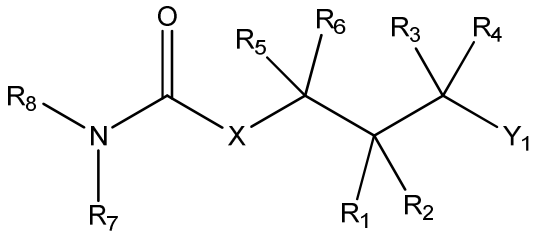
SUMMARY

[003a] In one aspect, the present disclosure refers to a compound of formula I, or a salt, solvate or hydrate thereof,



(I)

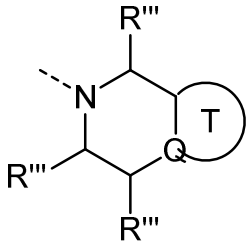
wherein,

R_1, R_3, R_4, R_5 and R_6 are each independently selected from hydrogen and C_{1-3} alkyl;

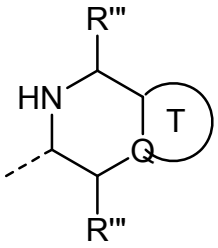
R_2 is selected from hydrogen and R_{14};

X is O or NR_9, where R_9 is hydrogen or a C_{1-3} alkyl;

Y_1 is a group selected from one of formula A and B,



(A)



(B)

where each R'" is independently selected from H or C_{1-3} alkyl;

Q is C or N;

T is selected from a fused phenyl group and a fused 5- or 6-membered heteroaryl group, wherein each group is optionally substituted with one or more substituents selected from halo and C_{1-3} alkyl; and

R_7 and R_8 are taken together with the intervening nitrogen atom to form a 3-12 membered heterocycloalkyl ring, wherein the 3-12 membered heterocycloalkyl ring is optionally substituted with one or more R_{10}; and/or optionally fused to one or more C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl rings, wherein each fused C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl ring is optionally substituted with one or more R_{14};

R_{10} is selected from a group of the formula L_1-L_2-R_{11} or L_2-L_1-$R_{11,}$ where L_1 is a linker of the formula $–[CR_{12}R_{13}]_n$-, where n is an integer of from 0 to 3 and R_{12} and R_{13} are in each instance each independently selected from H or C_1 to C_2 alkyl,

where L_2 is absent or a linker that is selected from O, S, SO, SO_2, N(R'), C(O), C(O)O, $[O(CH_2)_r]_s$, $[(CH_2)_rO]_s$, OC(O), CH(OR'), C(O)N(R'), N(R')C(O), N(R')C(O)N(R'), $SO_2N(R')$ or $N(R')SO_2$, where R' and R" are each independently selected from hydrogen and a C_1 to C_2 alkyl, and where r is 1 or 2 and s is 1 to 4,

R_{11} is independently selected from hydrogen, CN, NO_2, hydroxyl, =O, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, O-C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl, 3-10 membered heterocycloalkyl, $–C(=O)R^d$, $–C(=O)OR^d$, $–C(=O)NR^eR^d$, $–C(O)C(=O)R^d$, $–NR^eR^d$, $–NR^eC(=O)R^d$, $–NR^eC(=O)OR^d$, $–NR^eC(=O)NR^eR^d$, $–NR^eS(=O)_2R^d$, $–NR^eS(=O)_2NR^eR^d$, $–OR^d$, $–SR^d$, $–OC(=O)R^d$, $–OC(=O)NR^eR^d$, $–OC(=O)OR^d$, $–S(=O)_2R^d$, $–S(=O)R^d$, $–OS(=O)R^d$, $–OS(=O)_2R^d$, $–OS(=O)_2OR^d$, $–S(=O)NR^eR^d$, $–OS(=O)_2NR^eR^d$, and $–S(=O)_2NR^eR^d$, wherein, where R_{11} is independently selected from C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl and 3-10 membered heterocycloalkyl, each C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl and 3-10 membered heterocycloalkyl is optionally substituted with one or more R_{14};

each R^a and R^b is independently selected from hydrogen and C_{1-6} alkyl;

each R^d is independently selected from hydrogen, hydroxyl, halogen, CN, C_{1-6} haloalkyl, 3-7 membered heterocycloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, O-C_{1-6} alkyl and C_{6-11} aryl, wherein said C_{1-6} alkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl and C_{3-6} cycloalkyl are optionally substituted with one or more groups selected from hydroxyl, =O, halogen, CN, COR^a, NR^aR^b, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl;

each R^e is independently selected from hydrogen, hydroxyl, halogen, CN, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl; or

R^e and R^d, when attached to the same atom, together with the atom to which they are attached form a 3-7 membered heterocycloalkyl ring, optionally substituted with one or more substituent selected from hydroxyl, =O, halogen, CN, COR^a, NR^aR^b, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl;

and

R^{14} is independently selected from halo, CN, NO_2, hydroxyl, =O, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, O-C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, 5-6 membered heteroaryl, 3-7 membered heterocycloalkyl, C_{1-6}alkylC_{6-12}aryl, $–C(=O)R^d$, $–C(=O)OR^d$, $–C(=O)NR^eR^d$, $–C(O)C(=O)R^d$, $–NR^eR^d$, $–NR^eC(=O)R^d$, $–NR^eC(=O)OR^d$, $–NR^eC(=O)NR^eR^d$, $–NR^eS(=O)_2R^d$, $–NR^eS(=O)_2NR^eR^d$, $–OR^d$, $–SR^d$, $–OC(=O)R^d$, $–OC(=O)NR^eR^d$, $–OC(=O)OR^d$,

$-S(=O)_2R^d$, $-S(=O)R^d$, $-OS(=O)R^d$, $-OS(=O)_2R^d$, $-OS(=O)_2OR^d$, $-S(=O)NR^eR^d$, $-OS(=O)_2NR^eR^d$, and $-S(=O)_2NR^eR^d$.

[003b] In another aspect, the present disclosure refers to a pharmaceutical composition which comprises a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable excipients.

[003c] In another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

[003d] In yet another aspect, the present disclosure refers to the use of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 16 in the manufacture of a medicament for:

(a) treating or preventing a PRMT5-mediated disorder;
(b) treating a proliferative disorder;
(c) treating a cancer;
(d) inhibiting the activity of PRMT5; or
(e) altering gene expression in a cell.

[003e] In yet another aspect, the present disclosure refers to *in vitro* method of inhibiting the activity of PRMT5, said method comprising that a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as disclosed herein is to be administered to a subject in need thereof.

[003f] In yet another aspect, the present disclosure refers to an *in vitro* method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as disclosed herein.

[004] In one example, the present disclosure provides a compound of Formula I as defined herein, and/or a salt, hydrate or solvate thereof.

[005] In another example, the present disclosure provides a pharmaceutical composition which comprises a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable excipients.

[006] In another example, the present disclosure provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in therapy.

[007] In another example, the present disclosure provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment or prevention of a PRMT5-mediated disorder.

[008] In another example, the present disclosure provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment of a proliferative disorder.

[009] In another example, the present disclosure provides a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein, for use in the treatment cancer.

[0010] In another example, the present disclosure provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment or prevention of a PRMT5-mediated disorder.

[0011] In another example, the present disclosure provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment of a proliferative disorder.

[0012] In another example, the present disclosure provides the use of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, in the manufacture of a medicament for the treatment of cancer.

[0013] In another example, the present disclosure provides a method of treating or preventing a PRMT5-mediated disorder, said method comprising administering to a subject in need thereof

an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0014] In another example, the present disclosure provides a method of treating a proliferative disorder, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

[0015] In another example, the present disclosure provides a method of treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0016] In another example, the present disclosure provides a method of inhibiting the activity of PRMT5 *in vivo* or *in vitro*, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0017] In another example, the present disclosure provides a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula I as defined herein, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition as defined herein.

[0018] In another example, the present disclosure provides a combination comprising a compound of Formula I, or a pharmaceutically acceptable salt, hydrate or solvate thereof, as defined herein, with one or more additional therapeutic agents.

[0019] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

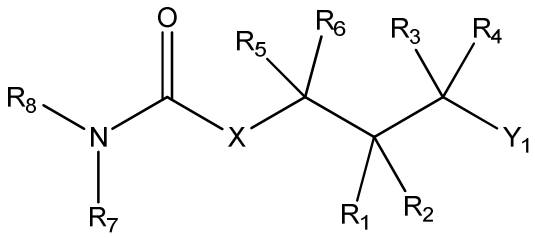
DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0020] The compounds and intermediates described herein may be named according to either the IUPAC (International Union for Pure and Applied Chemistry) or CAS (Chemical Abstracts Service) nomenclature systems. It should be understood that unless expressly stated to the contrary, the terms “compounds of Formula I” and the more general term “compounds” refer to and include any and all compounds described by and/or with reference to Formula I. It

CLAIMS

1. A compound of formula I, or a salt, solvate or hydrate thereof,



(I)

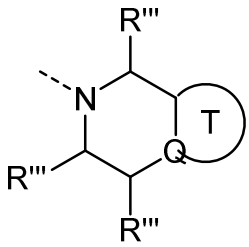
wherein,

R_1, R_3, R_4, R_5 and R_6 are each independently selected from hydrogen and C_{1-3} alkyl;

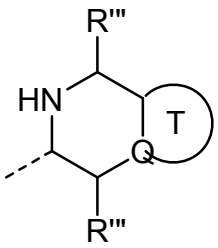
R_2 is selected from hydrogen and R_{14};

X is O or NR_9, where R_9 is hydrogen or a C_{1-3} alkyl;

Y_1 is a group selected from one of formula A and B,



(A)



(B)

where each R'" is independently selected from H or C_{1-3} alkyl;

Q is C or N;

T is selected from a fused phenyl group and a fused 5- or 6-membered heteroaryl group, wherein each group is optionally substituted with one or more substituents selected from halo and C_{1-3} alkyl; and

R_7 and R_8 are taken together with the intervening nitrogen atom to form a 3-12 membered heterocycloalkyl ring, wherein the 3-12 membered heterocycloalkyl ring is optionally substituted with one or more R_{10}; and/or optionally fused to one or more C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl rings, wherein each fused C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl ring is optionally substituted with one or more R_{14};

R_{10} is selected from a group of the formula L_1-L_2-R_{11} or L_2-L_1-$R_{11,}$ where L_1 is a linker of the formula $–[CR_{12}R_{13}]_n$-, where n is an integer of from 0 to 3 and R_{12} and R_{13} are in each instance each independently selected from H or C_1 to C_2 alkyl,

where L_2 is absent or a linker that is selected from O, S, SO, SO_2, N(R'), C(O), C(O)O, $[O(CH_2)_r]_s$, $[(CH_2)_rO]_s$, OC(O), CH(OR'), C(O)N(R'), N(R')C(O), N(R')C(O)N(R'), SO_2N(R') or N(R')SO_2, where R' and R" are each independently selected from hydrogen and a C_1 to C_2 alkyl, and where r is 1 or 2 and s is 1 to 4,

R_{11} is independently selected from hydrogen, CN, NO_2, hydroxyl, =O, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, O-C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl, 3-10 membered heterocycloalkyl, $–C(=O)R^d$, $–C(=O)OR^d$, $–C(=O)NR^eR^d$, $–C(O)C(=O)R^d$, $–NR^eR^d$, $–NR^eC(=O)R^d$, $–NR^eC(=O)OR^d$, $–NR^eC(=O)NR^eR^d$, $–NR^eS(=O)_2R^d$, $–NR^eS(=O)_2NR^eR^d$, $–OR^d$, $–SR^d$, $–OC(=O)R^d$, $–OC(=O)NR^eR^d$, $–OC(=O)OR^d$, $–S(=O)_2R^d$, $–S(=O)R^d$, $–OS(=O)R^d$, $–OS(=O)_2R^d$, $–OS(=O)_2OR^d$, $–S(=O)NR^eR^d$, $–OS(=O)_2NR^eR^d$, and $–S(=O)_2NR^eR^d$, wherein, where R_{11} is independently selected from C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl and 3-10 membered heterocycloalkyl, each C_{3-6} cycloalkyl, C_{6-12} aryl, C_{5-12} heteroaryl and 3-10 membered heterocycloalkyl is optionally substituted with one or more R_{14};

each R^a and R^b is independently selected from hydrogen and C_{1-6} alkyl;

each R^d is independently selected from hydrogen, hydroxyl, halogen, CN, C_{1-6} haloalkyl, 3-7 membered heterocycloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl, O-C_{1-6} alkyl and C_{6-11} aryl, wherein said C_{1-6} alkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl and C_{3-6} cycloalkyl are optionally substituted with one or more groups selected from hydroxyl, =O, halogen, CN, COR^a, NR^aR^b, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl;

each R^e is independently selected from hydrogen, hydroxyl, halogen, CN, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl; or

R^e and R^d, when attached to the same atom, together with the atom to which they are attached form a 3-7 membered heterocycloalkyl ring, optionally substituted with one or more substituent selected from hydroxyl, =O, halogen, CN, COR^a, NR^aR^b, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{6-11} aryl, 3-7 membered heterocycloalkyl, C_{1-6} alkyl and O-C_{1-6} alkyl;

and

R^{14} is independently selected from halo, CN, NO_2, hydroxyl, =O, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkyl, O-C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-12} aryl, 5-6 membered heteroaryl, 3-7 membered heterocycloalkyl, C_{1-6}alkylC_{6-12}aryl, $–C(=O)R^d$, $–C(=O)OR^d$, $–C(=O)NR^eR^d$, $–C(O)C(=O)R^d$, $–NR^eR^d$, $–NR^eC(=O)R^d$, $–NR^eC(=O)OR^d$, $–NR^eC(=O)NR^eR^d$, $–NR^eS(=O)_2R^d$, $–NR^eS(=O)_2NR^eR^d$, $–OR^d$, $–SR^d$, $–OC(=O)R^d$, $–OC(=O)NR^eR^d$, $–OC(=O)OR^d$,

$-S(=O)_2R^d$, $-S(=O)R^d$, $-OS(=O)R^d$, $-OS(=O)_2R^d$, $-OS(=O)_2OR^d$, $-S(=O)NR^eR^d$, $-OS(=O)_2NR^eR^d$, and $-S(=O)_2NR^eR^d$.

2. A compound according to claim 1, or a salt, solvate or hydrate thereof, wherein:

(a) X is NH or O;

(b) R_1, R_3, R_4, R_5 and R_6 are each hydrogen;

(c) Y_1 is a group of the formula A; and/or

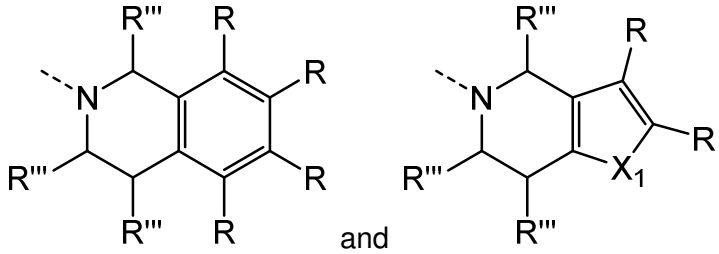
(d) Q is C.

3. A compound according to claim 1 or claim 2, or a salt, solvate or hydrate thereof, wherein T is either:

(a) a fused phenyl which is optionally substituted with one or more substituents selected from halo and C_1 to C_3 alkyl; or

(b) a fused 5- or 6-membered heteroaryl group optionally substituted with one or more substituents selected from halo and C_1 to C_3 alkyl.

4. A compound according to claim 1 or claim 2, or a salt, solvate or hydrate thereof, wherein Y_1 is selected from



wherein each R and R''' is selected from H and C_1 to C_3 alkyl, and X_1 is S.

5. A compound according to any preceding claim, or a salt, solvate or hydrate thereof, wherein the 3-12 membered heterocycloalkyl ring formed by R_7 and R_8 taken together with the intervening nitrogen atom is a 4-7 membered heterocycloalkyl ring, and optionally wherein the intervening nitrogen atom is the sole heteroatom in the 4-7 membered heterocycloalkyl ring.

6. A compound according to claim 5, or a salt, solvate or hydrate thereof, wherein either:

(a) the 4-7 membered heterocycloalkyl ring is selected from a pyrrolidinyl, piperidinyl and azepanyl ring; or

(b) the 4-7 membered heterocycloalkyl ring comprises a second heteroatom, and optionally wherein the second heteroatom is selected from O, S and N, and further optionally wherein the 5-7 membered heterocycloalkyl ring is selected from a piperizinyl, morpholinyl and diazepanyl ring.

7. A compound according to any preceding claim, or a salt, solvate or hydrate thereof, wherein the 3-12 membered heterocycloalkyl ring formed by R_7 and R_8 taken together with the intervening nitrogen atom is a 4-7 membered heterocycloalkyl ring, which is either:

(a) unsubstituted; or

(b) substituted with one or more R_{10}, and optionally wherein (i) R_{11} is independently selected from hydroxyl, C_{1-6} alkyl, C_{6-12} aryl, C_{5-12} heteroaryl and $–C(=O)R^d$, wherein, where R_{11} is selected from C_{6-12} aryl and/or C_{5-12} heteroaryl, the C_{6-12} aryl and/or C_{5-12} heteroaryl is optionally substituted with R_{14}, and further optionally wherein (ii) R_{11} is independently selected from C_{6-12} aryl and/or C_{5-12} heteroaryl that is optionally substituted with R_{14}, and optionally wherein R_{11} is independently selected from phenyl that is optionally substituted with R_{14}.

8. A compound according to any preceding claim, or a salt, solvate or hydrate thereof, wherein L_1 is a linker of the formula $–[CR_{12}R_{13}]_n-$, where n is an integer of from 0 to 3, and R_{12} and R_{13} are in each instance each independently selected from H or C_1 to C_2 alkyl, and where L_2 is absent or a linker that is selected from O.

9. A compound according to any preceding claim, or a salt, solvate or hydrate thereof, wherein the 3-12 membered heterocycloalkyl ring formed by R_7 and R_8 taken together with the intervening nitrogen atom is fused to one or more C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl rings, wherein each fused C_{6-12} aryl, C_{5-12} heteroaryl, C_{3-8} cycloalkyl and 3-12 membered heterocycloalkyl ring is optionally substituted with R_{14}.

10. A compound according to claim 9, or a salt, solvate or hydrate thereof, wherein R_{14} is absent or selected from C_{1-3} alkyl, halo or hydroxyl.

11. A compound according to claim 9 or 10, or a salt, solvate or hydrate thereof, wherein the 3-12 membered heterocycloalkyl ring is fused to one or more C_{6-12} aryl groups and/or C_{5-12} heteroaryl groups, said C_{6-12} aryl groups and/or C_{5-12} heteroaryl groups being optionally substituted with R_{14}, and optionally wherein the 3-12 membered heterocycloalkyl ring is fused to a phenyl group that is optionally substituted with R_{14}.

12. A compound according to any one of claims 9 to 11, or a salt, solvate or hydrate thereof, wherein the 3-12 membered heterocycloalkyl ring is selected from a pyrrolidinyl, piperidinyl and azepanyl ring.

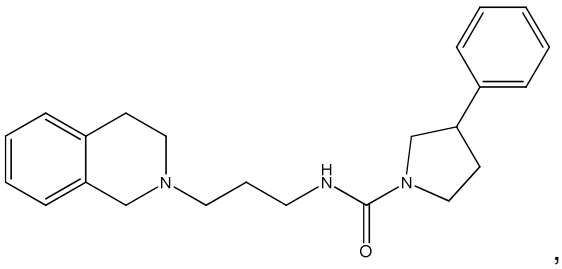
13. A compound according to any preceding claim, or a salt, solvate or hydrate thereof, wherein R_7 and R_8 are taken together with the intervening nitrogen atom to form a 4-7 membered heterocycloalkyl ring, wherein the 4 to 7 membered heterocycloalkyl ring is

(i) unsubstituted, or either

(ii) substituted with at least one R_{10}, where R_{10} is L_1-L_2-R_{11} or L_2-L_1-R_{11}, where L_1 is a linker of the formula $–[CR_{12}R_{13}]_n$-, where n is an integer of from 0 to 3 and R_{12} and R_{13} are in each instance each independently selected from H or C_1 to C_2 alkyl, and where L_2 is absent or a linker that is selected from O, C(O) or N(R'), where R' is H or C_1 to C_2 alkyl, and R_{11} is $-S(=O)_2R_d$, C_{6-12} aryl (e.g. phenyl), 3 – 10 membered heterocycloalkyl or C_{5-12} heteroaryl, wherein the C_{6-12} aryl, 3 – 10 membered heterocycloalkyl and/or C_{5-12} heteroaryl is optionally substituted with one or more R_{14}; and/or

(iii) fused to at least one C_{6-12} aryl (e.g. phenyl), or C_{5-12} heteroaryl; wherein the C_{6-12} aryl and/or C_{5-12} heteroaryl is optionally substituted with one or more R_{14}.

14. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein the compound is not any of the following compounds: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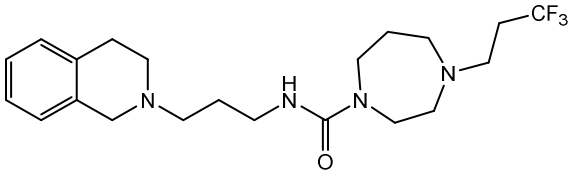
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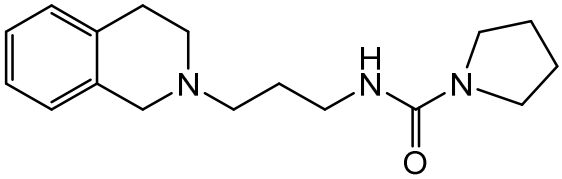
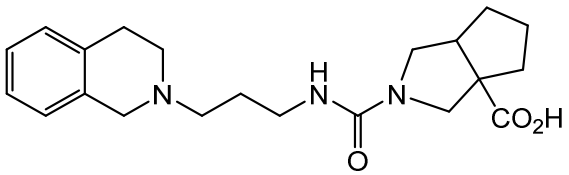

or

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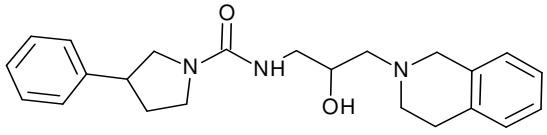
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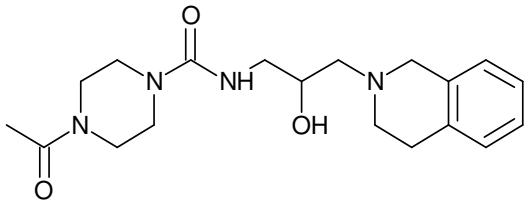
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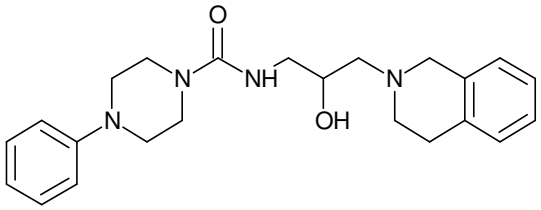
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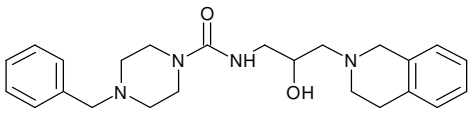
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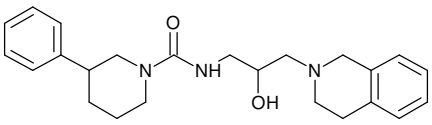
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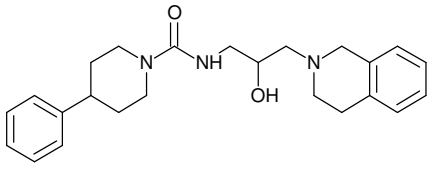
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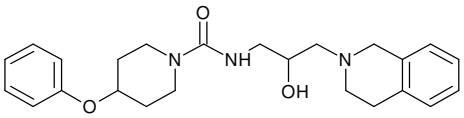
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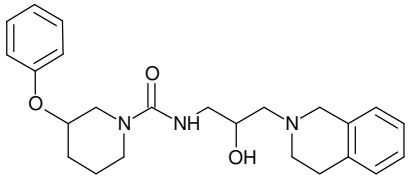
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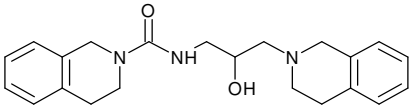
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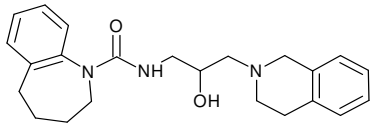
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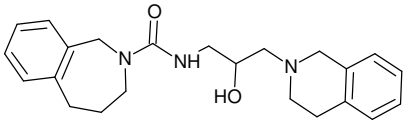
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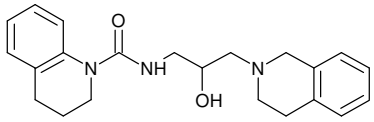
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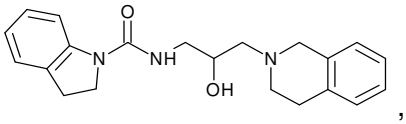
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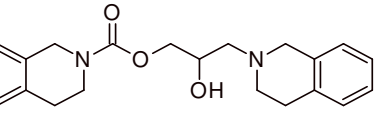
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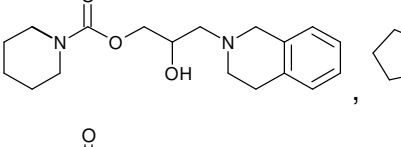
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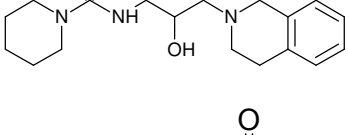
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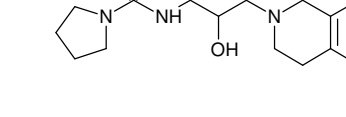
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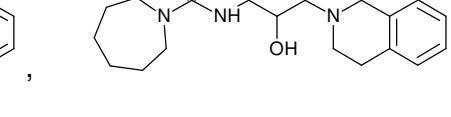
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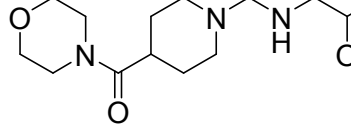
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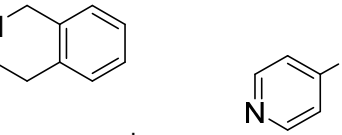
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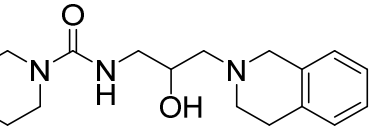
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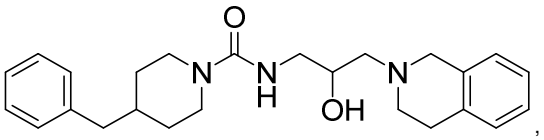
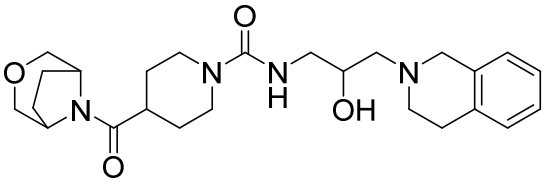
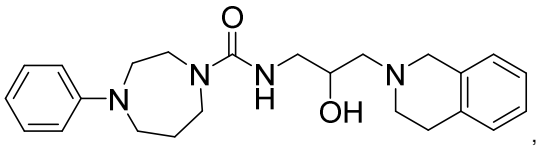
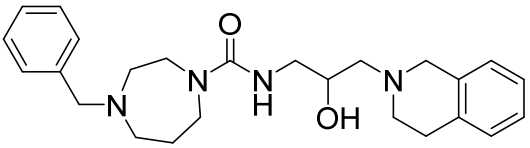
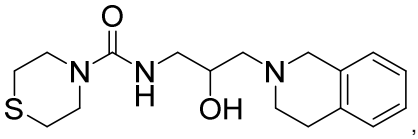
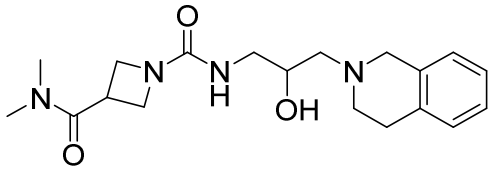
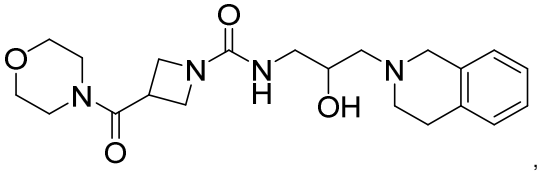
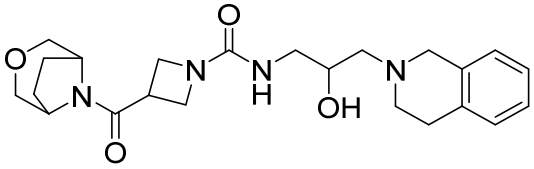
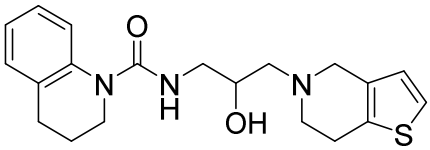
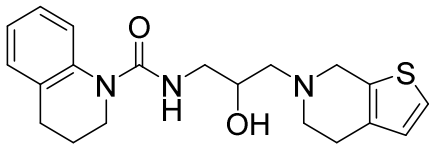
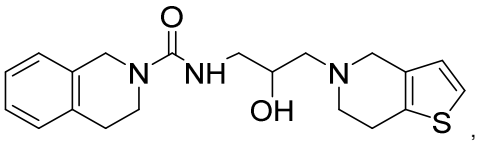
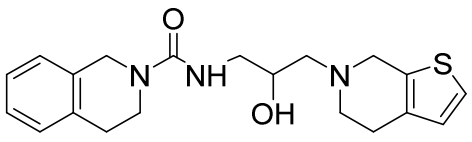
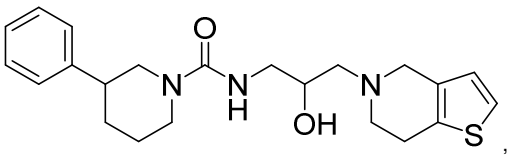
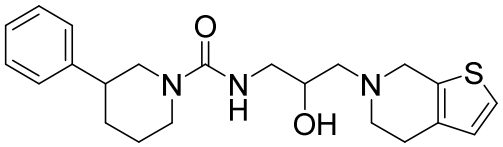
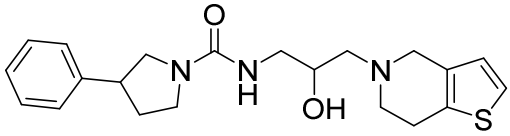
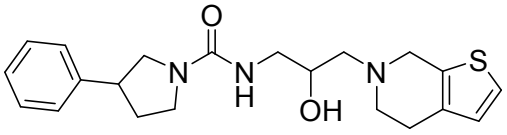
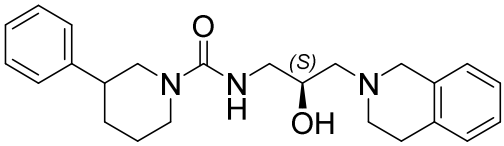
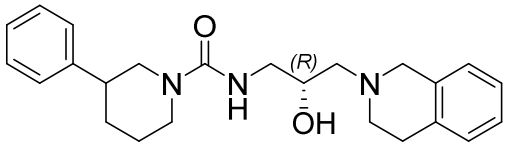
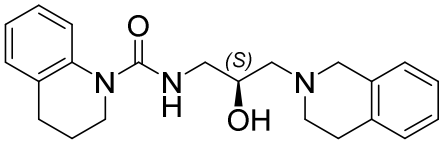
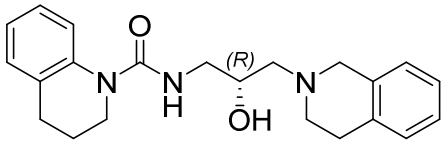
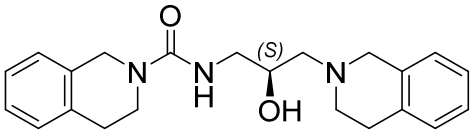
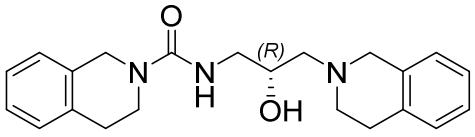
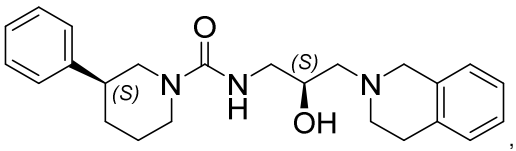
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,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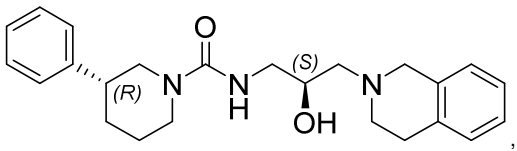
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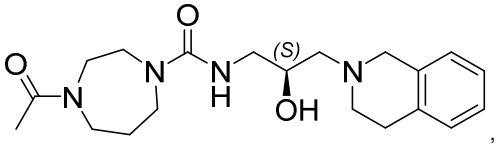
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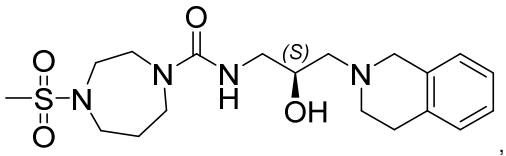
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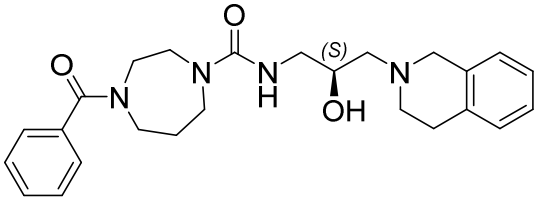
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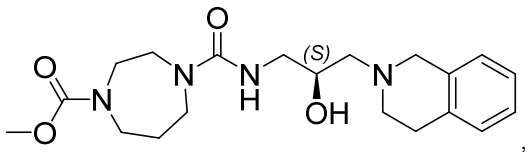
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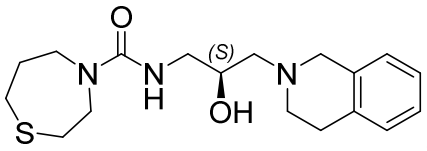
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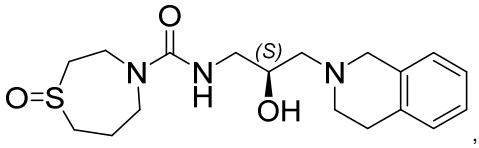
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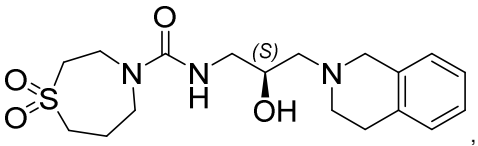
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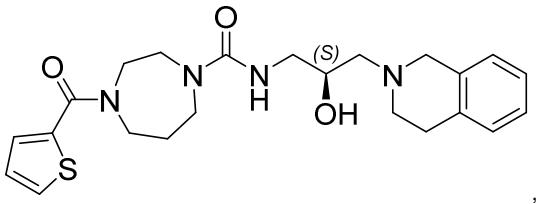
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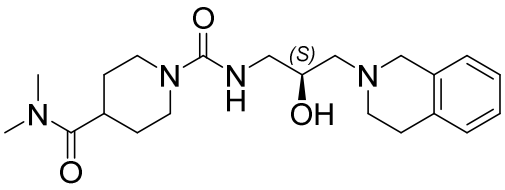
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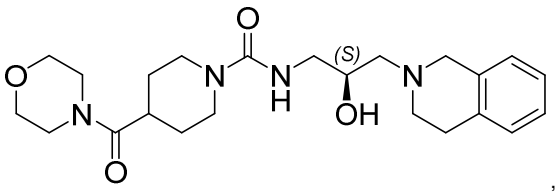
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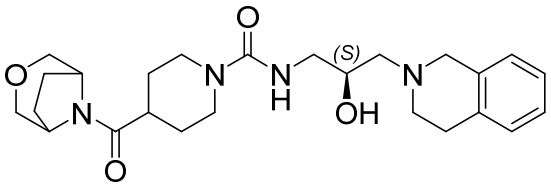
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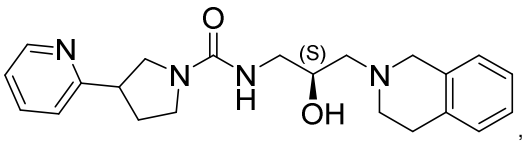
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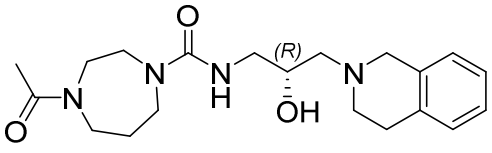
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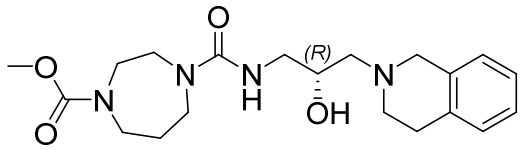
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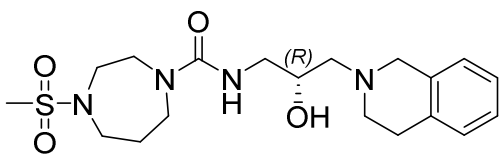
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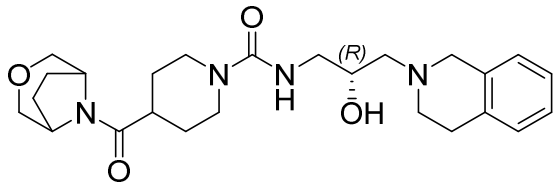
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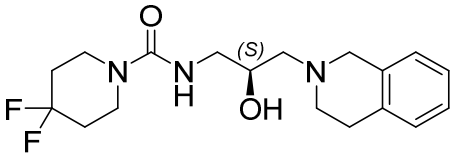
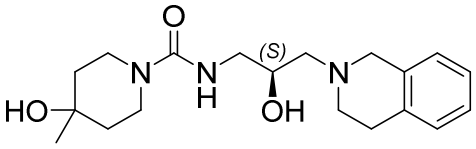
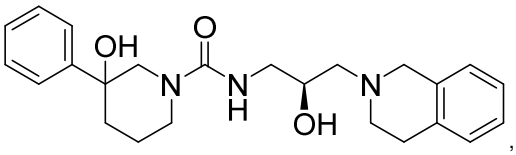
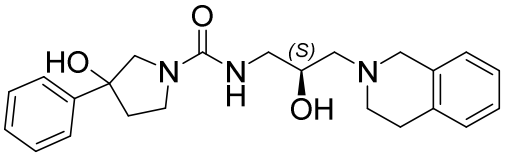
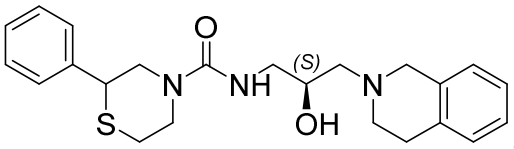
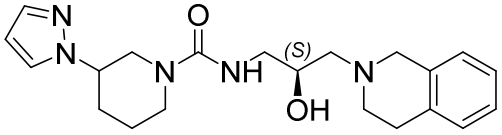


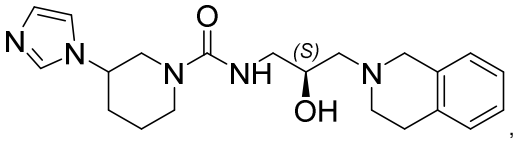


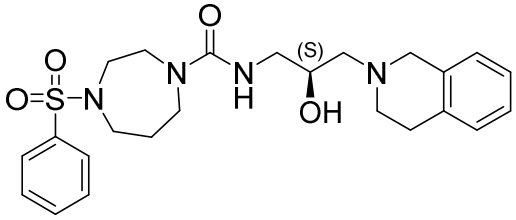


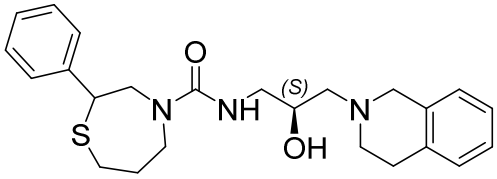


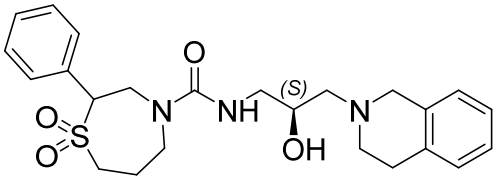


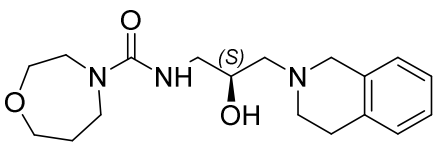


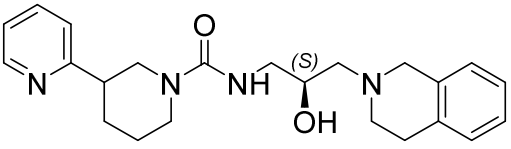


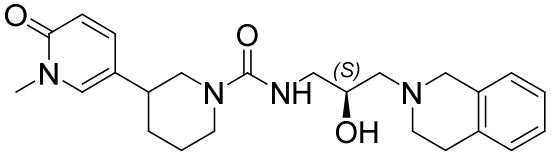


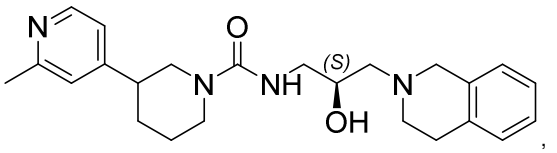


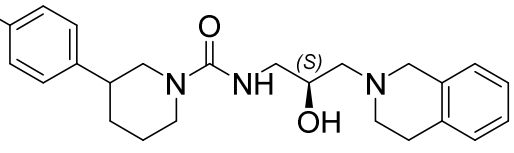


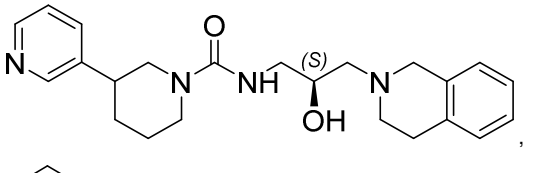


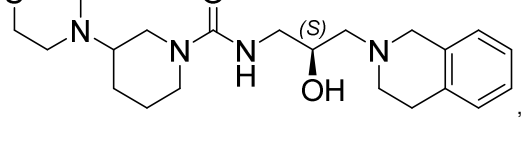


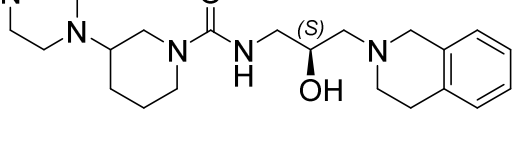


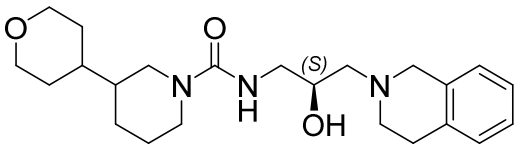


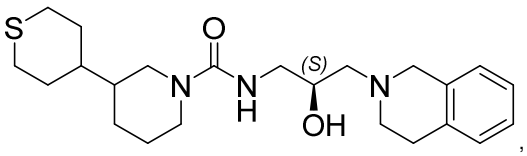


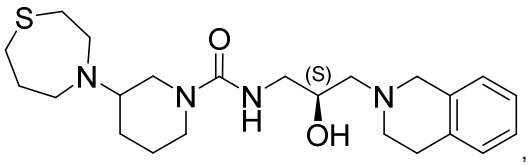


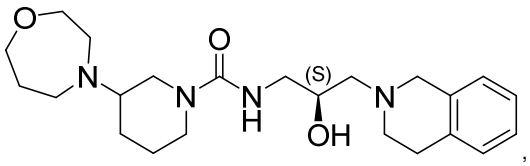


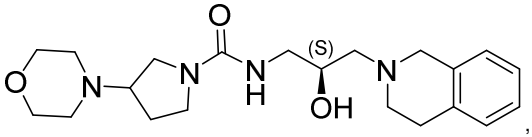


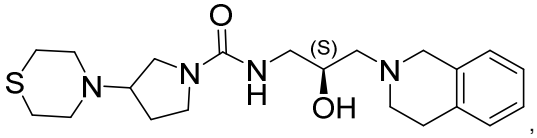
 ,

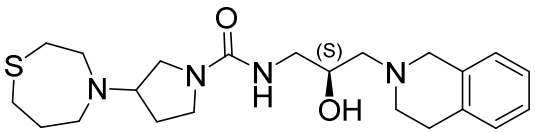
 ,

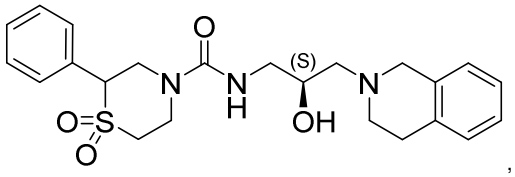
 ,

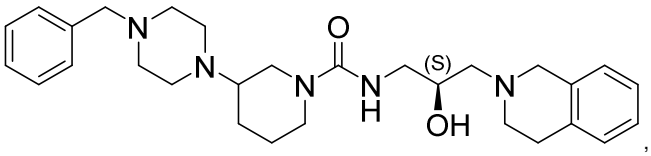
 ,

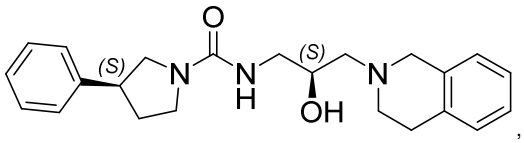
 ,

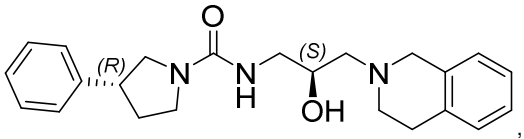
 ,

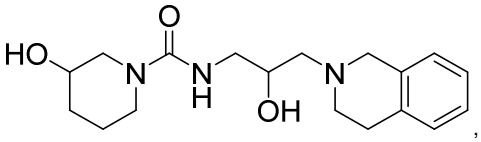
 ,

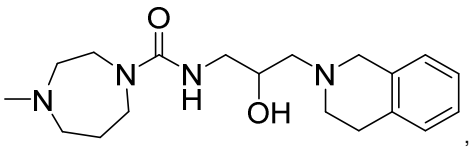
 ,

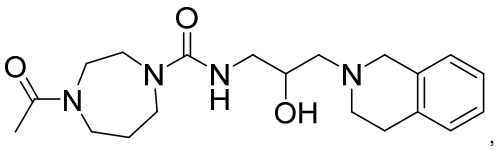
 ,

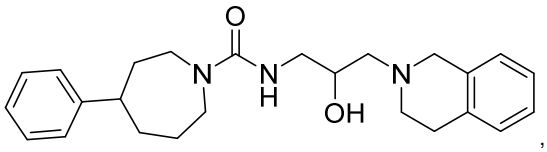
 ,

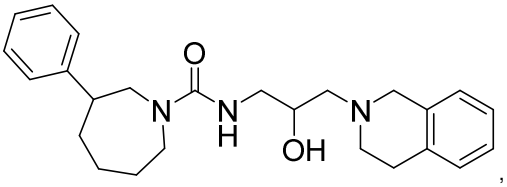
 ,

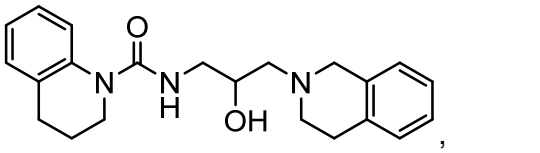
 ,

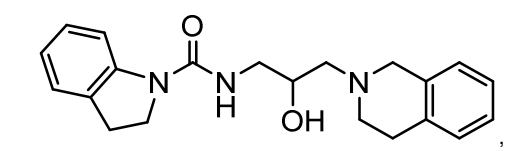
 ,

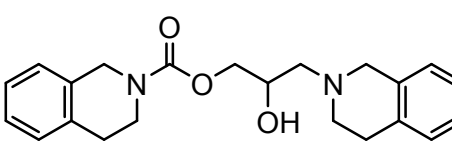
 ,

 ,

 ,

 ,

 ,

 ,

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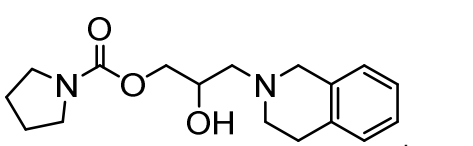
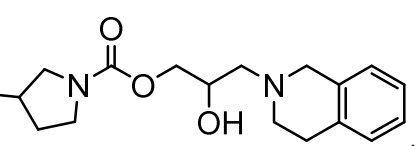
 ,

 ,

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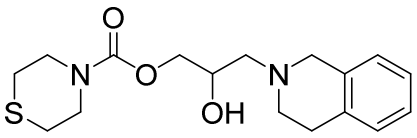
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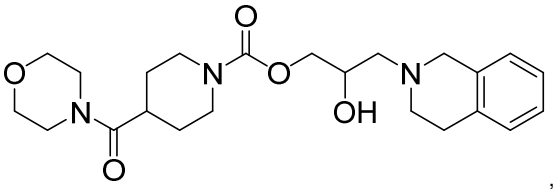
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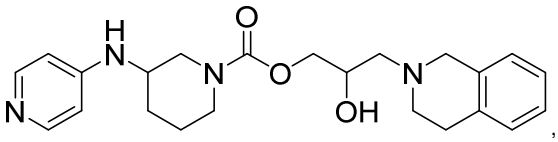
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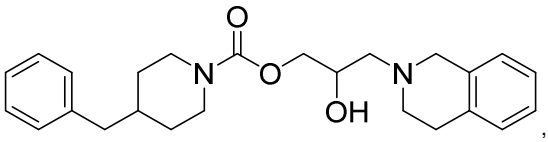
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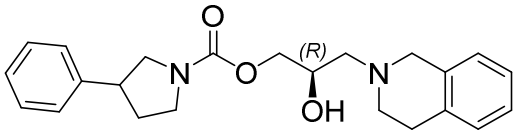
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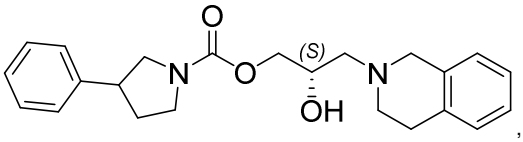
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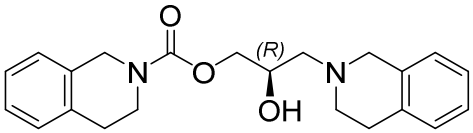
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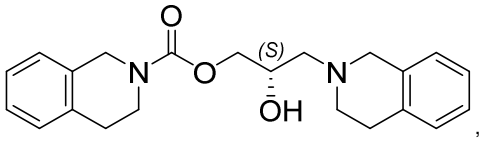
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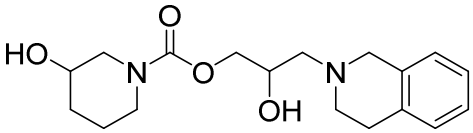
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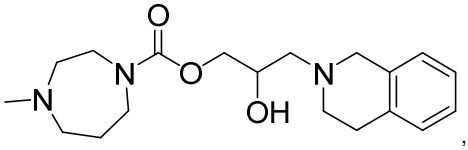
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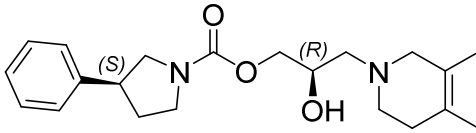
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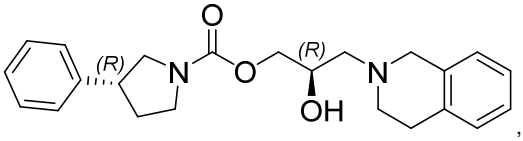
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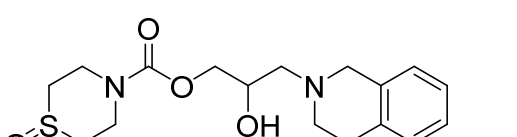
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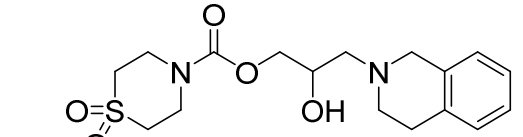
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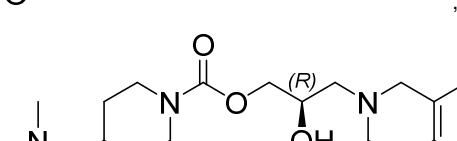
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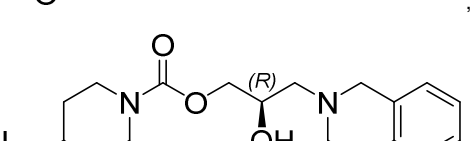
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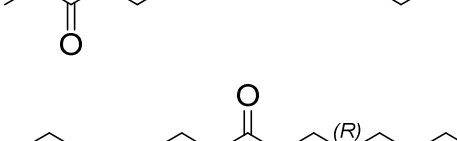
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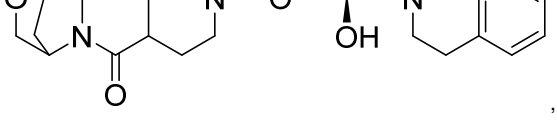
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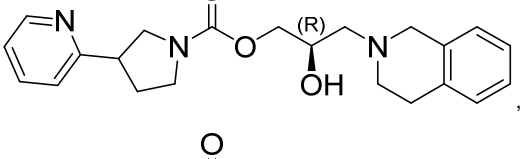
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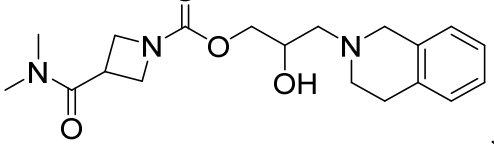
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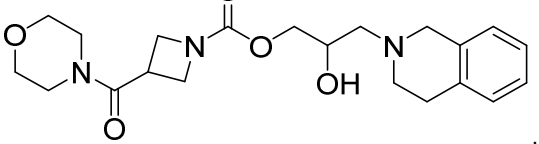
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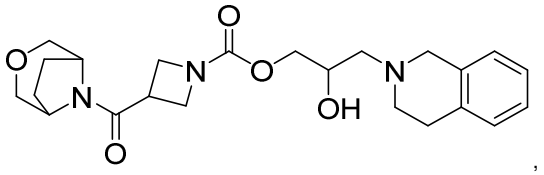
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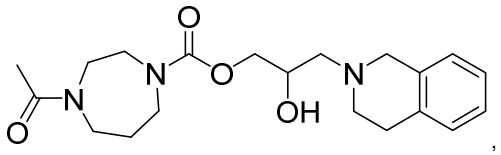
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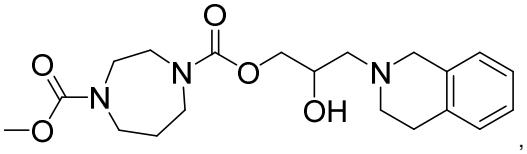
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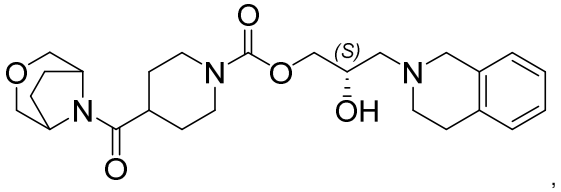
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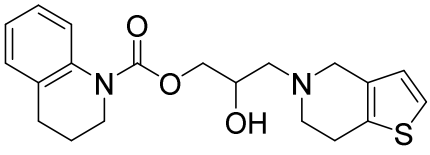
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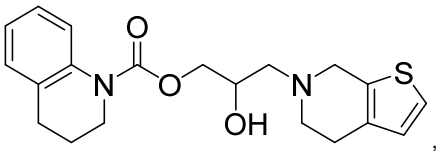
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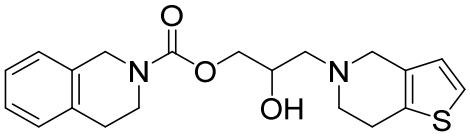
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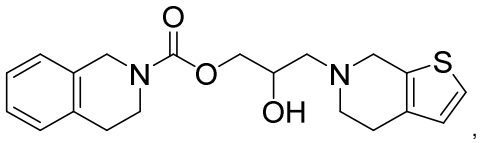
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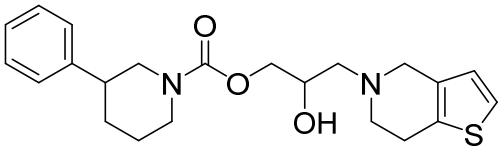
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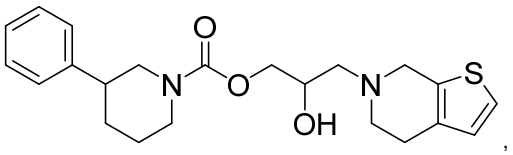
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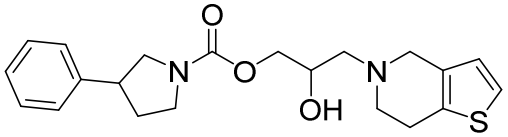
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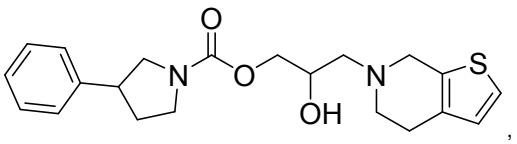
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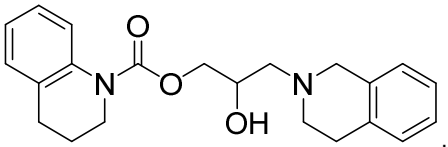
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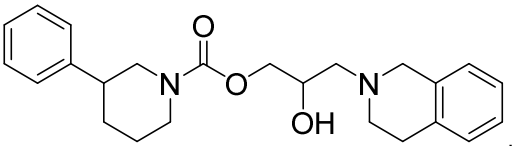
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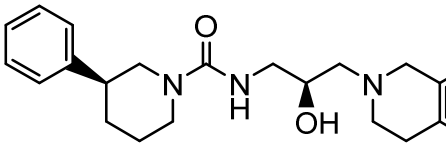
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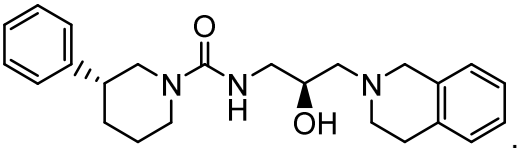
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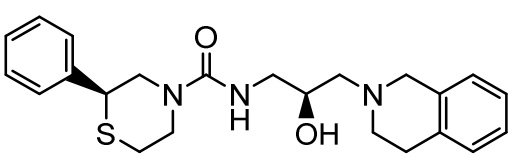
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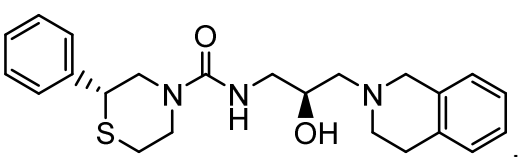
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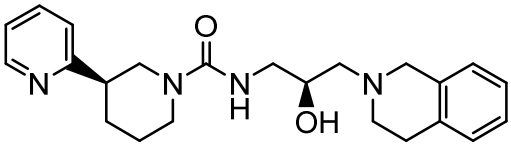
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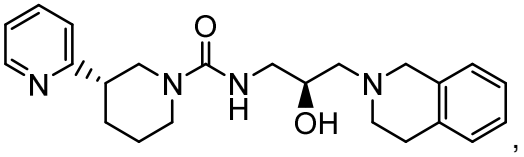
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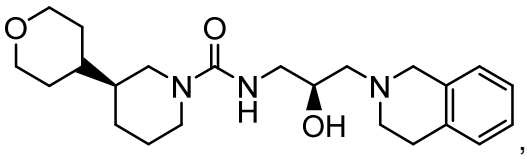
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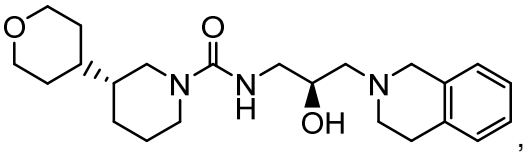
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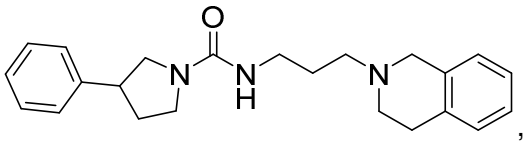
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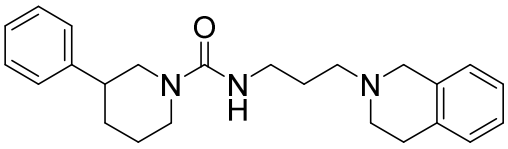
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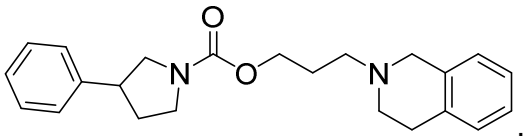
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16. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, and one or more pharmaceutically acceptable excipients.

17. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 16, for use in therapy.

18. Use of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 16 in the manufacture of a medicament for:

(a) treating or preventing a PRMT5-mediated disorder;
(b) treating a proliferative disorder;
(c) treating a cancer;
(d) inhibiting the activity of PRMT5; or
(e) altering gene expression in a cell.

19. An *in vitro* method of inhibiting the activity of PRMT5 , said method comprising that a therapeutically effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 16 is to be administered to a subject in need thereof.

20. An *in vitro* method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt, hydrate or solvate thereof, or a pharmaceutical composition according to claim 16.