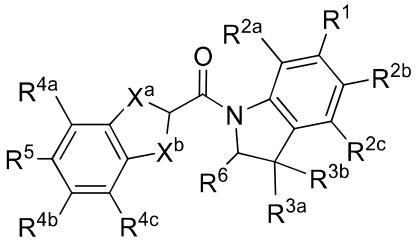
[0006] There is a need for new agents that are more effective and safer with improved pharmacokinetics. Inhibition of viral helicase-primase interferes with viral replication and thus could lead to the development of drugs with desirable selectivity, potency, metabolic stability, or reduced detrimental effects.

SUMMARY

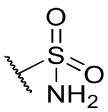
[0007] The present disclosure relates to indolinyl compounds. The present disclosure also relates to compounds that inhibit viral helicase-primase. The present disclosure further relates to use of the compounds for the treatment and/or prevention of diseases and/or conditions.

[0008] In an aspect, provided herein is a compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is  or  ;

R^{2a}, R^{2b}, and R^{2c} are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, C_{1-6} haloalkoxy, or $-SCF_3$;

R^{3a} and R^{3b} are each independently H, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

or R^{3a} and R^{3b} together with the carbon to which they are attached form C_{3-6} cycloalkyl; wherein the cycloalkyl formed from R^{3a} and R^{3b} may be optionally substituted with one to three Z^3, which may be the same or different;

X^a and X^b are each independently O or $CR^{7a}R^{7b}$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

or R^{7a} and R^{7b} together with the carbon to which they are attached form C_{3-6} cycloalkyl; wherein the C_{3-6} cycloalkyl formed from R^{7a} and R^{7b} may be optionally substituted with one to three Z^7, which may be the same or different;

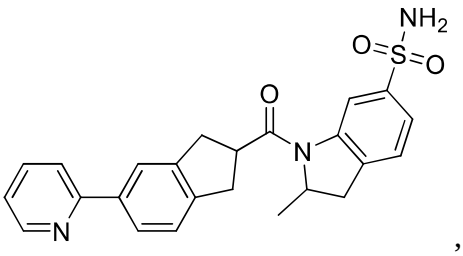
R^{4a}, R^{4b}, and R^{4c} are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, $-SCF_3$, or C_{3-6} cycloalkyl optionally substituted with Z^4;

R^5 is C_{6-10} aryl or heteroaryl; wherein the aryl or heteroaryl of R^5 may be optionally substituted with one to three Z^5, which may be the same or different; the heteroaryl of R^5 is 5 to 10 membered heteroaryl having one to three heteroatoms each independently N, O, or S;

R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, or C_{3-6} cycloalkyl, wherein the cycloalkyl of R^6 is optionally substituted with one to three Z^6; and

each Z^3, Z^4, Z^5, Z^6, and Z^7 is independently halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy.

[0008a] In another aspect, there is provided a compound selected from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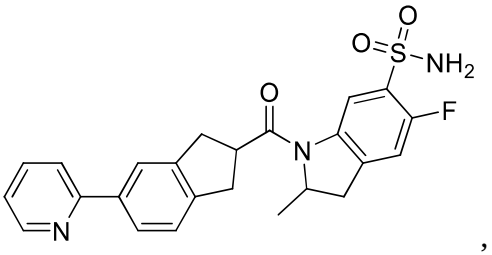
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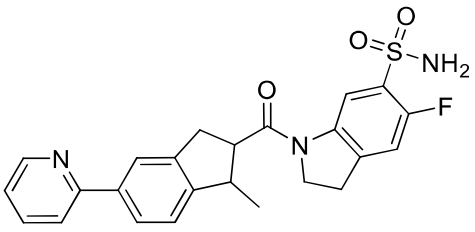
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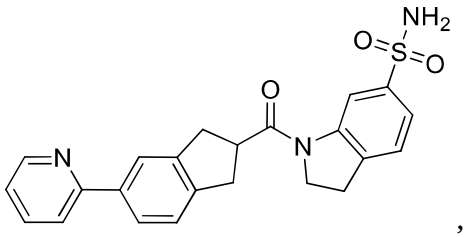
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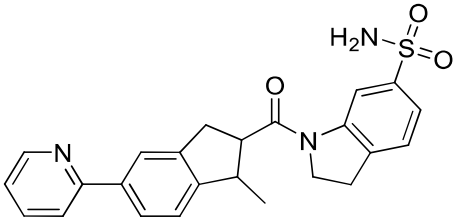
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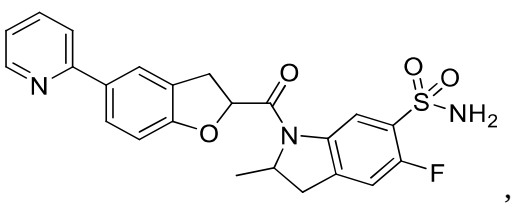
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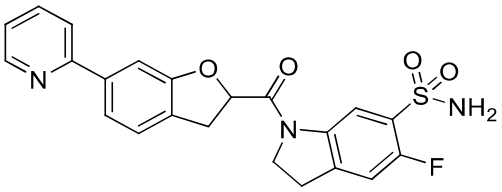
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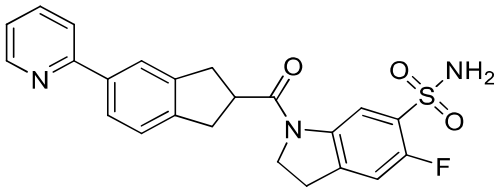
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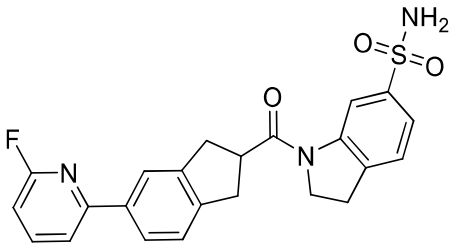
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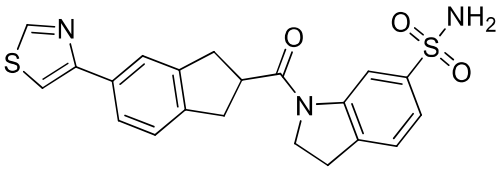
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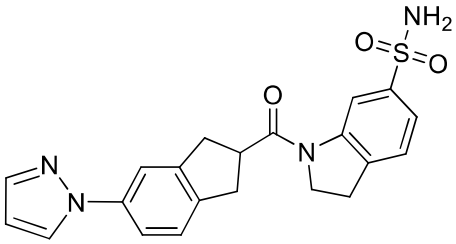
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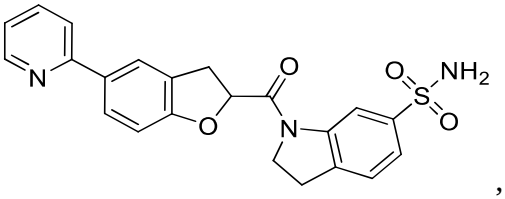
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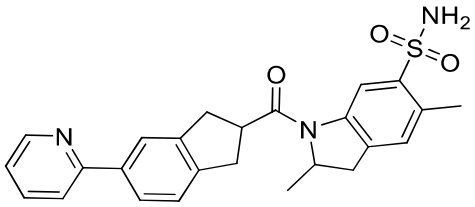
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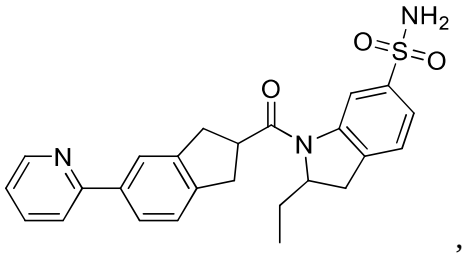
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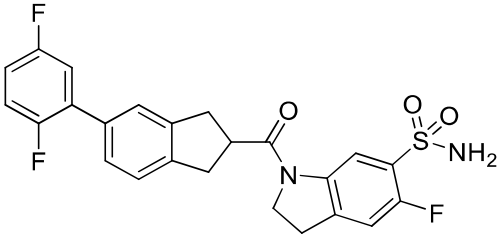
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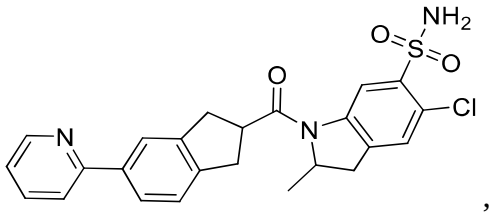
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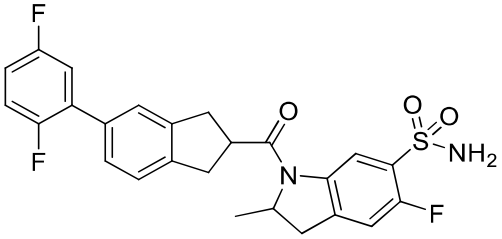
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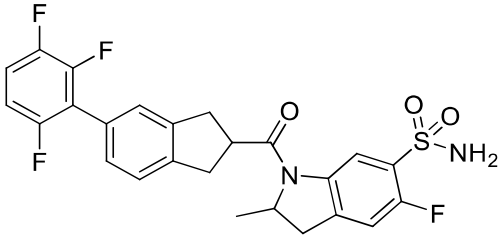
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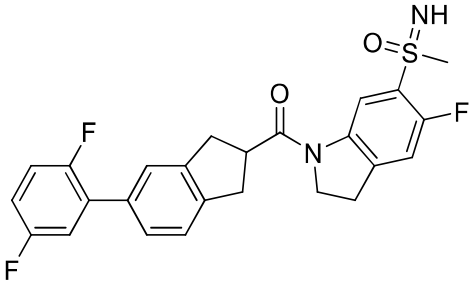
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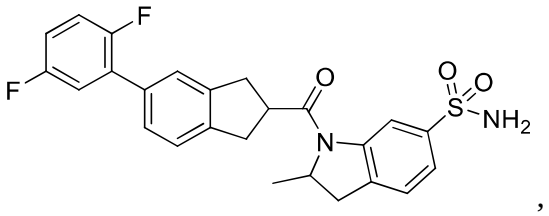
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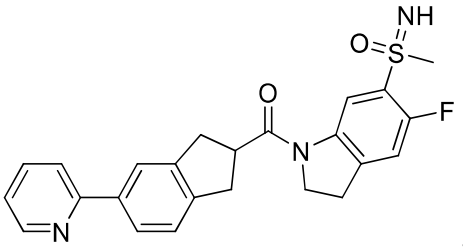
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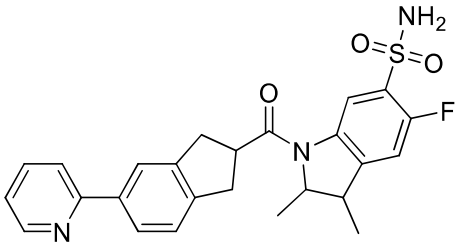
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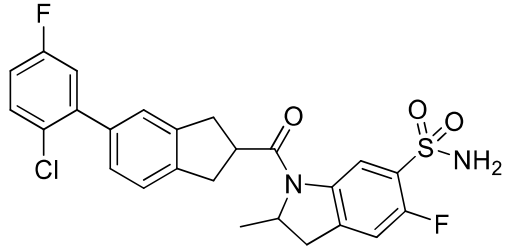
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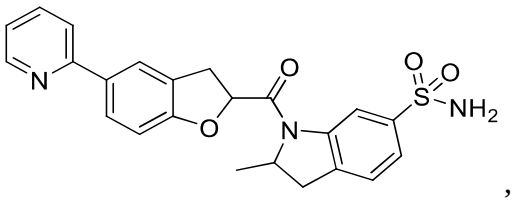
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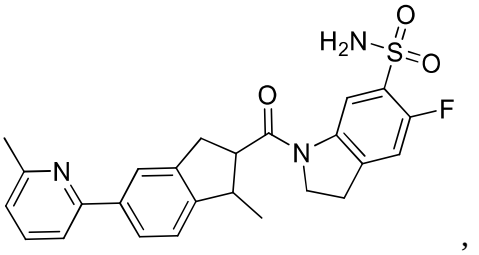
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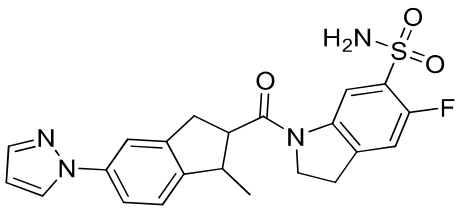
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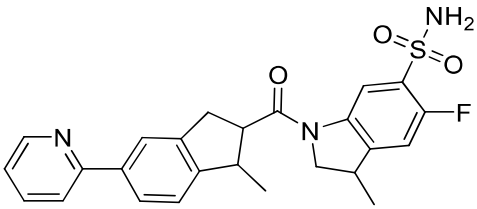
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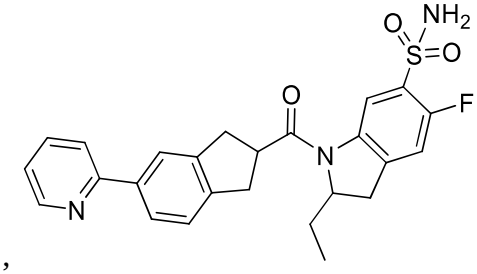
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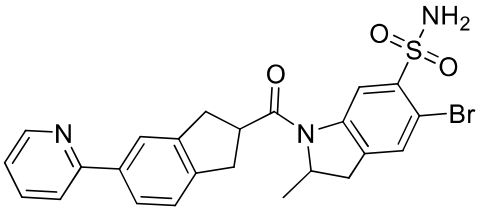
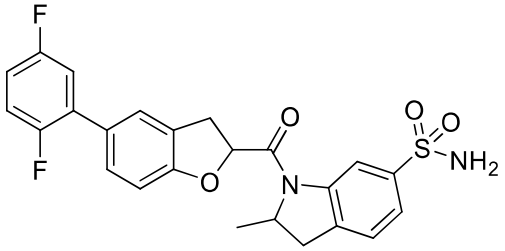

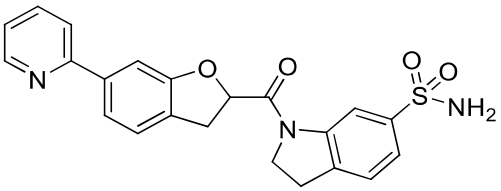
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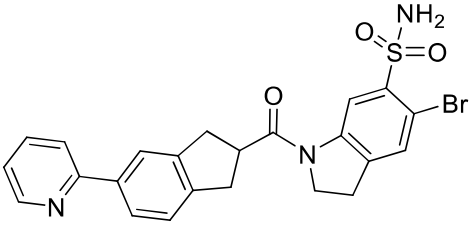
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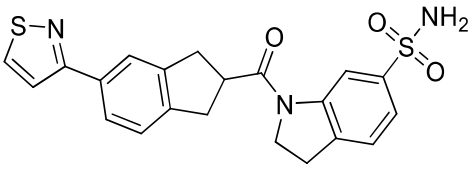
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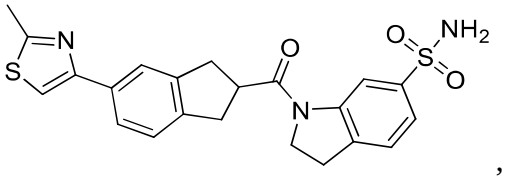
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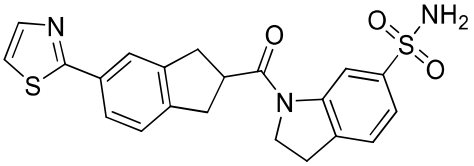
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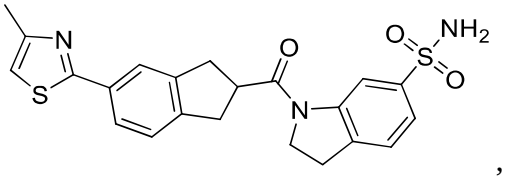
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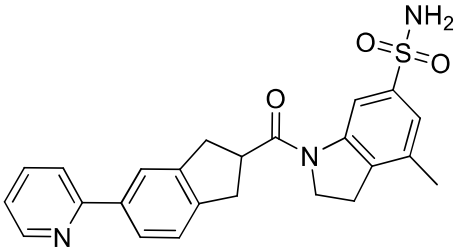
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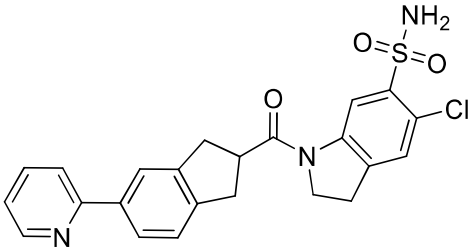
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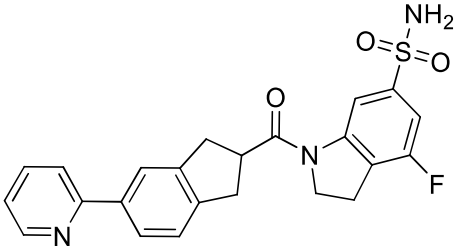
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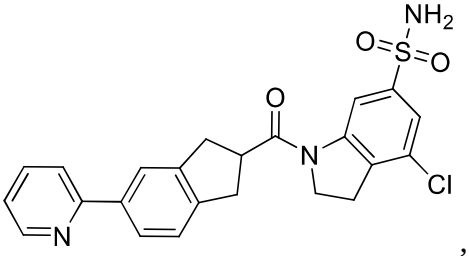
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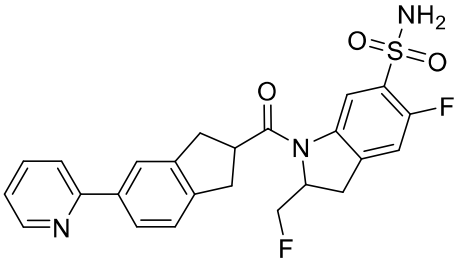
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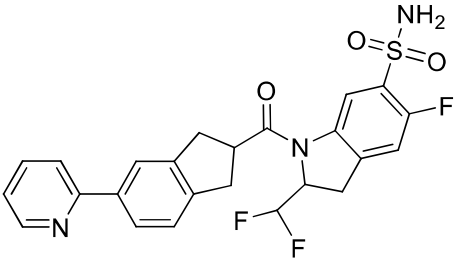
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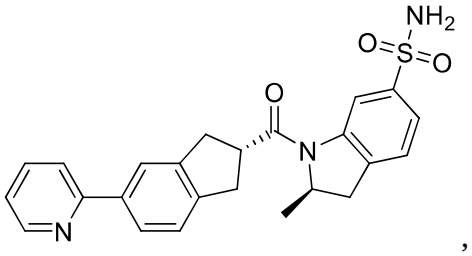
[0008b] In another aspect, there is provided a compound selected from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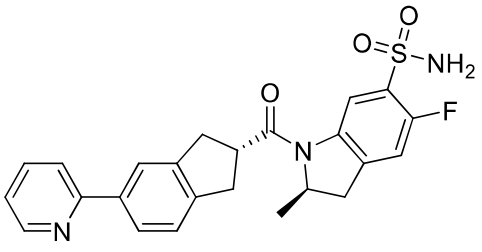
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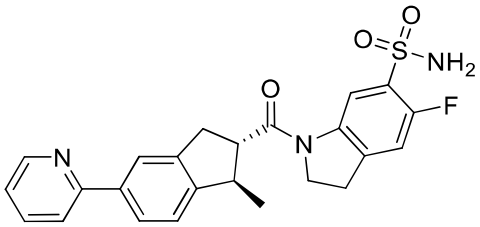
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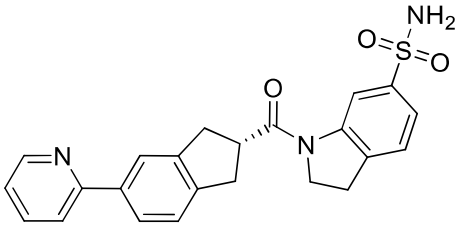
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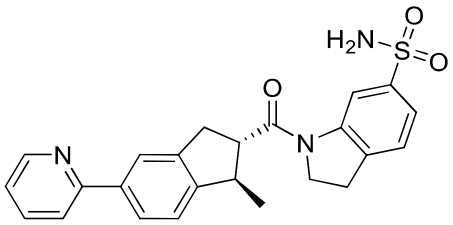
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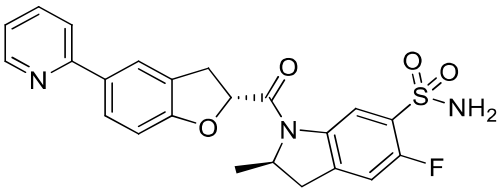
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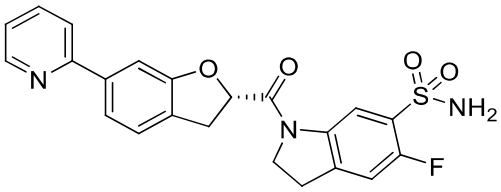
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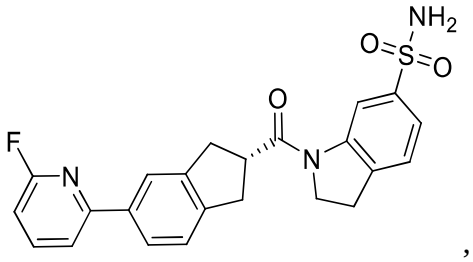
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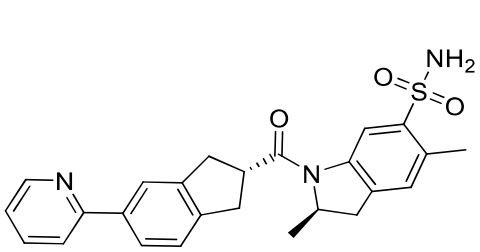
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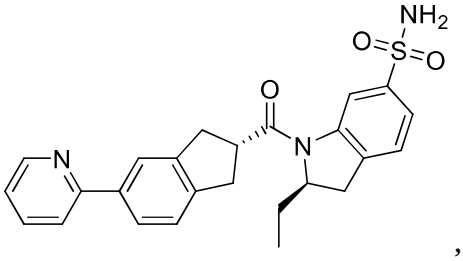
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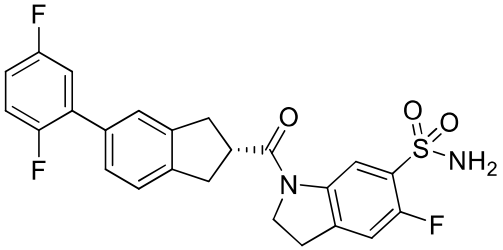
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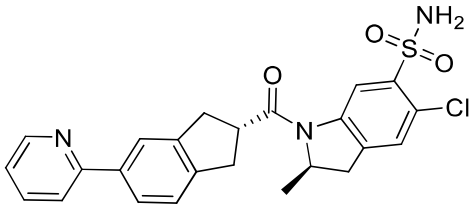
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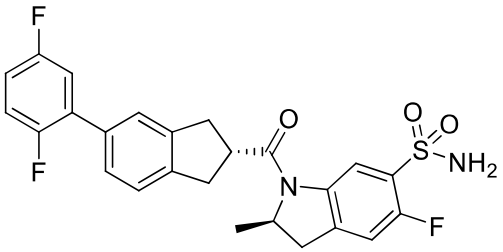
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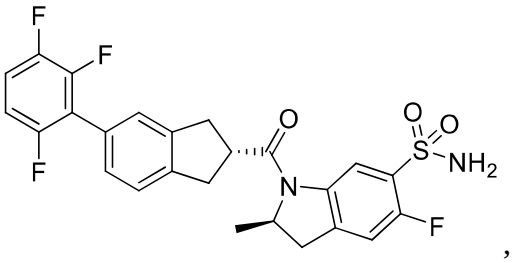
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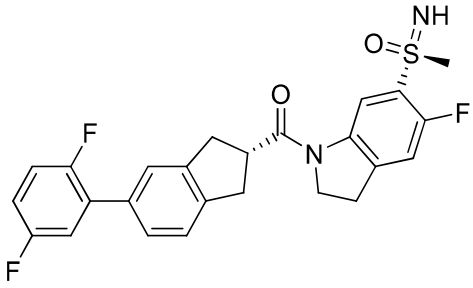
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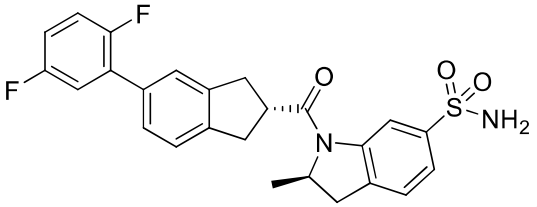
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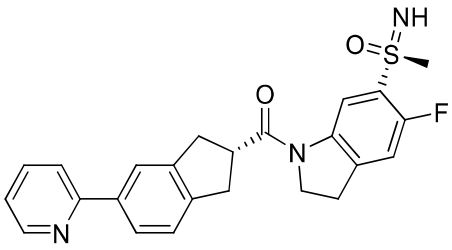
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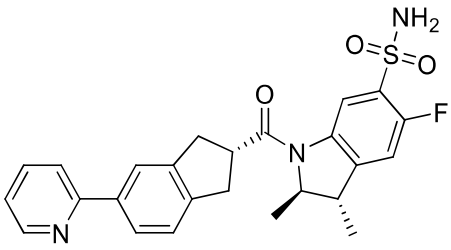
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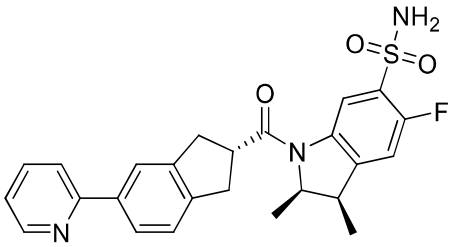
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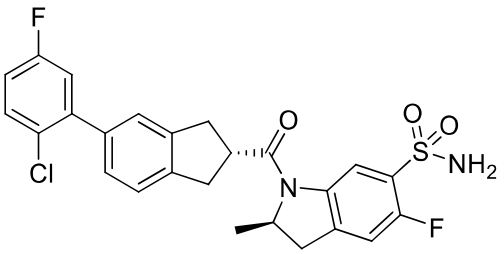
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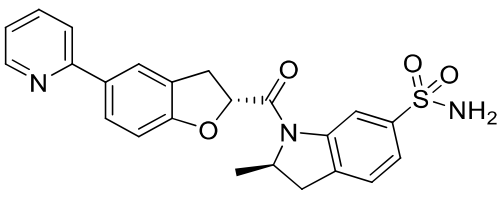
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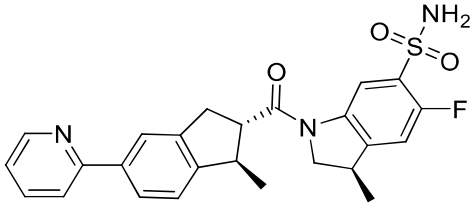
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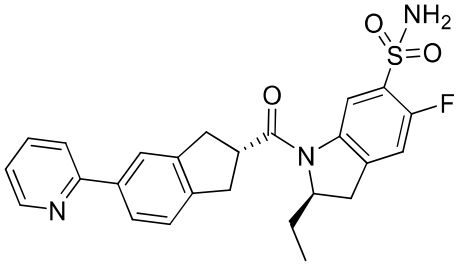
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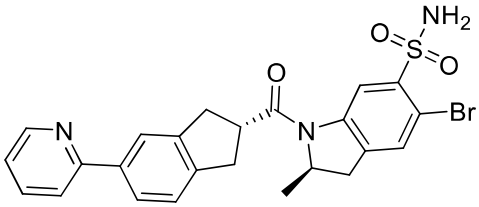
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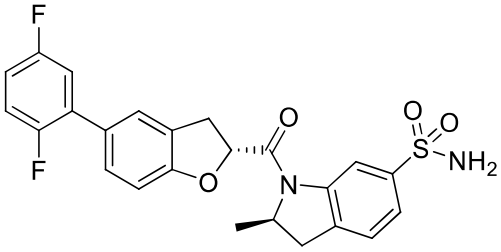
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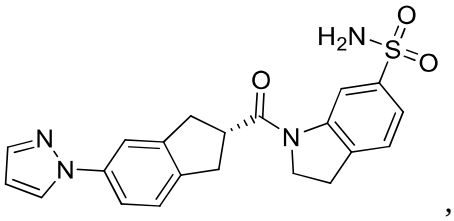
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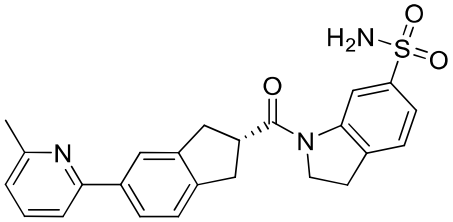
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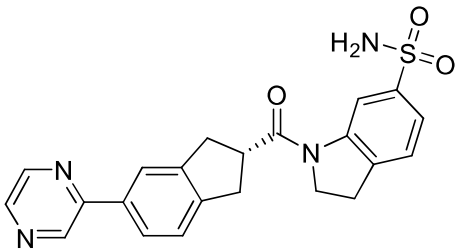
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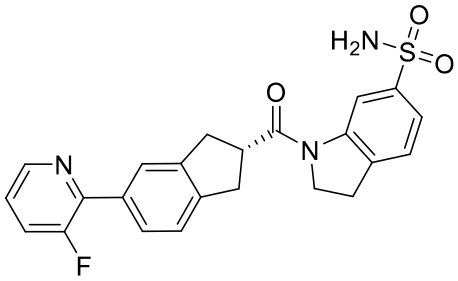
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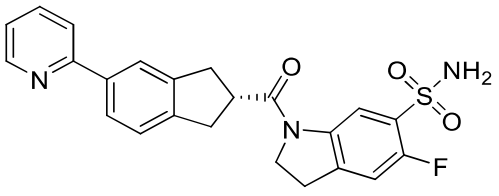
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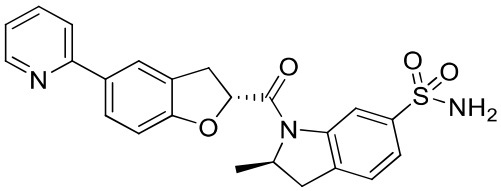
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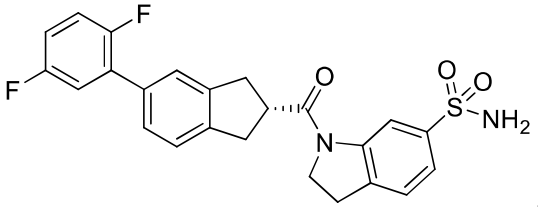
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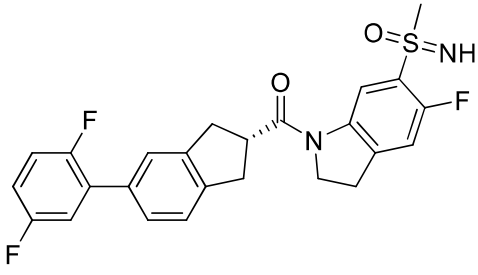
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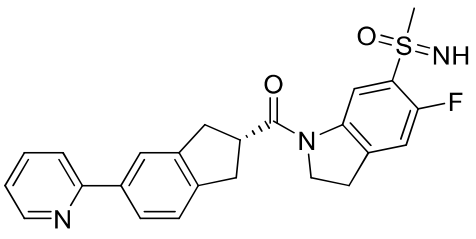
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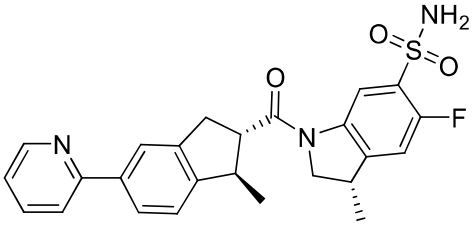
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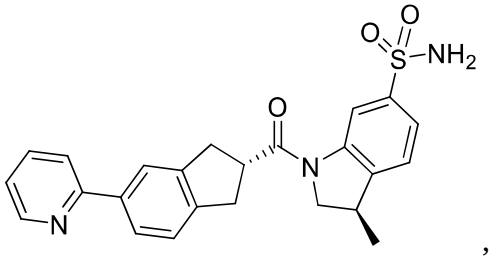
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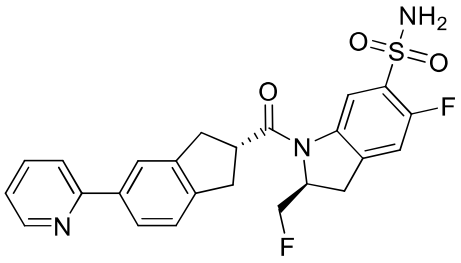
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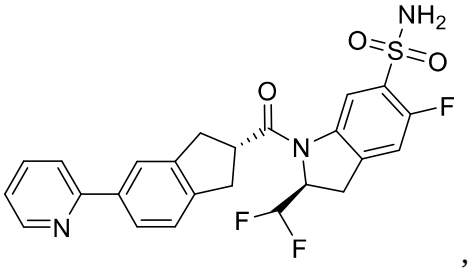
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or a pharmaceutically acceptable salt thereof.

[0008c] In another aspect, there is provided a compound selected from Examples 1-20, 22-29, 31, 33-41, 43-53, 56-65, 68-83, 85-119, 123, and 125-141.

[0009] In some other aspects, provided herein are pharmaceutical compositions comprising a compound provided herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier. In some examples, the pharmaceutical compositions comprise a therapeutically effective amount of a compound provided herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

[0010] In some examples, the pharmaceutical compositions provided herein further comprise one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or pharmaceutically acceptable salts thereof. In some examples, the pharmaceutical compositions further comprise a therapeutically effective amount of the one or more (*e.g.*, one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, or pharmaceutically acceptable salts thereof.

[0010a] In another aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof, or a composition as defined above, in the manufacture of a medicament for treating a herpesvirus infection.

[0010b] In another aspect, there is provided the use of a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof, or a composition as defined above, in the manufacture of a medicament for treating a disorder induced, exacerbated or accelerated by herpesvirus.

[0010c] In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection.

[0010d] In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection caused by herpesviruses.

[0010e] In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection caused by HSV-1 or HSV-2.

[0010f] In another aspect, there is provided the compound or pharmaceutically acceptable salt thereof as defined above or the pharmaceutical composition as defined above for use in treating a viral infection caused by HSV-1 or HSV-2.

[0010g] In another aspect, there is provided the compound or pharmaceutically acceptable salt thereof as defined above for use in therapy.

[0011] In some examples, the present disclosure provides methods of inhibiting the helicase-primase of herpesviruses in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (IIa), (IIb), (IIc), (IId), (IIe), or (IIf)), or pharmaceutically acceptable salt thereof, or a pharmaceutical composition provided herein.

[0012] In some examples, the present disclosure provides methods of treating a patient having a herpesvirus mediated condition, comprising administering to the patient a therapeutically effective amount of a compound provided herein (*e.g.*, a compound of Formula (I), (IIa), (IIb), (IIc), (IId), (IIe), or (IIf)), or pharmaceutically acceptable salt thereof, or a pharmaceutical composition provided herein.

DETAILED DESCRIPTION

[0013] The present disclosure relates to compounds that inhibit the helicase primase of herpesviruses. In one embodiment, the present disclosure relates to indolinyl compounds. The present disclosure further relates to use of the compounds for the treatment and/or prevention of diseases and/or conditions by said compounds. The disclosure also relates to compositions and methods of treating and/or preventing viral infections that include an inhibitor of herpesvirus helicase primase in combination with one or more additional therapeutic agents.

[0014] Patients infected with herpesviruses can benefit from the treatment with an inhibitor of herpesvirus helicase primase and optionally one or more additional therapeutic agents.

Definitions and General Parameters

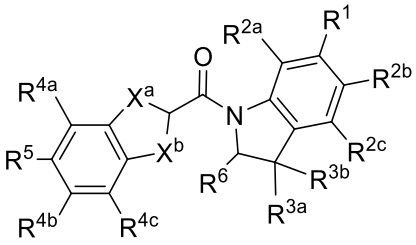
[0015] The description below is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter and is not intended to limit the appended claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0016] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. It must be noted that as used herein and in the appended claims, the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, *e.g.*, reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art, and so forth.

[0017] As used in the present specification, the following terms and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

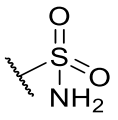
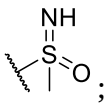
CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is  or  ;

R^{2a}, R^{2b}, and R^{2c} are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, C_{1-6} haloalkoxy, or $-SCF_3$;

R^{3a} and R^{3b} are each independently H, halogen, C_{1-6} alkyl, or C_{1-6} haloalkyl;

or R^{3a} and R^{3b} together with the carbon to which they are attached form C_{3-6} cycloalkyl; wherein the cycloalkyl formed from R^{3a} and R^{3b} may be optionally substituted with one to three Z^3, which may be the same or different;

X^a and X^b are each independently O or $CR^{7a}R^{7b}$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl;

or R^{7a} and R^{7b} together with the carbon to which they are attached form C_{3-6} cycloalkyl; wherein the C_{3-6} cycloalkyl formed from R^{7a} and R^{7b} may be optionally substituted with one to three Z^7, which may be the same or different;

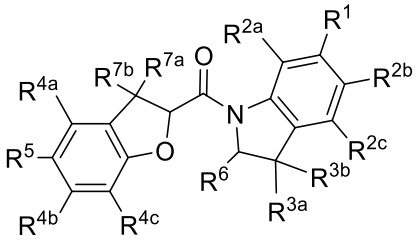
R^{4a}, R^{4b}, and R^{4c} are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -CN, $-SCF_3$, or C_{3-6} cycloalkyl optionally substituted with Z^4;

R^5 is C_{6-10} aryl or heteroaryl; wherein the aryl or heteroaryl of R^5 may be optionally substituted with one to three Z^5, which may be the same or different; the heteroaryl of R^5 is 5 to 10 membered heteroaryl having one to three heteroatoms each independently N, O, or S;

R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-8} alkoxyalkyl, or C_{3-6} cycloalkyl, wherein the cycloalkyl of R^6 is optionally substituted with one to three Z^6; and

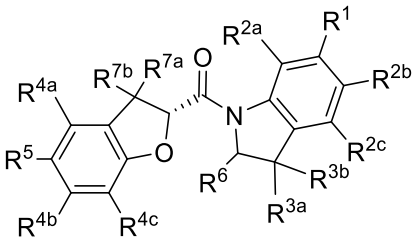
each Z^3, Z^4, Z^5, Z^6, and Z^7 is independently halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{1-6} haloalkoxy.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IIa)



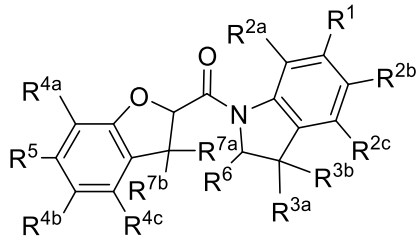
(IIa).

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IIb)



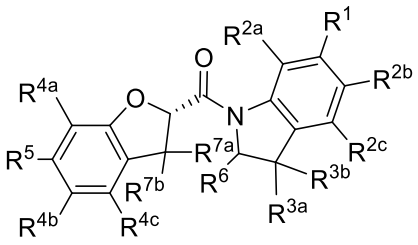
(IIb).

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IIc)



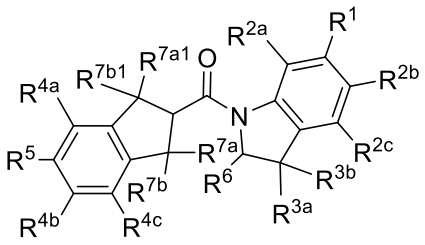
(IIc).

5. The compound of claim 1 or 4, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IId)



(IId).

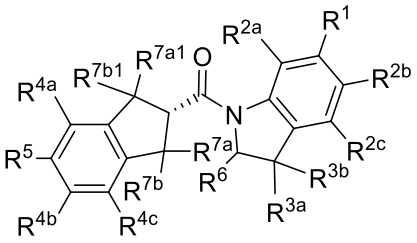
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IIe)



(IIe).

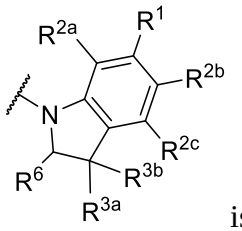
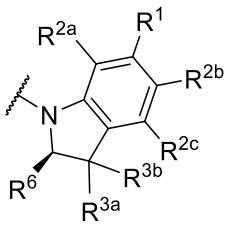
wherein R^{7a1} and R^{7b1} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl; or R^{7a1} and R^{7b1} together with the carbon to which they are attached form C_{3-6} cycloalkyl; wherein the C_{3-6} cycloalkyl formed from R^{7a1} and R^{7b1} may be optionally substituted with one to three Z^7, which may be the same or different.

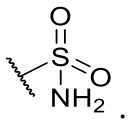
7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is represented by Formula (IIf)

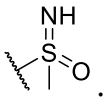


(IIf).

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof,

wherein  is  .

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

10. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^1 is  .

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H.

12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is halogen or C_{1-6} alkyl.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H.

14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is halogen.

15. The compound of any one of claims 1-12, and 14, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is F, Cl, or Br.

16. The compound of any one of claims 1-12, 14, and 15, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is F.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is H.

18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is halogen or C_{1-6} alkyl.

19. The compound of any one of claims 1-16 and 18, or a pharmaceutically acceptable salt thereof, wherein R^{2c} is F.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is H.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein R^{3a} is C_{1-6} alkyl.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is H.

23. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^{3b} is C_{1-6} alkyl.

24. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} together with the carbon to which they are attached form C_{3-6} cycloalkyl.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is H.

26. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, wherein R^{4a} is halogen.

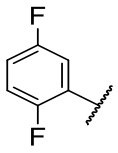
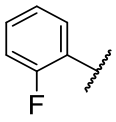
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is H.

28. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^{4b} is halogen.

29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is H.

30. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein R^{4c} is halogen.

31. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_{6-10} aryl optionally substituted with one to three Z^5 which may be the same or different, each Z^5 is independently halogen, -CN, C_{1-6} alkyl, or C_{1-6} haloalkyl.

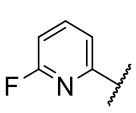
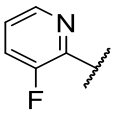
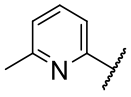
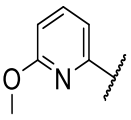
32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein R^5 is phenyl,  , or  .

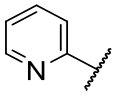
33. The compound of any one of claims 1-30, or a pharmaceutically acceptable salt thereof, wherein R^5 is heteroaryl; wherein the heteroaryl of R^5 may be optionally substituted with one to three Z^5, which may be the same or different.

34. The compound of any one of claims 1-30 and 33, or a pharmaceutically acceptable salt thereof, wherein R^5 is heteroaryl selected from thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, and pyrimidinyl; the heteroaryl of R^5 may be optionally substituted with one to three Z^5, which may be the same or different.

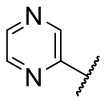
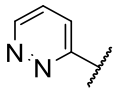
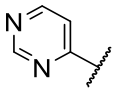
35. The compound of any one of claims 1-30, 33, and 34, or a pharmaceutically acceptable salt thereof, wherein R^5 is pyridyl optionally substituted with one to three Z^5, which may be the same or different.

36. The compound of any one of claims 1-30 and 33-35, or a pharmaceutically acceptable salt thereof, wherein R^5 is pyridyl optionally substituted with halogen, C_{1-3} alkyl, -CN, or $-OCH_3$.

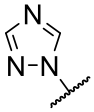
37. The compound of any one of claims 1-30 and 33-36, or a pharmaceutically acceptable salt thereof, wherein R^5 is pyridyl,  ,  ,  , or  .

38. The compound of any one of claims 1-30 and 33-37, or a pharmaceutically acceptable salt thereof, wherein R^5 is  .

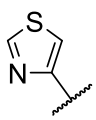
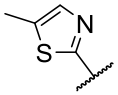
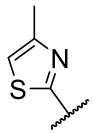
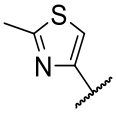
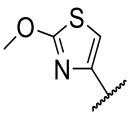
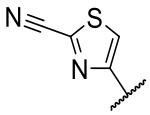
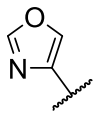
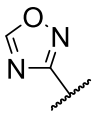
39. The compound of any one of claims 1-30, 33, and 34, or a pharmaceutically acceptable salt thereof, wherein R^5 is diazinyl optionally substituted with halogen, C_{1-3} alkyl, -CN, or $-OCH_3$.

40. The compound of any one of claims 1-30, 33, 34, and 39, or a pharmaceutically acceptable salt thereof, wherein R^5 is  ,  ,  , or  .

41. The compound of any one of claims 1-30, 33, and 34, or a pharmaceutically acceptable salt thereof, wherein R^5 is triazolyl or pyrazolyl, wherein the triazolyl or pyrazolyl is each optionally substituted with halogen, -CN, C_{1-3} alkyl, or -OCH_3.

42. The compound of any one of claims 1-30, 33, 34, and 41, or a pharmaceutically acceptable salt thereof, wherein R^5 is  or  .

43. The compound of any one of claims 1-30, 33, and 34, or a pharmaceutically acceptable salt thereof, wherein R^5 is thiazolyl, isothiazolyl, oxazolyl, or isoxazolyl; the thiazolyl, isothiazolyl, oxazolyl, isoxazolyl of R^5 is each optionally substituted with halogen, C_{1-3} alkyl, -CN, or -OCH_3.

44. The compound of any one of claims 1-30, 33, 34, and 43, or a pharmaceutically acceptable salt thereof, wherein R^5 is  ,  ,  ,  ,  ,  ,  ,  ,  ,or  .

45. The compound of any one of claims 1-44, or a pharmaceutically acceptable salt thereof, wherein R^{7a} and R^{7b} are each independently H or C_{1-6} alkyl.

46. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, wherein R^{7a} is H.

47. The compound of any one of claims 1-45, or a pharmaceutically acceptable salt thereof, wherein R^{7a} is C_{1-3} alkyl.

48. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, wherein R^{7b} is H.

49. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, wherein R^{7b} is C_{1-3} alkyl.

50. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt thereof, wherein R^{7b} is $-CH_3$.

51. The compound of any one of claims 1, 6-50, or a pharmaceutically acceptable salt thereof, wherein R^{7a1} and R^{7b1} are each independently H or C_{1-6} alkyl.

52. The compound of any one of claims 6-51, or a pharmaceutically acceptable salt thereof, wherein R^{7a1} is H.

53. The compound of any one of claims 6-51, or a pharmaceutically acceptable salt thereof, wherein R^{7a1} is C_{1-3} alkyl.

54. The compound of any one of claims 6-53, or a pharmaceutically acceptable salt thereof, wherein R^{7b1} is H.

55. The compound of any one of claims 6-53, or a pharmaceutically acceptable salt thereof, wherein R^{7b1} is C_{1-3} alkyl.

56. The compound of any one of claims 6-53, or a pharmaceutically acceptable salt thereof, wherein R^{7b1} is $-CH_3$.

57. The compound of any one of claims 1 and 8-44, or a pharmaceutically acceptable salt thereof, wherein X^a and X^b are O.

58. The compound of any one of claims 1-7 and 9-57, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

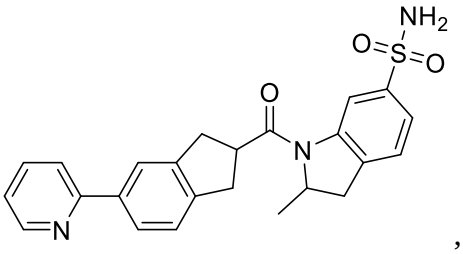
59. The compound of any one of claims 1-57, or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-6} alkyl or C_{1-6} haloalkyl.

60. The compound of any one of claims 1-57 and 59, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-CH_3$ optionally substituted with 1 to 3 halo.

61. The compound of any one of claims 1-57, 59, and 60, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-CH_3$, $-CHF_2$, $-CH_2F$, $-CF_3$, $-CHCl_2$, or $-CH_2Cl$.

62. The compound of any one of claims 1-57 and 59-61, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-CH_3$.

63. A compound selected from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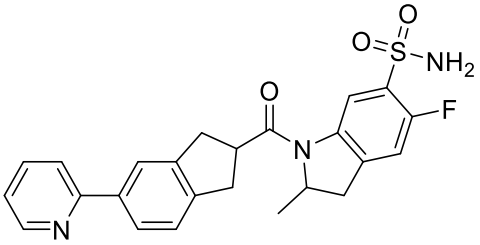
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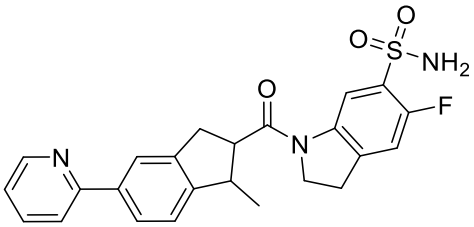
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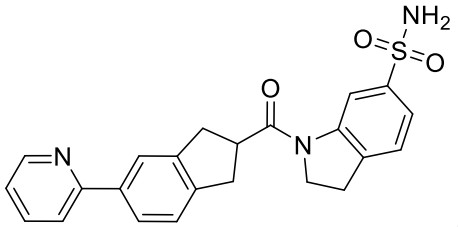
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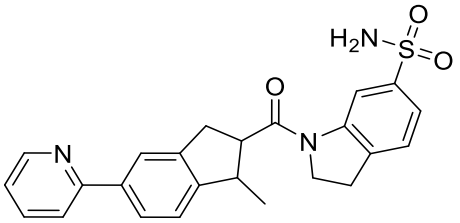
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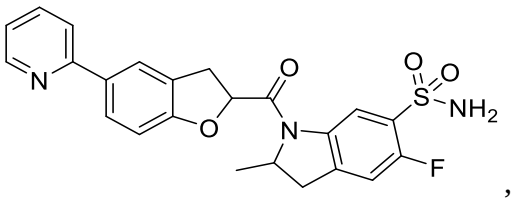
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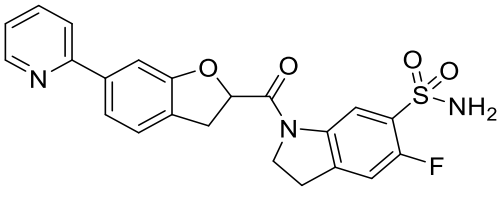
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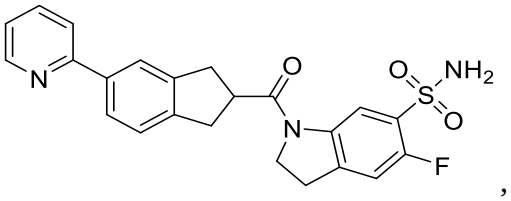
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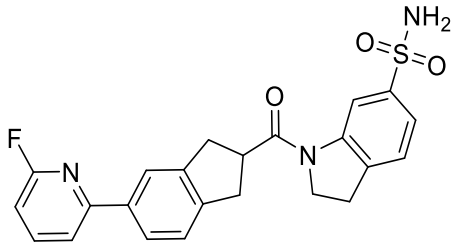
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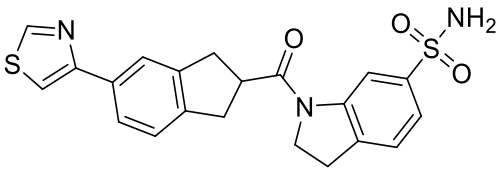
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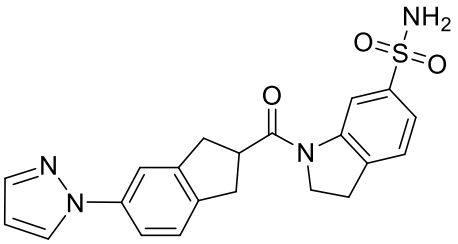
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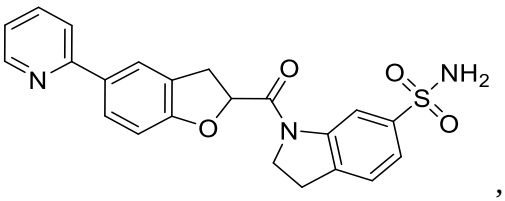
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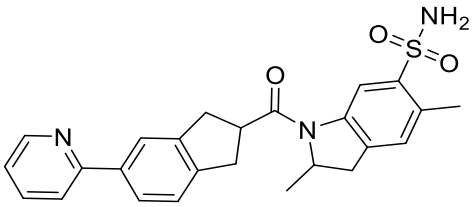
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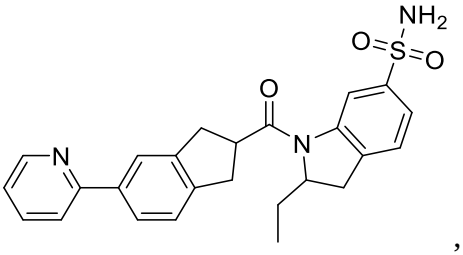
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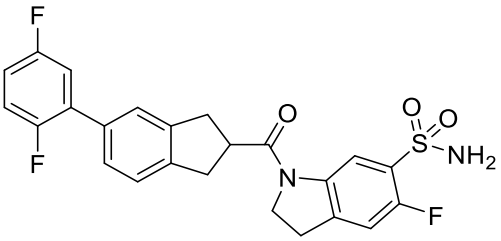
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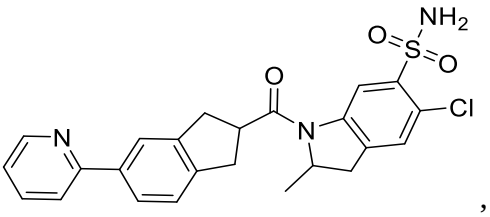
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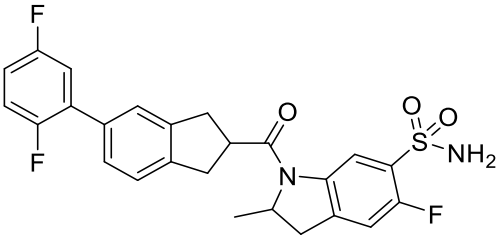
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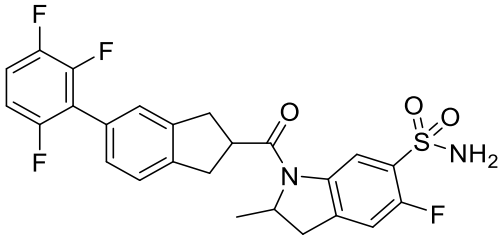
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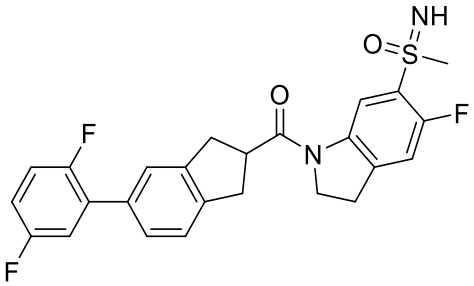
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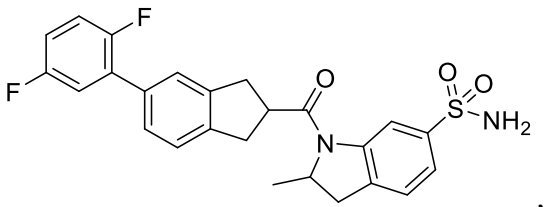
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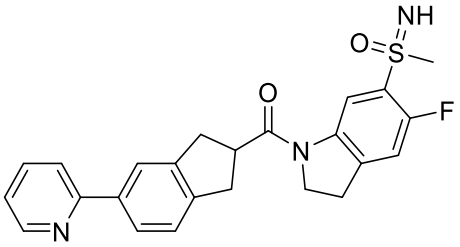
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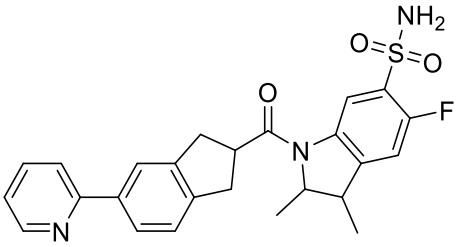
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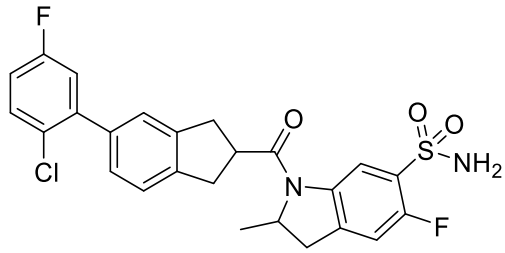
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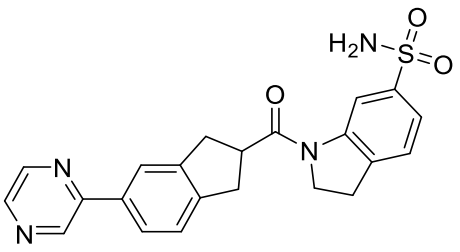
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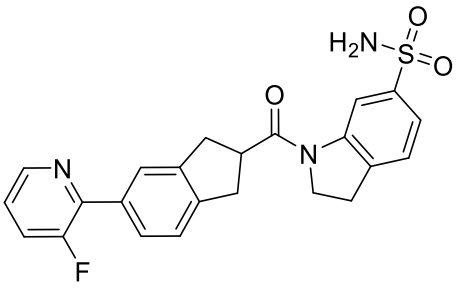
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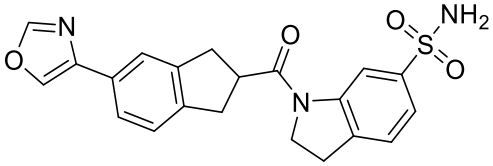
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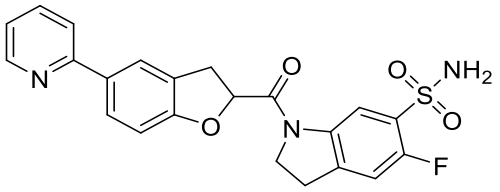
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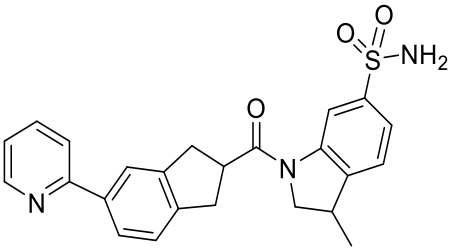
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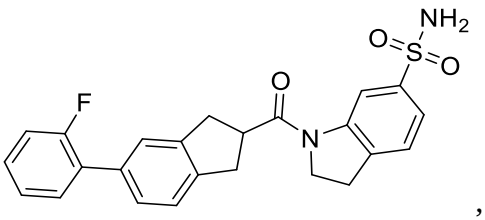
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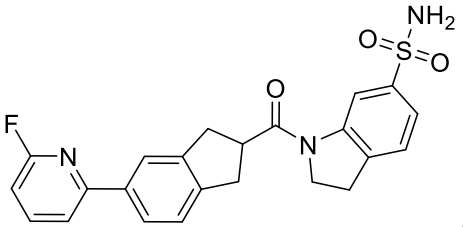
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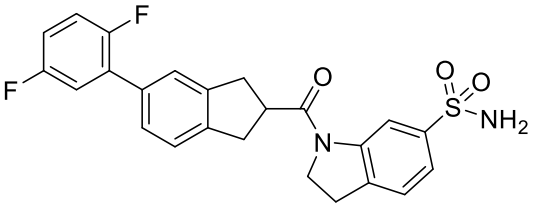
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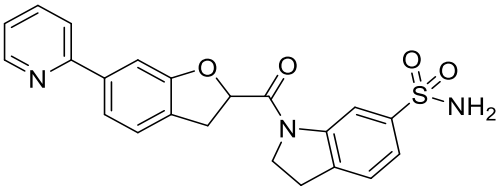
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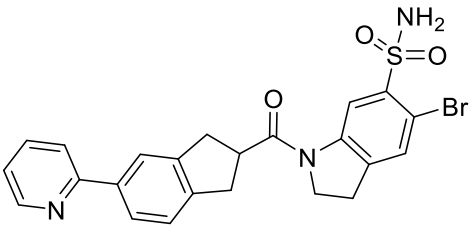
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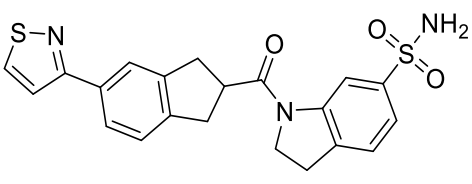
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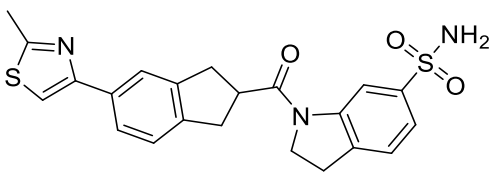
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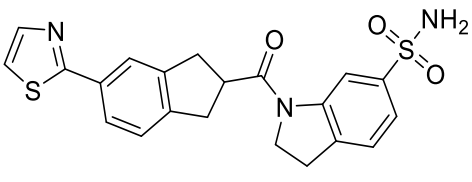
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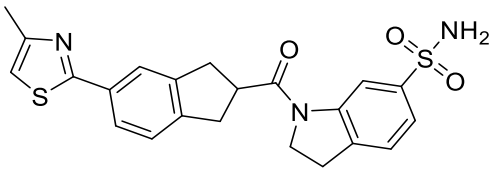
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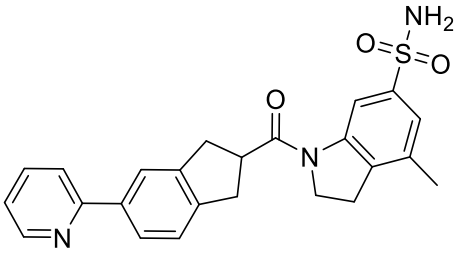
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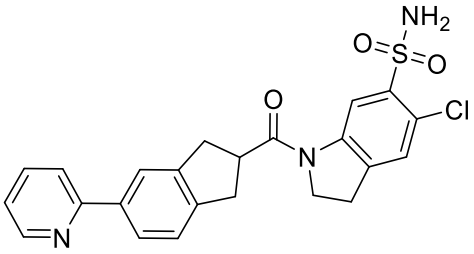
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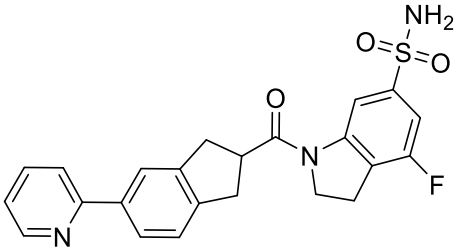
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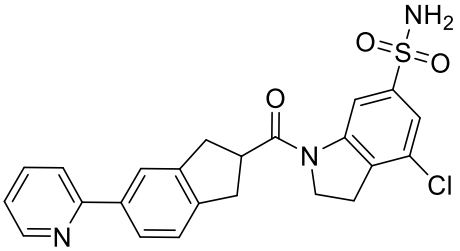
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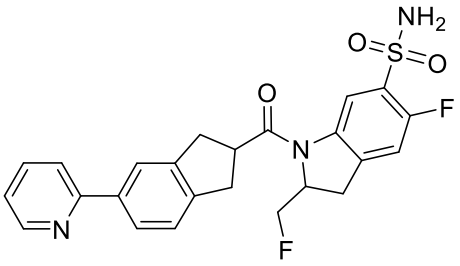
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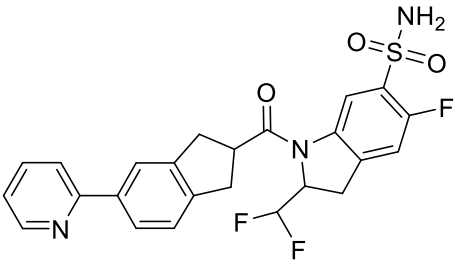
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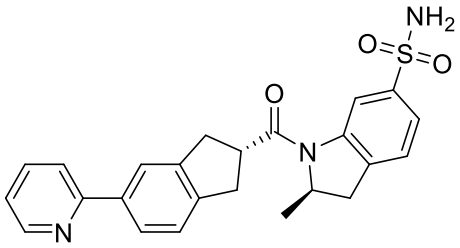
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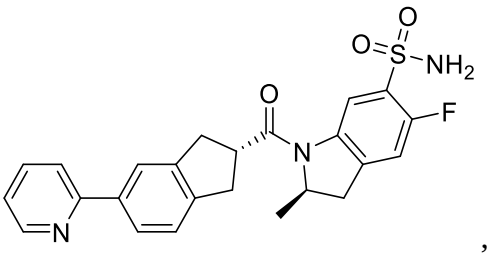
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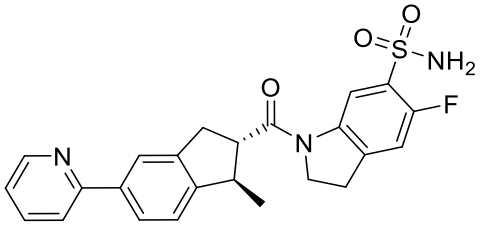
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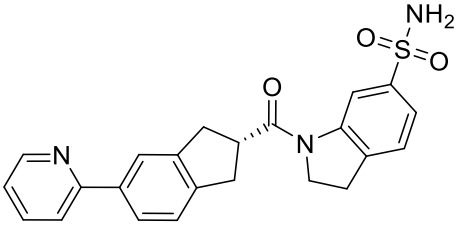
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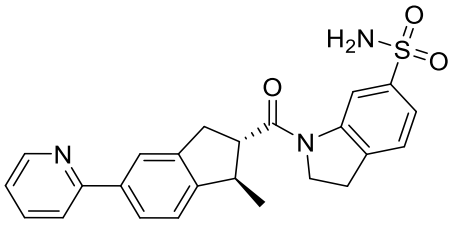
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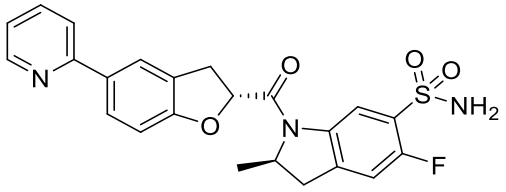
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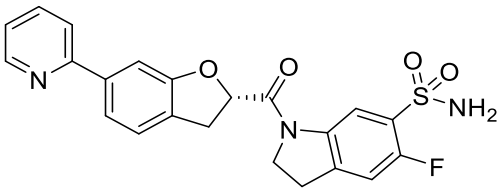
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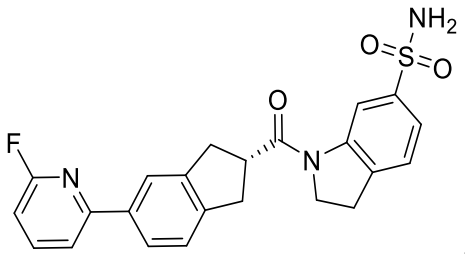
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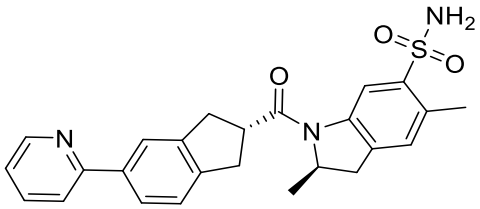
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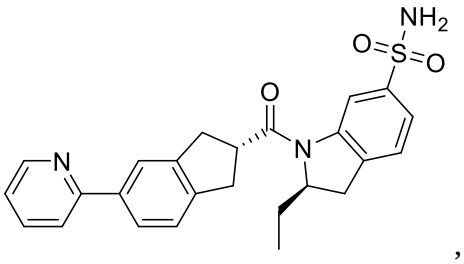
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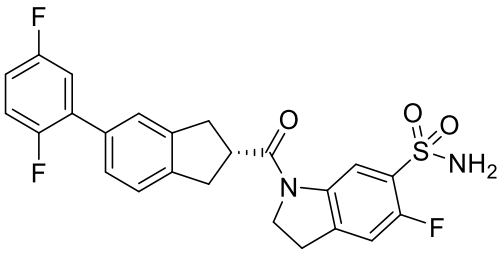
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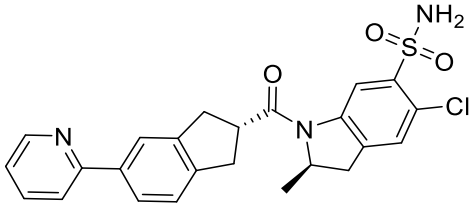
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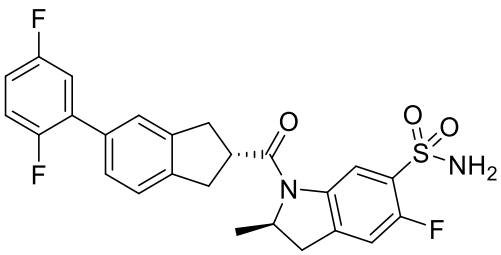
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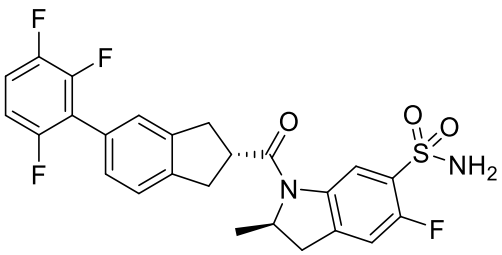
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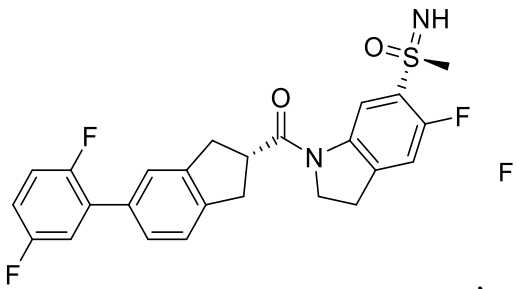
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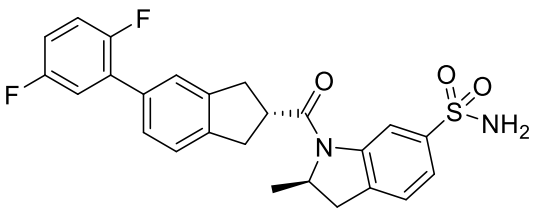
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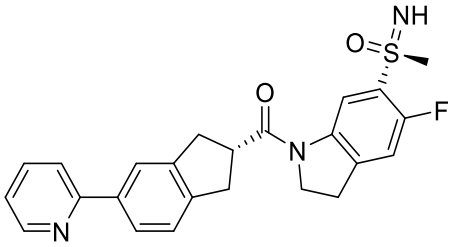
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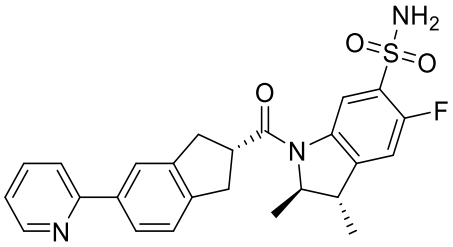
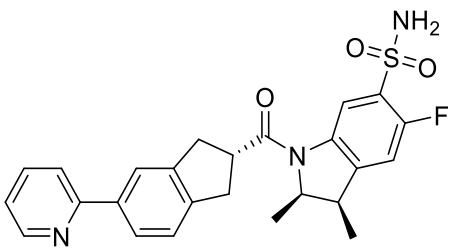
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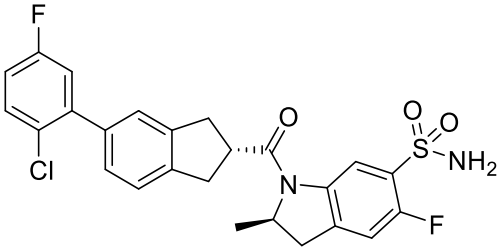
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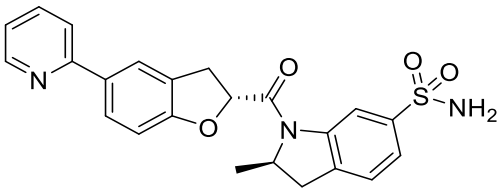
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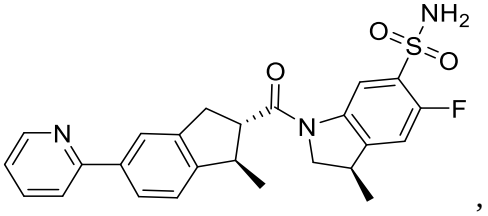
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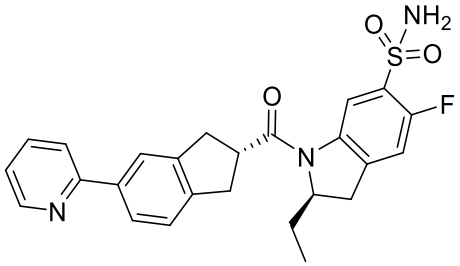
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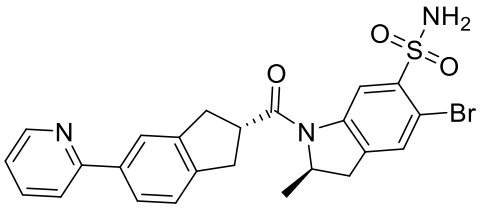
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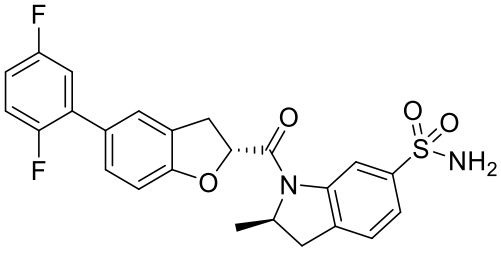
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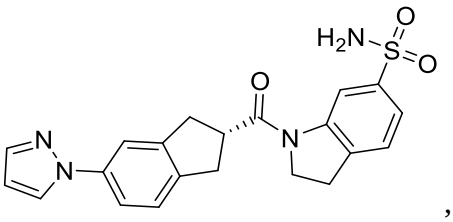
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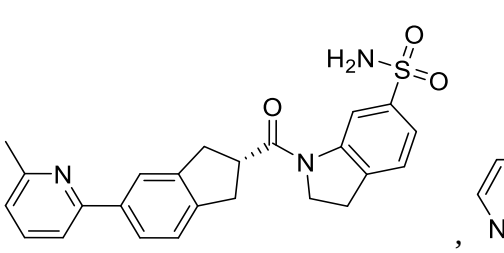
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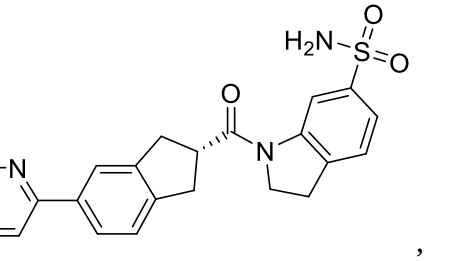
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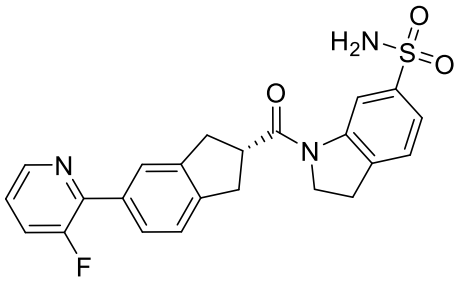
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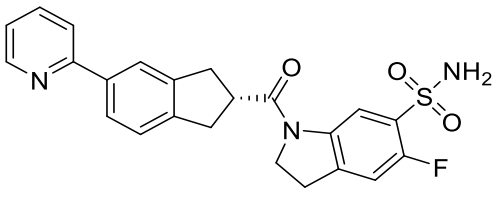
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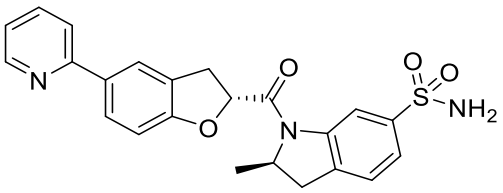
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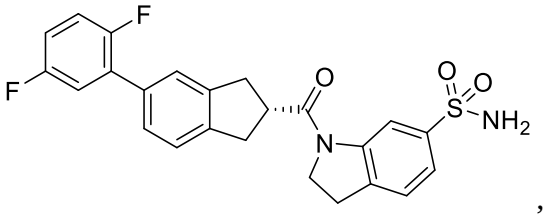
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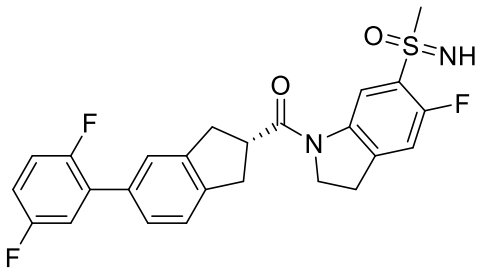
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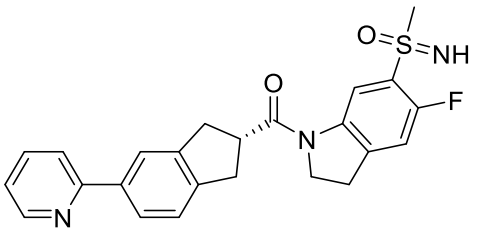
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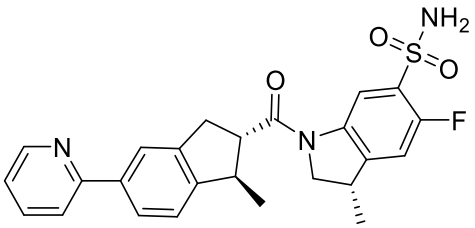
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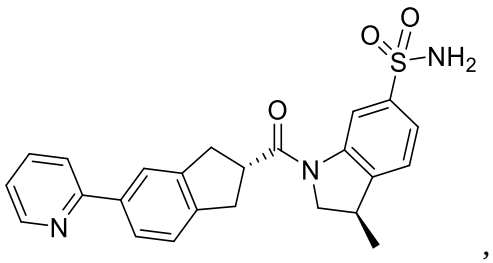
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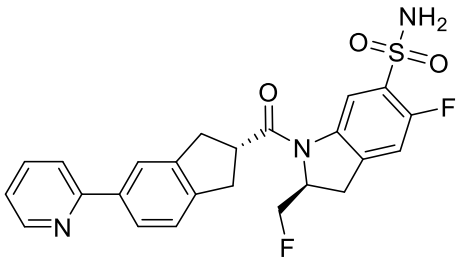
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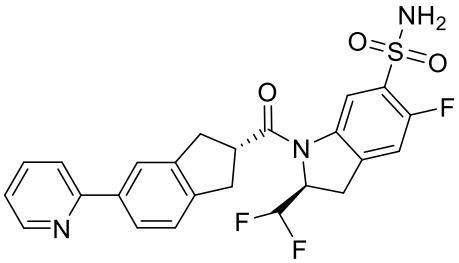
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or a pharmaceutically acceptable salt thereof.

65. A compound selected from Examples 1-20, 22-29, 31, 33-41, 43-53, 56-65, 68-83, 85-119, 123, and 125-141, or a pharmaceutically acceptable salt thereof.

66. A compound selected from Examples 1-20, 22-29, 31, 33-41, 43-53, 56-65, 68-83, 85-119, 123, and 125-141.

67. A pharmaceutical composition comprising a compound of any one of claims 1-66 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

68. The pharmaceutical composition of claim 67, further comprising one, two, three, or four additional therapeutic agents.

69. The pharmaceutical composition of claim 68, wherein the additional therapeutic agents are selected from famciclovir, acyclovir, and valacyclovir.

70. Use of a compound of any one of claims 1-66 or a pharmaceutically acceptable salt thereof, or a composition of any one of claim 67-69, in the manufacture of a medicament for treating a herpesvirus infection.

71. The use of claim 70, wherein a compound of any one of claims 1-65 or a pharmaceutically acceptable salt thereof, or a composition of any one of claim 66-68, is to be administered in combination with one, two, three, or four additional therapeutic agents.

72. The use of claim 70 or 71, wherein the herpesvirus is HSV-1 or HSV-2.

73. Use of a therapeutically effective amount of a compound of any one of claims 1-66 or a pharmaceutically acceptable salt thereof, or a composition of any one of claim 67-69, in the manufacture of a medicament for treating a disorder induced, exacerbated or accelerated by herpesvirus.

74. The use of claim 73, wherein a compound of any one of claims 1-65 or a pharmaceutically acceptable salt thereof, or a composition of any one of claim 66-68, is to be administered in combination with one, two, three, or four additional therapeutic agents.

75. The use of claim 73 or 74, wherein the disorder is genital herpes, herpes labialis, HSV keratitis, HSV encephalitis, or disseminated HSV.

76. Use of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection.

77. Use of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection caused by herpesviruses.

78. Use of a compound of any one of claims 1-66, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing/treating a viral infection caused by HSV-1 or HSV-2.

79. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-66 or the pharmaceutical composition of any one of claim 67-69 for use in treating a viral infection caused by HSV-1 or HSV-2.

80. The compound, pharmaceutically acceptable salt thereof, or pharmaceutical composition for use of claim 79, wherein the viral infection is genital herpes, herpes labialis, HSV keratitis, HSV encephalitis, or disseminated HSV.

81. The compound, pharmaceutically acceptable salt thereof, or pharmaceutical composition for use of claim 79 or 80, wherein the compound or pharmaceutically acceptable salt thereof is to be administered in combination with an additional therapeutic agent.

82. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-66 for use in therapy.