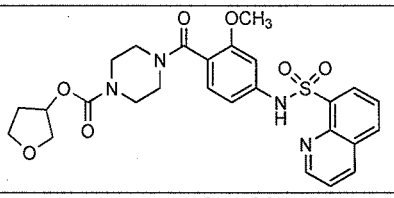
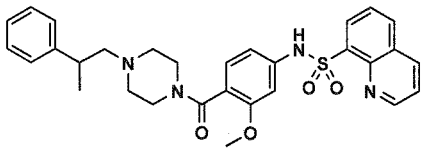
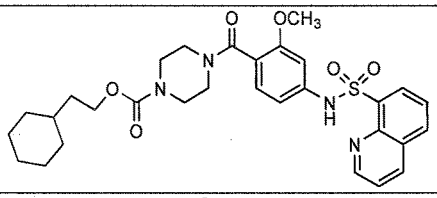
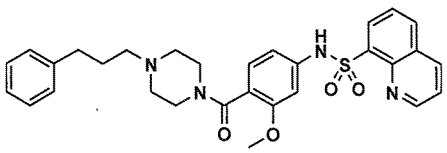
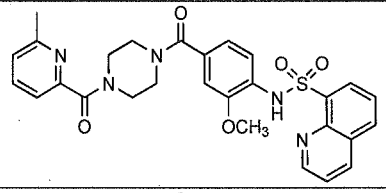
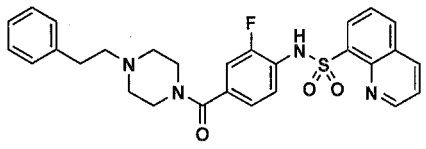
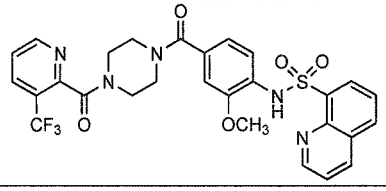
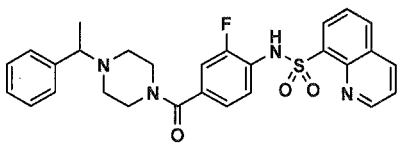
	
	
	
	
	
	
	
	

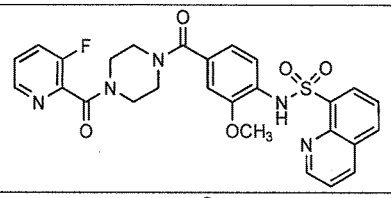
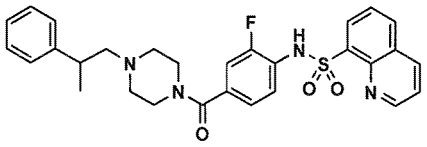
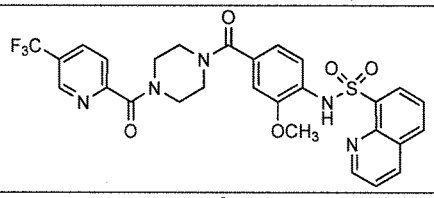
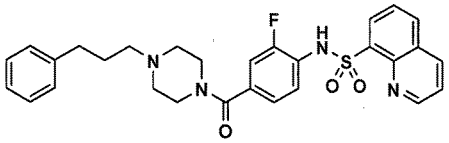
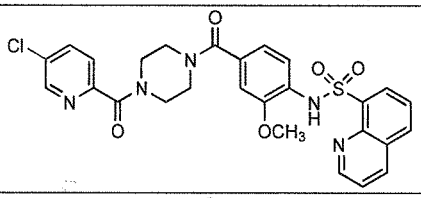
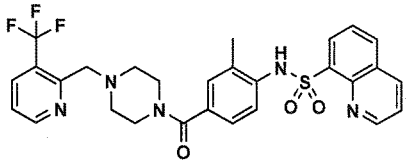
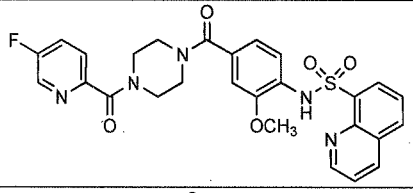
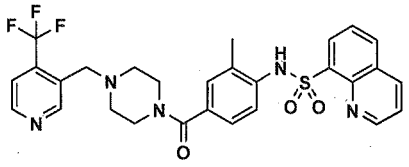
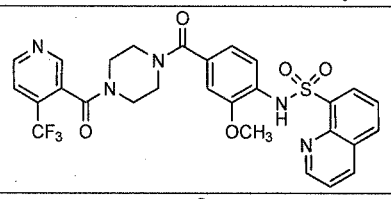
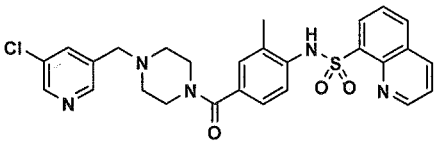
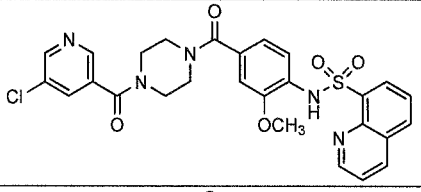
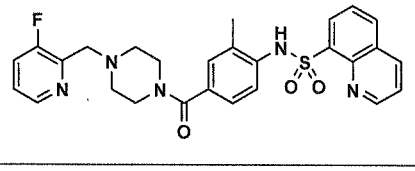
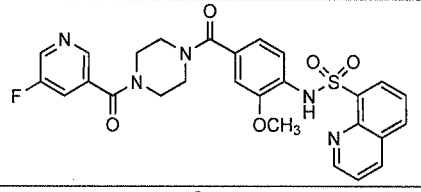
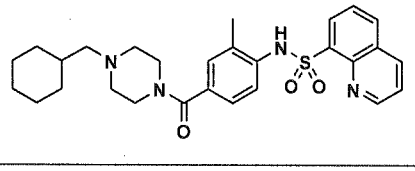
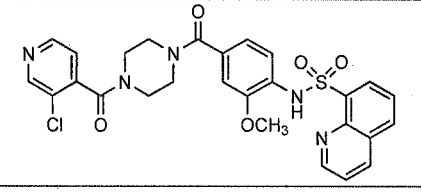
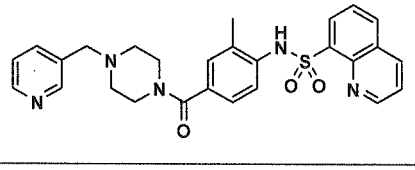
	
	
	
	
	
	
	
	

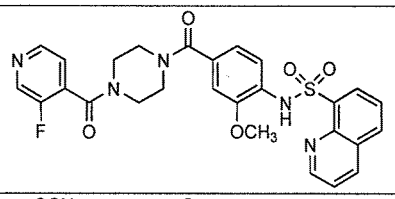
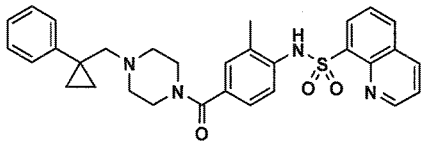
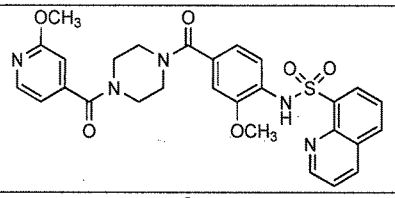
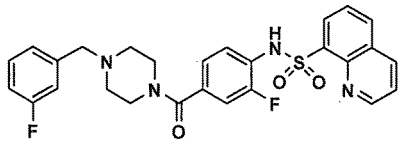
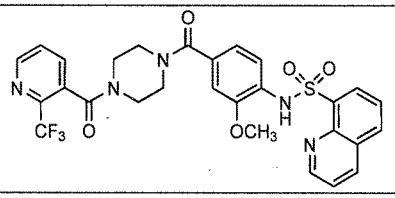
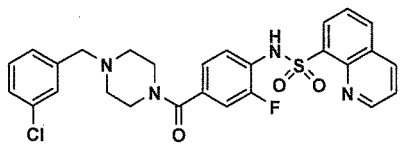
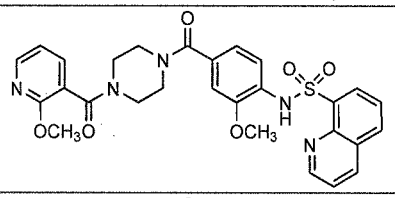
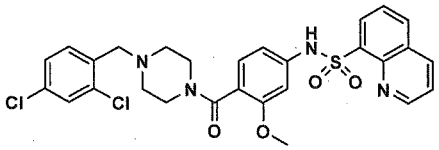
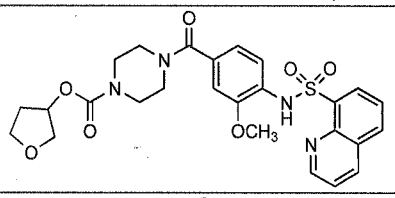
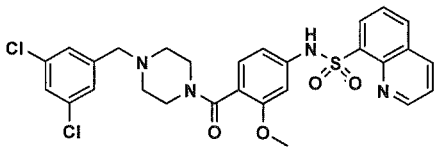
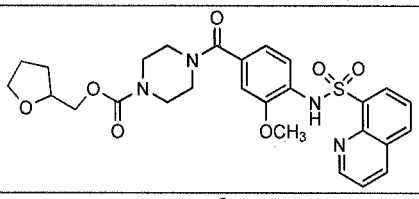
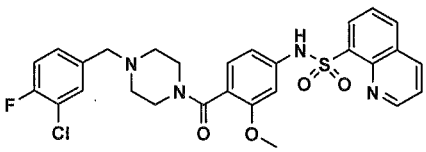
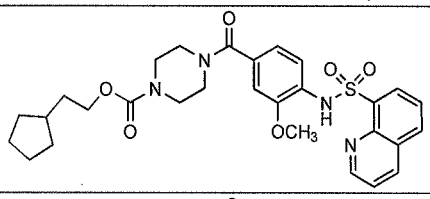
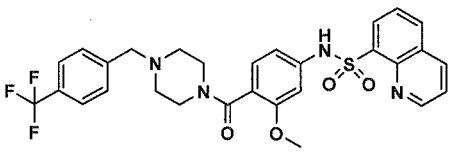
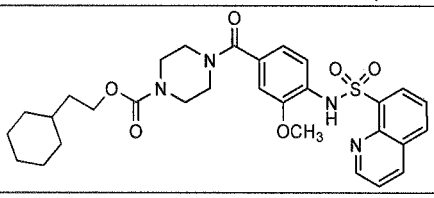
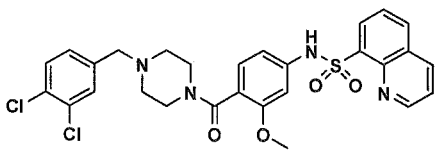
	
	
	
	
	
	
	
	

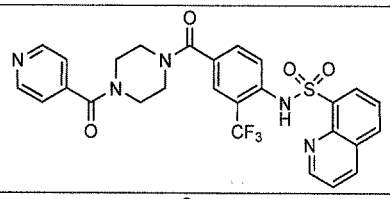
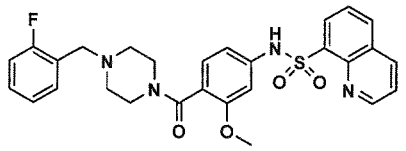
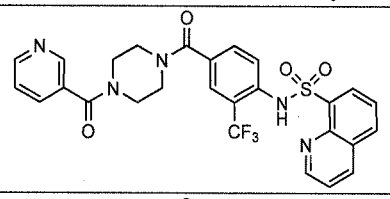
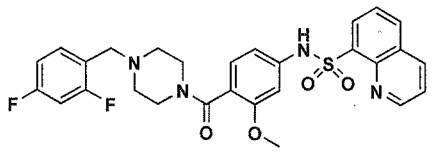
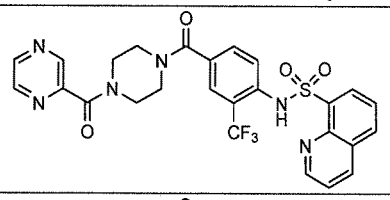
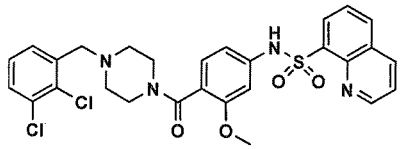
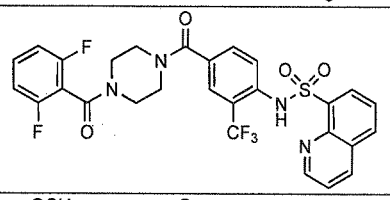
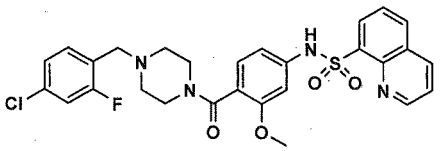
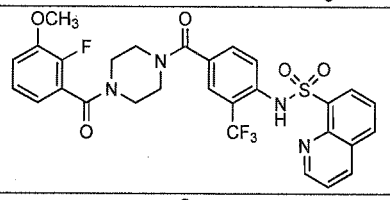
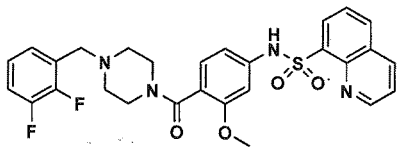
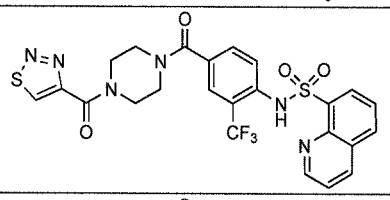
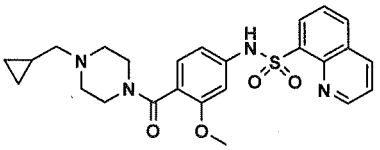
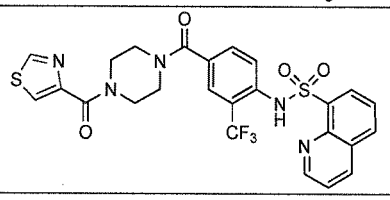
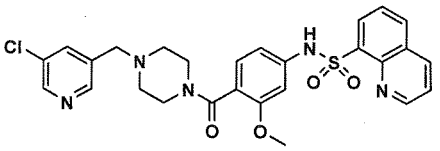
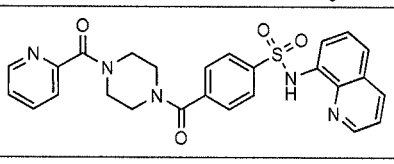
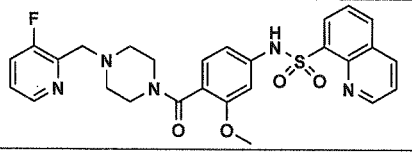
	
	
	
	
	
	
	
	

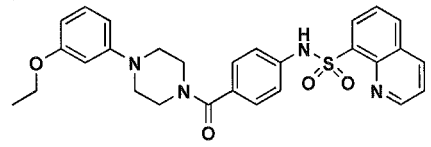
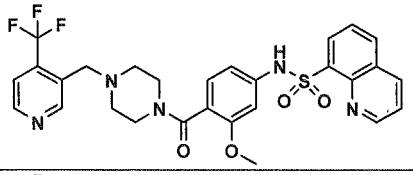
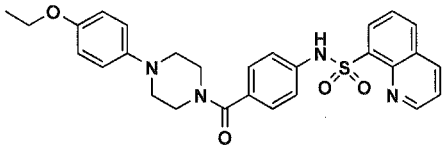
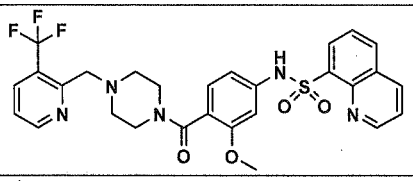
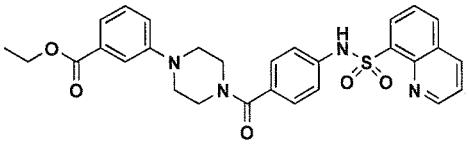
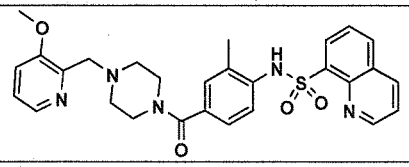
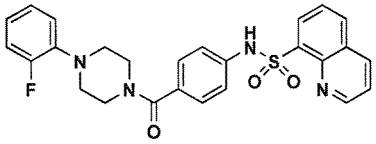
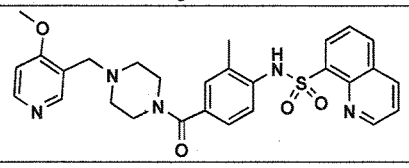
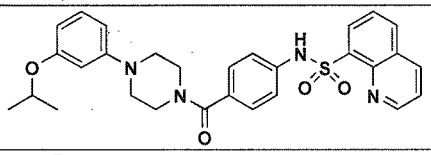
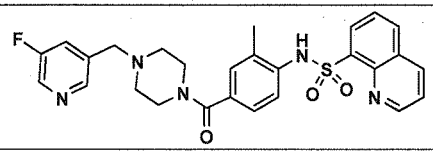
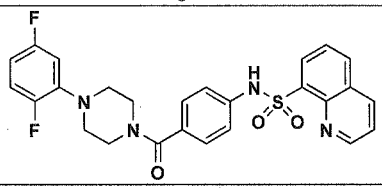
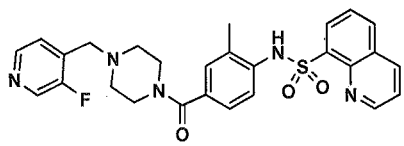
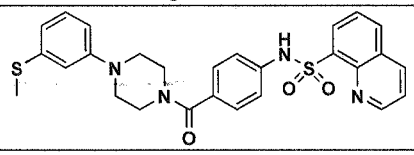
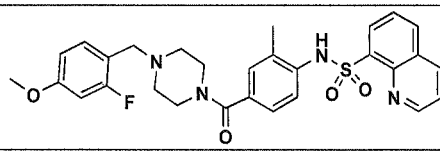
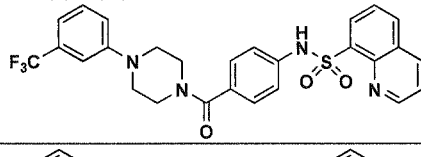
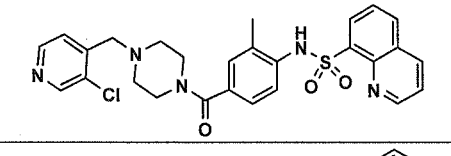
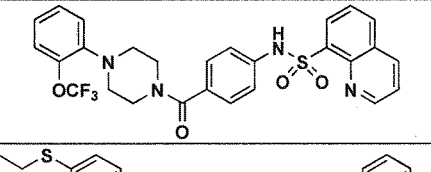
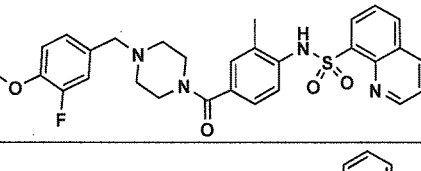
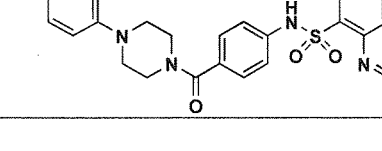
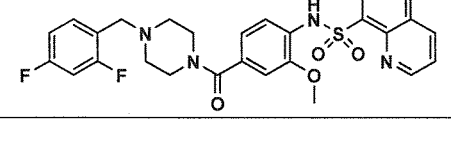
	
	
	
	
	
	
	
	

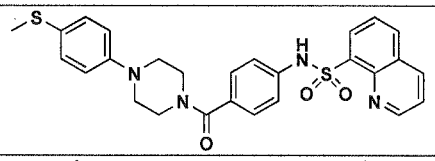
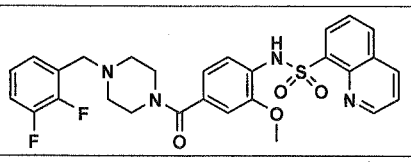
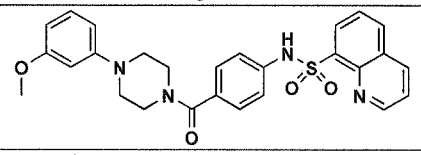
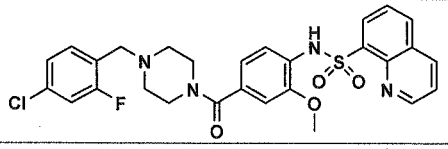
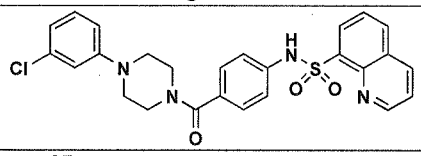
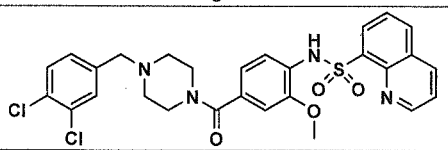
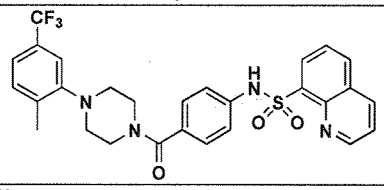
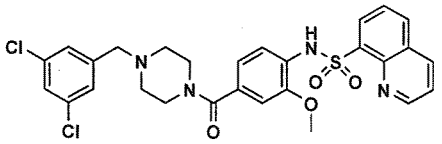
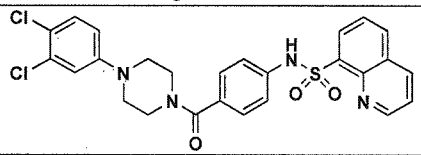
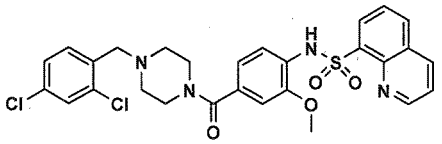
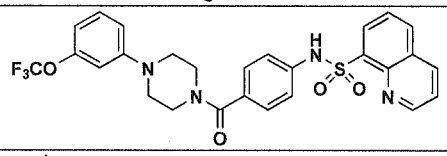
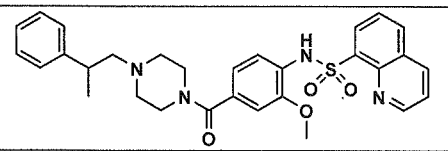
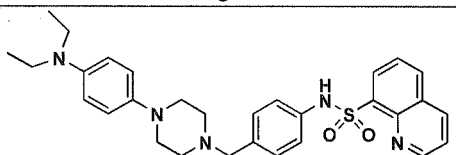
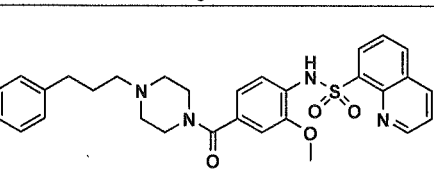
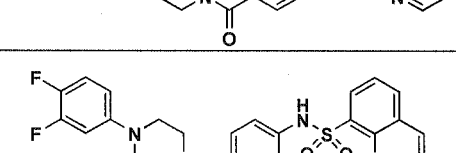
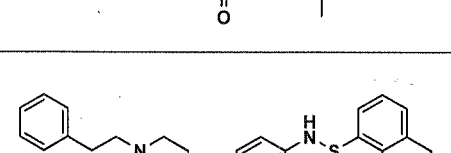
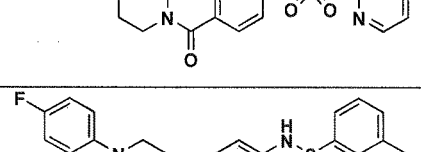
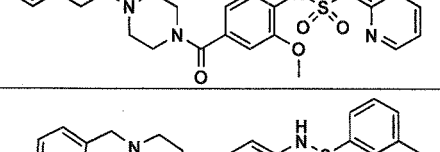
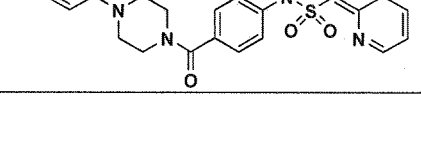
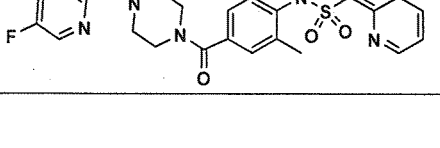
	
	
	
	
	
	
	
	

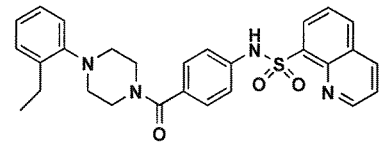
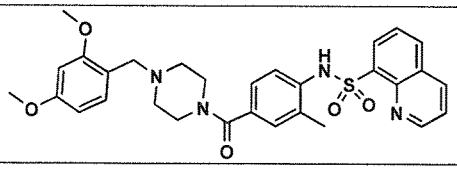
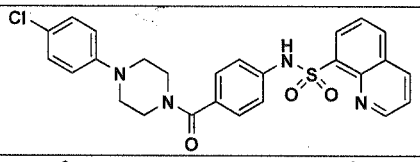
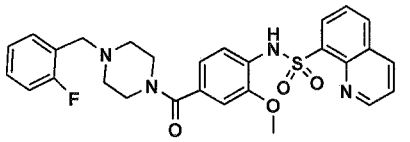
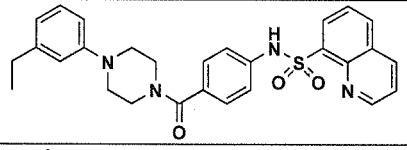
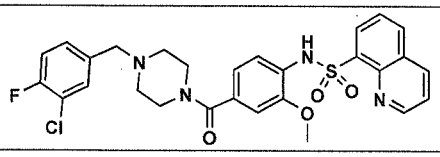
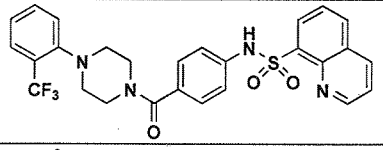
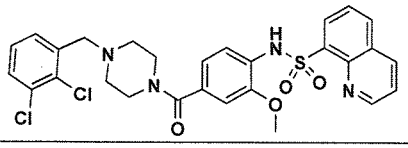
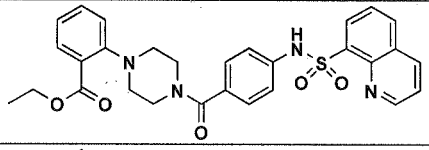
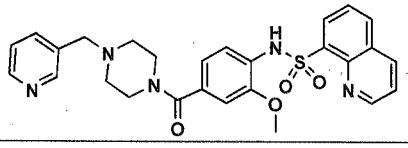
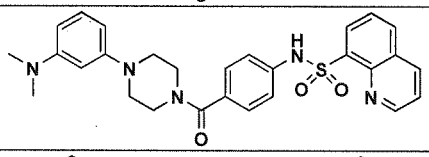
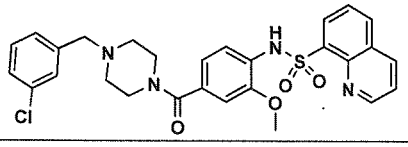
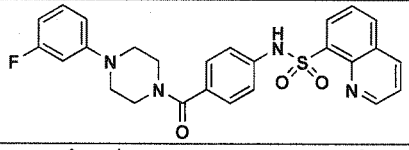
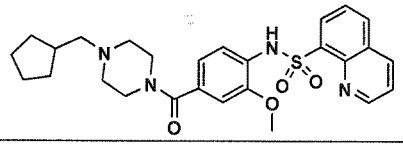
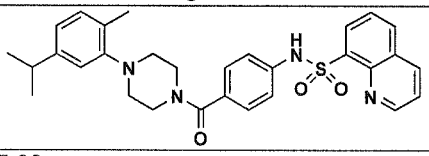
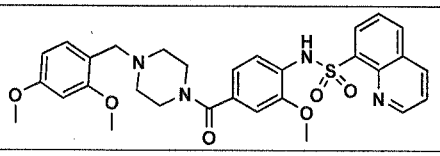
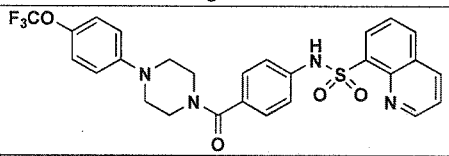
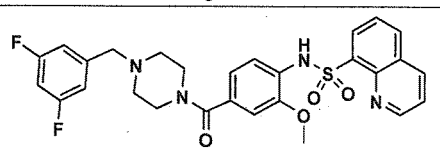
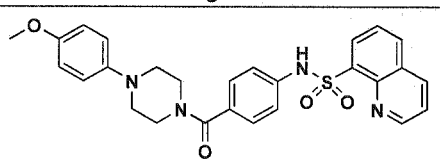
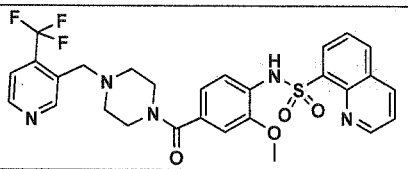
	
	
	
	
	
	
	
	

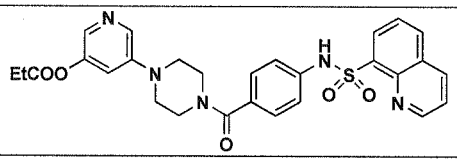
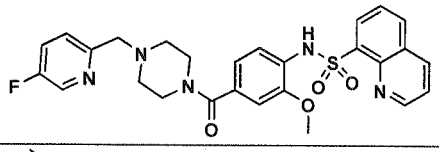
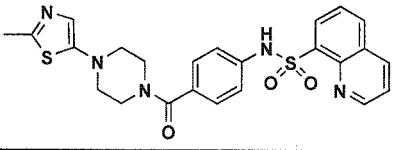
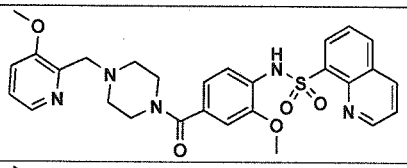
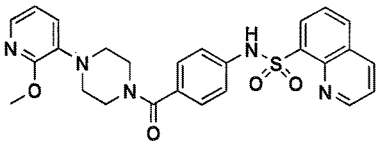
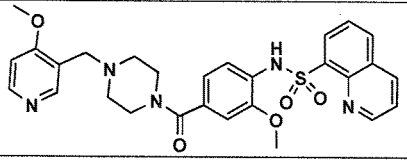
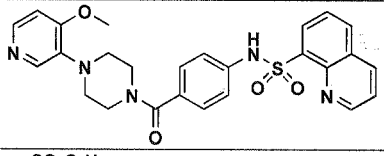
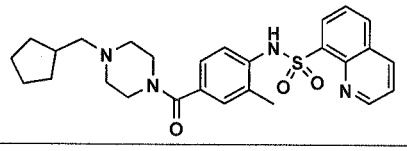
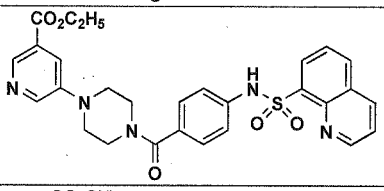
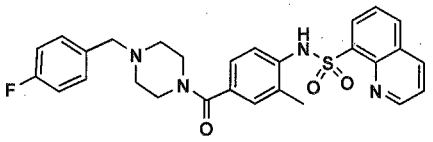
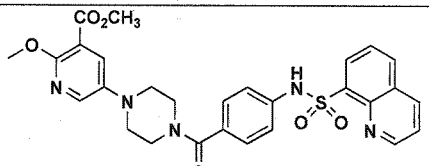
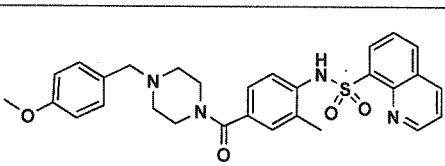
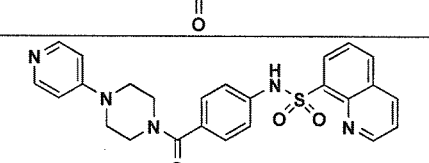
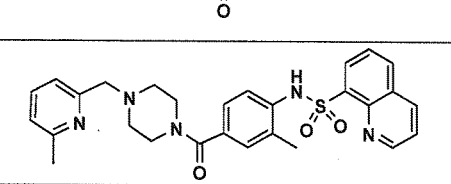
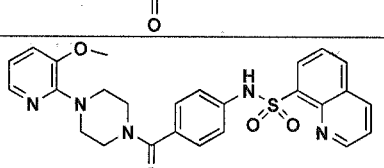
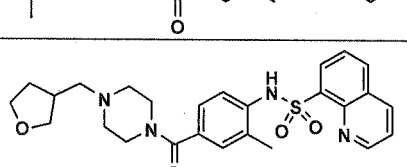
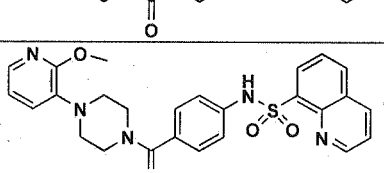
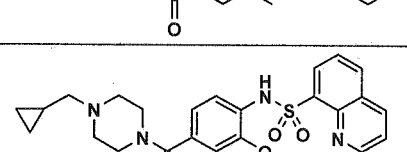
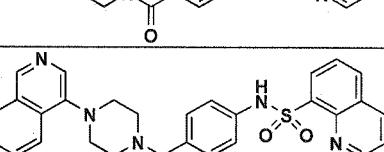
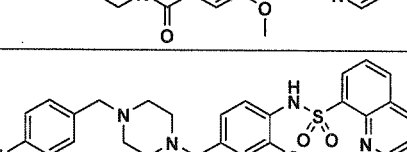
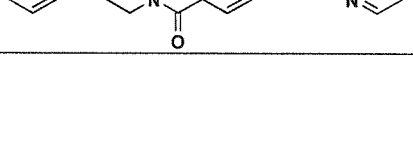
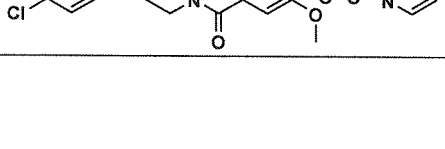
	
	
	
	
	
	
	
	

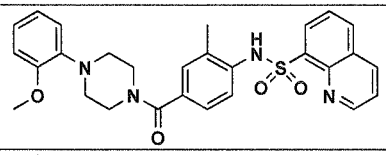
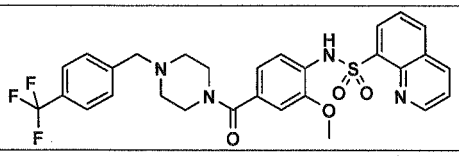
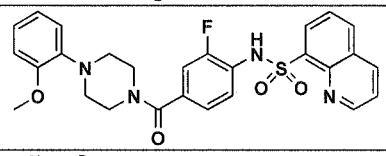
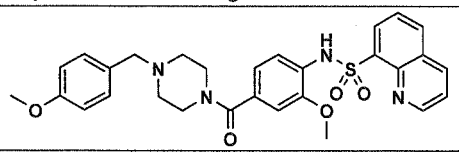
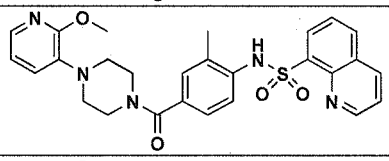
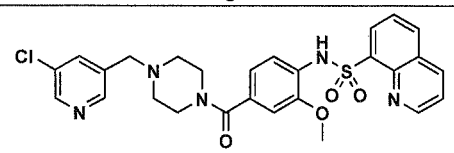
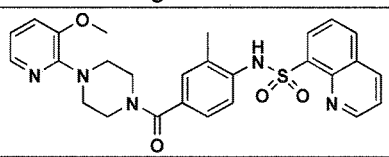
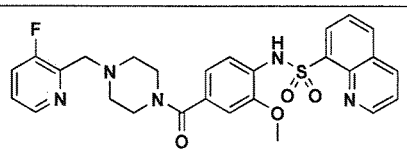
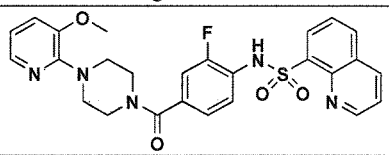
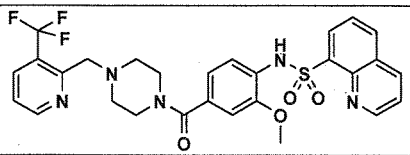
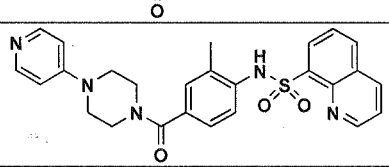
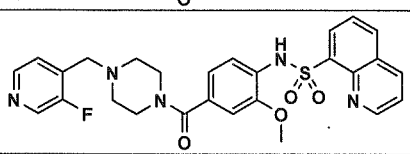
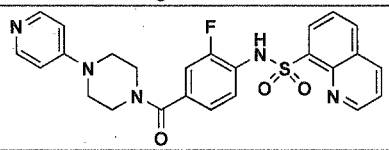
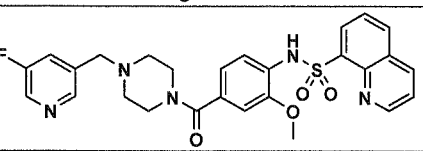
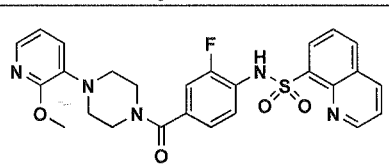
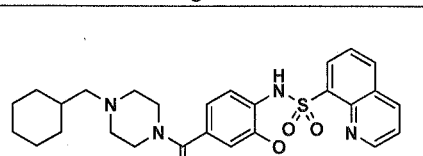
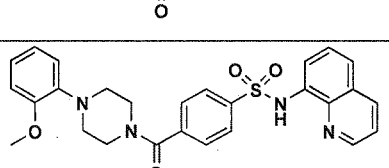
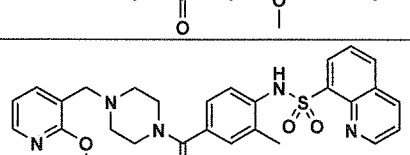
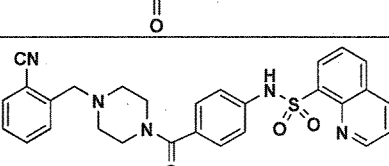
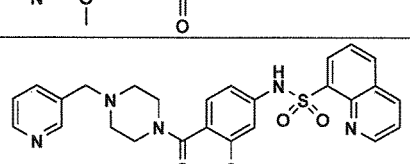
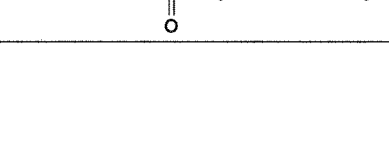
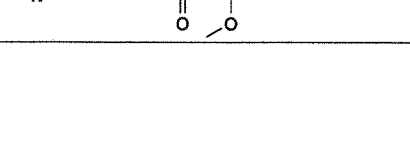
	
	
	
	
	
	
	
	

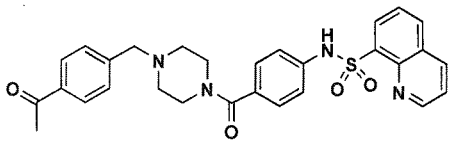
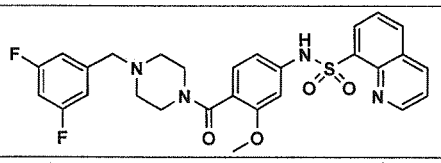
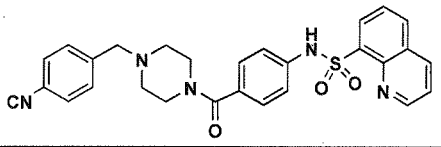
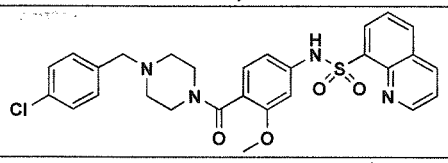
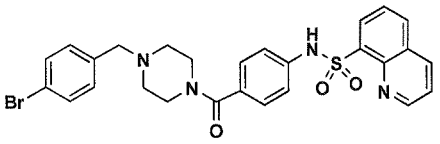
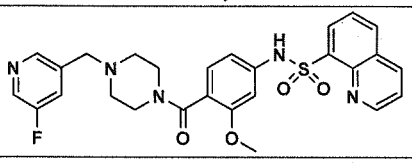
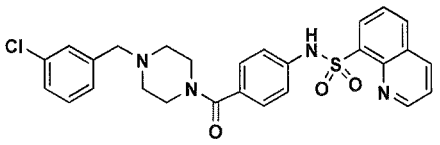
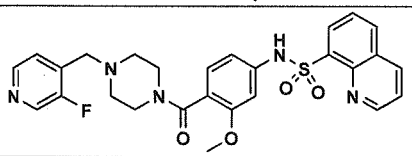
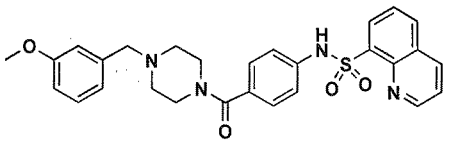
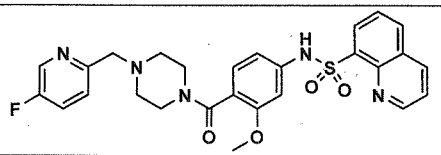
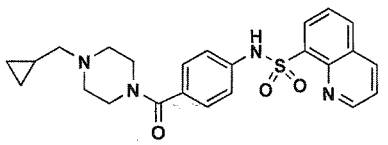
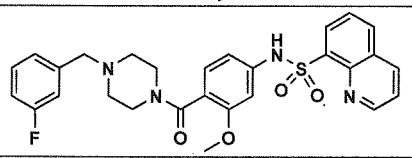
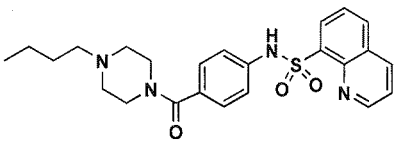
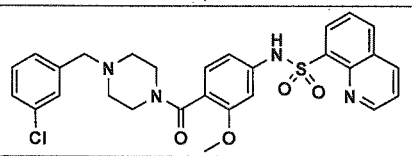
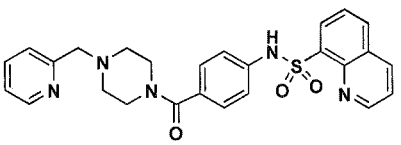
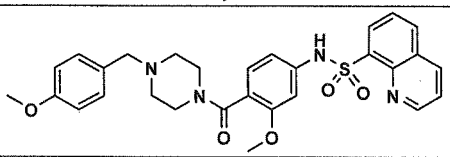
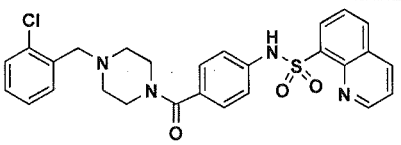
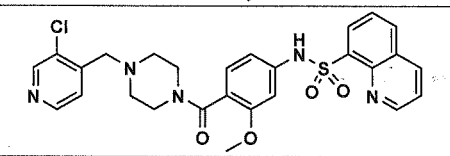
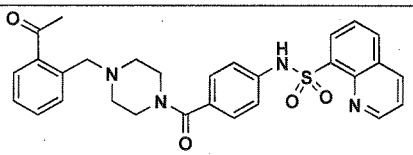
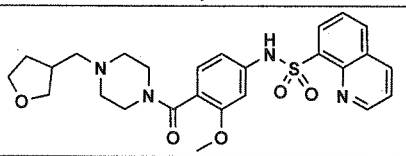
	
	
	
	
	
	
	
	
	
	

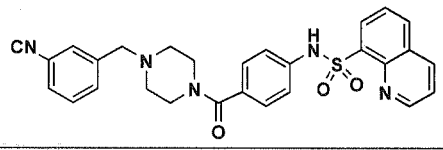
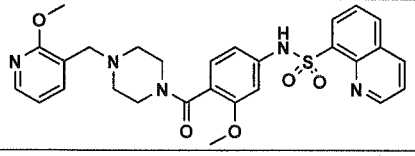
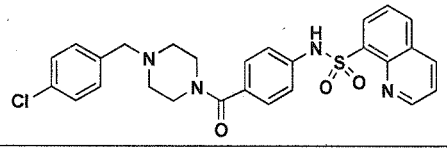
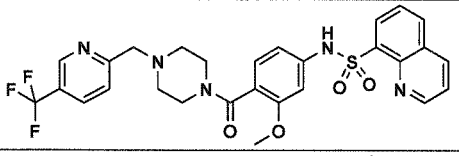
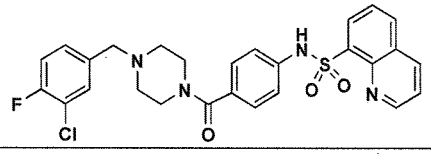
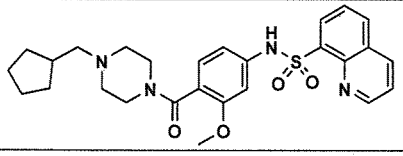
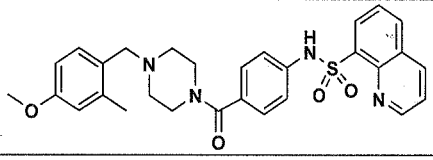
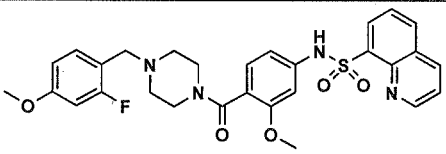
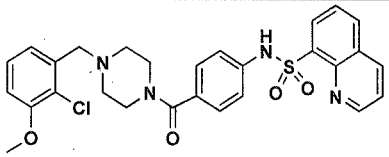
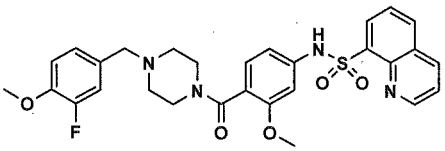
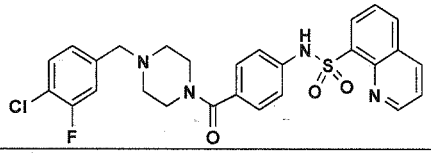
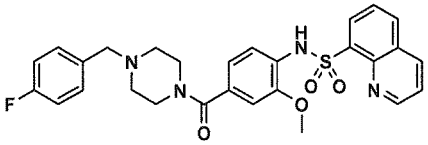
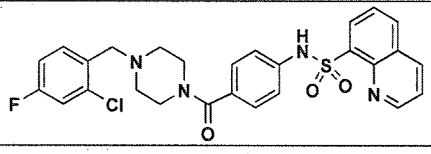
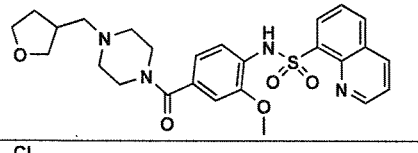
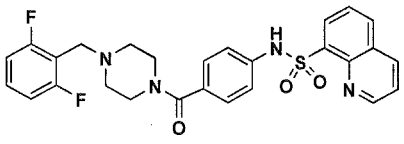
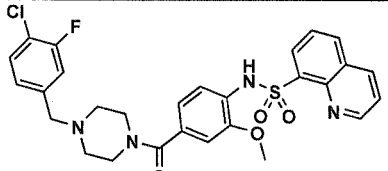
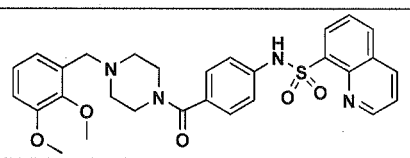
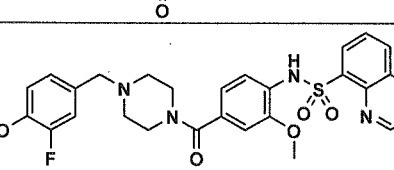
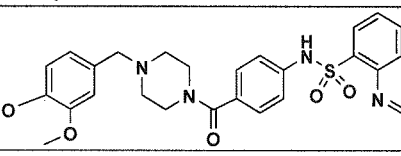
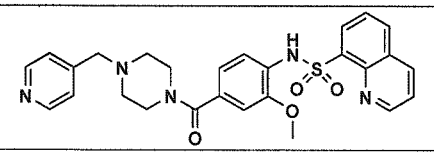
	
	
	
	
	
	
	
	
	
	

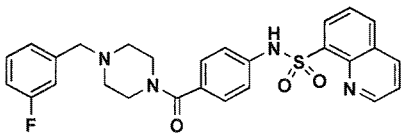
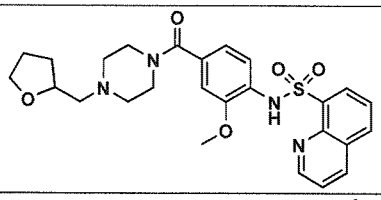
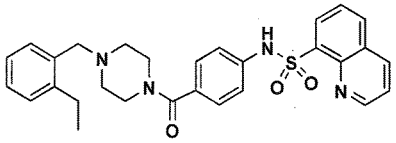
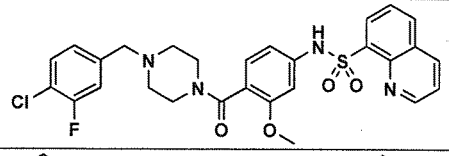
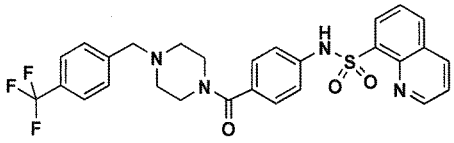
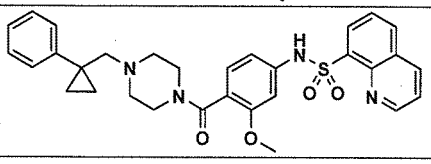
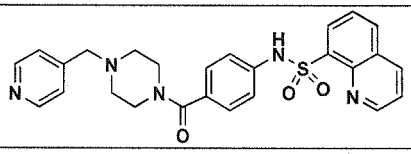
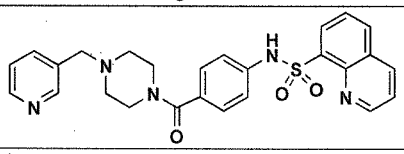
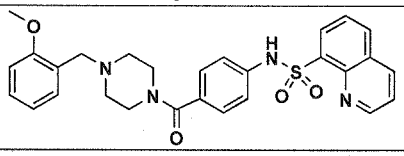
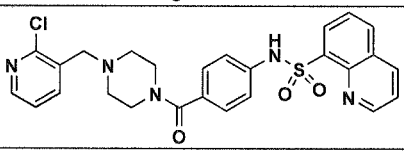
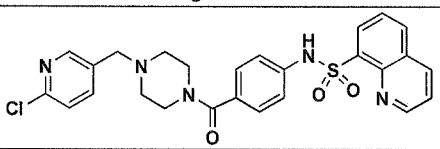
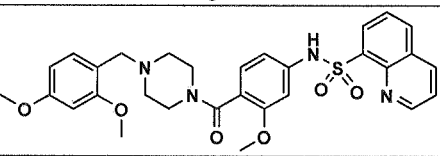
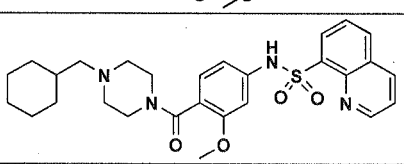
	
	
	
	
	
	
	
	
	
	

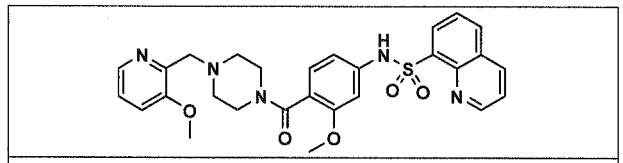
	
	
	
	
	
	
	
	
	
	
	

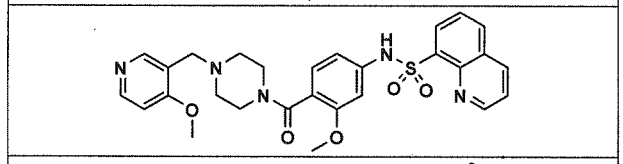
	
	
	
	
	
	
	
	
	
	
	

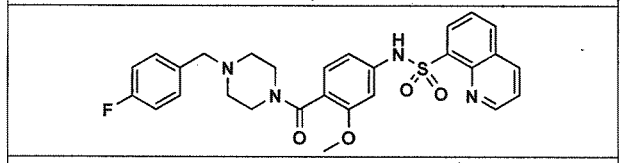
	
	
	
	
	
	
	
	
	
	

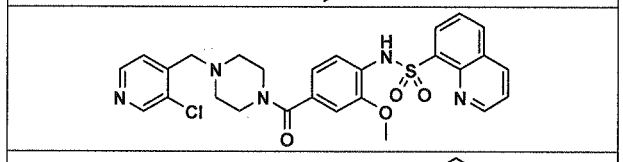
	
	
	
	
	
	
	
	
	
	

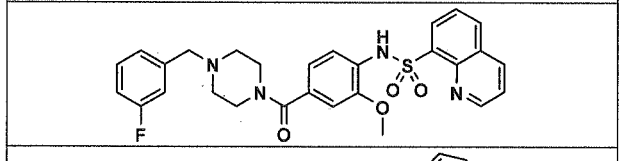
	
	
	
	
	
	
	
	
	
	

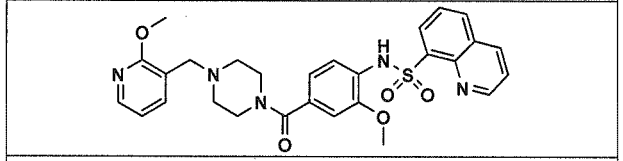


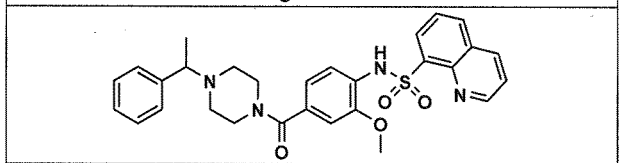


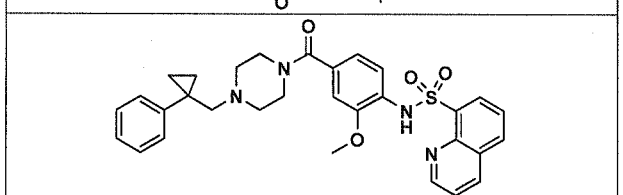


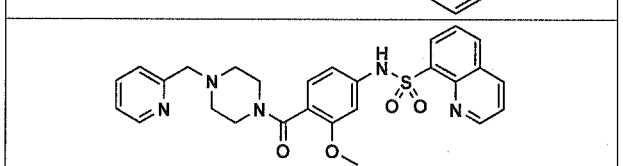


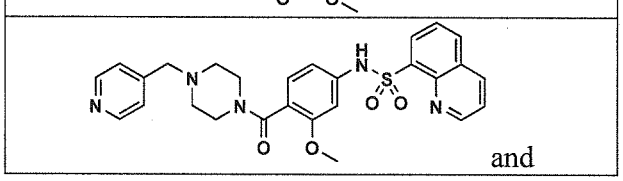












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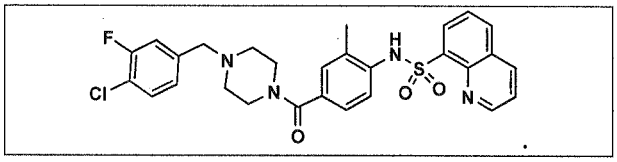

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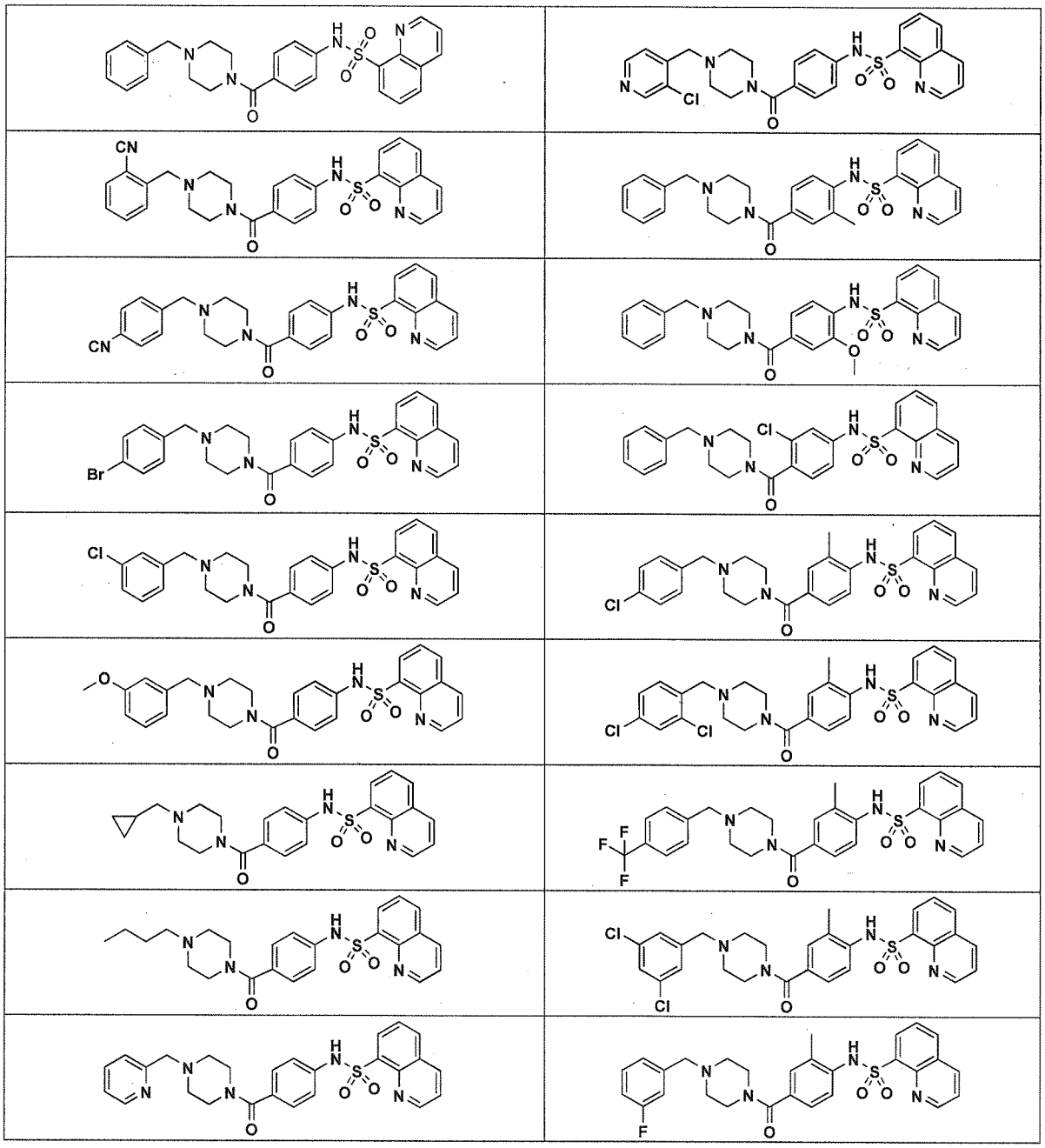
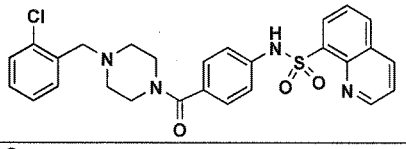
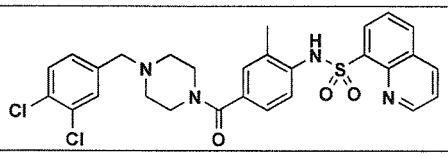
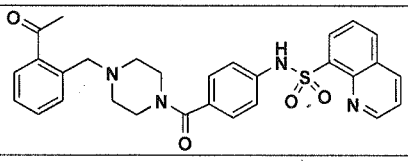
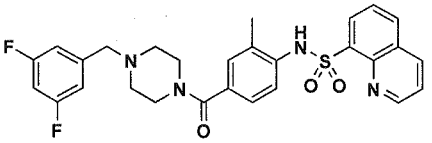
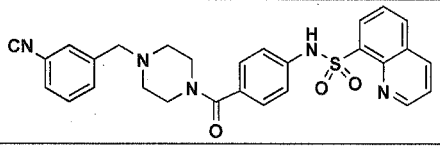
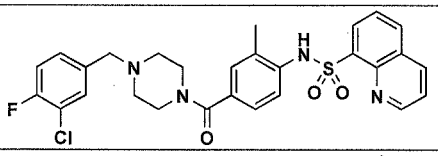
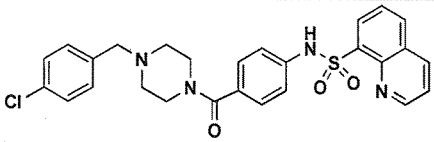
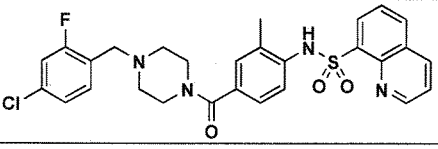
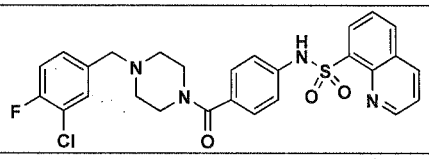
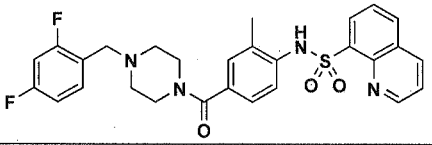
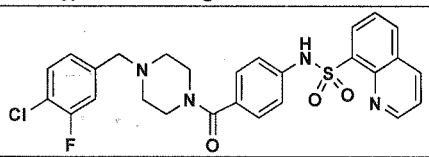
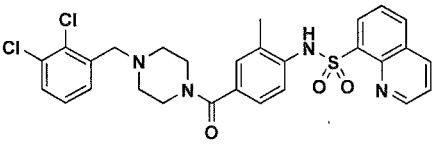
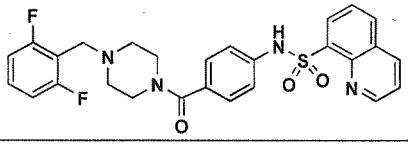
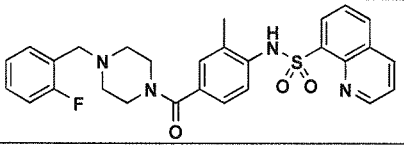
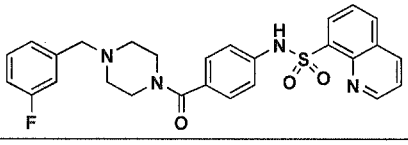
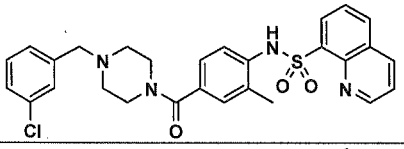
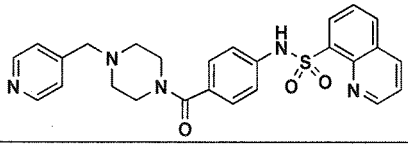
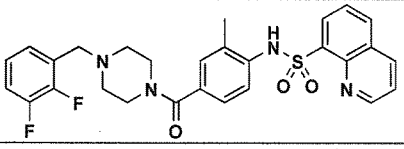
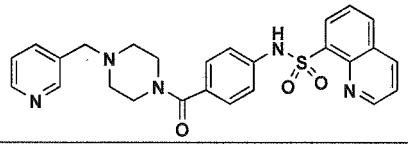
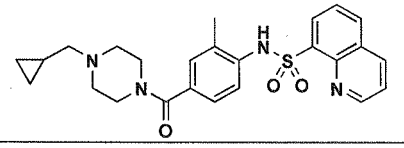
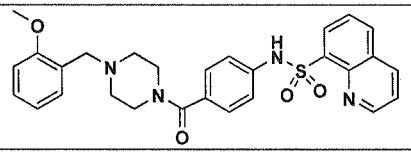
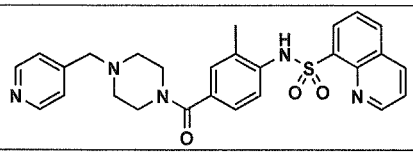
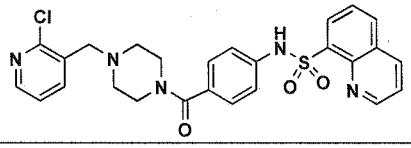
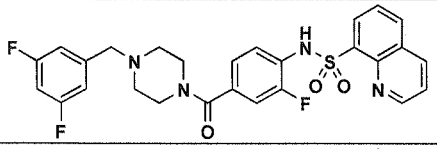
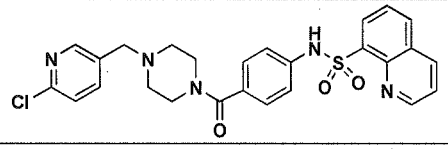
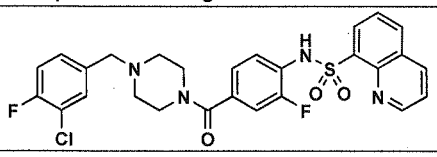
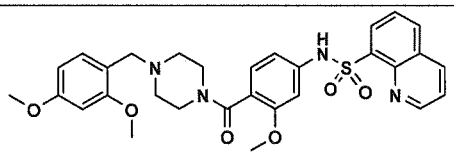
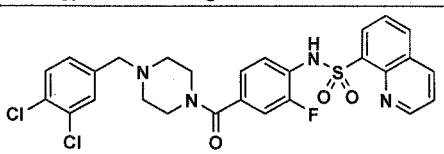
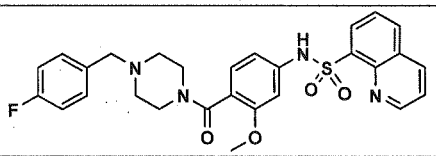
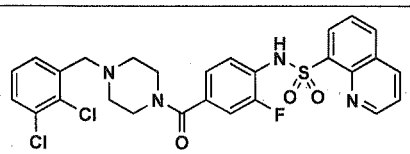
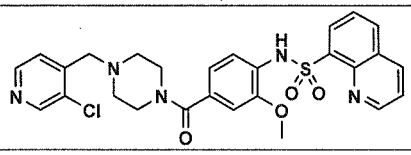
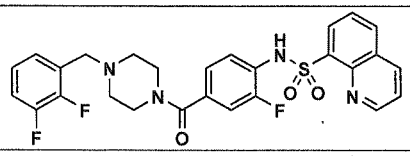
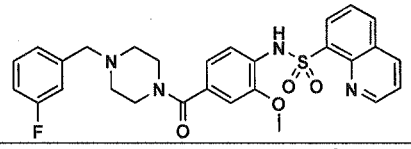
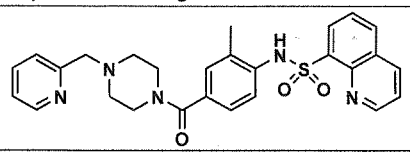
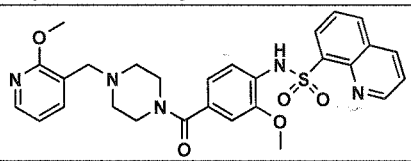
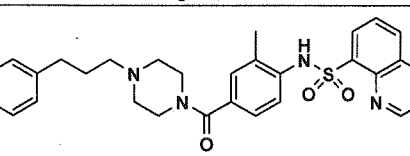
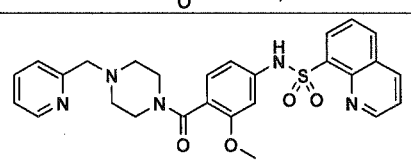
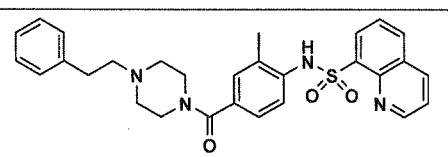
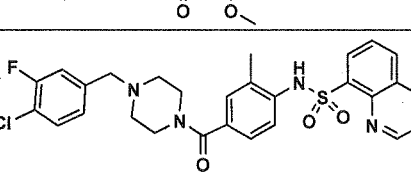
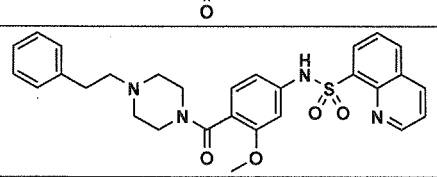
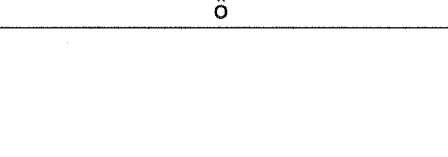
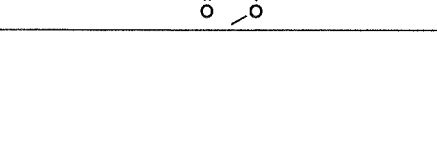
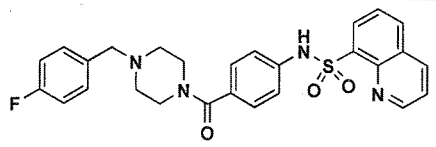
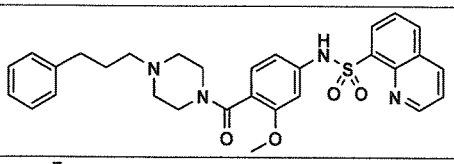
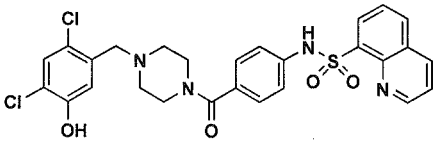
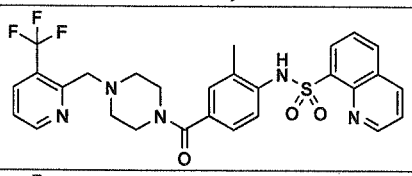
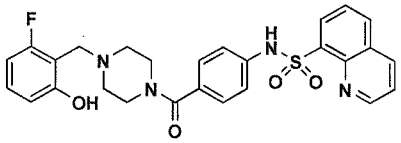
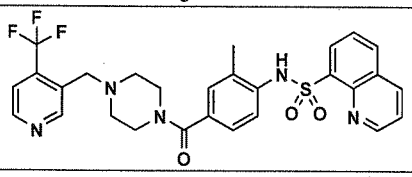
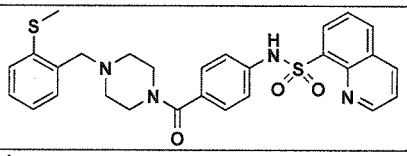
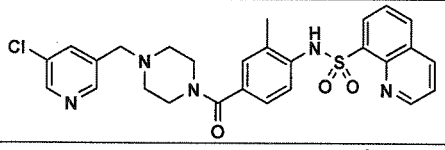
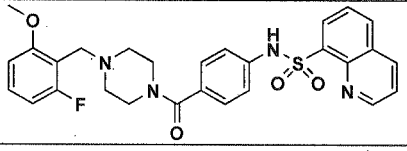
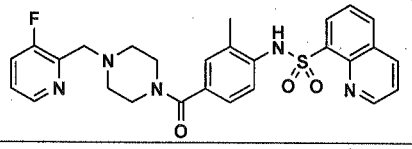
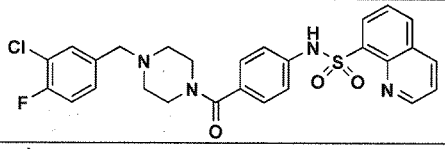
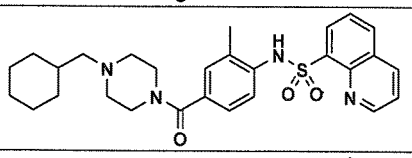
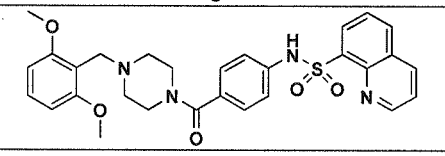
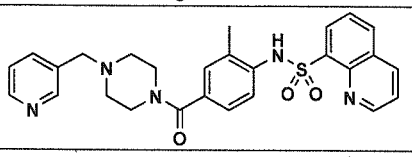
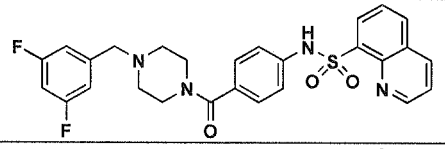
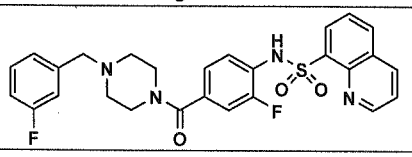
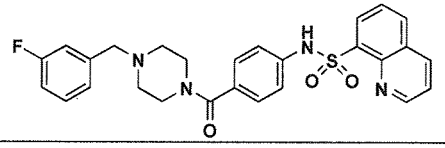
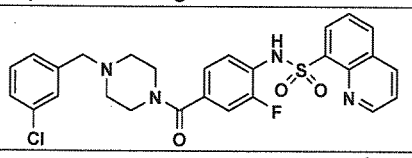
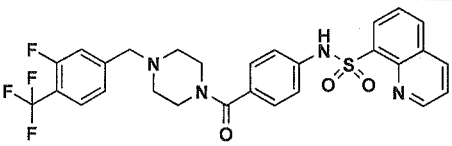
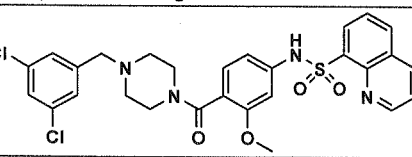
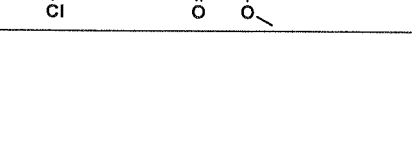
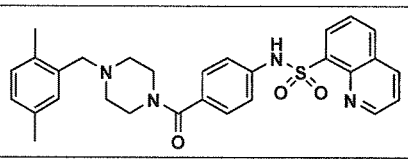
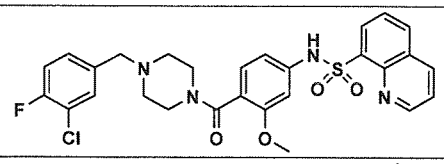
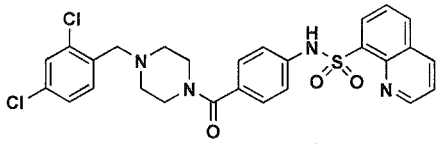
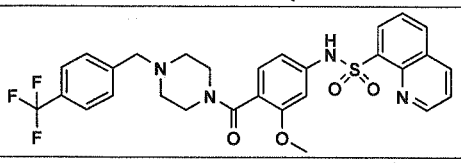
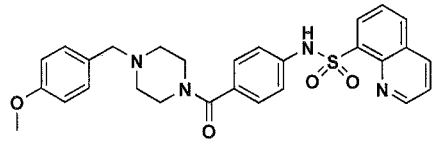
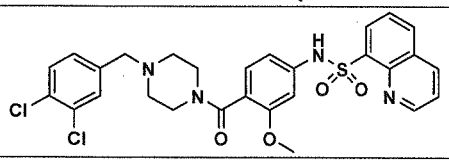
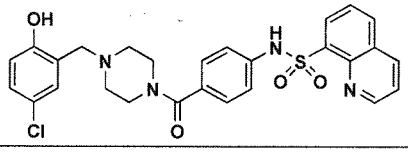
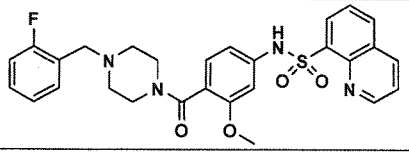
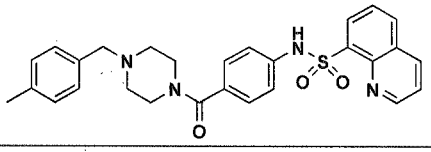
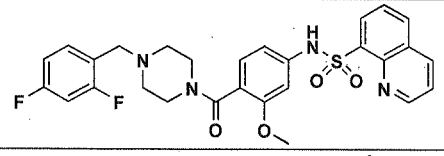
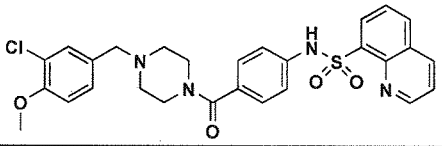
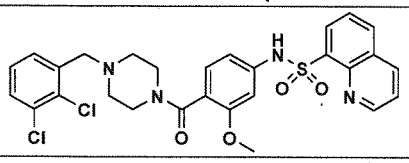
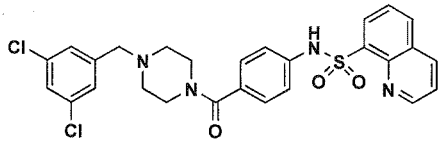
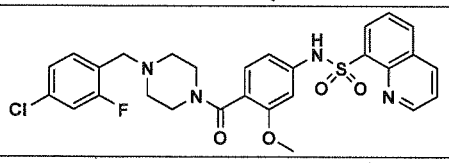
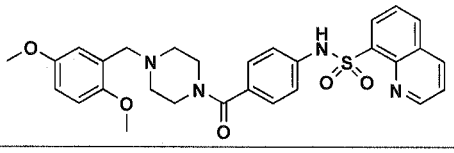
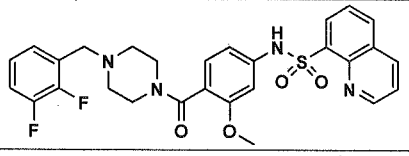
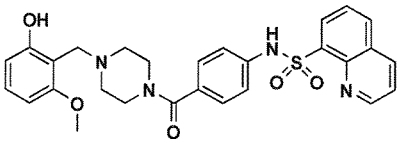
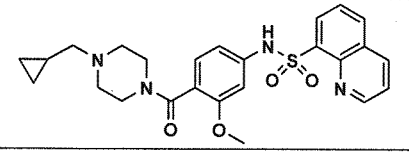
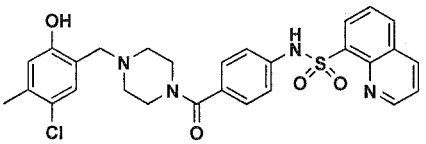
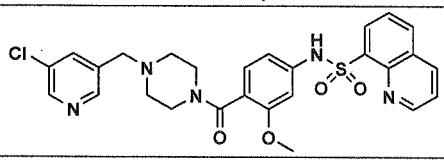
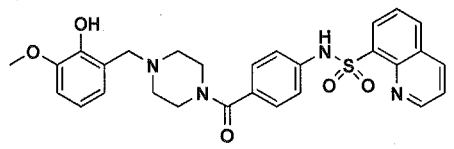
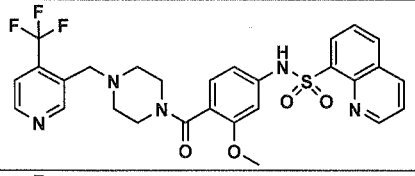
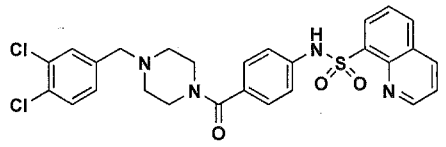
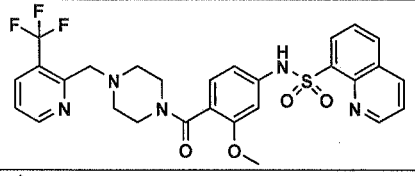
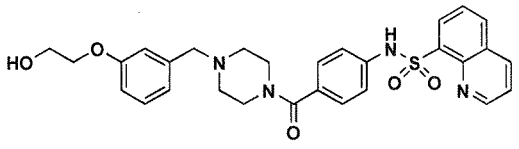
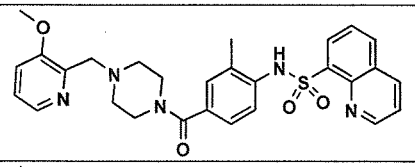
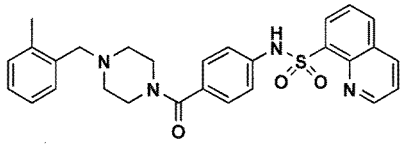
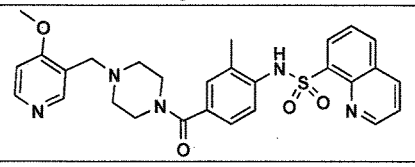
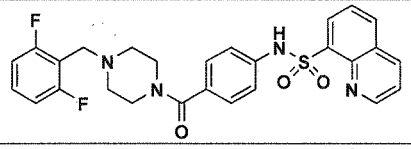
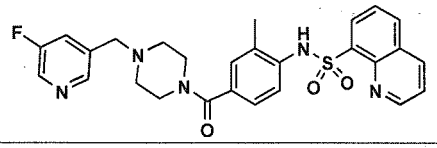
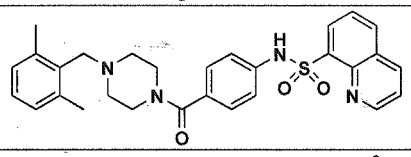
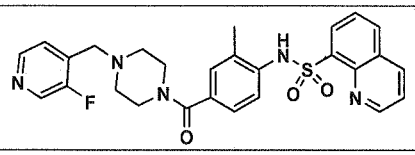
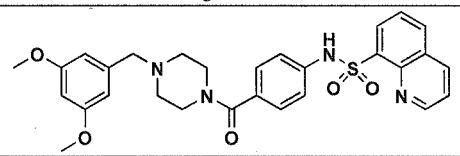
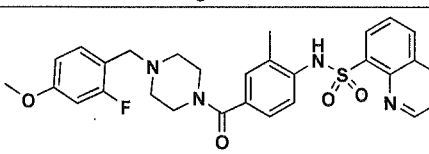
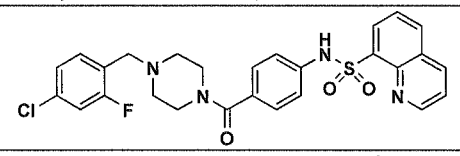
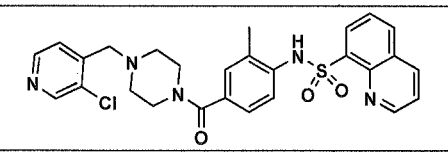
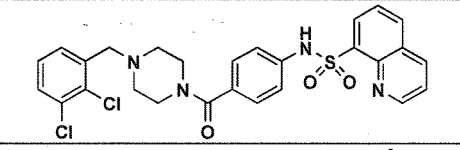
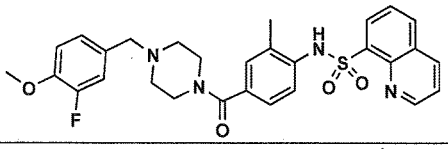
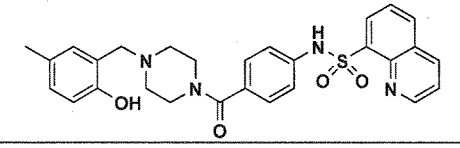
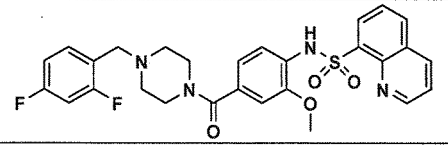


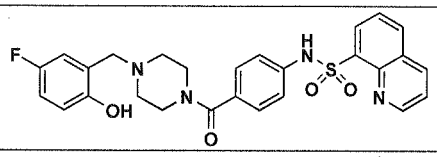
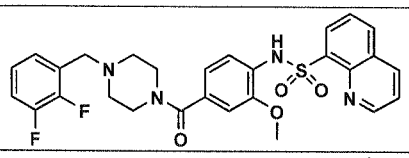
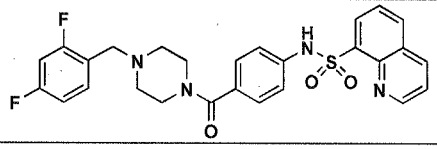
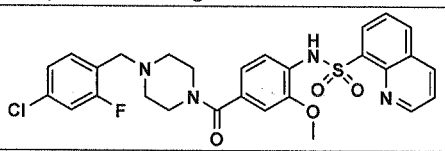
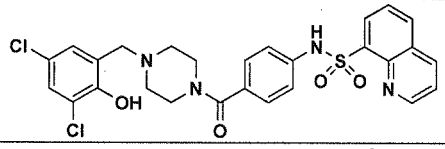
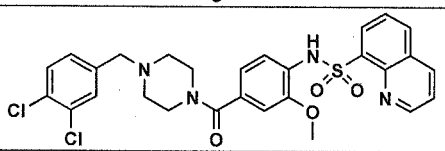
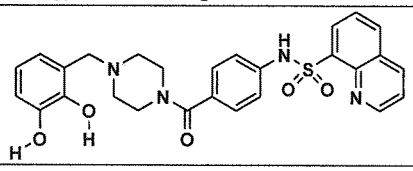
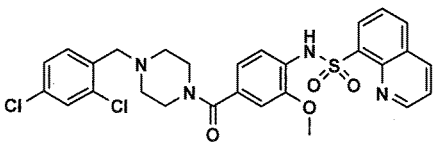
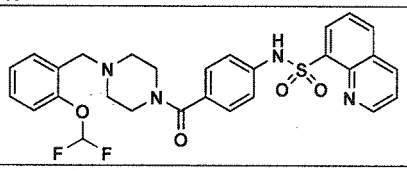
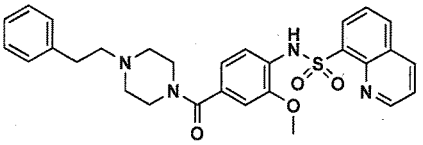
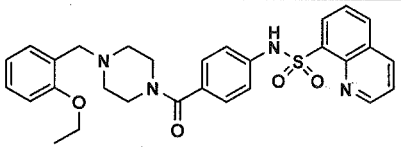
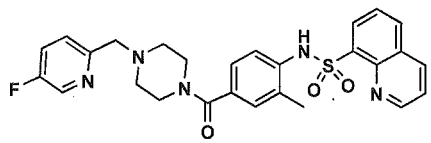
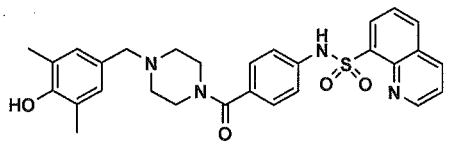
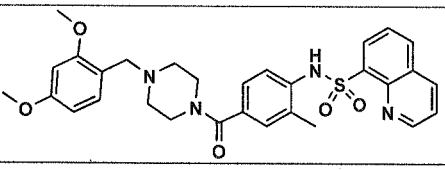
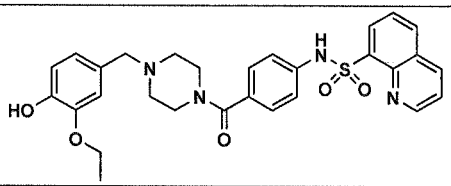
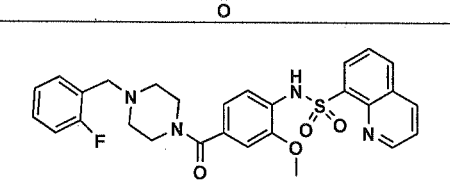
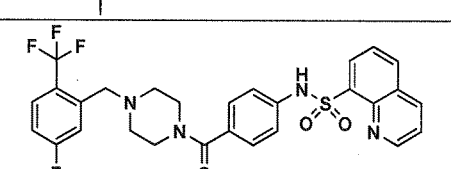
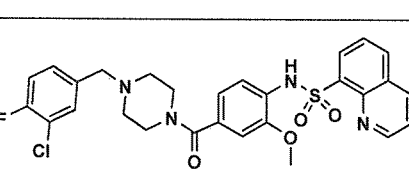
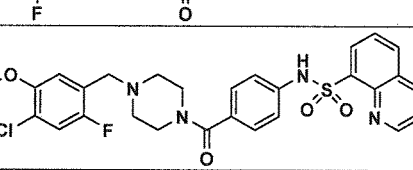
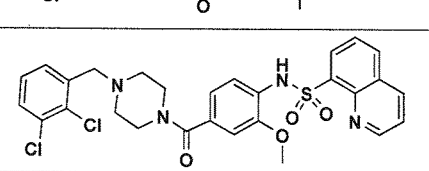
	
	
	
	
	
	
	
	
	
	

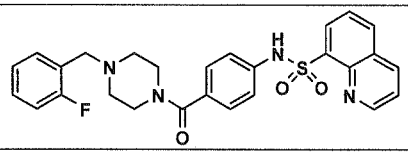
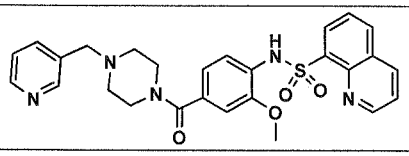
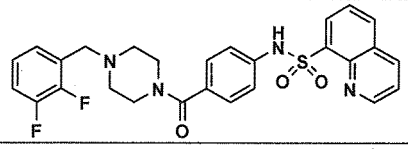
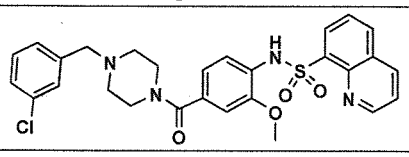
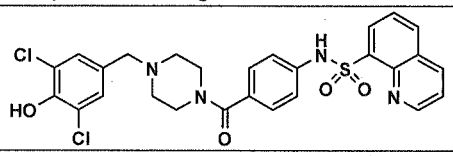
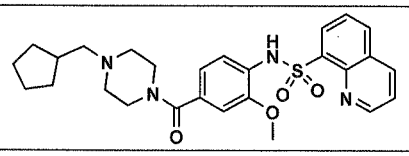
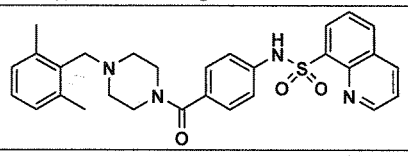
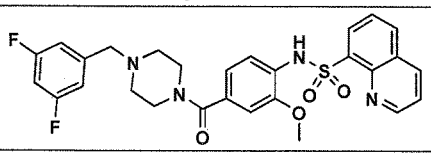
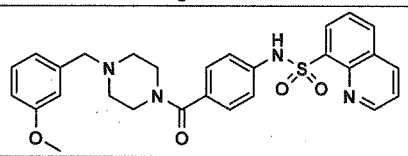
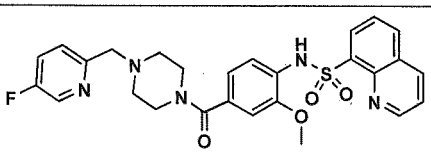
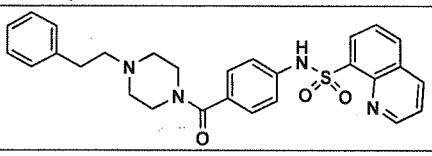
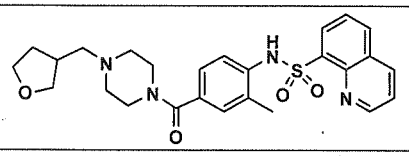
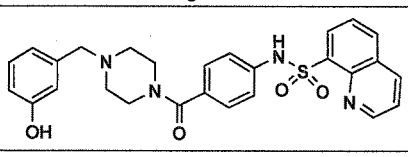
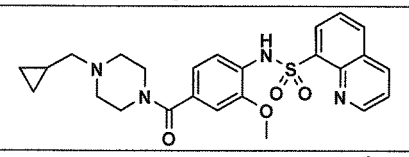
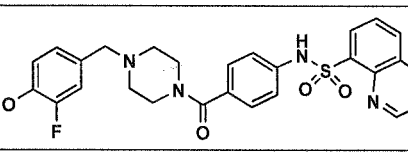
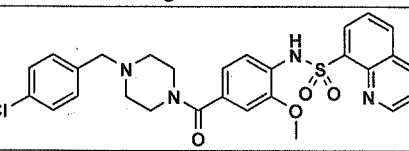
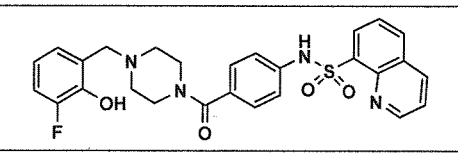
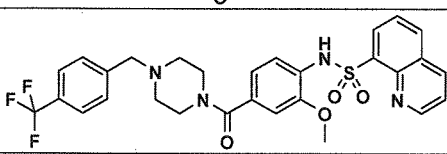
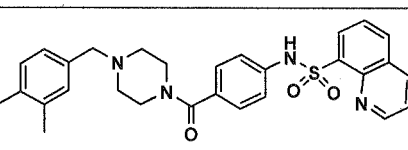
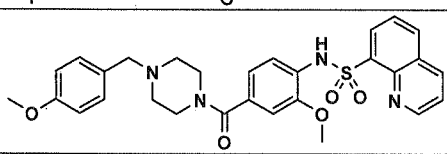
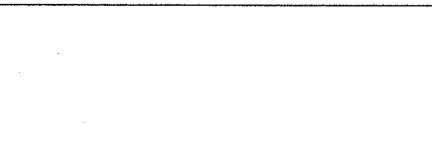
	
	
	
	
	
	
	
	
	
	
	

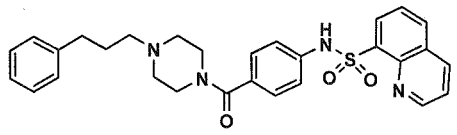
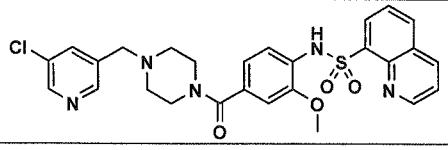
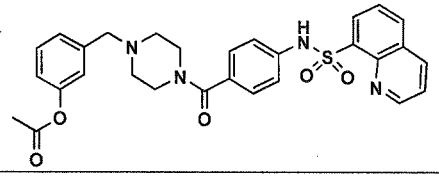
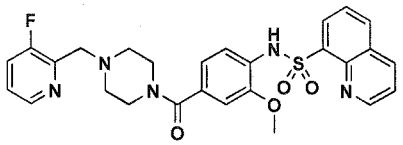
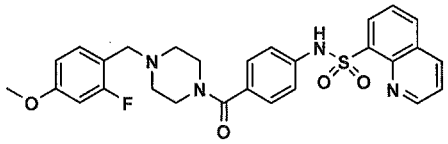
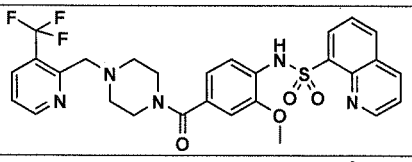
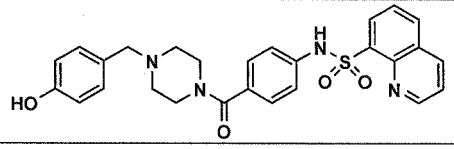
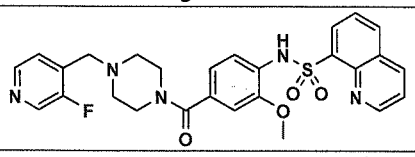
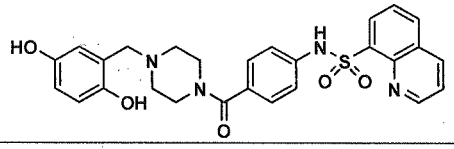
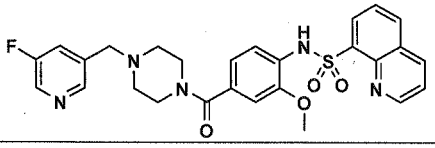
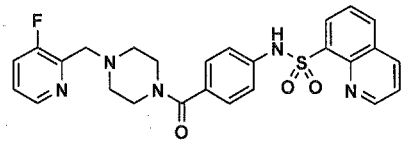
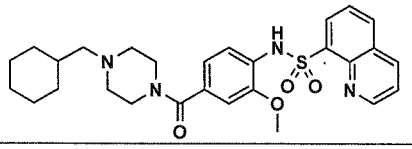
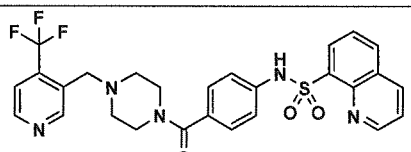
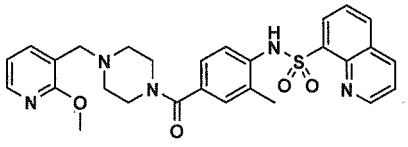
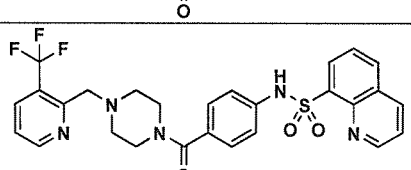
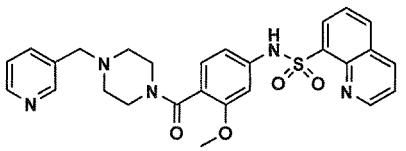
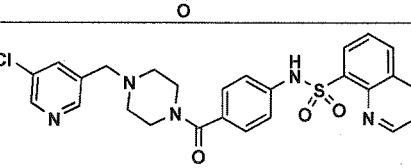
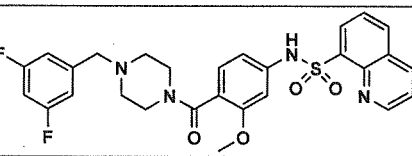
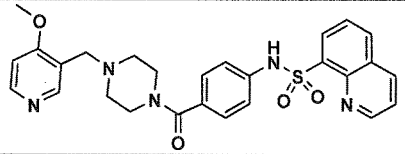
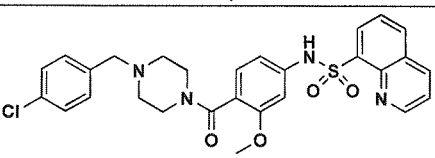
	
	
	
	
	
	
	
	
	
	
	

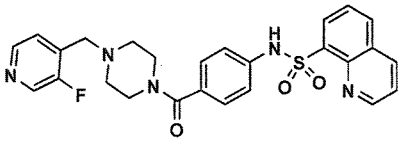
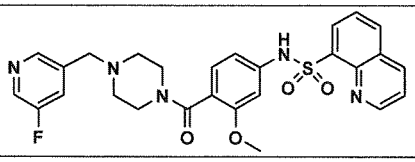
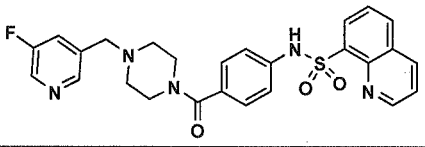
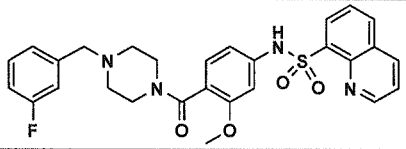
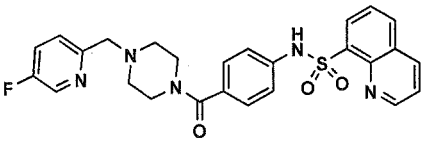
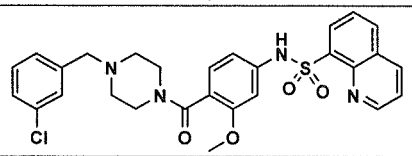
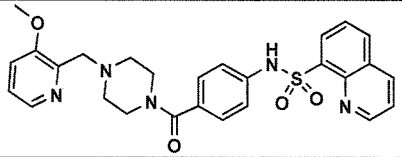
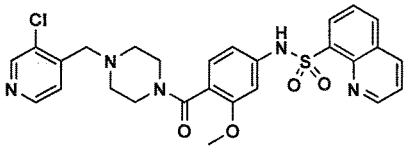
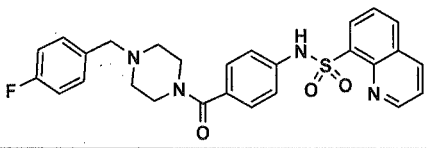
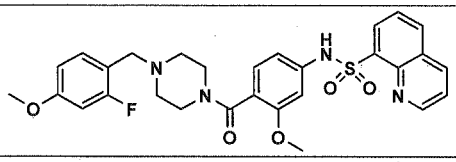
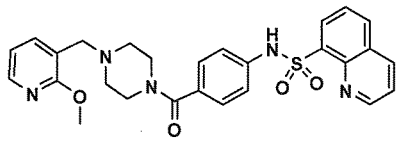
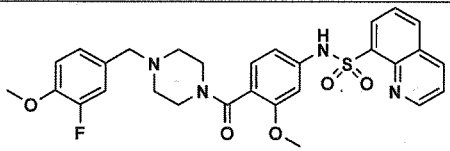
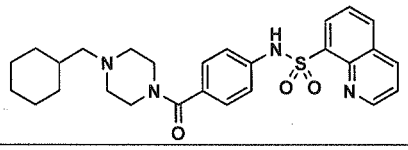
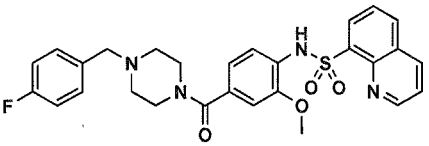
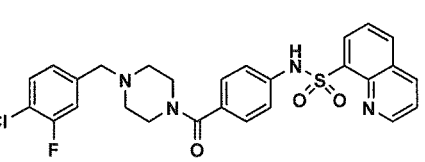
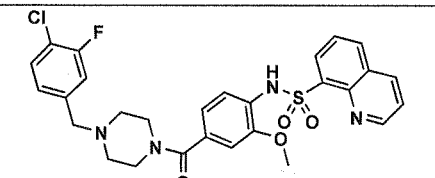
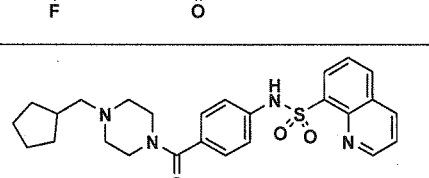
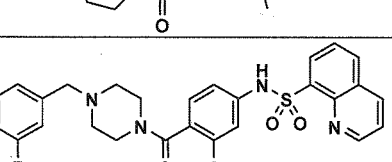
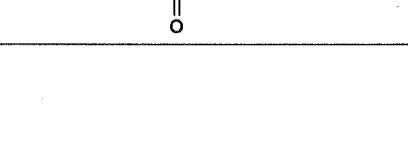
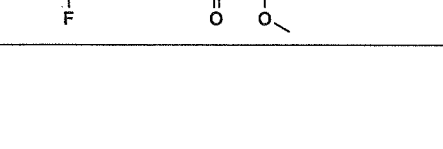
	
	
	
	
	
	
	
	
	
	

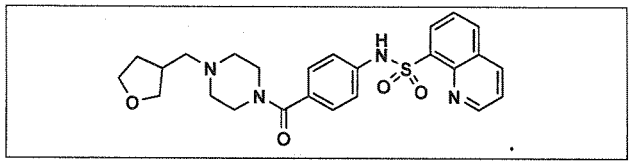
	
	
	
	
	
	
	
	
	
	

	
	
	
	
	
	
	
	
	
	 and



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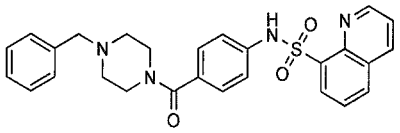

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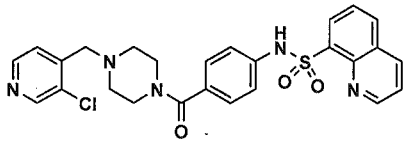

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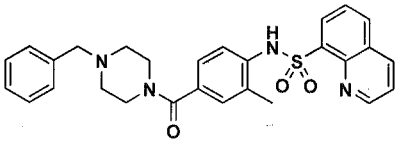

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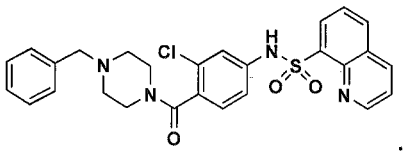

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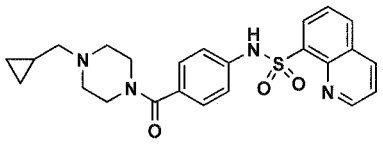

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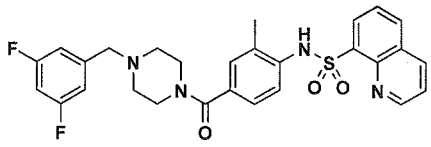

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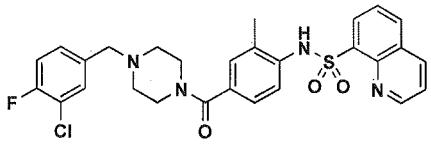

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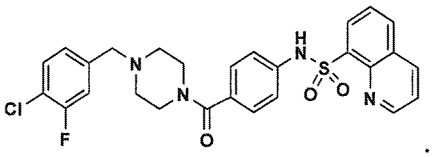

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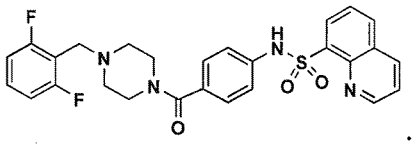

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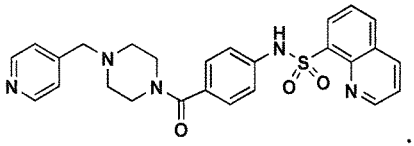

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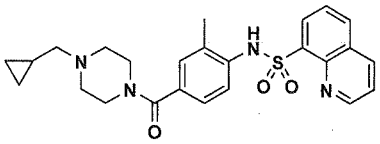

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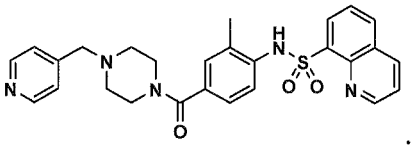

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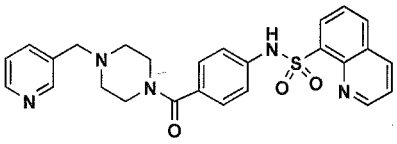

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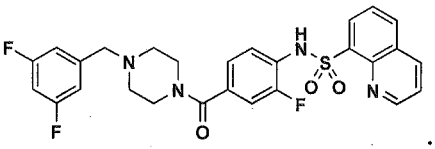

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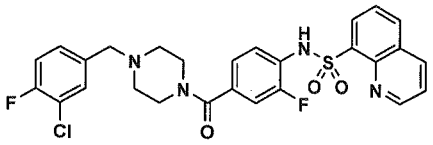

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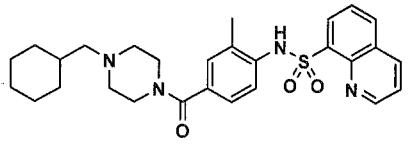

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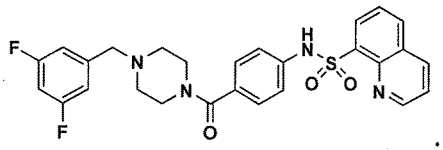

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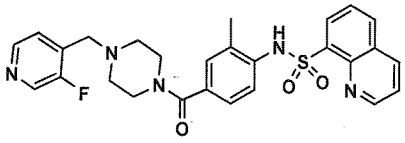

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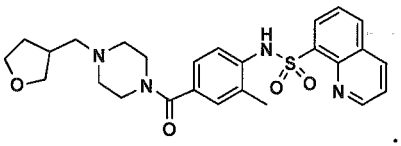

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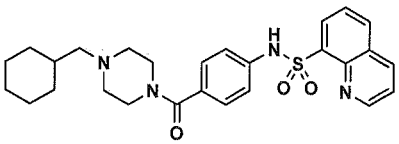
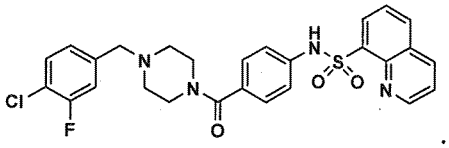
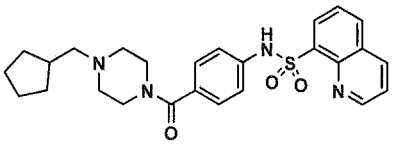


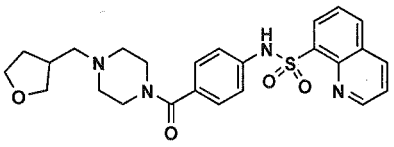
46. The compound of claim 1 selected from:



47. The compound of claim 1 selected from:



48. The compound of claim 1 selected from:



49. A pharmaceutical composition comprising a compound of any one of claims 2 to 21, or a pharmaceutically acceptable salt thereof.

50. A pharmaceutical composition comprising a compound of claim 24, or a pharmaceutically acceptable salt thereof.