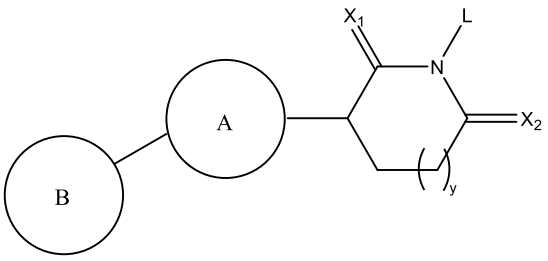
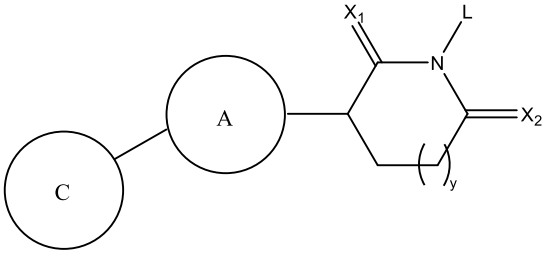
CLAIMS

1. A compound of Formula (Ia) or (Ib):



(Ia)



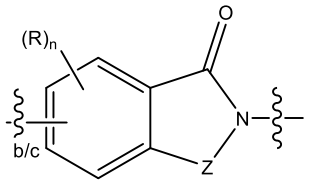
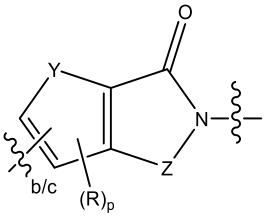
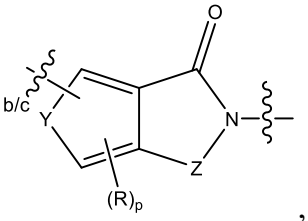
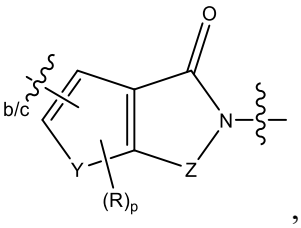
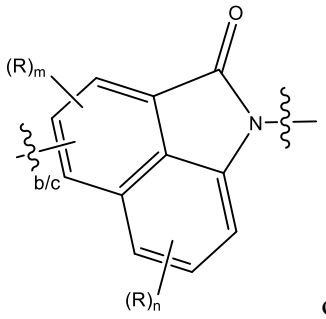
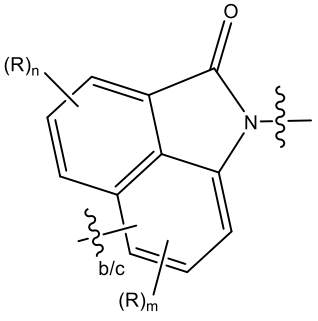
(Ib)

in which:

y is 0, 1 or 2;

each of X_1 and X_2 is independently O or S;

L is H, -C(O)alkyl, or -CH_2(O)COR';

A is , , , , , or 

in which

each Z is independently C=O, CH_2 or CH($C_{1\text{-}2}$ alkyl);

Y is S, O or NH;

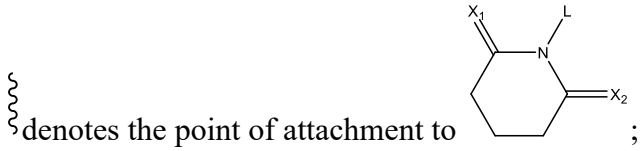
each R is independently halogen, alkyl, haloalkyl, hydroxy, alkoxy, $-NH_2$, -NHR' or $-NR'_2$;

each R' is independently alkyl or aryl;

each n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

p is 0 or 1;



denotes the point of attachment to ; and

b/c denotes the point of attachment to B in Formula (Ia) or C in Formula (Ib);

B is a heterocycloalkyl group having a heteroatom adjacent to the point of attachment b/c, and

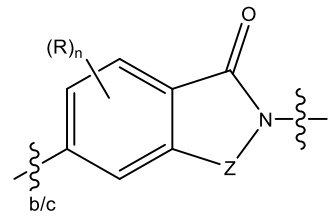
C is a 6-membered monocyclic heteroaryl group or a 10-membered fused bicyclic heteroaryl group, in which

C is either unsubstituted or is substituted with one or more R^3,

no substituents other than the one or more R^3 are present on C; and

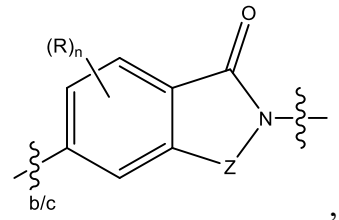
each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, cycloalkyl, hydroxy, OR^1, aryl, benzyl, $-C(O)R^1$, or $-NR^2C(O)R^1$, in which each R^1 is independently unsubstituted alkyl, cycloalkyl, or aryl and each R^2 is independently H, unsubstituted alkyl, or cycloalkyl;

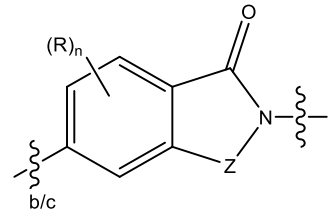
in which in formula (Ib):

(i) when A is  , Z is CH_2 and n = 0, then:

(a) C is substituted with one or more R^3 or

(b) y is 2;

(ii) when A is  , Z is CH_2, n = 0, and C is a 6-membered monocyclic heteroaryl group having two heteroatoms, the two heteroatoms are not adjacent to each other,

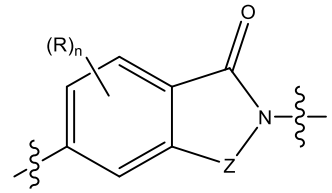
(iii) when A is  , Z is CH_2, n = 0 and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then:

(a) carbon atoms adjacent to the carbon atom through which C is attached to A are unsubstituted;

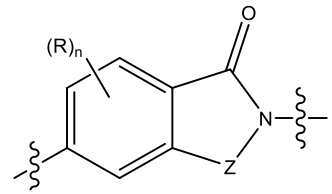
(b) when R^3 is alkyl or O(alkyl), then C is monosubstituted;

(c) when R^3 is O(alkyl), then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group; and

(d) when R^3 is aryl or $-NR^2C(O)R^1$, then the substitution is at a position *meta* to a heteroatom of the heteroaryl group,

(iv) when A is 

, Z is C=O, n = 0 and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then when R^3 is hydroxy, then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group; and

(v) when A is 

, Z is CH_2, n = 0 and C is a 10-membered fused bicyclic heteroaryl group substituted with one or more R^3, then:

each R^3 is present on the ring which contains the point of attachment to A,

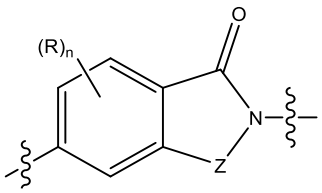
each R^3 is positioned *ortho* or *meta* to a heteroatom of the heteroaryl group;

R^3 is not Cl, methyl, iPr, cyclopropane, unsubstituted phenyl, hydroxy or OMe;

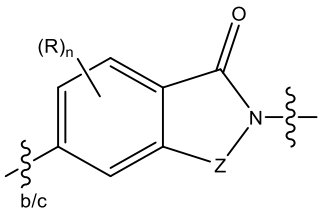
when R^3 is OEt, then R^3 is positioned *ortho* to the heteroatom of the heteroaryl group; and

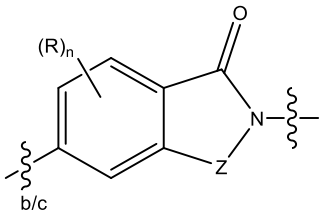
when R3 is NR2COMe, then R3 is positioned meta to the heteroatom of the heteroaryl group.

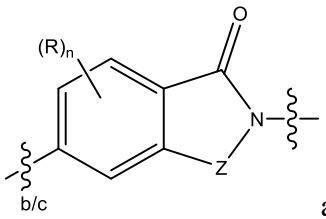
2. A compound according to Claim 1, in which in formula (Ib),

(a) when A is 

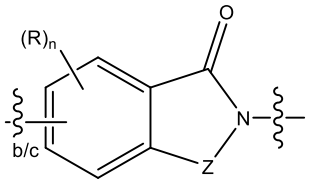
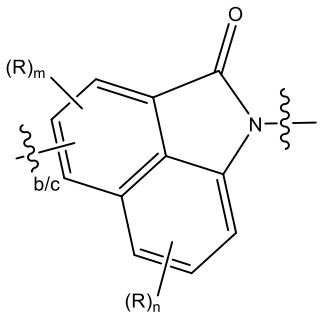
, Z is CH_2 and n = 0, then C is substituted with one or more R^3;

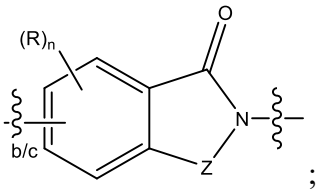
(b) when A is  , Z is C=O or CH_2, n = 0 and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then when R^3 is hydroxy or O(alkyl), then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group;

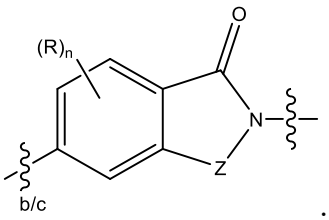
(c) when A is  and n = 0, then Z is CH($C_{1\text{-}2}$ alkyl) or C=O, and

(d) when A is  and Z is CH_2, then n is 1, 2, or 3.

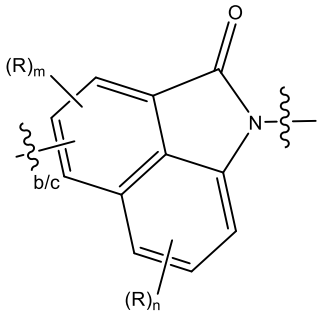
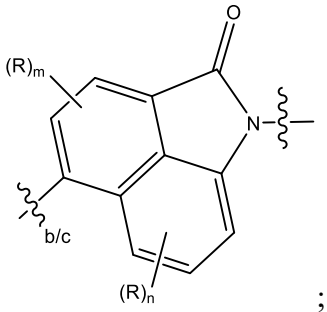
3. A compound according to Claim 1 or 2, in which A is

 or  ;

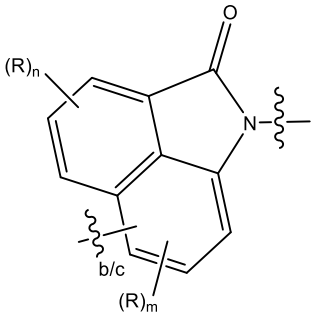
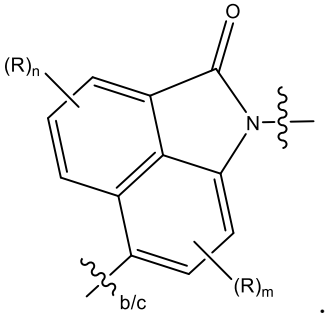
optionally in which A is  ;

further optionally in which  is .

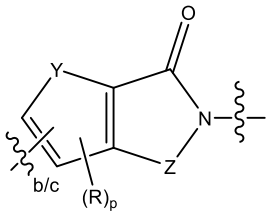
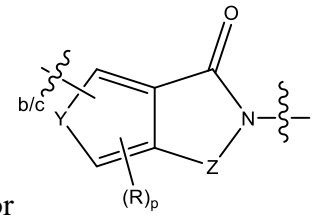
4. A compound according to Claim 1, 2 or 3, in which  is:

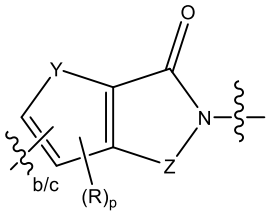
(a) , optionally in which  is ;

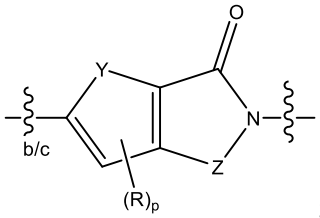
or

(b) , optionally in which  is .

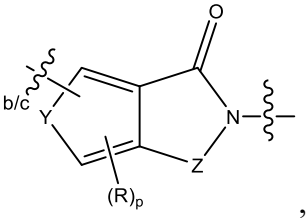
5. A compound according to Claim 1 or 2, in which  is

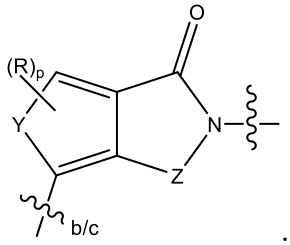
 or , optionally in which  is:

(a) , optionally



; or

(b) 

, optionally 

.

6. A compound according to any preceding claim, in which 

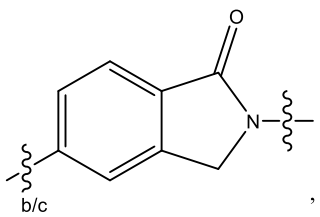
contains (a) one heteroatom, or (b) two heteroatoms.

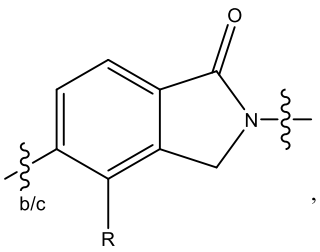
7. A compound according to any preceding claim, in which 

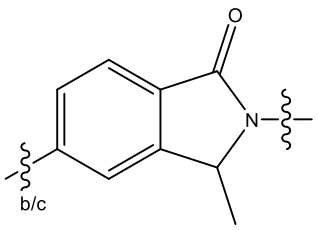
is a 5-10 membered heterocycloalkyl group, optionally a 5- or 6-membered heterocycloalkyl group.

8. A compound according to any preceding claim, in which 

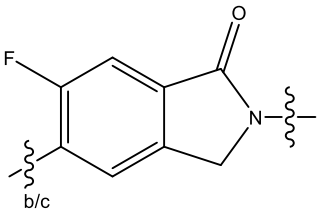
is

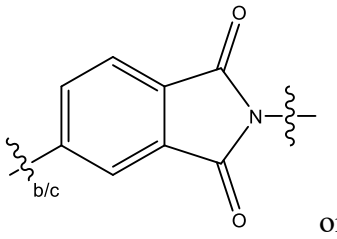


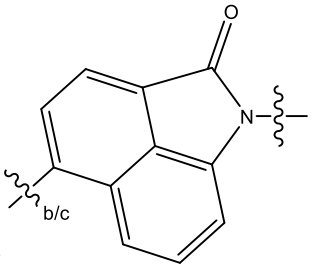
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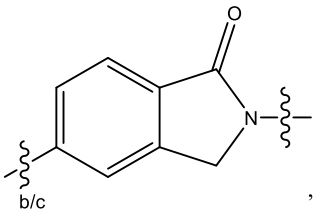


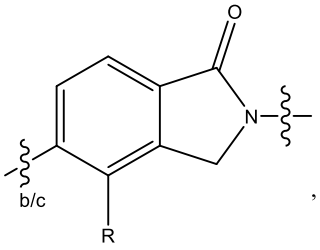
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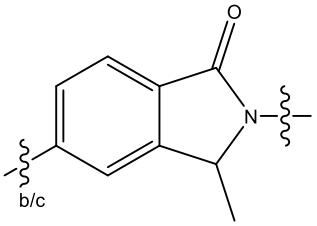
or 

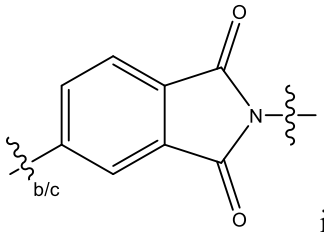
in which R is F or alkyl; optionally in which 

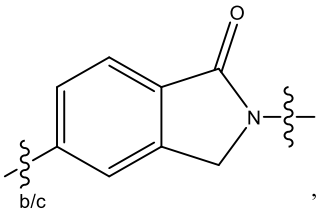
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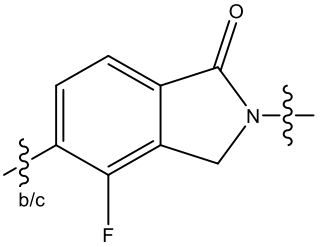


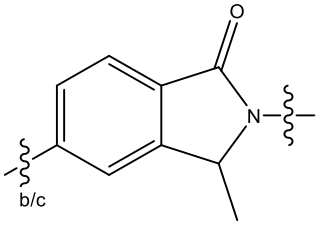
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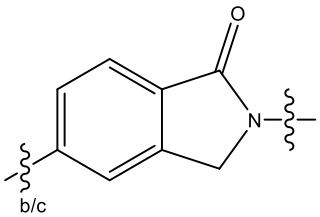
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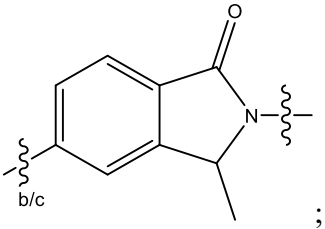
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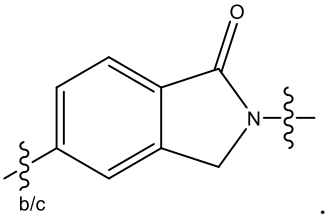
or in which R is F; further optionally in which A is


,


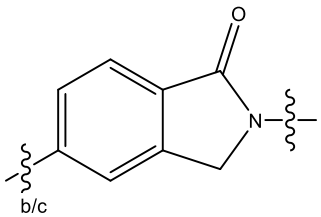
or


,
optionally


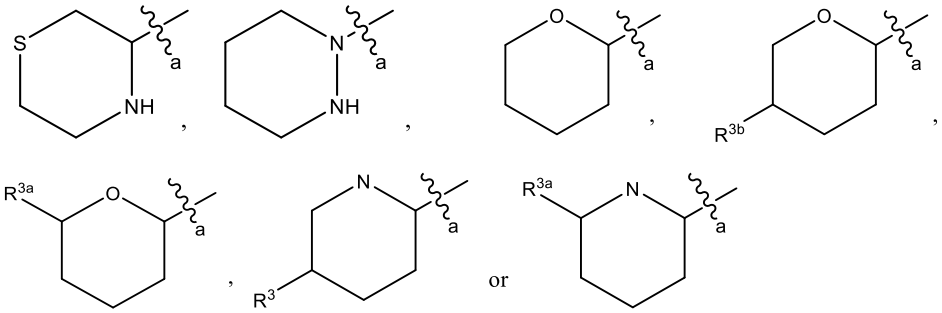
or


; further optionally


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9. A compound according to Claim 8, in which A is


, and B is

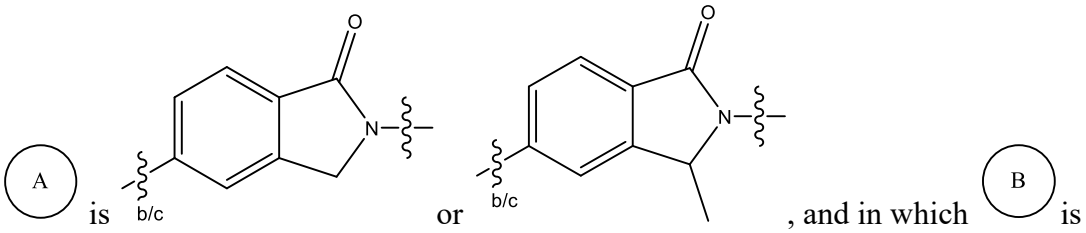


in which

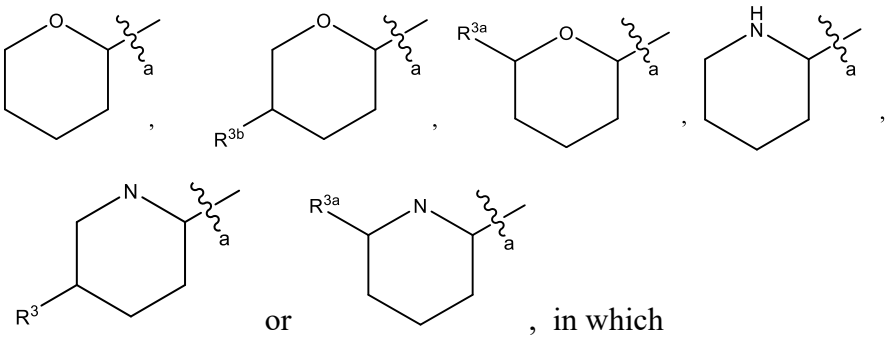
R^3 is unsubstituted alkyl, benzyl, -NHC(O)Ph or -NHC(O)Me,

R^{3a} is unsubstituted alkyl, and

R^{3b} is aryl; or in which



, and in which is



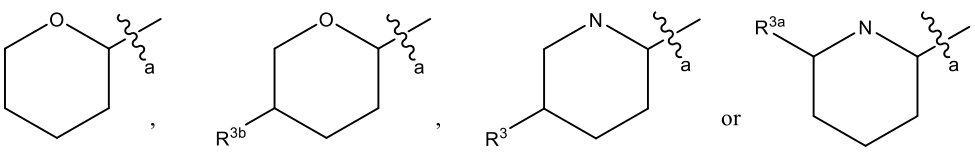
, in which

R^3 is unsubstituted alkyl, aryl, benzyl or -NHC(O)Ph,

R^{3a} is unsubstituted alkyl, and

R^{3b} is aryl or unsubstituted alkyl; optionally

in which  is



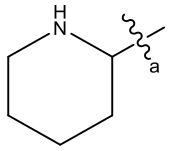
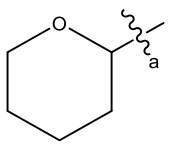
in which

R^3 is unsubstituted alkyl, benzyl or -NHC(O)Ph,

R^{3a} is unsubstituted alkyl, and

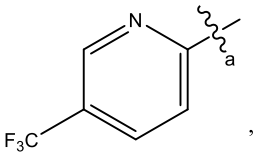
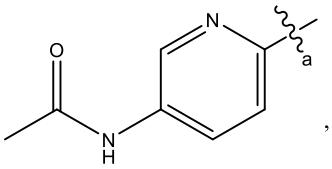
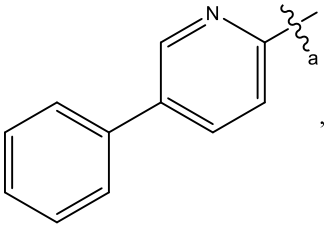
R^{3b} is aryl.

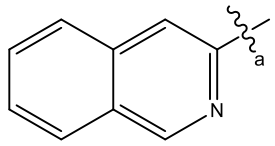
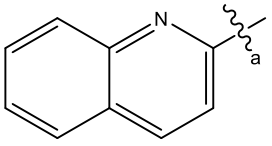
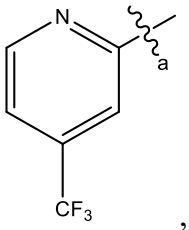
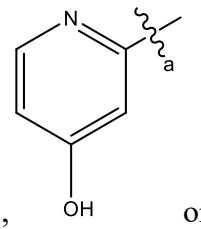
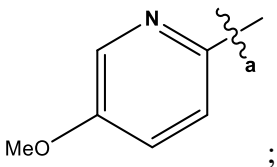
10. A compound according to Claim 9, in which is

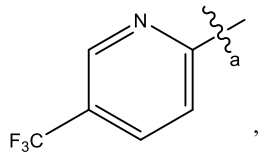
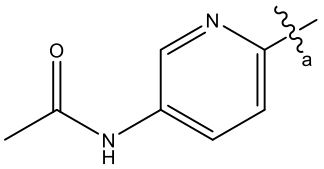
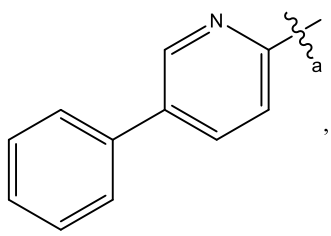
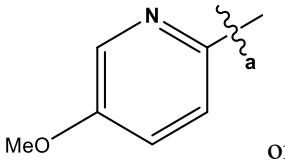
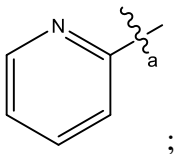
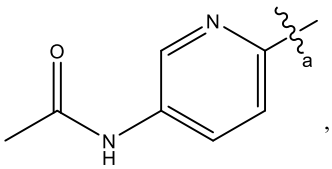
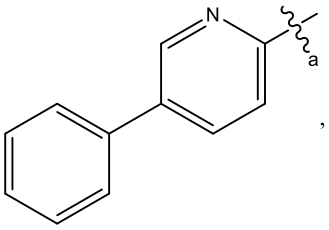
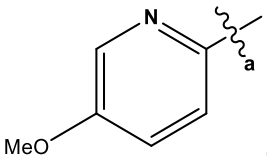
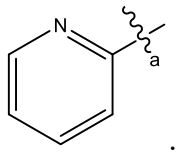
 or .

11. A compound according to any preceding claim, in which  contains (a) one heteroatom, or (b) two heteroatoms.

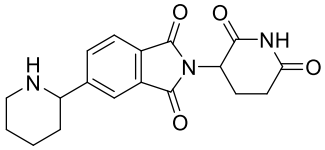
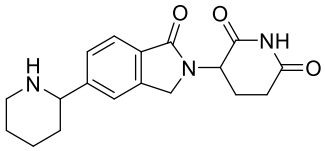
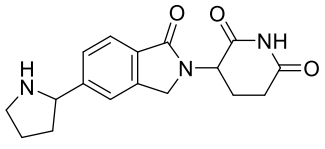
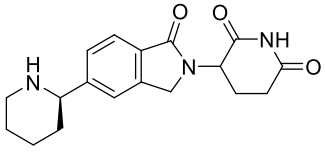
12. A compound according to any preceding claim, in which  is

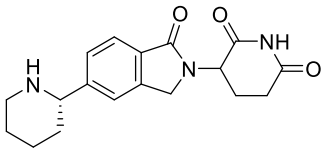
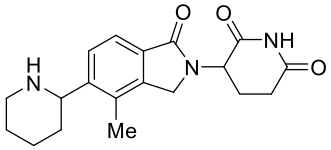
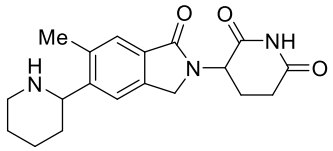
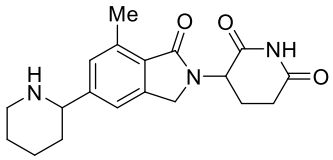
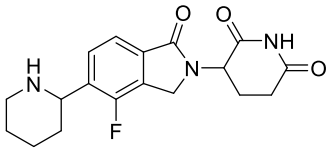
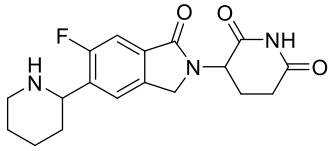
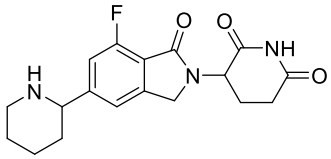
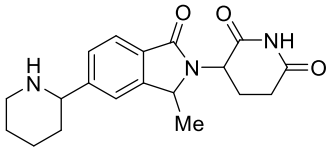
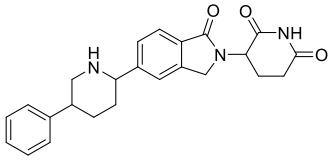
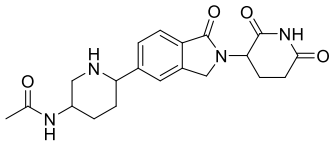
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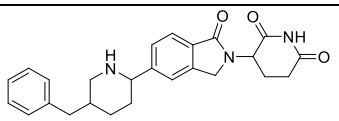
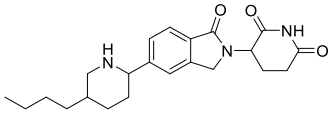
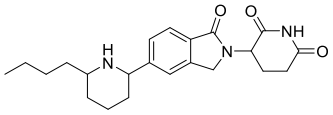
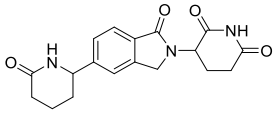
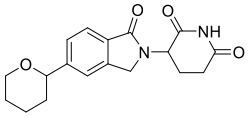
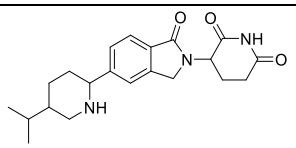
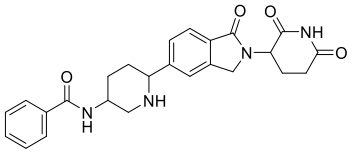
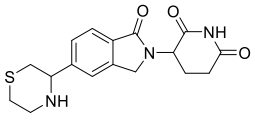
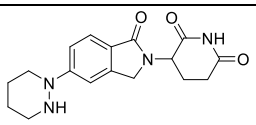
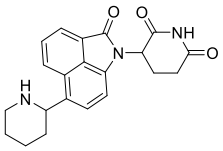
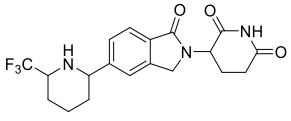
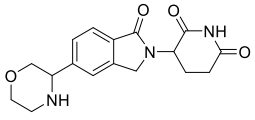
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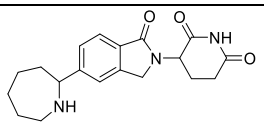
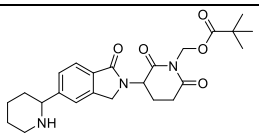
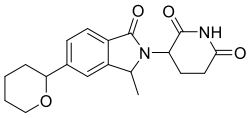
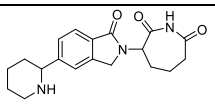
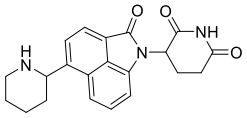
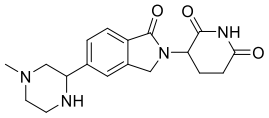
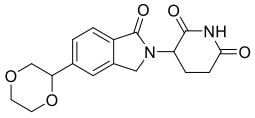
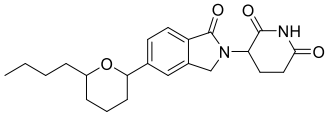
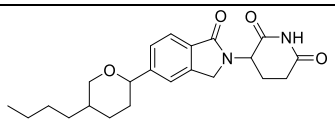
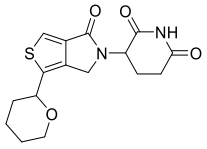
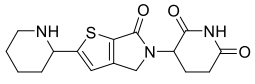
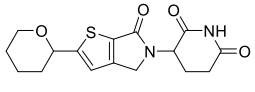
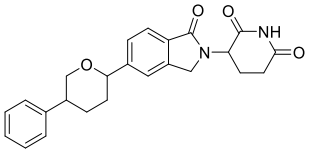





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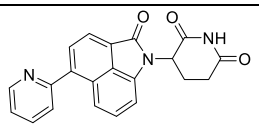
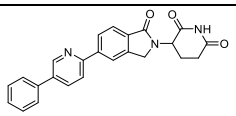
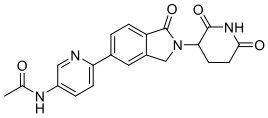
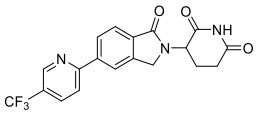
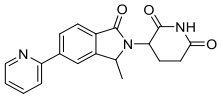
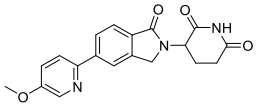
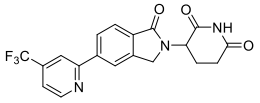
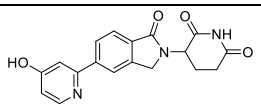
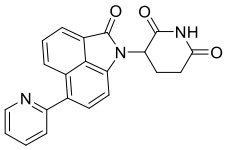
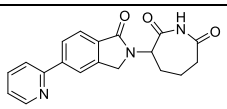
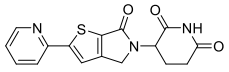
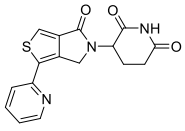
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Compound number	Structure
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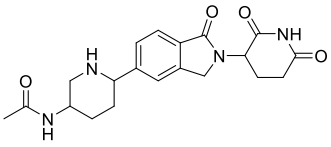
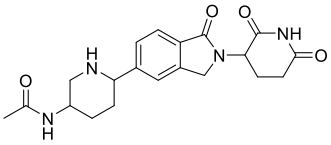
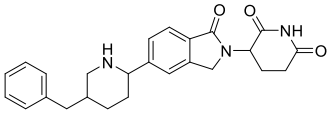
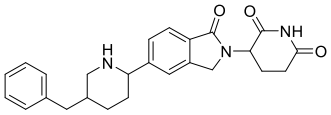
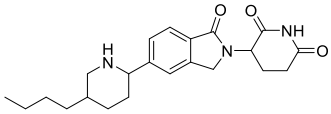
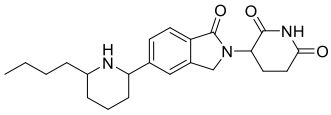
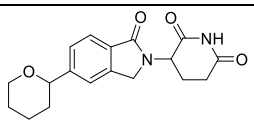
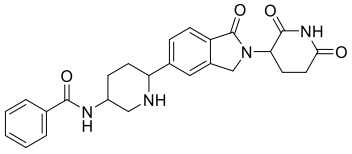
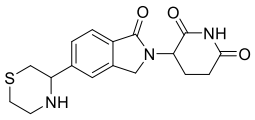
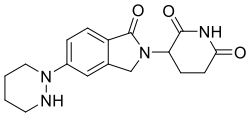
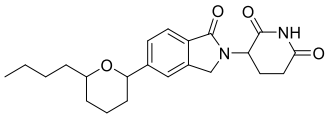
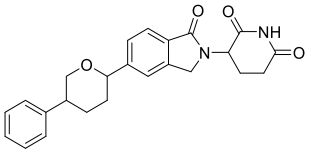
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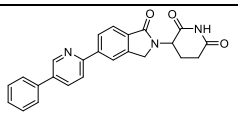
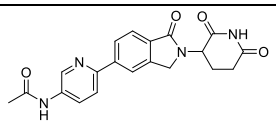
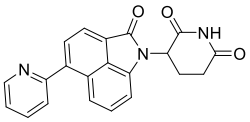
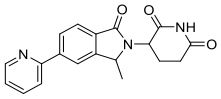
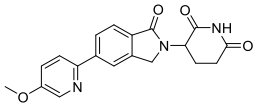
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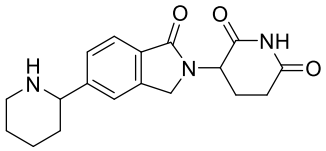
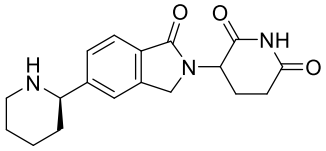
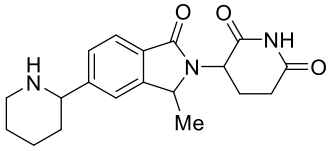
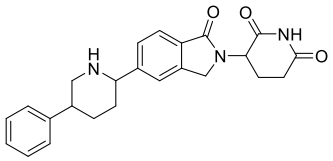
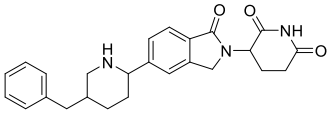
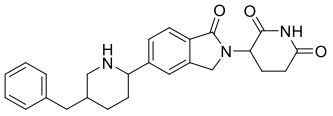
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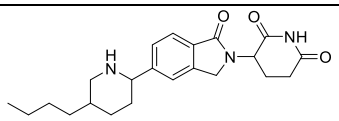
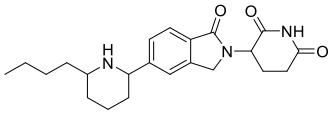
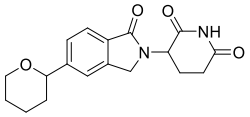
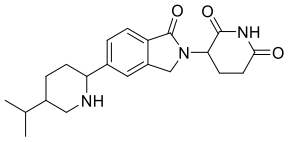
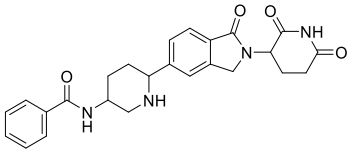
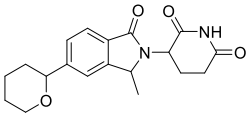
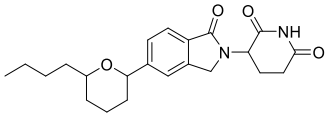
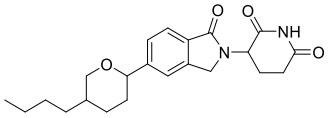
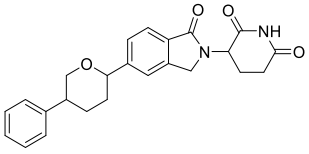
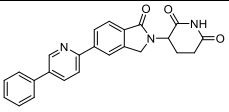
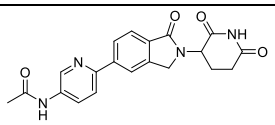
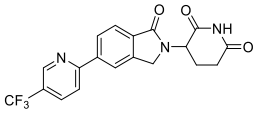
Compound number	Structure

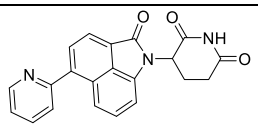
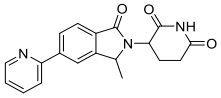
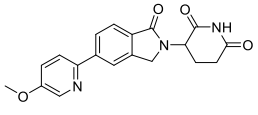
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33 Isomer 2	 Isomer 2
35 Isomer 1	 Isomer 1
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74 Isomer 2	 Isomer 2

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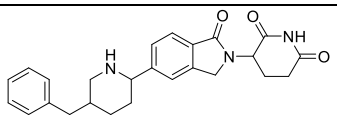
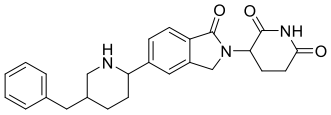
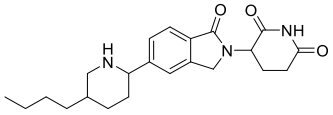
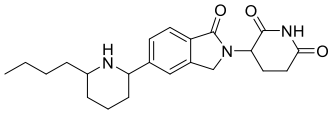
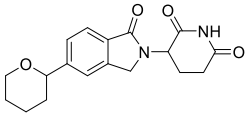
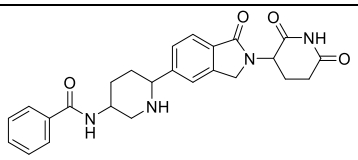
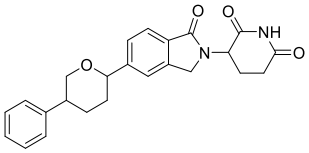
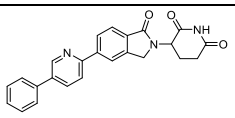
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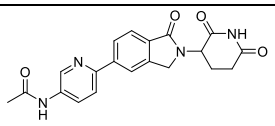
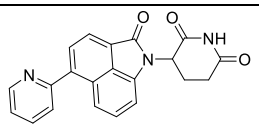
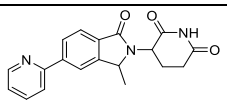
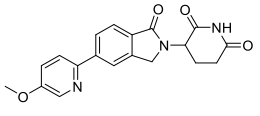
Compound number	Structure
2	
9	
25	
32 Isomer 2	 Isomer 2
35 Isomer 1	 Isomer 1
35 Isomer 2	 Isomer 2

37	
40	
54	
55 Isomer 2	 Isomer 2
56	
64	
69 Isomer 1	 Isomer 1
70 Isomer 2	 Isomer 2
74 Isomer 2	 Isomer 2
4(2)	
7(2)	
16(2)	

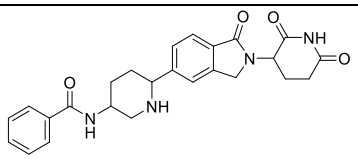
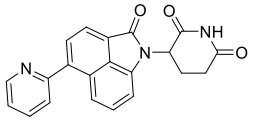
23(2)	
24(2)	
25(2)	

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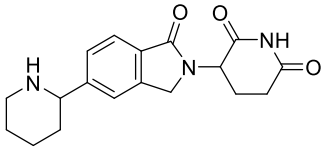
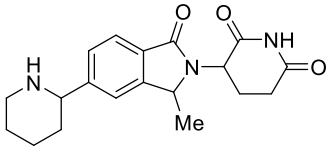
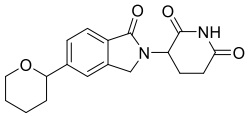
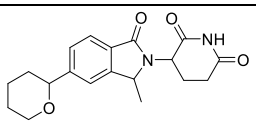
Compound number	Structure
35 Isomer 1	 Isomer 1
35 Isomer 2	 Isomer 2
37	
40	
54	
56	
74 Isomer 2	 Isomer 2
4(2)	

7(2)	
23(2)	
24(2)	
25(2)	

(d) selected from:

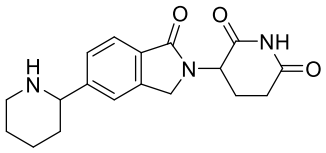
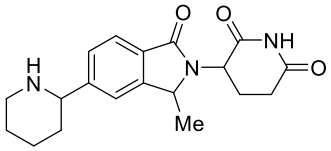
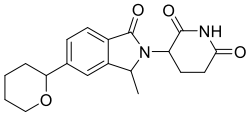
Compound number	Structure
56	
23(2)	

(e) selected from:

2	
25	
54	
64	

or

(f) selected from:

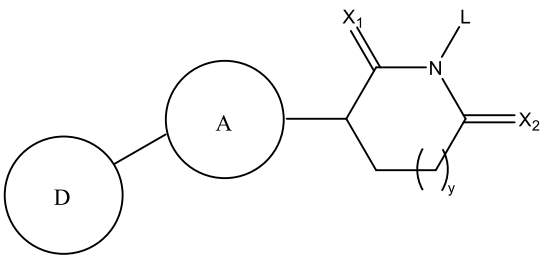
2	
25	
64	

14. A pharmaceutical composition comprising a compound according to any preceding claim.

15. A compound according to any of Claims 1 to 13 or the pharmaceutical composition of claim 14 for use in medicine.

16. A compound according to any of Claims 1 to 13 or a pharmaceutical composition according to Claim 14 for use in the treatment of an inflammatory disease or condition, an autoinflammatory disease or conditions, an auto-immune disease or condition, a respiratory disease or condition, a cardiovascular disease or condition, a gastro-intestinal disease or condition, a renal disease or condition, a disease or condition of the central nervous system (CNS), a disease or condition of the endocrine system, an infection, a metabolic disease or condition, a liver disease or condition, an ocular disease or condition, a skin disease or condition, a lymphatic disease or condition, a psychological disease or condition, graft versus host disease or condition, allodynia, pain, a condition associated with diabetes, a condition associated with arthritis, a wound or burn, or cancer.

17. A compound of Formula (I):



(I)

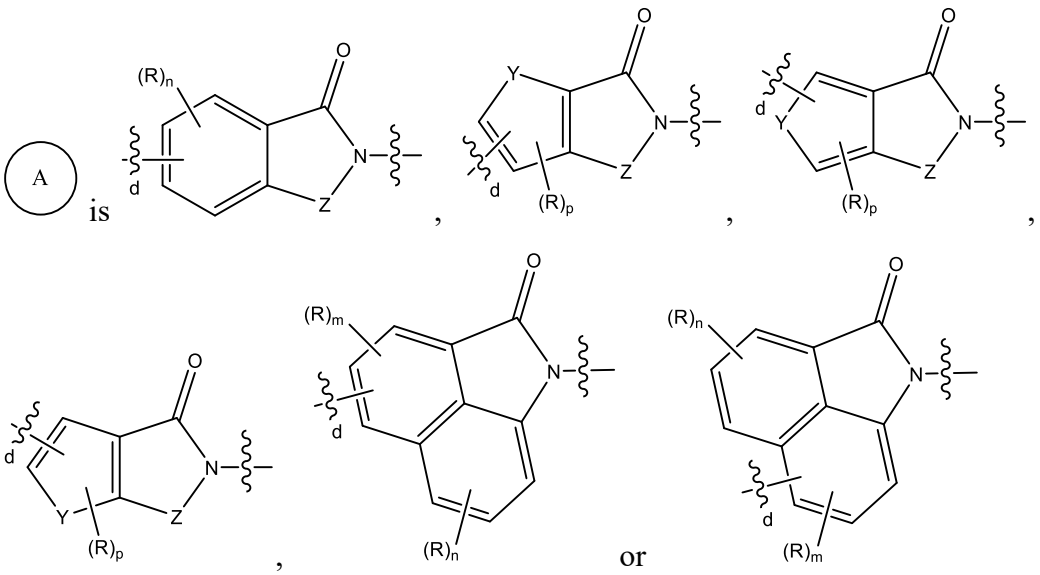
for use in a method of treating a disease or condition in a subject in need thereof,

in which:

y is 0, 1 or 2;

each of X_1 and X_2 is independently O or S;

L is H, -C(O)alkyl, or -CH_2(O)COR';

A is 

in which

each Z is independently C=O, CH_2 or CH(C_{1-2} alkyl);

Y is S, O or NH;

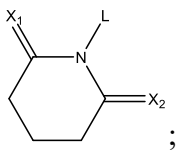
each R is independently halogen, alkyl, haloalkyl, hydroxy, alkoxy, -NH_2, -NHR' or -NR'$_2$;

each R' is independently alkyl or aryl

each n is independently 0, 1, 2 or 3;

m is 0, 1 or 2;

p is 0 or 1;

denotes the point of attachment to ;

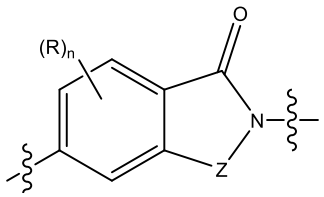
d denotes the point of attachment to D; and

D is a heterocyclic group selected from

(i) B, in which B is a heterocycloalkyl group, or

(ii) C, in which C is a 6-membered monocyclic heteroaryl group or a 10-membered fused bicyclic heteroaryl group which is either unsubstituted or is substituted with one or more R^3, in which no substituents other than the one or more R^3 are present on C; and in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, cycloalkyl, hydroxy, OR^1, aryl, benzyl, $-C(O)R^1$, or $-NR^2C(O)R^1$, in which each R^1 is independently unsubstituted alkyl, cycloalkyl, or aryl and each R^2 is independently H, unsubstituted alkyl, or cycloalkyl;

in which

when A is 

, Z is CH_2 or C=O, n = 0, D is C, C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, and R^3 is hydroxy or O(alkyl), then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group;

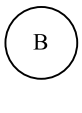
in which the disease or condition is an inflammatory disease or condition, an autoinflammatory disease or conditions, an auto-immune disease or condition, a respiratory disease or condition, a cardiovascular disease or condition, a gastro-intestinal disease or condition, a renal disease or condition, a disease or condition of the central nervous system (CNS), a disease or condition of the endocrine system, a metabolic disease or condition, a liver disease or condition, an ocular disease or condition, a skin disease or condition, a lymphatic disease or condition, a psychological disease or

condition, graft versus host disease or condition, allodynia, pain, a condition associated with diabetes, a condition associated with arthritis, or a wound or burn.

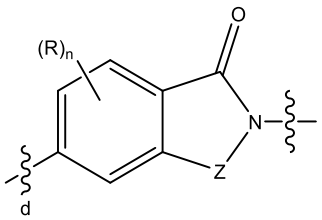
18. A compound for use according to Claim 17, in which the disease or condition is:

(a) an inflammatory disease or condition, an autoinflammatory disease or conditions, an auto-immune disease or condition, a respiratory disease or condition, a cardiovascular disease or condition, a renal disease or condition, a disease or condition of the central nervous system (CNS), a disease or condition of the endocrine system, a metabolic disease or condition, a liver disease or condition, an ocular disease or condition, a lymphatic disease or condition, a psychological disease or condition, graft versus host disease or condition, allodynia, pain, a condition associated with diabetes, a condition associated with arthritis, or a wound or burn; or

(b) cryopyrin-associated periodic syndromes (CAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disease (NOMID), familial Mediterranean fever (FMF), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), Tumour Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS), systemic juvenile idiopathic arthritis, adult-onset Still's disease (AOSD), relapsing polychondritis, Schnitzler's syndrome, Sweet's syndrome, Behcet's disease, anti-synthetase syndrome, deficiency of interleukin 1 receptor antagonist (DIRA), haploinsufficiency of A20 (HA20), lupus nephritis, pulmonary arterial hypertension, idiopathic pulmonary fibrosis, amyotrophic lateral sclerosis, rheumatoid arthritis, gout, Alzheimer's disease, Parkinson's disease, Huntington's diseases, spinal cord injury, atherosclerosis, heart failure, dilated cardiomyopathy (DCM), nonalcoholic steatohepatitis (NASH), liver cirrhosis, inflammatory bowel disease (IBD), ulcerative colitis (UC) or Crohn's disease.

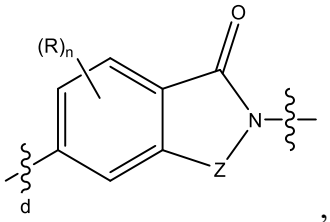
19. A compound for use according to Claim 17 or 18, in which  is a heterocycloalkyl group having a heteroatom adjacent to the point of attachment .

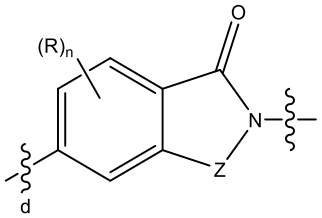
20. A compound for use according to Claim 17, 18 or 19, in which:

(i) when A is  , Z is CH_2, n = 0 and D is C, then

(a) C is substituted with one or more R^3 or

(b) y is 2;

(ii) when A is  , Z is CH_2, n = 0, D is C, and C is a 6-membered monocyclic heteroaryl group having two heteroatoms, the two heteroatoms are not adjacent to each other;

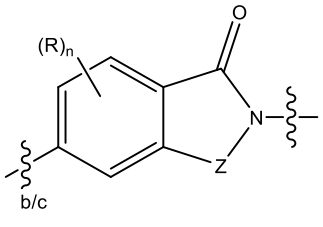
(iii) when A is  , Z is CH_2, n = 0, D is C, and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then:

(a) carbon atoms adjacent to the carbon atom through which C is attached to A are unsubstituted;

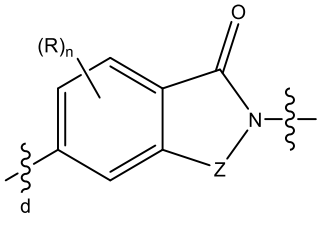
(b) when R^3 is alkyl or O(alkyl), then C is monosubstituted;

(c) when R^3 is O(alkyl), then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group; and

(d) when R^3 is aryl or $-NR^2C(O)R^1$, then the substitution is at a position *meta* to a heteroatom of the heteroaryl group;

(iv) when A is 

, Z is C=O, n = 0, D is C, and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then when R^3 is hydroxy, then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group; and

(v) when A is 

, Z is CH_2, n = 0, D is C, and C is a 10-membered fused bicyclic heteroaryl group substituted with one or more R^3, then:

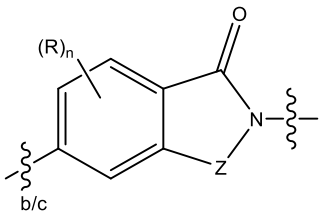
each R^3 is present on the ring which contains the point of attachment to A, each R^3 is positioned *ortho* or *meta* to a heteroatom of the heteroaryl group;

R^3 is not Cl, methyl, iPr, cyclopropane, unsubstituted phenyl, hydroxy or OMe;

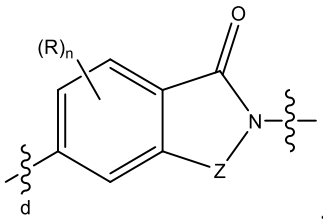
when R^3 is OEt, then R^3 is positioned *ortho* to the heteroatom of the heteroaryl group; and

when R^3 is NR^2COMe, then R^3 is positioned *meta* to the heteroatom of the heteroaryl group.

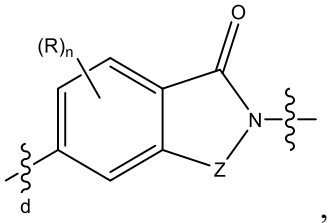
21. A compound for use according to Claim 20, in which:

(a) when A is 

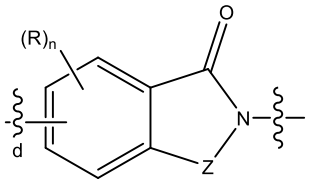
, Z is C=O or CH_2, n = 0, D is C, and C is a 6-membered monocyclic heteroaryl group substituted with one or more R^3, then when R^3 is hydroxy or O(alkyl), then the substitution is at a position *meta* or *para* to a heteroatom of the heteroaryl group;

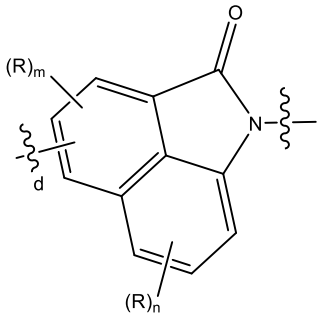
(b) when A is 

, n = 0 and D is C, then Z is $CH(C_{1\text{-}2}$ alkyl) or C=O, and

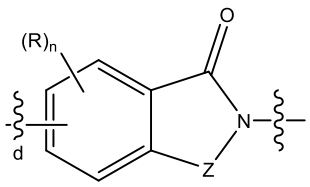
(c) when A is 

, Z is CH_2 and D is C, then n is 1, 2, or 3.

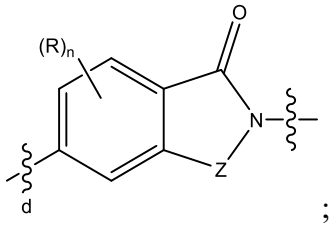
22. A compound for use according to any of Claims 17 to 21, in which A is 

or 

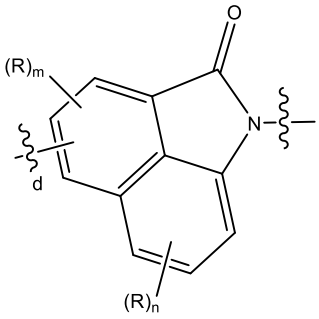
; optionally in which

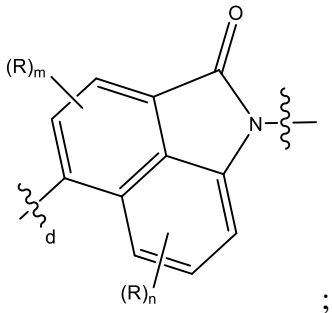
(a) A is 

; optionally



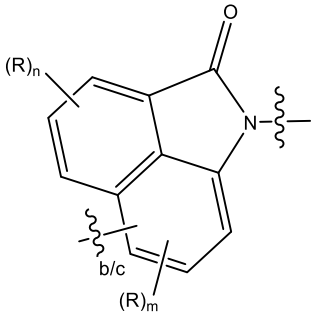
;

(b) A is  ; optionally

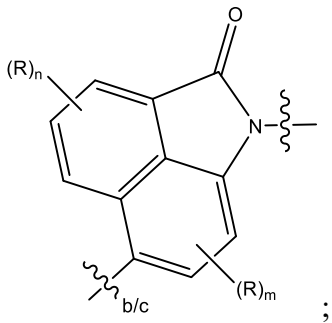


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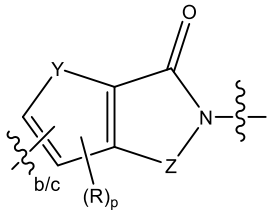
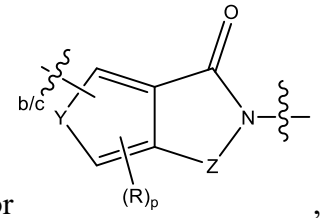
(c) A is

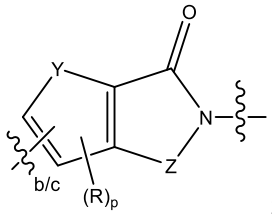
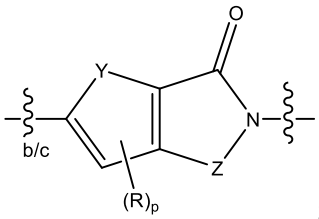


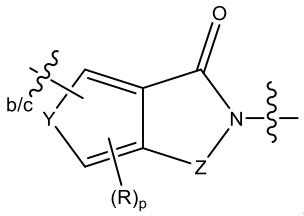
; optionally

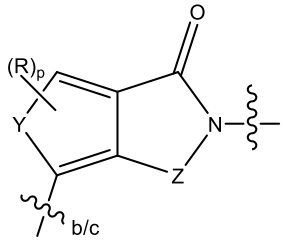


;

(d) A is  or , optionally in which

(i) A is ; optionally ; or

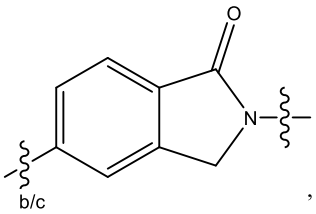
(ii) A is ; or

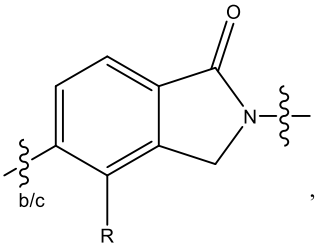
(e) A is 

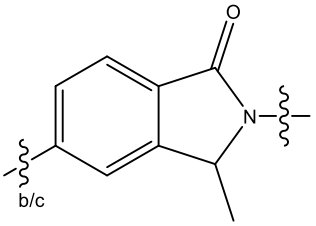
23. A compound for use according to any of Claims 17 to 22, in which D contains (a) one heteroatom, or (b) two heteroatoms.

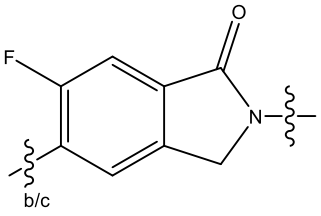
24. A compound for use according to any of Claims 17 to 23, in which D is B, in which B is a heterocycloalkyl group, optionally in which B is a 5-10 membered heterocycloalkyl group, further optionally in which B is a 5- or 6-membered heterocycloalkyl group.

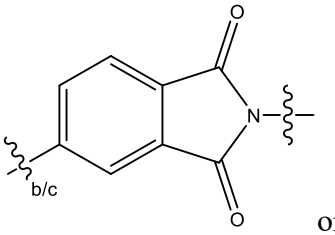
25. A compound for use according to any of Claims 17 to 24, in which A is

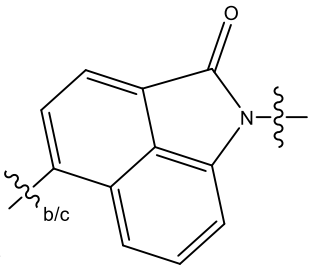


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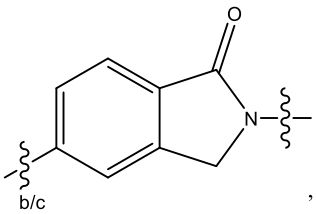
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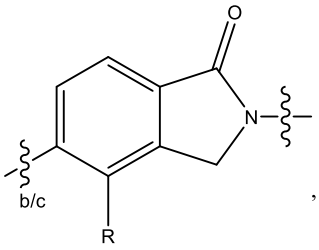


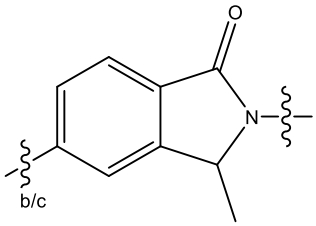
,


or


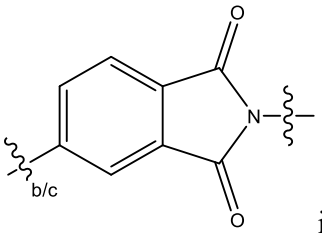
in which R is F or alkyl, optionally in which A is



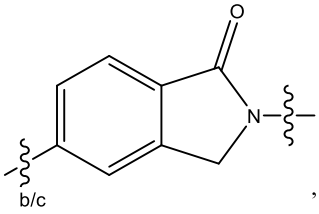
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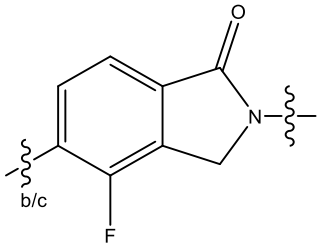
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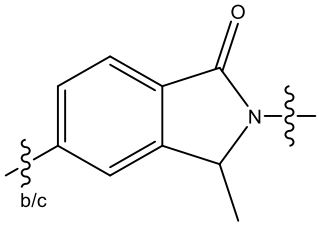
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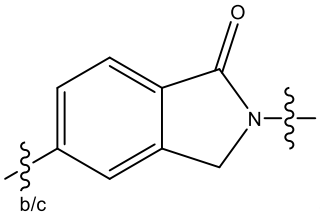
or in which R is F, further optionally in which A is

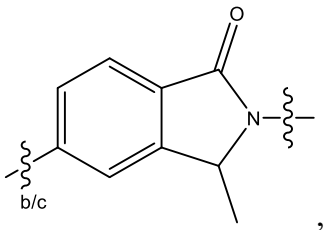


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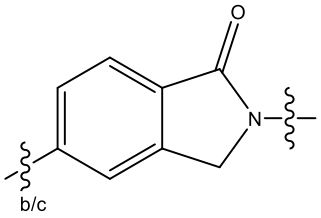
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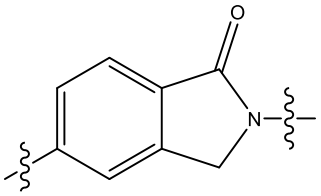
optionally 

or 

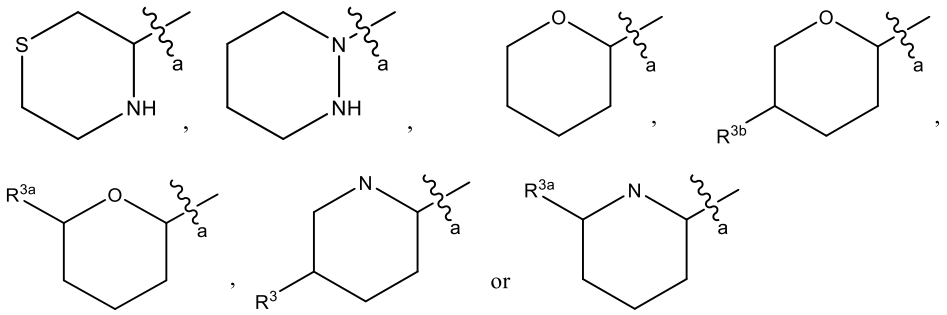
, further optionally



.

26. A compound for use according to Claim 25, in which (A) is 

, and (B) is:



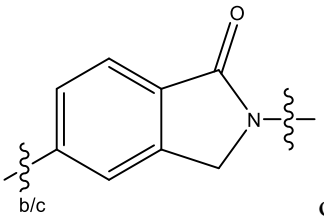
or

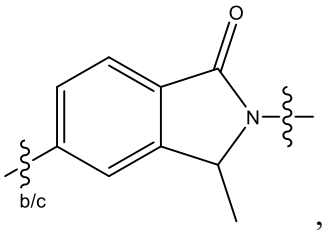
in which

R^3 is unsubstituted alkyl, benzyl, -NHC(O)Ph or -NHC(O)Me,

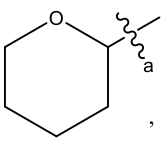
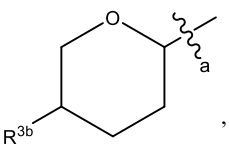
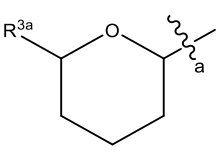
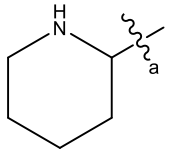
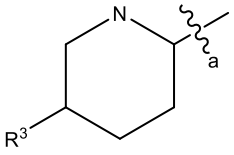
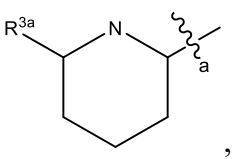
R^{3a} is unsubstituted alkyl, and

R^{3b} is aryl;

or in which (A) is 

or 

, and in which (B) is

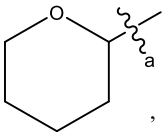
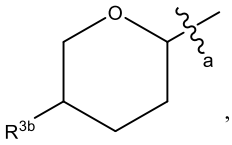
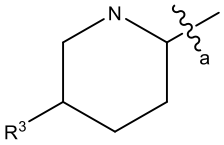
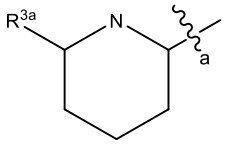
or , in which

R^3 is unsubstituted alkyl, aryl, benzyl or -NHC(O)Ph,

R^{3a} is unsubstituted alkyl, and

R^{3b} is aryl or unsubstituted alkyl;

optionally in which  is




or


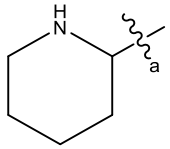
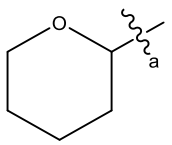
in which

R^3 is unsubstituted alkyl, benzyl or -NHC(O)Ph,

R^{3a} is unsubstituted alkyl, and

R^{3b} is aryl.

27. A compound for use according to Claim 26, in which  is

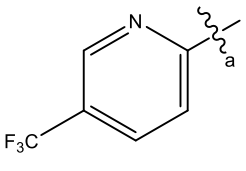
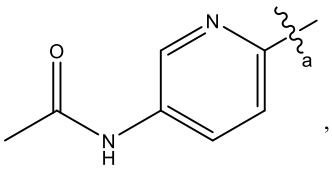
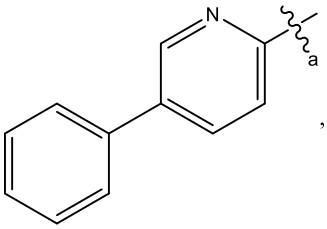

or

.

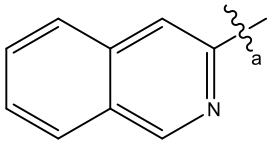
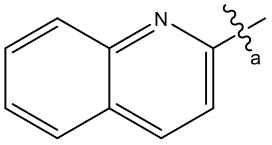
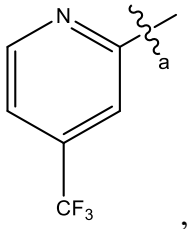
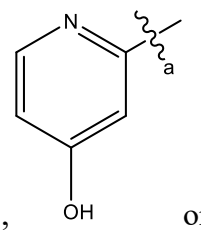
28. A compound for use according to any of Claims 17 to 23 and 25, in which  is

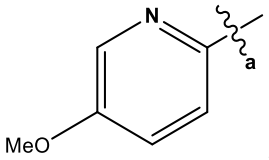

, in which  is a 6-membered monocyclic heteroaryl group or a 10-membered fused bicyclic heteroaryl group which is either unsubstituted or is substituted with one or more R^3,

in which no substituents other than the one or more R^3 are present on ; and in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, cycloalkyl, hydroxy, OR^1, aryl, benzyl, $-C(O)R^1$, or $-NR^2C(O)R^1$, in which each R^1 is independently unsubstituted alkyl, cycloalkyl, or aryl and each R^2 is independently H, unsubstituted alkyl, or cycloalkyl.

29. A compound for use according to Claim 28, in which  is

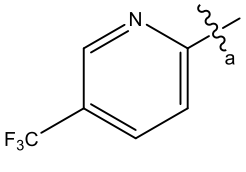
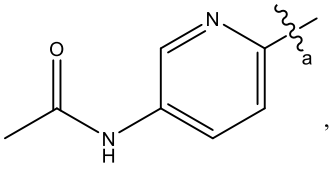
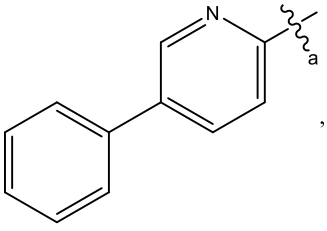
, , ,

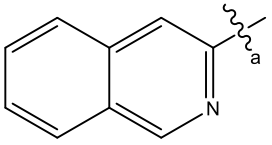
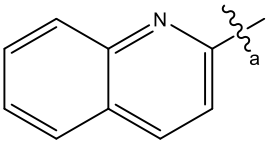
, , ,  or

;

optionally in which  is

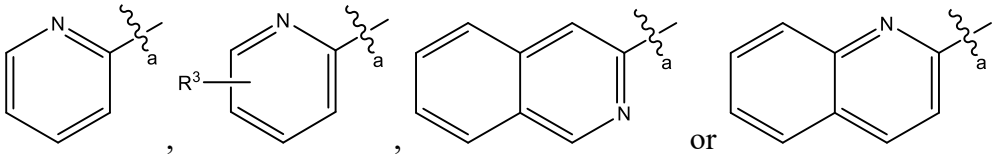
(a)

, , ,

 or 

or

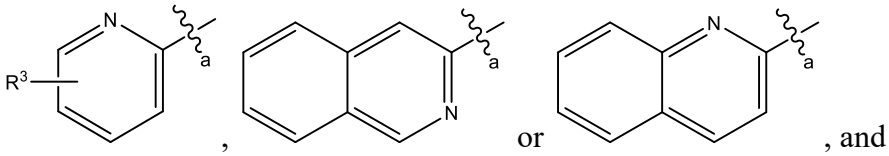
(b)



in which  denotes the point of attachment to , and

in which R^3 is aryl, haloalkyl or $-NR^2C(O)R^1$;

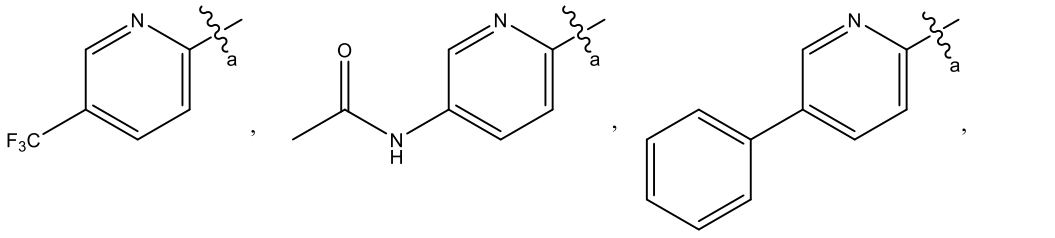
optionally in which  is



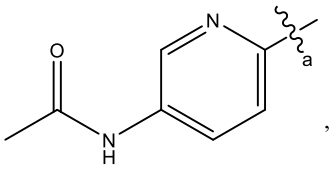
in which R^3 is aryl or $-NR^2C(O)R^1$;

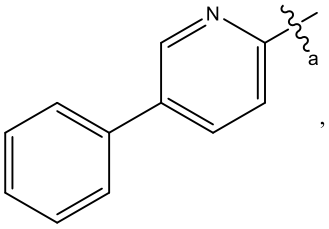
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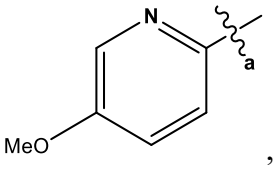
(c)

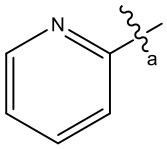


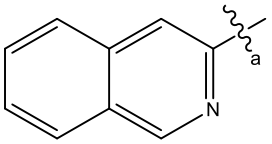
optionally in which  is

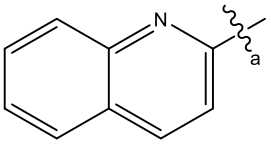


,


,


,


,


or


.

30. A compound for use according to any of Claims 1 to 12, or a compound for use according to any of Claims 15 to 29, in which L is hydrogen.

31. A compound or compound for use according to any preceding claim, in which:

(a) X_1 and X_2 are O;

(b) X_1 is O and X_2 is S;

(c) X_1 is S and X_2 is O; or

(d) X_1 and X_2 are S.

32. A compound or compound for use according to any preceding claim, in which Y is S.

33. A compound or compound for use according to any preceding claim, in which Z is C=O, CH_2 or CHMe; optionally in which Z is CH2 or CH(C1-2 alkyl); further optionally in which Z is CH_2 or CHMe; still further optionally in which Z is CH_2.

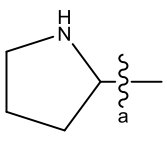
34. A compound or compound for use according to any preceding claim, in which 

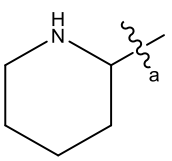
is:

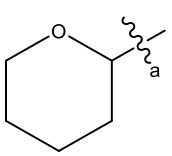
(a) a pyrrolidine, piperidine, or oxane group;

optionally in which 

is

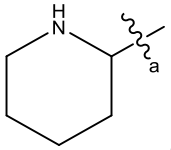


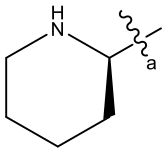
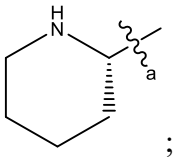
,


or


,

in which  denotes the point of attachment to ;

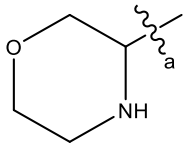
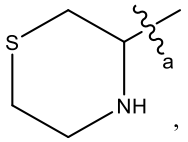
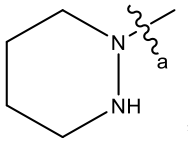
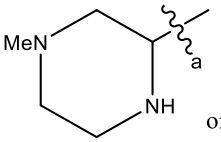
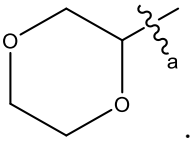
optionally in which  is , further optionally in which  is

 or ;

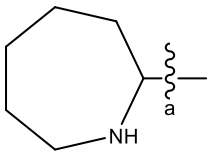
or

(b) a dioxane, diazinane, morpholine or thiomorpholine; optionally in which the dioxane is a 1,4-dioxane and the diazinane is a 1,2-diazinane or a 1,4-diazinane.

further optionally in which  is

, , ,  or ;

or

(c) an azepane, optionally .

35. A compound or compound for use according to any preceding claim, in which  is:

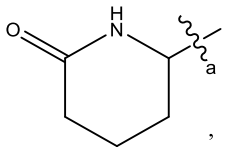
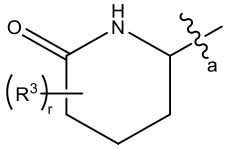
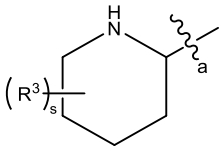
(a) unsubstituted; or

(b) substituted with one or more R^3, in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, cycloalkyl, hydroxy, OR^1, aryl, benzyl, $-C(O)R^1$, or $-NR^2C(O)R^1$, in which each R^1 is independently unsubstituted alkyl, cycloalkyl or aryl and each R^2 is independently H, unsubstituted alkyl or cycloalkyl; or in which two R^3 on adjacent atoms of the heterocycloalkyl group, together with the atoms to which they are attached, form an aromatic ring; or in which two R^3 on the same carbon atom of the

heterocycloalkyl group, together with the carbon atom to which they are attached, form a C=O group;

optionally in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, aryl, benzyl or -NHC(O)R^1; or in which two R^3 on the same carbon atom of the heterocycloalkyl group, together with the carbon atom to which they are attached, form a C=O group.

36. A compound or compound for use according to Claim 35, in which is

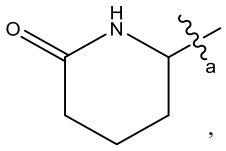
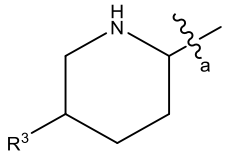
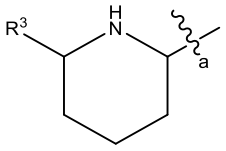

, 
or 

in which  denotes the point of attachment to ,

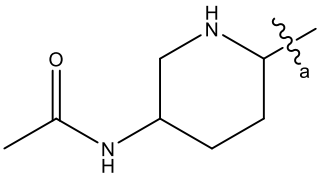
r is an integer from 1-7, optionally from 1-3, and

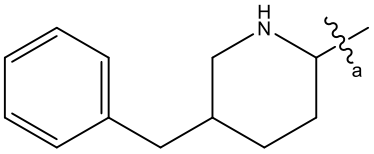
s is an integer from 1-9, optionally from 1-4;

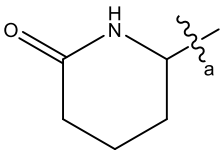
optionally in which  is

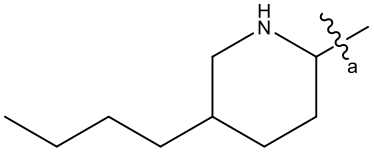

, 
or 
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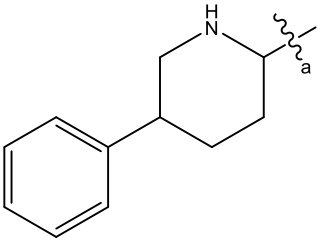
further optionally in which  is

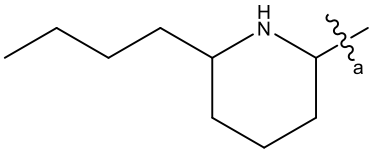


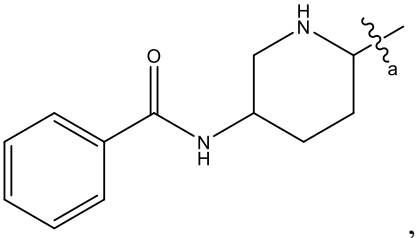
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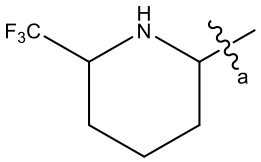
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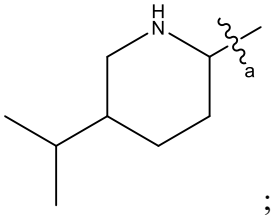
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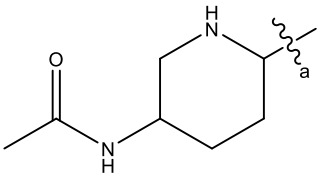
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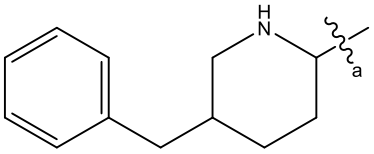
or


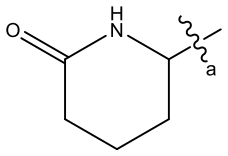
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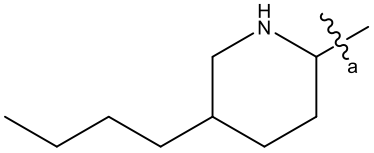
optionally in which 

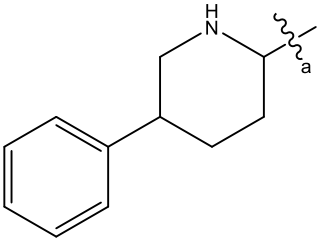
is

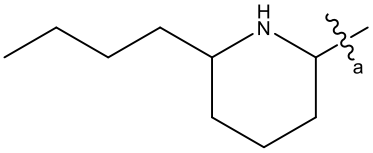


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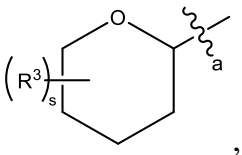
,


,


,


or


in which  denotes the point of attachment to .

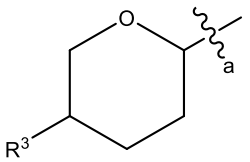
or (b) 

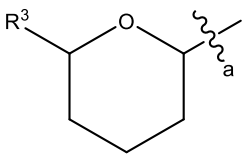
,

in which  denotes the point of attachment to , and

s is an integer from 1-9, optionally from 1-4;

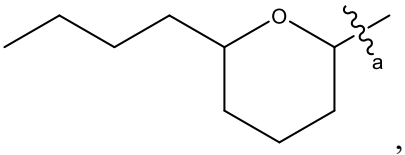
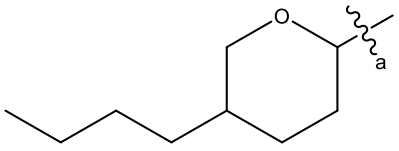
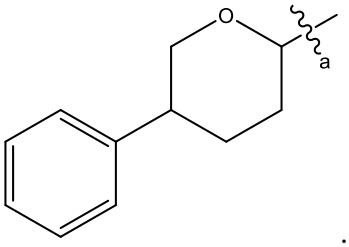
optionally in which  is



or


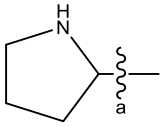
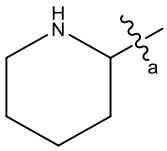
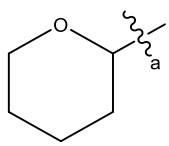
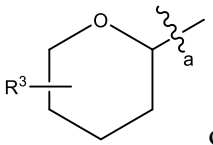
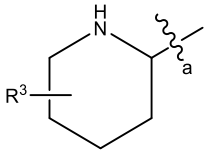
.

further optionally in which  is



or

.

37. A compound or compound for use according to any of Claims 1 to 34, in which  is

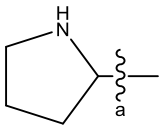
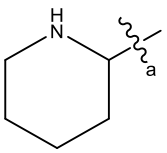
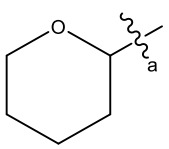
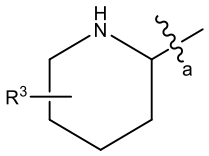
(a)


,

,


or


in which  denotes the point of attachment to ,

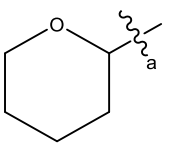
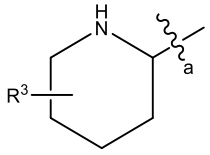
and in which R^3 is unsubstituted alkyl, haloalkyl, aryl, benzyl, or $-NR^2C(O)R^1$;

optionally in which  is


,

,

or


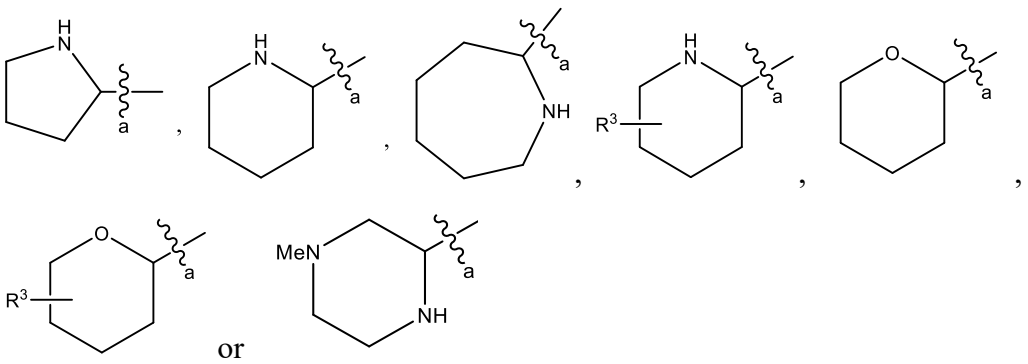
in which R^3 is unsubstituted alkyl, aryl, benzyl, or $-NR^2C(O)R^1$;.

further optionally in which  is:


or


and in which R^3 is unsubstituted alkyl, benzyl, or $-NR^2C(O)R^1$, optionally in which R^3 is unsubstituted alkyl or benzyl; or

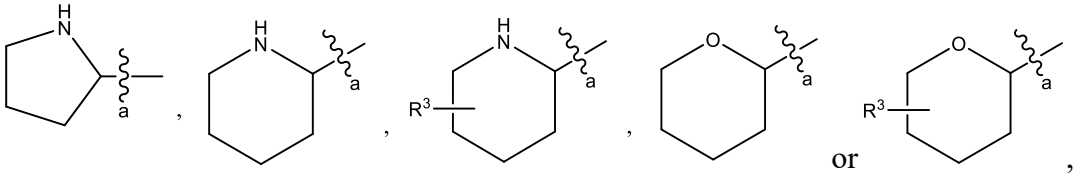
(b)



or

in which R^3 is unsubstituted alkyl, aryl, benzyl, -NHC(O)Me or -NHC(O)Ph;

optionally in which  is

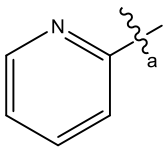


in which R^3 is unsubstituted alkyl, aryl, -NHC(O)Me or -NHC(O)Ph.

38. A compound or compound for use according to any preceding claim, in which:

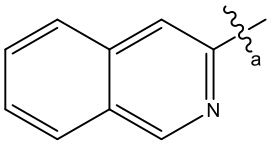
(a)  is a 6-membered monocyclic heteroaryl group, optionally a pyridine group,

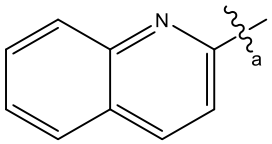
further optionally in which  is



in which  denotes the point of attachment to ; or

(b) C is a 10-membered fused bicyclic heteroaryl group, optionally a quinoline or isoquinoline group, further optionally in which C is



or


in which a denotes the point of attachment to A.

39. A compound or compound for use according to any preceding claim, in which C is

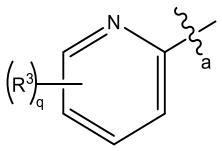
(a) unsubstituted; or

(b) substituted with one or more R^3, in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, cycloalkyl, hydroxy, OR^1, aryl, benzyl, $-C(O)R^1$, or $-NR^2C(O)R^1$, in which each R^1 is independently unsubstituted alkyl, cycloalkyl or aryl and each R^2 is independently H, unsubstituted alkyl or cycloalkyl;

optionally in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, hydroxy, OR^1, aryl, benzyl or $-NHC(O)R^1$; further optionally in which each R^3 is independently halogen, unsubstituted alkyl, haloalkyl, aryl, benzyl or $-NHC(O)R^1$.

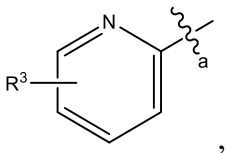
40. A compound or compound for use according to any preceding claim, in which each R^1 is independently unsubstituted alkyl or aryl and each R^2 is independently H or unsubstituted alkyl.

41. A compound or compound for use according to Claim 39 or 40, in which C is



in which a denotes the point of attachment to A, and q is an integer from 1-4, optionally from 1-3;

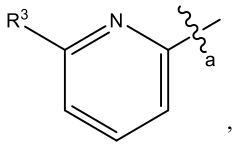
optionally in which  is



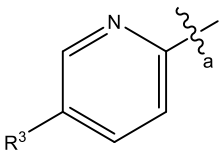
,

in which R^3 is aryl, haloalkyl, hydroxy, OR^1 or $-NR^2C(O)R^1$;

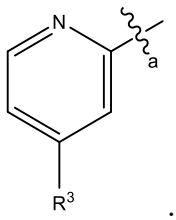
further optionally in which  is



,



or



.

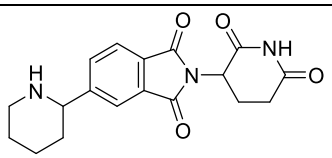
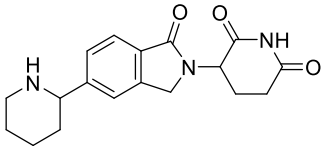
42. A compound or compound for use according to Claim 41, in which R^3 is aryl, haloalkyl or $-NR^2C(O)R^1$; optionally in which R^3 is (a) aryl or $-NR^2C(O)R^1$, or (b) aryl or haloalkyl.

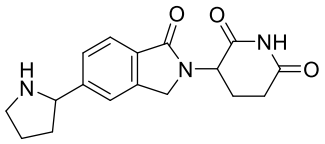
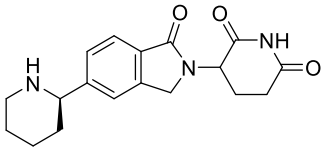
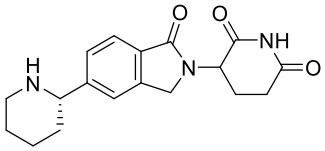
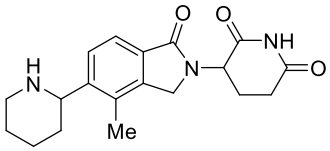
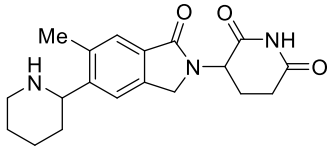
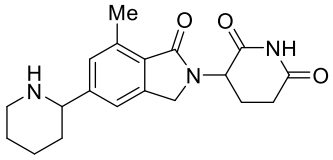
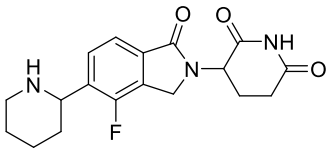
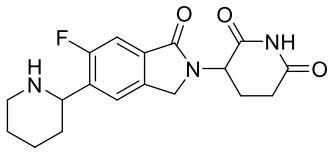
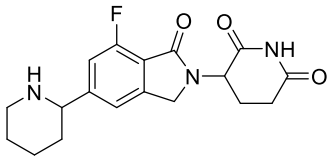
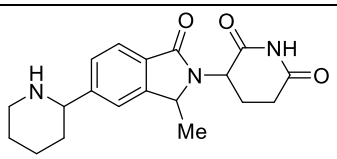
43. A compound or compound for use according to any preceding claim, in which each R is independently unsubstituted alkyl or halogen, optionally Me or F.

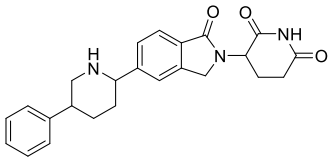
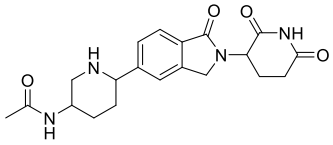
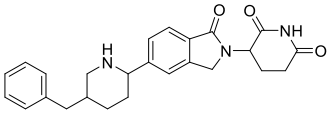
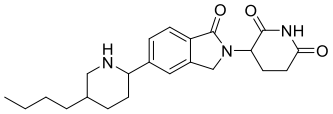
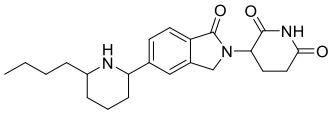
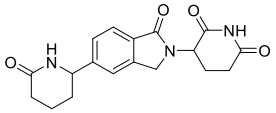
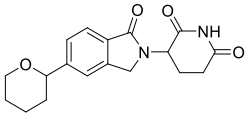
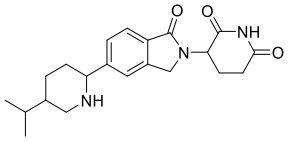
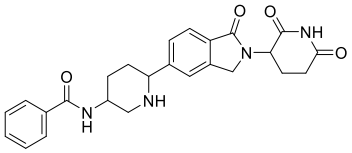
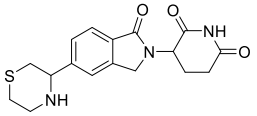
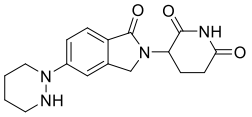
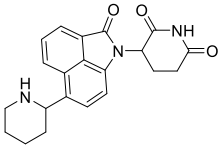
44. A compound or compound for use according to any preceding claim, in which n is 0 or 1 and/or in which m is 0.

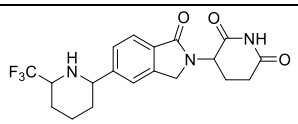
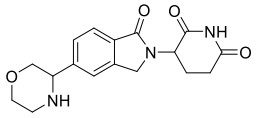
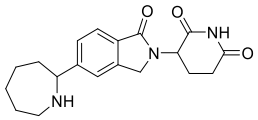
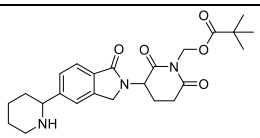
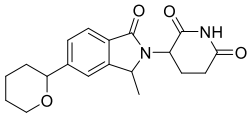
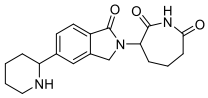
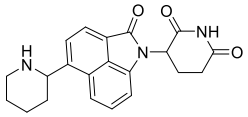
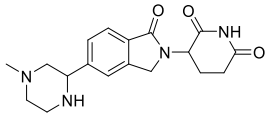
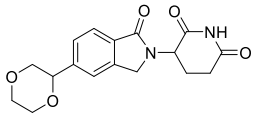
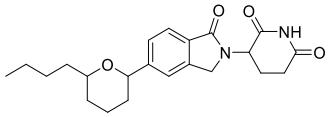
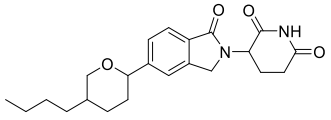
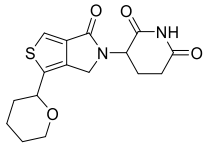
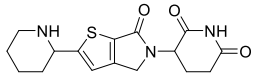
45. A compound or compound for use according to any preceding claim, in which y = 1.

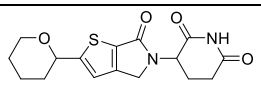
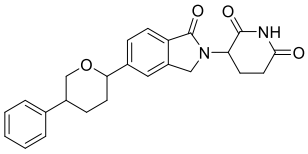
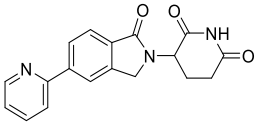
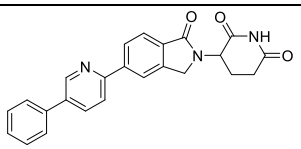
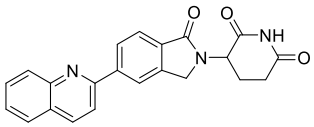
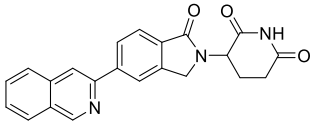
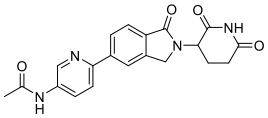
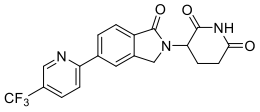
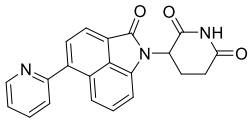
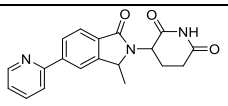
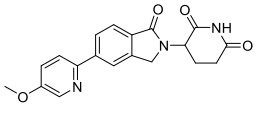
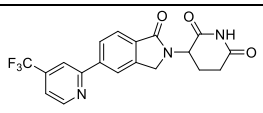
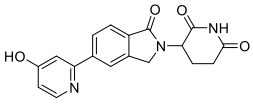
46. A compound or compound for use according to Claim 17, in which the compound is selected from:

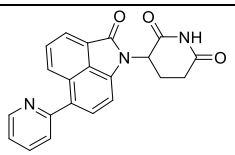
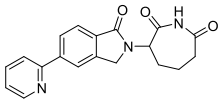
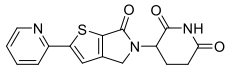
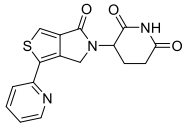
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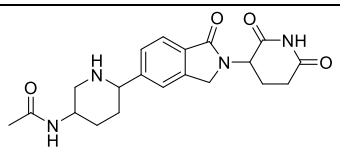
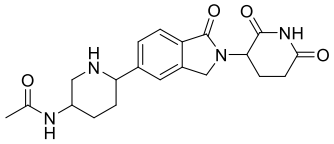
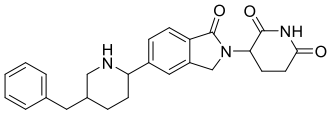
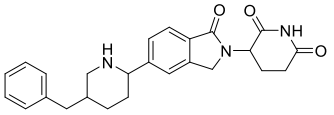
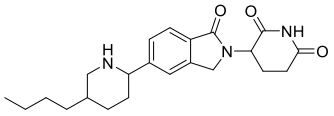
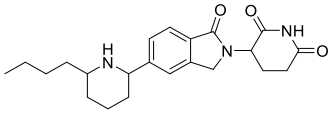
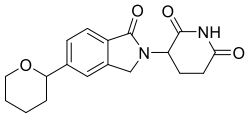
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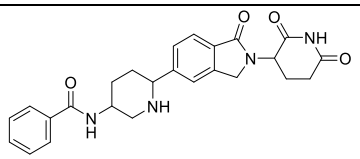
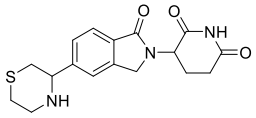
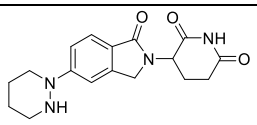
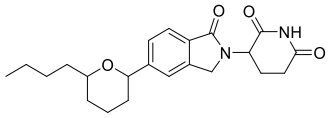
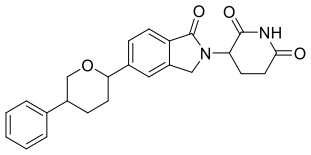
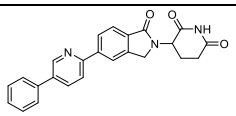
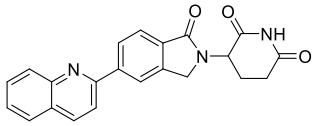
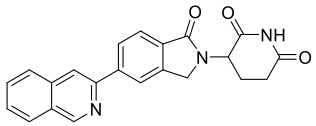
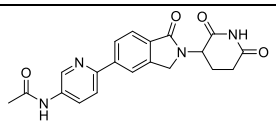
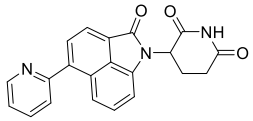
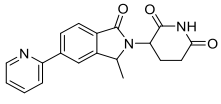
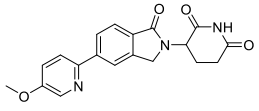
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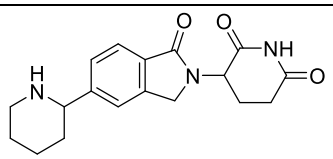
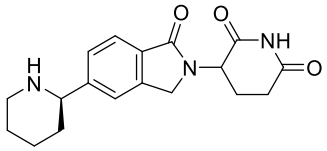
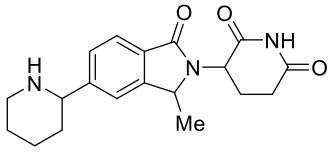
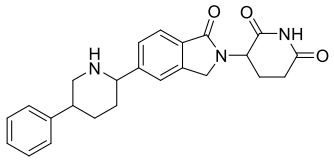
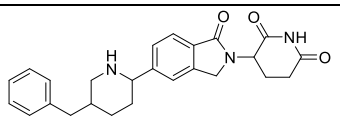
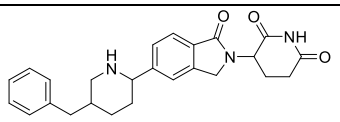
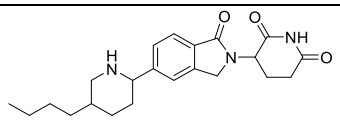
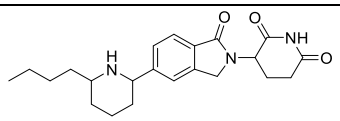
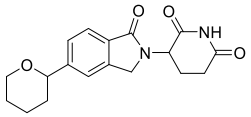
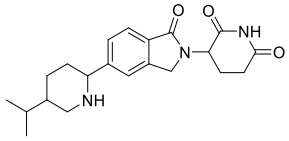
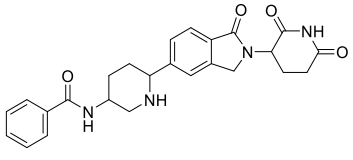
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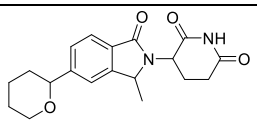
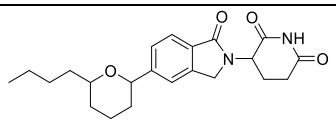
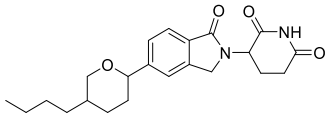
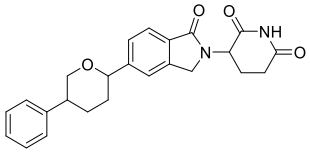
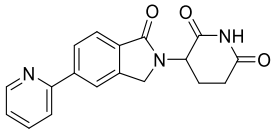
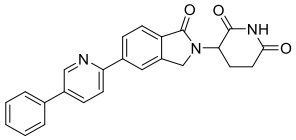
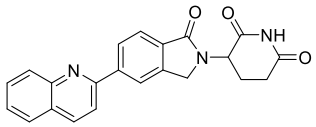
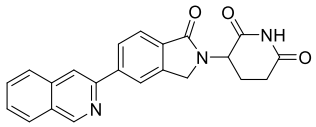
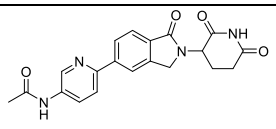
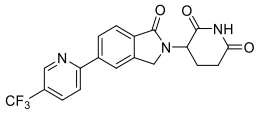
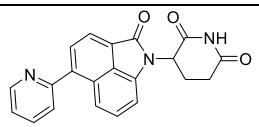
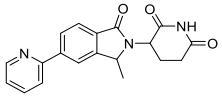
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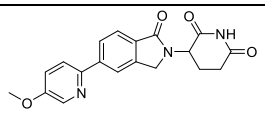
Compound number	Structure
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69 Isomer 2	 Isomer 2
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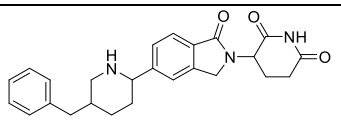
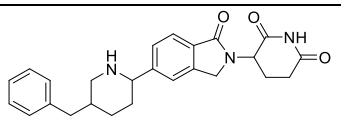
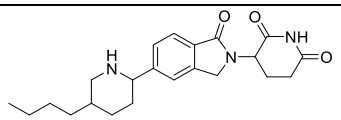
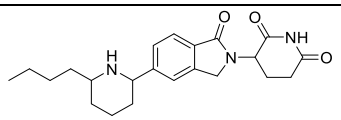
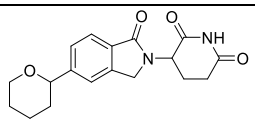
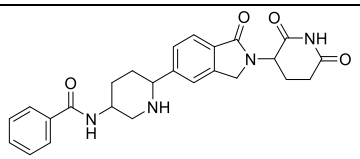
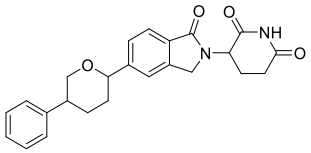
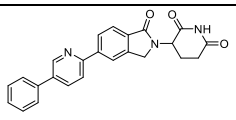
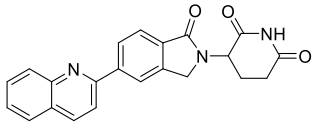
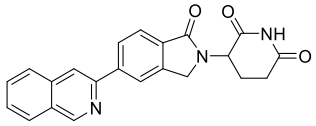
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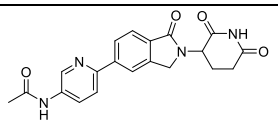
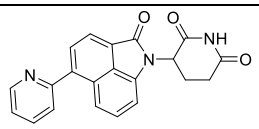
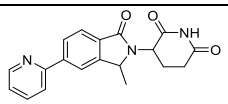
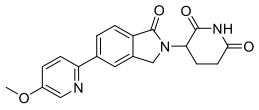
Compound number	Structure
2	
9	
25	
32 Isomer 2	 Isomer 2
35 Isomer 1	 Isomer 1
35 Isomer 2	 Isomer 2
37	
40	
54	
55 Isomer 2	 Isomer 2
56	

64	
69 Isomer 1	 Isomer 1
70 Isomer 2	 Isomer 2
74 Isomer 2	 Isomer 2
2(2)	
4(2)	
5(2)	
6(2)	
7(2)	
16(2)	
23(2)	
24(2)	

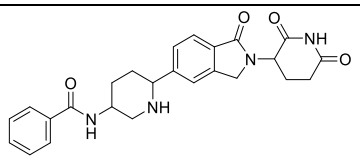
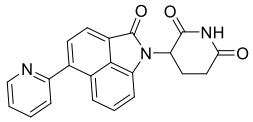
25(2)	

or in which the compound is selected from:

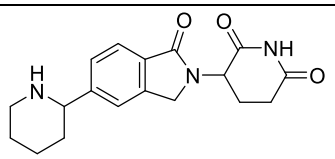
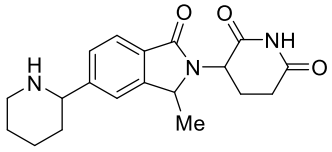
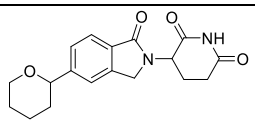
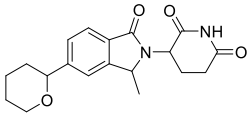
Compound number	Structure
35 Isomer 1	 Isomer 1
35 Isomer 2	 Isomer 2
37	
40	
54	
56	
74 Isomer 2	 Isomer 2
4(2)	
5(2)	
6(2)	

7(2)	
23(2)	
24(2)	
25(2)	

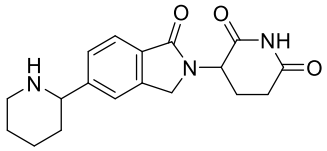
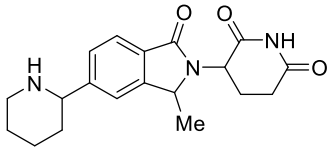
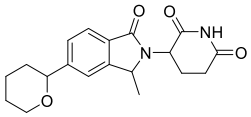
or is selected from:

Compound number	Structure
56	
23(2)	

or is selected from:

2	
25	
54	
64	

optionally selected from:

2	
25	
64	

47. A compound or compound for use according to any of Claims 17 to 46, in which the compound is formulated in a pharmaceutical composition.