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(54) Title: VIRAL POLYMERASE INHIBITORS

(57) Abstract: The present invention relates to viral polymerase inhibitors, in particular inhibitors of viral polymerases within the *Flaviviridae family* such as hepatitis C virus (HCV), processes for their preparation and their use in the treatment of infections.

VIRAL POLYMERASE INHIBITORS

FIELD

The present invention relates to viral polymerase inhibitors, in particular inhibitors of viral polymerases within the *Flaviviridae* family such as hepatitis C virus (HCV), processes for their preparation and their use in the treatment of infections.

BACKGROUND

The Flaviviridae is a group of positive single-stranded RNA viruses with a genome size from 9-15 kb. The Flaviviridae consists of various genera including:

1. Hepaciviruses: This genus contains only one species, the Hepatitis C virus (HCV), which is composed of many genotypes and subtypes.

2. Flaviviruses: This genus includes the Dengue virus, Japanese Tick-Borne and the Yellow Fever virus. Apart from these major groups, there are some additional Flaviviruses that are unclassified.

3. Pestiviruses: This genus includes three serotypes of bovine viral diarrhoea virus, but no known human pathogens.

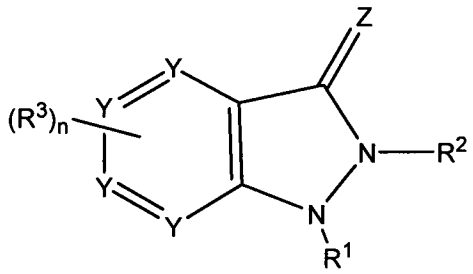
Hepatitis C virus (HCV), a major cause of viral hepatitis, has infected more than 200 million people worldwide. There is no vaccine to prevent HCV infection. Current approved treatment for HCV infection is restricted to immunotherapy with interferon-α alone or in combination with ribavirin, a nucleoside analog. This treatment has been reported to achieve a sustained response in fewer than 50% of cases and thus there is a

real need to find an alternative agent for the treatment of HCV infection.

SUMMARY

The present invention relates to compounds which are viral polymerase inhibitors , in particular inhibitors of viral polymerases within the *Flaviviridae* family such as HCV .

In a first aspect, there is provided a compound of formula I



I

in which

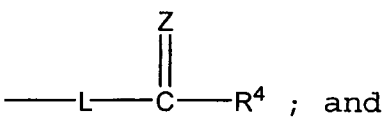
Y is independently selected from the group consisting of N, NO and CR in which R is selected from the group consisting of H, halogen, SH, S-optionally substituted C_{1-6}alkyl , OH, optionally substituted C_{1-6}alkoxy , NH_2, NH-optionally substituted C_{1-6}alkyl, N-di-optionally substituted C_{1-6}alkyl and NHCOR' in which R' is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

Z is selected from the group consisting of O, S and NR'' in which R'' is selected from the group consisting of H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

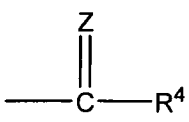
R^1 is selected from the group consisting of optionally substituted C_{2-6}alkyl, C_{1-6}alkylene optionally substituted C_{3-8}cycloalkyl, C_{1-6}alkylene optionally substituted aryl, C_{1-6}alkylene optionally substituted heterocyclyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

R^2 is -L-R"' in which L is absent or a linker and R"' is selected from the group consisting of optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

R^3 is selected from the group consisting of C_{2-6}alkyl; substituted C_{1-6}alkyl; halo; CN; optionally substituted aryl; optionally substituted heterocyclyl; NO_2; $NR^{12}R^{13}$ in which R^{12} and R^{13} are independently selected from the group consisting of H provided that not both are H, optionally substituted C_{1-6}alkyl, $S(O)_pR^{14}$ in which p is 0 to 2 and R^{14} is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl and COR^{25} in which R^{25} is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $S(O)_pR^{14}$ in which p and R^{14} are as defined above;



; and



in which
Z and L are as defined above;
R^4 is selected from the group consisting of amino acid; optionally substituted C_{3-8}cycloalkyl; optionally substituted aryl; optionally substituted heterocyclyl; OR^7 in which R^7 is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl; and NR^5R^6;
in which R^5 and R^6 are independently selected from the group consisting of H; optionally substituted C_{1-6}alkyl; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; optionally substituted $(CH_2)_m$ optionally substituted aryl; optionally substituted$(CH_2)_m$ optionally substituted heterocyclyl in which m is 0 to 4; $S(O)_pR^8$ in which p is as defined above and R^8 is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are as defined above; $CR^{17}R^{18}COR^{19}$ in which R^{17} and R^{18} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl or R^{17} and R^{18} together with the C to which they are attached form an optionally substituted 3 to 6-membered ring and R^{19} is selected from the group consisting of OR^{15}in which R^{15} is as defined above and $NR^{20}R^{21}$ in which R^{20} and R^{21} are selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted aryl and optionally substituted heterocyclyl; and $CR^{22}(CO_2R^{23})CH_2R^{24}$ in which R^{22} and R^{23} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl and R^{24} is selected from the group consisting of, optionally substituted aryl and optionally substituted heterocyclyl; or
R^5 and R^6 together with the N to which they are attached

form an optionally substituted 5 or 6-membered ring; and n is 0 to 4,

salts, solvates, derivatives, prodrugs, tautomers and/or isomers thereof.

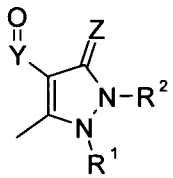
In a second aspect there is provided a process for the preparation of the compound of formula I defined above which comprises the steps of:

(a) substitution of a compound of formula II



II

in which R^1, R^2, and Z are as defined above to form a compound of formula III



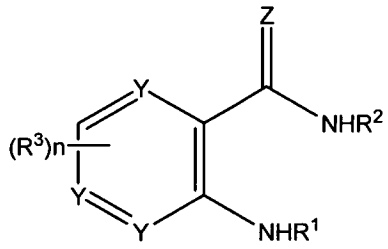
III

in which R^1, R^2, Y and Z are as defined above, provided that Y is not NO; and

(b) cycloaddition of the compound of formula III defined above followed by introduction of R^3 in which R^3 is as defined above.

In a third aspect there is provided a process for the preparation of the compound of formula I defined above which comprises the steps of:

(a) cyclisation of a compound of formula IV



IV

in which R^1, R^2, R^3, Y and Z are as defined above.

The compounds of formula I are inhibitors of hepatitis C. In particular, the compounds of formula I inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV (the NS5B protein encoded by HCV). NS5B inhibitors have been clinically validated as potential antiviral agents for the treatment of HCV infection.

In a fourth aspect, there is provided a HCV polymerase inhibitor such as a NS5B inhibitor comprising the compound of formula I defined above.

There is also provided use of the compound of formula I as a HCV polymerase inhibitor such as a NS5B inhibitor.

There is further provided the compound of formula I defined above for use as a HCV polymerase inhibitor such as a NS5B inhibitor.

In a fifth aspect, there is provided an antiviral agent comprising the compound formula I defined above.

There is also provided use of the compound of formula I defined above as an antiviral agent.

There is further provided the compound of formula I defined above for use as an antiviral agent.

The compound of formula I may be administered in the form of a pharmaceutical composition together with a pharmaceutically acceptable carrier.

In a sixth aspect, there is provided a pharmaceutical composition comprising the compound of formula I defined above and a pharmaceutically acceptable carrier.

According to one embodiment, the pharmaceutical composition additionally comprises a therapeutically effective amount of one or more antiviral agents such as

at least one other anti-HCV agent.

In a seventh aspect, there is provided a method for the treatment of a *Flaviviridae* viral infection such as a HCV infection which comprises administering an effective amount of the compound of formula I defined above to a subject in need thereof.

There is also provided use of the compound of formula I as defined above in the manufacture of a medicament for use in the treatment of a *Flaviviridae* viral infection such as a HCV infection.

There is further provided use of the compound of formula I as defined above in the treatment of a *Flaviviridae* viral infection such as a HCV infection.

There is still further provided the compound of the formula I defined above for use in the treatment of a *Flaviviridae* viral infection such as a HCV infection.

In an eighth aspect, there is provided a method of inhibiting the RNA-dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV, comprising exposing the enzyme NS5B to an effective amount of the compound of formula I defined above under conditions where the RNA-dependent RNA polymerase activity of the enzyme NS5B is inhibited.

In a ninth aspect, there is provided a method of inhibiting HCV replication, comprising exposing a cell infected with HCV to an effective amount of the compound of formula I defined above under conditions where replication of HCV is inhibited.

DETAILED DESCRIPTION

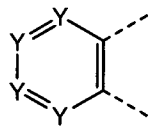
The present invention relates to compounds of formula I which inhibit viral polymerases and are useful in the treatment of *Flaviviridae* viral infections such as hepatitis C.

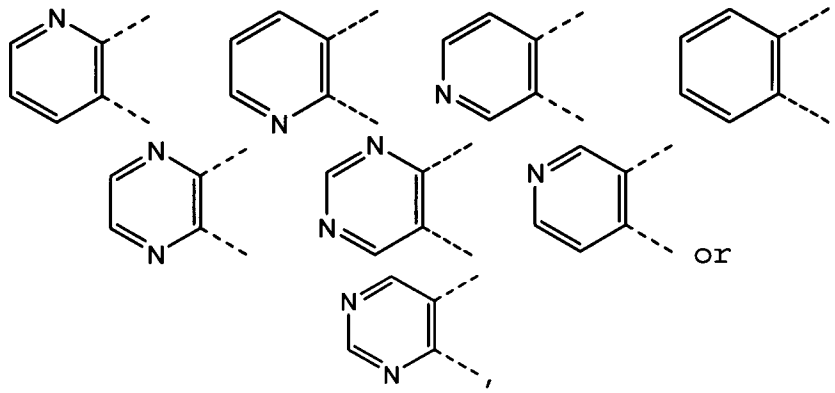
Compounds

The present invention relates to compounds of formula

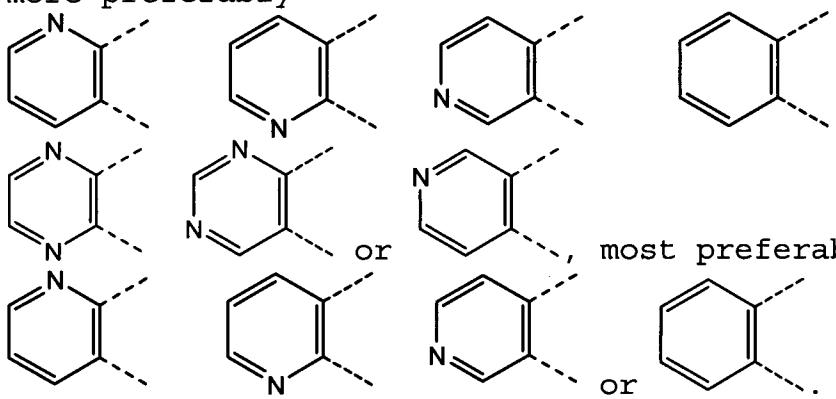
I, salts, solvates, derivatives, prodrugs, tautomers and/or isomers thereof as defined above.

In the compound of formula I, preferably each Y is CH or one or two of Y is N and the others are CH and n is 1 to 4, more preferably n is 1.

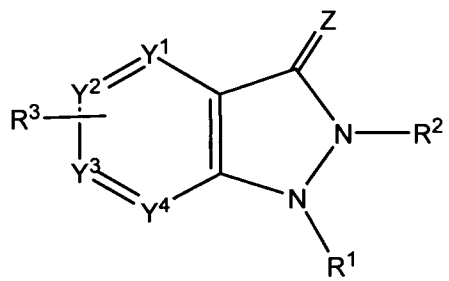
Preferred embodiments of  are as follows:



more preferably



In one embodiment, compounds of formula I have the formula Ia



Ia

in which

Z, R^1, R^2 and R^3 are as defined above;

Y^1 is CH;

Y^2 is CH; and

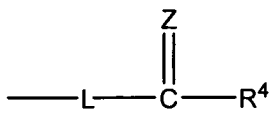
Y^3 and Y^4 are independently selected from the group consisting of N and CH.

R^1 is preferably optionally substituted C_{3-8} cycloalkyl such as cyclohexyl, optionally substituted aryl such as phenyl or optionally substituted heterocyclyl.

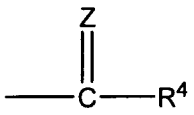
Preferably L is absent optionally substituted C_{1-6}alkylene or optionally substituted C_{1-6}acyl in R^2.

R^3 is preferably located at any one or more of positions 4, 5 or 6, preferably the 5 position.

Preferably R^3 is selected from the group consisting of C_{2-6}alkyl; substituted C_{1-6}alkyl; CN; optionally substituted aryl; optionally substituted heterocyclyl; $NR^{12}R^{13}$ in which R^{12} and R^{13} are independently selected from the group consisting of H provided that not both are H, optionally substituted C_{1-6}alkyl, $S(O)_pR^{14}$ in which p is 0 to 2 and R^{14} is selected from the group consisting of H, C_{2-6}alkyl, substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycoalkyl, optionally substituted aryl and optionally substituted heterocyclyl and COR^{25} in which R^{25} is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $S(O)_pR^{14}$ in which p and R^{14} are as defined above;



; and



in which

Z and L are as defined above;

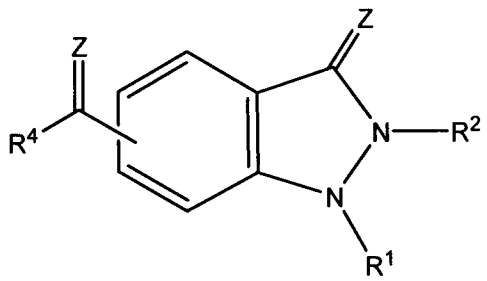
R^4 is selected from the group consisting of amino acid; optionally substituted C_{3-8}cycloalkyl; optionally substituted aryl; optionally substituted heterocyclyl; OR^7 in which R^7 is selected from the group consisting of C_{2-6}alkyl, substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl; and NR^5R^6; in which R^5 and R^6 are independently selected from the group consisting of H; optionally substituted C_{1-6}alkyl; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; optionally substituted $(CH_2)_m$ optionally substituted aryl; optionally substituted$(CH_2)_m$ optionally substituted heterocyclyl in which m is 0 to 4; $S(O)_pR^8$ in which p is as defined above and R^8 is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are as defined above; $CR^{17}R^{18}COR^{19}$ in which R^{17} and R^{18} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl or R^{17} and R^{18} together with the C to which they are attached form an optionally substituted 3 to 6-membered ring and R^{19} is selected from the group consisting of OR^{15}in which R^{15} is as defined above and $NR^{20}R^{21}$ in which R^{20} and R^{21} are selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted aryl and optionally substituted heterocyclyl; and $CR^{22}(CO_2R^{23})CH_2R^{24}$ in which R^{22} and R^{23} are independently selected from the group consisting of H and

optionally substituted C_{1-6}alkyl and R^{24} is selected from the group consisting of, optionally substituted aryl and optionally substituted heterocyclyl; or

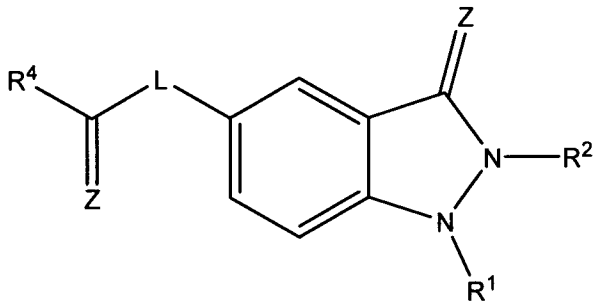
R^5 and R^6 together with the N to which they are attached form an optionally substituted 5 or 6-membered ring.

When R^3 is optionally substituted heterocyclyl, it is preferably a 5 or 6 membered N-containing heterocyclyl such as tetrazolyl.

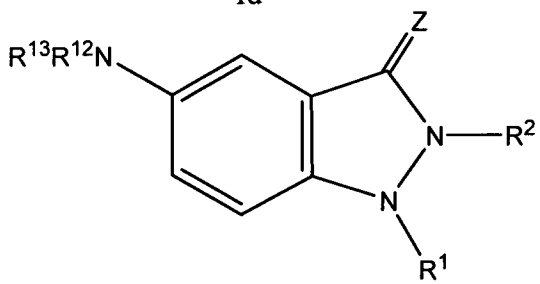
Subclasses of compounds of formula Ia are as follows:



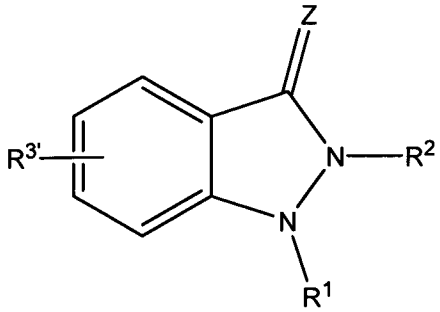
Ic



Id



Ie

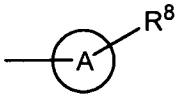


If

in which Z, L, R^1, R^2, R^4, R^{12} and R^{13} are as defined above; and

$R^{3'}$ is optionally substituted C_{1-6}alkyl, halo, CN, NO_2 or optionally substituted heterocyclyl.

In the compounds of formula Ic to If, R^2 may be



in which

A is selected from the group consisting of C_{3-8}cycloalkyl, aryl and heterocyclyl; and

R^8 is selected from the group consisting of hydrogen, halo, cyano, nitro, amino, optionally substituted C_{1-6} alkanoylamino, optionally substituted C_{1-6} alkylsulfonyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $COOR^9$ in which R^9 is hydrogen or optionally substituted C_{1-6} alkyl, $CONH-(CH_2)_n-R^{10}$ in which R^{10} is optionally substituted C_{1-6} alkyl, C_{1-6} alkoxycarbonyl or C_{1-6} alkanoylamino and n is 1 to 6 and OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl optionally substituted C_{3-8} cycloalkyl, optionally substituted aryl or optionally substituted heterocyclyl.

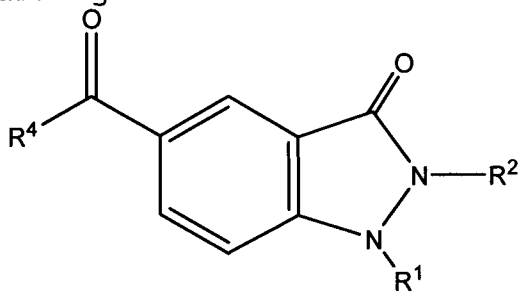
A is preferably cyclohexyl, phenyl or a 5 or 6 membered N-containing heterocyclyl such as pyridyl.

Preferably Z is O.

R^1 is preferably optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or C_{2-6}alkyl substituted with optionally substituted C_{3-8}cylcoalkyl, optionally substituted aryl or optionally substituted heterocyclyl.

Preferably R^8 is OR^{11} in which R^{11} is C_{1-6}alkyl or benzyl.

In one preferred embodiment the compound of formula Ic has the formula Ig

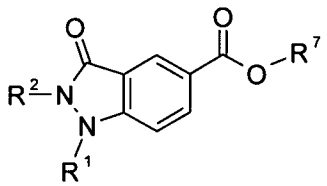


Ig

in which R^1, R^2 and R^4 are as defined above.

In the compound of formula Ig, preferably R^1 is C_{5-7}cycloalkyl such as cyclohexyl; phenyl; or a 5 or 6 membered N-containing heterocyclyl such as pyridyl and R^2 is C_{5-7}cycloalkyl such as cyclohexyl; optionally substituted phenyl; or heterocyclyl containing an N, O or S such as pyridyl, furyl or thienyl. Subclasses of compounds of this type are as follows:

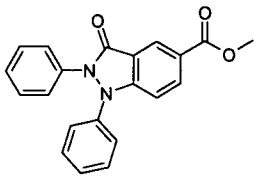
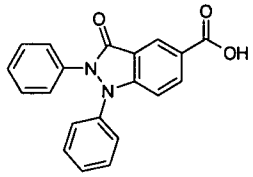
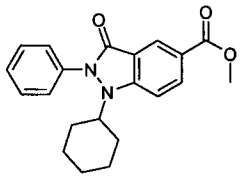
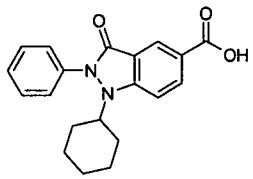
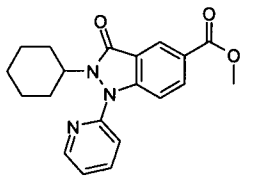
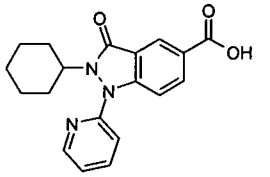
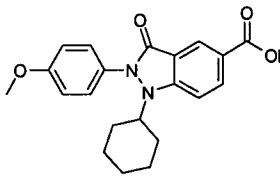
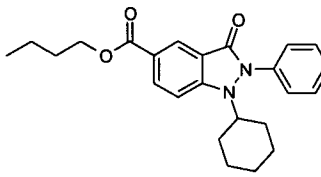
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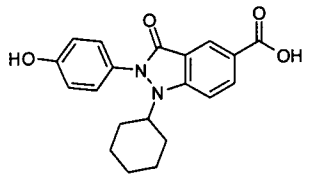
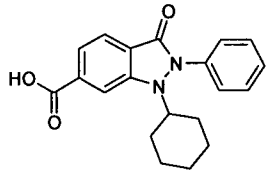
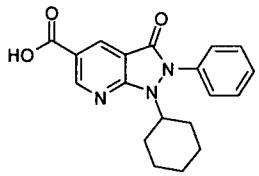
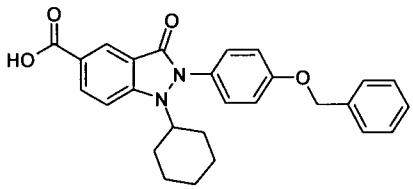


in which R^1, R^2 and R^7 are as defined above.

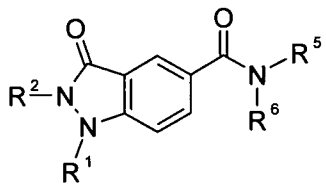
Preferably R^1 is cyclohexyl or phenyl, R^2 is phenyl optionally substituted with C_{1-6}alkoxy or benzyloxy and R^7 is H, C_{1-6}alkyl such as C_{1-4}alkyl for example methyl; optionally substituted aryl such as phenyl optionally substituted with a C_{1-6}alkyl which is substituted with amino, acyl and/or C_{1-6}alkoxy; or N-containing heterocyclyl such as indolyl optionally substituted with a C_{1-6}alkyl which is substituted with amino, acyl and/or C_{1-6}alkoxy. Representative examples are as follows:

Table 1

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
101		345.1	344.37	A
102		331.1	330.35	T (and alternatively B/J/L)
103		351.1	350.42	A (Example 1)
104		337.1	336.39	T (Example 28) (and alternatively D/J/L)
105		352.0	351.41	A
106		338.0	337.38	T
107		367.1	366.42	O (Example 19) (and alternatively D/J/L)
108		423.2	422.53	V (Example 32)

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
110		353.1	352.39	M (Example 17)
111		337.0	336.39	L (Example 15)
112		338.0	337.38	L (Example 16)
114		443.2	442.52	U (Example 31)

(ii)



in which R^1, R^2, R^5 and R^6 are as defined above.

Preferably R^1 is cyclohexyl or phenyl; R^2 is phenyl; and one of R^5 and R^6 is H and the other is C_{1-6}alkyl substituted with optionally substituted phenyl or optionally substituted heterocyclyl, both R^5 and R^6 are H or together with the N to which they are attached form an optionally substituted 5 or 6-membered heterocyclyl.

The optional substituents on the phenyl are preferably C_{1-6}alkyl, halo such as Cl or F, C_{1-6}alkoxy, hydroxy, C_{2-6}alkenyleneacylC_{1-6}alkoxy or acylC_{1-6}alkoxy.

The heterocyclyl is preferably an unsaturated 5 or 6-

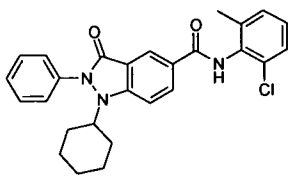
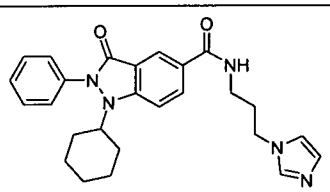
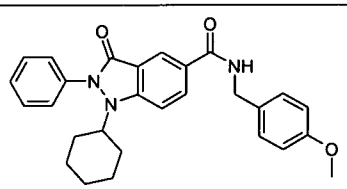
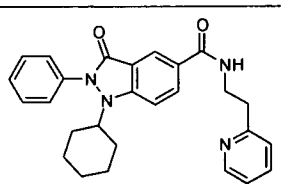
membered heteromonocyclic group containing 1 or 2 N atoms such as imidazolyl or pyridinyl; unsaturated condensed heterocyclyl containing 1 to 3 N atoms and optionally S and O atoms such as benzothiazol-2-yl, 5-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), benzoxazolyl and benzotriazolyl; unsaturated 5 or 6-membered heteromonocyclic group containing N and S such as thiazolyl; or unsaturated condensed heterocyclic group containing O atoms such as 2-oxo-2H-chromen-7-yl.

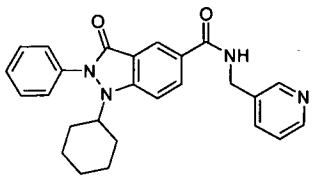
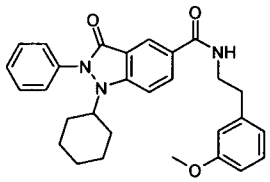
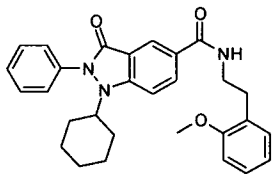
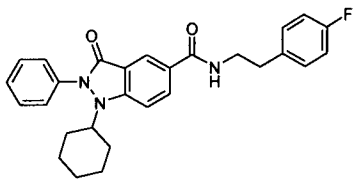
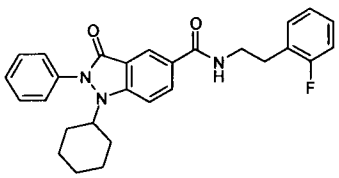
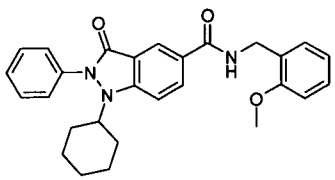
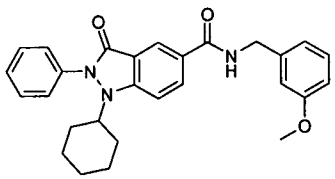
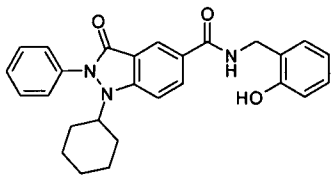
The optional substituents on the heterocyclyl are preferably C_{1-6}alkyl, C_{1-6}alkyleneacylC_{1-6}alkoxy, acylC_{1-6}alkoxy, CF_3, C_{1-6}alkyleneC_{1-6}alkoxy, carboxy or C_{1-6}alkenyenecarboxy.

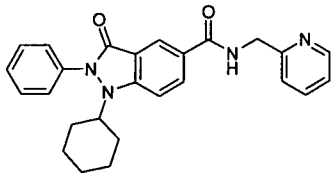
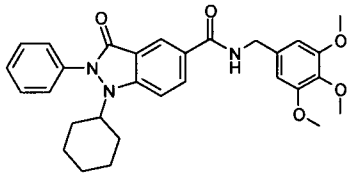
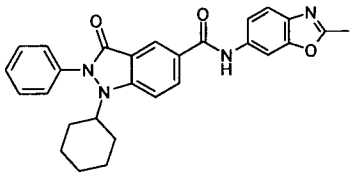
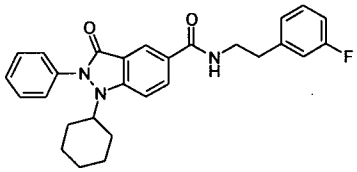
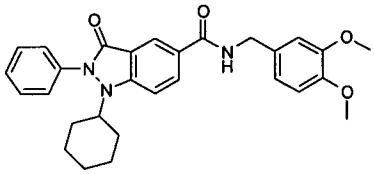
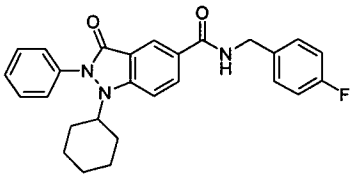
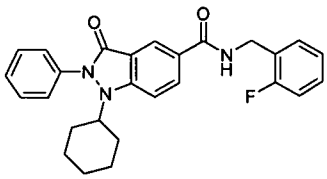
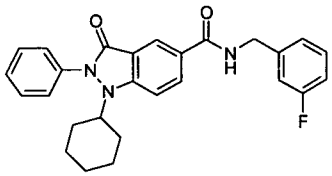
The optionally substituted 5 or 6-membered heterocyclyl is preferably a saturated N-containing 5 or 6-membered heterocyclyl such as pyrrolidinyl.

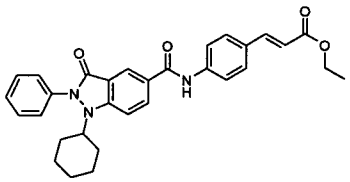
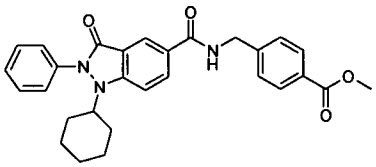
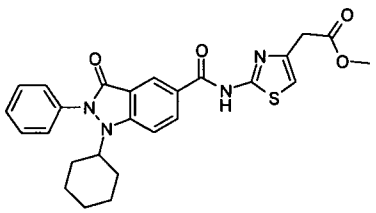
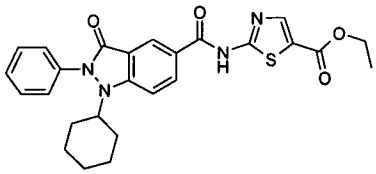
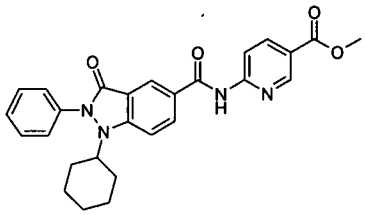
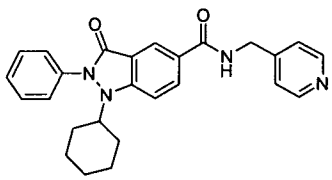
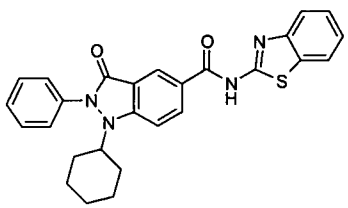
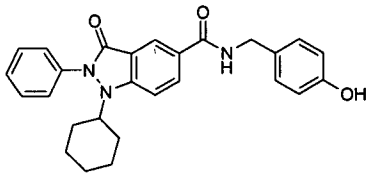
Representative examples are as follows:

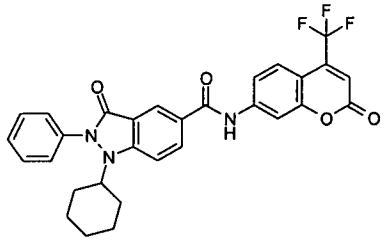
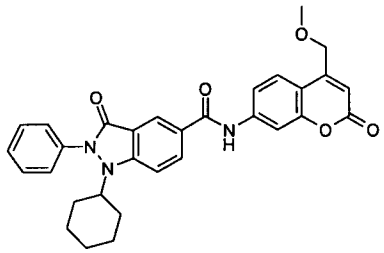
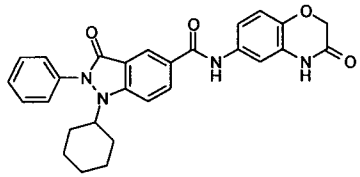
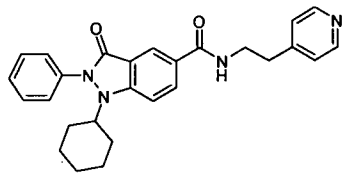
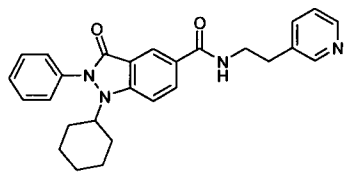
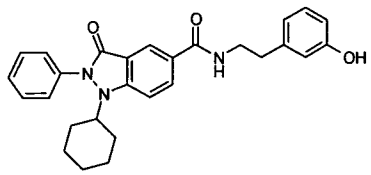
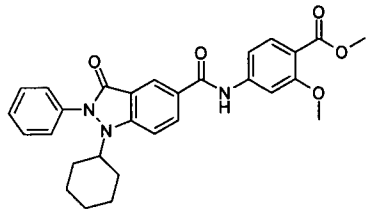
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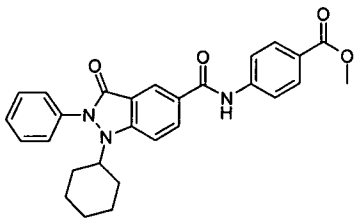
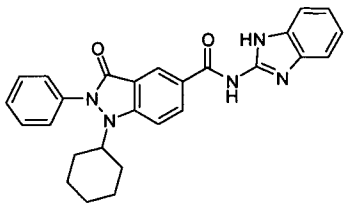
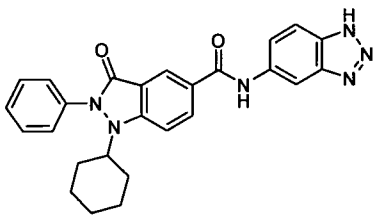
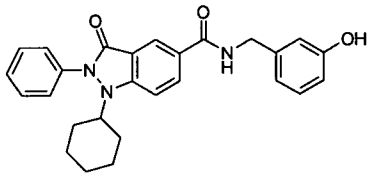
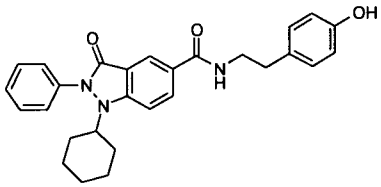
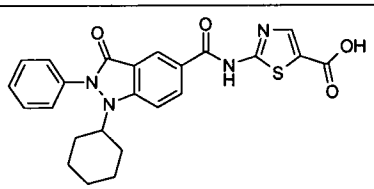
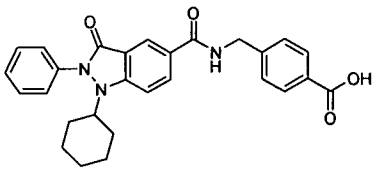
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
201		460.1	459.98	Q
202		444.2	443.55	Q
203		456.2	455.56	Q
204		441.2	440.55	Q

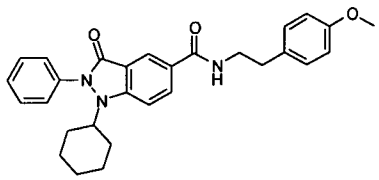
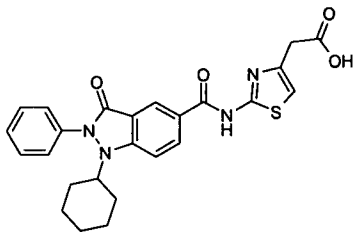
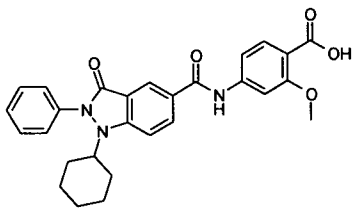
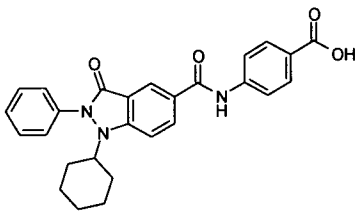
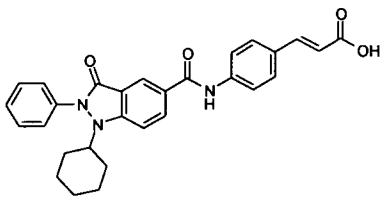
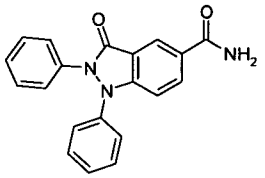
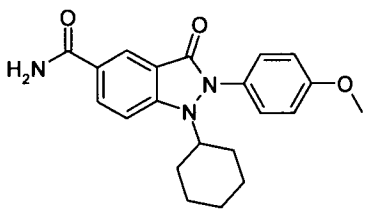
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
205		427.2	426.52	Q
206		470.2	469.59	Q
207		270.2	469.59	Q
208		458.2	457.55	Q
209		458.2	457.55	Q
210		456.2	455.56	Q
211		456.2	455.56	Q
212		442.2	441.53	Q

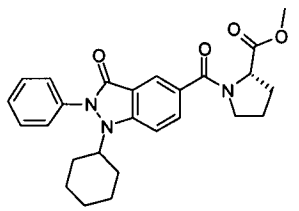
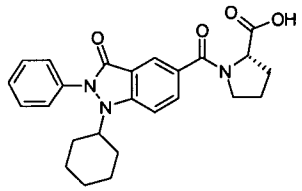
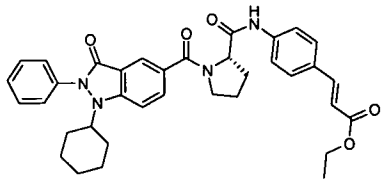
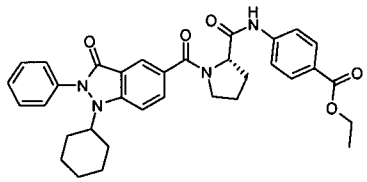
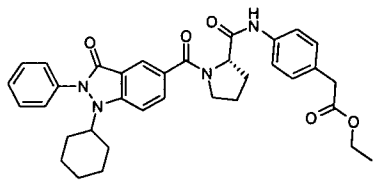
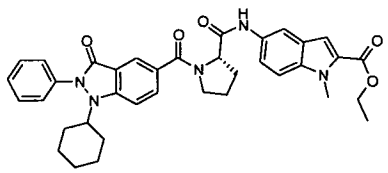
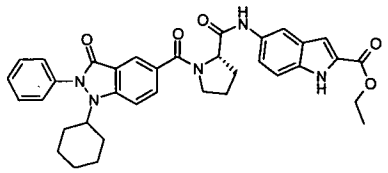
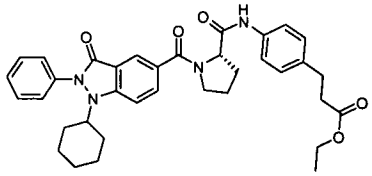
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
213		427.1	426.52	Q
214		516.2	515.61	Q
215		467.1	466.54	Q
216		458.2	457.55	Q
217		486.2	485.59	Q
218		444.1	443.53	Q
219		444.2	443.53	Q
220		444.2	443.53	Q

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
221		510.2	509.61	Q
222		484.2	483.57	Q
223		491.1	490.59	Q
224		491.1	490.59	Q
225		471.2	470.53	Q
226		427.2	426.52	Q
227		469.1	468.58	Q
228		442.2	441.53	Q

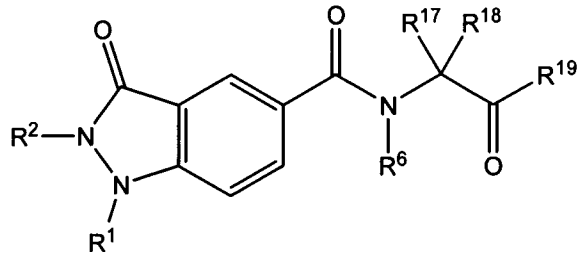
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
229		548.1	547.54	Q
230		524.1	523.59	Q
231		483.1	482.54	Q
232		441.2	440.55	Q
233		441.2	440.55	Q
234		456.2	455.56	Q
235		500.1	499.57	Q

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
236		470.2	469.55	Q
237		452.1	451.53	Q
238		453.1	452.52	Q
239		442.2	441.53	Q
240		456.2	455.56	Q
241		463.1	462.53	Q
242		470.2	469.55	Q

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
243		470.2	469.59	Q
244		477.1	476.56	Q
245		486.1	485.54	Q
246		456.2	455.52	Q
247		482.1	481.56	Q
248		330.1	329.36	Q
249		366.1	365.44	J (Partial hydrolysis product)

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
327		448.2	447.54	Q
328		434.1	433.51	T
351		607.1	606.73	Q
352		581.1	580.69	Q
353		595.1	594.72	Q
354		634.0	633.75	Q
365		620.0	619.73	Q
380		609.1	608.74	Q

(iii)



in which R^1, R^2, R^6, R^{17}, R^{18} and R^{19} are as defined above.

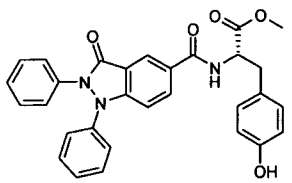
Preferably R^1 is cyclohexyl, phenyl or pyridyl; R^2 is cyclohexyl or phenyl; R^6 is H; R^{17} and R^{18} are both H or C_{1-6}alkyl, one is H and the other is C_{1-6}alkyl or C_{1-6}alkyl substituted with optionally substituted phenyl or optionally substituted heterocyclyl or together with the C to which they are attached form a 4-membered ring; and R^{19} is OR^{15} in which R^{15} is as defined above or $NR^{20}R^{21}$ in which one of R^{20} and R^{21} is H and the other is optionally substituted phenyl or optionally substituted heterocyclyl.

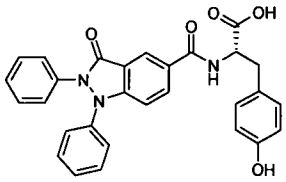
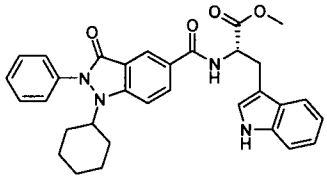
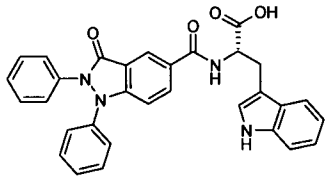
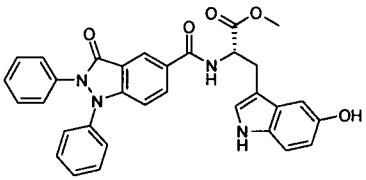
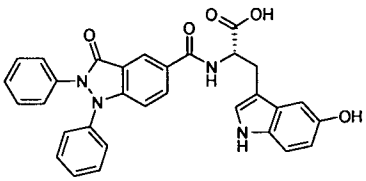
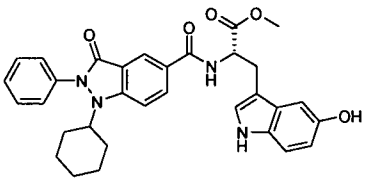
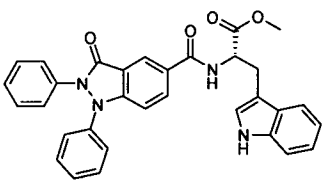
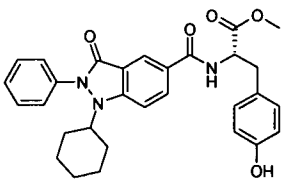
The optionally substituent on the phenyl or heterocyclyl is preferably hydroxy, acylC_{1-6}alkoxy, C_{2-6}alkenyleneacyl C_{1-6}alkoxy, C_{1-6}alkylenecarboxy, C_{1-6}alkylenecarboxy, carboxy or C_{1-6}alkylacylC_{1-6}alkoxy.

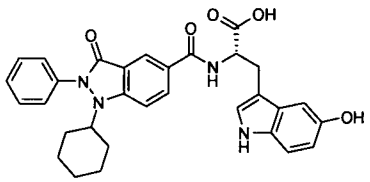
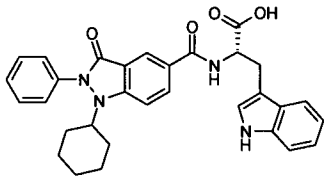
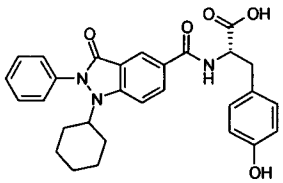
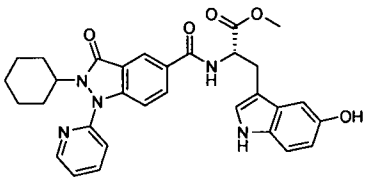
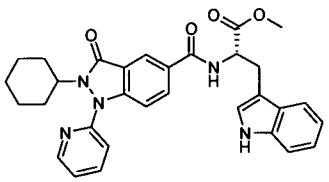
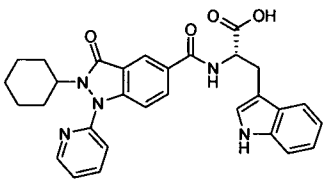
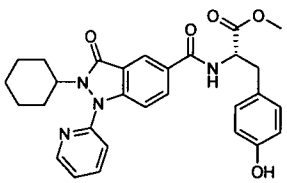
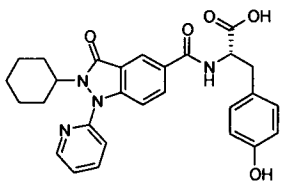
The heterocyclyl is preferably an unsaturated condensed heterocyclyl containing 1 to 3 N atoms such as indolyl or quinolinyl.

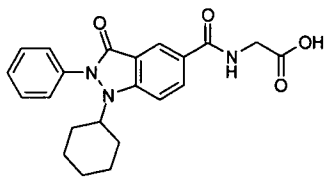
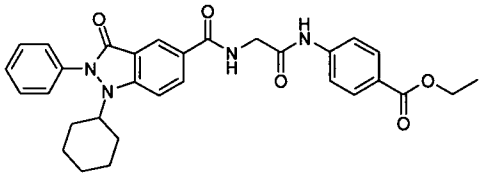
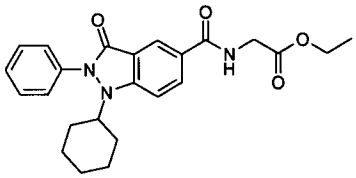
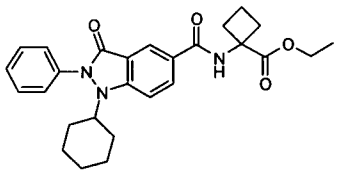
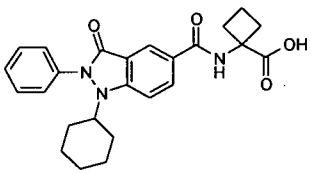
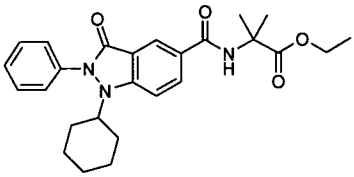
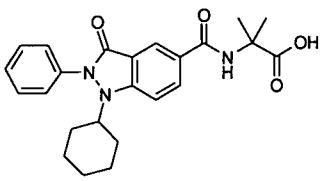
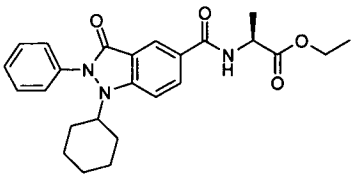
Representative examples are as follows:

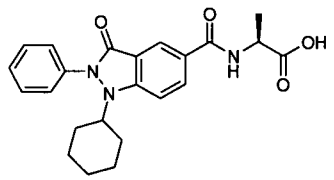
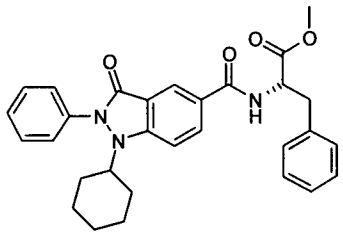
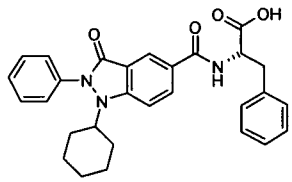
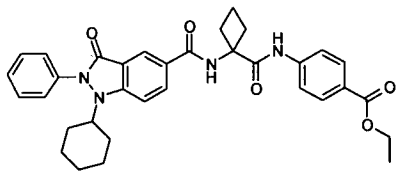
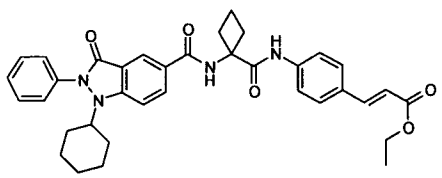
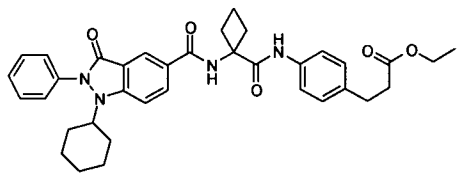
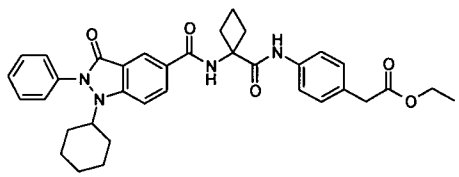
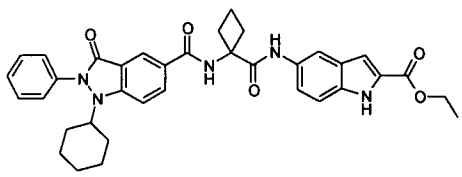
Table 3

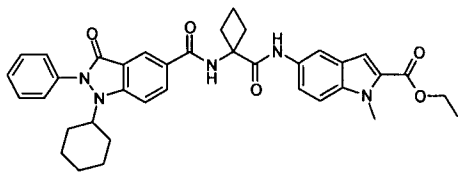
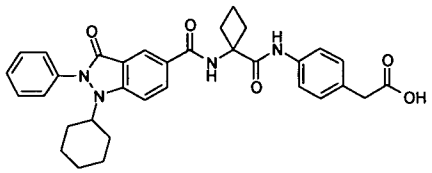
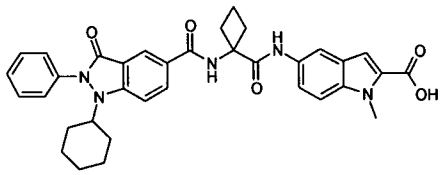
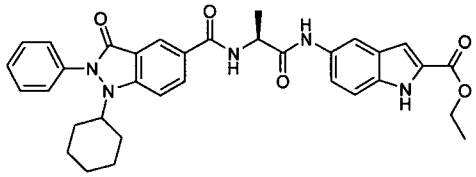
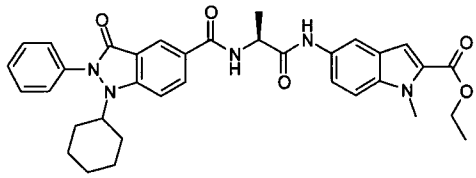
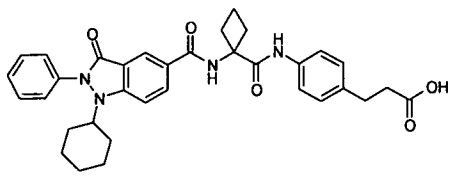
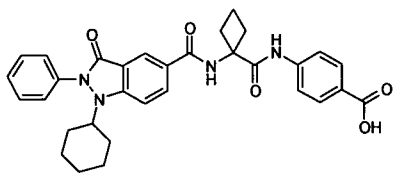
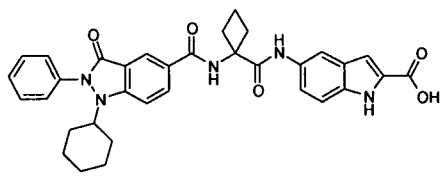
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
301		508.2	507.55	Q

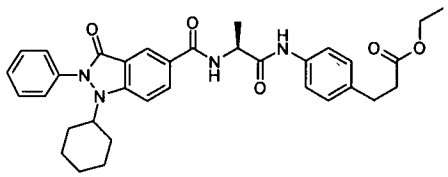
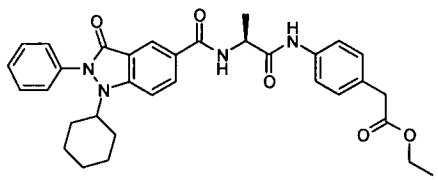
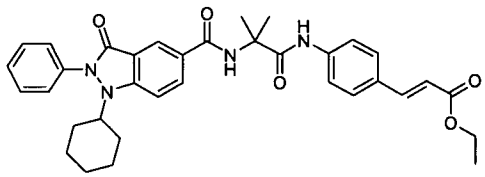
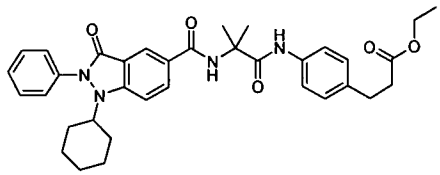
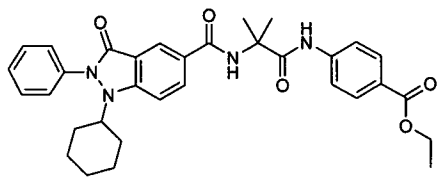
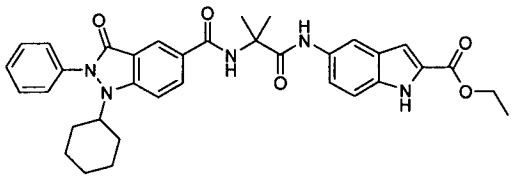
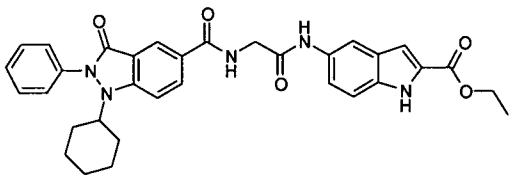
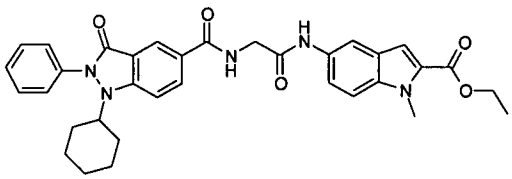
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
302		494.1	493.52	T
303		537.1	536.64	Q (Example 22)
304		517.1	516.56	T
305		547.1	546.59	Q
306		533.1	532.56	T
307		553.1	552.64	Q
308		531.1	530.59	Q
309		514.1	513.60	Q

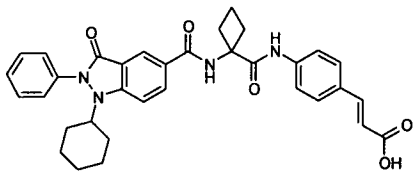
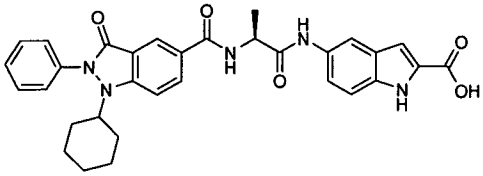
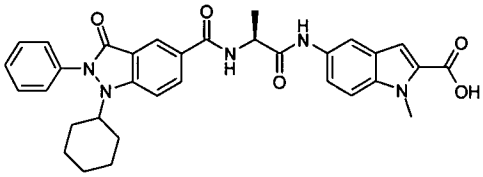
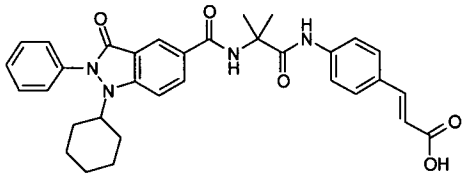
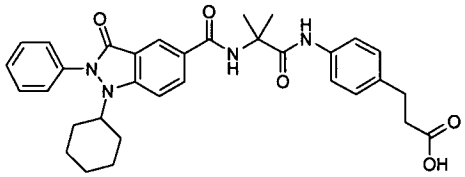
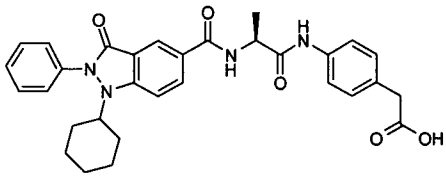
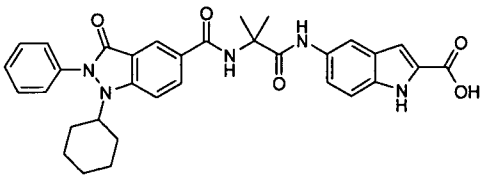
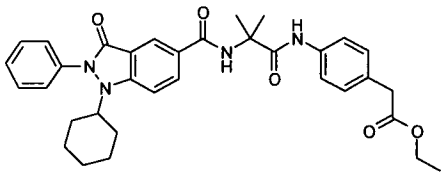
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
310		539.1	538.61	T
311		523.2	522.61	T (Example 29)
312		500.2	499.57	T
313		554.1	553.62	Q
314		538.1	537.62	Q
315		524.1	523.60	T
316		515.1	514.59	Q
317		501.1	500.56	T

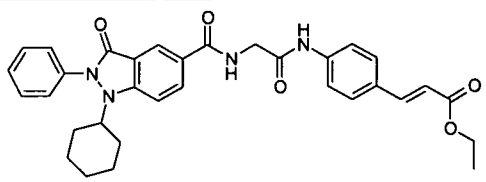
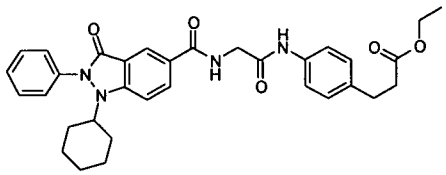
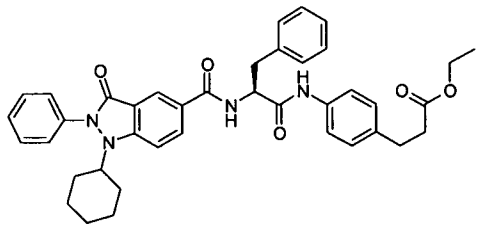
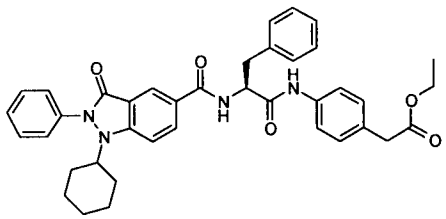
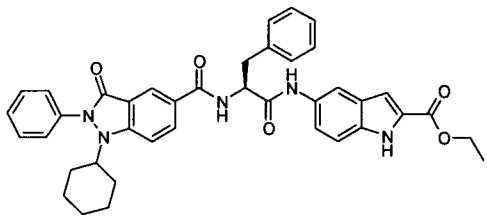
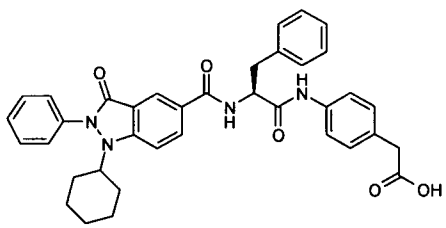
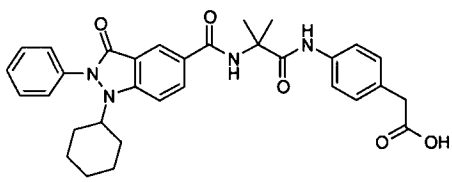
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
318		394.1	393.45	T
319		541.1	540.62	Q
320		422.1	421.50	Q
321		462.2	461.57	Q
322		434.2	433.51	T
323		450.2	449.55	Q
324		422.1	421.50	T
325		436.2	435.53	Q

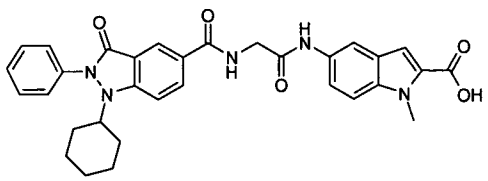
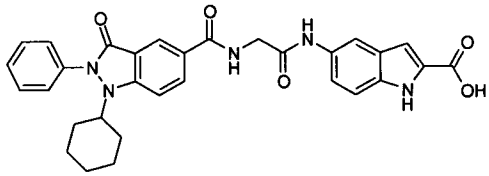
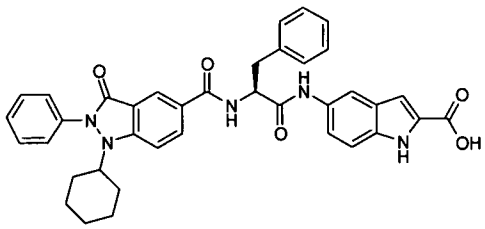
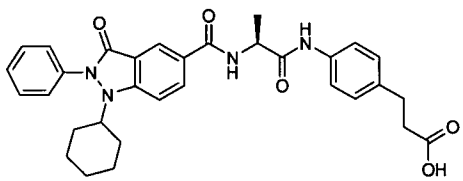
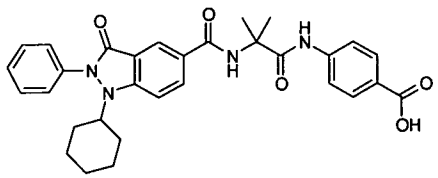
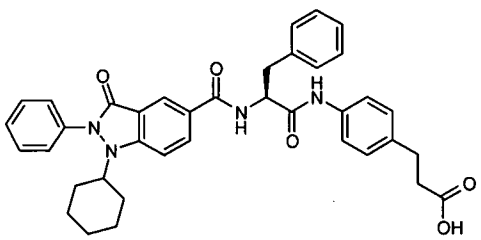
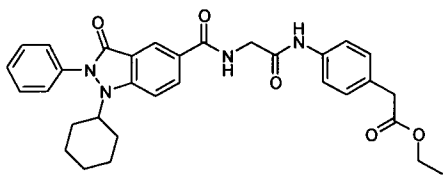
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
326		408.1	407.47	T
329		498.2	497.60	Q
330		484.1	483.57	T
331		581.1	580.69	Q
332		607.0	606.73	Q
333		609.1	608.74	Q
334		595.1	594.72	Q
336		619.9	619.73	Q

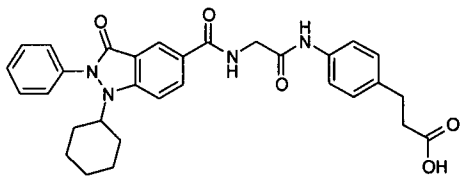
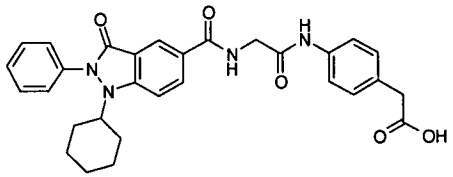
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
337		633.9	633.75	Q
338		566.9	566.66	Q
339		605.9	605.70	T
340		594.0	593.69	Q
341		608.0	607.72	Q
342		580.9	580.69	T
343		553.1	552.64	T
344		591.9	591.67	T

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
345		583.1	582.71	Q
346		569.1	568.68	Q
347		595.1	594.72	Q
348		597.1	596.73	Q
349		569.1	568.68	Q
350		608.0	607.72	Q
355		580.0	579.66	Q
356		594.1	593.69	Q

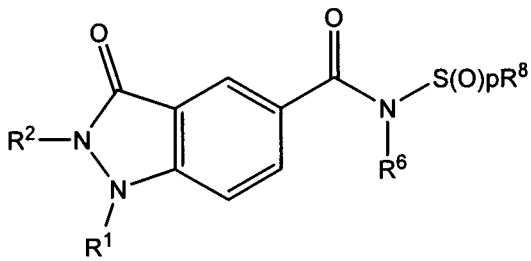
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
357		579.0	578.67	T
358		566.0	565.63	T
359		580.0	579.66	T
360		567.0	566.66	T
361		568.9	568.68	T
362		541.1	540.62	T
363		580.0	579.66	T
364		583.1	582.71	Q

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
366		567.1	566.66	Q
367		569.1	568.68	Q
368		659.1	658.80	Q
369		645.1	644.78	Q
370		670.1	669.79	Q
371		617.0	616.72	T
372		555.0	554.65	T

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
373		566.1	565.63	T
374		552.0	551.61	T
375		642.0	641.73	T
376		555.0	554.65	T
377		541.1	540.62	T
378		631.0	630.75	T
379		555.1	554.65	Q

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
381		541.1	540.62	T
382		527.1	526.60	T

(iv)



in which R^1, R^2, R^6, p and R^8 are as defined above.

Preferably R^1 is cyclohexyl or phenyl; R^2 is optionally substituted phenyl; R^6 is H; p is 2 and R^8 is optionally substituted C_{3-8}cycloalkyl, optionally substituted phenyl, optionally substituted heterocyclyl, C_{1-6}alkyl, C_{1-6}alkyl substituted with optionally substituted phenyl, C_{2-6}alkenyl substituted with optionally substituted phenyl or $NR^{15}R^{16}$ in which R^{15} and R^{16} are as defined above.

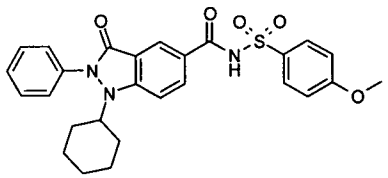
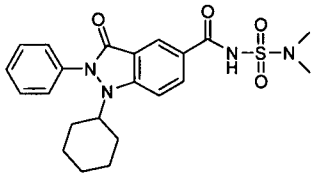
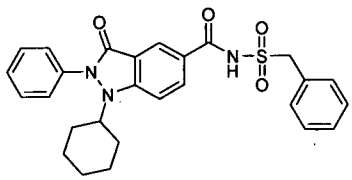
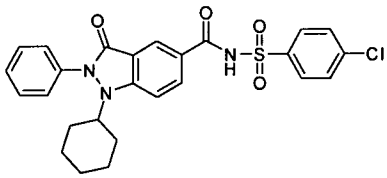
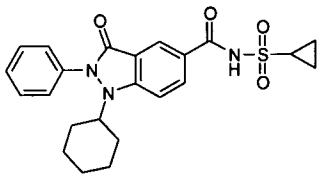
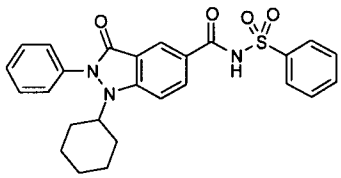
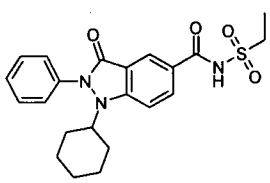
The optional substituents on the phenyl or heterocyclyl are preferably C_{1-6}alkoxy, halo such as Cl, Br or F, acylC_{1-6}alkoxy, nitro, carboxy, amidoC_{1-6}alkyl or CF_3.

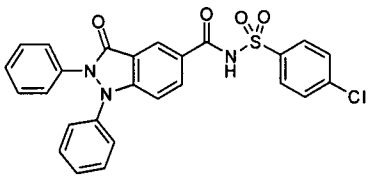
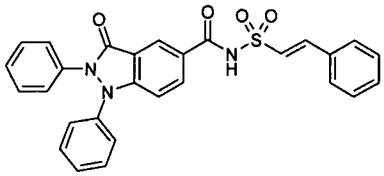
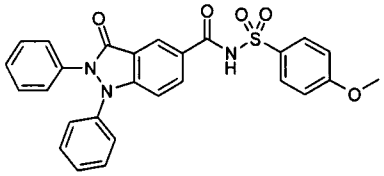
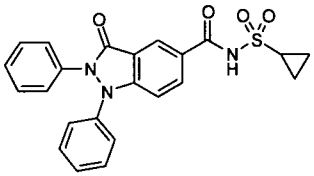
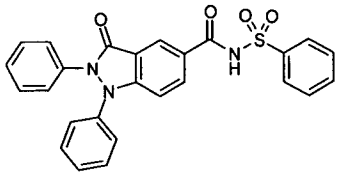
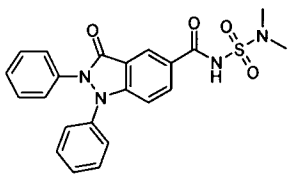
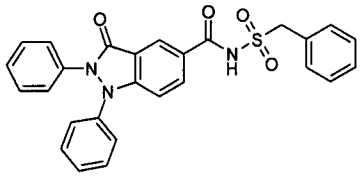
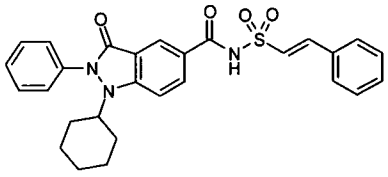
The C_{3-8}cycloalkyl is preferably C_3 cycloalkyl.

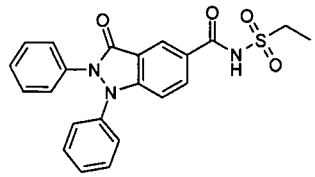
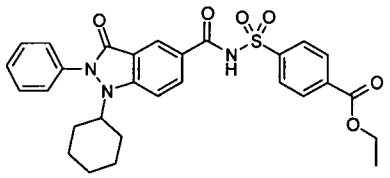
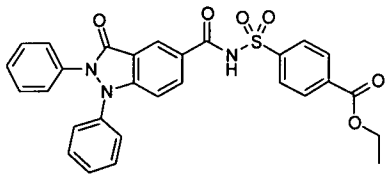
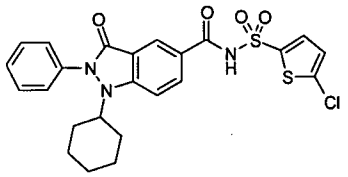
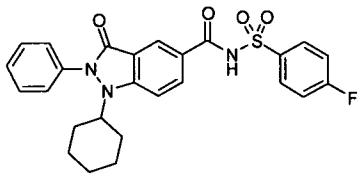
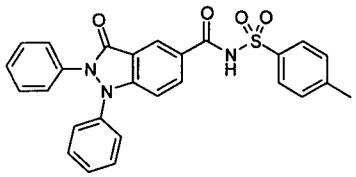
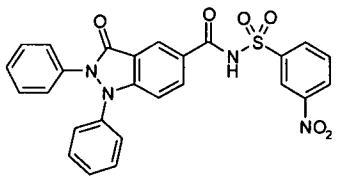
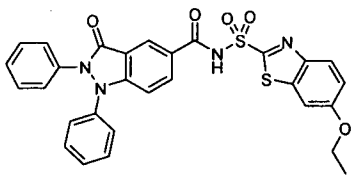
The heterocyclyl is preferably an unsaturated 5-membered heteromonocyclic group containing 1 to 2 S atoms such as thiophenyl; unsaturated condensed heterocyclyl containing 1 to 3 N atoms and optionally S atoms such as benzothiazol-2-yl,benzo[1,2,5]oxodiazol-4-yl and benzothiazol-2-yl or an unsaturated condensed heterocyclyl containing S atoms such as benzothiophenyl.

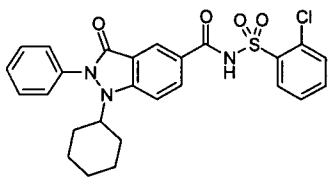
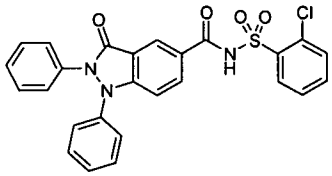
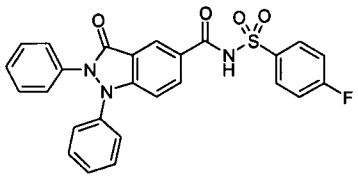
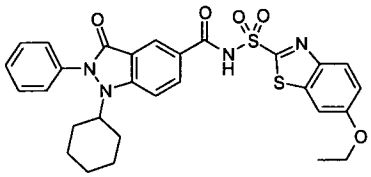
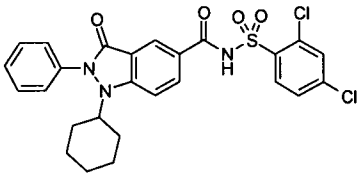
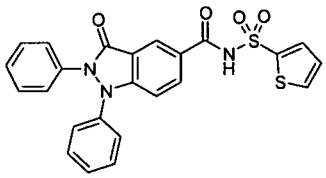
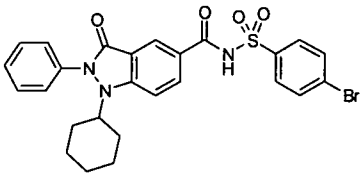
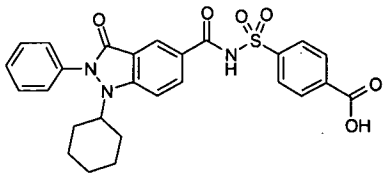
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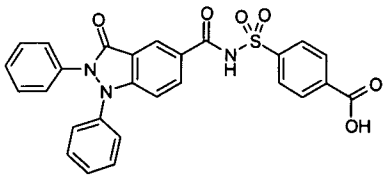
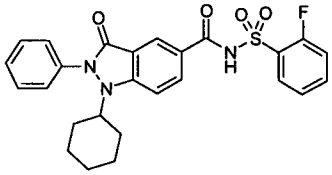
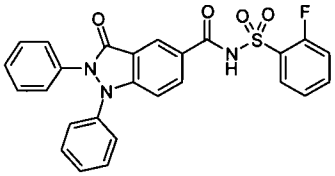
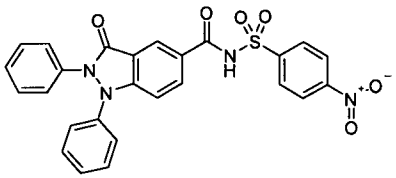
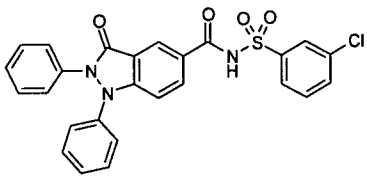
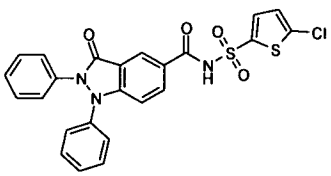
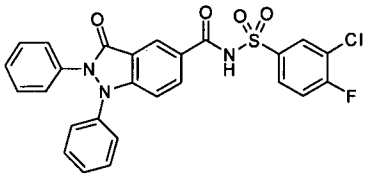
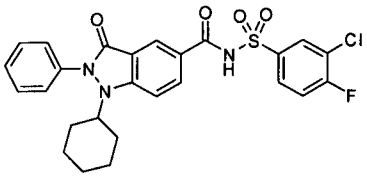
Table 4

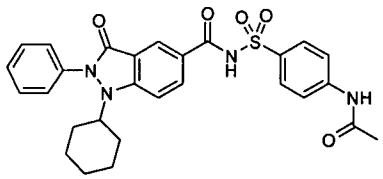
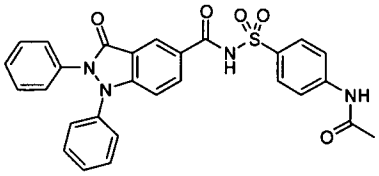
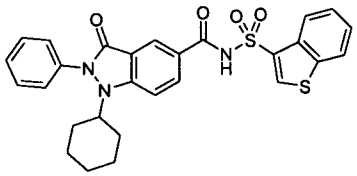
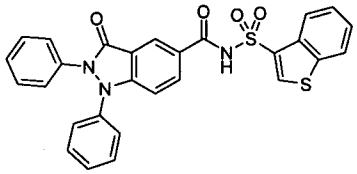
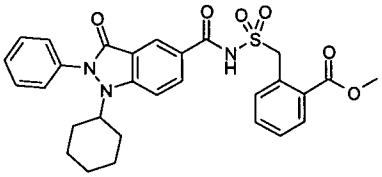
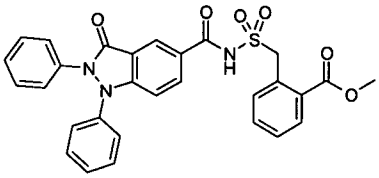
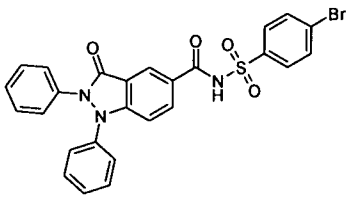
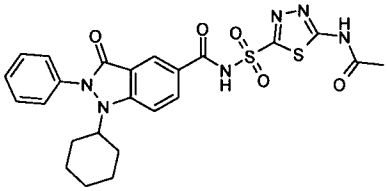
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
501		506.1	505.60	P (Example 20)
502		443.1	442.54	P
503		490.2	489.60	P
504		510.1	510.02	P
505		440.1	439.54	P
506		476.1	475.57	P
507		428.1	427.53	P

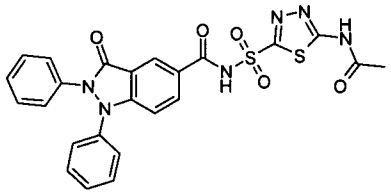
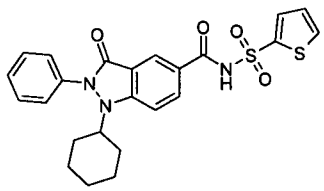
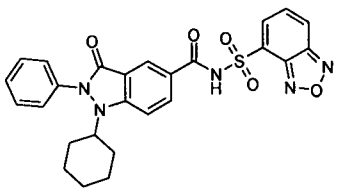
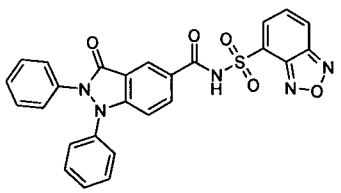
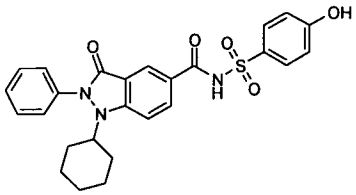
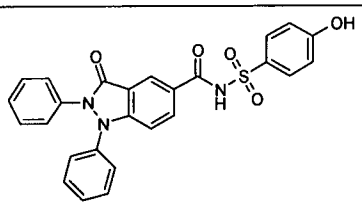
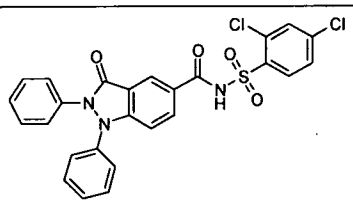
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
508		504.1	503.97	P
509		496.1	495.56	P
510		500.1	499.55	P
511		434.1	433.49	P
512		470.1	469.52	P
513		437.0	436.49	P
514		484.1	483.55	P
515		502.1	501.61	P

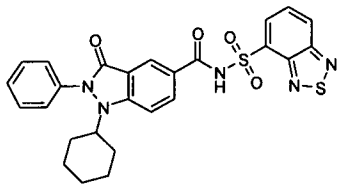
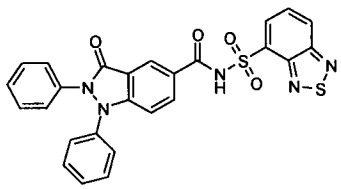
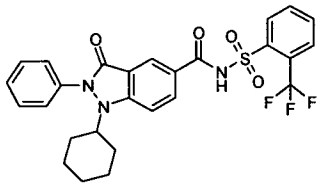
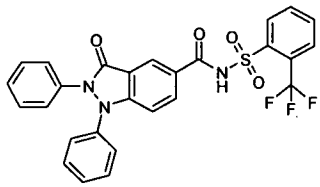
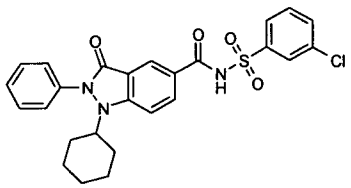
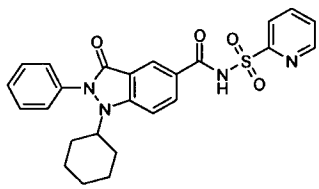
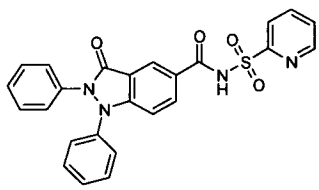
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
516		422.1	421.48	P
517		548.1	547.63	P
518		542.1	541.59	P
519		516.0	516.04	P
520		494.1	493.56	P
521		484.1	483.55	P
522		515.1	514.52	P
523		571.0	570.65	P

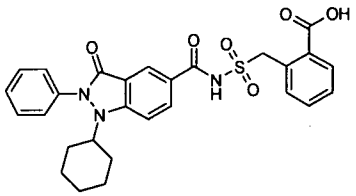
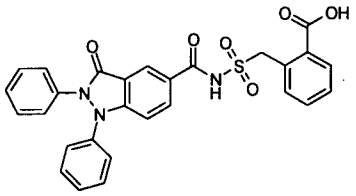
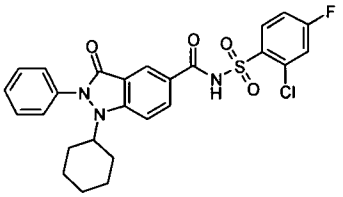
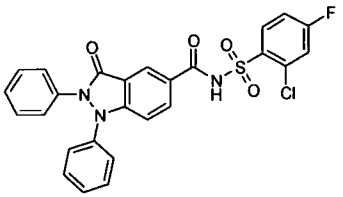
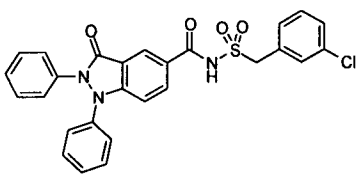
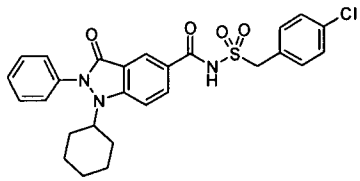
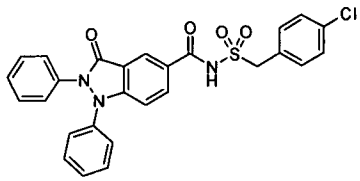
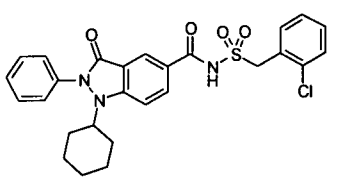
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
524		510.0	510.02	P (Example 21)
525		504.1	503.97	P
526		488.1	487.51	P
527		577.1	576.70	P
528		544.0	544.46	P
529		476.1	475.55	P
530		554.0	554.47	P
531		520.1	519.58	P

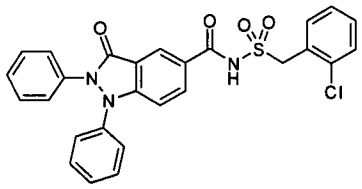
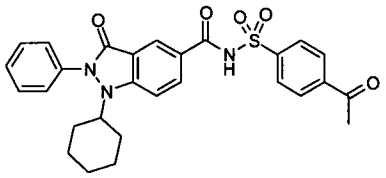
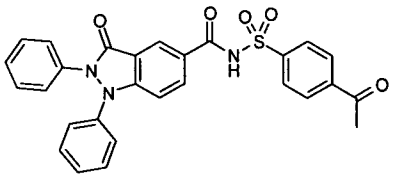
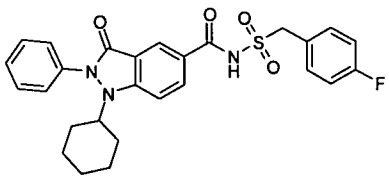
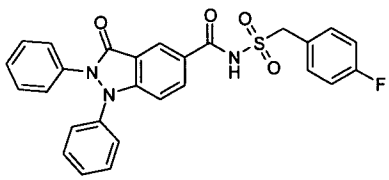
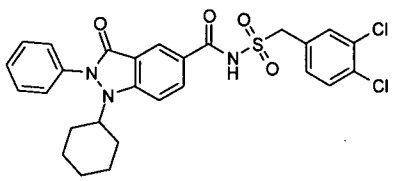
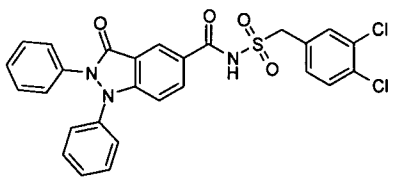
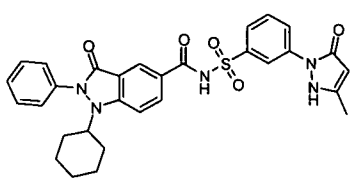
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
532		514.1	513.53	P
533		494.1	493.56	P
534		488.1	487.51	P
535		515.1	514.52	P
536		504.1	503.97	P
537		510.0	509.99	P
538		522.1	521.96	P
539		528.0	528.01	P

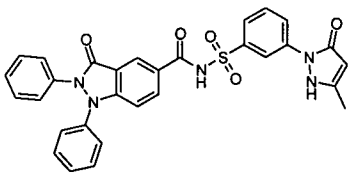
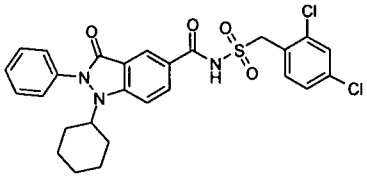
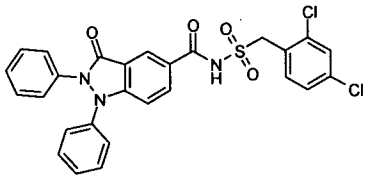
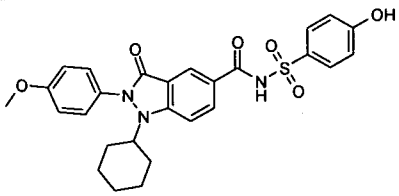
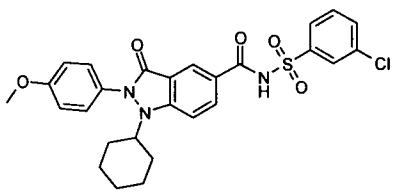
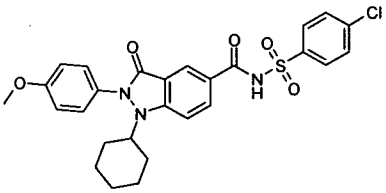
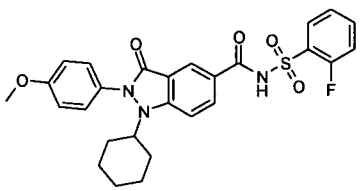
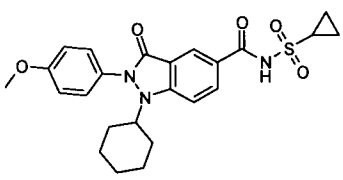
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
540		533.1	532.62	P
541		527.1	526.58	P
542		532.1	531.66	P
543		526.1	525.61	P
544		548.1	547.63	P
545		542.1	541.59	P
546		548.1	548.42	P
547		541.0	540.62	P

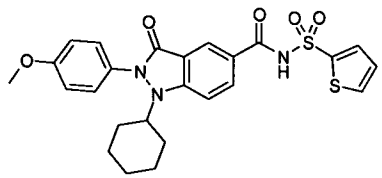
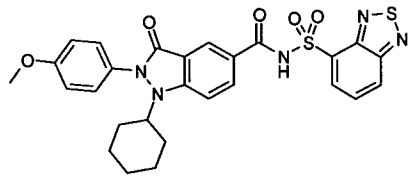
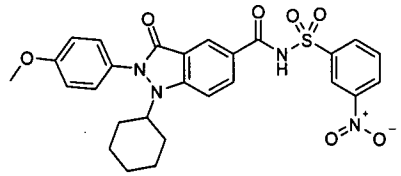
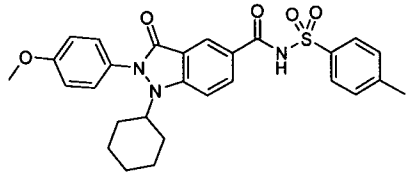
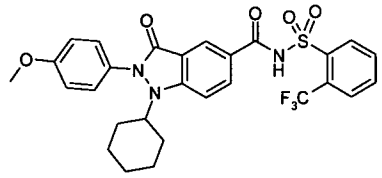
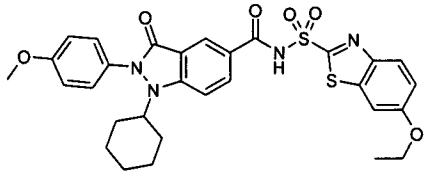
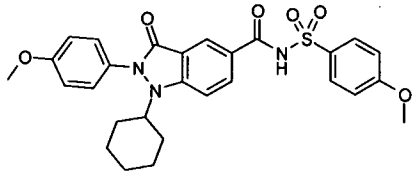
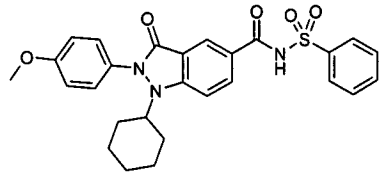
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
548		535.0	534.58	P
549		482.1	481.60	P
550		518.1	517.57	P
551		512.1	511.52	P
552		492.1	491.57	P
553		486.1	485.52	P
554		538.0	538.41	P

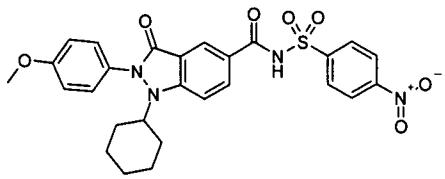
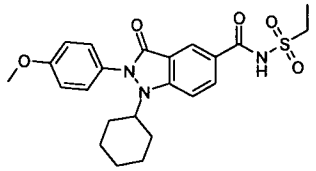
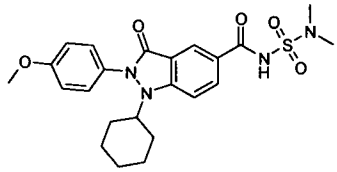
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
555		534.0	533.63	P
556		527.9	527.58	P
557		544.1	543.57	P
558		538.1	537.52	P
559		510.1	510.02	P
560		477.0	476.56	P
561		471.0	470.51	P

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
562		534.1	533.61	T
563		528.1	527.56	T
564		528.1	528.01	P
565		522.1	521.96	P
566		518.1	518.00	P
567		524.1	524.04	P
568		518.1	518.00	P
569		524.1	524.04	P

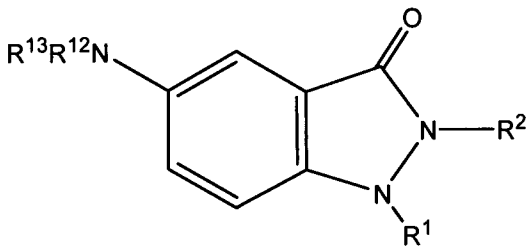
Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
570		518.1	518.00	P
571		518.1	517.61	P
572		512.1	511.56	P
573		508.1	507.59	P
574		502.1	501.54	P
575		558.1	558.49	P
576		552.1	552.44	P
577		572.1	571.66	P

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
578		566.0	565.61	P
579		558.1	558.49	P
580		552.1	552.44	P
581		522.1	521.60	P
582		540.1	540.04	P
583		540.1	540.04	P
584		524.1	523.59	P
585		470.1	469.56	P

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
586		512.1	511.62	P
587		564.0	563.66	P
588		551.1	550.59	P
589		520.1	519.62	P
590		574.1	573.60	P
591		607.1	606.72	P
592		536.1	535.62	P
593		506.1	505.60	P

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
594		551.1	550.59	P
595		458.1	457.55	P
596		473.1	472.57	P

In another preferred embodiment, the compounds are of formula Ih

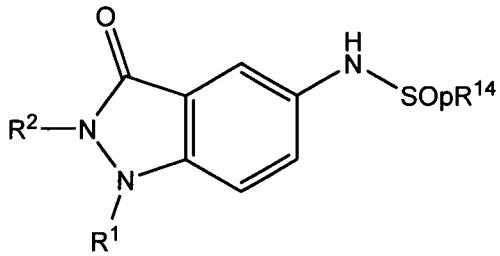


Ih

in which R^1, R^2, R^{12} and R^{13} are as defined above.

Preferably both R^1 and R^2 are phenyl and R^9 and R^{10} are both H or one is H and the other is SO_pR^{14} in which p and R^{14} are as defined above. Subclasses of compound of this type are as follows:

(i)



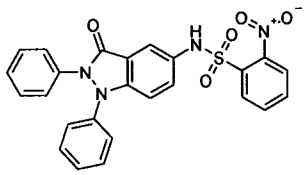
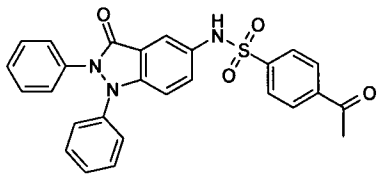
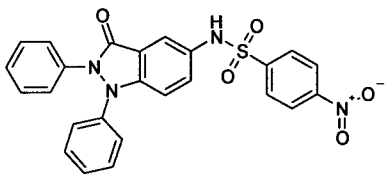
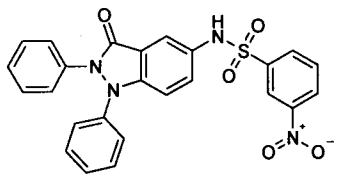
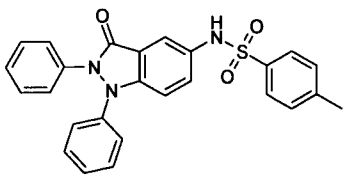
in which R^1, R^2, p and R^{14} are as defined above.

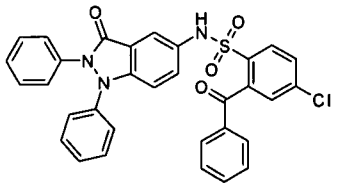
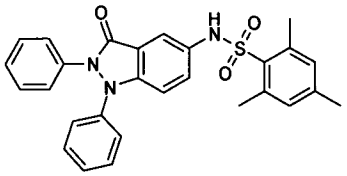
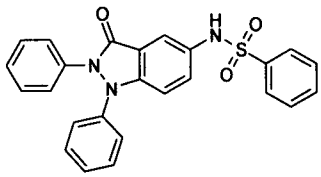
Preferably R^1 and R^2 are phenyl; p is 2; and R^{14} is optionally substituted phenyl.

The substituents on the phenyl are preferably nitro, acylC_{1-6}alkyl, C_{1-6}alkyl or halo such as Cl.

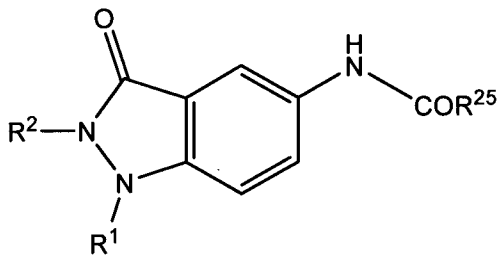
Representative examples are as follows:

Table 5

Cpd #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
701		487.1	486.51	S
702		484.1	483.55	S
703		487.1	486.51	S
704		487.1	486.51	S
705		456.1	455.54	S

Cpd #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
706		580.1	580.07	S
707		484.1	483.59	S
708		442.1	441.51	S (Example 24)

(ii)

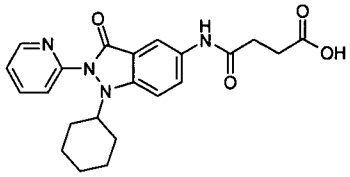


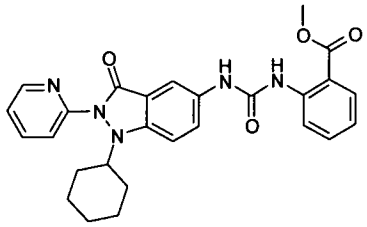
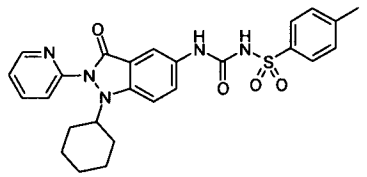
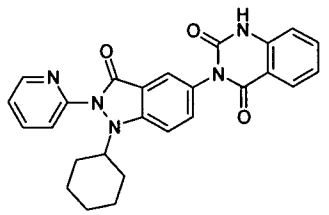
in which R^1, R^2 and R^{25} are as defined above.

Preferably R^1 is heterocyclyl such as pyridyl; R^2 is cyclohexyl; and R^{25} is C_{1-6}alkylene substituted with carboxylic acid or phenyl substituted with C_{1-6}alkyl, carboxylic acid or methoxy carboxylic acid.

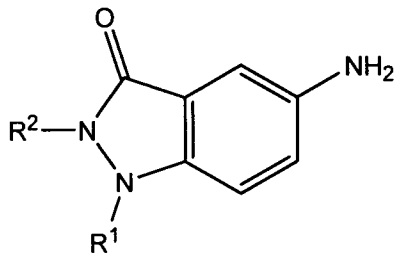
Representative examples are as follows:

Table 6

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
709		409.2	408.46	S (Example 25)

710		486.2	485.55	S (Example 26)
711		506.2	505.60	S (Example 27)
712		454.2	453.50	T (Example 30)

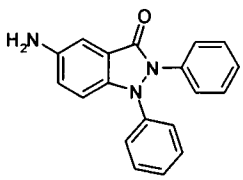
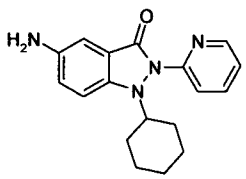
(iii)



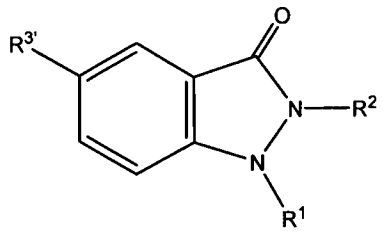
in which R^1 and R^2 are as defined above.

Representative examples are as follows:

Table 7

Cpd. #	Structure	Observed m/z [M+H]+	Formula weight	Synthetic method(s)
802		302.0	301.35	R (Example 23)
815		309.1	308.39	K (Example 14)

In a further preferred embodiment, the compounds are of the formula Ii



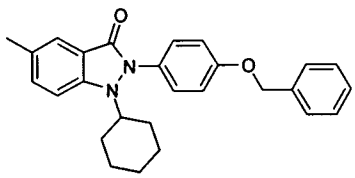
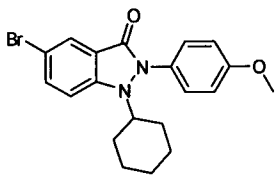
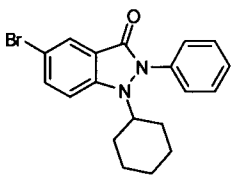
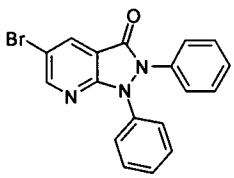
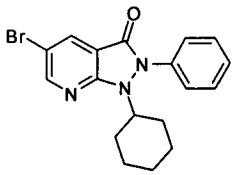
Ii

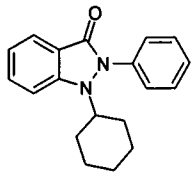
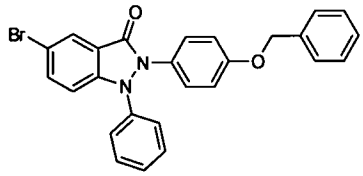
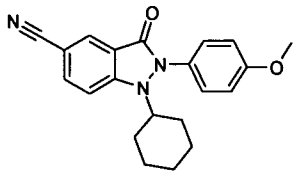
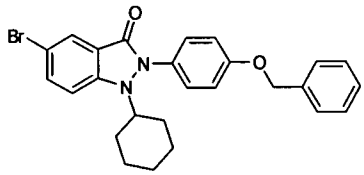
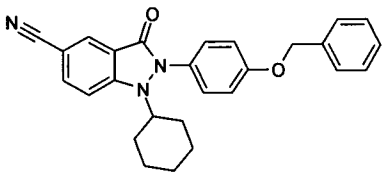
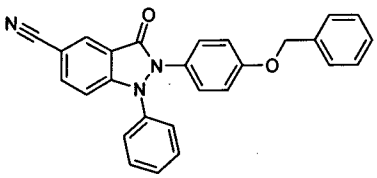
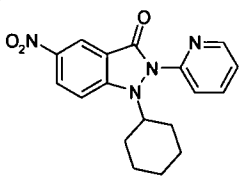
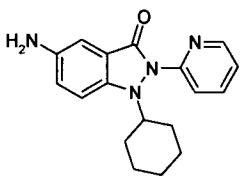
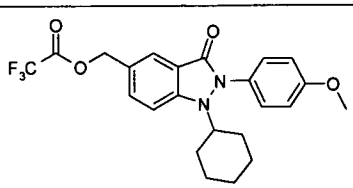
in which R^1, R^2 and $R^{3'}$ are as defined above

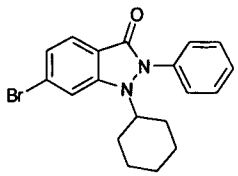
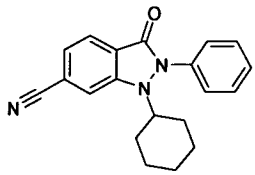
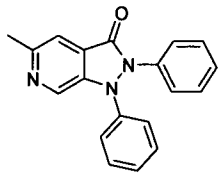
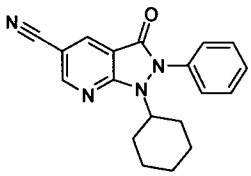
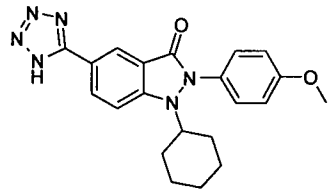
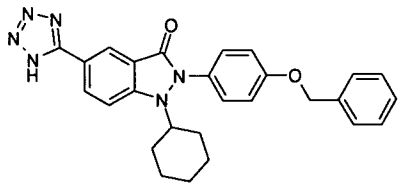
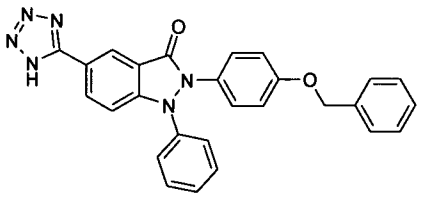
Preferably R^1 is phenyl or cyclohexyl; R^2 is optionally substituted phenyl; and $R^{3'}$ is C_{1-6}alkylene substituted with CO_2CF_3, Br, CN, NO_2 or tetrazolyl.

Representative examples are as follows:

Table 8

Cpd. #	Structure	Observed m/z $[M+H]^+$	Formula weight	Synthetic method(s)
803		413.2	412.54	D (Starting from 2-amino-5-methyl-benzoic acid)
804		401.0	401.31	D
805		373.0	371.28	D
806		365.9	366.22	H (aniline used in step 3)
807		374.0	372.27	H (Example 8)

808		293.1	292.38	D (Starting from 2-amino-benzoic acid)
809		473.0	471.36	B (Example 2)
810		348.1	347.42	J (Example 13)
811		477.1	477.41	D (Example 4)
812		424.1	423.52	J (Example 11)
813		418.1	417.47	J (Example 10)
814		339.1	338.37	C (Example 3)
815		309.1	308.39	K (Example 14)
816		449.1	448.45	G (Example 7)

817		370.9	371.28	E (Example 5)
818		318.0	317.39	J (Example 12)
819		302.0	301.35	F (Example 6)
820		319.0	318.38	J (Example 9)
821		391.1	390.45	N (Example 18)
822		467.2	466.55	N
823		461.1	460.50	N

The term "C_{1-6} alkyl" refers to straight chain or branched chain hydrocarbon groups having from 1 to 6 carbon atoms. Examples include ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

The term "C_{2-6} alkenyl" refers to straight chain or

branched chain hydrocarbon groups having at least one double bond of either E or Z stereochemistry where applicable and 2 to 6 carbon atoms. Examples include vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

The term "C_{2-6} alkynyl" refers to straight chain or branched chain hydrocarbon groups having at least one triple bond and 2 to 6 carbon atoms. Examples include ethynyl, 1- or 2-propynyl, 1-, 2- or 3- butynyl and methyl-2-propynyl.

The term "C_{3-8} cycloalkyl" refers to non-aromatic cyclic hydrocarbon groups having from 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloctyl, preferably cyclopentyl or cyclohexyl.

The term "C_{1-6} alkoxy" refers to an oxy-containing radical having C_{1-6} alkyl as defined above. Examples include methoxy, ethoxy, propoxy, butoxy, tert-butoxy and pentoxy.

The term "aryl" refers to single, polynuclear, conjugated or fused residues of aromatic hydrocarbons. Examples include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenxanthracenyl and phenanthrenyl. A preferred aryl is phenyl.

The term "heterocyclyl" refers to saturated or unsaturated, monocyclic or polycyclic hydrocarbon groups containing at least one heteroatom atom selected from the group consisting of nitrogen, sulphur and oxygen.

Suitable heterocyclyls include N-containing heterocyclic groups, such as, unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl,

imidazolidinyl, piperidino or piperazinyl;

unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolinyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl or thiophenyl;

unsaturated condensed heterocyclic groups containing 1 to 2 sulphur atoms such as benzothiophenyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl, benzoxadiazolyl or benzotriazolyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

Preferred heterocyclyls are pyridinyl, indolyl, benzoxazolyl, benzotriazolyl, thiazolyl, pyrrolidinyl, quinolinyl, thiophenyl, benzothiophenyl, tetrazolyl, furyl, morpholinyl, piperidinyl and 5-oxo-pyrrolidinyl.

The term "linker group" refers to a linear or branched chain of atoms connecting two distinct molecular subunits. Suitable linker groups include optionally

substituted C_{1-6}acyl, optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{3-8} cycloalkenylene, optionally substituted divalent aryl, optionally substituted divalent heterocyclyl, optionally substituted C_{1-6}sulfonamido, optionally substituted C_{1-6}amido and optionally substituted C_{1-6}acylamino. Preferred linker groups for R^2 are optionally substituted C_{1-6}alkylene or optionally substituted C_{1-6}acyl. Preferred linker groups for R^3 are optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted divalent aryl, optionally substituted divalent heterocyclyl, optionally substituted C_{1-6} acyl or optionally substituted C_{3-8} cycloalkyl.

The term "amino acid" refers to any of the twenty (20) common amino acids generally accepted in the peptide art. Examples include alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α–aminoadipic acid, α–amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α–methylserine, ornithine, pipecolic acid and thyroxine.

The term "halo" refers to fluorine, chlorine, bromine or iodine.

The term "C_{1-6} alkanoyl" refers to a radical provided by the residue after removal of hydroxyl from an organic acid. Examples include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and trifluoroacetyl.

The term "optionally substituted" refers to a group that may or may not be further substituted with one or more groups selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, CF_3, heterocyclyl, halo, haloC_{1-6}alkyl, haloC_{3-6}cycloalkyl, haloC_{2-6}alkenyl,

haloC$_{2-6}$alkynyl, haloaryl, haloheterocyclyl, hydroxy, C$_{1-6}$ alkoxy, C$_{2-6}$alkenyloxy, C$_{2-6}$alkynyloxy, aryloxy, heterocyclyloxy, carboxy, haloC$_{1-6}$alkoxy, haloC$_{2-6}$alkenyloxy, haloC$_{2-6}$alkynyloxy, haloaryloxy, nitro, nitroC$_{1-6}$,alkyl, nitroC$_{2-6}$alkenyl, nitroaryl, nitroheterocyclyl, azido, amino, C$_{1-6}$alkylamino, C$_{2-6}$alkenylamino, C$_{2-6}$alkynylamino, arylamino, heterocyclamino, acyl, C$_{1-6}$alkylacyl, C$_{2-6}$alkenylacyl, C$_{2-6}$alkynylacyl, arylacyl, heterocyclylacyl, acylamino, acyloxy, acylC$_{1-6}$alkoxy, aldehydo, C$_{1-6}$alkylsulphonyl, arylsulphonyl, C$_{1-6}$alkylsulphonylamino, arylsulphonylamino, C$_{1-6}$alkylsulphonyloxy, arylsulphonyloxy, C$_{1-6}$alkylsulphenyl, C$_{2-6}$alklysulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, C$_{1-6}$alkylthio, arylthio, acylthio, cyano and the like. Preferred optional substituents are selected from the group consisting of C$_{1-6}$ alkyl, CF$_3$, C$_{3-6}$ cycloalkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, aryl, heterocyclyl, halo, haloaryl, haloheterocycylyl, hydroxy, C$_{1-4}$ alkoxy, aryloxy, carboxy, amino, acyl, arylacyl, heterocyclylacyl, acylamino, acyloxy, acylC$_{1-6}$alkoxy, nitro, arylsulphonyl, cyano and the like.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of pharmaceutically acceptable cations such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium; acid addition salts of pharmaceutically acceptable inorganic acids such as hydrochloric, orthophosphoric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic and hydrobromic acids; or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, citric, lactic, mucic, gluconic, benzoic,

succinic, oxalic, phenylacetic, methanesulphonic, trihalomethanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

The salts may be formed by conventional means, such as by reacting the free base form of the compound with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The derivatives of the compound of formula I are preferably pharmaceutically acceptable. The term "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt, hydrate, ester, amide, active metabolite, analogue, residue or any other compound which is not biologically or otherwise undesirable and induces the desired pharmacological and/or physiological effect.

The term "pro-drug" refers to functional derivatives of the compound of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs" ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of the active compound that requires

transformation within the body in order to release the active compound, and that has improved delivery properties over the active compound. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The term "tautomer" refers to compounds of formula I which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound.

The term "isomer" refers to structural, geometric and stereo isomers. As the compound of formula I may have one or more chiral centres, it is capable of existing in enantiomeric forms.

Included within the scope of this invention are compounds of the formula I to which at least one of a detectable label, an affinity tag and a photoreactive group is linked.

Synthesis

The formylation step (a) may be carried out using any suitable known process such as a Vilsmeyer formylation or modified version thereof.

The cycloaddition step (b) may involve a diene and a dienophile or functionally equivalent groups thereof.

R^3 can be introduced using any suitable known technique such as aromatic substitution chemistry or by appropriate choice of reagents in the cycloaddition reaction.

NS5B Inhibition

The ability of the compounds of formula I to inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV (NS5B) can be demonstrated by any assay capable of measuring RNA dependent RNA polymerase activity. A

suitable assay is described in the examples.

To demonstrate that the compounds of formula I act by specific inhibition of NS5B, the compounds may be tested for the lack of inhibitory activity in an assay measuring the activity of an RNA-dependent RNA polymerase other than HCV polymerase or in a DNA dependent RNA polymerase assay.

Pharmaceutical Compositions

The administration of the compound of the present invention may be any suitable means that results in a concentration of the compound that is effective to yield the desired therapeutic or prophylactic response. The compound may be contained in any appropriate amount in any suitable carrier and is generally present in an amount of 1-95% by weight of the total weight of the composition. The carrier must be "pharmaceutically acceptable" in the sense of being compatible with other ingredients of the composition and not injurious to the subject. The pharmaceutical composition may additionally comprise a therapeutically effective amount of one or more antiviral agents such as ribavirin, an antiviral nucleoside, polymerase inhibitor, protease inhibitor and/or inhibitor of viral entry, assembly or egress. The composition may also additionally comprise at least one immunomodulatory agent for example an interferon or interferon derivative and/or an inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH).

The composition may be provided in a dosage form that is suitable for oral, parenteral (including intravenous, intramuscular, subcutaneous and intradermal), rectal, vaginal, nasal, inhalation, topical or ocular administration routes. Thus, the composition may be in form of tablets, capsules, pills, powders, granulates, suspensions, emulsions, liquids, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays or aerosols. The pharmaceutical compositions may

be formulated according to conventional pharmaceutical practice (see , *e.g.*, Remington: The Science and Practice of Pharmacy, (19th ed.). A.R. Gennaro, 1995, Mack Publishing Company, Easton, PA. and Encyclopedia of Pharmaceutical Technology, eds. J.Swarbrick and J.C. Boylan, 1988-1999, Marcel Dekker, New York).

Pharmaceutical compositions may be formulated to release the active compound substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the active compound within the body over an extended period of time; (ii) formulations that after a predetermined lay time create a substantially constant concentration of the active compound within the body over an extended period of time; (iii) formulations that sustain active compound action during a predetermined time period by maintaining a relatively, constant, effective active compound level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active compound (sawtooth kinetic pattern); (iv) formulations that localise active compound action by, *e.g.*, special placement of a controlled release composition adjacent to or in the diseased tissue or organ; and (v) formulations that target active compound action by using carriers or chemical derivatives to deliver the active compound to a particular target cell type.

Administration of compounds in the form of a controlled release formulation is especially preferred in cases in which the compound has (i) a narrow therapeutic index (*i.e.*, the difference between the plasma concentration leading to harmful side effects or toxic reactions and the plasma concentration leading to a therapeutic effect is small; in general, the therapeutic

index, TI, is defined as the ratio of median lethal dose (LD_{50}) to median effective dose (ED_{50})); (ii) a narrow absorption window in the gastro-intestinal tract; or (iii) a very short biological half-like so that frequent dosing during a day is required in order to sustain the plasma level at a therapeutic level.

Any number of strategies can be applied in order to obtain a controlled release formulation in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, *e.g.*, various types of controlled release compositions and coatings. Thus, the active compound is formulated with appropriate excipients into a pharmaceutical composition, that, upon administration to the subject, releases the active compound in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, patches and liposomes.

Solid Dosage Forms For Oral Use

Formulations for oral use include tablets containing the active compound in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (*e.g.*, sucrose, sorbitol, sugar, mannitol, mirocrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate or sodium phosphate); granulating and disintegrating agents (*e.g.*, cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates or alginic acid); binding agents(*e.g.*, sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminium silicate, carboxymethylcellulose

sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (*e.g.*, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils or talc). Other pharmaceutically acceptable excipients can be colourants, flavouring agents, plasticisers, humectants, buffering agents and the like.

The tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. The coating may be adapted to release the active compound in a predetermined pattern (*e.g.*, in order to achieve a controlled release formulation) or it may be adapted not to release the active compound until after passage of the stomach (enteric coating). The coating may be a sugar coating, a film coating (*e.g.*, based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (*e.g.*, based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac and/or ethylcellulose). Furthermore, a time delay material such as, glyceryl monostearate or glyceryl distearate may be employed.

The solid tablet compositions may include a coating adapted to protect the composition from unwanted chemical changes, (*e.g.*, chemical degradation prior to the release of the active compound). The coating may be applied on the solid dosage form in a similar manner as that described in Encyclopedia of Pharmaceutical Technology, *supra*.

Formulations for oral use may also be presented as chewing tablets or as hard gelatin capsules wherein the

active compound is mixed with an inert solid diluent (*e.g.*, potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active compound is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil. Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, *e.g*, a mixer, a fluid bed apparatus or a spray drying equipment.

Liquids for Oral Administration

Powders, dispersible powders, or granules suitable for preparation of an aqueous suspension by addition of water are convenient dosage forms for oral administration. Formulation as a suspension provides the active compound in a mixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents are, for example, naturally-occurring phosphatides (*e.g.*, lecithin or condensation products of ethylene oxide with a fatty acid, a long chain aliphatic alcohol or a partial ester derived from fatty acids) and a hexitol or a hexitol anhydride (*e.g.*, polyoxyethylene stearate, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitan monooleate and the like). Suitable suspending agents are, for example, sodium carboxymethylcellulose, methylcellulose, sodium alginate and the like.

Parenteral Compositions

The compound may be administered parenterally by injection, infusion or implantation (intravenous, intramuscular, subcutaneous or the like) in dosage forms, formulations or via suitable delivery devices or implants containing conventional, non-toxic pharmaceutically acceptable carriers. The formulation and preparation of such compositions is well known to those skilled in the

art of pharmaceutical formulation. Specific formulations can be found in Remington: The Science and Practice of Pharmacy, *supra*.

Compositions for parenteral use may be presented in unit dosage forms (*e.g.*, in single-dose ampoules) or in vials containing several doses and in which a suitable preservative may be added (see below). The composition may be in form of a solution, a suspension, an emulsion, an infusion device or a delivery device for implantation or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. Apart from the compound, the composition may include suitable parenterally acceptable carriers. The active compound may be incorporated into microspheres, microcapsules, nanoparticles, liposomes or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, stabilizing, pH-adjusting agents and/or dispersing agents.

As indicated above, the pharmaceutical compositions may be in the form suitable for sterile injection. To prepare such a composition, the suitable active compound is dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives (e.g., methyl, ethyl or n-propyl p-hydroxybenzoate). In cases where the compound is only sparingly or slightly soluble in water, a dissolution enhancing or solubilising agent can be added or the solvent may include 10- 60% w/w of propylene glycol or the like.

Rectal Compositions

For rectal application, suitable dosage forms for a

composition include suppositories (emulsion or suspension type) and rectal gelatin capsules (solutions or suspensions). In a typical suppository formulation, the active compound is combined with an appropriate pharmaceutically acceptable suppository base such as cocoa butter, esterified fatty acids, glycerinated gelatin and various water-soluble or dispersible bases like polyethylene glycols and polyoxyethylene sorbitan fatty acid esters. Various additives, enhancers or surfactants may be incorporated.

Vaginal Compositions

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Nasal and Inhalation Compositions

For administration to the respiratory tract, including intranasal administration, the active compound may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

Thus in general the active compound may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol or polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (*eg.* Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and

viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose and carboxymethyl cellulose sodium).

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the subject administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant, such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of active compound may be controlled by provision of a metered valve.

Alternatively the active compound may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form, for example in capsules or cartridges of *eg.* gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the active compound will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

When desired, formulations adapted to give sustained release of the active compound may be employed.

The active compound may be administered by oral inhalation as a free-flow powder via a "Diskhaler" (trade mark of Glaxo Wellcome plc or a meter dose aerosol inhaler.

Topical Compositions

The pharmaceutical compositions may also be administered topically on the skin for percutaneous absorption in dosage forms or formulations containing conventionally non-toxic pharmaceutical acceptable carriers and excipients including microspheres and liposomes. The formulations include creams, ointments, lotions, liniments, gels, hydrogels, solutions, suspensions, sticks, sprays, pastes, plasters and other kinds of transdermal drug delivery systems. The pharmaceutically acceptable carriers may include emulsifying agents, antioxidants, buffering agents, preservatives, humectants, penetration enhancers, chelating agents, gel forming agents, ointment bases, perfumes and skin protective agents.

Examples of emulsifying agents are naturally occurring gums (e.g., gum acacia or gum tragacanth) and naturally occurring phosphatides (e.g., soybean lecithin and sorbitan monooleate derivatives). Examples of antioxidants are butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, butylated hydroxy anisole and cysteine. Examples of preservatives are parabens, such as methyl or propyl p-hydroxybenzoate and benzalonium chloride. Examples of humectants are glycerin, propylene glycol, sorbitol and urea. Examples of penetration enhancers are propylene glycol, DMS0, triethanolamine, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone and derivatives thereof, tetrahydrofurfuryl alcohol and Azone.RTM. Examples of chelating agents are sodium EDTA, citric acid and

phosphoric acid. Examples of gel forming agents are Carbopol, cellulose derivatives, bentonite, alginates, gelatin and polyvinylpyrrolidone. Examples of ointment bases are beeswax, paraffin, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), polyethylene glycols and condensation products between sorbitan esters of fatty acids and ethylene oxide (*e.g.*, polyoxyethylene sorbitan monooleate (Tween)).

The pharmaceutical compositions described above for topical administration on the skin may also be used in connection with topical administration onto or close to the part of the body that is to be treated. The compositions may be adapted for direct application or for introduction into relevant orifice(s) of the body (*e.g.*, rectal, urethral, vaginal or oral orifices). The composition may be applied by means of special delivery devices such as dressings or alternatively plasters, pads, sponges, strips or other forms of suitable flexible material.

Ocular Compositions

For application to the eye, the active compound may be in the form of a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride, or chlorohexidine and thickening agents such as hypromellose may also be included.

Veterinary Compositions

The active compounds may also be presented for use in the form of veterinary compositions, which may be prepared, for example, by methods that are conventional in the art. Examples of such veterinary compositions include those adapted for:

(a) oral administration, external application, for example drenches (e.g. aqueous or non-aqueous solutions or suspensions); tablets or boluses; powders, granules or pellets for admixture with feed stuffs; pastes for application to the tongue;

(b) parenteral administration for example by subcutaneous, intramuscular or intravenous injection, e.g. as a sterile solution or suspension; or (when appropriate) by intramammary injection where a suspension or solution is introduced in the udder via the teat;

(c) topical applications, e.g. as a cream, ointment or spray applied to the skin; or

(d) rectally or intravaginally, e.g. as a pessary, cream or foam.

Methods of treatment

The compounds of formula I may be used in the treatment of a *Flaviviridae* viral infection such as a HCV infection.

Generally, the term "treatment" means affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect and include: (a) preventing the infection from occurring in a subject that may be predisposed to the infection, but has not yet been diagnosed as having it; (b) inhibiting the infection, i.e., arresting its development; or (c) relieving or ameliorating the effects of the infection, i.e., cause regression of the effects of the infection.

The prevention of hepatitis C means, for example, administration of a pharmaceutical agent to a subject found to carry a HCV by a test and the like but without a symptom of infection, or to a subject who shows an improved disease state of hepatitis after a treatment of hepatitis C, but who still carries a HCV and is associated with a risk of recurrence of hepatitis.

The term "subject" as used herein refers to any animal having a disease or condition which requires

treatment with a pharmaceutically-active agent. The subject may be a mammal, preferably a human, or may be a non-human primate or non-primates such as used in animal model testing. While it is particularly contemplated that the compounds are suitable for use in medical treatment of humans, it is also applicable to veterinary treatment, including treatment of companion animals such as dogs and cats, and domestic animals such as horses, ponies, donkeys, mules, llama, alpaca, pigs, cattle and sheep, or zoo animals such as primates, felids, canids, bovids and ungulates.

The term "viral infection" refers to the introduction of a virus into cells or tissues, e.g., hepatitis C virus (HCV). In general, the introduction of a virus is also associated with replication. Viral infection may be determined by measuring virus antibody titer in samples of a biological fluid, such as blood, using, e.g., enzyme immunoassay. Other suitable diagnostic methods include molecular based techniques, such as RT-PCR, direct hybrid capture assay, nucleic acid sequence based amplification, and the like. A virus may infect an organ, e.g., liver, and cause disease, e.g., hepatitis, cirrhosis, chronic liver disease and hepatocellular carcinoma.

The term "Flaviviridae virus" refers to a virus of the family Flaviviridae, which family includes the Hepacivirus Flavivirus and Pestivirus or hepatitis C-like virus genera. A representative species of the genus of hepatitis C-like viruses is hepatitis C virus.

Representative species of the genus Flavivirus include yellow fever virus, tick-bome encephalitis virus, Rio Bravo virus, Japanese encephalitis virus, Tyuleniy virus, Ntaya virus, Uganda S virus, Dengue virus and Modoc virus. Representative species of the genus Pestivirus include bovine diarrhea virus, border disease virus and hog cholera virus. Unassigned viruses in the family Flaviviridae are included in the meaning of Flaviviridae virus.

Dosages

The term "therapeutically effective amount" means an amount of the compound of formula I effective to yield a desired therapeutic response.

Dosage levels of the compound of formula I are of the order of about 0.5 mg to about 20 mg per kilogram body weight, with a preferred dosage range between about 0.5 mg to about 10 mg per kilogram body weight per day (from about 0.5 gms to about 3 gms per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the subject treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 5 mg to 1g of an active compound with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to 500 mg of active ingredient.

Optionally the compounds are administered in a divided dose schedule, such that there are at least two administrations in total in the schedule. Administrations are given preferably at least every two hours for up to four hours or longer; for example the compound may be administered every hour or every half hour. In one preferred embodiment, the divided-dose regimen comprises a second administration of the compound after an interval from the first administration sufficiently long that the level of active compound in the blood has decreased to approximately from 5-30% of the maximum plasma level reached after the first administration, so as to maintain an effective content of active compound in the blood. Optionally one or more subsequent administrations may be given at a corresponding interval from each preceding administration, preferably when the plasma level has decreased to approximately from 10-50% of the immediately-

preceding maximum.

It will be understood, however, that the specific dose level for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, active compound combination and the severity of the particular infection undergoing therapy.

EXAMPLES

The invention will now be described with reference to the following non-limiting examples.

Synthetic Methods

^1H NMR spectra were recorded on either a Bruker Avance DRX 400, AC 200 or AM 300 spectrometer. Spectra were recorded in $CDCl_3$, d_6-acetone, CD_3OD or d_6-DMSO using the residual solvent peak as a reference. Chemical shifts are reported on the δ scale in parts per million (ppm) using the following conventions to assign the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) and prefixed b (broad). Mass spectra (ESI) were recorded on either a Micromass Platform QMS or Finnigan LCQ Advantage spectrometer. Flash chromatography was performed on 40-63μm silica gel 60 (Merck No. 9385). Preparative HPLC was carried out using a Gilson 322 pump with a Gilson 215 liquid handler and a HP1100 PDA detector. The HPLC systems employed Phenomenex C8(2) columns using either acetonitrile or acetonitrile containing 0.06% TFA in water or water containing 0.1% TFA.

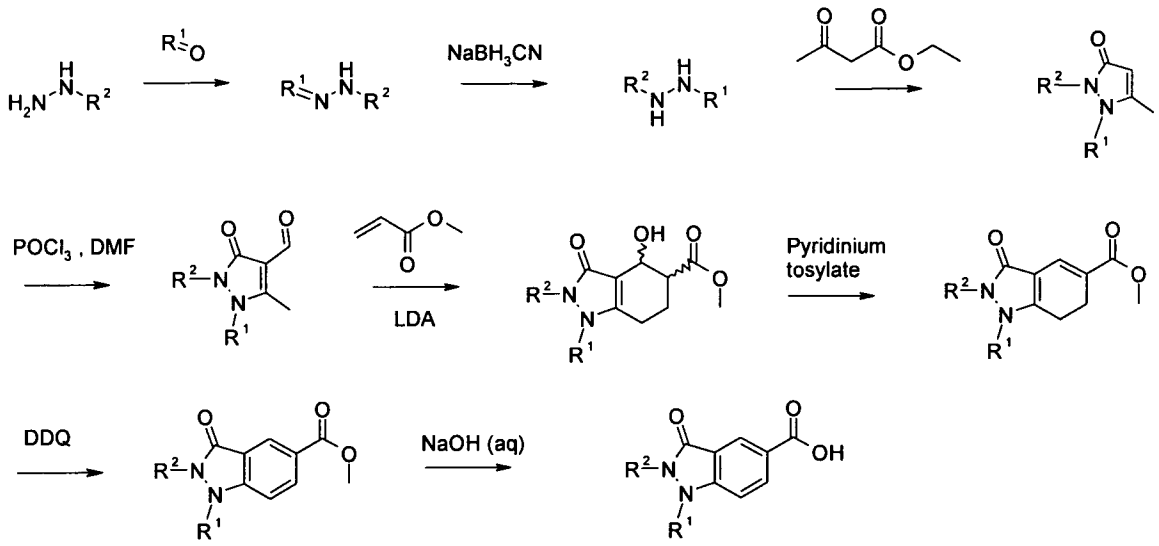
During the reactions a number of the moieties may need to be protected. Suitable protecting groups are well known in industry and have been described in many references such as Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981.

The abbreviations used in the Examples are as follows unless indicated otherwise:

Ac:	acetyl
acac:	acetylacetonate
BINAP:	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOP:	(benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate
Cy:	cyclohexyl
dba:	dibenzylideneacetone
DDQ:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA:	diisopropylethylamine
DMAP:	*N,N*-dimethylaminopyridine
DME:	1,2-dimethoxyethane
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
EDC:	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
eq:	molar equivalents
ESI:	electrospray ionisation
Et:	ethyl
HATU:	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU:	*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMBC:	heteronuclear multiple bond correlation
HPLC:	high performance liquid chromatography
LCMS:	liquid chromatography coupled mass spectrometry
LDA:	lithium diisopropylamide
Me:	methyl
MS:	mass spectrometry
NMP:	*N*-methylpyrrolidinone
NMR:	nuclear magnetic resonance
Ph:	phenyl
PIFA:	[bis(trifluoroacetoxy)iodo]benzene
PMDTA:	*N,N,N',N",N"*-pentamethyldiethylenetriamine
TFA:	trifluoroacetic acid
TFFH:	fluoro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate
THF:	tetrahydrofuran
TLC:	thin-layer chromatography

Example 1 (Method A)

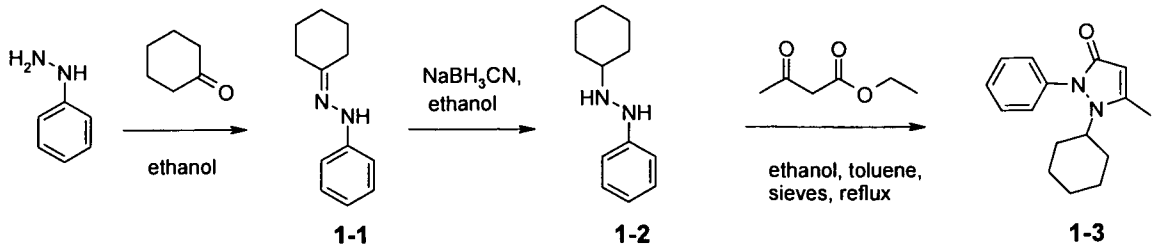
The scheme below depicts a non-limiting example of a process for manufacture of certain compounds of formula I.



In general, one equivalent of an appropriate hydrazine of general formula R^2-NH-NH_2 is treated with one equivalent of a suitable ketone or aldehyde of general formula R^1=O. The resulting hydrazone is reduced by treatment with approximately 1.2 equivalents of sodium cyanoborohydride. The crude *N,N'*-disubstituted hydrazine is then condensed with at least one equivalent of ethyl acetoacetate by heating under dehydrating conditions to yield a pyrazolone derivative. The pyrazolone is formylated by treatment with $POCl_3$ and DMF. A solution of the resulting aldehyde and approximately 1.1 equivalents of LDA is then treated with an excess of methyl acrylate or other suitable Diels-Alder substrate. The product thus obtained is then dehydrated with pyridinium tosylate and aromatised using DDQ. The ester may be hydrolysed by treatment with an aqueous base.

It will be appreciated by one skilled in the art that other compounds of formula I can be prepared by the addition, removal or modification of existing substituents. This could be achieved by using standard techniques for functional group inter-conversion that are well known, such as those described in "Comprehensive organic transformations: a guide to functional group preparations" by Larock R. C., New York, VCH Publishers, Inc. 1989.

1-Cyclohexyl-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-one

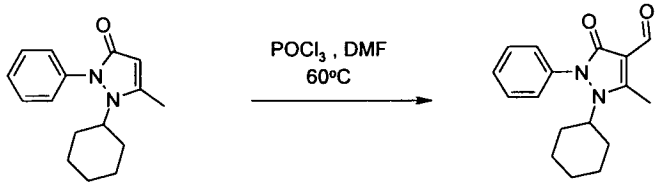


1-1 1-2 1-3

Phenylhydrazine (4.0 mL, 40.7 mmol) was treated with cyclohexanone (4.2 mL, 40.7 mmol, 1 eq) then dissolved in ethanol (20 mL) and stirred for 10 min at ambient temperature to give hydrazone **1-1**. Sodium cyanoborohydride (3.1 g, 40.8mmol, 1.2 eq) was added and the mixture was stirred. After 30 minutes LCMS showed complete reduction to the hydrazine **1-2**. Ethyl acetoacetate (5.2 mL, 40.7mmol, 1 eq) was added and the stirred mixture was heated to reflux under Dean-Stark conditions. More ethyl acetoacetate (5.2 mL, 40.7 mmol, 1 eq) was added and heating was continued overnight. The next morning, more ethyl acetoacetate (2 mL, 16.3 mmol, 0.4 eq) was added, along with molecular sieves (~10mL). After heating for a further 2 h, more ethyl acetoacetate (3 mL, 24.4 mmol, 0.6 eq) was added, along with more molecular sieves (~10mL). After another 2 h, more ethyl acetoacetate (1 mL, 8.1 mmol, 0.2 eq) was added and heating was continued for a final 1 h. After this time LCMS indicated almost complete conversion of the starting material. The mixture was allowed to cool, thinned with CH_2Cl_2 (50 mL) and filtered. After thoroughly washing the filter cake with CH_2Cl_2, the combined organic solutions were concentrated to yield a red syrup. The syrup was dissolved in CH_2Cl_2, adsorbed to silica and purified by flash chromatography using ethyl acetate as the eluent to give the title pyrazolone (**1-3**) as a yellow oil (3.1g, 12.1 mmol, 29% for three steps).

ESI-MS m/z calculated for $[M+H]^+$: 2; found: 257.1

1-Cyclohexyl-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde



1-3 1-4

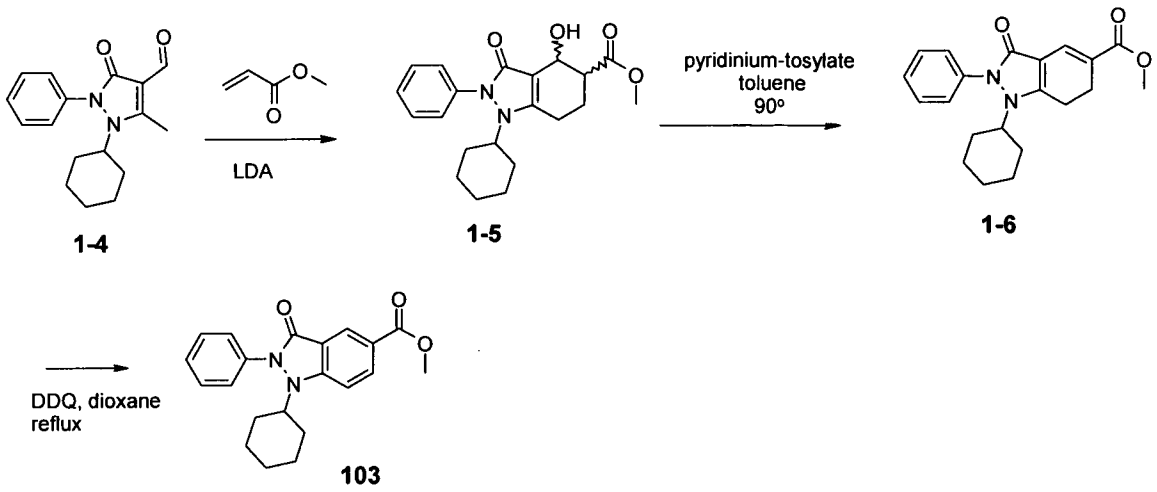
Dry chloroform (10 mL) and dry DMF (1.5 mL, 19.5 mmol, 2 eq) were stirred under a nitrogen atmosphere at ambient temperature. Phosphorus oxychloride (1.2 mL, 12.7 mmol, 1.3 eq) was added and the solution was stirred for 10 min. A solution of pyrazolone 1-3 (2.5 g, 9.8 mmol) in chloroform (10 mL) was added and the mixture was heated to 60°C and stirred overnight. More POCl3 (600 µL, 5.8 mmol, 0.6 eq) was added and the mixture was stirred at 60°C for a further 4 h, then the mixture was stirred at room temperature over the weekend. The reaction mixture was quenched with ice (20 mL) and 2 M NaOH (5 mL). Dichloromethane (150 mL) and water (70 mL) were added to dilute the mixture and then the organic layer was separated. The aqueous layer was extracted twice more with CH2Cl2 (2 x 50 mL). The combined organic layers were dried (MgSO4), filtered and concentrated. The residue was purified by flash chromatography to yield the title aldehyde (1-4) as a yellow solid (890mg, 3.12mmol, 32%).

ESI-MS m/z calculated for $[M+H]^+$: 285; found: 285.0

^{1}H-NMR (400 MHz, d6-acetone) δ 0.95-1.08 (m, 1H), 1.16-1.29 (m, 2H), 1.49-1.57 (m, 1H), 1.62 (ddd, 2H, *J* 3.4Hz, *J* 12.4Hz, *J* 16.5Hz), 1.70-1.76 (m, 2H), 1.89-1.95 (m, 2H), 2.74 (s, 3H), 3.98 (tt, 1H, *J* 3.6Hz, *J* 12.3Hz), 7.33-7.37 (m, 2H), 7.40-7.46 (m, 1H), 7.48-7.54 (m, 2H), 9.72 (s, 1H)

HMBC NMR experiments showed a long range ^{1}H,^{13}C correlation between the cyclohexyl methine proton and the methyl-substituted alkene carbon.

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carboxylic acid methyl ester (Compound 103, Table 1)



1-4 1-5 1-6 103

To a solution of diisopropylamine (370 µL, 2.64 mmol, 1.5 eq) in dry THF (2 mL) at 0°C under a nitrogen atmosphere was added n-BuLi (2.7 M in heptane, 720 µL, 1.93 mmol, 1.1 eq) and the reaction mixture was stirred for 20 min. The resulting solution of LDA was chilled to -78°C and a solution of 2-cyclohexyl-5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde 1-4 (500 mg, 1.76 mmol) in dry THF (3 mL) was cannulated in. Stirring was continued for 2 h, then methyl acrylate (1.6 mL, 17.6 mmol, 10 eq) was added. Stirring was continued and the reaction mixture was allowed to warm to room temperature overnight. The reaction flask was then immersed in a water bath at 50°C for 1h. The mixture was quenched with saturated ammonium chloride (15 mL) and extracted with ethyl acetate. The combined organic layers were dried (MgSO4) and concentrated to give Diels-Alder adduct 1-5. The Diels-Alder adduct was treated with pyridinium tosylate (530 mg, 2.11mmol, 1.2 eq) in toluene (30 mL) at 90°C for 30 min. The mixture was diluted with water, extracted with CH2Cl2, dried (MgSO4), filtered and concentrated to give dehydrated adduct 1-6. The dehydrated adduct was treated with DDQ (480 mg, 2.11mmol, 1.2 eq) in dioxane (50 mL) at reflux (~110°C) for 3 h. The mixture was cooled and allowed to stand overnight. It was then diluted with CH2Cl2 and concentrated to dryness. The residue was diluted with CH2Cl2 and purified by flash chromatography to yield the target indazolinone 103 as an off-white solid (106 mg, 0.302mmol, 17% for three steps).

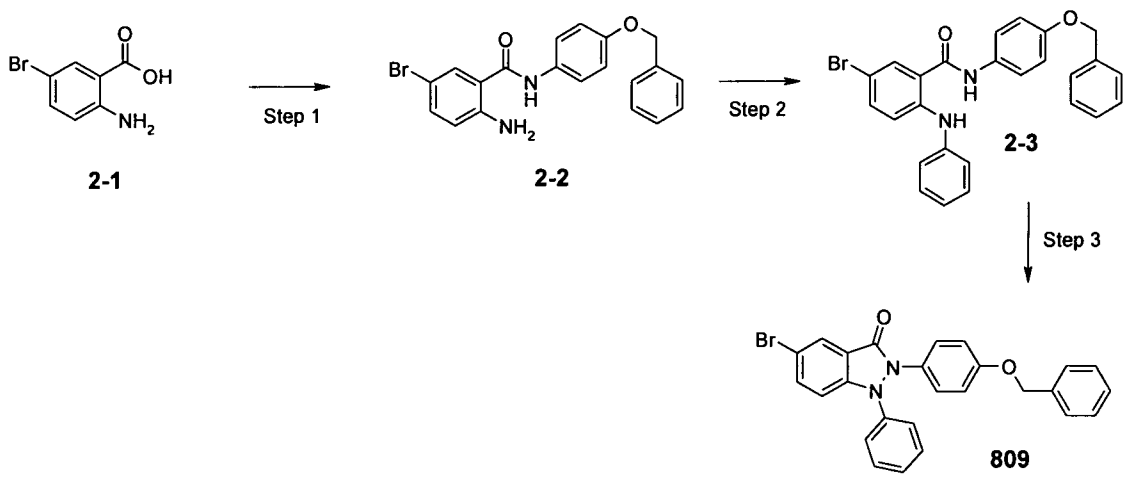
ESI-MS m/z calculated for $[M+H]^+$: 351; found: 351.1

^{1}H-NMR (300 MHz, d6-acetone) δ 0.85-0.95 (m, 1H), 1.01-1.16 (m, 1H), 1.13-1.30 (m, 2H), 1.57 (ddd, 1H, *J* 3.1Hz, *J* 12.4Hz, *J* 12.4 Hz), 1.71-1.81 (m, 2H), 1.83-1.91 (m, 2H),

3.77 (tt, 1H, *J* 3.6Hz, *J* 12.3Hz), 3.92 (s, 3H), 7.33-7.39 (m, 1H), 7.49-7.61 (m, 4H), 7.74 (dd, 1H, *J* 0.7Hz, *J* 8.8Hz), 8.23 (dd, 1H, *J* 1.8Hz, *J* 8.8Hz), 8.38 (dd, 1H, *J* 0.7Hz, *J* 1.8Hz)

Example 2 (Method B)

2-(4-Benzyloxyphenyl)-5-bromo-1-phenyl-1,2-dihydro-indazol-3-one (Compound 809, Table 8)



2-1 2-2

Step 1: HATU (1.25 eq) was added to 2-amino-5-bromobenzoic acid (5 g), 4-benzyloxyaniline hydrochloride (2 eq) and DIPEA (about 10 eq) in CH_2Cl_2 (about 200 mL) and the solution allowed to stand for 16 h. The mixture was concentrated and chromatographed on silica to yield amide **2-2**.

Step 2: $Pd_2(dba)_3$ (30 mg) and BINAP (30 mg) were added to toluene (10 mL) and the mixture stirred for 10 min. Bromobenzene (200 µL), KO^tBu (60 mg) and amine **2-2** (100 mg) were added and the mixture heated to reflux for 2 h. The mixture was filtered through Celite, concentrated and chromatographed on silica to yield compound **2-3** as a yellow powder (40 mg, 32%)

Step 3: PIFA (60 mg) was added to a solution of amide **2-3** (30 mg) in TFA (5 drops) and CH_2Cl_2 (5 mL). Progress was monitored by TLC and when the reaction was complete the mixture was concentrated and chromatographed on silica to yield indazolinone **809** as a yellow gum (18 mg, 60%).

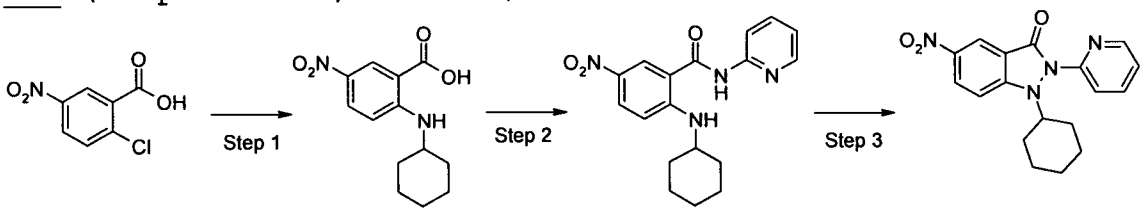
ESI-MS m/z calc. for $[M+H]^+$: 473 (Br isotope); found: 473.0

^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 2H), 6.95 (d, 2H, *J* 9.0Hz), 7.19-7.43 (m, 13H), 7.71 (dd, 1H, *J* 1.6Hz, *J* 8.6Hz), 8.30 (d, 1H, *J* 1.0Hz).

It will be apparent to one skilled in the art that the general procedure of Example 2 may be used to prepare other compounds of Formula I by replacing bromobenzene with an appropriate reagent of the formula R^1-Br, or by replacing 4-benzyloxyaniline with an appropriate reagent of the formula R^2-NH_2, where R^1 and R^2 are defined herein.

Example 3 (Method C)

1-Cyclohexyl-5-nitro-2-pyridin-2-yl-1,2-dihydroindazol-3-one (Compound 814, Table 8)



3-1 **3-2** **814**

Step 1: 2-Chloro-5-nitrobenzoic acid (1.5 g) was dissolved in cyclohexylamine (4 mL) with stirring and warming. The bright yellow solution was heated in a microwave reactor at 120 °C for 6 minutes. The resulting gel was diluted with CH_2Cl_2 (~100 mL) and extracted with 0.2M NaOH (4 × ~100 mL). The aqueous extracts were acidified with 5M HCl, causing precipitation of a white solid. The solid was recovered by filtration and dried. The solid was recrystallised from methanol/water to yield light yellow crystals of amine **3-1** (0.6 g, 31%).

Step 2: 2-Cyclohexylamino-5-nitrobenzoic acid (**3-1**) (0.6 g) was dissolved in CH_2Cl_2 (12 mL) and TEA (2 mL) and treated with BOP (1 g). After stirring for 2 minutes at room temperature, 2-aminopyridine (0.5 g) was added. The mixture was stirred for 64 h, then another portion of BOP (1 g) was added. After an additional 30 minutes, LCMS indicated almost complete reaction. The mixture was diluted with dichloromethane, washed with aqueous K_2CO_3 and the organic layer was dried, concentrated and the residue purified by flash chromatography on silica (eluting with 20:80 EtOAc/hexanes) to yield the target compound (**3-2**) as a yellow solid (280 mg, 36%).

Step 3: Compound **3-2** (270 mg) was dissolved in acetonitrile and treated with PIFA (341 mg, 1 eq) at room temperature. After 2h, TFA (1 mL) and additional PIFA (1 eq) were added. After 3h, more PIFA (1eq) was added and

the mixture was stirred at room temperature for 64 h. The mixture was concentrated to dryness, taken up in CH_2Cl_2 and washed with aqueous K_2CO_3. The organic layer was dried ($MgSO_4$), concentrated and purified by silica chromatography (eluting with EtOAc/hexanes) to yield the target (**814**) as a yellow solid (97 mg, 36%).

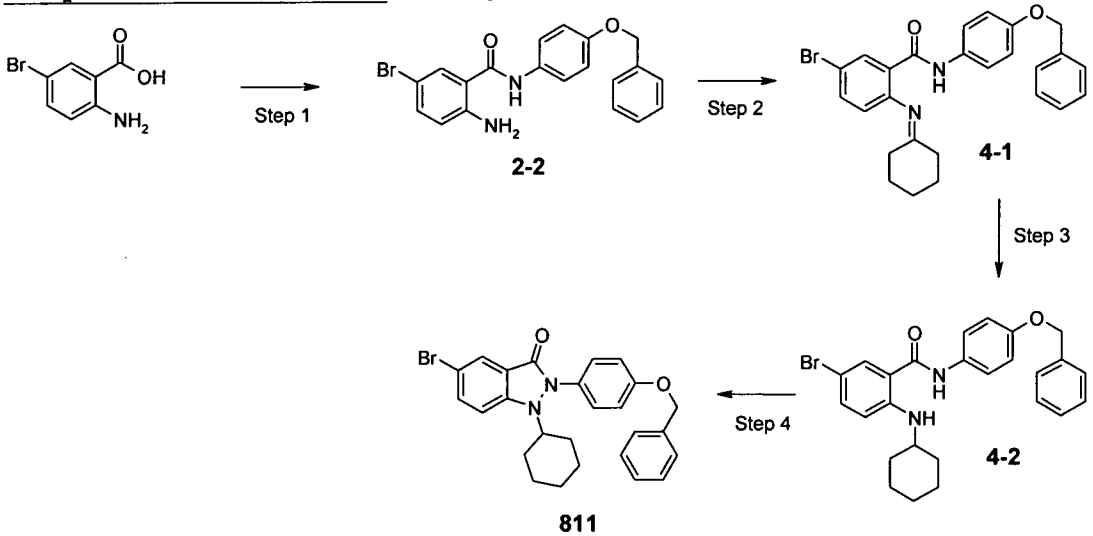
ESI-MS m/z calculated for $[M+H]^+$: 339; found: 339.1

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45-1.29 (m, 1H), 1.72-1.49 (m, 2H), 1.96-1.75 (m, 2H), 2.37-1.96 (m, 3H), 3.58 (ddd, 1H, *J* 15.7Hz, *J* 10.0Hz, *J* 6.7Hz), 4.03 (ddd, 1H, *J* 15.5Hz, *J* 7.4Hz, *J* 2.7Hz), 6.16 (dd, 1H, *J* 11.0Hz, *J* 4.1Hz), 6.74 (d, 1H, *J* 9.3Hz), 7.17 (ddd, 1H, *J* 7.3Hz, *J* 5.0Hz, *J* 0.8 Hz), 7.81 (ddd, 1H, *J* 8.6Hz, *J* 7.4Hz, *J* 1.9Hz), 8.20 (d, 1H, *J* 8.5Hz), 8.28 (dd, 1H, *J* 9.2Hz, *J* 2.7Hz), 8.44 (dd, 1H, *J* 5.0Hz, 2.0Hz), 8.97 (d, 1H, *J* 2.7Hz)

It will be apparent to one skilled in the art that the general procedure of Example 3 may be used to prepare other compounds of Formula I by replacing cyclohexylamine with an appropriate reagent of the formula R^1-NH_2, or by replacing 2-aminopyridine with an appropriate reagent of the formula R^2-NH_2, where R^1 and R^2 are defined herein.

Example 4 (Method D)

2-(4-Benzyloxy-phenyl)-5-bromo-1-cyclohexyl-1,2-dihydroindazol-3-one (Compound 811, Table 8)



Step 1: Amine **2-2** was prepared as described in Example 2.

Step 2: Amine **2-2** (9.3 g) was treated with an excess of cyclohexanone in acetic acid at reflux for 1 h. The

mixture was diluted with EtOAc, washed with aqueous NaOH, dried and concentrated to yield imine **4-1** (10.1 g).
Step 3: Imine **4-1** (10.1 g) was treated with sodium borohydride (~5 eq) in EtOH and the reaction heated at reflux for 3 h. Concentration and silica chromatography yielded the target amine **4-2** (8.2 g).
Step 4: Amide **4-2** was converted to indazolinone **811** using the analogous procedure to that described in Step 3 of Example 2.

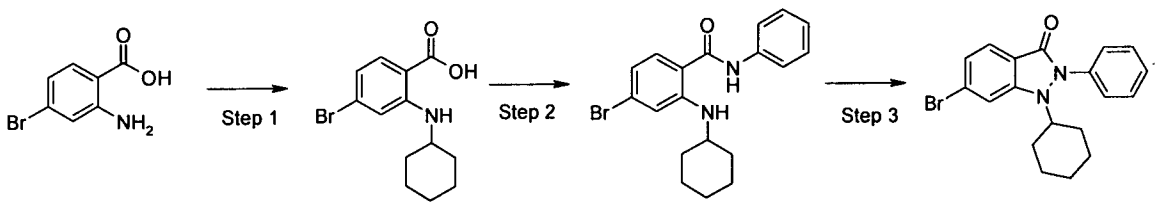
ESI-MS m/z calculated for $[M+H]^+$: 418; found: 418.1

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.87-1.21 (m, 1H), 1.36 (dd, 2H, *J* 21.9Hz, 12.2Hz), 1.51 (d, 1H, *J* = 11.8Hz), 1.67 (d, 4H, *J* 10.5 Hz, 4H), 3.61 (t, 1H, *J* 12.1Hz), 5.16 (s, 2H), 7.16 (d, 2H, *J* 8.9Hz), 7.31-7.52 (m, 7H), 7.66 (d, 1H, *J* 8.8Hz), 7.78 (dd, 1H, *J* 8.8Hz, 2.0Hz), 7.88 (d, 1H, *J* 1.9Hz)

It will be apparent to one skilled in the art that the general procedure of Example 4 may be used to prepare other compounds of Formula I by replacing cyclohexanone with an appropriate reagent of the formula R^1=O, or by replacing 4-benzyloxyaniline with an appropriate reagent of the formula R^2-NH_2, where R^1 and R^2 are defined herein.

Example 5 (Method E)

6-Bromo-1-cyclohexyl-2-phenyl-1,2-dihydroindazol-3-one
(Compound 817, Table 8)



5-1 **5-2** **817**

Step 1: To a stirred solution of 2-amino-4-bromobenzoic acid (1 g) in acetic acid (20 mL) was added cyclohexanone (1.2 eq) and the mixture was stirred at room temperature for 1h. Sodium borohydride (3 eq) was added in portions over 2 h at 40°C and the reaction mixture was stirred for an additional 2 h. Concentration gave an oil, which was diluted with water. The precipitated solids were isolated by filtration and purified by chromatography to yield the target **5-1** (1.2 g, 86%).

Step 2: Compound **5-2** was prepared from acid **5-1** by the procedure in Step 1 of Example 2, using aniline in place of 4-benzyloxyaniline hydrochloride.
Step 3: Amide **5-2** was converted to indazolinone **817** using the analogous procedure to that described in Step 3 of Example 2.

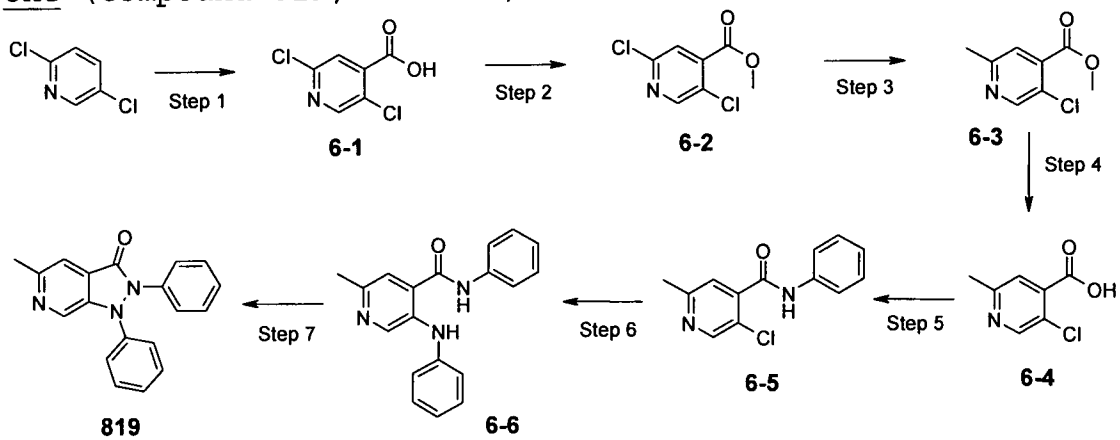
ESI-MS m/z calculated for $[M+H]^+$: 371; found: 370.9

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02-1.68 (m, 6H), 1.73-1.89 (m, 4H), 3.51 (tt, 1H, *J* 3.3Hz, 11.8Hz), 7.27-7.38 (m, 2H), 7.48 (t, 2H, *J* 8.1Hz), 7.59 (s, 1H), 7.75 (d, 1H, *J* 8.2Hz).

It will be apparent to one skilled in the art that the general procedure of Example 5 may be used to prepare other compounds of Formula I by replacing cyclohexanone with an appropriate reagent of the formula R^1=O, or by replacing aniline with an appropriate reagent of the formula R^2-NH_2, where R^1 and R^2 are defined herein.

Example 6 (Method F)

5-Methyl-1,2-diphenyl-1,2-dihydropyrazolo[3,4-c]pyridin-3-one (Compound 819, Table 8)



Step 1: 2,5-Dichloropyridine was added to a THF solution of n-BuLi and PMDTA and stirred for 2 hours at -78°C before quenching with dry ice. The product was isolated by acid-base work-up in 47% yield.
Step 2: To a methanolic solution of 2,5-dichloro-isonicotinic acid was added H_2SO_4 (conc) (0.5 mL) and the solution was heated to reflux for 12 h. The mixture was cooled to room temperature, neutralized with aqueous $NaHCO_3$, extracted into EtOAc and evaporated to afford the methyl ester (**6-2**) in 89% yield.

Step 3: To a THF solution of methyl 2,5-dichloro-isonicotinate was added $Fe(acac)_3$ (0.05 eq) and NMP (~10 vol). After cooling to 0°C, CH_3MgBr (1.2 eq) was added and the mixture was stirred at 0°C for 1 h. After aqueous workup, the organic extracts were purified by silica chromatography to yield nicotinate **6-3**.

Step 4: Methyl 5-chloro-2-methylisonicotinate was suspended in a solution of THF/MeOH/water (1:1:1) and to that LiOH (3 eq) was added. The mixture was stirred for 1 h and the resultant carboxylic acid was isolated by aqueous workup.

Step 5: To a CH_2Cl_2 solution of acid **6-4** (0.8 g) was added EDC (1.3 eq) and aniline (2 eq) at room temperature. After 10 minutes, the reaction was diluted with CH_2Cl_2 and washed with dilute HCl. The organic layer was dried and concentrated to yield amide **6-5** (0.9 g, 80%).

Step 6: Amide **6-5** was taken up in DME and to this was added NaO^tBu (1.4 eq), $Pd(OAc)_2$ (0.05 eq), $CyPF(^tBu)$ (0.05 eq) and aniline (1.2 eq). The mixture was heated at 100°C in a sealed tube for 12 hours and the product was purified by column chromatography.

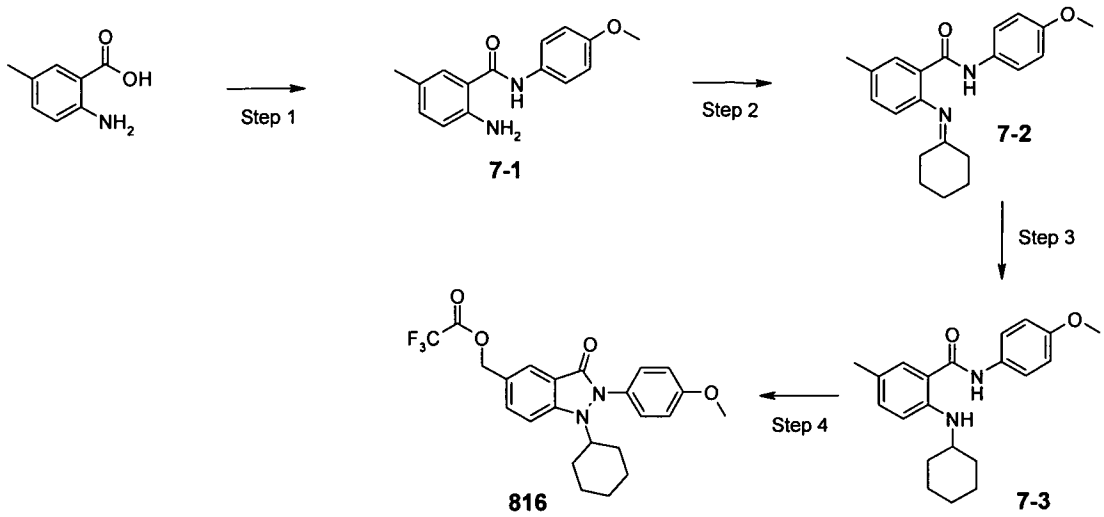
Step 7: Amide **6-6** was converted to indazolinone **819** using the analogous procedure to that described in Step 3 of Example 2 but using MeCN as the solvent instead of CH_2Cl_2.

ESI-MS m/z calculated for $[M+H]^+$: 302; found: 302.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H), 7.07 (dd, 1H, *J* 2.1Hz, 8.0Hz), 7.18 (t, 1H, *J* 7.1Hz), 7.25-7.38 (m, 2H, 7.63 (t, 1H, *J* 7.8 Hz), 7.71 (d, 2H, *J* 8.2Hz), 7.92 (d, 1H, *J* 8.1Hz), 8.04 (d, 1H, *J* 8.3Hz), 8.51 (s, 1H), 8.57 (s, 1H), 10.07 (br s, 1H).

Example 7 (Method G)

Acetic acid 1-cyclohexyl-2-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-indazol-5-ylmethyl ester (Compound 816, Table 8)



Step 1: Compound **7-1** was prepared from 2-amino-5-methylbenzoic acid using the analogous procedure set out in Step 1 of Example 2, using p-anisidine in place of 4-benzyloxyaniline hydrochloride.

Step 2: Imine **7-2** was prepared from amine **7-1** by the analogous procedure set out in Step 2 of Example 4.

Step 3: Imine **7-2** was reduced to amine **7-3** by the analogous procedure set out in Step 3 of Example 4.

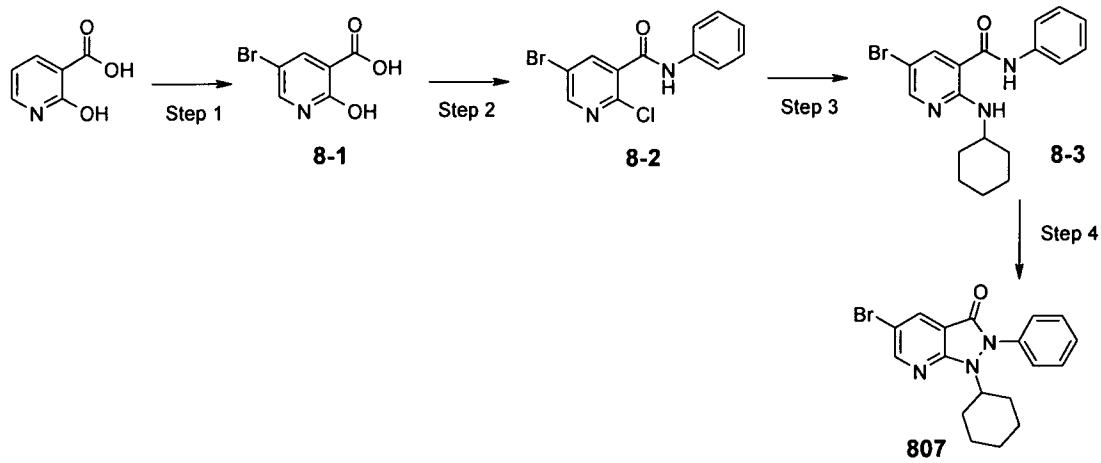
Step 4: Amide **7-3** was converted to an indazolinone using the analogous procedure to that described in Step 3 of Example 2 but in the current example, the substrate was observed to have simultaneously undergone both ring-closure and partial benzylic oxidation to yield trifluoroacetoxy derivative **816**.

ESI-MS m/z calculated for $[M+H]^+$: 449; found: 449.1.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96-1.27 (m, 3H), 1.35-1.68 (m, 3H), 1.70-1.89 (m, 4H), 3.54 (tt, 1H, *J* 3.2Hz, *J* 12.2Hz), 3.86 (s, 3H), 5.41 (s, 2H), 7.00 (d, 2H, *J* 9.0Hz), 7.26 (s, 1H), 7.42 (dd, 2H, *J* 1.4Hz, 9.0Hz), 7.58 (dd, 1H, *J* 1.7Hz, 8.5Hz), 7.94 (s, 1H)

Example 8 (Method H)

5-Bromo-1-cyclohexyl-2-phenyl-1,2-dihydropyrazolo[3,4-b]pyridin-3-one (Compound 807, Table 8)



Step 1: 2-Hydroxynicotinic acid (100 g) was converted to 5-bromo-2-hydroxynicotinic acid (**8-1**) in 79% yield using the procedure reported in Letavic, M.A. *et al.*, *Bioorganic and Medicinal Chemistry Letters*, 17, 2007, 2566-2569.

Step 2: A stirred suspension of 5-bromo-2-hydroxy-nicotinic acid (**8-1**)(67 g) in $POCl_3$ (1 vol) was heated to 100°C for 14 h. The reaction mixture was cooled to room temperature and quenched by stirring with ice-water for 10 min. The product was extracted into CH_2Cl_2 and treated with aniline for 1 h. After washing with water, concentration of the organic layer gave crude amide **8-2**.

Step 3: A solution of **8-2** (10 g) in cyclohexylamine (10 eq) was heated to 100°C for 14 h, after which time TLC indicated complete conversion of the starting material. The mixture was diluted with dilute HCl solution and the product extracted into CH_2Cl_2. The organic extracts were concentrated and recrystallised from diethyl ether to give amine **8-3** (6.5 g, 54%).

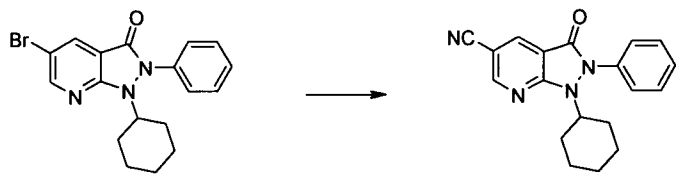
Step 4: Amide **8-3** was converted to indazolinone **807** using the analogous procedure to that described in Step 3 of Example 2.

ESI-MS m/z calc. for $[M+H]^+$: 374 (Br isotope); found: 374.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03-1.35 (m, 3H), 1.53-1.66 (m, 1H), 1.71-1.94 (m, 6H), 3.70-3.83 (m, 1H), 7.32-7.41 (m, 1H), 7.44-7.59 (m, 4H), 8.30 (s, 1H), 8.65 (s, 1H).

Example 9 (Method J)

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (Compound 820, Table 8)



807 820

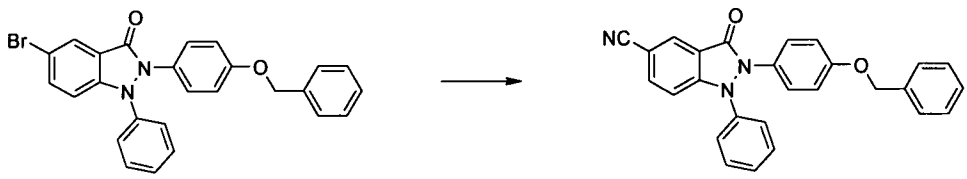
Bromide **807** (10.5 g) was suspended in NMP (30 vol), CuCN (1.8 eq) was added and the mixture was sealed in a vessel and heated to 210°C for 14 h. The reaction mixture was cooled to room temperature, poured into a solution of ethylenediamine (10 vol) and water (30 vol) and warmed to 85°C for 1 h. The mixture was cooled and the product extracted with EtOAc. The organic extracts were washed with dilute HCl, dried over sodium sulfate and concentrated to yield the nitrile (**820**)(4.2 g).

ESI-MS m/z calculated for $[M+H]^+$: 319; found: 319.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.08-1.22 (m, 3H), 1.53-1.66 (m, 1H), 1.74-2.02 (m, 6H), 3.85 (tt, 1H, *J* 3.6Hz, 12.7Hz), 7.38-7.61 (5H, m), 8.44 (d, 1H, *J* 2.1 Hz), 8.82 (d, 1H, *J* 2.0 Hz).

Example 10 (Method J)

2-(4-Benzyloxyphenyl)-3-oxo-1-phenyl-2,3-dihydro-1H-indazole-5-carbonitrile (Compound 813, Table 8)



809 813

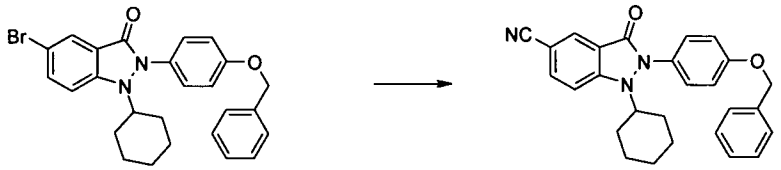
Bromide **809** was converted to nitrile **813** using the procedure described for Example 9, except that DMF was used as the solvent instead of NMP and the mixture was heated only to 140°C.

ESI-MS m/z calculated for $[M+H]^+$: 418; found: 418.1

^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 2H), 6.94 (d, 2H, *J* 9.1Hz), 7.03 (d, 1H, *J* 8.7Hz), 7.22-7.45 (m, 12H), 7.58 (dd, 1H, *J* 2.0Hz, *J* 8.7Hz), 8.09 (d, 1H, *J* 1.9Hz).

Example 11 (Method J)

1-Cyclohexyl-2-(4-benzyloxyphenyl)-3-oxo-2,3-dihydro-1H-indazole-5-carbonitrile (Compound 812, Table 8)



811 812

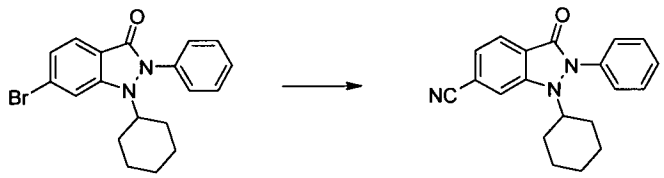
Bromide **811** was converted to nitrile **812** using the procedure described for Example 9, except that DMF was used as the solvent instead of NMP and the mixture was heated only to 140°C.

ESI-MS m/z calculated for $[M+H]^+$: 424; found: 424.1

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.90-1.24 (m, 3H), 1.37-1.57 (m, 3H), 1.64-1.75 (m, 4H), 3.76 (t, 1H, *J* = 12.1Hz), 5.17 (s, 2H), 7.17 (d, 2H, *J* = 9.0Hz), 7.31-7.46 (m, 5H), 7.49 (d, 2H, *J* 8.4Hz), 7.86 (d, 1H, *J* 8.8Hz), 8.00 (dd, 1H, *J* 8.7Hz, 1.7Hz), 8.27 (d, 1H, *J* 1.3Hz)

Example 12 (Method J)

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-6-carbonitrile (Compound 818, Table 8)



817 818

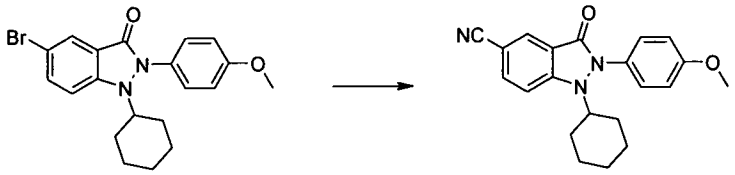
Bromide **817** was converted to nitrile **818** using the procedure described for Example 9.

ESI-MS m/z calculated for $[M+H]^+$: 318; found: 318.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02-1.30 (m, 4H), 1.44 (q, 1H, *J* 11.8Hz), 1.63 (d, 1H, *J* 10.0Hz), 1.83 (dd, 4H, *J* 8.8Hz, 13.1Hz), 3.57 (tt, 1H, *J* 3.2 Hz,12.5Hz), 7.36 (t, 1H, *J* 7.0Hz), 7.42-7.59 (m, 5H), 8.00 (d, 1H, *J* 7.0Hz).

Example 13 (Method J)

1-Cyclohexyl-2-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-indazole-5-carbonitrile (Compound 810, Table 8)



804 810

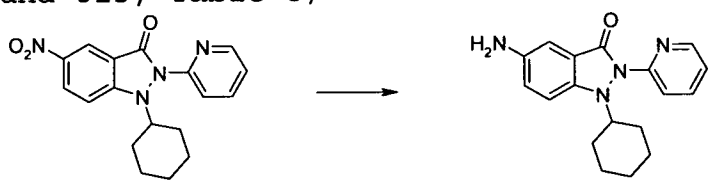
Bromide **804** was converted to nitrile **810** using the procedure described for Example 9, except that DMF was used as the solvent instead of NMP and the mixture was heated only to 140°C.

ESI-MS m/z calculated for $[M+H]^+$: 348; found: 348.1

^{1}H-NMR (300 MHz, d_6-DMSO) δ 0.96-1.20 (m, 3H), 1.39-1.54 (m, 3H), 1.67-1.71 (m, 4H), 3.72-3.80 (m, 1H), 3.82 (s, 3H), 7.09 (d, 2H, *J* 9.0Hz), 7.39 (d, 2H, *J* 9.0Hz), 7.86 (d, 2H, *J* 1.8Hz), 8.02 (d, 2H, *J* 1.8Hz), 8.28 (d, 2H, *J* 1.2Hz).

Example 14 (Method K)

5-Amino-1-cyclohexyl-2-pyridin-2-yl-1,2-dihydro-indazol-3-one (Compound 815, Table 8)



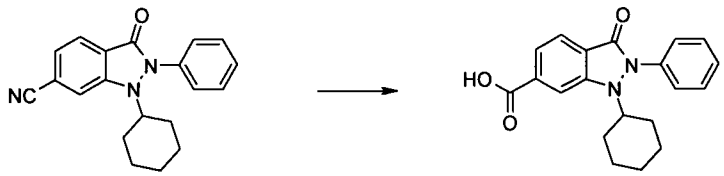
814 815

Nitro-indazolinone **814** (90 mg) was dissolved in ethanol (30 mL), treated with 10%Pd/C (5 mg) and placed under an atmosphere of hydrogen. The mixture was stirred vigourously for 16 h before filtering through celite. The filtrate was concentrated to dryness and the residue purified by silica chromatography (eluting with EtOAc/hexanes) to yield amine **815** (70 mg)

ESI-MS m/z calculated for $[M+H]^+$: 309; found: 309.1

Example 15 (Method L)

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-6-carboxylic acid (Compound 111, Table 1)



818 111

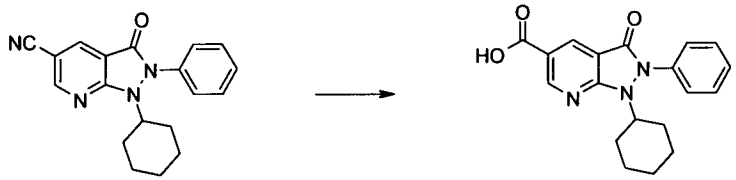
Nitrile **818** (2.6 g) was added to a solution of sulfuric acid and water (1:1) and the reaction mixture was heated to 100°C for 1 h. The mixture was diluted with water and the product extracted into chloroform. The organic extracts were concentrated and purified by silica chromatography to yield acid **111** (1.0g, 35%).

ESI-MS m/z calculated for $[M+H]^+$: 337; found: 337.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.03-1.30 (m, 4H), 1.50 (q, 1H, *J* 11.0Hz), 1.61 (d, 1H, *J* 10.2Hz), 1.79 (d, 1H, *J* 12.3Hz), 1.88 (d, 1H, *J* 11.1Hz), 3.61 (t, 1H, *J* 11.9Hz), 7.36 (t, 1H, *J* 7.1Hz), 7.51 (t, 2H, *J* 7.1Hz), 7.61 (d, 2H, *J* 7.3Hz), 7.98 (d, 1H, *J* 7.9Hz), 8.01 (d, 1H, *J* 7.9Hz), 8.22 (s, 1H), 10.23 (br s, 1H).

Example 16 (Method L)

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (Compound 112, Table 1)



820 112

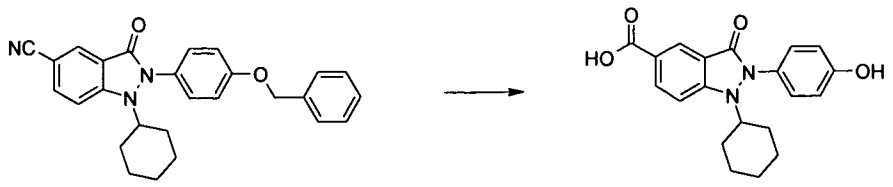
Nitrile **820** was converted to acid **112** using the procedure described for Example 15.

ESI-MS m/z calculated for $[M+H]^+$: 338; found: 338.0

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92-1.19 (m, 3H), 1.53 (d, 1H, *J* 11.9Hz), 1.64-1.90 (m, 6H), 3.79 (q, 1H, *J* 7.3Hz), 7.43 (t, 1H, *J* 7.1Hz), 7.48-7.61 (m, 4H), 8.54 (s, 1H), 9.17 (s, 1H).

Example 17 (Method M)

1-Cyclohexyl-2-(4-hydroxy-phenyl)-3-oxo-2,3-dihydro-1H-indazole-5-carboxylic acid (Compound 110, Table 1)



812 110

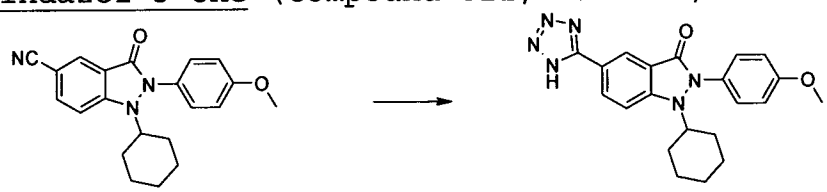
Nitrile **812** (130 mg) was treated with acetic acid (0.5 mL and concentrated HCl (3 mL) and stirred at reflux for 50 h. After cooling, the mixture was diluted with water and the product extracted into CH_2Cl_2. The organic layer was concentrated and the residue purified by silica chromatography to yield acid **110** (48 mg, 54%).

ESI-MS m/z calculated for $[M+H]^+$: 353; found: 353.1

^{1}H-NMR (300 MHz, DMSO) δ 0.86-1.24 (m, 3H), 1.32-1.58 (m, 3H), 1.58-1.79 (m, 4H), 3.70 (t, 1H, *J* 12.2Hz), 6.88 (d, 2H, *J* 9.0Hz), 7.26 (d, 2H, *J* 9.0Hz), 7.74 (d, 1H, *J* 9.1Hz), 8.26 (d, 1H, *J* 9.2Hz), 8.23 (s, 1H), 9.80 (br s, 1H).

Example 18 (Method N)

1-Cyclohexyl-2-(4-methoxyphenyl)-5-(1H-tetrazol-5-yl)-1,2-dihydroindazol-3-one (Compound 821, Table 8)



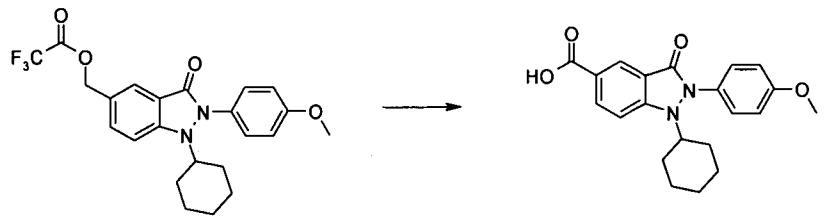
810 821

Nitrile **810** was converted to the title tetrazole using trimethylaluminium and trimethylsilylazide according to the analogous procedure reported in B. E. Huff and M. A. Staszak, *Tetrahedron Letters*, 34, 8011 (1993).

ESI-MS m/z calculated for $[M+H]^+$: 391; found: 391.1

Example 19 (Method O)

1-Cyclohexyl-2-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-indazole-5-carboxylic acid (Compound 107, Table 1)



816 107

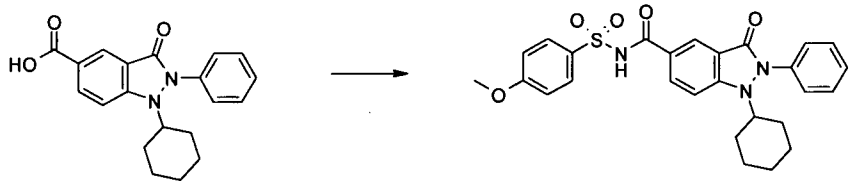
Indazolinone **816** (40 mg) and NaOH (100 mg) were dissolved in acetone/water (3:1, 4 mL) and heated to reflux. Portions of $KMnO_4$ were added whenever the purple colouration subsided. After 3 h, TLC indicated that the benzylic oxidation was complete. The mixture was filtered through celite, rinsing the filter with 5M NaOH and acetone. The acetone was removed in vacuo and the resulting aqueous solution was washed with CH_2Cl_2. The aqueous layer was then acidified with conc. HCl and extracted with CH_2Cl_2, which was dried and concentrated to give acid **107** as a pale tan powder (18 mg, 53%).

ESI-MS m/z calculated for $[M+H]^+$: 367; found: 367.1

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.01-1.29 (m, 3H), 1.43-1.68 (m, 3H), 1.81 (t, *J* 11.9Hz , 3.62 (t, 1H, *J* 12.1Hz), 3.86 (s, 3H), 5.30 (s, 2H), 7.02 (dd, 2H, *J* 2.2Hz, 6.8 Hz),7.37-7.42 (m, 3H), 8.24 (dd, 1H, *J* 1.7Hz, 8.7 Hz), 8.72 (s, 1H).

Example 20 (Method P)

N-(1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carbonyl)-4-methoxybenzenesulfonamide (Compound 501, Table 4)



104 501

In general, a solution of an appropriate indazolinone-carboxylic acid in an inert solvent is treated with the desired sulfonamide (at least 1 equivalent), an activating agent such as EDC (about 1 to 2 eq) and, if required, DMAP (~2 eq), such as in the manner reported by Stansfield *et al.* in *Bioorg Med Chem Lett* 17(18), 2007, 5143. If desired, a non-nucleophilic base, such as DIPEA, may be added.

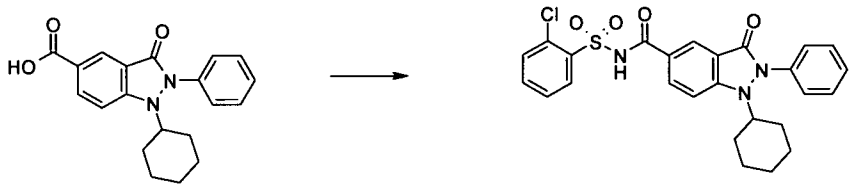
In this example, a dichloromethane solution of 1-cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carboxylic acid (**104**) was treated with EDC (2 eq) and DMAP (2 eq) and then 4-methoxybenzenesulfonamide (2 eq) to yield the title compound (**501**), which was isolated by silica chromatography.

ESI-MS m/z calculated for $[M+H]^+$: 506; found: 506.1

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.99-1.23 (m, 3H), 1.41-1.64 (m, 3H), 1.93-1.67 (m, 4H), 3.59 (tt, 1H, *J* 12.3Hz, 3.2Hz), 3.87 (s, 3H), 6.98 (d, 2H, *J* 9.0 Hz), 7.36 (tt, 1H, *J* 7.1 Hz, 1.5Hz), 7.40-7.59 (m, 5H), 8.02 (d, 2H, *J* 9.0Hz), 8.08 (dd, 1H, *J* 8.8Hz, 1.8Hz), 8.56 (s, 1H), 9.76 (s, 1H, N*H*)

Example 21 (Method P)

2-Chloro-*N*-(1-cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carbonyl)-benzenesulfonamide (Compound 524, Table 4)



104 **524**

A dichloromethane solution of 1-cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carboxylic acid (**104**) was treated at room temperature with HATU (1.2 eq), DIPEA (3 eq) and then 2-chlorobenzenesulfonamide to yield the title compound (**524**), which was isolated by silica chromatography.

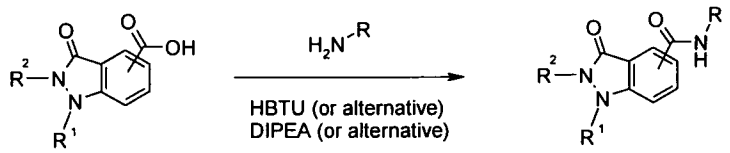
ESI-MS m/z calculated for $[M+H]^+$: 510; found: 510.0

^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.93-1.20 (m, 3H), 1.31-1.55 (m, 3H), 1.69 (t, 4H, *J* 11.5 Hz,), 3.59 (t, 1H, *J* 12.1Hz), 7.31-7.41 (m, 1H), 7.52 (d, 4H, *J* 3.9Hz), 7.59 (d, 1H, *J* 8.6Hz), 7.71 (t, 1H, *J* 8.0Hz), 8.34-8.12 (m, 4H), 8.61 (s, 1H)

Other sulfonamides may be purchased or prepared from their corresponding sulfonyl chlorides using techniques that are well known to those skilled in the art. It will also be apparent to one skilled in the art that the general procedure of Examples 20 and 21 may be used to prepare other compounds of Formula I by replacing 2-chlorobenzene-sulfonamide (Example 21) or 4-methoxybenzenesulfonamide

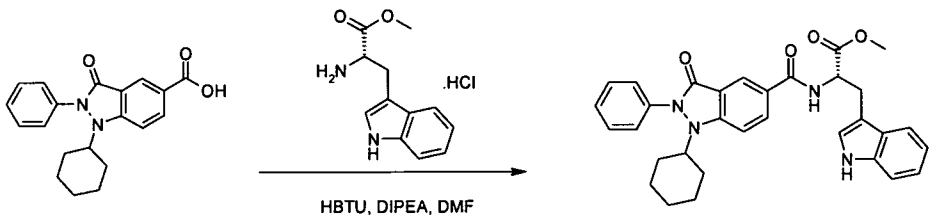
(Example 20) with alternative nucleophiles of the formula R^6-NHS(O)$_p$$R^8$, where R^6, R^8 and p are defined herein.

Example 22 (Method Q)



In general, certain amides of formula I may be prepared from an appropriate carboxylic acid as set out in the scheme above. The indazolinone-carboxylic acid and approximately 1.2 equivalents of an activating agent such as HBTU are dissolved in an appropriate solvent. A suitable non-nucleophilic base is added together with the desired amine and the solution is allowed to stand at room temperature until condensation has occurred. The products may be isolated by chromatography.

(S)-2-[(1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carbonyl)-amino]-3-(1H-indol-3-yl)-propionic acid methyl ester (Compound 303, Table 3)



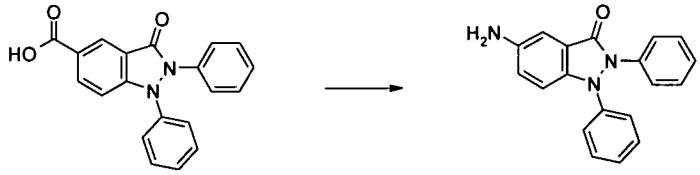
104 303

In the above example, carboxylic acid 104 (40.5 mg, 0.12 mmol) and HBTU (55 mg, 0.14 mmol, 1.2 eq) were dissolved in DMF (400 µL). DIPEA (105 µL, 0.6 mmol, 5 eq) was added followed by L-tryptophan methyl ester hydrochloride (37 mg, 0.14 mmol, 1.2 eq). The solution was allowed to stand at room temperature. After 20 min the reaction mixture was diluted with CH2Cl2 (2 mL) and washed with water (3 x 1 mL). The organic layer was filtered through cotton wool and concentrated. The crude residue was purified by flash chromatography using ethyl acetate:hexanes (1:1) as eluent to yield the target amide 303 as a white solid (60 mg, 0.11 mmol, 93%).

ESI-MS m/z calculated for $[M+H]^+$: 537.0; found: 537.1.

Example 23 (Method R)

5-Amino-1,2-diphenyl-1,2-dihydroindazol-3-one (Compound 802, Table 7)



In general, a suitable carboxylic acid substrate is dissolved in H_2SO_4, treated with sodium azide and heated to approximately 70° C until the reaction is complete. The reaction mixture is then poured onto an aqueous solution of NaOH and extracted with a suitable organic solvent.

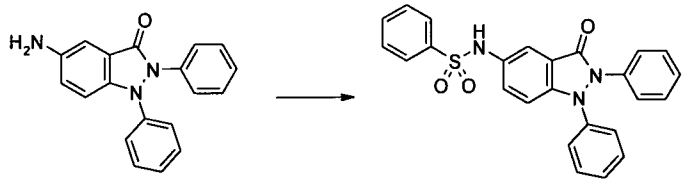
In the above example, sodium azide (20 mg) was added to a solution of 3-oxo-1,2-diphenyl-2,3-dihydro-1H-indazole-5-carboxylic acid (50 mg) in H_2SO_4 (1 mL) and heated to 70°C for 2 h. The reaction was cooled, poured into 2M NaOH and extracted into dichloromethane. The organic layer was dried ($MgSO_4$), filtered and concentrated to furnish the title compound (8 mg, 18%).

ESI-MS m/z calculated for $[M+H]^+$: 302; found: 302.0

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.72 (br s, 2H), 6.91 (dd, 1H, *J* 2.3Hz, *J* 8.7Hz), 7.01 (d, 1H, d, *J* 8.7Hz), 7.10-7.35 (m, 9H), 7.62 (d, 2H, *J* 4.8Hz).

Example 24 (Method S)

N-(3-Oxo-1,2-diphenyl-2,3-dihydro-1H-indazol-5-yl)-benzenesulfonamide (Compound 708, Table 5)



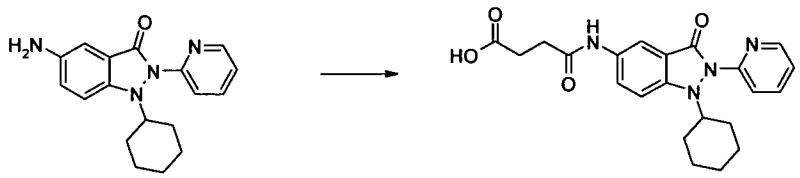
In general, the amine substrate is dissolved in a suitable solvent such as THF, CH_2Cl_2 or pyridine and treated with an excess of a suitable electrophile, such as a carboxylic acid halide, an anhydride, a sulfonyl halide or an isocyanate. If required, a non-nucleophilic base such as TEA may be added and the mixture may be heated. When the reaction is complete, the volatile components are evaporated and the residue may be purified by chromatography.

In the above example, a stirred solution of the indazolinone (5 mg) in pyridine (100 µl) was treated with benzenesulfonyl chloride (5 µl). The reaction mixture was then heated at 60 °C for 18 h, cooled to room temperature and the volatiles removed *in vacuo*. The residue was filtered through a plug of silica gel, eluting with EtOAc. The material was purified further by preparative HPLC to yield the title compound (**708**).

ESI-MS m/z calculated for $[M+H]^+$: 442.0; found: 442.1

Example 25 (Method S)

N-(1-Cyclohexyl-3-oxo-2-pyridin-2-yl-2,3-dihydro-1H-indazol-5-yl)-succinamic acid (Compound 709, Table 6)



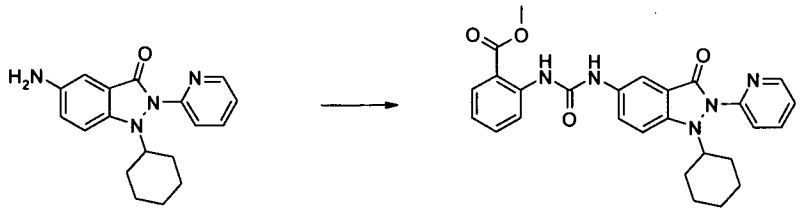
815 **709**

A THF solution of amine **815** was treated with succinic anhydride (1.2 eq) and DIPEA (3 eq) at room temperature. After 1 h, LCMS indicated complete conversion to the desired amide. The solution was diluted with 1M $NaHCO_3$ and washed with CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and the solvent was evaporated to yield crude amide **709**.

ESI-MS m/z calculated for $[M+H]^+$: 409; found: 409.2

Example 26 (Method S)

2-[3-(1-Cyclohexyl-3-oxo-2-pyridin-2-yl-2,3-dihydro-1H-indazol-5-yl)-ureido]-benzoic acid methyl ester (Compound 710, Table 6)



815 **710**

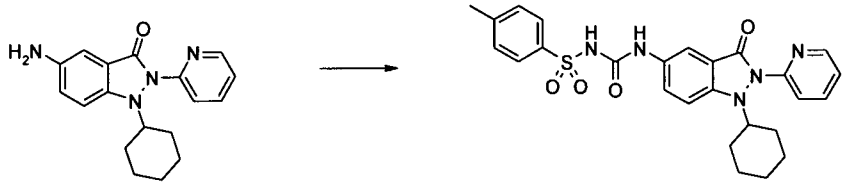
A THF solution of amine **815** was treated with 2-isocyanato-benzoic acid methyl ester (1.2 eq) at room temperature. After 1 h, LCMS indicated complete conversion to the desired urea. The solution was diluted with 1M $NaHCO_3$ and washed with CH_2Cl_2. The organic extracts were dried

($MgSO_4$), evaporated and purified by flash chromatography to yield amide **710**.

ESI-MS m/z calculated for $[M+H]^+$: 486; found: 486.2

Example 27 (Method S)

1-(1-Cyclohexyl-3-oxo-2-pyridin-2-yl-2,3-dihydro-1H-indazol-5-yl)-3-[(4-methylphenyl)sulfonyl]-urea (Compound 711, Table 6)



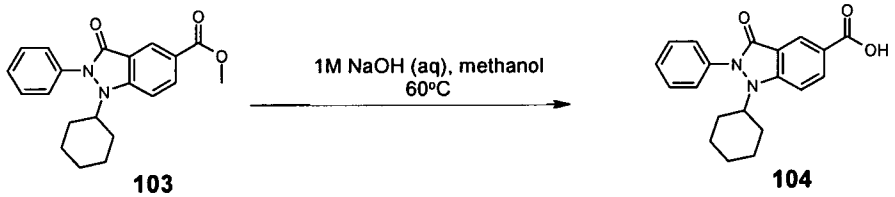
815 **711**

A THF solution of amine **815** was treated with 4-methyl-benzenesulfonyl isocyanate (1.2 eq) at room temperature. After 1 h, LCMS indicated complete conversion to the desired urea. The solution was diluted with 1M $NaHCO_3$ and washed with CH_2Cl_2. The organic extracts were dried ($MgSO_4$), evaporated and purified by flash chromatography to yield sulfonylurea **711**.

ESI-MS m/z calculated for $[M+H]^+$: 506; found: 506.2

Example 28 (Method T)

1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carboxylic acid (Compound 104, Table 1)



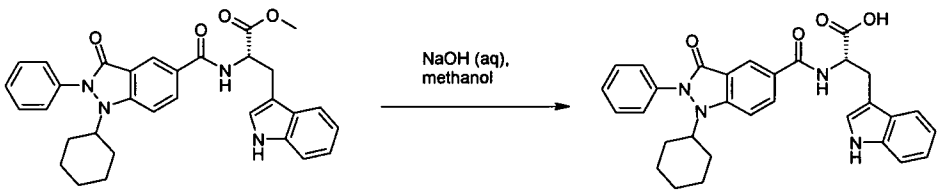
103 **104**

Indazolinone **103** (68 mg, 0.194mmol) was dissolved in a mixture of methanol (5 mL) and 1 M aqueous NaOH (2 mL) and warmed to 60°C for 1 h. The mixture was evaporated to dryness and the residue partitioned between 1 M HCl(aq) and CH2Cl2. The organic layer was filtered through cotton wool and concentrated to yield carboxylic acid 104 as a light brown solid (64 mg, 0.190mmol, 98%).

ESI-MS m/z calculated for $[M+H]^+$: 337.0; found: 337.1.

^{1}H-NMR (300 MHz, d6-acetone) δ 1.01-1.27 (m, 3H), 1.50-1.67 (m, 3H), 1.72-1.82 (m, 2H), 1.82-1.93 (m, 2H), 3.77 (tt, 1H, *J* 3.5Hz, *J* 12.2Hz), 7.33-7.39 (m, 1H), 7.49-7.61 (m, 4H), 7.74 (dd, 1H, *J* 0.7Hz, *J* 8.8Hz), 8.27 (dd, 1H, *J* 1.8Hz, *J* 8.7Hz), 8.43 (dd, 1H, *J* 0.7Hz, *J* 1.8Hz)

Example 29 (Method T)
(S)-2-[(1-Cyclohexyl-3-oxo-2-phenyl-2,3-dihydro-1H-indazole-5-carbonyl)-amino]-3-(1H-indol-3-yl)-propionic acid (Compound 311, Table 3)

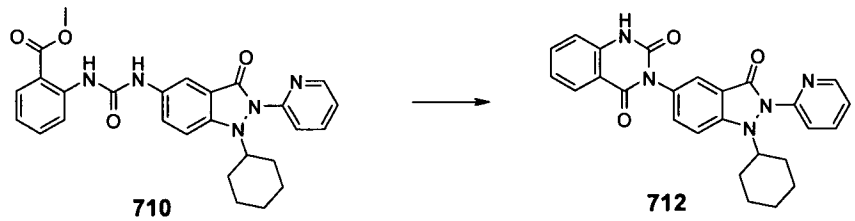


308 311

Amide **308** (60mg, 0.112 mmol) was dissolved in methanol (5 mL) and treated with 1 M NaOH (aq) (3 mL). The solution was warmed to 60°C for 30 min. LCMS indicated complete hydrolysis of the ester functionality. The solution was concentrated to dryness, treated with excess 1 M HCl (6 mL) and water (2 mL) and extracted with ethyl acetate (6 mL and then 2 x 2 mL). The organic extracts were filtered through cotton wool and concentrated to yield carboxylic acid 311 as a white solid (41 mg, 0.078 mmol, 68%).

ESI-MS m/z calculated for $[M+H]^+$: 523.0; found: 523.2.

Example 30 (Method T)
3-(1-Cyclohexyl-3-oxo-2-pyridin-2-yl-2,3-dihydro-1H-indazol-5-yl)-1H-quinazoline-2,4-dione (Compound 712, Table 6)



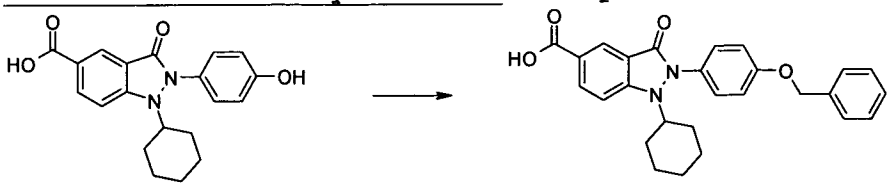
710 712

Compound **710** was treated according to the procedure described for example 29, except that acetonitrile was used as the co-solvent instead of methanol. Hydrolysis of the ester and concomitant cyclisation yielded indazolinone **712**.

ESI-MS m/z calculated for $[M+H]^+$: 454; found: 454.2

Example 31 (Method U)

2-(4-Benzyloxyphenyl)-1-cyclohexyl-3-oxo-2,3-dihydro-1H-indazole-5-carboxylic acid (Compound 114)



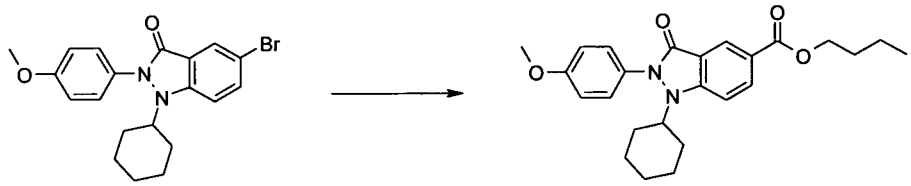
110 114

The phenol **110** was dissolved in acetone and treated with benzyl bromide (2 eq) and K_2CO_3 (excess). After 1 h at room temperature, LCMS indicated complete conversion to the desired ether. The mixture was concentrated, resuspended in dichloromethane and washed with water. The organic phase was dried ($MgSO_4$) and concentrated to yield the target phenol, **114**.

ESI-MS m/z calculated for $[M+H]^+$: 443; found: 443.2

Example 32 (Method V)

1-Cyclohexyl-2-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-indazole-5-carboxylic acid butyl ester (Compound 108, Table 1)



804 108

Indazolinone **804** (50 mg) was dissolved in 1-butanol (0.5 mL), treated with DIPEA (3 eq), $Pd(OAc)_2$ (0.2 eq) and Xantphos (0.2 eq) and placed under an atmosphere of carbon monoxide. The mixture was stirred and heated to 100°C for 3 days. After liquid-liquid work-up, the major product was purified by flash chromatography to yield the title ester (**108**) as a colourless, waxy solid.

ESI-MS m/z calculated for $[M+H]^+$: 401; found: 401.0.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J* 7.4 Hz, 3H), 1.02-1.27 (m, 3H), 1.40-1.69 (m, 6H), 1.71-1.86 (m, 5H), 3.58 (tt, 1H, *J* 12.3, 3.3 Hz), 3.87 (s, 3H), 4.34 (t, *J* 6.6 Hz, 2H), 7.01 (d, 2H, *J* 9.0 Hz), 7.39-7.45 (m, 3H), 8.23 (d, 1H, *J* 8.8 Hz), 8.60 (s, 1H)

Example 33 - HCV Polymerase Inhibition Assay - Poly C

HCV polymerase reactions were carried out using a modified method of Howe et al., Antimicrobial Agents and Chemotherapy 2004 48(12): 4813-4821. Reactions contained 50 nM NS5BbΔ21, 20 mM Tris-HCl pH 7.5, 5 mM MgCl2, 3 mM DTT, 25 mM KCl, 0.05% BSA, 0.5% DMSO, 0.4U/µL RNasin, and 20 nM Poly r(C) (Amersham). GTP was present at Km concentration including 0.04 µCi/µL 33P-GTP, with a total reaction volume of 50 µL. Reactions were initiated with the addition of template and GTP following pre-incubation of the test compound with NS5bΔ21. Reactions were terminated after 2 ½ hours with 50 µL 0.2 M EDTA. Terminated reactions were transferred to DEAE 96-well filter plates (Millipore), and unincorporated nucleotides were washed from the filters using 0.5 M sodium phosphate buffer. The filters were dried and 50 µL scintillation fluid was added to each well prior to reading on a scintillation counter.

The results of the Poly C assay are set out in Table 9 below. The calculated IC_{50} is quoted as A(< 10 µM), B(10 to 100 µM) or C(> 100 µM).

Table 9

Cpd. #	IC_{50}
241	B
245	B
246	B
247	B
302	B
304	B
306	B
310	B
311	B
312	B
316	B
317	C
339	B
344	B
357	B
358	B
359	B
360	B
371	B
378	B
504	A

Cpd. #	IC_{50}
508	B
509	B
514	B
515	B
517	B
518	B
519	B
523	B
538	B
539	B
542	B
543	B
546	B
547	B
550	B
554	B
557	B
558	B
559	B
566	B
567	B

Cpd. #	IC_{50}
568	B
569	B
573	B
574	B
575	B
576	B
579	B
580	B
582	B
583	B
584	B
586	B
587	B
588	A
589	B
590	A
591	A
592	B
593	B
594	B

Example 34 -HCV replicon assays

Ava5 cells (Huh7 cells containing a genotype 1b subgenomic HCV replicon, Blight et al., *Science* 2000 290: 1972-1974) were used in these studies. Cultures were maintained in a sub-confluent state in DMEM with glutamine, non-essential amino acids, 10% heat-inactivated foetal bovine serum and G418.

Cells for HCV RNA analysis were seeded at a concentration of 2000 cells per well into 96 well tissue culture trays and grown overnight in the presence of G418. The following day the cell monolayers were exposed to dilutions of compound. Stock solutions (50mM) of each compound were made in DMSO and diluted in culture media lacking G418 on the day of addition. Compounds were tested in a final concentration range of 20-100 uM downwards. Cells were treated for three consecutive days with the test compounds. Medium was replaced daily with fresh test compounds. Analysis of HCV RNA was performed 24 h following the last addition of test compound.

Example 35 -HCV RNA analysis

Cellular RNA was isolated using commercially available 96 well extraction method. HCV replicon RNA was assayed by real-time reverse transcription (RT-PCR) using primers located in the HCV NS5B gene and quantified on the basis of HCV RNA standards and relative amounts of cellular actin mRNA.

Example 36 -Cytotoxicity analysis

Cytotoxicity of compounds against Ava5 cells was assessed using the MTT assay (Watanabe et al., *Journal of Virological Methods* 1994 48:257-265). Plates were prepared as described for the HCV Replicon assay, and cytotoxicity analysis was performed 24 h following the last addition of test compound. Culture media in each test well was replaced with 1mg/mL MTT solution, and the cells incubated at 37°C for several hours. The MTT solution was then

replaced with isopropanol, and cytotoxicity assessed by reading the plates at 540/690 nm and determining colour development in each test well.

Example 37 -HCV Polymerase Inhibition Assay - Heteropolymer

HCV polymerase reactions were carried out using a modified method of Howe et al., *Antimicrobial Agents and Chemotherapy* 2004 48(12): 4813-4821. Reactions contained 25 nM NS5bΔ21, 20 mM Tris-HCl pH 7.5, 5 mM $MgCl_2$, 3 mM DTT, 0.05% BSA, 0.4U/μL RNasin, and 5 nM RNA (500 nt template). All NTPs used were at Km concentrations, and 0.04 μCi/μL ^{33}P-UTP, with a total reaction volume of 50 μL. Reactions were initiated with the addition of NTPs, and terminated after 1 hour with 50 μL 0.2 M EDTA. Terminated reactions were transferred to DEAE 96-well filter plates (Millipore), and unincorporated nucleotides were washed from the filters using 0.5 M sodium phosphate buffer. The filters were dried and 50 μL scintillation fluid was added to each well prior to reading on a scintillation counter.

Example 38 -*In vivo* Assays

The *in vivo* efficacy of the compounds may be evaluated using known methods such as those described in: Lanford, R.E. "The chimpanzee model of hepatitis C virus. Framing the Knowledge of Viral Hepatitis", 197-218 IHL Press, 2006; Lanford, R. E., Bigger, C., Bassett, S., Klimpel, G., "The chimpanzee model of hepatitis C virus infections", *Institute for Laboratory Animal Research Journal* 42(2), 2001, 117; or Lamarre, D., "An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus", *Nature* 426, 2003, 186. As an alternative to evaluating *in vivo* efficacy in chimpanzee or human subjects, a model that employs a surrogate virus – in particular GB virus B – may be used according to known methods such as described in Haqshenas, G. et al.,

"A chimeric GB virus B encoding the hepatitis C virus hypervariable region 1 is infectious *in vivo*", Journal of General Virology 88, 2007, 895 and Bright, H. et al., "Development of a GB Virus B Marmoset Model and Its Validation with a Novel Series of Hepatitis C Virus NS3 Protease Inhibitors", Journal of Virology, 78(4), 2004, 2062.

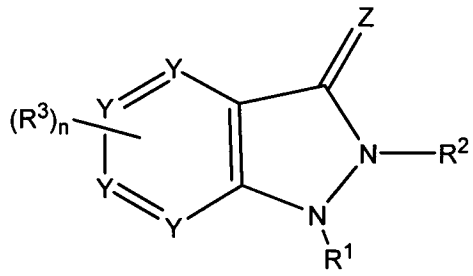
It must be noted that, as used in the subject specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise.

In the subject specification except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It will be understood to persons skilled in the art of the invention that many modifications may be made without departing from the spirit and scope of the invention.

CLAIMS

1. A compound of formula I



I

in which

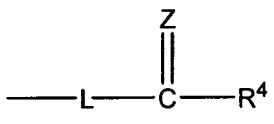
Y is independently selected from the group consisting of N, NO and CR in which R is selected from the group consisting of H, halogen, SH, S-optionally substituted C_{1-6}alkyl , OH, optionally substituted C_{1-6}alkoxy , NH_2, NH-optionally substituted C_{1-6}alkyl, N-di-optionally substituted C_{1-6}alkyl and NHCOR' in which R' is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

Z is selected from the group consisting of O, S and NR'' in which R'' is selected from the group consisting of H, OH, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

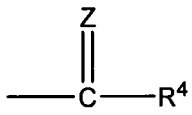
R^1 is selected from the group consisting of optionally substituted C_{2-6}alkyl, C_{1-6}alkylene optionally substituted C_{3-8}cycloalkyl, C_{1-6}alkylene optionally substituted aryl, C_{1-6}alkylene optionally substituted heterocyclyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

R^2 is -L-R"' in which L is absent or a linker and R"' is selected from the group consisting of optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl;

R^3 is selected from the group consisting of C_{2-6}alkyl; substituted C_{1-6}alkyl; halo; CN; optionally substituted aryl; optionally substituted heterocyclyl; NO_2; $NR^{12}R^{13}$ in which R^{12} and R^{13} are independently selected from the group consisting of H provided that not both are H, optionally substituted C_{1-6}alkyl, $S(O)_pR^{14}$ in which p is 0 to 2 and R^{14} is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-6}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl and COR^{25} in which R^{25} is selected from the group consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $S(O)_pR^{14}$ in which p and R^{14} are as defined above;



; and



in which

Z and L are as defined above;

R^4 is selected from the group consisting of amino acid; optionally substituted C_{3-8}cycloalkyl; optionally substituted aryl; optionally substituted heterocyclyl; OR^7 in which R^7 is selected from the group consisting of H,

optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl; and NR^5R^6;

in which R^5 and R^6 are independently selected from the group consisting of H; optionally substituted C_{1-6}alkyl; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; optionally substituted $(CH_2)_m$ optionally substituted aryl; optionally substituted$(CH_2)_m$ optionally substituted heterocyclyl in which m is 0 to 4; $S(O)_pR^8$ in which p is as defined above and R^8 is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are as defined above; $CR^{17}R^{18}COR^{19}$ in which R^{17} and R^{18} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl or R^{17} and R^{18} together with the C to which they are attached form an optionally substituted 3 to 6-membered ring and R^{19} is selected from the group consisting of OR^{15}in which R^{15} is as defined above and $NR^{20}R^{21}$ in which R^{20} and R^{21} are selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted aryl and optionally substituted heterocyclyl; and $CR^{22}(CO_2R^{23})CH_2R^{24}$ in which R^{22} and R^{23} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl and R^{24} is selected from the group consisting of, optionally substituted aryl and optionally substituted heterocyclyl; or

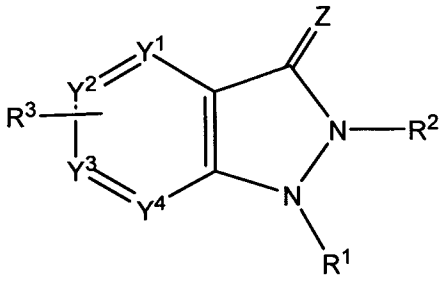
R^5 and R^6 together with the N to which they are attached form an optionally substituted 5 or 6-membered ring; and

n is 0 to 4,

salts, solvates, derivatives, prodrugs, tautomers and/or isomers thereof.

2. The compound according to claim 1, in which the

compound of formula I has the formula Ia



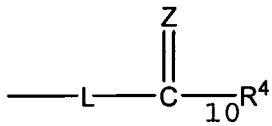
Ia

in which
Z, R^1, R^2 and R^3 are as defined in claim 1;
Y^1 is CH;
Y^2 is CH; and
Y^3 and Y^4 are independently selected from the group consisting of N and CH.

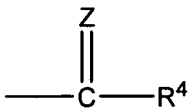
3. The compound according to claim 1 or 2, in which R^3 is located at position 5.

4. The compound according to any one of the preceding claims, in which R^3 is selected from the group consisting of C_{2-6}alkyl; substituted C_{1-6}alkyl; CN; optionally substituted aryl; optionally substituted heterocyclyl; $NR^{12}R^{13}$ in which R^{12} and R^{13} are independently selected from the group consisting of H provided that not both are H, optionally substituted C_{1-6}alkyl, $S(O)_pR^{14}$ in which p is 0 to 2 and R^{14} is selected from the group consisting of H, C_{2-6}alkyl, substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are independently selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycoalkyl, optionally substituted aryl and optionally substituted heterocyclyl and COR^{25} in which R^{25} is selected from the group

consisting of optionally substituted C_{1-6}alkyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $S(O)_pR^{14}$ in which p and R^{14} are as defined above;



; and



in which

Z and L are as defined above;

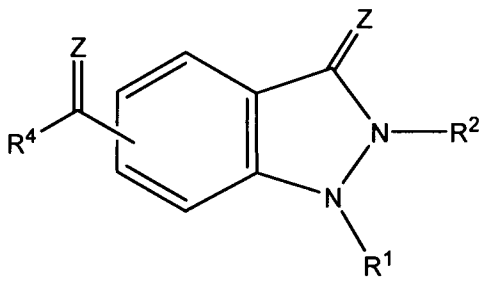
R^4 is selected from the group consisting of amino acid; optionally substituted C_{3-8}cycloalkyl; optionally substituted aryl; optionally substituted heterocyclyl; OR^7 in which R^7 is selected from the group consisting of C_{2-6}alkyl, substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl; and NR^5R^6;

in which R^5 and R^6 are independently selected from the group consisting of H; optionally substituted C_{1-6}alkyl; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; optionally substituted $(CH_2)_m$ optionally substituted aryl; optionally substituted$(CH_2)_m$ optionally substituted heterocyclyl in which m is 0 to 4; $S(O)_pR^8$ in which p is as defined above and R^8 is selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-6}alkynyl, optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl and $NR^{15}R^{16}$ in which R^{15} and R^{16} are as defined above; $CR^{17}R^{18}COR^{19}$ in which R^{17} and R^{18} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl or R^{17} and R^{18} together with the C to

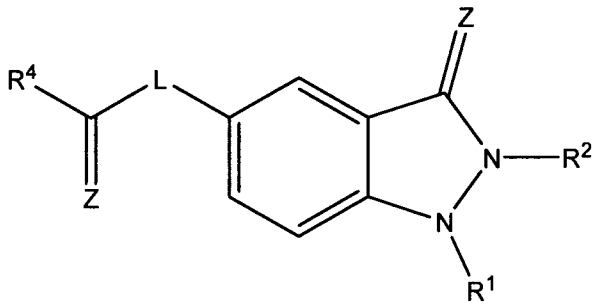
which they are attached form an optionally substituted 3 to 6-membered ring and R^{19} is selected from the group consisting of OR^{15}in which R^{15} is as defined above and $NR^{20}R^{21}$ in which R^{20} and R^{21} are selected from the group consisting of H, optionally substituted C_{1-6}alkyl, optionally substituted aryl and optionally substituted heterocyclyl; and $CR^{22}(CO_2R^{23})CH_2R^{24}$ in which R^{22} and R^{23} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl and R^{24} is selected from the group consisting of, optionally substituted aryl and optionally substituted heterocyclyl; or
R^5 and R^6 together with the N to which they are attached form an optionally substituted 5 or 6-membered ring.

5. The compound according to any one of the preceding claims, in which L in R^2 is selected from the group consisting of optionally substituted C_{1-6}alkylene and optionally substituted C_{1-6}acyl.

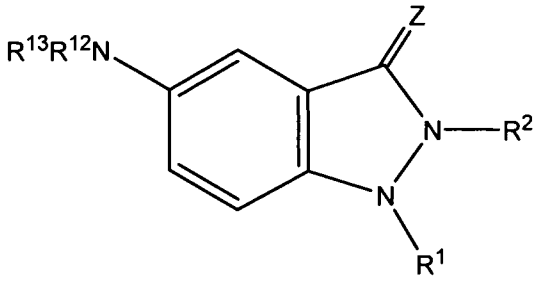
6. The compound according to claim 2, in which the compound of formula Ia has the formula Ic, Id, Ie or If



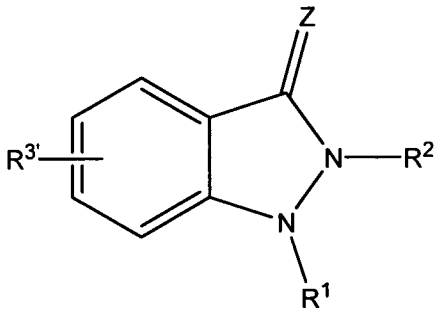
Ic



Id



Ie

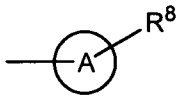


If

in which Z, L, R^1, R^2, R^4, R^{12} and R^{13} are as defined in claim 1; and

$R^{3'}$ is optionally substituted C_{1-6}alkyl, halo, CN, NO_2 or optionally substituted heterocyclyl.

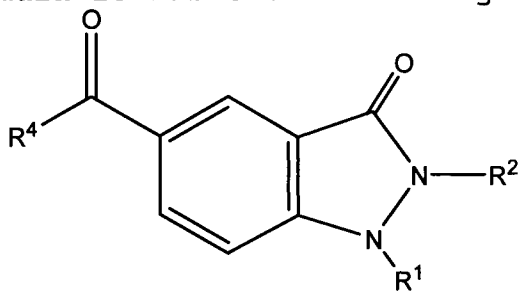
7. The compound according to claim 3 in which R^2 is



in which A is selected from the group consisting of C_{3-8}cycloalkyl, aryl and heterocyclyl; and

R^8 is selected from the group consisting of hydrogen, halo, cyano, nitro, amino, optionally substituted C_{1-6} alkanoylamino, optionally substituted C_{1-6} alkylsulfonyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $COOR^9$ in which R^9 is hydrogen or optionally substituted C_{1-6} alkyl, $CONH-(CH_2)_n-R^{10}$ in which R^{10} is optionally substituted C_{1-6} alkyl, C_{1-6} alkoxycarbonyl or C_{1-6} alkanoylamino and n is 1 to 6 and OR^{11} in which R^{11} is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl optionally substituted C_{3-8} cycloalkyl, optionally substituted aryl or optionally substituted heterocyclyl.

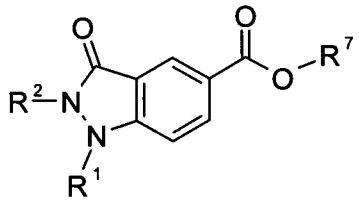
8. The compound according to claim 3, in which the compound of formula Ic has the formula Ig



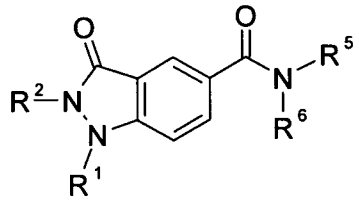
Ig

in which R^1, R^2 and R^4 are as defined in claim 1.

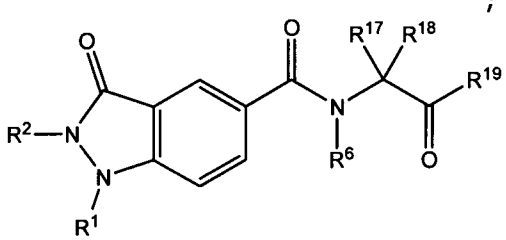
9. The compound according to claim 8, in which the compound of formula Ig has the following formula:



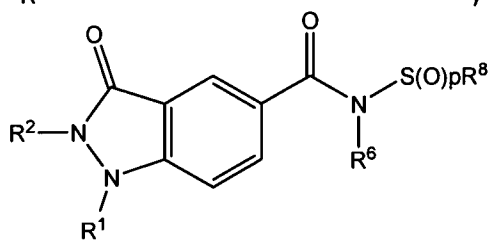
;



;



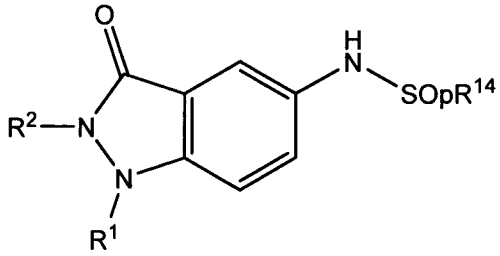
; or



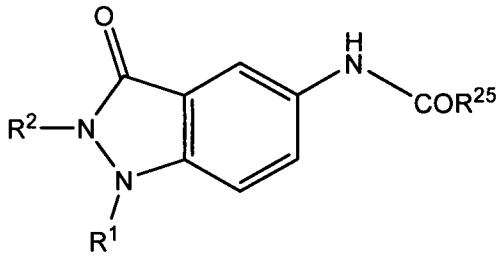
in which R^1, R^2, R^5, R^6, R^7, R^8, R^{17}, R^{18}, R^{19} and p are as defined in claim 1.

10. The compound according to claim 3, in which the

compound of formula Ie has the following formula:

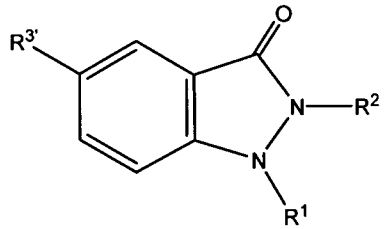


; or



in which R^1, R^2, R^{14}, R^{25} and p are as defined in claim 1.

11. The compound according to claim 3, in which the compound of formula If has the formula Ii



Ii

in which R^1 and R^2 are as defined in claim 1 and $R^{3'}$ is as defined in claim 3.

12. The compound according to any one of the preceding claims, in which R^1 is selected from the group consisting of optionally substituted C_{3-8}cycloalkyl, optionally substituted aryl and optionally substituted heterocyclyl.

13. The compound according to any one of the preceding claims, in which the cycloalkyl in R^1 is cyclohexyl and the aryl in R^1 is phenyl.

14. The compound according to any one of the preceding claims, in which R^2 is optionally substituted cyclohexyl, optionally substituted phenyl or optionally substituted

or 6 membered N-containing heterocyclyl.

15. The compound according to any one of the preceding claims which is a HCV polymerase inhibitor or an antiviral agent.

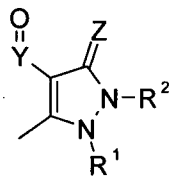
16. A process for the preparation of the compound of formula I according to any one of claims 1 to 14 which comprises the steps of:

(a) substitution of a compound of formula II



II

in which R^1, R^2, and Z are as defined in claim 1 to form a compound of formula III



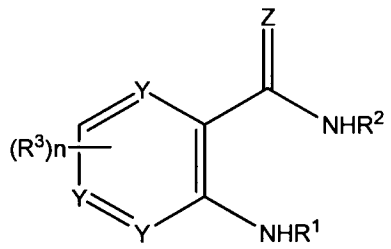
III

in which R^1, R^2, Y and Z are as defined in claim 1, provided that Y is not NO; and

(b) cycloaddition of the compound of formula III defined above, with concomitant or subsequent introduction of R^3 in which R^3 is as defined in claim 1.

17. A process for the preparation of the compound of formula I according to any one of claims 1 to 14 which comprises the step of:

(a) cyclisation of a compound of formula IV



IV

in which R^1, R^2, R^3, Y; Z and n are as defined in claim 1.

18. A pharmaceutical composition comprising the compound of formula I according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition according to claim 18 which further comprises a therapeutically effective amount of one or more antiviral agents and/or at least one immunomodulatory agent.

20. A method for the treatment of a *Flaviviridae* viral infection which comprises administering an effective amount of the compound of formula I according to any one of claims 1 to 14 to a subject in need thereof.

21. The method according to claim 20, in which the viral infection is hepatitis C.

22. A method of inhibiting the RNA-dependent RNA polymerase activity of the enzyme NS5B, encoded by HCV, comprising exposing the enzyme NS5B to an effective amount of the compound of formula I according to any one of claims 1 to 14 under conditions where the RNA-dependent RNA polymerase activity of the enzyme NS5B is inhibited.

23. A method of inhibiting HCV replication, comprising exposing a cell infected with HCV to an effective amount of the compound of formula I according to any one of claims 1 to 14 under conditions where replication of HCV

is inhibited.

24. Use of the compound of formula I according to any one of claims 1 to 14 in the manufacture of a medicament for use in the treatment of a Flaviviridae viral infection.

25. Use of the compound of formula I according to any one of claims 1 to 14 in the treatment of a Flaviviridae viral infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000714

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.
Int. Cl.

C07D 231/56 (2006.01) ***A61K 31/427*** (2006.01) ***C07D 401/12*** (2006.01)
[*continued in Supplemental Box*]

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Substructure of formula I searched on Registry and CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 580 402 A2 (E.R. SQUIBB & SONS, INC.) 26 January 1994 See compound 250d and abstract	1-2,5,12,15 18,19-25
X	WO 2004/093872 A1 (ELI LILLY AND COMPANY) 4 November 2004 See examples 79-98 and abstract	1-2,4-6,8-9,18
X	US 6,180,637 B1 (SCHINDLER ET AL.) 30 January 2001 See whole document, formula I, abstract, examples 26-35	1-4,6,8-12,18

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
07 July 2008	14 AUG 2008
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **Keith Wagg** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6225 6161

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000714

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,448,777 A (HEINEMANN ET AL.) 15 May 1984 See whole document, table on columns 11-14.	1-6,11-13,18
X	ROY, AMRITA ET AL. *Anionic [4+2] cycloaddition reactions of dihydropyrazolin-5-one dienolate with dienophiles: a novel approach for substituted and fused indazolones.* Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1999), (20), 3001-3004 See experimental compound 3, 14, 15 and 18	1-4,6-7,14,16
X	CORREA, A. ET AL. *An advantageous synthesis of new indazolone and pyrazolone derivatives.* Tetrahedron (2006), 62 (48), 11100-11105 See compounds 1a-d scheme 2	1-4,6-7,11-14,17
X	CORREA, A. ET AL. *Novel Alternative for the N-N Bond Formation through a PIFA-Mediated Oxidative Cyclization and Its Application to the Synthesis of Indazol-3-ones.* Journal of Organic Chemistry (2006), 71 (9), 3501-3505 See compounds 3a-3d, 3h-3k, 3m-3n	1-4,6-7,11-14,17
X	ARAN, V. ET AL. *Analogs of cytostatic, fused indazolinones: synthesis, conformational analysis and cytostatic activity against HeLa cells of some 1-substituted indazolols, 2-substituted indazolinones, and related compounds.* Liebigs Annalen (1996), (5), 683-691 See compound 13g	1-3,5-7,11-12
P,X	US 2007/0254892 A1 (SAGARA ET AL.) 1 November 2007 See abstract and examples	1,4,5,7,12-14,18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000714

Supplemental Box
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No: A classification of the subject matter. Int. Cl.

A61K 31/416 (2006.01)
A61K 31/4162 (2006.01)
A61K 31/4178 (2006.01)
A61K 31/4184 (2006.01)
A61K 31/4192 (2006.01)
A61K 31/423 (2006.01)
A61K 31/4245 (2006.01)
C07D 471/04 (2006.01)
A61K 31/428 (2006.01)
A61K 31/433 (2006.01)
A61K 31/437 (2006.01)
A61K 31/4439 (2006.01)
A61K 31/517 (2006.01)
A61P 31/14 (2006.01)
C07D 401/04 (2006.01)
C07D 401/14 (2006.01)
C07D 403/10 (2006.01)
C07D 403/12 (2006.01)
C07D 405/12 (2006.01)
C07D 409/12 (2006.01)
C07D 413/12 (2006.01)
C07D 417/12 (2006.01)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/000714

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	0580402	AU	41659/93	BG	97961	CA	2100894
		CN	1085546	CZ	9301437	FI	933277
		HU	67090	HU	9500679	JP	6206857
		MX	9304351	NO	932620	PL	299738
		SK	76093	US	5559256	US	5760036
		US	5776933	ZA	9305243		
WO	2004/093872	EP	1610779	US	2006211755		
US	6180637	AU	42576/99	BG	104910	BR	9911772
		CA	2271837	CN	1309642	DE	19821003
		EP	1077948	HU	0101707	NO	20005698
		NZ	508646	PL	344254	SK	17082000
		WO	1999/058504	ZA	200006151		
US	4448777	AU	87425/82	CA	1207774	DD	202566
		DE	3132916	DK	372482	EP	0072961
		ES	8400743	FI	822884	IL	66579
		JP	58039669	NO	822828	NZ	201642
		PH	18226	PT	75354	US	4537975
		ZA	8205380				
US	2007/0254892	WO	2007/126122	WO	2007/126128		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX