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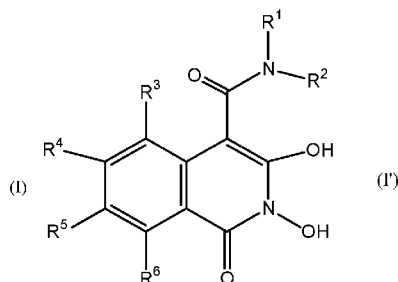
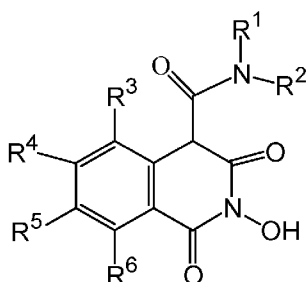
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(54) Title: 2-HYDROXYISOQUINOLINE-1,3(2H,4H)-DIONES AND RELATED COMPOUNDS USEFUL AS HIV REPLICATION INHIBITORS



(57) Abstract: The present invention relates to compounds and compositions acting as inhibitors of HIV integrase. The compound of the invention is of Formula (I), or a tautomer (I') thereof, or a pharmaceutically acceptable salt, or solvate of said compound or tautomer thereof, wherein R¹, R², R³, R⁴, R⁵ and R⁶ have defined meanings.

**2-HYDROXYISOQUINOLINE- 1 , 3 (2H , 4H) - DIONES AND RELATED COMPOUNDS
USEFUL AS HIV REPLICATION INHIBITORS**

FIELD OF THE INVENTION

5 The present invention relates to compounds and compositions containing said compounds acting as inhibitors of HIV integrase. The invention also provides processes for the preparation of the disclosed compounds and compositions and methods of using them, for instance as a medicine.

10 BACKGROUND OF THE INVENTION

Human immunodeficiency virus type 1 (HIV-1) is the causative agent of acquired immune deficiency syndrome (AIDS). Despite decades of research and the successful development of combination therapies known as highly active antiretroviral therapy (HAART), HIV-1
15 remains one of the most serious health problems in the world. Currently, 22 drugs are approved by FDA for the treatment of HIV infection. These compounds that have been licensed for clinical use for the treatment of HIV infections fall into one of the following four categories: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), and
20 (iv) entry inhibitors. The standard combination therapy consists of a PI compound or a NNRTI compound combined with two NRTIs compounds. HAART can suppress virus titers to undetectable levels but the virus persists in reservoirs such as peripheral blood mononuclear cells or resting T-lymphocytes. While HAART is undeniably effective, it is strongly limited by several factors like lack of therapy adherence, occurrence of important
25 side effects and the development of resistance (multidrug resistance and cross-resistance) causing the loss of drug effectiveness. In the last decade, viral entry inhibitors and, most importantly, HIV-1 integrase inhibitors have been pursued as novel anti-HIV agents.

HIV-1 integrase (IN) has emerged as an attractive target since it is necessary for stable
30 infection and has no cellular equivalent. This enzyme is essential for viral replication, and mediates the insertion of viral DNA within the host cell genome via a multistep process that occurs in discrete biochemical stages: (i) assembly of a stable-DNA enzyme complex with specific DNA sequences at the end of the HIV-1 long terminal repeat (LTR) regions, (ii) endonucleolytic process of the viral DNA to remove the terminal dinucleotide from

each 3'-end (3'-processing), (iii) strand transfer in which the viral DNA 3'-ends are covalently linked to the cellular DNA, (iv) removal of the two unpaired nucleotides at the 3'-ends of the viral DNA and (v) gap-filling, probably accomplished by cellular enzymes. Structural studies showed that the IN catalytic domain contains a triad of invariant carboxylate residues, D64, D116 and E152 (the so-called DDE motif), which are required for catalysis. One Mg^{2+} ion is coordinated by D64 and D116 along with water molecules whereas E152 that lies closely to D64 does not participate in metal binding. However it is largely accepted that this enzyme requires two metal divalent ions for catalysis. A great number of HIV-1 IN inhibitors have been described. Two IN inhibitors, GS-9137 (Elvitegravir) and MK-0518 (Raltegravir), demonstrated promising clinical trial results and advanced into later stage trials, the latter being the first US FDA-approved drug targeting IN. Raltegravir is the successful result of continued efforts to optimise HIV-1 IN inhibitory properties of the β -diketo acid class of compounds directed to two-metal ion enzyme catalytic sites.

US3726875 issued on 10 April 1973 discloses isoquinoline-1,3(2*H*,4*H*)-diones with anti-inflammatory activity.

US3886163 issued on 27 May 1975 discloses isoquinoline-1,3(2*H*,4*H*)-diones with anti-inflammatory activity.

WO200400472 published on 15 January 2004 discloses 3,4-dihydroisoquinolin-1-one derivatives as inducers of apoptosis.

WO200707578 published on 5 July 2005 discloses substituted isoquinoline-1,3(2*H*, 4*H*)-diones for the prevention of cancer.

Billamboz et al. (J. Med. Chem. 2008, 51, 7717-7730) disclose the design, synthesis, and biological evaluation of a series of 2-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones as dual inhibitors of human immunodeficiency virus type 1 integrase and the reverse transcriptase RNase H domain.

Billamboz et al. (European Journal of Medicinal Chemistry, 2011, 46, 535-546; available online 27 November 2010) disclose 2-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones as inhibitors of HIV-1 integrase and reverse transcriptase RNase H domain and the influence of the alkylation of position 4.

There is a stringent need in the art for potent inhibitors of HIV. In particular, there is a need for compounds which either complement existing drugs such that the resulting cocktail has improved activity or resistance to virus mutation or compounds which are themselves effective against many or all viable mutations of a virus.

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Unexpectedly the present novel hydroxyisoquinolinediones derivatives act as selective inhibitors of HIV-1 integrase. They inhibit the overall catalytic activity of HIV-integrase and act as inhibitors of HIV-1 replication. More in particular they act as strand transfer inhibitors.

10

Even more unexpectedly the present compounds act as 3'processing inhibitors. Thus they have a strong activity against both strand transfer activity and 3'processing and inhibit the viral integrase in a unique way. The compounds inhibit the overall integrase reaction, the strand transfer reaction and the 3'processing reaction with similar potency.

15

Hence, the present invention satisfies the urgent need for efficient and non-harmful pharmaceutically compounds and combinations for the treatment of retroviral infections, in particular lentiviral infections, and more particularly HIV infections, in mammals and in humans.

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SUMMARY OF THE INVENTION

In the present invention, new anti-viral, more in particular anti-HIV compounds are provided. The compounds are novel hydroxyisoquinolinediones derivatives of formula (I) and it has been shown that they possess anti-viral activity, more specifically against HIV. The present invention demonstrates that the compounds inhibit the replication of HIV. Therefore, these compounds constitute a new potent class of anti-viral agents that can be used in the treatment and prevention of viral infections in animals, mammals and humans, more specifically for the treatment and prevention of HIV.

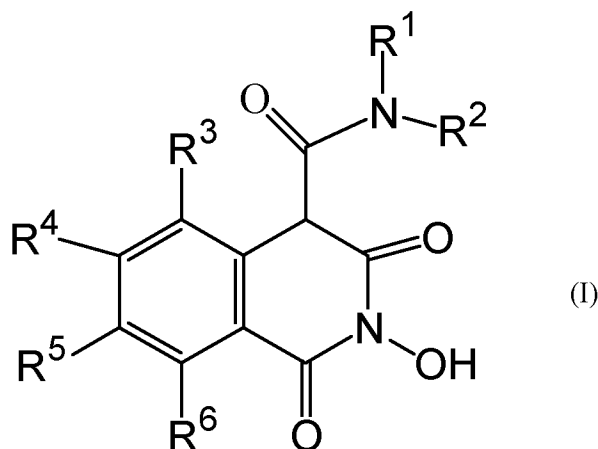
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The present invention relates to novel hydroxyisoquinolinediones derivatives of formula (I). The invention further relates to compounds having anti-viral activity, more specifically to novel hydroxyisoquinolinediones derivatives of formula (I) thereof having viral replication inhibitory properties, more in particular of HIV (Human Immunodeficiency

Virus), which is the etiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans, and consequently may be useful for the treatment of individuals infected by HIV. The present invention also relates to compounds of formula (I) having antiviral activities with respect to other viruses, such as Hepatitis C Virus. Present invention furthermore relates to the use of the compounds of formula (I) as a medicine and more specifically to the use of the compounds of formula (I) as an anti-viral agent. The invention also relates to methods for preparation of all such compounds and pharmaceutical compositions comprising them. The invention further relates to the use of said compounds in the manufacture of a medicament useful for the treatment of subjects suffering from HIV infection, as well as for treatment of other viral, retroviral or lentiviral infections, treatment of animals suffering from FIV, viral, retroviral, lentiviral infections or treatment of tumour or cancer cells. The present invention also relates to a method of treatment or prevention of viral infections, by using said compounds.

One aspect of the present invention is the provision of hydroxyisoquinolinediones derivatives and analogues thereof.

The present invention relates to hydroxyisoquinolinediones and derivatives or analogues thereof, corresponding to the formula (I),



or a tautomer thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof,

wherein

R¹ and R² are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₁₂alkyl, C₂₋₁₂alkenyl or C₂₋₁₂alkynyl which are optionally substituted with halo,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³;
 5 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl which are optionally substituted with halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹ or Ar³; Ar¹;
 Het¹; or

R¹ and R² together form a bivalent radical of formula

10 -(CH₂)₃- (a-1),
 -(CH₂)₄- (a-2), or
 -(CH₂)₅- (a-3);

R³, R⁴, R⁵ and R⁶ are each independently selected from:

15 hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₆alkyl which is optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN,
 -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C₁₋₆alkyloxy; C₁₋₆alkylthio;
 Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl; NHC(=O)C₁₋₆alkyl,
 which is optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸,
 20 C(=O)OC₁₋₆alkyl, Het¹ or Ar³; NHC(=O)Ar² or NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl which is optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; or C(=O)R⁹;

25 each R⁹ is hydrogen; OH; C₁₋₆alkyl which is optionally substituted with halo, C₁₋₆alkyl,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C₁₋₆alkoxy;
 NR¹⁰R¹¹; Ar⁴; or Het⁴;

each R¹⁰ and R¹¹ is independently selected from hydrogen; OH; C₁₋₆alkyl which is optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃,

30 C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

each Ar¹, Ar², Ar³, or Ar⁴ is independently phenyl or naphthyl and is optionally substituted with 1 to 5 substituents each of which is independently halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃ or CF₃;

- 5 each Het¹, Het², Het³ or Het⁴ is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of: O, N, and S and is optionally substituted with 1 to 4 substituents each of which is independently halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃ or CF₃.

- 10 In an embodiment, the present invention also relates to a compound of formula (I) or a tautomer thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof,

wherein

R¹ and R² are each independently selected from:

- 15 hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹; C₁₋₁₂alkyl, C₁₋₁₂alkenyl or C₁₋₁₂alkynyl which are optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl which are optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹ or Ar³, Ar¹,
20 Het¹; or

R¹ and R² together form a bivalent radical of formula



- 25 R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹; C₁₋₆alkyl which is optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl; NHC(=O)C₁₋₆alkyl, which is optionally substituted with halogen, C(=O)OC₁₋₆alkyl or Ar³; NHC(=O)Ar² or NHC(=O)Het²;

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each R^7 and R^8 is independently selected from hydrogen; C_{1-6} alkyl which is optionally substituted with halo, C_{1-6} alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; or C(=O)R⁹;

each R^9 is hydrogen; OH; C_{1-6} alkyl which is optionally substituted with halo, C_{1-6} alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C_{1-6} alkoxy; NR¹⁰R¹¹; Ar⁴; or Het⁴;

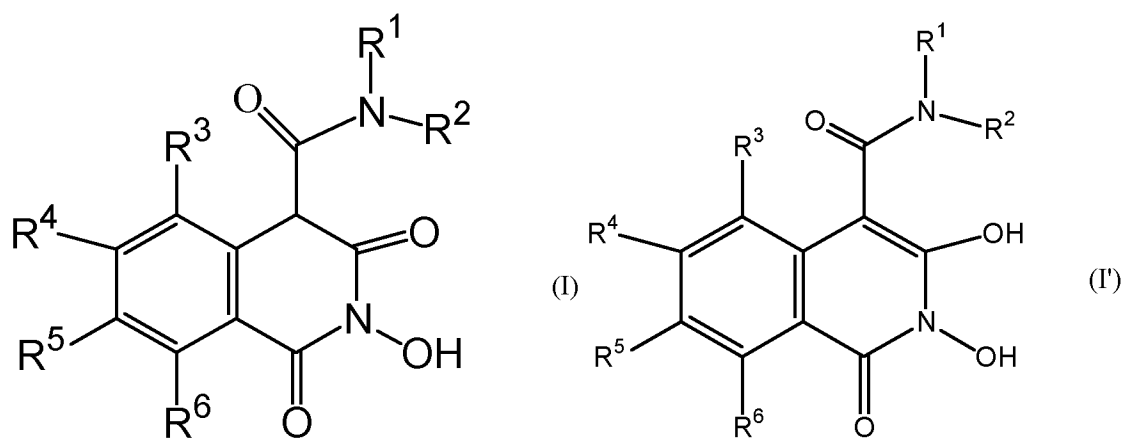
each R^{10} and R^{11} is independently selected from hydrogen; OH; C_{1-6} alkyl which is optionally substituted with halo, C_{1-6} alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³ or Het³; C_{1-6} alkoxy; Ar⁴; or Het⁴;

each Ar¹, Ar², Ar³, or Ar⁴ is independently phenyl or naphthyl and is optionally substituted with 1 to 5 substituents each of which is independently halo, C_{1-6} alkyl, OH, C_{1-6} alkyloxy, NO₂, -OCF₃ or CF₃;

each Het¹, Het², Het³ or Het⁴ is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of:

O, N, and S and is optionally substituted with 1 to 4 substituents each of which is independently halo, C_{1-6} alkyl, OH, C_{1-6} alkyloxy, NO₂, -OCF₃ or CF₃.

The present invention also relates to hydroxyisoquinolinediones and derivatives or analogues thereof, corresponding to the formula (I),



or a tautomer (I') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof,

wherein

R^1 and R^2 are each independently selected from:

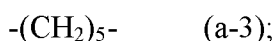
hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³; Ar¹;

Het¹; or

R¹ and R² together form a bivalent radical of formula



R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

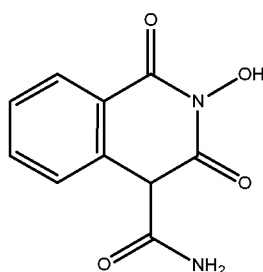
each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents)

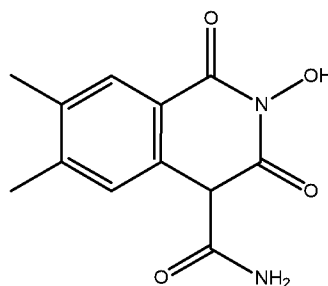
independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃;

provided that the following compounds are excluded:



2-Hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



2-Hydroxy-6,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide.

- One embodiment of the present invention relates to the compounds of formula (I) or (I') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, or for use as a treatment of infection by HIV, or for treating AIDS.

One embodiment of the present invention relates to the compounds of formula (I) or (I') as defined just hereinbefore or 2-Hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide, or 2-Hydroxy-6,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide for use as an antiviral agent, or for use as a treatment of infection by HIV, or for treating AIDS.

One aspect of the present invention relates to hydroxyisoquinolinediones and derivatives or analogues thereof, corresponding to the formula (I), or a tautomer (I') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof, wherein

5 R^1 is selected from:

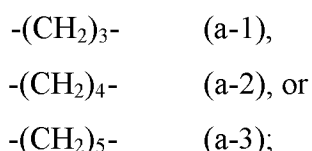
hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with
 one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;
 10 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
 Ar¹;
 Het¹;

15 R^2 is selected from:

halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with
 one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;
 20 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
 Ar¹;
 Het¹;

25 or

R^1 and R^2 together form a bivalent radical of formula



30 R^3 , R^4 , R^5 and R^6 are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

- 5 -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³; -NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

- 10 each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H,

- 15 C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

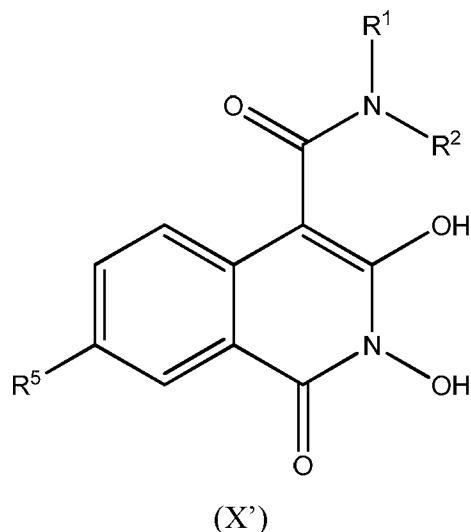
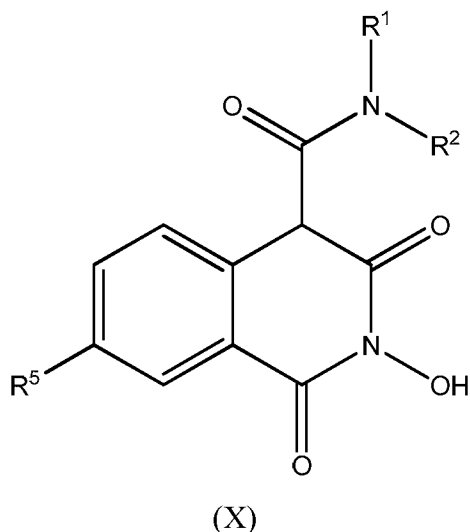
each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

- 20 each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and
25 -CF₃.

One embodiment of the present invention relates to the compounds of formula (I) or (I') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

30

Another aspect of the present invention relates to hydroxyisoquinolinediones and derivatives or analogues thereof, corresponding to the formula (X),



or a tautomer (X') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof, wherein

5 R¹ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

10 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
Ar¹;
Het¹;

15 R² is selected from:

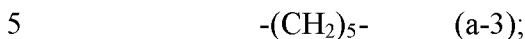
halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

20 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
Ar¹;
Het¹;

or

R¹ and R² together form a bivalent radical of formula



R⁵ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

10 C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

15 each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

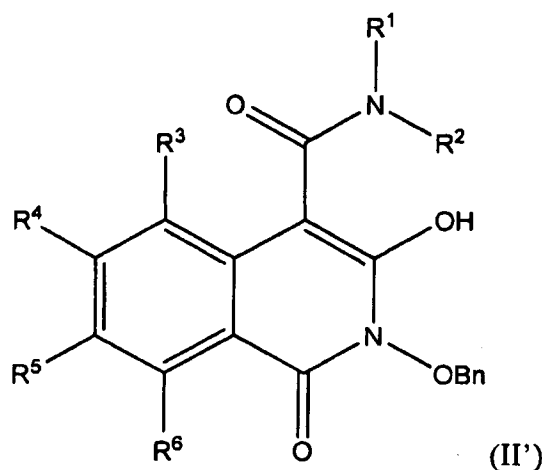
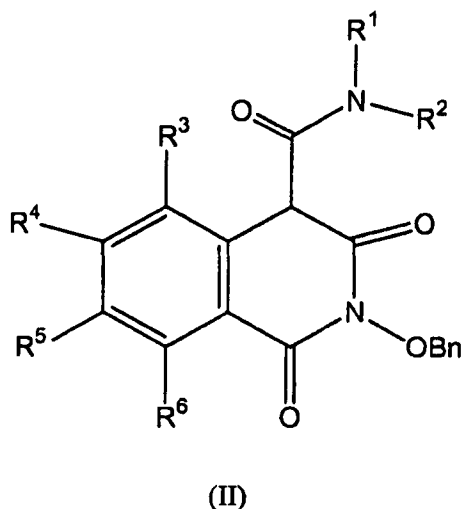
20 each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

25 each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃; and

30 each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃.

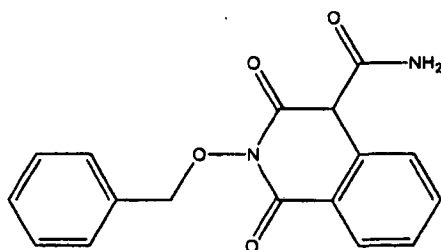
One embodiment of the present invention relates to the compounds of formula (X) or (X') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

- 5 Another aspect of the present invention is the provision of 2-benzyloxy-4-carboxamidoisoquinoline-1,3(2*H*,4*H*)-diones of formula (II) or (II') wherein the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , are as defined above.

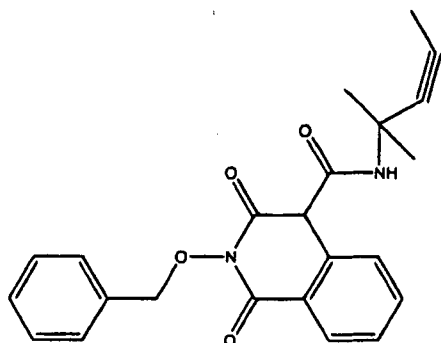


- 10 One embodiment of the present invention relates to the compounds of formula (II) or (II') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

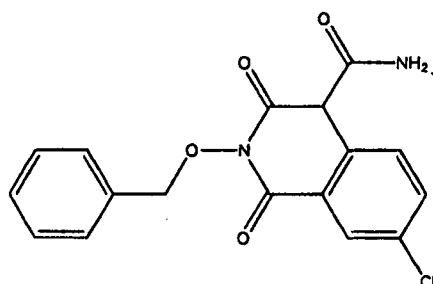
- Another aspect of the present invention relates to 2-benzyloxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamides of formula (II) or (II') wherein the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , are as defined above, provided that the following compounds are excluded:
- 15



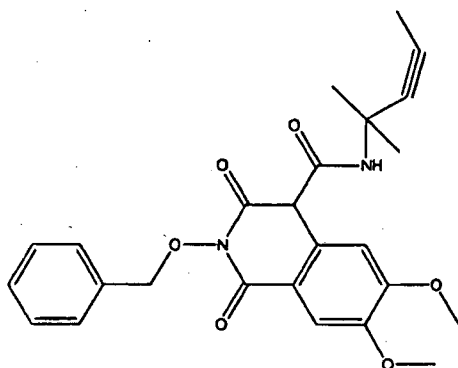
2-Benzyloxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



N-(1,1-dimethyl-but-2-ynyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,



5 2-Benzyloxy-7-chloro-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



N-(1,1-dimethyl-but-2-ynyl)-2-benzyloxy-6,7-dimethoxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide.

10 One embodiment of the present invention relates to the compounds of formula (II) or (II') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

Another aspect of the present invention relates to 2-benzyloxy-4-carboxamidoisoquinoline-1,3(2*H*,4*H*)-diones of formula (II) or a tautomer (II') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof,

15

wherein

R¹ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with
 5 one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹;

R² is selected from:

halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, C₂₋₅alkynyl, or C₇₋₁₂alkynyl, which are each optionally
 15 substituted with one or more substituents (for example 1, 2, 3 or 4 substituents)
 selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³,
 and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 20 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹;

or

R¹ and R² together form a bivalent radical of formula

25 -(CH₂)₃- (a-1),

-(CH₂)₄- (a-2), or

-(CH₂)₅- (a-3);

R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

30 C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,
 -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

5 each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or
10 Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally
15 substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group
20 consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃.

25 One embodiment of the present invention relates to the compounds of formula (II) or (II') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

Another aspect of the present invention relates to 2-benzyloxy-4-carboxamidoisoquinoline-
30 1,3(2*H*,4*H*)-diones of formula (II) or a tautomer (II') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof, wherein R¹ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with
 one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

5 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
 Ar¹;
 Het¹;

10 R² is selected from:

halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₁₂alkyl or C₂₋₁₂alkenyl, which are each optionally substituted with one or more
 substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH,
 -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

15 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one
 or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo,
 C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
 Ar¹;
 Het¹;

20 or

R¹ and R² together form a bivalent radical of formula



25 R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,
 -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio;

30 C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

each R^7 and R^8 is independently selected from hydrogen; C_{1-6} alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

5 each R^9 is hydrogen; OH; C_{1-6} alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C_{1-6} alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

each R^{10} , R^{11} , and R^{12} is independently selected from hydrogen; OH; C_{1-6} alkyl optionally substituted with halo, C_{1-6} alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C_{1-6} alkoxy; Ar⁴; or Het⁴;

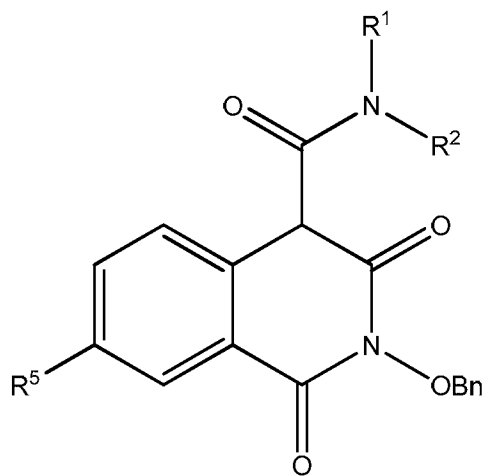
10 each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents) independently selected from halo, C_{1-6} alkyl, OH, C_{1-6} alkyloxy, NO₂, -OCF₃, and CF₃;

15 each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C_{1-6} alkyl, OH, C_{1-6} alkyloxy, NO₂, -OCF₃, and -CF₃.

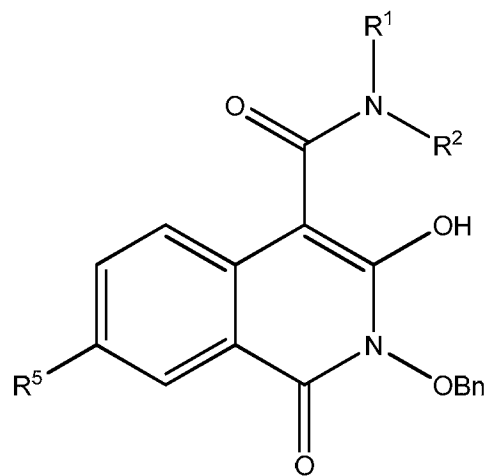
20

One embodiment of the present invention relates to the compounds of formula (II) or (II') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

25 Another aspect of the present invention relates to 2-benzyloxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamides of formula (XI)



(XI)



(XI')

or a tautomer (XI') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof,

5 wherein

R¹ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹;

R² is selected from:

halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹;

or

R¹ and R² together form a bivalent radical of formula

-(CH₂)₃- (a-1),

5 -(CH₂)₄- (a-2), or

 -(CH₂)₅- (a-3);

R⁵ is selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

10 C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,
-NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio;
C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;
-NHC(=O)Ar²; or -NHC(=O)Het²;

15 each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted
with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or
Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂,
-NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or
20 Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally
substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H,
C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

25 each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally
substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents)
independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and
CF₃; and

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring
system containing 1, 2, 3, or 4 heteroatoms independently selected from the group
30 consisting of O, N, and S, and said heterocyclic ring system is optionally
substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents)

independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃.

One embodiment of the present invention relates to the compounds of formula (XI) or (XI') as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

Interesting group of compounds are those compounds of formula (I), (I'), (II), or (II'), wherein

R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C(=O)R⁹, Ar³, and Het³; C₃₋₁₀cycloalkyl; or Ar¹;

R² is hydrogen or C₁₋₆alkyl; or

R¹ and R² together form the bivalent radical of formula (a-3);

R³, R⁴, R⁵ and R⁶ are each, independently, hydrogen, NO₂, -NR⁷R⁸, C₁₋₆alkoxy, -NHC(=O)C₁₋₆alkyl optionally substituted with -C(=O)OC₁₋₆alkyl or Ar³, -NHC(=O)Ar², or -NHC(=O)Het²;

R⁷ and R⁸ are each, independently, hydrogen or C₁₋₆alkyl;

R⁹ is C₁₋₆alkoxy; and

Ar¹ and Ar³ are each optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆alkyl, OH, and C₁₋₆alkyloxy;

Het² is pyridinyl; and

Het³ is thienyl.

Interesting group of compounds are those compounds of formula (I), (I'), (II), or (II') wherein

R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -C(=O)OC₂H₅, phenyl, and thienyl; C₅cycloalkyl; or phenyl;

R² is hydrogen, methyl, or ethyl; or

R¹ and R² together form the bivalent radical of formula (a-3);

R^3 , R^4 , R^5 and R^6 are each, independently, hydrogen, NO_2 , or NH_2 , methoxy, $-NHCOCH_3$, $-NHCOCH_2phenyl$, $-NHCOphenyl$, $-NHCOpyridinyl$, or $-NHCOCH_2thienyl$; and

each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, and methoxy.

One embodiment of the present invention relates to the compounds of formula (I), (I'), (II), or (II'), as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

Interesting group of compounds are those compounds of formula (I), (I'), (X), (X'), (II), (II'), (XI), or (XI'), wherein

R^1 is hydrogen, $C_{1-12}alkyl$, phenylmethyl, phenylethyl, or phenyl;

R^2 is hydrogen; and

R^5 is hydrogen, methoxy, $-NHCOCH_2phenyl$, $-NHCOphenyl$, $-NHCOpyridinyl$, or $-NHCOCH_2thienyl$; and

each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, and methoxy.

One embodiment of the present invention relates to the compounds of formula (I), (I'), (X), (X'), (II), (II'), (XI), or (XI'), as defined just hereinbefore for use as a medicine, or for use as an antiviral agent, for treating infection by HIV, or for treating AIDS.

Interesting group of compounds are those compounds of formula (I), (I'), (II), or (II'), wherein one or more of the following restrictions apply:

a) R^1 is hydrogen; $C_{1-12}alkyl$ or $C_{2-12}alkenyl$ which are optionally substituted with halo, $C(=O)R^9$, Ar^3 or Het^3 ; $C_{3-10}cycloalkyl$; or Ar^1 ;

b) R^2 is hydrogen or $C_{1-6}alkyl$;

b) R^1 and R^2 together form the bivalent radical of formula (a-3);

c) R^3 , R^4 , R^5 and R^6 are each hydrogen, halo, NO_2 or $-NR^7R^8$;

d) R^7 and R^8 are each $C_{1-6}alkyl$;

e) R^9 is $C_{1-6}alkoxy$;

f) Ar¹ and Ar³ are each optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆alkyl, OH, or C₁₋₆alkyloxy.

Further interesting compounds are those interesting compounds of formula (I), (I'), (II), or (II'), wherein one or more of the following restrictions apply:

- a) R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl which are optionally substituted with halo, C(=O)OC₂H₅, phenyl or thienyl; C₅cycloalkyl; or phenyl;
- b) R² is hydrogen or ethyl;
- b) R¹ and R² together form the bivalent radical of formula (a-3);
- c) R³, R⁴, R⁵ and R⁶ are each hydrogen, halo, NO₂ or NH₂ ;
- e) R⁹ is ethyloxy;
- f) each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, or methyloxy.

Even further interesting compounds are those interesting and further interesting compounds of formula (I), (I'), (X), (X'), (II), (II'), (XI), or (XI'), wherein one or more of the following restrictions apply:

- a) R¹ is hydrogen;
- b) R² is halophenylmethyl;
- c) and R⁵ is hydrogen or NO₂.

Preferred compounds are those compounds of formula (I), (I'), (II), or (II') wherein

R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl which are optionally substituted with halo, C(=O)R⁹, Ar³ or Het³; C₃₋₁₀cycloalkyl; or Ar¹; R² is hydrogen or C₁₋₆alkyl; R¹ and R² together form the bivalent radical of formula (a-3); R³, R⁴, R⁵ and R⁶ are each hydrogen, NO₂ or -NR⁷R⁸ ; R⁷ and R⁸ are each C₁₋₆alkyl; R⁹ is C₁₋₆ alkoxy; and Ar¹ and Ar³ are each optionally substituted with 1 or 2 substituents independently selected from halo, C₁₋₆alkyl, OH, or C₁₋₆alkyloxy.

More preferred compounds are those compounds of formula (I), (I'), (II), or (II') wherein R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl which are optionally substituted with halo, C(=O)OC₂H₅, phenyl or thienyl; C₅cycloalkyl; or phenyl; R² is hydrogen or ethyl; R¹

and R² together form the bivalent radical of formula (a-3); R³, R⁴, R⁵ and R⁶ are each hydrogen, NO₂ or NH₂; R⁹ is ethyloxy; and each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, or methyloxy.

- 5 Even more preferred compounds are compounds of formula (I), (I'), (II), or (II') wherein R¹ is hydrogen; R² is halophenylmethyl; and R⁵ is hydrogen or NO₂.

Even more preferred compounds are those selected from

- N*-(3-Chloropropyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 10 *N*-Hexyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
N-(3-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
N-(3-Chloro-4-methoxyphenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-
 carboxamide,
N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 15 *N*-(2,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-
 carboxamide,
N-(2,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-
 carboxamide,
N-(3,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide,
 20 *N*-Dodecyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
N-Benzyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
N-(4-Fluorobenzyl)-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide,
N-(4-Fluorobenzyl)-7-amino-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-
 carboxamide,
 25 *N*-Phenyl-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,
N-(4-Fluorophenyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-
 carboxamide,
N-Benzyl-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,
N-(4-Methoxybenzyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-
 30 carboxamide,
N-(4-Fluorophenethyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-
 carboxamide,

N-(4-Fluorobenzyl)-7-acetamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-phenylacetamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

5 *N*-(4-Fluorobenzyl)-7-benzamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-picolinamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-(2-(thiophen-2-yl)acetamido-1,2,3,4-

10 tetrahydroisoquinoline-4-carboxamide, and

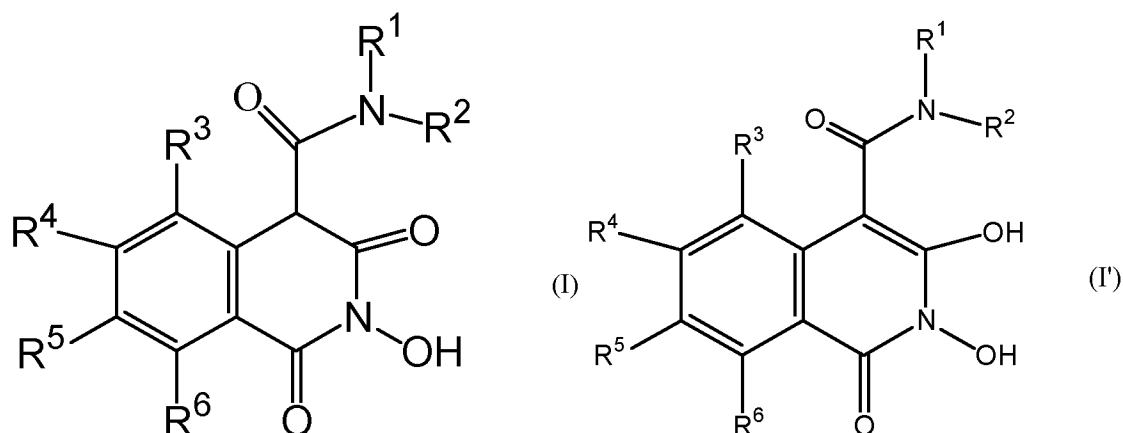
N-(4-Fluorobenzyl)-2-hydroxy-7-methoxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide.

The most preferred compounds are selected from

15 *N*-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-isoquinoline-4-carboxamide, or

N-(4-Fluorobenzyl)-2-hydroxy-7-nitro-1,3-dioxo-isoquinoline-4-carboxamide.

One embodiment of the present invention relates to a compound of formula (I),



20 or a tautomer (I') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof, wherein

R¹ and R² are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³; Ar¹;

Het¹; or

R¹ and R² together form a bivalent radical of formula

-(CH₂)₃- (a-1),

-(CH₂)₄- (a-2), or

-(CH₂)₅- (a-3);

R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

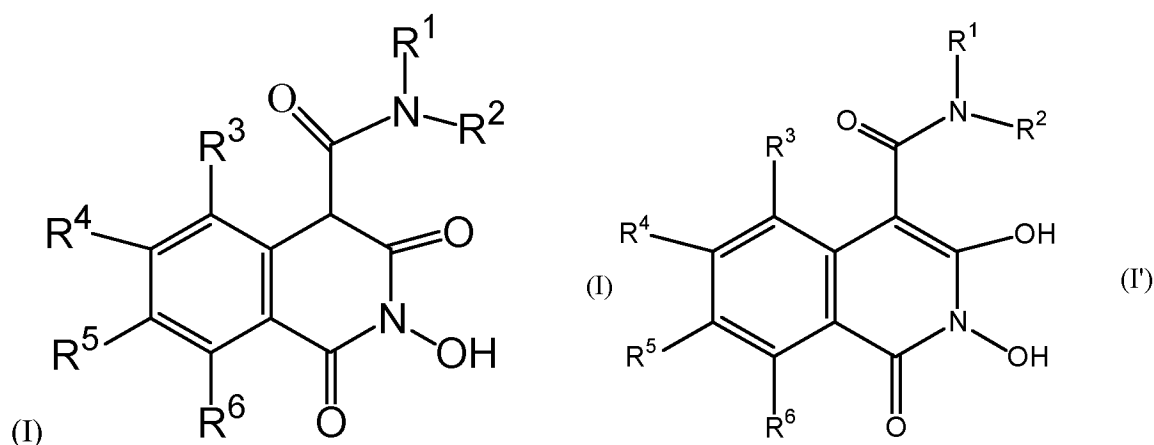
each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents)

independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃;

for use as an antiviral agent or for treating AIDS.

One embodiment of the present invention relates to the use of a compound of formula



or a tautomer (I') thereof, or a pharmaceutically acceptable salt, solvate or prodrug of said compound or tautomer thereof, wherein

R¹ and R² are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

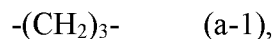
C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹; or

R^1 and R^2 together form a bivalent radical of formula



5 R^3 , R^4 , R^5 and R^6 are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,
-NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio;

10 C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted
with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or

15 Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂,
-NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or
Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally
20 substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H,
C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally
substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents)
independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and
25 CF₃;

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring
system containing 1, 2, 3, or 4 heteroatoms independently selected from the group
consisting of O, N, and S, and said heterocyclic ring system is optionally
substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents)
30 independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and
-CF₃;

for the manufacture of a medicament for the prevention or treatment of viral infections in mammals.

According to a second aspect, the invention relates the compounds of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, for use as a medicine, more particularly as antiviral compounds, even more particularly as compounds active against HIV. The invention also relates to the use of the compounds of the formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, for the manufacture of a medicament or as a pharmaceutically active ingredient, especially as a virus replication inhibitor, preferably a retrovirus replication inhibitor, for instance for the manufacture of a medicament or pharmaceutical composition having antiviral activity for the prevention and/or treatment of viral, preferably retroviral, infections in humans and mammals. The present invention further relates to a method of treatment of a viral infection, preferably a retroviral infection in a mammal, including a human, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, as an active ingredient, preferably in admixture with at least a pharmaceutically acceptable carrier.

The invention further relates to methods for the preparation of compounds of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof. The invention also relates to pharmaceutical compositions comprising the compounds of the invention according to formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, in admixture with at least a pharmaceutically acceptable carrier, the active ingredient preferably being in a concentration range of about 0.1 to 100% by weight, and to the use of these derivatives namely as drugs useful for the treatment of subjects suffering from HIV infection.

The invention further relates to the use of a composition comprising (a) one or more derivatives of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, and (b) one or more viral inhibitors as biologically

active agents in respective proportions such as to provide a synergistic effect against a viral infection, preferably a lentiviral infection and more preferably a retroviral infection in a mammal, for instance in the form of a combined preparation for simultaneous, separate or sequential use in retroviral infection therapy. Within the framework of this embodiment of the invention, the retroviral enzyme inhibitors used as a therapeutically active ingredients (b) may belong to categories already known in the art and include, among others,

- HIV integrase inhibitors such as for instance, elvitegravir and raltegravir,
- Nucleoside, non-nucleoside and nucleotide reverse transcriptase inhibitors such as for instance, dideoxyadenosine, stavudine, zalcitabine, zidovudine, lamivudine, didanosine, nevirapine, delavirdine, efavirenz, tenofovir, foscarnet sodium and the like,
- HIV protease inhibitors such as for instance saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and the like,
- HIV fusion inhibitors such as enfuvirtide.

Hence the present invention also relates to a pharmaceutical composition according to the invention further comprising a therapeutically effective amount of an HIV/AIDS treatment agent selected from the group consisting of: an HIV/AIDS antiviral agent; an anti-infective agent; and an immunomodulator.

The invention also relates to a process for preparing a pharmaceutical composition of the invention wherein a therapeutically effective amount of a compound of formula (I) is intimately mixed with a pharmaceutically acceptable carrier.

The invention also relates to a process for preparing a pharmaceutical composition of the invention wherein a therapeutically effective amount of a compound of formula (I) and a therapeutically effective amount of an HIV/AIDS treatment agent as defined herein are intimately mixed with a pharmaceutically acceptable carrier

The invention also relates to the compounds of the invention according to formula (I) being used for inhibition of the proliferation of other viruses than HIV, preferably the inhibition of viral activity of hepatitis B virus, hepatitis C virus or flaviviruses, with in particular yellow fever virus or Dengue virus.

More generally, the invention relates to the compounds of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, being useful as agents having biological activity (preferably antiviral or antitumoral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

Another aspect of the invention relates to a pharmaceutical composition comprising a compound of the formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, more in particular having antiviral activity, yet more in particular against HIV.

A further aspect of the invention provides for a method of treatment or prevention of a viral infection in a mammal, comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the invention.

The compounds of the present invention can act as inhibitors of HIV-1 integrase, strand transfer inhibitors and/or 3' processing inhibitors.

Accordingly the present invention includes a method of inhibiting HIV-1 integrase in a subject in need of such inhibition which comprises administering to the subject an effective amount of a compound of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In each of the following definitions, the number of carbon atoms represents the maximum number of carbon atoms generally optimally present in the substituent or linker; it is understood that where otherwise indicated in the present application, the number of carbon

atoms represents the optimal maximum number of carbon atoms for that particular substituent or linker.

“C₁₋₆alkyl” as used herein refers to a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of C₁₋₆alkyl include, but are not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and the like. “C₇₋₁₁alkyl” as used herein refers to a straight or branched chain hydrocarbon containing from 7 to 11 carbon atoms. Representative examples of C₇₋₁₁alkyl include, but are not limited to 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undyl, and the like.

“C₁₋₁₂alkyl”, as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 12 carbon atoms and includes but is not limited to C₁₋₆alkyl, the examples given under these definitions, include, but are not limited to, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undyl, and the like.

“C₂₋₆alkenyl” as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 6 carbons, and containing at least one carbon-carbon double bond, formed structurally, for example, by the replacement of two hydrogens. Representative examples of "alkenyl" include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, and the like.

“C₂₋₆alkynyl” as used herein, refers to a straight or branched chain hydrocarbon group containing from 2 to 6 carbon atoms, and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butylnyl, 2-pentylnyl, 1-butylnyl and the like.

As used herein and unless otherwise stated, the term “C₃₋₁₀cycloalkyl” means a monocyclic saturated hydrocarbon monovalent radical having from 3 to 10 carbon atoms, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. As used herein and unless otherwise stated, the term “cycloalkylene” refers to a cyclic hydrocarbon radical of 3-10 carbon atoms, and having two monovalent radical centers

derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane; i.e. the divalent hydrocarbon radical corresponding to the above defined C₃₋₁₀cycloalkyl.

- 5 The term “C₃₋₁₀cycloalkenyl” as used herein refers to a cyclic hydrocarbon having 3 to 10 carbon atoms with at least one site (usually 1 to 3, preferably 1) of unsaturation, i.e. a carbon-carbon, sp² double bond.

The term “monocyclic heterocyclic ring system” refers to any 5 or 6 member ring
10 containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of: O, N, and S. The 5 member ring has from 0 to 2 double bonds, and the 6 member ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine,
15 isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine,
20 thiomorpholine sulfone, sulfoxide, thiopyran, triazine, triazole, trithiane, and the like.

The term “bicyclic heterocyclic ring system” refers to any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic
25 ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiaazole, benzothiophene, benzoxadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxane, 1,3- benzodioxane, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, pyranopyridine, quinoline, quinolizine, quinoxaline, quinazoline,
30 tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like.

As used herein and unless otherwise stated, the terms “C₁₋₆ alkoxy”, “C₁₋₆alkylthio”, “Aroxy”, “Arthio”, “Hetoxy”, “Hetthio”, “thio C₃₋₁₀ cycloalkyl”, “arylthio”, “arylalkylthio” and “thioheterocyclic ring” refer to substituents wherein a C₁₋₆alkyl radical Ar or Het radical (each of them such as defined herein), are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl and the like.

As used herein and unless otherwise stated, the term halo means any atom selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

Substituents optionally are designated with or without bonds. Regardless of bond indications, if a substituent is polyvalent (based on its position in the structure referred to), then any and all possible orientations of the substituent are intended.

The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography separations, depending on the nature of the groups of the compounds, for example compounds with aryl are useful in hydrophobic affinity separations.

In an embodiment, the present invention encompasses compounds of formula (I) or (I'), wherein

R¹ and R² are each independently selected from:

hydrogen; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹;

preferably R¹ and R² are each independently selected from:

hydrogen; C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, -OH, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents (for example 1, 2, 3 or 4 substituents) selected from halo, C₁₋₆alkyl, -OH, and Ar³; Ar¹; and Het¹;

or

R¹ and R² together form a bivalent radical of formula

-(CH₂)₃- (a-1),

-(CH₂)₄- (a-2), or

-(CH₂)₅- (a-3); preferably (a-2) or (a-3); preferably (a-3);

R³, R⁴, and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³; -NHC(=O)Ar²; or -NHC(=O)Het²;

preferably R³, R⁴, and R⁶ are each independently selected from hydrogen; halo; -OH;

-CN; -NO₂; -OCF₃; CF₃; C₁₋₆alkyl; C₁₋₆alkyloxy; Ar²; Ar²oxy; Het²; Het²oxy;

C₃₋₆cycloalkyl; -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³; -NHC(=O)Ar²; or -NHC(=O)Het²; preferably R³, R⁴, and R⁶

are each independently selected from: hydrogen; halo; -OH; -NO₂; -OCF₃; CF₃; C₁₋₆alkyl; C₁₋₆alkyloxy; Ar²; preferably R³, R⁴, and R⁶ are each independently selected from: hydrogen;

R⁵ is selected from: hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³; C₁₋₆alkyloxy;

- C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio; C₃₋₆cycloalkyl; -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³; or Het³; -NHC(=O)Ar²; or -NHC(=O)Het²; preferably R⁵ is selected from: hydrogen; halo; -OH; -SH; -CN; -NO₂; -NH₂; -OCF₃; CF₃; C₁₋₆alkyl; C₁₋₆alkyloxy; Ar²; Ar²oxy; Het²; Het²oxy; C₃₋₆cycloalkyl; -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³; or Het³; -NHC(=O)Ar²; or -NHC(=O)Het²; preferably R⁵ is selected from: hydrogen; halo; -OH; -NO₂; -NH₂; CF₃; C₁₋₄alkyl; C₁₋₄alkyloxy; C₃₋₆cycloalkyl; -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or phenyl; or Het³; -NHC(=O)phenyl; or -NHC(=O)Het²;
- each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²; preferably R⁷ and R⁸ is independently selected from hydrogen; or C₁₋₆alkyl ;
- each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴; preferably R⁹ is selected from hydrogen; OH; or C₁₋₆alkyl or C₁₋₆alkoxy;
- each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴; preferably each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl; C₁₋₆alkoxy;
- each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃; preferably each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl, and is optionally substituted with 1 to 5 substituents (for example 1, 2, 3, 4 or 5 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;
- each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents (for example 1, 2, 3 or 4 substituents) independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃; preferably each of Het¹, Het², Het³, and Het⁴, is independently a mono- or

bicyclic heterocyclic ring system containing 1 or 2 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃;

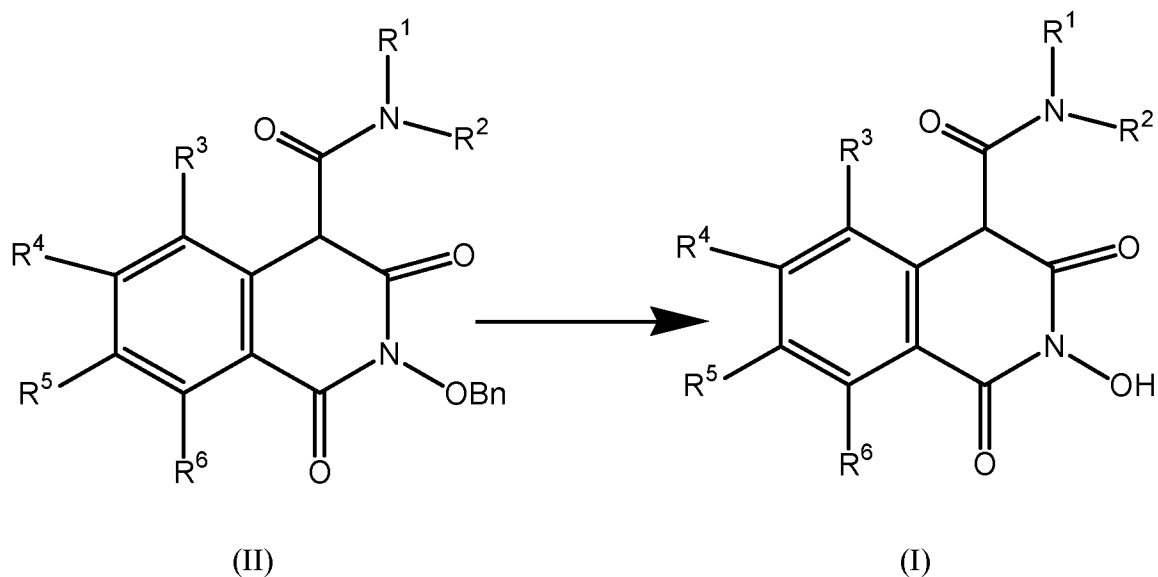
- 5 with the proviso that said compound is not 2-Hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide, or 2-Hydroxy-6,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide.

Another embodiment of the present invention is a process for preparing compounds of
10 formula (I). They can be readily prepared according to the following reaction scheme and examples, or modifications thereof, using readily available starting materials and reagents. In the reactions below, it is possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the
15 person of ordinary skill in the art in light of the following reaction scheme and examples.

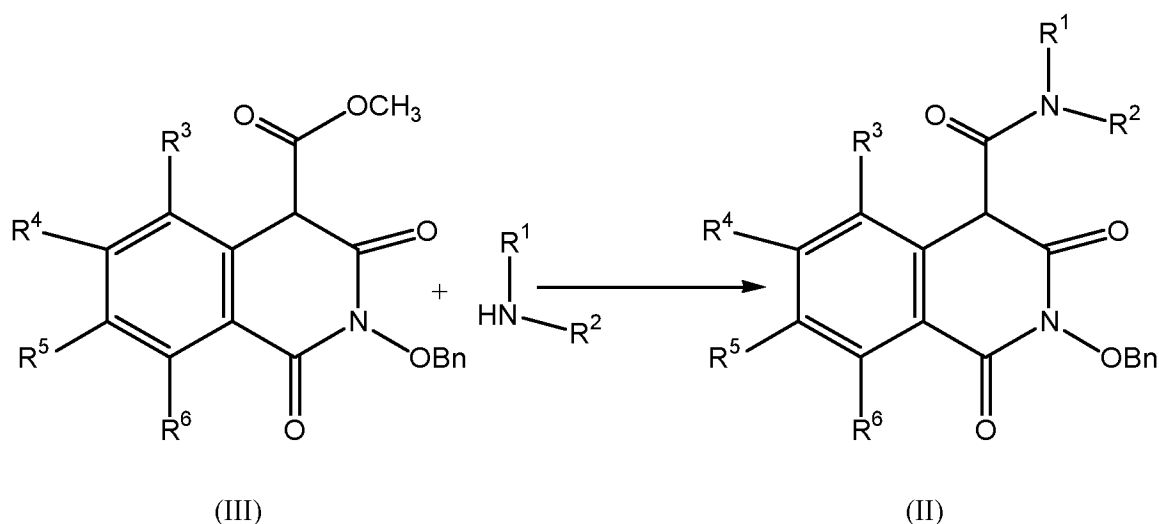
Abbreviations used in the instant specification, particularly the Scheme and Examples, include the following: Bn = benzyl, BOP = (benzotriazol-1-
yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, DMSO =
20 dimethylsulfoxide, ESI-MS = electrospray ionization mass spectrometry, EtOAc = ethyl acetate, h = hour(s); LDA = lithium diisopropyl amide, MeOH = methanol, NMM = 4-methylmorpholine, NMR = nuclear magnetic resonance, rt = room temperature, THF = tetrahydrofuran.

The present invention encompasses a process for making a compound of formula (I)
25 wherein

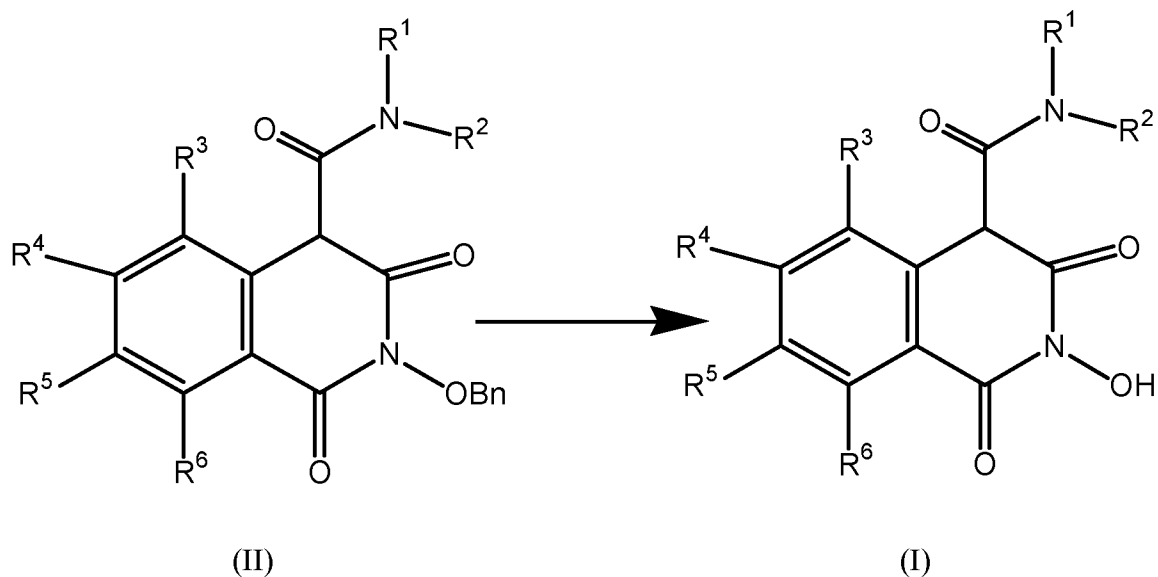
- a) the intermediate of formula (II) is reacted with a boron halide or is deprotected by catalytic dehydrogenation with the formation of a compound of formula (I),



b) wherein the intermediate of formula (II) is obtained by reacting the intermediate of formula (III) with a suitable amine with the formation of an intermediate of formula (II)

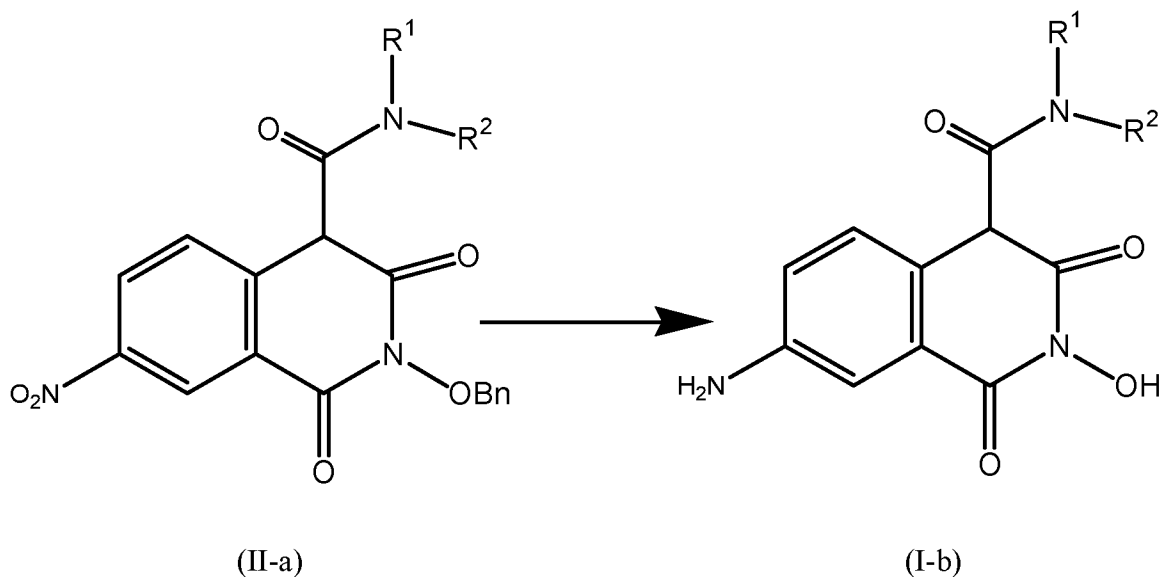


- 5 The 4-carboxamido-2-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones of formula (I) can be prepared by reacting an intermediate of formula (II) with a boron halide (BX₃) such as for example boron tribromide or boron trichloride at room or low temperature. Use of boron tribromide allows for a complete deprotection of the intermediates of formula (II) (deprotection of the benzyloxy function as well as of the alkoxy functions in aromatic rings) whereas boron trichloride only affects the benzyloxy function. Deprotection may
- 10 also be performed by catalytic hydrogenation on Pd/C 5%.



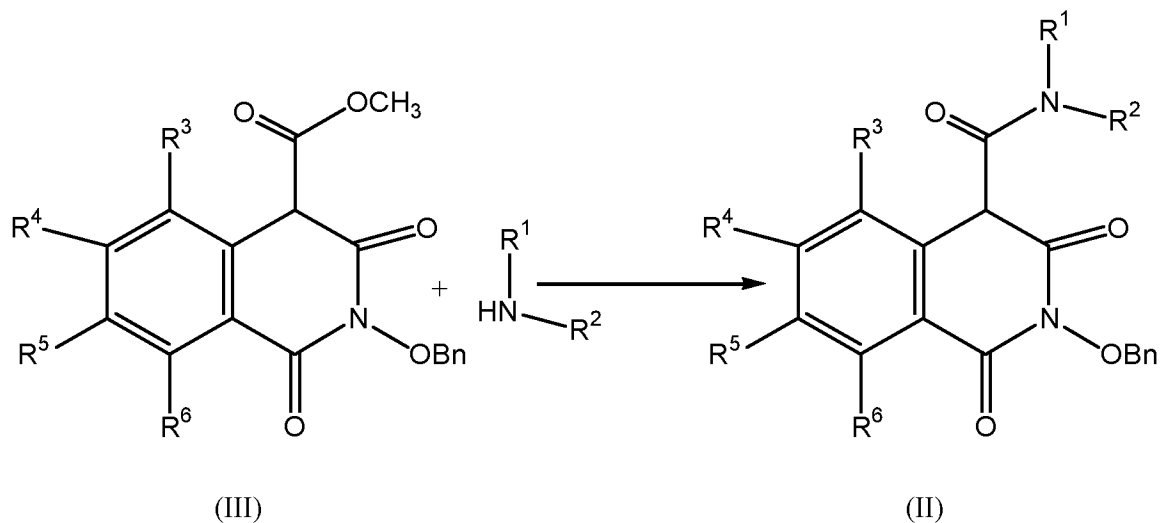
The 4-carboxamido-2-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones of formula (I) wherein R³, R⁴ and R⁶ are hydrogen and R⁵ is a nitro function herein referred to as compounds of formula (I-a) can be prepared by deprotecting an intermediate of formula (II) wherein R³, R⁴ and R⁶ are hydrogen and R⁵ is a nitro function, herein referred to as an intermediate of formula (II-a) with boron trichloride or tribromide.

The 4-carboxamido-2-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones of formula (I) wherein R³, R⁴ and R⁶ are hydrogen and R⁵ is aminated herein referred to as compounds of formula (I-b) can be prepared by catalytic hydrogenation on Pd/C of an intermediate of formula (II-a).

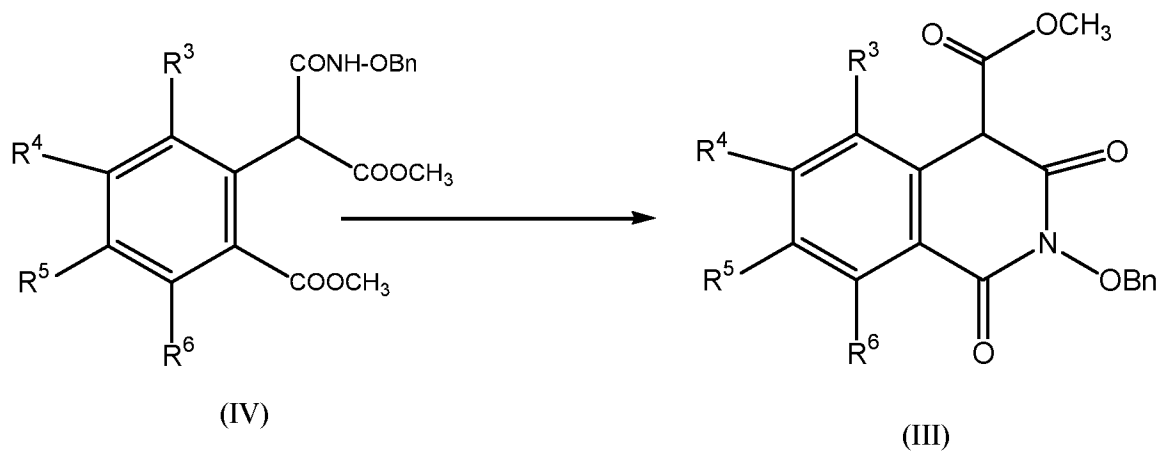


The 2-benzyloxy-4-carboxamidoisoquinoline-1,3(2*H*,4*H*)-diones of formula (II) can be

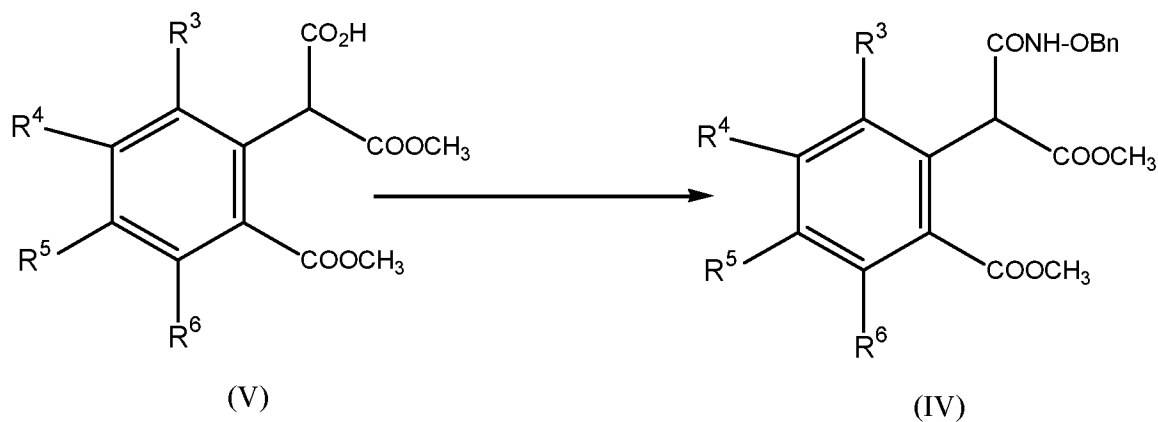
prepared by reacting the methyl esters of formula (III) with variously suitable amines of formula R^1NHR^2 for example, by refluxing in toluene using a Dean Stark apparatus.



Surprisingly, the basic treatment of an intermediate of formula (IV) does not yield an homophthalic acid derivative but a cyclized 2-benzyloxy-4-methoxycarbonylisoquinoline-1,3(2*H*,4*H*)-dione of formula (III). Hence, the intermediates of formula (III) can be prepared by cyclization of an intermediate of formula (IV). This cyclization can be performed quantitatively using 2.5 M potassium hydroxide in a suitable solvent such as aqueous methanol, at room temperature for 5 min.

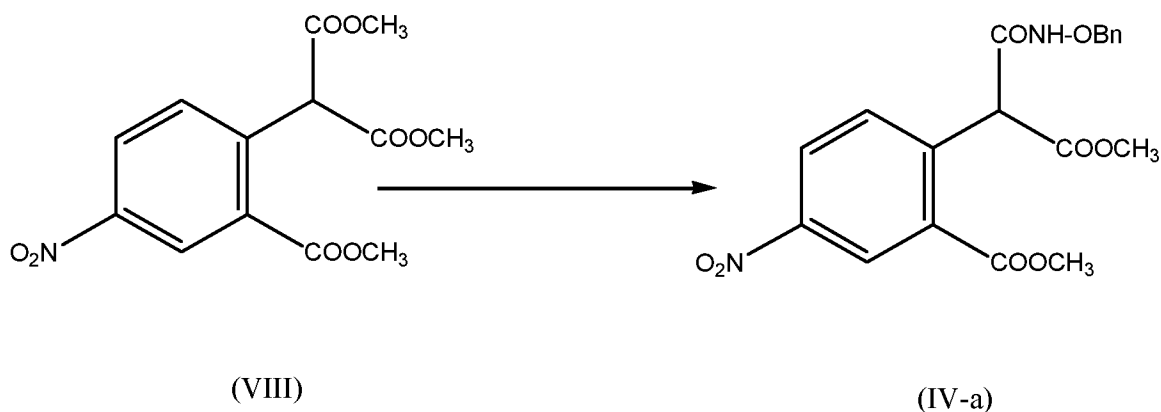


the benzyloxycarboxamide of formula (IV) can be prepared by coupling the intermediate of formula (V) with *O*-benzylhydroxylamine, after activation with the BOP reagent and *N*-methylmorpholine. The coupling can be performed in a suitable solvent such as CH_2Cl_2 .

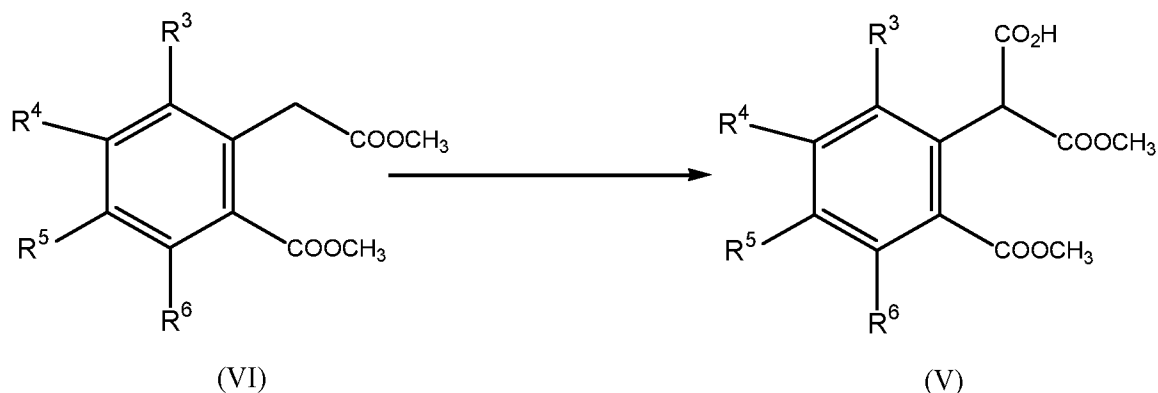


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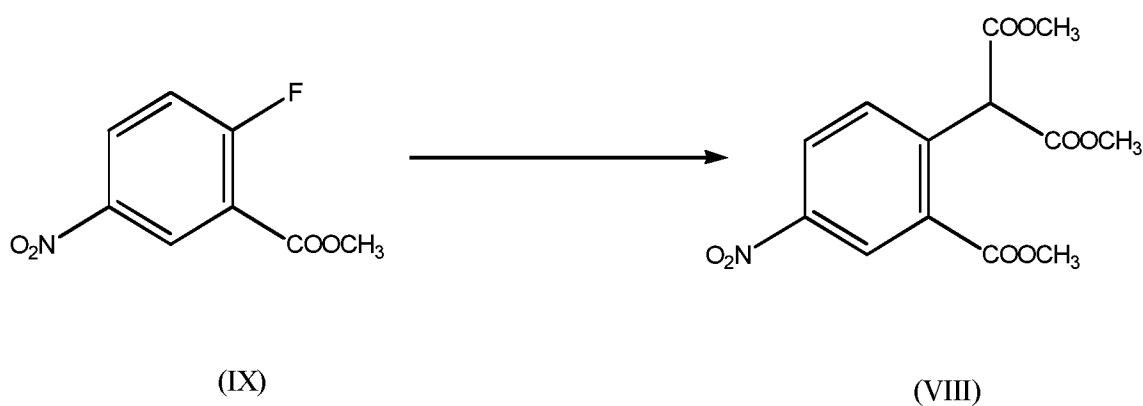
he benzyloxycarboxamide of formula (IV) wherein R^3 , R^4 and R^6 are hydrogen and R^5 is a nitro function herein referred to as compounds of formula (IV-a) can be prepared by coupling the intermediate of formula (VIII), wherein R^3 , R^4 and R^6 are hydrogen and R^5 is a nitro function with *O*-benzylhydroxylamine by refluxing in toluene using a Dean Stark apparatus.



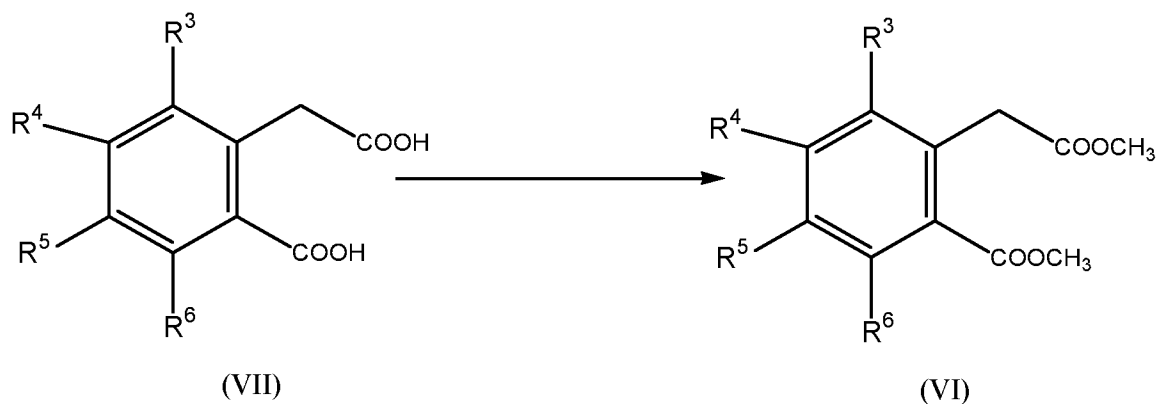
The methyl 2-(2-methoxycarbonylphenyl) malonate monoester of formula (V) can be prepared by reacting the anion of the homophthalic diester of formula (VI) with carbon dioxide. This reaction is possible after treatment of the homophthalic diester of formula (VI) with LDA according to the method described in Lazer *et al.*, *J. Med. Chem.* 1979, 22, 845. The reaction can be performed in a suitable solvent such as for example tetrahydrofuran.



The triester of formula (VIII) can be prepared by aromatic nucleophilic substitution of intermediate (IX) with dimethyl malonate in the presence of NaH and under reflux in a suitable solvent such as, for example, THF.

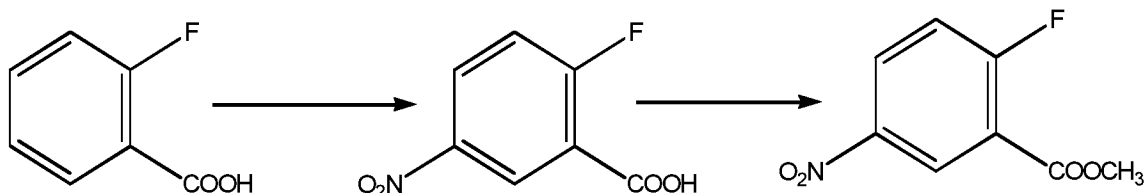


The methyl diester of formula (VI) can be prepared by reacting the commercially available homophthalic acid of formula (VII) with thionyl chloride in a suitable solvent such as, for example, methanol.



The intermediate of formula (IX) can be prepared by esterification of 2-fluoro-5-nitrobenzoic acid with thionyl chloride in a suitable solvent such as, for example,

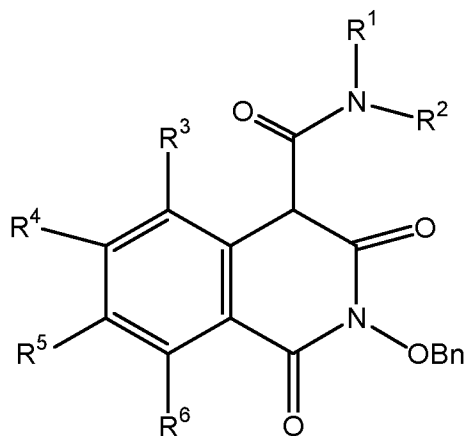
methanol. 2-fluoro-5-nitrobenzoic acid can be prepared by nitrating the commercial 2-fluorobenzoic acid in a mixture of sulfuric acid and nitric acid.



(IX) T

The above described reactions that can be applied to homophthalic acids containing substituents at any ring position, like the homophthalic acid derivatives previously described in Billamboz *et al.*, J. Med. Chem. 2008, 24, 7717 are exemplified in Examples 1-24. The more specific reactions described for compounds being only nitrated or aminated at position 7 are exemplified in Examples B35-B47.

The present invention also encompasses an intermediate of formula (II) wherein the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , are as defined hereinabove.



(II)

Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state, any and all protonated forms of the compounds are intended to fall within the scope of the invention.

The resulting compounds may be optionally converted into a pharmaceutically acceptable salt or vice versa according to the methods known by the skilled in the art. Further, the resulting compounds may be converted into each other following art-known functional group transformation reactions. For example, amino groups may be N-alkylated, nitro groups reduced to amino groups, a halo atom may be exchanged for another halo.

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms which the compounds according to the formulas of the application like (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, are able to form. Therefore, the compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+ , Li^+ , K^+ , Ca^{2+} and Mg^{2+} . Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include,

for instance, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the solvates which the compounds according to the formulas of the application like (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, as well as their salts are able to form, such as for example hydrates, alcoholates and the like. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C1-C4alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X typically is independently selected from H or a C₁₋₄alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for

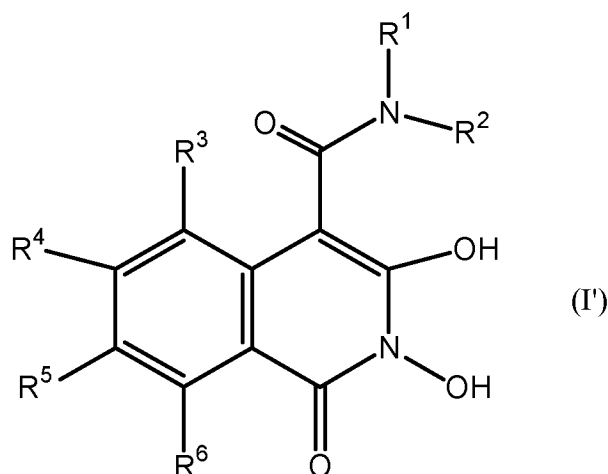
example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

5 As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

10

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and stereochemical forms, which the compounds of formula (I), (X), (II), (XI), or any other compounds disclosed herein, groups, subgroups, and tautomers thereof, may possess, but not including position isomers. Typically, the structures shown herein exemplify only one
15 tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well.

The compounds of the present invention may also occur as tautomers thereof, such as the following tautomer (I') of a compound of formula (I):



20

It is understood that the present invention includes all tautomers of 2-hydroxyisoquinoline-1,3(2*H*,4*H*)-dione compounds of Formula I (or I'), as well as the tautomers of its intermediates of Formula II (or II'), both singly and in mixtures.

Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds according to the formulas of the application like (I) may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers

of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched compounds of the invention. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCelTM CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and ChiralpakTM AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents on a ring moiety.

The absolute stereochemical configuration of the compounds according to the formulas of the application like (I) or (II) may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction or NMR.

The compounds of the invention are employed for the treatment or prophylaxis of viral infections, more particularly HIV infections. When using one or more compounds of formula (I) as defined herein:

- 5 - the active ingredients of the compound(s) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- 10 - the therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is a retroviral enzyme inhibiting amount. More preferably, it is a retroviral replication inhibiting amount or a retroviral enzyme inhibiting amount of the derivative(s) of formula (I) as defined herein corresponds to an amount which ensures a plasma level of between 1 µg/ml and 100 mg/ml, optionally of 10 mg/ml. This can be achieved by
15 administration of a dosage of in the range of 0.001 mg to 2000 mg, in particular 0.01 mg to 1000 mg, more in particular 0.1 mg to 500 mg, or 0.1 mg to 100 mg, or 0.1 mg to 20 mg, or 0.1 mg to 5 mg, or 0.1 to 1 mg per day per kg bodyweight for humans. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be
20 administered at more than one day intervals.

The present invention further relates to a method for preventing or treating a viral infection in a subject or patient by administering to the patient in need thereof a therapeutically effective amount of a compound of formula (I). The therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans
25 and other mammals, preferably is HIV protein/enzyme inhibiting amount. More preferably, it is a HIV replication inhibiting amount or a HIV enzyme inhibiting amount of the derivative(s) of the formulas as defined herein. Suitable dosage is usually in the range of 0.001 mg to 20 mg, in particular 0.01 mg to 5 mg, more in particular 0.1 mg to 1 mg per
30 day per kg bodyweight for humans. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in *Adv. Enzyme Reg.* (1984) 22:27. Briefly, this principle states that interactions (synergism, additivity, antagonism) between two drugs can be quantified using the combination index (hereinafter referred as CI) defined by the following equation:

$$CI_x = \frac{ED_x^{1c}}{ED_x^{1a}} + \frac{ED_x^{2c}}{ED_x^{2a}}$$

wherein ED_x is the dose of the first or respectively second drug used alone (1a, 2a), or in combination with the second or respectively first drug (1c, 2c), which is needed to produce a given effect. The said first and second drug have synergistic or additive or antagonistic effects depending upon $CI < 1$, $CI = 1$, or $CI > 1$, respectively.

Synergistic activity of the pharmaceutical compositions or combined preparations of this invention against viral infection may also be readily determined by means of one or more tests such as, but not limited to, the isobologram method, as previously described by Elion et al. in *J. Biol. Chem.* (1954) 208:477-488 and by Baba et al. in *Antimicrob. Agents Chemother.* (1984) 25:515-517, using EC_{50} for calculating the fractional inhibitory concentration (hereinafter referred as FIC). When the minimum FIC index corresponding to the FIC of combined compounds (e.g., $FIC_x + FIC_y$) is equal to 1.0, the combination is said to be additive; when it is between 1.0 and 0.5, the combination is defined as subsynergistic, and when it is lower than 0.5, the combination is defined as synergistic. When the minimum FIC index is between 1.0 and 2.0, the combination is defined as subantagonistic and, when it is higher than 2.0, the combination is defined as antagonistic.

This principle may be applied to a combination of different antiviral drugs of the invention or to a combination of the antiviral drugs of the invention with other drugs that exhibit anti-HIV activity.

The invention thus relates to a pharmaceutical composition or combined preparation having synergistic effects against a viral infection and containing:

(a) a combination of two or more of the compounds of formula (I), and

(b) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

for simultaneous, separate or sequential use in the treatment or prevention of a viral infection, or

5 (c) one or more anti-viral agents, and

(d) at least one of the compounds of formula (I), and

(e) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

for simultaneous, separate or sequential use in the treatment or prevention of a viral
10 infection.

Suitable anti-viral agents for inclusion into the synergistic antiviral compositions or combined preparations of this invention include practically all known anti-HIV compounds known at this moment such as nucleoside and non-nucleoside reverse transcriptase
15 inhibitors, protease inhibitors and integrase inhibitors.

The pharmaceutical composition or combined preparation with synergistic activity against viral infection according to this invention may contain the compounds of the present invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the compounds of formula (I) of the
20 combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

According to a particular embodiment of the invention, the compounds of the invention may be employed in combination with other therapeutic agents for the treatment or
25 prophylaxis of HIV infections. The invention therefore relates to the use of a composition comprising:

(f) one or more compounds of formula (I), and

(g) one or more HIV /protein-enzyme inhibitors as biologically active agents in respective proportions such as to provide a synergistic effect against a viral infection, particularly a
30 HIV infection in a mammal, for instance in the form of a combined preparation for simultaneous, separate or sequential use in viral infection therapy, such as HIV.

When using a combined preparation of (f) and (g):

- the active ingredients (f) and (g) may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- the therapeutically effective amount of the combined preparation of (f) and (g), especially for the treatment of viral infections in humans and other mammals, particularly is a HIV enzyme inhibiting amount. More particularly, it is a HIV replication inhibiting amount of derivative (f) and a HIV enzyme inhibiting amount of inhibitor (g). Still more particularly when the said HIV enzyme inhibitor (g) is a reverse transcriptase inhibitor, its effective amount is a reverse transcriptase inhibiting amount. When the said HIV enzyme inhibitor (g) is a protease inhibitor, its effective amount is a protease inhibiting amount. When the said HIV enzyme inhibitor (g) is an integrase inhibitor, its effective amount is a integrase inhibiting amount.
- ingredients (f) and (g) may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

The invention also relates to the compounds of the invention, for inhibition of the proliferation of other viruses than HIV, particularly for the inhibition of other retroviruses and lentiviruses and also for the inhibition of flaviviruses or picornaviruses such as BVDV, HCV, HBV or Cocksackie virus, with in particular yellow fever virus, Dengue virus, hepatitis B virus, hepatitis G virus, Classical Swine Fever virus or the Border Disease Virus. Other viruses may be inhibited such as HSV, CMV and Sars-virus.

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

More generally, the invention relates to the compounds of formula (I) being useful as agents having biological activity (particularly antiviral activity) or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-
5 medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

The compounds of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain
10 excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin,
15 hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving,
20 dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or
25 powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention. They may also include additives such as
30 wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like, provided

the same are consistent with pharmaceutical practice, i.e. carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material and, where appropriate, the other additives such as surface-active agents may also be prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of about 1 to 10 μ m, namely for the manufacture of microcapsules for controlled or sustained release of the active ingredients.

Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the pharmaceutical compositions of the present invention are non-ionic, cationic and/or anionic materials having good emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10-22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alkanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphthalenesulphonic acid or a naphthalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g.

phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl -choline and their mixtures.

- 5 Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10
10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100
15 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and
20 pentaerythritol are also suitable non-ionic surfactants.

- Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl
25 or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C₈-C₂₂ alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

- 30 A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Corp.,

Ridgewood, New Jersey, 1981), "Tensid-Taschenbucw", 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants, (Chemical Publishing Co., New York, 1981).

Compounds of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent.

5 Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active
10 ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be
15 formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances
20 absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known
25 ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without
30 stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations

suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

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

Formulations suitable for parenteral administration include aqueous and non-aqueous
sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and
10 solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example
15 water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose,
20 as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral
25 administration may include flavoring agents.

Compounds of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be
30 controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted

for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

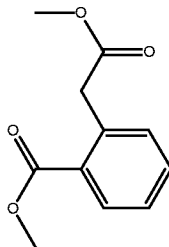
In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Examples

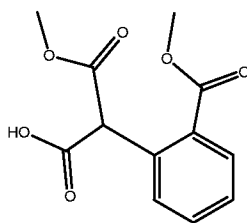
The following examples are provided for the purpose of illustrating the present invention and should in no way be interpreted as limiting the scope thereof.

A INTERMEDIATES

EXAMPLE A1

A1-a intermediate 1: Methyl 2-(2-methoxy-2-oxoethyl)benzoate

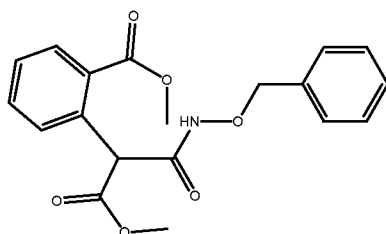
2-Carboxymethyl-benzoic acid (5 g, 28.0 mmol) was dissolved in MeOH (100 mL) and thionyl chloride (5.5 mL, 62.0 mmol) was added dropwise. The solution was heated under reflux for 2 h and concentrated *in vacuo*. The residue was dissolved in AcOEt and washed several times with 10% NaHCO₃. After drying over Na₂SO₄, the solvent was evaporated *in vacuo* to yield **intermediate 1** as a yellow oil (99%). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.60 (s, 3 H, OCH₃), 3.78 (s, 3 H, OCH₃), 4.00 (s, 2 H, CH₂), 7.36 (m, 3 H, H_{Ar}), 7.92 (1 H, H_{Ar}, dd, ³J = 8.2 Hz, ⁴J = 2.0 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 36.7 (CH₂), 51.4 (OCH₃), 51.8 (OCH₃), 127.4 (CH), 129.5 (C), 130.3 (CH), 132.4 (CH), 132.6 (CH), 135.9 (C), 166.9 (CO), 172.4 (CO).

A1-b intermediate 2: 3-Methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid

A solution of freshly distilled diisopropylamine (0.75 mL, 5.35 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to -78 °C and 3.34 mL of 1.6 M *n*-butyllithium (5.35 mmol) was added. After 30 min reaction at -78 °C, a solution of **intermediate 1** (0.79 g, 3.8 mmol) in 10.0 mL of THF was added dropwise. After stirring the solution for 30 min, temperature was risen to -5 °C and the argon inlet was removed. CO₂ formed from addition of sulfuric acid on anhydrous barium carbonate was bubbled through the reaction mixture for 20 min. The mixture was acidified with 2.0 M HCl and then extracted with CHCl₃. The combined organic extracts were extracted with 10% Na₂CO₃. The basic extracts were made acidic by the careful addition of 2.0 M HCl and the

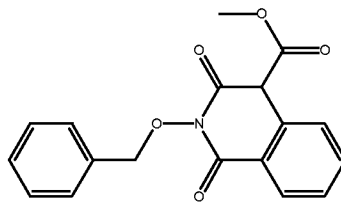
product was extracted into CHCl_3 (3 x 100 mL). The combined CHCl_3 extracts were dried over Na_2SO_4 . The solvent was removed under reduced pressure to give an oily residue **intermediate 2** which crystallized on cooling. Orange solid (0.49 g; 62%); mp 100 °C; ^1H NMR (300 MHz, CDCl_3): δ = 3.75 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.16 (s, 1 H, CH), 7.38 (1 H, H_{Ar} , dd, 3J = 7.7 Hz, 4J = 1.2 Hz), 7.44 (1 H, H_{Ar} , td, 3J = 7.7 Hz, 4J = 1.2 Hz), 7.57 (1 H, H_{Ar} , td, 3J = 7.7 Hz, 4J = 1.2 Hz), 8.07 (1 H, H_{Ar} , dd, 3J = 7.7 Hz, 4J = 1.2 Hz), 11.22 (br s, 1 H, COOH); ^{13}C NMR (75 MHz, CDCl_3): δ = 52.5 (OCH_3), 53.3 (OCH_3), 55.5 (CH), 128.5 (CH), 128.6 (C), 131.3 (CH), 132.3 (CH), 132.9 (CH), 134.4 (C), 167.7 (CO), 170.6 (CO), 170.8 (CO).

10 A1-c intermediate 3: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl} benzoate



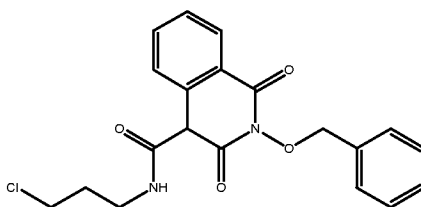
BOP (1.69 g, 4.0 mmol) was added at -25 °C to a solution of **intermediate 2** (1.00 g, 4.0 mmol) and 4-methylmorpholine (2.2 mL, 20.0 mmol) in a minimum of CH_2Cl_2 . After 30 min stirring at -25 °C, *O*-benzylhydroxylamine hydrochloride (0.64 g, 4.0 mmol) was added and after 12 h stirring at room temperature, the mixture was washed with 1.0 M HCl, 1.0 M NaHCO_3 solutions and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography of the residue (eluent: petroleum ether/AcOEt, 70/30), **intermediate 3** was obtained as a yellow oil (69%); ^1H NMR (300 MHz, CDCl_3): δ = 3.63 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.79 (s, 2 H, CH_2), 5.20 (s, 1 H, CH), 7.18-7.28 (m, 5 H, H_{Ar}), 7.33 (1 H, H_{Ar} , td, 3J = 7.5 Hz, 4J = 1.2 Hz), 7.48 (1 H, H_{Ar} , td, 3J = 7.5 Hz, 4J = 1.2 Hz), 7.57 (1 H, H_{Ar} , dd, 3J = 7.5 Hz, 4J = 1.2 Hz), 7.87 (1 H, H_{Ar} , dd, 3J = 7.5 Hz, 4J = 1.2 Hz), 9.64 (s, 1 H, NH); ^{13}C NMR (75 MHz, CDCl_3): δ = 52.5 (OCH_3), 52.7 (OCH_3), 52.8 (CH), 78.0 (OCH_2), 116.7 (C), 128.1 (CH), 128.5 (2CH), 128.6 (CH), 128.8 (C), 129.3 (2CH), 130.8 (CH), 131.9 (CH), 132.8 (CH), 134.5 (C), 165.4 (CO), 168.3 (CO), 169.3 (CO); ESI-MS: m/z = 358 ($\text{M}+\text{H}$)⁺

25 A1-d intermediate 4: Methyl 2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline -4-carboxylate



Intermediate 3 (0.337 g, 1.0 mmol) was dissolved in a solution of methanol (10.0 mL) and 2.0 M KOH (10.0 mL). After 5 min stirring, the solution was acidified with 2.0 M HCl and extracted three times with ether (20.0 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to **intermediate 4** as white crystals (0.323 g, 99%); mp 126 °C; 82% enol, 18% keto form. We give the ¹H NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ¹H NMR (300 MHz, CDCl₃): δ = 3.77 (s, 3 H, OCH₃), 4.11 (s, 3 H, OCH₃), 5.03 (s, 1 H, CH), 7.29-7.65 (m, 7 H, H_{Ar}), 5.29 (s, 2 H, CH₂), 6.37 (1 H, H_{Ar}, dd, ³J = 8.5 Hz, ⁴J = 1.5 Hz), 7.25 (1 H, H_{Ar}, dd, ³J = 7.7 Hz, ⁴J = 1.5 Hz), 8.45 (m, 2 H, H_{Ar}); **Enol form**; ¹³C NMR (75 MHz, CDCl₃): δ = 53.1 (CH₃), 79.0 (CH₂), 84.3 (C), 121.2 (C), 124.3 (CH), 124.6 (CH), 128.3 (CH), 128.6 (2CH), 129.4 (CH), 130.1 (2CH), 132.9 (C), 133.5 (C), 133.8 (CH), 158.8 (CO), 163.0 (CO), 173.5 (CO); **Keto form**; ¹³C NMR (75 MHz, CDCl₃): δ = 53.8 (CH₃), 54.8 (CH), 78.5 (CH₂), 119.3 (C), 123.5 (C), 127.3 (CH), 128.5 (2CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 130.0 (2CH), 131.4 (C), 133.5 (C), 134.4 (CH), 160.7 (CO), 162.9 (CO), 171.6 (CO); ESI-MS: *m/z* = 326 (M+H)⁺.

A1-e intermediate 5: N-(3-Chloropropyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



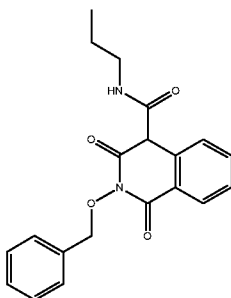
Intermediate 4 (0.325 g, 1.0 mmol) and 3-chloropropylamine hydrochloride (0.26 g, 2.0 mmol) were dissolved in toluene (100 mL). The mixture was refluxed for 12 h using a Dean Stark apparatus. After cooling, the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc. The organic layer was washed with 2.0 M HCl and dried over Na₂SO₄. After concentration *in vacuo*, the residue was triturated with ether and the precipitate was filtered and dried at room temperature giving **intermediate 5**. White crystals (82%); mp 126 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.08

(quin, 2 H, CH₂, ³J = 7.0 Hz), 3.60 (t, 2 H, CH₂, ³J = 7.0 Hz), 4.67 (t, 2 H, CH₂, ³J = 7.0 Hz), 5.05 (s, 2 H, OCH₂), 7.15 (td, 1 H, H_{Ar}, ³J = 8.0 Hz, ⁴J = 1.5 Hz), 7.39-7.50 (m, 3 H, H_{Ar}), 7.54 (td, 1 H, H_{Ar}, ³J = 8.0 Hz, ⁴J = 1.5 Hz), 7.59-7.67 (m, 2 H, H_{Ar}), 8.11 (dd, 1 H, H_{Ar}, ³J = 8.0 Hz, ⁴J = 1.5 Hz), 8.22 (dd, 1 H, H_{Ar}, ³J = 8.0 Hz, ⁴J = 1.5 Hz), 12.05 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 20.1 (CH₂), 37.9 (CH₂), 67.6 (CH₂), 77.4 (OCH₂), 88.8 (C_{IV}, C₄), 119.9 (C_{IV}), 122.2 (CH), 123.8 (CH), 128.0 (CH), 128.8 (2CH), 129.1 (CH), 129.8 (2CH), 133.2 (CH), 135.5 (C_{IV}), 135.6 (C_{IV}), 161.0 (CO), 164.2 (CO), 166.8 (CO); ESI-MS: *m/z* = 387 ((M+H)⁺, 100%, ³⁵Cl); 389 ((M+H)⁺, 32%, ³⁷Cl).

EXAMPLE A2

The process followed in this example is the same as described in example A1

A2-e intermediate 6: *N*-Propyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

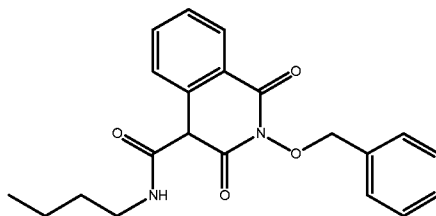


Intermediate 6: white solid (80%); mp 166 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 0.86 (t, 3 H, CH₃, ³J = 7.3 Hz), 1.45 (sext, 2 H, CH₂, ³J = 7.1 Hz), 3.06 (q, 2 H, NH-CH₂, ³J = 6.3 Hz), 4.98 (d, 1 H, OCH₂, ²J = 9.8 Hz), 5.03 (d, 1 H, OCH₂, ²J = 9.8 Hz), 5.12 (s, 1 H, CH), 7.38-7.45 (m, 4 H, H_{Ar}), 8.10 (d, 1 H, H_{Ar}, ³J = 7.8 Hz), 8.80 (t, 1 H, NH, ³J = 5.4 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 11.3 (CH₃), 22.2 (CH₂), 40.9 (CH₂), 55.8 (CH), 77.4 (OCH₂), 125.3 (C_{IV}), 126.6 (CH), 128.1 (CH), 128.3 (CH), 128.4 (2 CH), 128.9 (CH), 129.4 (2 CH), 134.2 (CH), 134.5 (C_{IV}), 133.9 (C_{IV}), 161.1 (CO), 164.6 (CO), 167.0 (CO); ESI-MS: *m/z* = 353 (M+H)⁺; Anal. (C₂₀H₂₀N₂O₄) C, H, N.

EXAMPLE A3

The process followed in this example is the same as described in example A1

A3-e intermediate 7: *N*-Butyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

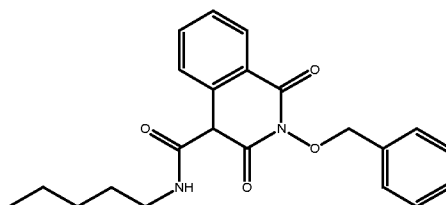


Intermediate 7: white solid (83%); mp 166 °C; 100% keto form; ^1H NMR (300 MHz, CDCl_3): δ = 0.85 (t, 3 H, CH_3 , 3J = 7.0 Hz), 1.12-1.40 (m, 4 H, 2 CH_2), 3.28 (q, 2 H, NH-CH_2 , 3J = 6.9 Hz), 4.80 (s, 1 H, CH), 5.14 (s, 2 H, OCH_2), 6.47 (t, 1 H, NH, 3J = 7.0 Hz), 7.40 (d, 1 H, H_{Ar} , 3J = 7.7 Hz), 7.52 (t, 1 H, H_{Ar} , 3J = 7.6 Hz), 7.69 (t, 1 H, H_{Ar} , 3J = 7.4 Hz), 8.07 (d, 1 H, H_8 , 3J = 6.8 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 13.7 (CH_3), 20.0 (CH_2), 31.3 (CH_2), 40.3 (CH_2), 55.7 (CH), 78.5 (OCH_2), 125.3 (C_{IV}), 128.1 (CH), 128.5 (2 CH), 128.7 (CH), 129.0 (CH), 129.2 (CH), 130.0 (2CH), 133.0 (C_{IV}), 133.8 (C_{IV}), 134.0 (CH), 161.1 (CO), 164.6 (CO), 165.1 (CO); ESI-MS: m/z = 367 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$) C, H, N.

EXAMPLE A4

The process followed in this example is the same as described in example A1

A4-e intermediate 8: *N*-Pentyl-2-benzoyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

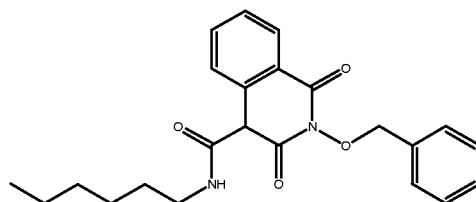


Intermediate 8: white solid (45%); mp 134 °C; 100% keto form; ^1H NMR (300 MHz, CDCl_3): δ = 0.90 (t, 3 H, CH_3 , 3J = 6.4 Hz), 1.32-1.65 (m, 6 H, 3 CH_2), 3.25 (q, 2 H, NH-CH_2 , 3J = 7.0 Hz), 4.79 (s, 1 H, CH), 5.11 (d, 1 H, OCH_2 , 2J = 9.0 Hz), 5.15 (d, 1 H, OCH_2 , 2J = 9.0 Hz), 6.50 (s, 1 H, NH), 7.34-7.66 (m, 8 H, H_{Ar}), 8.24 (d, 1 H, H_8 , 3J = 7.3 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 13.9 (CH_3), 22.2 (CH_2), 28.9 (2 CH_2), 40.5 (CH_2), 55.7 (CH), 78.5 (OCH_2), 125.3 (C_{IV}), 127.8 (CH), 128.5 (2 CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.9 (2 CH), 133.1 (C_{IV}), 133.8 (C_{IV}), 134.0 (CH), 161.1 (CO), 164.9 (CO), 165.0 (CO); ESI-MS: m/z = 381 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$) C, H, N.

EXAMPLE A5

The process followed in this example is the same as described in example A1

A5-e intermediate 9: N-Hexyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

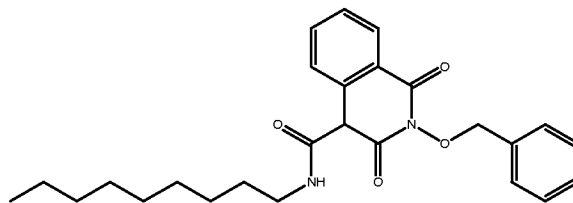


Intermediate 9: white crystals (83%); mp 139-140 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.88 (t, 3 H, CH₃, ³J = 7.0 Hz), 1.29 (m, 6 H, CH₂), 1.51 (quin, 2 H, CH₂, ³J = 7.0 Hz), 3.25 (t, 2 H, CH₂, ³J = 7.0 Hz), 4.80 (s, 1 H, CH), 5.12 (d, 1 H, OCH₂, ²J = 9.2 Hz), 5.16 (d, 1 H, OCH₂, ²J = 9.2 Hz), 6.51 (t, 1 H, NH, ³J = 6.0 Hz), 7.28 (dd, 1 H, H₅, ³J = 8.0 Hz, ⁴J = 1.5 Hz), 7.30-7.40 (m, 3 H, H_{Ar}), 7.51-7.68 (m, 4 H, H_{Ar}), 8.23 (dd, 1 H, H₈, ³J = 8.0 Hz, ⁴J = 1.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.0 (CH₃), 22.5 (CH₂), 26.4 (CH₂), 29.2 (CH₂), 31.4 (CH₂), 40.6 (CH₂), 55.5 (CH), 78.6 (OCH₂), 125.2 (C_{IV}), 128.5 (2CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.2 (CH), 130.0 (2CH), 132.7 (C_{IV}), 133.7 (C_{IV}), 133.9 (CH), 160.5 (CO), 164.0 (CO), 165.1 (CO); ESI-MS: m/z = 395 (M+H)⁺.

EXAMPLE A6

The process followed in this example is the same as described in example A1

A6-e intermediate 10: N-Nonyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

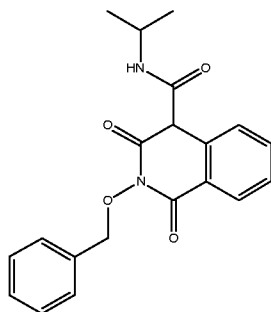


Intermediate 10: white solid (65%); mp 146 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.89 (t, 3 H, CH₃, ³J = 7.0 Hz), 1.28-1.60 (m, 14 H, 7 CH₂), 3.28 (q, 2 H, NH-CH₂, ³J = 6.0 Hz), 4.78 (s, 1 H, CH), 5.14 (m, 2 H, OCH₂), 6.43 (m, 1 H, NH), 7.30-7.68 (m, 8 H, H_{Ar}), 8.25 (d, 1 H, H₈, ³J = 7.6 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.1 (CH₃), 22.6 (CH₂), 26.8 (2 CH₂), 29.2 (3 CH₂), 29.5 (CH₂), 31.8 (CH₂), 40.5 (CH₂), 55.7 (CH), 78.5 (OCH₂), 125.3 (C_{IV}), 127.9 (CH), 128.5 (2 CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.9 (2 CH), 133.1 (C_{IV}), 133.8 (C_{IV}), 134.0 (CH), 161.1 (CO), 164.8 (CO), 165.0 (CO); ESI-MS: m/z = 437 (M+H)⁺; Anal. (C₂₆H₃₂N₂O₄) C, H, N.

EXAMPLE A7

The process followed in this example is the same as described in example A1

A7-e intermediate 11: *N*-Isopropyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

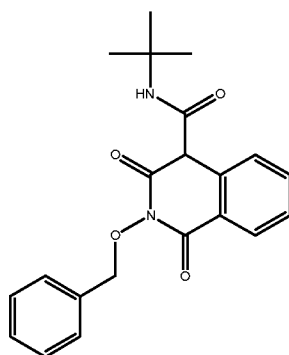


Intermediate 11: white solid (74%); mp 158 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.07 (d, 3 H, CH₃, ³*J* = 6.4 Hz), 1.14 (d, 3 H, CH₃, ³*J* = 6.4 Hz), 3.76 (sext, 1 H, CH, ³*J* = 6.6 Hz), 4.99 (d, 1 H, OCH₂, ²*J* = 9.6 Hz), 5.04 (d, 1 H, OCH₂, ²*J* = 9.6 Hz), 5.08 (s, 1 H, CH), 7.42-7.45 (m, 4 H, H_{Ar}), 7.57-7.60 (m, 3 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.10 (d, 1 H, H₈, ³*J* = 7.7 Hz), 8.74 (d_{app}, 1 H, NH, ³*J* = 7.4 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.0 (2 CH₃), 41.3 (CH), 55.7 (CH), 77.3 (OCH₂), 125.2 (CH), 128.0 (CH), 128.3 (3 CH), 128.8 (CH), 129.4 (2 CH), 134.1 (CH), 134.4 (C_{IV}), 134.9 (C_{IV}), 161.1 (CO), 164.5 (CO), 165.0 (CO); ESI-MS: *m/z* = 353 (M+H)⁺; Anal. (C₁₂₀H₂₀N₂O₄) C, H, N.

EXAMPLE A8

The process followed in this example is the same as described in example A1

A8-e intermediate 12: *N*-*Tert*-butyl-2-benzyloxy-1,3-dioxo-1,2,3,4- tetrahydroisoquinoline -4-carboxamide



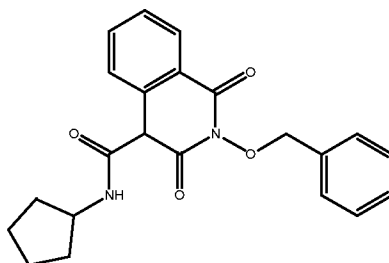
Intermediate 12: beige solid (70%); mp 143 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.31 (s, 9 H, 3 CH₃), 5.04 (d, 1 H, OCH₂, ²*J* = 9.3 Hz), 5.08 (d, 1 H, OCH₂,

$^2J = 9.3$ Hz), 5.19 (s, 1 H, CH), 7.48 (m, 3 H, H_{Ar}), 7.51 (d, 1 H, H_{Ar} , $^3J = 7.7$ Hz), 7.60-7.65 (m, 3 H, H_{Ar}), 7.80 (t, 1 H, H_{Ar} , $^3J = 7.7$ Hz), 8.15 (d, 1 H, H_8 , $^3J = 7.7$ Hz), 8.55 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 28.1$ (3 CH_3), 50.9 (C_{IV}), 56.2 (CH), 77.3 (OCH_2), 125.2 (C_{IV}), 126.4 (CH), 128.0 (CH), 128.3 (2 CH), 128.8 (CH), 129.3 (2 CH), 134.0 (CH), 134.5 (C_{IV}), 135.1 (C_{IV}), 161.1 (CO), 164.6 (CO), 165.2 (CO); ESI-MS: $m/z = 367$ (M+H) $^+$; Anal. ($C_{21}H_{22}N_2O_4$) C, H, N.

EXAMPLE A9

The process followed in this example is the same as described in example A1

A9-e intermediate 13: *N*-Cyclopentyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

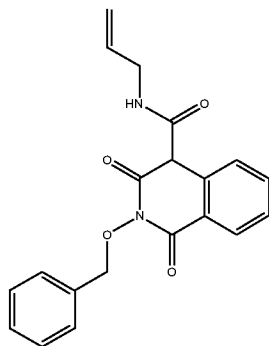


Intermediate 13: white solid (77%); mp 188 °C; 100% keto form; 1H NMR (300 MHz, DMSO- d_6): $\delta = 1.40$ -1.90 (m, 8 H, 4 CH_2), 3.95 (sext, 1 H, CH, $^3J = 6.3$ Hz), 4.99 (d, 1 H, OCH_2 , $^2J = 9.6$ Hz), 5.04 (d, 1 H, OCH_2 , $^2J = 9.6$ Hz), 5.10 (s, 1 H, CH), 7.40-7.43 (m, 4 H, H_{Ar}), 7.55-7.59 (m, 3 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar} , $^3J = 7.6$ Hz), 8.09 (d, 1 H, H_8 , $^3J = 7.9$ Hz), 8.79 (d_{app}, 1 H, NH, $^3J = 7.3$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 23.4$ (CH_2), 23.5 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 50.9 (CH), 55.6 (CH), 77.3 (OCH_2), 125.2 (C_{IV}), 126.4 (CH), 128.0 (CH), 128.2 (CH), 128.3 (2 CH), 128.8 (CH), 129.3 (2 CH), 134.1 (CH), 134.4 (C_{IV}), 134.9 (C_{IV}), 161.0 (CO), 164.5 (CO), 165.3 (CO); ESI-MS: $m/z = 379$ (M+H) $^+$; Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

EXAMPLE A10

The process followed in this example is the same as described in example A1

A10-e intermediate 14: *N*-Allyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

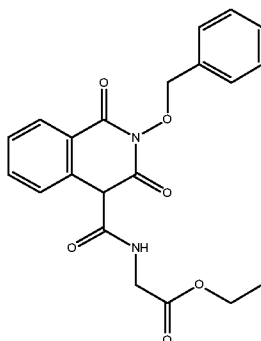


Intermediate 14: white solid (70%); mp 186 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.76 (m, 2 H, $\text{CH}_2\text{-CH=CH}_2$), 4.85 (d, 1 H, OCH_2 , 2J = 9.6 Hz), 4.95 (d, 1 H, OCH_2 , 2J = 9.6 Hz), 5.02-5.20 (m, 3 H, C_4H , $\text{CH}_2\text{-CH=CH}_2$), 5.80 (m, 1 H, $\text{CH}_2\text{-CH=CH}_2$), 7.43 (d, 1 H, H_{Ar} , 3J = 7.5 Hz), 7.55 (t, 1 H, H_{Ar} , 3J = 7.2 Hz), 7.71 (t, 1 H, H_{Ar} , 3J = 7.2 Hz), 8.07 (d, 1 H, H_8 , 3J = 7.5 Hz), 9.00 (m, 1 H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 41.7 ($\text{CH}_2\text{-CH=CH}_2$), 55.7 (CH), 77.3 (OCH_2), 115.4 ($\text{CH}_2\text{-CH=CH}_2$), 125.3 (C_{IV}), 126.7 (CH), 128.0 (CH), 128.3 (CH), 128.4 (2 CH), 128.8 (CH), 129.3 (2 CH), 134.1 (CH), 134.3 (CH), 134.4 (C_{IV}), 134.7 (C_{IV}), 161.0 (CO), 164.4 (CO), 165.9 (CO); ESI-MS: m/z = 351.1 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$) C, H, N.

EXAMPLE A11

The process followed in this example is the same as described in example A1

A11-e intermediate 15 : Ethyl 2-[(2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)formamido]acetate



15

Intermediate 15: orange oil (78%); 100% keto form; ^1H NMR (300 MHz, CDCl_3): δ = 1.22 (t, 3 H, CH_3 , 3J = 7.0 Hz), 4.01-4.12 (m, 4 H, CH_2), 5.10 (m, 3 H, CH, OCH_2), 7.28-7.40 (m, 4 H, NH, 3 H_{Ar}), 7.43-7.70 (m, 5 H, H_{Ar}), 8.22 (dd, 1 H, H_8 , 3J = 8.0 Hz, 4J = 1.5 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 14.1 (CH_3), 42.0 (CH_2), 55.3 (CH), 61.7 (OCH_2), 78.5 (OCH_2), 125.3 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.7 (2CH), 129.0 (CH), 129.1 (CH),

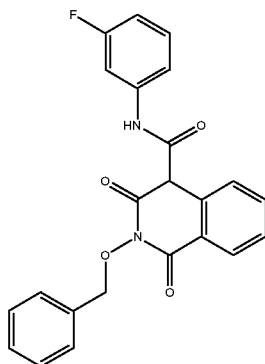
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130.0 (2CH), 132.8 (C_{IV}), 133.8 (C_{IV}), 134.1 (CH), 161.1 (CO), 164.8 (CO), 165.6 (CO), 169.4 (CO); ESI-MS: m/z = 397 (M+H)⁺; Anal. (C₂₁H₂₀N₂O₆) C, H, N.

EXAMPLE A12

The process followed in this example is the same as described in example A1

5 A12-e intermediate 16 : *N*-(3-Fluorophenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

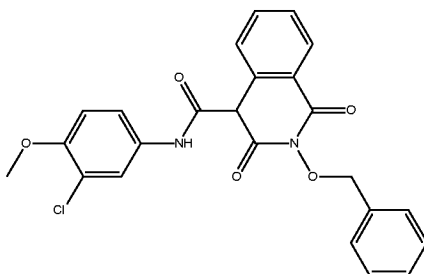


Intermediate 16: green oil (78%); 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 4.17 (s, 1 H, CH), 5.16 (s, 2 H, OCH₂), 6.82 (t, 1 H, H_{Ar}, ³*J* = 7.6 Hz), 7.00-7.59 (m, 12 H, NH, 10 11 H_{Ar}), 8.23 (dd, 1 H, H₈, ³*J* = 8.0 Hz, ⁴*J* = 1.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 55.9 (CH), 78.5 (OCH₂), 109.1 (d, CH, C_{2'}, ²*J*_{C-F} = 28.0 Hz), 110.7 (d, CH, C_{4'}, ²*J*_{C-F} = 28.0 Hz), 118.4 (d, CH, C_{6'}, ⁴*J*_{C-F} = 3.0 Hz), 126.9 (C_{IV}), 127.0 (CH), 127.6 (CH), 128.1 (CH), 128.6 (d, CH, C_{5'}, ³*J*_{C-F} = 8.0 Hz), 128.7 (2CH), 129.0 (CH), 129.1 (CH), 130.0 (2CH), 131.6 (C_{IV}), 134.8 (C_{IV}), 136.1 (d, C_{IV}, C_{1'}, ³*J*_{C-F} = 10.0 Hz), 161.1 (d, C_{IV}, C_{3'}, ¹*J*_{C-F} = 15 255.0 Hz), 161.6 (CO), 162.3 (CO), 165.4 (CO); ESI-MS: m/z = 405 (M+H)⁺; Anal. (C₂₃H₁₇FN₂O₄) C, H, N.

EXAMPLE A13

The process followed in this example is the same as described in example A1.

20 A13-e intermediate 17: *N*-(3-Chloro-4-methoxyphenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

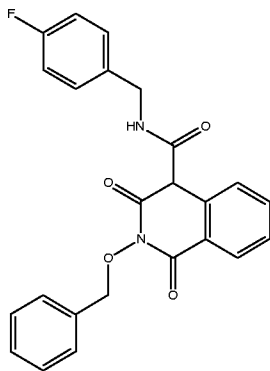


Intermediate 17: purple oil (67%); 100% keto form; ^1H NMR (300 MHz, CDCl_3): δ = 3.79 (s, 3 H, OCH_3), 4.17 (s, 1 H, CH), 5.15 (s, 2 H, OCH_2), 6.80 (d, 1 H, $\text{H}_{5''}$, $^3J = 7.2$ Hz), 7.20-7.70 (m, 9 H, NH, 8 H_{Ar}), 8.23 (m, 2 H, H_{Ar}), 8.78 (d, 1 H, $\text{H}_{2''}$, $^4J = 1.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 55.4 (OCH_3), 56.0 (CH), 115.1 (CH), 116.1 (C_{IV}), 120.5 (CH), 120.8 (CH), 126.9 (C_{IV}), 127.1 (CH), 127.6 (CH), 128.1 (CH), 128.2 (C_{IV}), 128.8 (2CH), 129.0 (CH), 129.1 (CH), 129.8 (2CH), 131.3 (C_{IV}), 134.8 (C_{IV}), 148.6 (C_{IV}), 161.3 (CO), 163.3 (CO), 166.4 (CO); ESI-MS: m/z = 451 ($(\text{M}+\text{H})^+$, 100%, ^{35}Cl); 453 ($(\text{M}+\text{H})^+$, 32%, ^{37}Cl); Anal. ($\text{C}_{24}\text{H}_{19}\text{ClN}_2\text{O}_5$) C, H, N.

EXAMPLE A14

10 The process followed in this example is the same as described in example A1.

A14-e intermediate 18: *N*-(4-Fluorobenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

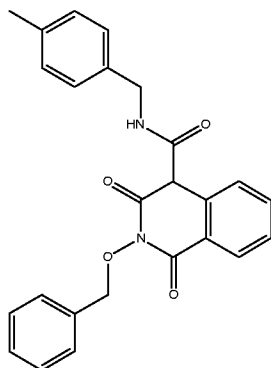


Intermediate 18: beige solid (81%); mp 119-121 °C; 100% enol form; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 4.46 (d, 2 H, CH_2 , $^3J = 5.8$ Hz), 5.13 (s, 2 H, OCH_2), 6.84-7.20 (m, 4 H, H_{Ar}), 7.36-7.50 (m, 6 H, H_{Ar}), 7.68 (td, 1 H, H_{Ar} , $^3J = 8.0$ Hz, $^4J = 1.5$ Hz), 8.06 (dd, 1 H, H_{Ar} , $^3J = 8.0$ Hz, $^4J = 1.5$ Hz), 8.34 (dd, 1 H, H_{Ar} , $^3J = 8.0$ Hz, $^4J = 1.5$ Hz), 10.65 (t, 1 H, NH, $^3J = 5.8$ Hz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 42.5 (CH_2), 76.7 (OCH_2), 83.7 (C_{IV} , C_4), 115.0 (d, 2CH, $\text{C}_{3''}$, $\text{C}_{5''}$, $^2J_{\text{C-F}} = 21.4$ Hz), 126.2 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (2CH), 130.1 (d, 2 CH, $\text{C}_{2''}$, $\text{C}_{6''}$, $^3J_{\text{C-F}} = 8.6$ Hz), 130.2 (2 CH), 131.1 (CH), 132.1 (CH), 133.8 (C_{IV}), 133.8 (d, C_{IV} , $\text{C}_{1''}$, $^4J_{\text{C-F}} = 3.1$ Hz), 135.1 (C_{IV}), 159.1 (CO), 161.2 (d, C_{IV} , $\text{C}_{4''}$, $^1J_{\text{C-F}} = 245.0$ Hz), 161.3 (CO), 165.4 (CO); ESI-MS: m/z = 419 ($\text{M}+\text{H})^+$; Anal. ($\text{C}_{24}\text{H}_{19}\text{FN}_2\text{O}_4$) C, H, N.

EXAMPLE A15

25 The process followed in this example is the same as described in example A1.

A15-e intermediate 19 : *N*-(4-Methylbenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

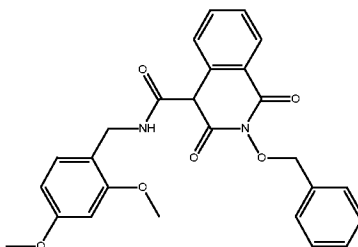


Intermediate 19: white crystals (85%); mp 149-150 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.28 (s, 3 H, CH₃), 4.42 (d, 2 H, ³*J* = 5.3 Hz), 5.01 (s, 2 H, OCH₂), 6.84 (td, 1 H, H_{Ar}, ³*J* = 7.0 Hz, ⁴*J* = 1.5 Hz), 7.13 (d, 2 H, ³*J* = 7.8 Hz), 7.20-7.38 (m, 6 H, H_{Ar}), 7.62 (d, 2 H, H_{Ar}, ³*J* = 7.8 Hz), 7.94 (dd, 1 H, H_{Ar}, ³*J* = 8.0 Hz, ⁴*J* = 1.5 Hz), 8.38 (dd, 1 H, H₈, ³*J* = 8.0 Hz, ⁴*J* = 1.5 Hz), 10.65 (t, 1 H, NH, ³*J* = 5.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 21.2 (CH₃), 42.1 (CH₂), 76.6 (OCH₂), 86.8 (C_{IV}, C₄), 118.5 (C_{IV}), 118.6 (CH), 124.0 (CH), 126.9 (CH), 127.8 (2CH), 128.6 (2 CH), 128.7 (CH), 129.2 (2 CH), 129.3 (2CH), 131.2 (C_{IV}), 131.3 (CH), 136.3 (C_{IV}), 138.3 (C_{IV}), 140.5 (C_{IV}), 159.8 (CO), 161.3 (CO), 169.6 (CO); ESI-MS: *m/z* = 415 (M+H)⁺; Anal. (C₂₅H₂₂N₂O₄) C, H, N.

EXAMPLE A16

The process followed in this example is the same as described in example A1.

A16-e intermediate 20: *N*-(2,4-Dimethoxybenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 20: salmon solid (88%); mp 176-177 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 3.75 (s, 3 H, OCH₃), 3.84 (s, 3 H, OCH₃), 4.35 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 4.38 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 4.82 (s, 1 H, CH), 5.01 (d, 1 H, OCH₂, ²*J* = 9.2 Hz), 5.08 (d, 1 H, OCH₂, ²*J* = 9.2 Hz), 6.40 (dd, 1 H, H_{5''}, ³*J*_{5''-6''} = 7.5 Hz, ⁴*J*_{5''-3''} = 1.2 Hz), 6.45 (d, 1 H, H_{3''}, ⁴*J*_{3''-5''} = 1.2 Hz), 7.05 (t, 1 H, NH, ³*J* = 5.1 Hz),

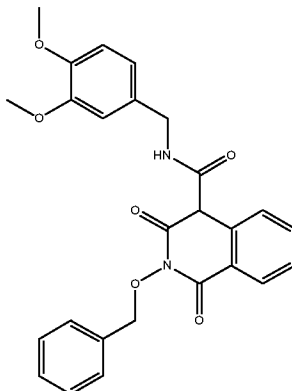
7.14 (d, 1 H, $H_{6''}$, $^3J_{6''-5''} = 7.6$ Hz), 7.28-7.39 (m, 5 H, H_{Ar}), 7.51-7.70 (m, 3 H, H_{Ar}), 8.21 (dd, 1 H, H_8 , $^3J = 7.6$ Hz, $^4J = 1.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 40.3$ (CH_2), 55.3 (CH_3), 55.4 (CH_3), 55.7 (CH), 78.4 (OCH_2), 98.6 (CH, $C_{3''}$), 103.9 (CH, $C_{5''}$), 118.5 (C_{IV} , $C_{1''}$), 125.6 (C_{IV}), 126.1 (CH), 128.5 (CH), 128.6 (2CH), 128.7 (CH), 129.0 (CH), 129.9 (2CH), 130.6 (CH), 133.8 (C_{IV}), 133.9 (CH), 135.0 (C_{IV}), 158.5 (CO), 160.8 (CO), 163.9 (CO), 165.0 (CO), 166.6 (CO); ESI-MS: $m/z = 461$ ($M+H$) $^+$; Anal. ($C_{26}H_{24}N_2O_6$) C, H, N.

EXAMPLE A17

The process followed in this example is the same as described in example A16.

EXAMPLE A18

10 The process followed in this example is the same as described in example A1
A18-e intermediate 21: *N*-(3,4-Dimethoxybenzyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 21: white crystals (48%); mp 186-188 °C; 100% keto form; 1H NMR (300 MHz, $CDCl_3$): $\delta = 3.74$ (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.27 (dd, 1 H, CH_2 , $^2J = 11.9$ Hz, $^3J = 5.1$ Hz), 4.36 (dd, 1 H, CH_2 , $^2J = 11.9$ Hz, $^3J = 5.1$ Hz), 4.73 (s, 1 H, CH), 4.98 (d, 1 H, OCH_2 , $^2J = 9.2$ Hz), 5.02 (d, 1 H, OCH_2 , $^2J = 9.2$ Hz), 6.50-6.62 (m, 3 H, H_{Ar}), 6.96 (t, 1 H, H_{Ar} , $^3J = 7.6$ Hz), 7.20-7.32 (m, 4 H, H_{Ar}), 7.40-7.54 (m, 3 H, H_{Ar}), 8.13 (dd, 1 H, H_8 , $^3J = 7.6$ Hz, $^4J = 1.5$ Hz), 9.01 (t, 1 H, NH, $^3J = 5.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 44.2$ (CH_2), 55.6 (CH), 55.8 (CH_3), 55.9 (CH_3), 78.6 (OCH_2), 110.8 (CH), 111.1 (CH), 118.5 (C_{IV}), 120.0 (CH), 125.6 (C_{IV}), 128.1 (CH), 128.5 (2CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.9 (2CH), 132.7 (C_{IV}), 134.0 (CH), 134.1 (C_{IV}), 158.8 (CO), 160.8 (CO), 163.9 (CO), 164.5 (CO), 166.6 (CO); ESI-MS: $m/z = 461$ ($M+H$) $^+$; Anal. ($C_{26}H_{24}N_2O_6$) C, H, N.

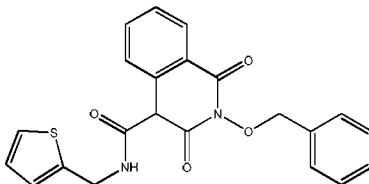
EXAMPLE A19

The process followed in this example is the same as described in example A18

EXAMPLE A20

The process followed in this example is the same as described in example A1

A20-e intermediate 22: *N*-((Thiophen-2-yl)methyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

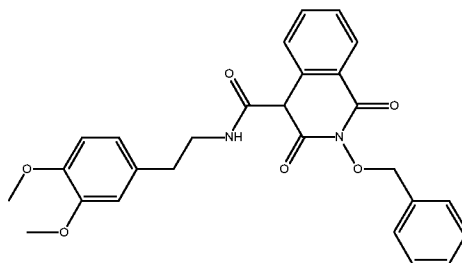


Intermediate 22: beige solid (74%); mp 190 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.56 (m, 2 H, CH₂), 5.08 (s, 2 H, OCH₂), 5.24 (s, 1 H, CH), 6.75-6.81 (m, 2 H, CH Thioph), 6.90 (d, 1 H, CH Thioph, ³*J* = 5.0 Hz), 7.00-7.70 (m, 7 H, H_{Ar}), 7.78 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.16 (d, 1 H, H₈, ³*J* = 7.7 Hz), 9.48 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 37.6 (CH₂), 55.4 (CH), 77.2 (OCH₂), 125.2 (C_{IV}), 125.4 (CH), 125.7 (CH), 126.7 (2 CH), 128.1 (CH), 128.4 (3 CH), 128.8 (CH), 129.4 (2 CH), 134.1 (CH), 134.4 (2 C_{IV}), 141.2 (C_{IV}), 161.0 (CO), 164.3 (CO), 165.8 (CO); ESI-MS: *m/z* = 407.1 (M+H)⁺; Anal. (C₂₂H₁₈N₂O₄S) C, H, N.

EXAMPLE A21

The process followed in this example is the same as described in example A1

A21-e intermediate 23 : *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 23: white solid (53%); mp 191-192 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.70 (m, 2 H, CH₂), 3.35 (m, 2 H, CH₂), 3.71 (s, 3 H, OCH₃), 3.72 (s, 3 H, OCH₃), 4.95 (d, 1 H, OCH₂, ²*J* = 9.2 Hz), 5.04 (d, 1 H, OCH₂, ²*J* = 9.2 Hz), 5.19 (s, 1 H, CH), 6.20 (d, 1 H, H₅, ³*J* = 7.8 Hz), 6.85-6.92 (m, 2 H, H_{Ar}), 7.31 (dd, 1 H, H_{Ar}, ³*J* = 7.8 Hz, ⁴*J* = 1.5 Hz), 7.40-7.51 (m, 3 H, H_{Ar}), 7.53-7.60 (m, 3 H, H_{Ar}), 7.65 (td, 1 H, H_{Ar}, ³*J* = 7.8 Hz, ⁴*J* = 1.5 Hz), 8.08 (dd, 1 H, H₈, ³*J* = 7.8 Hz, ⁴*J* = 1.5 Hz), 9.06 (t, 1 H, NH, ³*J* = 5.2 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 34.6 (CH₂), 41.3 (CH₂), 55.8 (OCH₃), 55.9

(OCH₃), 55.9 (CH), 77.8 (OCH₂), 112.2 (CH), 113.0 (CH), 121.0 (CH), 125.6 (C_{IV}), 127.2 (CH), 128.4 (CH), 128.7 (CH), 128.8 (2CH), 129.3 (CH), 129.8 (2CH), 131.9 (C_{IV}), 134.4 (CH), 134.9 (C_{IV}), 135.2 (C_{IV}), 147.7 (C_{IV}), 149.0 (C_{IV}), 161.5 (CO), 165.0 (CO), 166.4 (CO); ESI-MS: m/z = 475 (M+H)⁺; Anal. (C₂₇H₂₆N₂O₆) C, H, N.

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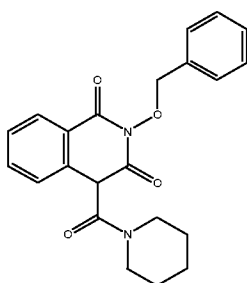
EXAMPLE A22

The process followed in this example is the same as described in example A21

EXAMPLE A23

The process followed in this example is the same as described in example A1

A23-e intermediate 24: (2-Benzyloxy-1,3-dioxoisoquinolin-4-yl)(piperidin-1-yl)methanone



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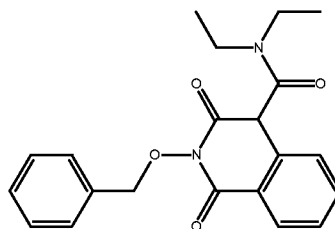
Intermediate 24: white solid (67%); mp 132 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.48-1.62 (m, 6 H, 3 CH₂), 3.35 (t, 2 H, N-CH₂, ³*J* = 5.1 Hz), 3.66 (t, 2 H, N-CH₂, ³*J* = 5.1 Hz), 5.00 (s, 2 H, OCH₂), 5.93 (s, 1 H, CH), 7.30 (d, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 7.42-7.56 (m, 6 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.12 (d, 1 H, H₈, ³*J* = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 23.8 (CH₃), 25.3 (CH₂), 26.1 (CH₂), 43.2 (CH₂), 47.5 (CH₂), 51.0 (CH), 77.5 (OCH₂), 125.4 (C_{IV}), 126.9 (CH), 128.1 (CH), 128.3 (CH), 128.4 (2 CH), 128.9 (CH), 129.4 (2 CH), 134.2 (CH), 134.3 (C_{IV}), 135.1 (C_{IV}), 160.9 (CO), 164.4 (CO), 164.6 (CO); ESI-MS: m/z = 379 (M+H)⁺; Anal. (C₂₂H₂₂N₂O₄) C, H, N.

15

EXAMPLE A24

20 The process followed in this example is the same as described in example A1

A24-e intermediate 25: *N,N*-Diethyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

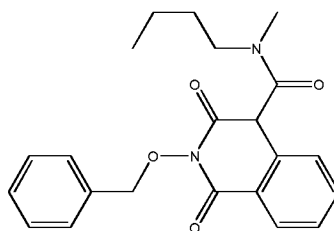


Intermediate 25: white solid (67%); mp 114 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.11 (t, 3 H, CH₃, ³*J* = 6.7 Hz), 1.29 (t, 3 H, CH₃, ³*J* = 6.5 Hz), 3.24-3.43 (m, 2 H, NH-CH₂), 3.61-3.76 (m, 2 H, NH-CH₂), 5.00 (s, 2 H, OCH₂), 5.80 (s, 1 H, CH), 6.50 (s, 1 H, NH), 7.28 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.30-7.40 (m, 3 H, H_{Ar}), 7.56-7.61 (m, 3 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.11 (d, 1 H, H₈, ³*J* = 7.6 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 12.7 (CH₃), 14.7 (CH₃), 40.5 (CH₂), 42.8 (CH₂), 51.1 (CH), 77.4 (OCH₂), 125.5 (C_{IV}), 126.6 (CH), 128.1 (CH), 128.2 (CH), 128.4 (2 CH), 128.9 (CH), 129.4 (2 CH), 134.3 (CH), 135.3 (2 C_{IV}), 160.9 (CO), 164.5 (CO), 165.7 (CO); ESI-MS: *m/z* = 367 (M+H)⁺; Anal. (C₂₁H₂₂N₂O₄) C, H, N.

EXAMPLE A25

The process followed in this example is the same as described in example A1

A25-e intermediate 26: *N*-Butyl-*N*-methyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

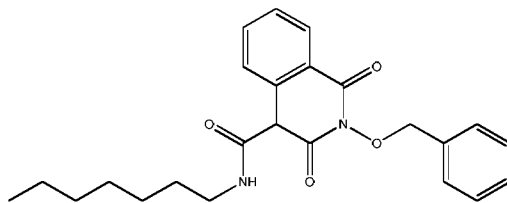


Intermediate 26: white solid (69%); mp 117-120 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.83 (t, 3 H, CH₃, ³*J* = 8.4 Hz), 1.20-1.59 (m, 4 H, 2 CH₂), 2.88 (s, 3 H, NH-CH₃), 3.07 (s, 3 H, NH-CH₃), 3.30 (t, 2 H, NH-CH₂, ³*J* = 6.7 Hz), 3.56 (t, 2 H, NH-CH₂, ³*J* = 6.7 Hz), 4.99 (s, 1 H, CH), 5.23 (s, 1 H, CH), 7.06 (m, 1 H, H_{Ar}), 7.23-7.25 (m, 3 H, H_{Ar}), 7.36-7.47 (m, 4 H, H_{Ar}), 8.10 (d, 1 H, H₈, ³*J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 13.8 (CH₃), 19.9 (CH₂), 20.0 (CH₂), 29.0 (CH₂), 30.9 (CH₂), 34.6 (NHCH₃), 36.5 (NHCH₃), 48.6 (NHCH₂), 51.0 (NHCH₂), 51.7 (CH), 52.5 (CH), 78.4 (OCH₂), 125.9 (C_{IV}), 126.1 (C_{IV}), 126.4 (CH), 128.4 (2 CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 129.9 (2 CH), 133.9 (C_{IV}), 134.2 (CH), 161.1 (CO), 164.2 (CO), 165.9 (CO); ESI-MS: *m/z* = 381 (M+H)⁺; Anal. (C₂₂H₂₄N₂O₄) C, H, N.

EXAMPLE A26

The process followed in this example is the same as described in example A1

A26-e intermediate 27: *N*-Heptyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

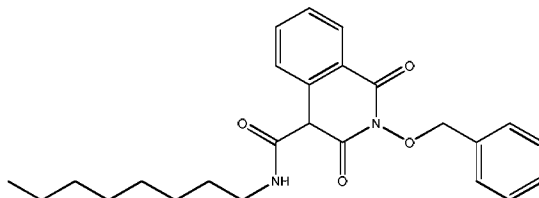


Intermediate 27: white solid (48%); mp 131-134 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.80 (t, 3 H, CH₃, ³J = 7.0 Hz), 1.19-1.21 (m, 8 H, 4 CH₂), 1.43-1.45 (m, 2 H, CH₂), 3.14 (q, 2 H, NH-CH₂, ³J = 7.1 Hz), 4.71 (s, 1 H, CH), 5.05 (m, 2 H, OCH₂), 6.40 (m, 1 H, NH), 7.19 (d, 1 H, H_{Ar}, ³J = 7.2 Hz), 7.26-7.30 (m, 3 H, H_{Ar}), 7.44-7.56 (m, 4 H, H_{Ar}), 8.16 (d, 1 H, H₈, ³J = 8.3 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.1 (CH₃), 22.6 (CH₂), 26.8 (CH₂), 28.9 (CH₂), 29.3 (CH₂), 31.7 (CH₂), 40.5 (CH₂), 55.7 (CH), 78.5 (OCH₂), 125.3 (C_{IV}), 127.8 (CH), 128.5 (3 CH), 129.0 (CH), 129.2 (CH), 129.9 (2 CH), 133.2 (C_{IV}), 133.8 (C_{IV}), 134.0 (CH), 161.2 (CO), 165.0 (CO), 165.1 (CO); ESI-MS: *m/z* = 409 (M+H)⁺; Anal. (C₂₄H₂₈N₂O₄) C, H, N.

EXAMPLE A27

The process followed in this example is the same as described in example A1

A27-e intermediate 28: N-Octyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

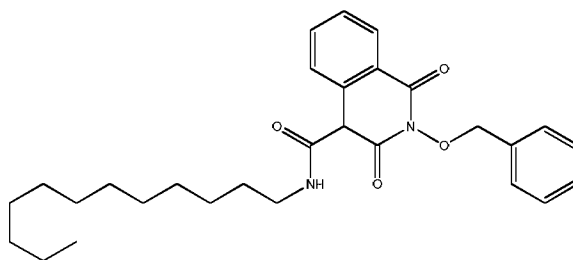


Intermediate 28: white solid (49%); mp 137-139 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.80 (t, 3 H, CH₃, ³J = 7.3 Hz), 1.18-1.22 (m, 10 H, 5 CH₂), 1.43-1.45 (m, 2 H, CH₂), 3.18 (q, 2 H, NH-CH₂, ³J = 7.5 Hz), 4.71 (s, 1 H, CH), 5.07 (m, 2 H, OCH₂), 6.37 (m, 1 H, NH), 7.20 (d, 1 H, H_{Ar}, ³J = 8.0 Hz), 7.31-7.33 (m, 3 H, H_{Ar}), 7.44-7.59 (m, 4 H, H_{Ar}), 8.16 (d, 1 H, H₈, ³J = 7.7 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.1 (CH₃), 22.6 (CH₂), 26.8 (CH₂), 29.2 (3 CH₂), 31.8 (CH₂), 40.5 (CH₂), 55.7 (CH), 78.5 (OCH₂), 125.3 (C_{IV}), 127.8 (CH), 128.5 (3 CH), 128.9 (CH), 129.2 (CH), 129.9 (2 CH), 133.2 (C_{IV}), 133.8 (C_{IV}), 134.0 (CH), 161.1 (CO), 165.0 (CO), 165.1 (CO); ESI-MS: *m/z* = 423 (M+H)⁺; Anal. (C₂₅H₃₀N₂O₄) C, H, N.

EXAMPLE A28

The process followed in this example is the same as described in example A1

A28-e intermediate 29: *N*-Dodecyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

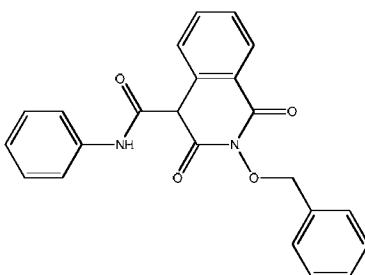


Intermediate 29: grey solid (57%); mp 143-145 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 0.80 (t, 3 H, CH₃, ³J = 6.6 Hz), 1.15-1.29 (m, 20 H, 10 CH₂), 3.10 (q, 2 H, NH-CH₂, ³J = 6.7 Hz), 4.80 (s, 1 H, CH), 5.05 (m, 2 H, OCH₂), 6.37 (m, 1 H, NH), 7.18 (d, 1 H, H_{Ar}, ³J = 7.2 Hz), 7.28-7.33 (m, 4 H, H_{Ar}), 7.47 (t, 1 H, H_{Ar}, ³J = 8.5 Hz), 7.49-7.52 (m, 1H, H_{Ar}), 7.58 (t, 1 H, H_{Ar}, ³J = 7.2 Hz), 8.17 (d, 1 H, H₈, ³J = 8.0 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.1 (CH₃), 22.7 (CH₂), 26.9 (CH₂), 29.3 (CH₂), 29.4 (CH₂), 29.7 (5 CH₂), 31.9 (CH₂), 40.6 (CH₂), 55.7 (CH), 78.6 (OCH₂), 125.3 (C_{IV}), 128.0 (CH), 128.5 (2 CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 129.9 (2 CH), 133.1 (C_{IV}), 133.7 (C_{IV}), 134.0 (CH), 161.1 (CO), 164.9 (CO), 165.3 (CO); ESI-MS: *m/z* = 479 (M+H)⁺; Anal. (C₂₉H₃₈N₂O₄) C, H, N.

EXAMPLE A29

The process followed in this example is the same as described in example A1.

A29-e intermediate 30: *N*-Phenyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



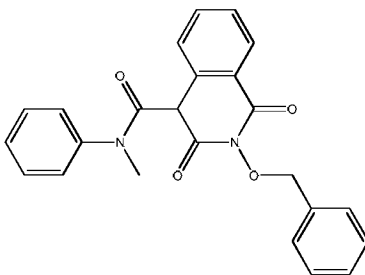
Intermediate 30: grey solid (60%); mp 143-146 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 5.04 (d, 1 H, CH₂, ²J = 9.6 Hz), 5.09 (d, 1 H, CH₂, ²J = 9.6 Hz), 5.39 (s, 1 H, CH), 7.13 (t, 1 H, H_{Ar}, ³J = 7.3 Hz), 7.36 (t, 1 H, H_{Ar}, ³J = 7.7 Hz), 7.42-7.44 (m, 4 H, H_{Ar}), 7.59-7.61 (m, 5H, H_{Ar}), 7.76 (t, 1 H, H_{Ar}, ³J = 7.3 Hz), 8.15 (d, 1 H, H_{Ar}, ³J = 7.3 Hz), 10.93 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 56.5 (CH), 77.4 (OCH₂), 119.4 (2 CH), 124.3 (CH), 125.3 (C_{IV}), 126.7 (CH), 128.2 (CH), 128.4 (2 CH), 128.5 (CH), 128.9

(CH), 129.0 (2 CH), 129.4 (2 CH), 134.36 (CH), 134.39 (C_{IV}), 134.5 (C_{IV}), 138.1 (C_{IV}), 161.0 (CO), 164.3 (CO), 164.7 (CO); ESI-MS: $m/z = 387$ (M+H)⁺; Anal. (C₂₃H₁₈N₂O₄) C, H, N.

EXAMPLE A30

5 The process followed in this example is the same as described in example A1.

A30-e intermediate 31: *N*-Methyl-*N*-phenyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

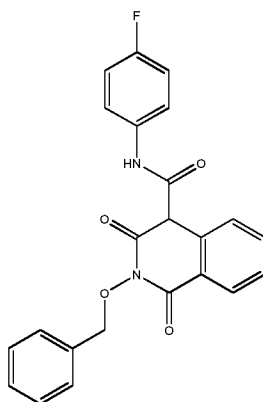


Intermediate 31: white solid (77%); mp 177-180 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 3.31 (s, 3 H, CH₃), 3.43 (s, 3 H, CH₃), 5.05 (m, 2 H, OCH₂), 5.13 (s, 1 H, CH), 7.05-7.07 (m, 1 H, H_{Ar}), 7.20 (t, 1 H, H_{Ar}, ³J = 7.3 Hz), 7.32-7.42 (m, 8 H, H_{Ar}), 7.53-7.55 (m, 3 H, H_{Ar}), 8.11 (d, 1 H, H_{Ar}, ³J = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 38.3 (CH₃), 52.0 (CH), 78.4 (OCH₂), 125.8 (C_{IV}), 126.3 (CH), 128.5 (5 CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 130.0 (2 CH), 130.4 (2 CH), 134.0 (C_{IV}), 134.1 (CH), 142.8 (C_{IV}), 161.0 (CO), 164.3 (CO), 166.3 (CO); ESI-MS: $m/z = 401$ (M+H)⁺; Anal. (C₂₄H₂₀N₂O₄) C, H, N.

EXAMPLE A31

The process followed in this example is the same as described in example A1

A31-e intermediate 32: *N*-(4-Fluorophenyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

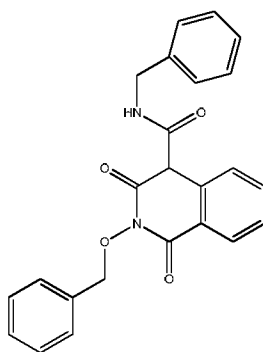


Intermediate 32: beige solid (78%); mp 177-180 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 5.04 (d, 1 H, CH₂, ²J = 9.6 Hz), 5.09 (d, 1 H, CH₂, ²J = 9.6 Hz), 5.37 (s, 1 H, CH), 7.20 (t, 2 H, H_{Ar}, ³J = 8.8 Hz), 7.41-7.43 (m, 3 H, H_{Ar}), 7.53-7.66 (m, 6 H, H_{Ar}), 7.76 (t, 1 H, H_{Ar}, ³J = 7.7 Hz), 8.15 (d, 1 H, H_{Ar}, ³J = 7.7 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 56.5 (CH), 77.4 (OCH₂), 115.6 (d, 2 CH, C_{3''}, C_{5''}, ²J_{C-F} = 22.5 Hz), 121.3 (d, 2 CH, C_{2''}, C_{6''}, ³J_{C-F} = 8.2 Hz), 125.3 (C_{IV}), 126.7 (CH), 128.2 (CH), 128.3 (2 CH), 128.5 (CH), 118.4 (d, CH, C_{6''}, ⁴J_{C-F} = 3.0 Hz), 127.6 (CH), 128.1 (CH), 128.9 (CH), 129.4 (2 CH), 134.3 (CH), 134.4 (2 C_{IV}), 134.5 (d, C_{IV}, C_{1''}, ⁴J_{C-F} = 2.2 Hz), 158.5 (d, C_{IV}, C_{4''}, ¹J_{C-F} = 240.0 Hz), 160.9 (CO), 164.3 (CO), 164.6 (CO); ESI-MS: *m/z* = 405 (M+H)⁺; Anal. (C₂₃H₁₇FN₂O₄) C, H, N.

EXAMPLE A32

The process followed in this example is the same as described in example A1

A32-e intermediate 33: *N*-Benzyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

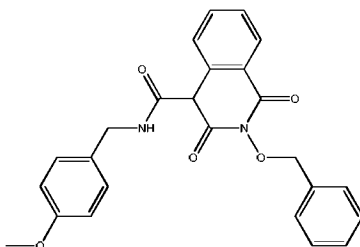


Intermediate 33: white solid (52%); mp 153-155 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 4.33 (s, 2 H, CH₂), 5.01-5.03 (m, 2 H, OCH₂), 5.21 (s, 1 H, CH), 7.18-7.52 (m, 12 H, H_{Ar}), 7.73 (t, 1 H, H_{Ar}, ³J = 7.0 Hz), 8.10 (d, 1 H, H_{Ar}, ³J = 7.7 Hz), 9.33 (s, 1 H, NH); ¹³C NMR (75 MHz, CDCl₃): δ = 42.6 (CH₂), 55.7 (CH), 77.4 (OCH₂), 125.3 (C_{IV}), 126.7 (CH), 127.08 (CH), 127.17 (2 CH), 128.1 (CH), 128.4 (5 CH), 128.9 (CH), 129.4 (2 CH), 134.1 (CH), 134.4 (C_{IV}), 134.6 (C_{IV}), 138.4 (C_{IV}), 161.0 (CO), 164.5 (CO), 166.1 (CO); ESI-MS: *m/z* = 401 (M+H)⁺; Anal. (C₂₄H₂₀N₂O₄) C, H, N.

EXAMPLE A33

The process followed in this example is the same as described in example A1.

A33-e intermediate 34: *N*-4-Methoxybenzyl-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

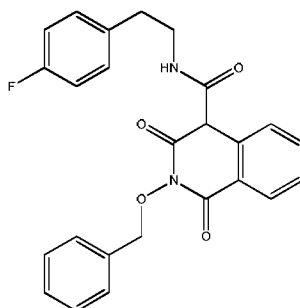


Intermediate 34: grey solid (61%); mp 163-167 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 3.74 (s, 3 H, OCH₃), 4.24 (dd, 1 H, CH₂, ²J = 14.7 Hz, ³J = 5.6 Hz), 4.29 (dd, 1 H, CH₂, ²J = 14.7 Hz, ³J = 5.6 Hz), 5.00 (d, 1 H, OCH₂, ²J = 9.6 Hz), 5.05 (d, 1 H, OCH₂, ²J = 9.6 Hz), 5.19 (s, 1 H, CH), 6.91 (d, 2 H, H_{Ar}, ³J = 8.5 Hz), 7.19 (d, 2 H, H_{Ar}, ³J = 8.5 Hz), 7.40-7.44 (m, 4 H, H_{Ar}), 7.56-7.58 (m, 3 H, H_{Ar}), 7.74 (t, 1 H, H_{Ar}, ³J = 7.4 Hz), 8.10 (d, 1 H, H₈, ³J = 7.6 Hz), 9.25 (t, 1 H, NH, ³J = 5.3 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 42.1 (CH₂), 55.3 (OCH₃), 56.1 (CH), 77.8 (OCH₂), 113.8 (2 CH), 125.2 (C_{IV}), 126.6 (CH), 128.0 (CH), 128.30 (CH), 128.37 (2CH), 128.6 (2 CH), 128.8 (CH), 129.3 (2CH), 130.2 (C_{IV}), 134.1 (CH), 134.4 (C_{IV}), 134.7 (C_{IV}), 158.4 (CO), 161.0 (CO), 164.4 (CO), 165.9 (CO); ESI-MS: *m/z* = 431 (M+H)⁺; Anal. (C₂₅H₂₂N₂O₅) C, H, N.

EXAMPLE A34

The process followed in this example is the same as described in example A1.

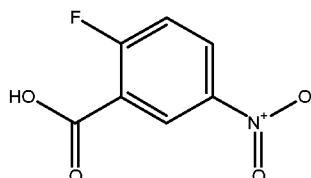
A34-e intermediate 35: *N*-(4-Fluorophenethyl)-2-benzyloxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



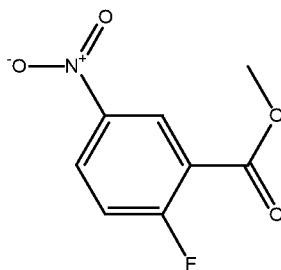
Intermediate 35: white solid (61%); mp 155-165 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.73 (t, 2 H, CH₂, ³J = 5.0 Hz), 3.36 (q, 2 H, CH₂, ³J = 5.0 Hz), 4.97 (d, 1 H, OCH₂, ²J = 9.5 Hz), 5.00 (d, 1 H, OCH₂, ²J = 9.5 Hz), 5.09 (s, 1 H, CH), 7.12 (t, 2 H, H_{Ar}, ³J = 8.8 Hz), 7.24-7.28 (m, 4 H, H_{Ar}), 7.41-7.43 (m, 3 H, H_{Ar}), 7.54-7.58 (m, 3 H, H_{Ar}), 7.68 (t, 1 H, H_{Ar}, ³J = 7.6 Hz), 8.08 (d, 1 H, H_{Ar}, ³J = 7.7 Hz), 8.85 (t, 1 H, NH, ³J = 5.0 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 33.8 (CH₂), 40.6 (CH₂), 54.2 (CH), 77.6 (OCH₂), 115.7 (d, 2 CH, C_{3'}, C_{5'}, ²J_{C-F} = 21.0 Hz), 125.2 (C_{IV}), 126.9 (CH), 127.6 (CH),

128.0 (CH), 129.2 (2CH), 129.6 (2 CH), 130.7 (d, 2 CH, C_{2'}, C_{6'}, ³J_{C-F} = 8.3 Hz), 133.7 (2 CH), 134.7 (CH), 135.28 (C_{IV}), 135.30 (d, C_{IV}, C_{1'}, ⁴J_{C-F} = 2.8 Hz), 136.4 (C_{IV}), 162.0 (d, C_{IV}, C_{4'}, ¹J_{C-F} = 241.5 Hz), 165.2 (CO), 167.5 (CO), 169.2 (CO); ESI-MS: *m/z* = 433 (M+H)⁺; Anal. (C₂₅H₂₁FN₂O₄) C, H, N.

5

EXAMPLE A35**A35-a intermediate 36: 2-Fluoro-5-nitrobenzoic acid**

Nitric acid (60% solution, 5.0 mL) was carefully added to a cooled solution of concentrate sulfuric acid (5.0 mL) so that the temperature did not exceed 10 °C. 2-fluorobenzoic acid
 10 (2.1 g, 15.0 mmol) was added by small portions while maintaining temperature between 15 and 25 °C. The mixture was stirred for 2 h at room temperature. Ice was added and the precipitate was filtered. After drying at room temperature, **intermediate 36** was obtained as a white powder. Yield: 93%; mp 135-137 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.32 (t, 1 H, H₃, ³J_{H3-H4} = ³J_{H3-F} = 9.2 Hz), 8.43 (dt, 1 H, H₄, ³J_{H4-H3} = 9.2 Hz, ⁴J_{H4-F} = ⁴J_{H4-H6} =
 15 3.5 Hz), 8.89 (dd, 1H, H₆, ⁴J_{H6-F} = 5.8 Hz, ⁴J_{H6-H4} = 3.0 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 118.7 (d, C₁, ²J_{C-F} = 10.9 Hz), 118.7 (d, C₃, ²J_{C-F} = 25.0 Hz), 128.9 (d, C₆, ³J_{C-F} = 2.2 Hz), 130.6 (d, C₄, ³J_{C-F} = 10.9 Hz), 143.9 (C₅), 165.7 (d, C₂, ¹J_{C-F} = 272.0 Hz), 166.7 (d, COOH, ³J_{C-F} = 3.8 Hz).

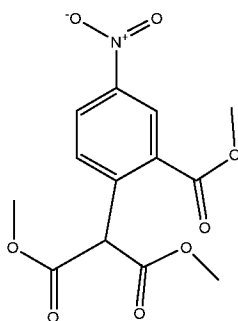
A35-b intermediate 37: Methyl 2-fluoro-5-nitrobenzoate

20

Intermediate 36 (3.7 g, 20.0 mmol) was dissolved at 0 °C in MeOH (100 mL) and thionyl chloride (5.3 mL, 60.0 mmol) was added dropwise. The solution was heated under reflux for 24 h and concentrated *in vacuo*. The residue was dissolved in EtOAc and washed several times with 1.0 M NaOH. After drying over Na₂SO₄, the solvent was evaporated *in*
 25 *vacuo* to yield **intermediate 37** as a yellow oil, which crystallized upon standing as light

yellow needles. Yield: 90%; mp 47-49 °C; ^1H NMR (300 MHz, CDCl_3) δ = 4.01 (s, 3 H, OCH_3), 7.35 (t, 1H, H_3 , $^3J_{\text{H}3-\text{H}4} = ^3J_{\text{H}3-\text{F}} = 9.2$ Hz), 8.44 (dt, 1H, H_4 , $^3J_{\text{H}4-\text{H}3} = 9.2$ Hz, $^4J_{\text{H}4-\text{F}} = ^4J_{\text{H}4-\text{H}6} = 3.5$ Hz), 8.87 (dd, 1H, H_6 , $^4J_{\text{H}6-\text{F}} = 5.9$ Hz, $^4J_{\text{H}6-\text{H}4} = 2.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 47.7 (OCH_3), 113.2 (d, C_3 , $^2J_{\text{C}-\text{F}} = 25.1$ Hz), 114.5 (d, C_1 , $^2J_{\text{C}-\text{F}} = 12.0$ Hz),
 5 122.9 (d, C_6 , $^3J_{\text{C}-\text{F}} = 3.3$ Hz), 124.3 (d, C_4 , $^3J_{\text{C}-\text{F}} = 10.9$ Hz), 138.6 (C_5), 157.4 (d, COOCH_3 , $^3J_{\text{C}-\text{F}} = 3.8$ Hz), 159.8 (d, C_2 , $^1J_{\text{C}-\text{F}} = 269.0$ Hz).

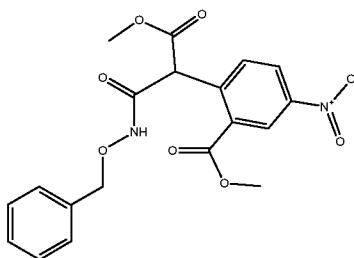
A35-c intermediate 38: Methyl 2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}-5-nitrobenzoate



An argon stream was passed on a suspension of sodium hydride (60% dispersion in
 10 mineral oil, 1.2 g, 25.1 mmol) in petroleum ether to discard mineral oil. Then sodium
 hydride was dispersed in THF (30.0 mL) and a solution of methyl malonate (2.9 mL, 25.1
 mmol) in THF (20.0 mL) was added dropwise under argon inert atmosphere. After 30 min
 stirring at room temperature, a solution of **intermediate 37** (5.0 g, 25.1 mmol) in THF
 (20.0 mL) was added dropwise and the solution was heated under reflux for 12 h. The
 15 solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed several
 times with water. After column chromatography of the residue (eluent: petroleum
 ether/EtOAc, 80/20), the product **intermediate 38** was obtained as a yellow oil, which
 crystallized upon standing as light yellow needles. Yield: 67%; mp 63-65 °C; ^1H NMR
 (300 MHz, CDCl_3) δ = 3.73 (s, 6 H, 2 OCH_3), 3.90 (s, 3 H, OCH_3), 5.81 (s, 1 H, CH), 7.61
 20 (d, 1H, H_3 , $^3J_{\text{H}3-\text{H}4} = 8.6$ Hz), 8.31 (dd, 1H, H_4 , $^3J_{\text{H}4-\text{H}3} = 8.6$ Hz, $^4J_{\text{H}4-\text{H}6} = 2.2$ Hz), 8.80 (dd,
 1H, H_6 , $^4J_{\text{H}6-\text{H}4} = 2.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 52.9 (2 OCH_3), 54.7 (OCH_3),
 59.7 (CH), 125.0 (CH), 126.8 (CH), 131.1 (C_{IV}), 132.5 (CH), 140.3 (C_{IV}), 146.9 (C_{IV} , C_5),
 165.2 (CO), 167.4 (2 CO).

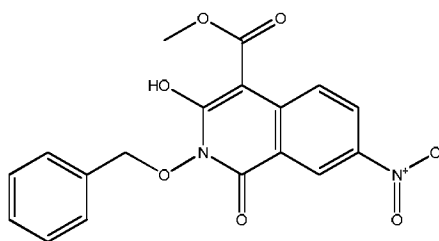
A35-d intermediate 39: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-nitrobenzoate

25



A solution of **intermediate 38** (0.31 g, 1.0 mmol) and *O*-benzylhydroxylamine (0.15 g, 1.2 mmol) in toluene (15.0 mL) was refluxed for 8 h using a Dean Stark apparatus. After cooling, the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc. The organic layer was washed with 2.0 M HCl and dried over Na₂SO₄. After concentration *in vacuo* and column chromatography of the residue (eluent: petroleum ether/EtOAc, 70/30), the product **intermediate 39** was obtained as an orange oil. Yield: 50%; ¹H NMR (300 MHz, CDCl₃) δ = 3.65 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.83 (s, 2 H, OCH₂), 5.22 (s, 1 H, CH), 7.26 (m, 5 H, H_{Ar}), 7.75 (d, 1H, H₃, ³*J*_{H3-H4} = 8.6 Hz), 8.32 (dd, 1H, H₄, ³*J*_{H4-H3} = 8.6 Hz, ⁴*J*_{H4-H6} = 2.2 Hz), 8.75 (dd, 1H, H₆, ⁴*J*_{H6-H4} = 2.2 Hz), 9.62 (s, 1 H, NH); ¹³C NMR (75 MHz, CDCl₃): δ = 52.9 (CH), 53.2 (2 OCH₃), 78.8 (OCH₂), 125.8 (CH), 126.8 (CH), 128.5 (2 CH), 128.7 (CH), 129.3 (2 CH), 130.2 (C_{IV}), 133.7 (CH), 135.0 (C_{IV}), 141.3 (C_{IV}), 147.2 (C_{IV}, C₅), 164.1 (CO), 166.2 (CO), 168.4 (CO); ESI-MS: *m/z* = 403 (M+H)⁺.

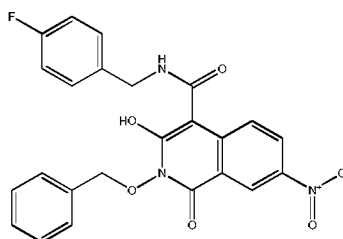
A35-e intermediate 40: Methyl 2-(benzyloxy)-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxylate



Intermediate 39 (0.40 g, 1.0 mmol) was dissolved in a solution of methanol (10.0 mL) and 2.0 M KOH (10.0 mL). After 12 h stirring, the solution was acidified with 2.0 M HCl and extracted three times with dichloromethane (20.0 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was triturated in ether to afford **intermediate 40** as a yellow solid. Yield: 89%; mp 190-196 °C; 100% enol form; ¹H NMR (300 MHz, CDCl₃) δ = 4.17 (s, 3 H, OCH₃), 5.31 (s, 2 H, OCH₂), 7.45 (m, 3 H, H_{Ar}), 7.63 (m, 2 H, H_{Ar}), 8.43 (dd, 1H, H₆, ³*J*_{H6-H5} = 9.4 Hz, ⁴*J*_{H6-H8} = 2.0 Hz), 8.60 (d, 1H, H₅, ³*J*_{H5-H6} = 9.4 Hz), 9.26 (d, 1H, H₈, ⁴*J*_{H8-H4} = 1.9 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 53.7 (OCH₃), 79.4 (OCH₂), 84.5 (C_{IV}), 121.2 (C_{IV}), 124.6 (CH), 125.6 (CH), 127.4 (CH),

128.7 (2 CH), 129.6 (CH), 130.1 (2 CH), 133.0 (C_{IV}), 138.0 (C_{IV}), 144.0 (C_{IV}, C₇), 157.5 (CO), 164.8 (CO), 173.1 (CO); Anal. (C₁₈H₁₄N₂O₇) C, H, N.

A35-f intermediate 41: N-(4-Fluorobenzyl)-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydro-isoquinoline-4-carboxamide



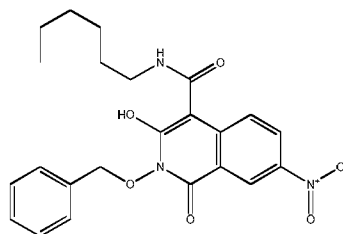
A solution of **intermediate 40** (0.37 g, 1.0 mmol) and 4-fluorobenzylamine (0.62 g, 5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. After cooling, the solution was concentrated *in vacuo*. The residue was dissolved in EtOAc. The organic layer was washed with 2.0 M HCl and dried over Na₂SO₄. During the washings, an amount of **intermediate 41** precipitated and was isolated by filtration. After concentration *in vacuo*, the residue was triturated with ether and the precipitate was filtered and dried at room temperature. Orange solid. Yield: 75%; mp 183-185 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.48 (d, 2 H, NHCH₂, ³J = 5.6 Hz), 5.06 (s, 2 H, OCH₂), 7.15 (t, 2 H, H_{Ar}, ³J_{H-H} = ³J_{H-F} = 8.8 Hz), 7.40 (m, 5 H, H_{Ar}), 7.62 (m, 2 H, H_{Ar}), 8.01 (dd, 1 H, H₆, ³J_{H6-H5} = 9.7 Hz, ⁴J_{H6-H8} = 2.3 Hz), 8.78 (d, 1H, H₈, ⁴J_{H8-H6} = 2.3 Hz), 9.40 (d, 1H, H₅, ³J_{H5-H6} = 9.7 Hz), 10.35 (t, 1H, NH, ³J = 5.6 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 41.2 (NHCH₂), 76.6 (OCH₂), 90.2 (C₄), 114.9 (d, 2 CH, ²J_{C-F} = 20.7 Hz), 115.8 (C_{IV}), 123.6 (CH), 124.1 (CH), 124.6 (CH), 128.2 (2 CH), 128.5 (CH); 129.21 (2 CH), 129.22 (d, 2 CH, ³J_{C-F} = 7.6 Hz), 135.3 (C_{IV}), 137.0 (d, C_{IV}, ⁴J_{C-F} = 3.3 Hz), 137.7 (C_{IV}), 144.5 (C₇), 159.2 (CO), 161.0 (d, C_{IV}, ¹J_{C-F} = 240.0 Hz), 161.5 (CO), 167.8 (CO); ESI-MS: *m/z* = 464 (M+H)⁺; Anal. (C₂₄H₁₈FN₃O₆) C, H, N.

EXAMPLE A36

The process followed in this example is the same as described in example A35

EXAMPLE A37

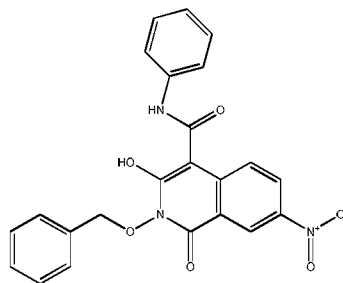
A37-a intermediate 42: N-Hexyl-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



A solution of **intermediate 40** (0.37 g, 1.0 mmol) and hexylamine (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Orange solid. Yield: 97%; mp 155-156 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.88 (m, 3 H, CH₃), 1.31 (m, 6 H, CH₂), 1.49 (m, 2 H, CH₂), 3.24 (t, 2 H, CH₂, $^3J_{\text{H-H}}$ = 6.3 Hz), 5.03 (s, 2 H, OCH₂), 7.40-7.42 (m, 2 H, H_{Ar}), 7.61-7.63 (m, 3 H, H_{Ar}), 7.97 (d, 1 H, H₆, $^3J_{\text{H(6)-H(5)}}$ = 10.3 Hz), 8.74 (s, 1H, H₈), 9.32 (d, 1H, H₅, $^3J_{\text{H(5)-H(6)}}$ = 10.3 Hz); ^{13}C NMR(75 MHz, DMSO- d_6): δ = 14.4 (CH₃), 22.6 (CH₂), 26.9 (CH₂), 29.9 (CH₂), 31.5 (CH₂), 38.9 (CH₂), 77.1 (OCH₂), 90.6 (C₄), 116.4 (C_{IV}), 124.1 (CH_{Ar}), 124.6 (CH_{Ar}), 125.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 128.9 (CH_{Ar}), 129.7 (2 CH_{Ar}), 135.7 (C_{IV}), 138.3 (C_{IV}), 144.6 (C₇), 159.6 (CO), 161.8 (CO), 168.2 (CO); ESI-MS: m/z = 440 (M+H)⁺; Anal. (C₂₃H₂₅N₃O₆) C, H, N.

EXAMPLE A38

A38-a intermediate 43: *N*-Phenyl-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



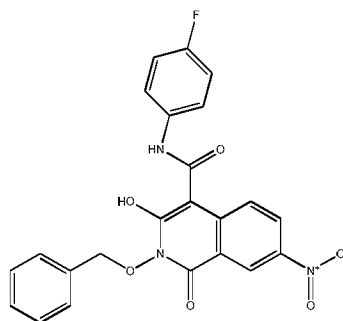
A solution of **intermediate 40** (0.37 g, 1.0 mmol) and aniline (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Yellow solid. Yield: 77%; mp 169-171 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 5.10 (s, 2 H, OCH₂), 6.98 (t, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 7.2 Hz), 7.30 (t, 2 H, H_{Ar}, $^3J_{\text{H-H}}$ = 7.9 Hz), 7.40-7.47 (m, 3 H, H_{Ar}), 7.65-7.69 (m, 4 H, H_{Ar}), 8.08 (dd, 1 H, H₆, $^3J_{\text{H(6)-H(5)}}$ = 9.8 Hz, $^4J_{\text{H(6)-H(8)}}$ = 2.5 Hz), 8.79 (d, 1 H, H₈, $^4J_{\text{H(8)-H(6)}}$ = 2.5 Hz), 9.42 (d, 1 H, H₅, $^3J_{\text{H(5)-H(6)}}$ = 9.8 Hz), 12.41 (s, 1 H, OH);

^{13}C NMR (75MHz, DMSO- d_6): δ = 76.7 (OCH₂), 90.1 (C₄), 116.5 (C_{1'}), 119.3 (2 CH_{Ar}), 121.9 (CH_{Ar}), 123.8 (CH_{Ar}), 123.9 (CH_{Ar}), 124.9 (CH_{Ar}), 128.3 (3 CH_{Ar}), 128.7 (2 CH_{Ar}), 129.3 (2 CH_{Ar}), 135.2 (C_{IV}), 138.4 (C_{IV}), 140.2 (C_{IV}), 144.3 (C₇), 159.0 (CO), 161.8 (CO), 166.0 (CO); ESI-MS: m/z = 432 (M+H)⁺; Anal. (C₂₃H₁₇N₃O₆) C, H, N.

5

EXAMPLE A39

A39-a intermediate 44: *N*-(4-Fluorophenyl)-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

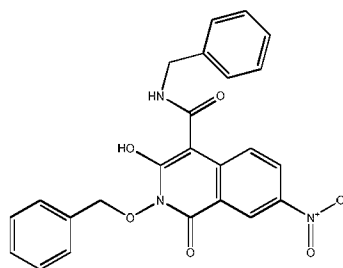


A solution of **intermediate 40** (0.37 g, 1.0 mmol) and aniline (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Beige solid. Yield: 89%; mp 189-190 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 5.11 (s, 2 H, OCH₂), 7.11-7.13 (m, 2 H, H_{Ar}), 7.31-7.43 (m, 5 H, H_{Ar}), 7.65-7.71 (m, 2 H, H_{Ar}), 8.09 (d, 1 H, H₆, $^3J_{\text{H}(6)\text{-H}(5)}$ = 9.8 Hz), 8.80 (s, 1 H, H₈), 9.42 (d, 1 H, H₅, $^3J_{\text{H}(5)\text{-H}(6)}$ = 9.8 Hz); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 77.2 (OCH₂), 90.3 (C₄), 115.6 (d, C_{3'} et C_{5'}, $^2J_{\text{C-F}}$ = 21.3 Hz), 117.0 (C_{IV}), 121.3 (d, C_{2'} and C_{6'}, $^3J_{\text{C-F}}$ = 7.6 Hz), 124.2 (CH_{Ar}), 124.4 (CH_{Ar}), 125.5 (CH_{Ar}), 128.8 (2 CH_{Ar}), 129.0 (CH_{Ar}), 129.8 (2 CH_{Ar}), 135.7 (C_{IV}), 137.1 (C_{IV}), 138.9 (C_{IV}), 144.9 (C₇), 156.2 (CO), 159.6 (CO), 161.0 (d, C_{4'}, $^1J_{\text{C-F}}$ = 252.0 Hz), 166.5 (CO); ESI-MS: m/z = 450 (M+H)⁺; Anal. (C₂₃H₁₆FN₃O₆) C, H, N.

20

EXAMPLE A40

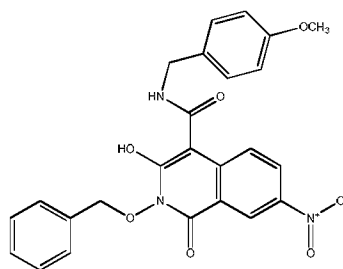
A40-a intermediate 45: *N*-Benzyl-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



A solution of **intermediate 40** (0.37 g, 1.0 mmol) and benzylamine (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Orange solid. Yield: 62%; mp 178-181 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.49 (s, 2 H, CH₂), 5.04 (s, 2 H, OCH₂), 7.31- 7.44 (m, 8 H, H_{Ar}), 7.61 (d, 2 H, H_{Ar}, ³J_{H-H} = 7.3 Hz), 8.00 (dd, 1 H, H₆, ³J_{H(6)-H(5)} = 9.5 Hz, ⁴J_{H(6)-H(8)} = 1.8 Hz), 8.76 (d, 1H, H₈, ⁴J_{H(8)-H(6)} = 1.8 Hz), 9.38 (d, 1 H, H₅, ³J_{H(5)-H(6)} = 9.5 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 42.6 (CH₂), 77.1 (OCH₂), 90.5 (C₄), 116.5 (C_{IV}), 124.2 (CH_{Ar}), 124.5 (CH_{Ar}), 125.2 (CH_{Ar}), 127.1 (CH_{Ar}), 127.8 (3 CH_{Ar}), 128.7 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 129.8 (2 CH_{Ar}), 135.7 (C_{IV}), 138.4 (C_{IV}), 141.0 (C_{IV}), 144.7 (C₇), 159.6 (CO), 162.0 (CO), 168.3 (CO); ESI-MS: *m/z* = 446 (M+H)⁺; Anal. (C₂₄H₁₉N₃O₆) C, H, N.

EXAMPLE A41

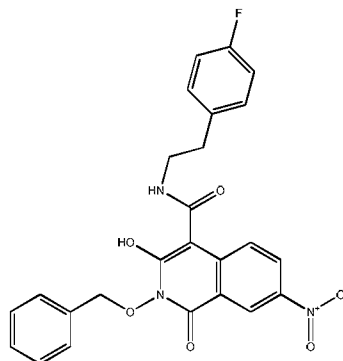
A41-a intermediate 46: *N*-(4-Methoxybenzyl)-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



A solution of **intermediate 40** (0.37 g, 1.0 mmol) and 4-methoxybenzylamine (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Yellow solid. Yield: 74%; mp 180 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.74 (s, 3 H, OCH₃), 4.41 (s, 2 H, CH₂), 5.03 (s, 2 H, OCH₂), 6.90 (d, 2 H, H_{Ar}, ³J_{H-H} = 8.3 Hz), 7.28 (d, 2 H, H_{Ar}, ³J_{H-H} = 8.3 Hz), 7.40-7.42 (m, 3 H, H_{Ar}), 7.59-7.62 (m, 2 H, H_{Ar}), 8.00 (dd, 1 H, H₆, ³J_{H(6)-H(5)} = 9.8 Hz, ⁴J_{H(6)-H(8)} = 2.0 Hz), 8.76 (d, 1 H, H₈, ⁴J_{H(8)-H(6)} = 2.0 Hz), 9.38 (d, 1 H, H₅, ³J_{H(5)-H(6)} = 9.8 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 42.1 (CH₂), 55.5 (OCH₃), 77.1 (OCH₂), 90.5 (C₄), 114.2 (C_{3'} and C_{5'}), 116.6 (C_{IV}), 124.2 (CH_{Ar}), 124.6 (CH_{Ar}), 125.2 (CH_{Ar}), 128.7 (2 CH_{Ar}), 129.0 (CH_{Ar}), 129.2 (C_{2'} and C_{6'}), 129.7 (2 CH_{Ar}), 132.8 (C_{IV}), 135.7 (C_{IV}), 138.4 (C_{IV}), 144.8 (C₇), 158.6 (CO), 159.6 (CO), 161.9 (CO), 168.2 (CO); ESI-MS: *m/z* = 476 (M+H)⁺; Anal. (C₂₅H₂₁N₃O₇) C, H, N.

EXAMPLE A42

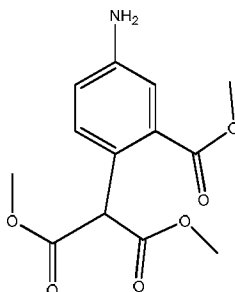
A42-a intermediate 47: *N*-(4-Fluorophenethyl)-2-benzyloxy-3-hydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



A solution of **intermediate 40** (0.37 g, 1.0 mmol) and 4-fluorophenethylamine (5.0 mmol) in toluene (15.0 mL) was refluxed for 12 h using a Dean Stark apparatus. The work-up is identical to the one reported for the synthesis of **intermediate 41** (A35-f). Yellow solid. Yield: 81%; mp 171-173 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.81 (t, 2 H, ³J_{H-H} = 6.8 Hz), 3.48 (t, 2 H, ³J_{H-H} = 6.8 Hz), 5.03 (s, 2 H, OCH₂), 7.13 (t, 2 H, H_{3'} and H_{5'}, ³J_{H-H} = ³J_{H-F} = 8.8 Hz), 7.30-7.34 (m, 2 H, H_{Ar}), 7.39-7.45 (m, 3 H, H_{Ar}), 7.61-7.63 (m, 2 H, H_{Ar}), 7.99 (d, 1 H, H₆, ³J_{H(6)-H(5)} = 9.4 Hz), 8.75 (s, 1 H, H₈), 9.32 (d, 1 H, H₅, ³J_{H(5)-H(6)} = 9.4 Hz), 9.77 (s, 1 H, OH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 35.4 (CH₂), 40.7 (CH₂), 77.1 (OCH₂), 90.7 (C₄), 115.4 (d, C_{3'} and C_{5'}, ²J_{C-F} = 20.7 Hz), 116.3 (C_{IV}), 124.1 (CH_{Ar}), 124.6 (CH_{Ar}), 125.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 129.0 (CH_{Ar}), 129.8 (2 CH_{Ar}), 130.9 (d, C_{2'} and C_{6'}, ³J_{C-F} = 7.6 Hz), 135.7 (C_{IV}), 136.6 (d, C_{1'}, ⁴J_{C-F} = 1.6 Hz), 138.2 (C_{IV}), 144.8 (C₇), 159.6 (CO), 161.2 (d, C_{4'}, ¹J_{C-F} = 242.7 Hz), 161.8 (CO), 168.2 (CO); ESI-MS: *m/z* = 478 (M+H)⁺; Anal. (C₂₅H₂₀FN₃O₆) C, H, N.

EXAMPLE A43

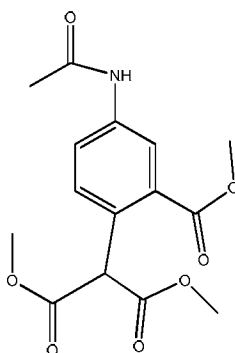
A43-a intermediate 48: Methyl 5-amino-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate



Intermediate 38 (4.0 g, 12.9 mmol) was dissolved in methanol (100 mL) and hydrogenated for 12 h at room temperature over Pd/C 5% (0.4 g). The catalyst was filtered and the solvent was removed *in vacuo*. Pink solid. Yield: 95%; mp 89-90 °C; ¹H NMR

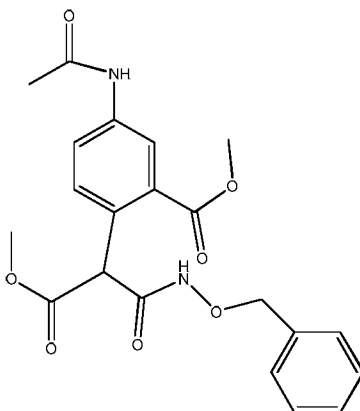
(300 MHz, CDCl₃): δ = 3.79 (s, 6 H, 2 OCH₃), 3.88 (s, 3 H, OCH₃), 5.63 (s, 1 H, CH), 6.84 (d, 1 H, H₃, $^3J_{H(3)-H(4)}$ = 8.3 Hz), 7.21 (dd, 1 H, H₄, $^3J_{H(4)-H(3)}$ = 8.3 Hz and $^4J_{H(4)-H(6)}$ = 2.2 Hz), 7.32 (d, 1 H, H₆, $^4J_{H(6)-H(4)}$ = 2.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 52.2 (2 OCH₃), 52.7 (OCH₃), 54.1 (CH), 116.9 (CH_{Ar}), 118.7 (CH_{Ar}), 123.2 (C_{IV}), 130.1 (C_{IV}), 131.0 (CH_{Ar}), 146.6 (C₅), 167.5 (CO), 169.6 (2 CO).

A43-b intermediate 49: Methyl 5-acetamido-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate



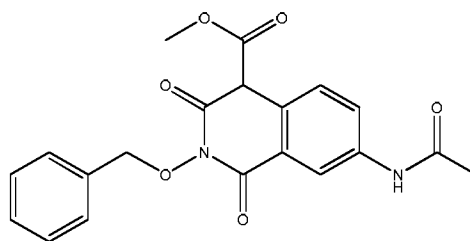
Acetyl chloride (1.1 mL, 16.0 mmol) was added to a solution of **intermediate 48** (3.0 g, 10.7 mmol) in dichloromethane (50 mL). After stirring for 4 h at room temperature, the solution was washed with aqueous 1.0 M HCl. The organic phase was dried over Na₂SO₄. The solvent was removed under reduced pressure to give an oily residue, which was triturated in ether. After filtration, a white powder was obtained (96%); mp 81-83 °; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.06 (s, 3 H, CH₃), 3.68 (s, 6 H, 2 OCH₃), 3.80 (s, 3 H, OCH₃), 5.49 (s, 1 H, CH), 7.26 (d, 1 H, H₃, $^3J_{H(3)-H(4)}$ = 8.5 Hz), 7.80 (dd, 1 H, H₄, $^3J_{H(4)-H(3)}$ = 8.5 Hz and $^4J_{H(4)-H(6)}$ = 1.9 Hz), 8.20 (d, 1 H, H₆, $^4J_{H(6)-H(4)}$ = 1.9 Hz), 10.24 (s, 1H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 23.9 (CH₃), 52.3 (OCH₃), 52.6 (2 OCH₃), 54.3 (CH), 120.6 (CH_{Ar}), 122.6 (CH_{Ar}), 128.0 (C_{IV}), 129.6 (C_{IV}), 130.7 (CH_{Ar}), 139.1 (C₅), 166.6 (CO), 168.4 (2 CO), 168.7 (CO).

A43-c intermediate 50: Methyl 5-acetamido-2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate



The process followed in this step is the same as described in example A35d. White powder (28%); mp 60-62 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.06 (s, 3 H, CH₃), 3.63 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 4.81 (s, 2 H, OCH₂), 5.11 (s, 1 H, CH), 7.36 (s, 6 H, H₃ and H_{Ar}), 7.73 (dd, 1 H, H₄, $^3J_{\text{H}(4)\text{-H}(3)}$ = 8.5 Hz and $^4J_{\text{H}(4)\text{-H}(6)}$ = 1.9 Hz), 8.20 (d, 1H, H₆, $^4J_{\text{H}(6)\text{-H}(4)}$ = 1.9 Hz), 10.20 (s, 1 H, NH), 11.46 (s, 1 H, NH), NMR ^{13}C (75 MHz, DMSO- d_6): δ = 23.9 (CH₃), 52.1 (OCH₃), 52.24 (OCH₃), 52.25 (CH), 76.8 (OCH₂), 120.4 (CH_{Ar}), 122.5 (CH_{Ar}), 128.27 (2 CH_{Ar}), 128.32 (CH_{Ar}), 128.9 (2 CH_{Ar}), 129.0 (C_{IV}), 129.6 (C_{IV}), 129.9 (CH_{Ar}), 135.7 (C_{IV}), 138.7 (C₅), 164.4 (CO), 166.7 (CO), 168.7 (2 CO); ESI-MS: m/z = 415 (M+H)⁺.

A43-d intermediate 51: Methyl 7-acetamido-2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate

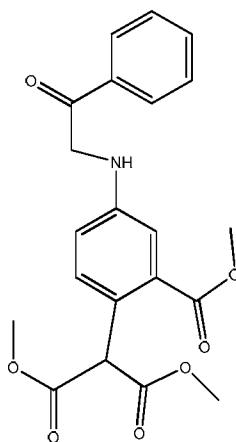


The process followed in this step is the same as described in example A35e. Yellow powder (70%); 100% keto form; mp 197-199 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.09 (s, 3 H, CH₃), 3.71 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 5.37 (s, 1 H, H₄), 7.36 – 7.42 (m, 4 H, H_{Ar}), 7.54-7.57 (m, 2 H, H_{Ar}), 7.89 (d, 1 H, H₃, $^3J_{\text{H}(3)\text{-H}(4)}$ = 8.6 Hz), 8.40 (d, 1 H, H₆, $^4J_{\text{H}(6)\text{-H}(4)}$ = 1.9 Hz), 11.34 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 24.0 (CH₃), 53.5 (OCH₃), 54.0 (C₄), 77.5 (OCH₂), 117.7 (CH_{Ar}), 124.7 (CH_{Ar}), 125.0 (C_{IV}), 126.3 (C_{IV}), 127.9 (CH_{Ar}), 128.4 (2 CH_{Ar}), 129.0 (CH_{Ar}), 129.5 (2 CH_{Ar}), 134.2 (C_{IV}), 139.8 (C₅), 160.4 (CO), 163.0 (CO), 167.3 (CO), 168.8 (CO); ESI-MS: m/z = 383 (M+H)⁺; Anal. (C₂₀H₁₈N₂O₆) C, H, N.

CC(=O)Nc1ccc2c(c1)c(=O)n(COCc3ccccc3)c(=O)c2C(=O)NCc4ccc(F)cc4

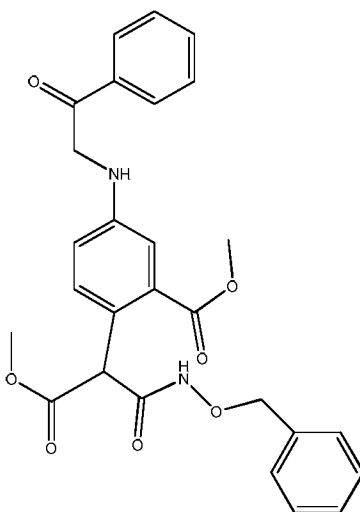
5 (78%); 100% keto form; mp 218-220 °C; ^1H NMR (300 MHz, DMSO- d_6): δ =
2.10 (s, 3 H, CH₃), 4.37 (dd, 1 H, CH₂, $^2J_{\text{H-H}} = 14.6$ Hz and $^3J_{\text{H-H}} = 5.4$ Hz), 4.38 (dd, 1 H,
CH₂, $^2J_{\text{H-H}} = 14.6$ Hz and $^3J_{\text{H-H}} = 5.4$ Hz), 5.02 (s, 2 H, OCH₂), 5.18 (s, 1 H, H₄), 7.23 (t, 2
H, H_{3'} and H_{5'}, $^3J_{\text{H-H}} = 8.9$ Hz and $^3J_{\text{H-F}} = 8.9$ Hz), 7.34 – 7.63 (m, 8 H, H_{Ar}), 7.94 (d, 1 H,
H_{Ar}, $^3J_{\text{H-H}} = 8.0$ Hz), 8.41 (s, 1 H, H_{Ar}), 9.33 (t, 1 H, NH, $^3J_{\text{H-H}} = 5.4$ Hz), 10.36 (s, 1 H, NH);
10 NMR ^{13}C (75 MHz, DMSO- d_6): δ = 24.5 (CH₃), 42.4 (CH₂), 55.7 (C₄), 77.8 (OCH₂), 115.6
(d, C_{3'} and C_{5'}, $^2J_{\text{C-F}} = 21.8$ Hz), 118.1 (CH_{Ar}), 125.0 (CH_{Ar}), 126.1 (C_{IV}), 127.8 (CH_{Ar}),
128.9 (2 CH_{Ar}), 129.2 (C_{IV}), 129.4 (CH_{Ar}), 129.7 (2 CH_{Ar}), 129.8 (d, C_{2'} and C_{6'}, $^3J_{\text{C-F}} = 8.2$
Hz), 131.0 (C_{IV}), 135.0 (C_{IV}), 139.8 (C_{IV}), 161.4 (CO), 161.8 (d, C_{4'}, $^1J_{\text{C-F}} = 240.5$ Hz),
165.0 (CO), 166.7 (CO), 169.0 (CO); ESI-MS: m/z = 476 (M+H)⁺; Anal. (C₂₆H₂₂FN₃O₅) C,
15 H, N.

A44-a intermediate 53: Methyl 2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}-5-
(phenylacetamido)benzoate



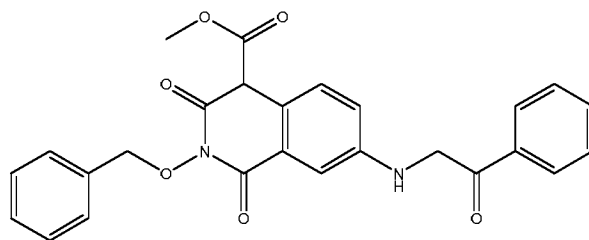
The process followed in this step is the same as described in example A43b using phenylacetyl chloride (instead of acetyl chloride). White powder (76%); mp 126-128 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.36 (s, 6 H, 2 OCH₃), 3.68 (s, 3 H, OCH₃), 3.80 (s, 2 H, OCH₂), 5.51 (s, 1 H, CH), 7.27 (d, 1 H, H₃, ³J_{H(3)-H(4)} = 8.2 Hz), 7.33 (s, 5 H, H_{Ar}), 7.82 (dd, 1 H, H₄, ³J_{H(4)-H(3)} = 8.5 Hz and ⁴J_{H(4)-H(6)} = 1.9 Hz), 8.24 (d, 1H, H₆, ⁴J_{H(6)-H(4)} = 1.9 Hz), 10.49 (s, 1H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 43.7 (CH₂), 52.8 (OCH₃), 53.1 (2 OCH₃), 54.8 (CH), 121.2 (CH_{Ar}), 123.2 (CH_{Ar}), 127.1 (CH_{Ar}), 128.8 (C_{IV}), 128.8 (2 CH_{Ar}), 129.6 (2 CH_{Ar}), 130.2 (C_{IV}), 131.2 (CH_{Ar}), 136.1 (C_{IV}), 139.5 (C₅), 167.1 (CO), 168.9 (2 CO), 170.1 (CO).

10 A44-b intermediate 54: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-(2-phenylacetamido)benzoate



The process followed in this step is the same as described in example A35d. Light yellow powder (25%); mp 65-70 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.63 (s, 3 H, OCH₃), 3.66 (s, 2 H, CH₂), 3.79 (s, 3 H, OCH₃), 4.81 (s, 2 H, OCH₂), 5.13 (s, 1H, CH), 7.33-7.39 (m, 11 H, H₃ and H_{Ar}), 7.76 (dd, 1 H, H₄, ³J_{H(4)-H(3)} = 8.6 Hz and ⁴J_{H(4)-H(6)} = 2.3 Hz), 8.23 (d, 1 H, H₆, ⁴J_{H(6)-H(4)} = 2.3 Hz), 10.46 (s, 1 H, NH), 11.47 (s, 1 H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 43.7 (CH₂), 52.71 (CH), 52.73 (2 OCH₃), 77.3 (OCH₂), 121.0 (CH_{Ar}), 123.1 (CH_{Ar}), 127.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 128.8 (3 CH_{Ar}), 129.4 (2 CH_{Ar}), 129.6 (2 CH_{Ar}), 129.8 (C_{IV}), 130.1 (C_{IV}), 130.5 (CH_{Ar}), 136.1 (C_{IV}), 136.2 (C_{IV}), 139.1 (C₅), 164.9 (CO), 167.1 (CO), 169.4 (CO), 170.0 (CO); ESI-MS: *m/z* = 491 (M+H)⁺.

20 A44-c intermediate 55: Methyl 2-(benzyloxy)- 7-phenylacetamido -1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate

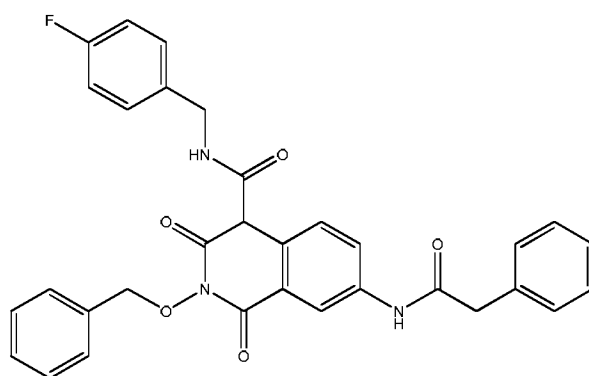


The process followed in this step is the same as described in example A35e. White powder (80%); 100% keto form; mp 187-196 °C; ^1H NMR (300 MHz, DMSO- d_6): δ =

3.70 (s, 3 H, OCH₃), 3.99 (s, 2 H, CH₂), 5.05 (s, 2 H, OCH₂), 5.38 (s, 1 H, H₄), 7.26-7.35 (m, 8 H, H_{Ar}), 7.54-7.56 (m, 3 H, H_{Ar}), 7.92 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}} = 8.2$ Hz), 8.42 (s, 1 H, H_{Ar}), 10.61 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 43.8 (CH₂), 54.0 (OCH₃), 54.5 (C₄), 77.9 (OCH₂), 118.4 (CH_{Ar}), 125.3 (CH_{Ar}), 125.6 (C_{IV}), 127.1 (CH_{Ar}), 128.5 (CH_{Ar}), 128.8 (2 CH_{Ar}), 128.9 (2 CH_{Ar}), 129.6 (3 CH_{Ar}), 130.0 (2 CH_{Ar}), 134.7 (C_{IV}), 136.1 (C_{IV}), 136.3 (C_{IV}), 140.1 (C₅), 160.8 (CO), 163.5 (CO), 167.7 (CO), 170.1 (CO);

ESI-MS: m/z = 459 (M+H)⁺.

A44-d intermediate 56: N-(4-fluorobenzyl)-2-(benzyloxy)-1,3-dioxo-7-phenylacetamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



The process followed in this step is the same as described in example A35f. White powder

(80%); 100% keto form; mp 225-229 °C; ^1H NMR (300 MHz, DMSO- d_6): δ =

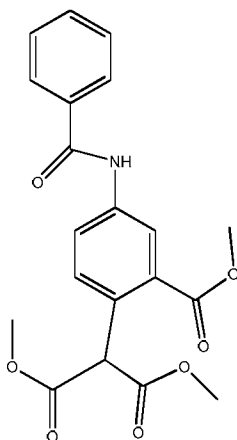
3.69 (s, 2 H, CH₂), 4.31 (dd, 1 H, CH₂, $^2J_{\text{H-H}} = 14.6$ Hz and $^3J_{\text{H-H}} = 5.7$ Hz), 4.32 (dd, 1 H, CH₂, $^2J_{\text{H-H}} = 14.6$ Hz and $^3J_{\text{H-H}} = 5.7$ Hz), 5.00 (s, 2 H, CH₂), 5.13 (s, 1 H, H₄), 7.17 (t, 2 H, H_{4'} and H_{6'}, $^3J_{\text{H-F}} = ^3J_{\text{H-H}} = 8.6$ Hz), 7.26 – 7.37 (m, 8 H, H_{Ar}), 7.41 – 7.43 (m, 3 H, H_{Ar}), 7.55 -7.58 (m, 2 H, H_{Ar}), 7.92 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}} = 8.3$ Hz), 8.36 (s, 1H, H₈), 9.27 (t, 1 H, NH, $^3J_{\text{H-H}} = 5.7$ Hz), 10.55 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 42.4 (CH₂), 43.7 (CH₂), 55.7 (C₄), 77.8 (OCH₂), 115.6 (d, C_{3'} and C_{5'}, $^2J_{\text{C-F}} = 21.3$ Hz), 118.2 (CH_{Ar}), 125.1 (CH_{Ar}), 126.1 (C_{IV}), 127.1 (CH_{Ar}), 127.8 (CH_{Ar}), 128.8 (2 CH_{Ar}), 128.9 (2 CH_{Ar}),

129.3 (CH_{Ar}), 129.5 (C_{IV}), 129.6 (2 CH_{Ar}), 129.7 (d, C_{2''} and C_{6''}, ³J_{C-F} = 7.6 Hz), 129.9 (2 CH_{Ar}), 134.9 (C_{IV}), 135.2 (d, C_{1''}, ⁴J_{C-F} = 2.7 Hz), 136.1 (C_{IV}), 139.6 (C_{IV}), 161.3 (CO), 161.8 (d, C_{4''}, ¹J_{C-F} = 241.1 Hz), 164.9 (CO), 166.6 (CO), 170.0 (CO); ESI-MS: *m/z* = 552 (M+H)⁺; Anal. (C₃₂H₂₆FN₃O₅) C, H, N.

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EXAMPLE A45

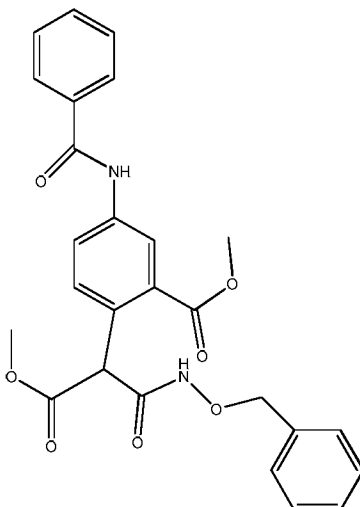
A45-a intermediate 57: Methyl 5-benzamido-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate



The process followed in this step is the same as described in example A43b using benzoyl chloride (instead of acetyl chloride). White powder (67%); mp 135-137 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.71 (s, 6 H, 2 OCH₃), 3.87 (s, 3 H, OCH₃), 5.60 (s, 1 H, CH), 7.35–7.37 (m, 1 H, H_{Ar}), 7.58–7.61 (m, 3 H, H_{Ar}), 8.02–8.06 (m, 3 H, H_{Ar}), 8.49 (s, 1 H, H_{Ar}), 10.59 (s, 1 H, NH), NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 52.3 (OCH₃), 52.6 (2 OCH₃), 54.4 (CH), 122.0 (CH_{Ar}), 123.9 (CH_{Ar}), 127.7 (2 CH_{Ar}), 128.4 (2 CH_{Ar}), 128.7 (C_{IV}), 129.6 (C_{IV}), 130.7 (CH_{Ar}), 131.9 (CH_{Ar}), 134.4 (C_{IV}), 139.1 (C₅), 165.8 (CO), 166.7 (CO), 168.5 (2 CO).

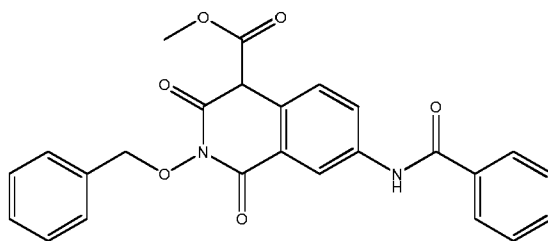
15

A45-b intermediate 58: Methyl 5-benzamido-2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate



The process followed in this step is the same as described in example A35d. Light yellow powder (23%); mp 85-94 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 3.66 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.84 (s, 2 H, OCH_2), 5.17 (s, 1 H, CH), 7.38 (m, 6 H, H_{Ar}), 7.56 (m, 3 H, H_{Ar}), 7.99 (m, 3 H, H_{Ar}), 8.43 (s, 1 H, H_{Ar}), 10.52 (s, 1 H, NH), 11.50 (s, 1 H, NH);
 NMR ^{13}C (75 MHz, $\text{DMSO}-d_6$): δ = 52.77 (2 OCH_3), 52.78 (CH), 77.3 (OCH_2), 122.3 (CH_{Ar}), 124.4 (CH_{Ar}), 128.2 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 128.9 (3 CH_{Ar}), 129.5 (2 CH_{Ar}), 130.0 (C_{IV}), 130.2 (C_{IV}), 130.4 (CH_{Ar}), 132.3 (CH_{Ar}), 134.9 (C_{IV}), 136.2 (C_{IV}), 139.2 (C_5), 164.9 (CO), 166.2 (CO), 167.2 (CO), 169.4 (CO); ESI-MS: m/z = 491 ($\text{M}+\text{H}$) $^+$.

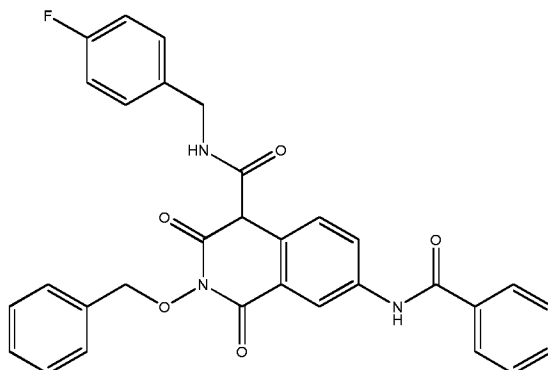
10 A45-c intermediate 59: Methyl 7-benzamido-2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



The process followed in this step is the same as described in example A35e. Orange powder (83%); 100% keto form; mp 185-187 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ =
 15 3.86 (s, 3 H, OCH_3), 5.07 (s, 2 H, OCH_2), 5.42 (s, 1 H, H_4), 7.29-7.42 (m, 3 H, H_{Ar}), 7.57-7.75 (m, 5 H, H_{Ar}), 7.91-8.02 (m, 3 H, H_{Ar}), 8.42 (d, 1 H, H_{Ar} , $^3J_{\text{H-H}}$ = 8.0 Hz), 8.62 (d, 1 H, H_{Ar} , $^4J_{\text{H-H}}$ = 2.5 Hz), 10.41 (s, 1 H, NH); NMR ^{13}C (75 MHz, $\text{DMSO}-d_6$): δ =
 54.0 (OCH_3), 54.5 (C_4), 78.0 (OCH_2), 119.6 (CH_{Ar}), 125.5 (C_{IV}), 126.5 (CH_{Ar}), 127.5 (C_{IV}), 128.2 (2 CH_{Ar}), 128.4 (CH_{Ar}), 128.9 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 129.4 (CH_{Ar}), 130.0

(2 CH_{Ar}), 132.4 (CH), 134.7 (C_{IV}), 134.8 (C_{IV}), 140.2 (C₇), 160.9 (CO), 163.5 (CO), 166.3 (CO), 167.8 (CO); ESI-MS: $m/z = 445$ (M+H)⁺.

A45-d intermediate 60: N-(4-fluorobenzyl)-7-benzamido-2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



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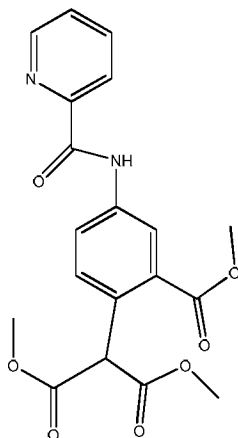
The process followed in this step is the same as described in example A35f. Beige powder (54%); 100% keto form; mp 242-244 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.33 (s, 2 H, CH₂), 5.03 (s, 2 H, OCH₂), 5.18 (s, 1 H, H₄), 7.20 (t, 2 H, H_{3''} and H_{5''}, ³J_{H-H} = ³J_{H-F} = 8.7 Hz), 7.31-7.58 (m, 11 H, H_{Ar}), 8.01-8.04 (m, 2 H, H_{Ar}), 8.14 (s, 1 H, H_{Ar}), 8.57 (s, 1 H, H_{Ar}), 9.30 (s, 1 H, NH), 10.62 (s, 1 H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.5 (CH₂), 55.7 (C₄), 77.8 (OCH₂), 115.6 (d, C_{3''} and C_{5''}, ²J_{C-F} = 21.3 Hz), 119.5 (CH_{Ar}), 126.1 (C_{IV}), 126.3 (CH_{Ar}), 127.6 (CH_{Ar}), 128.2 (2 CH_{Ar}), 128.9 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 129.3 (CH_{Ar}), 129.7 (d, C_{2''} and C_{6''}, ³J_{C-F} = 8.2 Hz), 129.9 (2 CH_{Ar}), 132.4 (CH_{Ar}), 134.8 (C_{IV}), 134.9 (C_{IV}), 135.1 (C_{IV}), 135.2 (d, C_{1''}, ⁴J_{C-F} = 2.7 Hz), 139.7 (C₇), 161.4 (CO), 161.8 (d, C_{4''}, ¹J_{C-F} = 241.0 Hz), 165.0 (CO), 166.2 (CO), 166.7 (CO); ESI-MS: $m/z = 538$ (M+H)⁺; Anal. (C₃₁H₂₄FN₃O₅) C, H, N.

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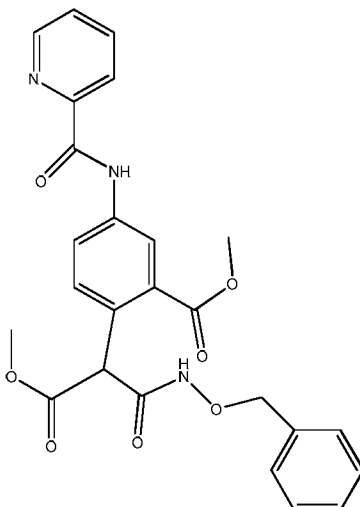
EXAMPLE A46

A46-a intermediate 61: Methyl 2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}-5-picolinamidobenzoate



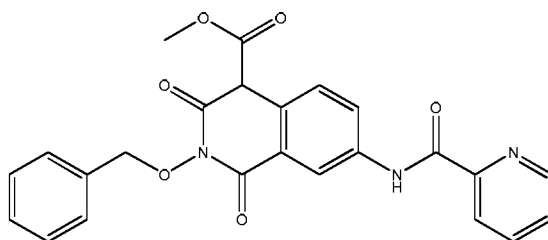
Thionyl chloride (1.1 mL, 15.7 mmol) was added dropwise to a cooled solution of 2-picolinic acid (1.05 g, 8.5 mmol) in a mixture of ethyl acetate (25 mL) and N,N-dimethylformamide (5 mL). After 1 h reflux, the volatiles were removed *in vacuo* and the crude acid chloride was dissolved in a mixture of ethyl acetate (25 mL) and N,N-dimethylformamide (5 mL). Diisopropylethylamine (3.5 mL, 21.4 mmol) and **intermediate 48** (2.0 g, 7.1 mmol) were added. After 12 h stirring at room temperature, the solution was washed several times with 1.0 M NaHCO₃ and 1.0 M HCl. The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. Organic residues were triturated with ether and insoluble materials were filtered. Pink solid (81%); mp 153-155 °C; ¹H NMR (300 MHz, CDCl₃): δ = 3.81 (s, 6 H, 2 OCH₃), 3.94 (s, 3 H, OCH₃), 5.77 (s, 1 H, CH), 7.47 (d, 1 H, H₃, ³J_{H(3)-H(4)}} = 8.5 Hz), 7.55 (ddd, 1 H, H_{Ar}, ³J_{H-H} = 7.7 Hz, ³J_{H-H} = 4.8 Hz and ⁴J_{H-H} = 1.2 Hz), 7.97 (td, 1 H, H_{Ar}, ³J_{H-H} = 7.7 Hz and ⁴J_{H-H} = 1.6 Hz), 8.06 (dd, 1 H, H₄, ³J_{H(4)-H(3)}} = 8.5 Hz and ⁴J_{H(4)-H(6)}} = 2.4 Hz), 8.34 (d, 1 H, H₂, ³J_{H(2')-H(3')}} = 7.7 Hz), 8.45 (d, 1 H, H₆, ⁴J_{H(6)-H(4)}} = 2.4 Hz), 8.66 (d, 1 H, H₅, ³J_{H(5')-H(4')}} = 4.7 Hz), 10.22 (s, 1 H, NH); NMR ¹³C (75 MHz, CDCl₃): δ = 52.9 (OCH₃), 53.2 (2 OCH₃), 54.9 (CH), 122.7 (CH_{Ar}), 123.1 (CH_{Ar}), 124.7 (CH_{Ar}), 127.6 (CH_{Ar}), 129.5 (C_{IV}), 130.2 (C_{IV}), 131.1 (CH_{Ar}), 138.7 (CH_{Ar}), 138.8 (C₅), 148.9 (CH_{Ar}), 150.0 (C_{1'}), 163.4 (CO), 167.2 (CO), 168.9 (2 CO); ESI-MS: *m/z* = 387 (M+H)⁺.

A46-b intermediate 62: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-picolinamidobenzoate



The process followed in this step is the same as described in example A35d. White powder (20%); mp 207-208 °C; ^1H NMR (300 MHz, CDCl_3): δ = 3.75 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.90 (s, 2 H, OCH_2), 5.27 (s, 1 H, CH), 7.33 (s, 5 H, H_{Ar}), 7.60 (dd, 1 H, H_{Ar} , $^3\text{J}_{\text{H-H}} = 6.1$ Hz and $^3\text{J}_{\text{H-H}} = 6.7$ Hz), 7.71 (d, 1 H, H_{Ar} , $^3\text{J}_{\text{H-H}} = 7.9$ Hz), 7.94-8.04 (m, 2 H, H_{Ar}), 8.38 (d, 1 H, H_{Ar} , $^3\text{J}_{\text{H-H}} = 7.9$ Hz), 8.55 (s, 1 H, H_{Ar}), 8.67 (d, 1 H, H_{Ar} , $^4\text{J}_{\text{H-H}} = 4.4$ Hz), 9.65 (s, 1 H, NH), 10.33 (s, 1 H, NH); ^{13}C (75 MHz, CDCl_3): δ = 52.7 (CH), 52.8 (2 OCH_3), 77.3 (OCH_2), 122.4 (CH_{Ar}), 123.0 (CH_{Ar}), 124.7 (CH_{Ar}), 127.6 (CH_{Ar}), 128.78 (2 CH_{Ar}), 128.84 (CH_{Ar}), 129.5 (2 CH_{Ar}), 130.1 (C_{IV}), 130.3 (CH_{Ar}), 130.5 (C_{IV}), 136.2 (C_{IV}), 138.4 (C_5), 138.7 (CH_{Ar}), 149.0 (CH_{Ar}), 150.1 (C_{I}), 163.4 (CO), 164.9 (CO), 167.2 (CO), 169.4 (CO); ESI-MS: m/z = 478 ($\text{M}+\text{H}$) $^+$.

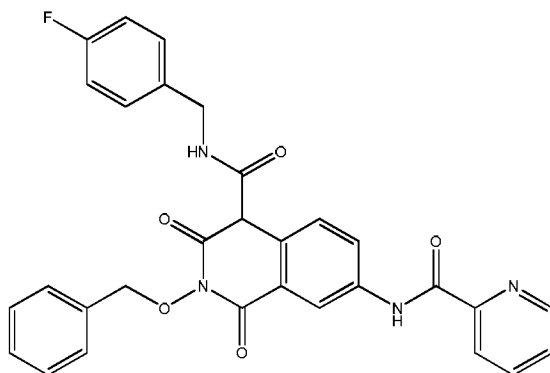
A46-c intermediate 63: Methyl 2-(benzyloxy)-1,3-dioxo-7-picolinamido-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



The process followed in this step is the same as described in example A35e. Beige powder (51%); 100% keto form; mp 177-180 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 4.13 (s, 3 H, OCH_3), 5.30 (s, 2 H, OCH_2), 5.31 (s, 1H, H_4), 7.42-7.43 (m, 4 H, H_{Ar}), 7.56 – 7.65 (m, 3 H, H_{Ar}), 7.98 (t, 1 H, H_{Ar} , $^3\text{J} = 7.6$ Hz), 8.36 (d, 1 H, H_{Ar} , $^3\text{J}_{\text{H-H}} = 7.7$ Hz), 8.41 – 8.49 (m, 2 H, H_{Ar}), 8.68 (s, 1 H, H_{Ar}), 10.32 (s, 1H, NH); ^{13}C (75 MHz, $\text{DMSO}-d_6$): δ = 54.1 (OCH_3), 54.5 (C_4), 78.0 (OCH_2), 119.9 (CH_{Ar}), 123.1 (CH_{Ar}), 125.5 (C_{IV}), 126.9

(CH_{Ar}), 127.7 (CH_{Ar}), 127.8 (C_{IV}), 128.3 (CH_{Ar}), 130.0 (2 CH_{Ar}), 129.4 (CH_{Ar}), 130.1 (2 CH_{Ar}), 134.7 (C_{IV}), 138.7 (CH_{Ar}), 139.5 (C_{IV}), 149.0 (CH_{Ar}), 150.0 (C_{I'}), 160.8 (CO), 163.5 (CO), 163.6 (CO), 167.7 (CO); ESI-MS: m/z = 446 (M+H)⁺; Anal. (C₂₄H₁₉N₃O₆) C, H, N.

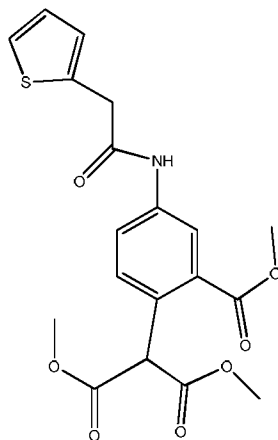
5 A46-d intermediate 64: N-(4-fluorobenzyl)-2-(benzyloxy)-1,3-dioxo-7-picolinamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



The process followed in this step is the same as described in example A35f. Beige powder (64%); 100% keto form; mp 240-243 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.33 (dd, 1 H, CH₂, ²J_{H-H} = 19.7 Hz and ³J_{H-H} = 5.7 Hz), 4.34 (dd, 1 H, CH₂, ²J_{H-H} = 19.7 Hz and ³J_{H-H} = 5.7 Hz), 5.02 (d, 1 H, OCH₂, ²J_{H-H} = 15.0 Hz), 5.03 (d, 1 H, OCH₂, ²J_{H-H} = 15.0 Hz), 5.17 (s, 1 H, H₄), 7.18 (t, 2 H, H₃ and H₅, ³J_{H-H} = ³J_{H-F} = 8.9 Hz), 7.31 (dd, 2 H, H_{Ar}, ³J_{H-H} = 8.3 Hz and ⁴J_{H-F} = 5.5 Hz), 7.40-7.44 (m, 4 H, H_{Ar}), 7.57-7.59 (m, 2 H, H_{Ar}), 7.72 (dd, 1 H, H_{Ar}, ³J_{H-H} = 7.1 Hz and ³J_{H-H} = 5.1 Hz), 8.10 (t, 1 H, H_{Ar}, ³J_{H-H} = 7.7 Hz), 8.16 – 8.21 (m, 2 H, H_{Ar}), 8.77-8.79 (m, 2 H, H_{Ar}), 9.30 (t, 1 H, NH, ³J_{H-H} = 5.7 Hz), 11.06 (s, 1 H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.5 (CH₂), 55.7 (C₄), 77.8 (OCH₂), 115.6 (d, C₃ and C₅, ²J_{C-F} = 21.3 Hz), 119.8 (CH_{Ar}), 123.1 (CH_{Ar}), 126.1 (C_{IV}), 126.7 (CH_{Ar}), 127.6 (CH_{Ar}), 127.7 (CH_{Ar}), 128.9 (2 CH_{Ar}), 129.3 (CH_{Ar}), 129.7 (d, C₂ and C₆, ³J_{C-F} = 8.2 Hz), 129.9 (2 CH_{Ar}), 130.2 (C_{IV}), 134.9 (C_{IV}), 135.2 (d, C₁, ⁴J_{C-F} = 2.7 Hz), 138.7 (CH_{Ar}), 138.9 (C_{IV}), 149.0 (CH_{Ar}), 150.0 (C_{I'}), 161.3 (CO), 161.8 (d, C₄, ¹J_{C-F} = 241.0 Hz), 163.5 (CO), 164.9 (CO), 166.7 (CO); ESI-MS: m/z = 539 (M+H)⁺; Anal. (C₃₀H₂₃FN₄O₅) C, H, N.

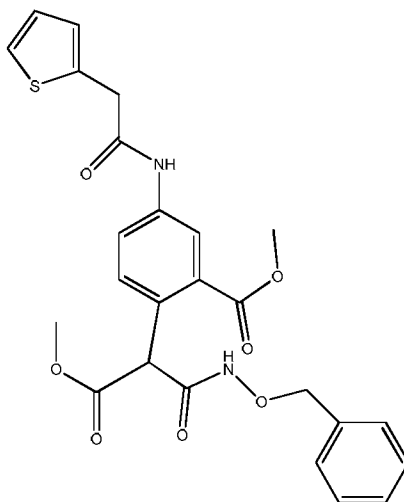
EXAMPLE A47

A47a intermediate 65: Methyl 2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}-5-(2-(thiophen-2-yl)acetamido)benzoate



The process followed in this step is the same as described in example A46a using 2-thienylacetic acid instead of picolinic acid. White powder (33%); mp 135-137 °C; ¹H NMR (300 MHz, CDCl₃): δ = 3.78 (s, 6 H, 2 OCH₃), 3.87 (s, 3 H, OCH₃), 3.95 (s, 2 H, CH₂), 5.68 (s, 1 H, CH), 7.05-7.08 (m, 2 H, H_{thiophen}), 7.32-7.34 (m, 2 H, H_{thiophen} and H₃), 7.70 (dd, 1 H, H₄, ³J_{H(4)-H(3)} = 8.5 Hz and ⁴J_{H(4)-H(6)} = 1.9 Hz), 8.02 (d, 1 H, H₆, ⁴J_{H(6)-H(4)} = 1.9 Hz), 9.82 (s, 1 H, NH); NMR ¹³C (75 MHz, CDCl₃): δ = 38.2 (CH₂), 52.5 (OCH₃), 53.0 (2 OCH₃), 54.5 (CH), 122.2 (CH_{Ar}), 123.8 (CH_{Ar}), 125.7 (CH_{Ar}), 127.4 (CH_{Ar}), 127.5 (CH_{Ar}), 129.7 (C_{IV}), 129.8 (C_{IV}), 130.7 (CH_{Ar}), 135.5 (C_{IV}), 137.8 (C₅), 167.0 (CO), 168.5 (CO);, 169.3 (2 CO); ESI-MS: m/z = 406 (M+H)⁺.

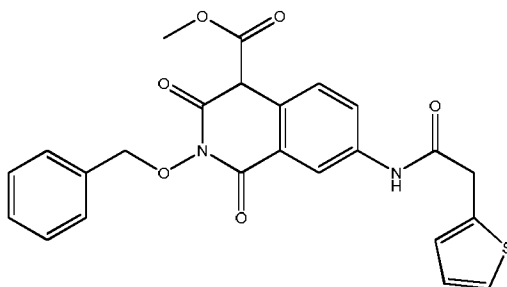
A47-b intermediate 66: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-(2-(thiophen-2-yl)acetamido)benzoate



The process followed in this step is the same as described in example A35d. Yellow powder (27%); mp 67-70 °C; ¹H NMR (300 MHz, CDCl₃): δ = 3.68 (s, 3 H, OCH₃), 3.78 (s, 3 H, OCH₃), 3.93 (s, 2 H, CH₂), 4.88 (s, 2 H, OCH₂), 5.12 (s, 1 H, CH), 7.02-7.03 (m, 2

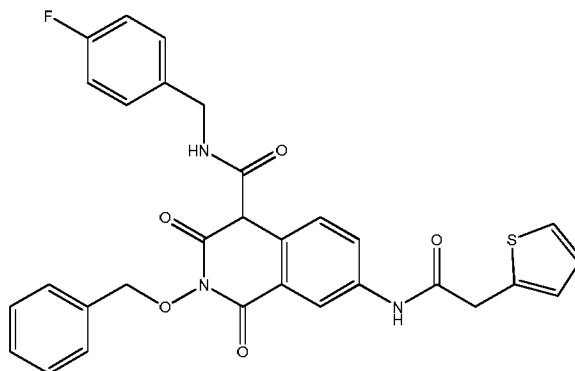
H, H_{Ar}), 7.31 (m, 5 H, H_{Ar}), 7.41-7.43 (m, 2 H, H_{Ar}), 7.93 (s, 1 H, H_{Ar}), 8.13 (s, 1 H, H_{Ar}), 9.82 (s, 1 H, NH), 10.25 (s, 1 H, NH); ¹³C NMR (75 MHz, CDCl₃): δ = 38.3 (CH₂), 52.6 (CH), 52.7 (OCH₃), 52.9 (OCH₃), 78.1 (OCH₂), 122.0 (CH_{Ar}), 123.8 (CH_{Ar}), 125.9 (CH_{Ar}), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 129.2 (C_{IV}), 129.3 (3 CH_{Ar}), 130.1 (C_{IV}), 132.5 (CH_{Ar}), 135.0 (C_{IV}), 135.5 (C_{IV}), 137.6 (C_{IV}), 165.5 (CO), 167.8 (CO), 168.3 (CO), 169.5 (CO); ESI-MS: m/z = 497 (M+H)⁺.

A47-c intermediate 67: Methyl 2-(benzyloxy)-1,3-dioxo-7-(2-(thiophen-2-yl)acetamido)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



The process followed in this step is the same as described in example A35e. White powder (92%); 100% keto form; mp 179-181 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.71 (s, 3 H, OCH₃), 3.93 (s, 2 H, CH₂), 5.05 (s, 2 H, OCH₂), 5.39 (s, 1 H, H₄), 6.99 – 7.01 (m, 2 H, H_{Ar}), 7.41 (m, 5 H, H_{Ar}), 7.55-7.56 (m, 2 H, H_{Ar}), 7.92 (d, 1 H, H_{Ar}, ³J = 7.7 Hz), 8.42 (s, 1 H, H_{Ar}), 10.63 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 38.0 (CH₂), 54.0 (OCH₃), 54.5 (C₄), 78.0 (OCH₂), 118.4 (CH_{Ar}), 125.4 (CH_{Ar}), 125.6 (C_{IV}), 125.7 (CH_{Ar}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (C_{IV}), 128.6 (CH_{Ar}), 128.9 (2 CH_{Ar}), 129.4 (CH_{Ar}), 130.0 (2 CH_{Ar}), 134.7 (C_{IV}), 137.1 (C_{IV}), 140.0 (C_{IV}), 160.8 (CO), 163.4 (CO), 167.7 (CO), 169.1 (CO); ESI-MS: m/z = 465 (M+H)⁺; Anal. (C₂₄H₂₀N₂O₆S) C, H, N.

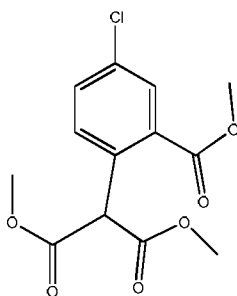
A47-d intermediate 68: N-(4-fluorobenzyl)- 2-(benzyloxy)-1,3-dioxo-7-(2-(thiophen-2-yl)acetamido)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



The process followed in this step is the same as described in example A35f. Beige powder (64%); 100% keto form; mp 240-243 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.92 (s, 2 H, CH₂), 4.31 (dd, 1 H, CH₂, $^2J_{\text{H-H}}$ = 19.5 Hz and $^3J_{\text{H-H}}$ = 5.8 Hz), 4.32 (dd, 1 H, CH₂, $^2J_{\text{H-H}}$ = 19.5 Hz and $^3J_{\text{H-H}}$ = 5.8 Hz), 5.00 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 15.0 Hz), 5.01 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 15.0 Hz), 5.13 (s, 1 H, H₄), 6.98 – 7.01 (m, 2 H, H_{Ar}), 7.18 (t, 2 H, H_{3''} and H_{5''}, $^3J_{\text{H-H}}$ = $^3J_{\text{H-F}}$ = 8.9 Hz), 7.30 (dd, 2 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.2 Hz and $^3J_{\text{H-F}}$ = 5.9 Hz), 7.36-7.43 (m, 5 H, H_{Ar}), 7.56-7.59 (m, 2 H, H_{Ar}), 7.90 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.3 Hz), 8.36 (s, 1 H, H_{Ar}), 9.28 (t, 1 H, NH, $^3J_{\text{H-H}}$ = 5.8 Hz), 10.59 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 38.0 (CH₂), 42.5 (CH₂), 55.7 (C₄), 77.8 (OCH₂), 115.6 (d, C_{3''} and C_{5''}, $^2J_{\text{C-F}}$ = 21.3 Hz), 118.3 (CH_{Ar}), 125.2 (CH_{Ar}), 125.7 (CH_{Ar}), 126.2 (C_{IV}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 127.8 (CH_{Ar}), 128.9 (2 CH_{Ar}), 129.3 (CH_{Ar}), 129.6 (C_{IV}), 129.7 (d, C_{2''} and C_{6''}, $^3J_{\text{C-F}}$ = 8.2 Hz), 129.9 (2 CH_{Ar}), 134.9 (C_{IV}), 135.2 (d, C_{1'}, $^4J_{\text{C-F}}$ = 3.3 Hz), 137.2 (C_{IV}), 139.5 (C_{IV}), 161.3 (CO), 161.8 (d, C_{4''}, $^1J_{\text{C-F}}$ = 241.1 Hz), 165.0 (CO), 166.7 (CO), 169.0 (CO); ESI-MS: m/z = 558 (M+H)⁺; Anal. (C₃₀H₂₄FN₃O₅S) C, H, N.

EXAMPLE A48

A48a intermediate 69: Methyl 5-chloro-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate

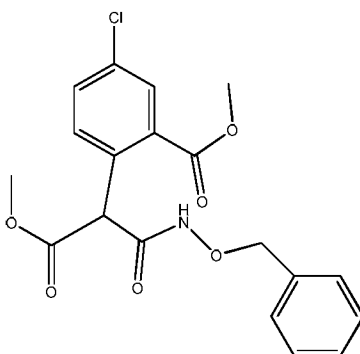


A solution of **intermediate 48** (1.0 g, 3.6 mmol) in concentrate hydrochloric acid (8.0 mL) was cooled at 0 -5 °C. A solution of sodium nitrite (0.25 g, 3.6 mmol) in water (3.0 mL) was added dropwise while maintaining temperature below 5 °C. After 10 min stirring, a pink solution of the diazonium salt was obtained. A cold solution of CuCl (0.5 g, 5.1 mmol) in concentrate HCl acid solution was added dropwise to the diazonium mixture while maintaining temperature below 5 °C. After temperature rising and 12 h stirring, water (10.0 mL) was added and the solution was extracted several times with ethyl acetate. Organic layers were dried over Na₂SO₄ and, after removal of the volatiles *in vacuo*, the crude residue was purified by column chromatography using petroleum ether / ethyl acetate (70/30, % v/v) as eluent. Yellow oil (48%); ^1H NMR (300 MHz, CDCl₃): δ = 3.80

(s, 6 H, 2 OCH₃), 3.92 (s, 3 H, OCH₃), 5.76 (s, 1 H, CH), 7.40 (d, 1 H, H₃, ³J_{H(3)-H(4)} = 8.3 Hz), 7.54 (dd, 1 H, H₄, ³J_{H(4)-H(3)} = 8.3 Hz, ⁴J_{H(4)-H(6)} = 1.7 Hz), 8.03 (d, 1 H, H₆, ⁴J_{H(6)-H(4)} = 1.7 Hz); NMR ¹³C (75 MHz, Acetone-*d*₆): δ = 53.0 (OCH₃), 53.2 (2 OCH₃), 54.7 (CH), 130.5 (CH), 131.9 (C_{IV}), 132.8 (2 CH), 133.2 (C_{IV}), 133.5 (C_{IV}), 166.1 (CO), 168.5 (2 CO);

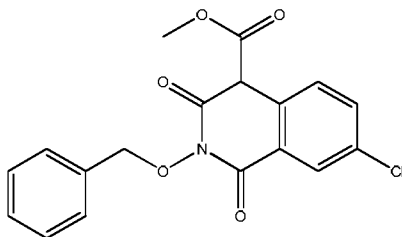
5 MALDI-TOF: m/z = 301 and 303 (M+H)⁺

A48-b intermediate 70: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-chlorobenzoate



The process followed in this step is the same as described in example A35d. White powder
 10 (35%); mp 112-113 °C; ¹H NMR (300 MHz, Acetone-*d*₆): δ = 3.56 (s, 3 H, OCH₃), 3.71 (s, 3 H, OCH₃), 4.76 (s, 2 H, OCH₂), 5.26 (s, 1 H, CH), 7.22 (m, 5 H, H_{Ar}), 7.53 (m, 2 H, H₄ and H₃), 7.78 (s, 1 H, H₆), 10.40 (s, 1 H, NH); NMR ¹³C (75 MHz, Acetone-*d*₆): δ = 52.0 (OCH₃), 52.1 (OCH₃), 52.2 (CH), 77.4 (OCH₂), 128.3 (2 CH_{Ar}), 128.4 (CH_{Ar}), 129.2 (2 CH_{Ar}), 130.0 (CH_{Ar}), 131.5 (C_{IV}), 132.0 (CH_{Ar}), 132.3 (CH_{Ar}), 133.2 (C_{IV}), 134.0 (C_{IV}),
 15 135.9 (C_{IV}), 164.5 (CO), 166.0 (CO), 168.5 (CO); MALDI-TOF: m/z = 392 and 394 (M+H)⁺.

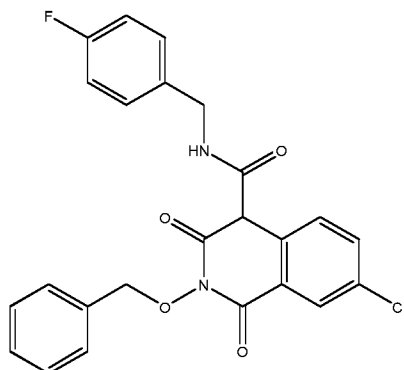
A48-c intermediate 71: Methyl 2-(benzyloxy)-7-chloro-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



20 The process followed in this step is the same as described in example A35e. White powder (69%); 100% keto form; mp 161-163 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.72 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 5.48 (s, 1 H, H₄), 7.42 (m, 4 H, H_{Ar}), 7.58 (m, 2 H, H_{Ar}), 8.08 (s, 1 H, H_{Ar}), 8.43 (d, 1 H, H_{Ar}, ³J_{H-H} = 8.8 Hz); NMR ¹³C (75 MHz, DMSO-

d_6): δ = 53.0 (OCH₃), 54.2 (C₄), 78.0 (OCH₂), 126.6 (CH_{Ar}), 127.2 (C_{IV}), 128.9 (3 CH_{Ar}), 129.5 (CH_{Ar}), 130.1 (2 CH_{Ar}), 131.8 (C_{IV}), 133.6 (CH_{Ar}), 134.7 (C_{IV}), 134.7 (C_{IV}), 161.3 (CO), 163.0 (CO), 167.3 (CO); MALDI-TOF: m/z = 360 and 362 (M+H)⁺; Anal. (C₁₈H₁₄ClNO₅) C, H, N.

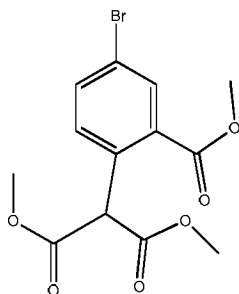
5 A48-d intermediate 72: N-(4-fluorobenzyl)- 2-(benzyloxy)-7-chloro-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



The process followed in this step is the same as described in example A35f. White powder (81%); 100% keto form; mp 216-218 °C; ¹H NMR (300 MHz, DMSO- d_6): δ = 4.31 (dd, 1 H, CH₂, ²J_{H-H} = 15.4 Hz and ³J_{H-H} = 5.0 Hz), 4.32 (dd, 1 H, CH₂, ²J_{H-H} = 15.4 Hz and ³J_{H-H} = 5.0 Hz), 5.01 (d, 1 H, OCH₂, ²J_{H-H} = 14.9 Hz), 5.02 (d, 1 H, OCH₂, ²J_{H-H} = 14.9 Hz), 5.20 (s, 1 H, H₄), 7.18 (t, 2 H, H_{3'} and H_{5'}, ³J_{H-H} = ³J_{H-F} = 8.3 Hz), 7.30 (t, 2 H, H_{Ar}, ³J_{H-H} = 7.6 Hz and ³J_{H-F} = 4.5 Hz), 7.42-7.47 (m, 4 H, H_{Ar}), 7.56-7.57 (m, 2 H, H_{Ar}), 7.84 (d, 1 H, H_{Ar}, ³J_{H-H} = 8.2 Hz), 8.05 (s, 1 H, H_{Ar}), 9.33 (t, 1 H, NH, ³J_{H-H} = 5.0 Hz); NMR ¹³C (75 MHz, DMSO- d_6): δ = 42.0 (CH₂), 55.3 (C₄), 77.4 (OCH₂), 115.2 (d, C_{3'} and C_{5'}, ²J_{C-F} = 21.3 Hz), 127.1 (C_{IV}), 127.2 (CH_{Ar}), 128.4 (2 CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 129.2 (d, C_{2'} and C_{6'}, ³J_{C-F} = 8.2 Hz), 129.4 (2 CH_{Ar}), 133.1 (C_{IV}), 133.5 (C_{IV}), 134.0 (CH_{Ar}), 134.3 (C_{IV}), 134.5 (d, C_{1'}, ⁴J_{C-F} = 2.7 Hz), 160.0 (CO), 161.3 (d, C_{4'}, ¹J_{C-F} = 241.6 Hz), 164.1 (CO), 165.7 (CO); MALDI-TOF: m/z = 453 and 455 (M+H)⁺; Anal. (C₂₄H₁₈ClFN₂O₄) C, H, N.

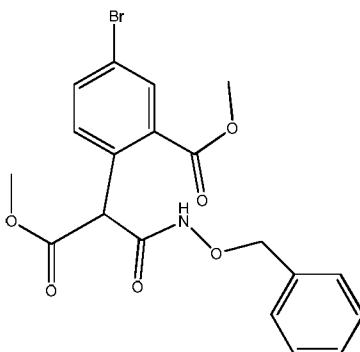
20 **EXAMPLE A49**

A49a intermediate 73: Methyl 5-bromo-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate



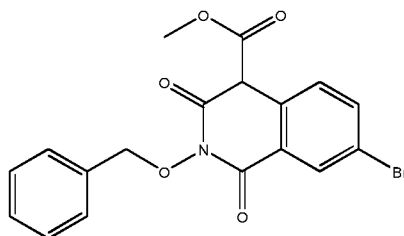
The process followed in this step is the same as described in example A48a, using hydrobromic acid instead of hydrochloric acid. White solid (61%); ^1H NMR (300 MHz, CDCl_3): δ = 3.80 (s, 6 H, 2 OCH_3), 3.92 (s, 3 H, OCH_3), 5.74 (s, 1 H, CH), 7.34 (d, 1 H, H_3 , $^3J_{\text{H}(3)-\text{H}(4)}$ = 8.3 Hz), 7.69 (dd, 1 H, H_4 , $^3J_{\text{H}(4)-\text{H}(3)}$ = 8.3 Hz, $^4J_{\text{H}(4)-\text{H}(6)}$ = 1.5 Hz), 8.18 (d, 1 H, H_6 , $^4J_{\text{H}(6)-\text{H}(4)}$ = 1.5 Hz); NMR ^{13}C (75 MHz, CDCl_3): δ = 52.7 (OCH_3), 53.0 (2 OCH_3), 54.2 (CH), 122.2 (C_5), 131.0 (C_{IV}), 131.9 (CH_{Ar}), 133.3 (C_{IV}), 133.9 (CH_{Ar}), 135.5 (CH_{Ar}), 166.1 (CO), 168.5 (2 CO); MALDI-TOF: m/z = 345 and 347 ($\text{M}+\text{H}$) $^+$.

A49-b intermediate 74: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-bromobenzoate



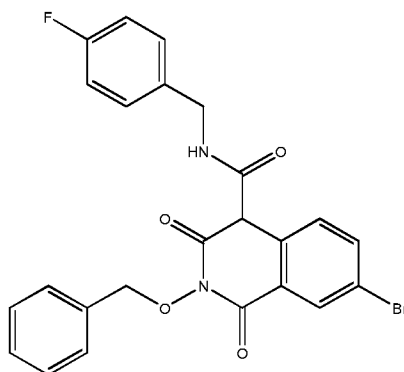
The process followed in this step is the same as described in example A35d. White powder (35%); mp 99-101 $^{\circ}\text{C}$; ^1H NMR (300 MHz, CDCl_3): δ = 3.64 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.81 (s, 2 H, OCH_2), 5.12 (s, 1 H, CH), 7.24 (m, 5 H, H_{Ar}), 7.45 (d, 1 H, H_{Ar} , $^3J_{\text{H-H}}$ = 8.6 Hz), 7.62 (d, 1 H, H_{Ar} , $^3J_{\text{H-H}}$ = 8.6 Hz), 8.02 (m, 1 H, H_6), 9.55 (s, 1 H, NH); NMR ^{13}C (75 MHz, CDCl_3): δ = 52.3 (CH), 52.8 (OCH_3), 53.0 (OCH_3), 78.0 (OCH_2), 122.1 (C_{IV}), 128.5 (2 CH_{Ar}), 128.7 (CH_{Ar}), 129.3 (3 CH_{Ar}), 130.39 (C_{IV}), 130.40 (C_{IV}), 133.6 (CH_{Ar}), 135.0 (C_{IV}), 135.6 (CH_{Ar}), 164.8 (CO), 167.0 (CO), 168.9 (CO); MALDI-TOF: m/z = 436 and 438 ($\text{M}+\text{H}$) $^+$.

A49-c intermediate 75: Methyl 2-(benzyloxy)-7-bromo-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



The process followed in this step is the same as described in example A35e. White powder (77%); 100% keto form; mp 160-162 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.71 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 5.46 (s, 1 H, H₄), 7.42-7.59 (m, 5 H, H_{Ar}), 7.76 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.2 Hz), 7.94 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.2 Hz), 8.20 (s, 1H, H₈); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 53.1 (OCH₃), 54.5 (C₄), 78.1 (OCH₂), 122.2 (C₇), 123.7 (C_{IV}), 126.6 (CH_{Ar}), 128.9 (3 CH_{Ar}), 129.5 (CH_{Ar}), 129.6 (CH_{Ar}), 130.0 (CH_{Ar}), 133.4 (C_{IV}), 134.6 (C_{IV}), 136.3 (CH_{Ar}), 161.4 (CO), 163.0 (CO), 167.2 (CO); MALDI-TOF: m/z = 404 and 406 (M+H)⁺; Anal. (C₁₈H₁₄BrNO₅) C, H, N.

10 A49-d intermediate 76: N-(4-fluorobenzyl)-2-(benzyloxy)-7-bromo-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

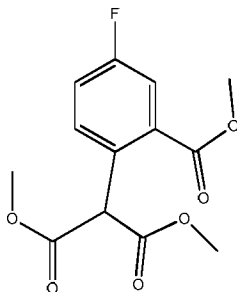


The process followed in this step is the same as described in example A35f. White powder (77%); 100% keto form; mp 171-177 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 4.33 (dd, 1 H, CH₂, $^2J_{\text{H-H}}$ = 15.4 Hz and $^3J_{\text{H-H}}$ = 5.4 Hz), 4.34 (dd, 1 H, CH₂, $^2J_{\text{H-H}}$ = 15.4 Hz and $^3J_{\text{H-H}}$ = 5.4 Hz), 5.02 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 9.1 Hz), 5.03 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 9.1 Hz), 5.20 (s, 1 H, H₄), 7.18 (t, 2 H, H_{3'} and H_{5'}, $^3J_{\text{H-H}}$ = $^3J_{\text{H-F}}$ = 8.6 Hz), 7.31 (dd, 2 H, H_{2'} and H_{6'}, $^3J_{\text{H-H}}$ = 8.0 Hz and $^4J_{\text{H-F}}$ = 5.7 Hz), 7.39 – 7.43 (m, 4 H, H_{Ar}), 7.56 – 7.58 (m, 2 H, H_{Ar}), 7.95 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.0 Hz), 8.18 (s, 1 H, H_{Ar}), 9.34 (t, 1 H, NH, $^3J_{\text{H-H}}$ = 5.4 Hz); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 42.5 (CH₂), 55.8 (C₄), 77.9 (OCH₂), 115.7 (d, C_{3'} and C_{5'}, $^2J_{\text{C-F}}$ = 20.7 Hz), 121.8 (C₇), 127.8 (C_{IV}), 128.9 (2 CH_{Ar}), 129.4 (CH_{Ar}), 129.5 (CH_{Ar}), 129.7 (d, C_{2'} and C_{6'}, $^3J_{\text{C-F}}$ = 8.2 Hz), 129.9 (2 CH_{Ar}), 130.6 (CH_{Ar}), 134.4 (C_{IV}), 134.8 (C_{IV}), 135.0

(d, C₁, ⁴J_{C-F} = 3.3 Hz), 137.3 (CH_{Ar}), 160.2 (CO), 161.8 (d, C₄, ¹J_{C-F} = 241.1 Hz), 164.5 (CO), 166.1 (CO); MALDI-TOF: m/z = 497 and 499 (M+H)⁺; Anal. (C₂₄H₁₈BrFN₂O₄) C, H, N.

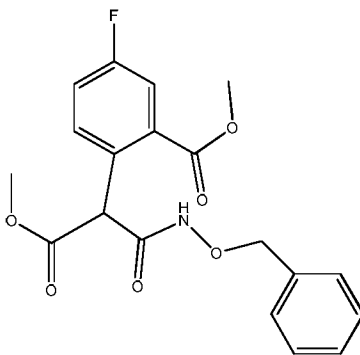
EXAMPLE A50

5 A50a intermediate 77: Methyl 5-fluoro-2-{1,3-dimethoxy-1,3-dioxopropan-2-yl}benzoate



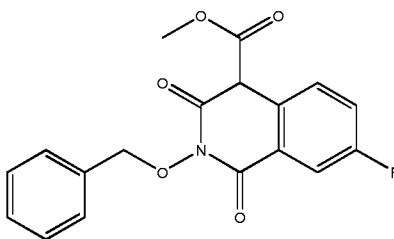
A solution of **intermediate 48** (1.00 g, 3.6 mmol) in aqueous 6.0 M HCl (5.0 mL) was cooled at 0 -5 °C. A solution of sodium nitrite (0.37 g, 5.4 mmol) in water (3.0 mL) was added dropwise while maintaining temperature below 5 °C. After 10 min stirring, a pink
 10 solution of the diazonium salt was obtained. Tetrafluoroboric acid (1.1 mL, 10.8 mmol) was added dropwise and the solution was stirred for 1 h at 5 °C. The formed precipitate was filtered and dried for 2 h at 50 °C in an oven. The residual powder was then heated at 80 °C for several minutes until end of gas evolution. The residue was dissolved in ethyl acetate and extracted several times with 1.0 M NaHCO₃. The organic layer was dried over
 15 Na₂SO₄ and, after removal of the volatiles *in vacuo*, the crude residue was purified by column chromatography using petroleum ether / ethyl acetate (70/30, % v/v) as eluent. Yellow oil (42%); ¹H NMR (300 MHz, Acetone-*d*₆): δ = 3.61 (s, 6 H, 2 OCH₃), 3.75 (s, 3 H, OCH₃), 5.54 (s, 1 H, CH), 7.30 (td, 1 H, H₄, ³J_{H(4)-H(3)}} = ³J_{H(4)-F} = 8.3 Hz and ⁴J_{H(4)-H(6)}} = 2.5 Hz), 7.36 (dd, 1 H, H₃, ³J_{H(3)-H(4)}} = 8.3 Hz, ⁴J_{H(3)-F} = 5.6 Hz), 7.58 (dd, 1 H, H₆, ³J_{H(6)-F} =
 20 9.7 Hz and ⁴J_{H(6)-H(4)}} = 2.5 Hz); NMR ¹³C (75 MHz, Acetone-*d*₆): δ = 53.0 (OCH₃), 53.1 (2 OCH₃), 55.0 (CH), 118.2 (d, CH_{Ar}, ²J_{C-F} = 24.0 Hz), 120.2 (CH_{Ar}, ²J_{C-F} = 21.3 Hz), 131.5 (C_{IV}), 132.8 (C_{IV}), 133.4 (C₃, ³J_{C-F} = 8.2 Hz), 162.6 (C₅, ¹J_{C-F} = 246.0 Hz), 166.9 (CO), 169.3 (2 CO).

25 A50-b intermediate 78: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-fluorobenzoate



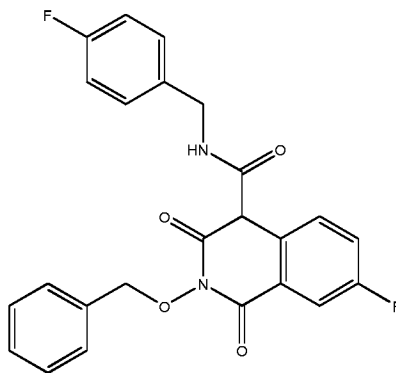
The process followed in this step is the same as described in example A35d. White powder (30%); mp 118-119 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.65 (s, 3 H, OCH₃), 3.81 (s, 3 H, OCH₃), 4.81 (s, 2 H, OCH₂), 5.15 (s, 1 H, CH), 7.36 (m, 5 H, H_{Ar}), 7.49-7.52 (m, 2 H, H_{Ar}), 7.64-7.67 (m, 1 H, H_{Ar}), 11.51 (s, 1 H, NH); NMR ^{13}C (75MHz, DMSO- d_6): δ = 52.2 (CH), 52.9 (OCH₃), 53.1 (OCH₃), 77.3 (OCH₂), 117.3 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 23.5 Hz), 119.8 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 20.7 Hz), 128.8 (2 CH_{Ar}), 128.9 (CH_{Ar}), 129.5 (2 CH_{Ar}), 131.4 (d, C₂, $^4J_{\text{C-F}}$ = 3.3 Hz), 131.9 (d, C₁, $^3J_{\text{C-F}}$ = 7.1 Hz), 132.3 (d, C₃, $^3J_{\text{C-F}}$ = 8.2 Hz), 136.1 (C_{IV}), 161.4 (d, C₅, $^1J_{\text{C-F}}$ = 244.4 Hz), 164.6 (CO), 166.3 (d, CO, $^4J_{\text{C-F}}$ = 2.7 Hz), 169.1 (CO); MALDI-TOF: m/z = 376 (M+H)⁺.

A50-c intermediate 79: Methyl 2-(benzyloxy)-7-fluoro-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



The process followed in this step is the same as described in example A35e. Yellow powder (77%); 100% keto form; mp 140-142 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.72 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 5.18 (s, 1 H, H₄), 7.42-7.43 (m, 3 H, H_{Ar}), 7.55-7.67 (m, 4 H, H_{Ar}), 7.86 (d, 1 H, H_{Ar}, 3J = 8.5 Hz); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 54.1 (CH₃), 54.3 (C₄), 78.0 (OCH₂), 114.9 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 24.0 Hz), 122.3 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 22.4 Hz), 127.5 (C_{IV}), 128.9 (2 CH_{Ar}), 129.2 (C_{IV}), 129.5 (CH_{Ar}), 130.0 (2 CH_{Ar}), 130.7 (d, C₅, $^3J_{\text{C-F}}$ = 8.2 Hz), 134.6 (C_{IV}), 160.1 (CO), 162.3 (d, C₇, $^1J_{\text{C-F}}$ = 245.7 Hz), 163.2 (CO), 167.5 (CO); MALDI-TOF: m/z = 344 (M+H)⁺; Anal. (C₁₈H₁₄FNO₅) C, H, N.

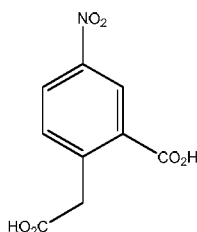
A50-d intermediate 80: N-(4-fluorobenzyl)- 2-(benzyloxy)-7-fluoro-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



The process followed in this step is the same as described in example A35f. White powder (75%); 100% keto form; mp 215-217 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 4.32 (d, 1 H, CH₂, $^2J_{\text{H-H}}$ = 15.6 Hz and $^3J_{\text{H-H}}$ = 5.3 Hz), 4.33 (d, 1 H, CH₂, $^2J_{\text{H-H}}$ = 15.6 Hz and $^3J_{\text{H-H}}$ = 5.3 Hz), 5.02 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 9.5 Hz), 5.03 (d, 1 H, OCH₂, $^2J_{\text{H-H}}$ = 9.5 Hz), 5.20 (s, 1 H, H₄), 7.18 (t, 2 H, H_{3'} and H_{5'}, $^3J_{\text{H-H}}$ = $^3J_{\text{H-F}}$ = 8.5 Hz), 7.30 (dd, 2 H, H_{2'} and H_{6'}, $^3J_{\text{H-H}}$ = 8.2 Hz and $^4J_{\text{H-F}}$ = 5.7 Hz), 7.42 – 7.52 (m, 4 H, H_{Ar}), 7.56 – 7.58 (m, 2 H, H_{Ar}), 7.64 (t, 1 H, H₆, $^3J_{\text{H-H}}$ = $^3J_{\text{H-F}}$ = 8.5 Hz), 7.84 (d, 1 H, H_{Ar}, $^3J_{\text{H-H}}$ = 8.5 Hz), 9.33 (t, 1 H, NH, $^3J_{\text{H-H}}$ = 5.3 Hz); NMR ^{13}C (75MHz, DMSO- d_6): δ = 42.0 (CH₂), 55.1 (C₄), 77.4 (OCH₂), 114.1 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 24.0 Hz), 115.2 (d, C_{3'} and C_{5'}, $^2J_{\text{C-F}}$ = 21.3 Hz), 121.6 (d, CH_{Ar}, $^2J_{\text{C-F}}$ = 22.9 Hz), 127.3 (d, C_{8a}, $^3J_{\text{C-F}}$ = 7.6 Hz), 128.4 (2 CH_{Ar}), 128.9 (CH_{Ar}), 129.2 (d, C₅, $^3J_{\text{C-F}}$ = 8.2 Hz), 129.3 (d, C_{2'} and C_{6'}, $^3J_{\text{C-F}}$ = 8.2 Hz), 129.4 (2 CH_{Ar}), 130.9 (d, C_{4a}, $^4J_{\text{C-F}}$ = 2.7 Hz), 134.3 (C_{IV}), 134.6 (d, C_{1'}, $^4J_{\text{C-F}}$ = 2.7 Hz), 160.1 (d, C₁, $^4J_{\text{C-F}}$ = 2.7 Hz), 161.3 (d, C₇, $^1J_{\text{C-F}}$ = 241.1 Hz), 161.5 (C_{4'}, $^1J_{\text{C-F}}$ = 244.9 Hz), 164.2 (CO), 165.9 (CO); MALDI-TOF: m/z = 437 (M+H)⁺; Anal. (C₂₄H₁₈F₂N₂O₄) C, H, N.

EXAMPLE A51

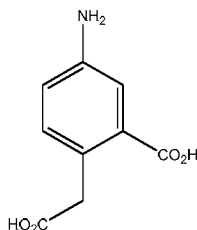
A51a intermediate 81: 2-Carboxymethyl-5-nitrobenzoic acid



Fuming nitric acid (20.0 mL) was cooled to 0 °C and 6.25 g of homophthalic acid (35.0 mmol) was carefully added while maintaining temperature below 22 °C. After 2 h, ice (20 g) was added. The precipitate was filtered and washed several times with distilled water. After drying at room temperature, the nitrated compound was obtained as a white powder (90%); mp 235 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 4.06 (s, 2 H, CH₂), 7.66 (d, 1 H,

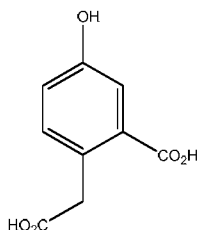
H_3 , $^3J_{H-H} = 8.5$ Hz), 8.34 (dd, 1 H, H_4 , $^3J_{H-H} = 8.5$ Hz, $^4J_{H-H} = 2.4$ Hz), 8.61 (d, 1H, H_6 , $^4J_{H-H} = 2.4$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 39.3$ (CH_2), 123.6 (CH), 125.5 (CH), 128.6 (CH), 131.0 (C_1), 139.6 (C_2), 150.2 (C_5), 164.3 (CO), 174.0 (CO).

A51b intermediate 82: 5-Amino-2-carboxymethylbenzoic acid



Intermediate 81 (2.25 g, 10.0 mmol) was solubilized in methanol (10.0 mL) and hydrogenated on 0.2 g Pd/C 5% under normal pressure. Water (50.0 mL) was added and the mixture was refluxed for 5 min. After filtration of the hot solution, **intermediate 82** slightly crystallized at room temperature as orange needles, which were washed with cold water and dried at room temperature (80%); mp 218 °C; 1H NMR (300 MHz, DMSO- d_6): $\delta = 3.70$ (s, 2 H, CH_2), 6.66 (dd, 1 H, H_4 , $^3J_{H-H} = 8.2$ Hz, $^4J_{H-H} = 2.4$ Hz), 6.92 (d, 1 H, H_3 , $^3J_{H-H} = 8.2$ Hz), 7.15 (d, 1 H, H_6 , $^4J_{H-H} = 2.4$ Hz); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 39.5$ (CH_2), 115.1 (CH), 117.2 (CH), 123.5 (C_2), 128.5 (CH), 131.0 (C_1), 148.4 (C_5), 161.3 (CO), 173.8 (CO).

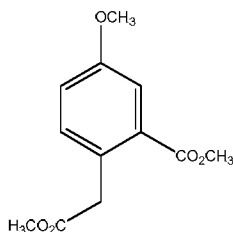
A51c intermediate 83: 2-Carboxymethyl-5-hydroxybenzoic acid



Intermediate 82 (1.00 g, 5.1 mmol) was dissolved at 5 °C in an aqueous sulfuric acid solution (3.0 mL of concentrate acid in 4.5 mL of water). A solution of sodium nitrite (0.53 g, 5.1 mmol) in water (3.0 mL) was slowly added while maintaining temperature below 5 °C to obtain a pink solution of the diazonium salt. This diazonium mixture was added dropwise to a boiling aqueous sulfuric solution (1.0 mL concentrate acid in 1.5 mL water) and the solution was kept in an ice bath for 2 h. The precipitate was filtered, washed with distilled water and dried at room temperature. Beige solid (47%); mp 212 °C; 1H NMR (300 MHz, DMSO- d_6): $\delta = 3.78$ (s, 2 H, CH_2), 6.87 (dd, 1 H, H_4 , $^3J_{H-H} = 8.2$ Hz, $^4J_{H-H} = 2.4$ Hz), 7.09 (d, 1 H, H_3 , $^3J_{H-H} = 8.2$ Hz), 7.30 (d, 1 H, H_6 , $^4J_{H-H} = 2.4$ Hz), 9.60 (s, 1 H, OH);

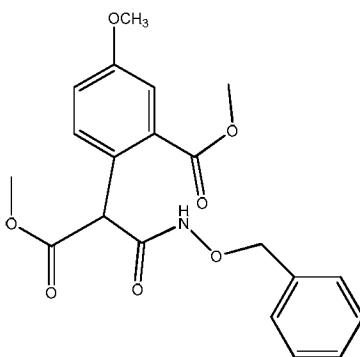
^{13}C NMR (75 MHz, DMSO- d_6): δ = 39.3 (CH₂), 115.7 (CH), 126.2 (C₂), 129.1 (CH), 131.6 (C₁), 154.3 (CO), 156.7 (C₅), 172.0 (CO).

A51d intermediate 84: Methyl 5-methoxy-2-(2-methoxy-2-oxoethyl)benzoate



- 5 Thionyl chloride (1.5 mL, 20.4 mmol) was added dropwise to a cooled solution of **intermediate 83** (1.00 g, 5.1 mmol). After 24 h reflux, the solvent was removed *in vacuo*. The crude residue was dissolved in dry acetone (50.0 mL) and potassium carbonate (4.20 g, 30.6 mmol) and methyl iodide (1.9 mL, 30.6 mmol) were added. After 12 h reflux, volatiles were removed *in vacuo*. The residue was taken up in ethyl acetate, washed several
- 10 times with 1.0 M NaOH and brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give an orange solid (43%); mp 212 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.48 (s, 3 H, OCH₃), 3.69 (s, 3 H, OCH₃), 3.72 (s, 3 H, OCH₃), 3.81 (s, 2 H, CH₂), 6.98 (dd, 1 H, H₄, $^3J_{\text{H-H}}$ = 8.4 Hz, $^4J_{\text{H-H}}$ = 2.7 Hz), 7.15 (d, 1 H, H₃, $^3J_{\text{H-H}}$ = 8.4 Hz), 7.36 (d, 1 H, H₆, $^4J_{\text{H-H}}$ = 2.7 Hz); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 39.6 (CH₂), 51.8
- 15 (OCH₃), 52.0 (OCH₃), 55.4 (OCH₃), 115.8 (CH), 118.3 (CH), 128.0 (C_{IV}), 130.4 (C_{IV}), 133.3 (CH), 158.6 (C₅), 167.2 (CO), 172.3 (CO).

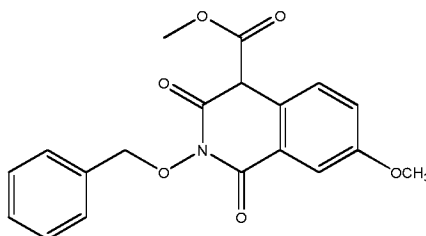
A51e intermediate 85: Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}-5-methoxybenzoate



- 20 A solution of freshly distilled diisopropylamine (0.77 mL, 5.5 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to -78 °C and 3.4 mL of 1.6 M *n*-butyllithium (5.5 mmol) was added. After 30 min reaction at -78 °C, a solution of intermediate **84** (1.00 g, 4.2 mmol) in 5.0 mL of dry THF was added dropwise. After stirring the solution for 40

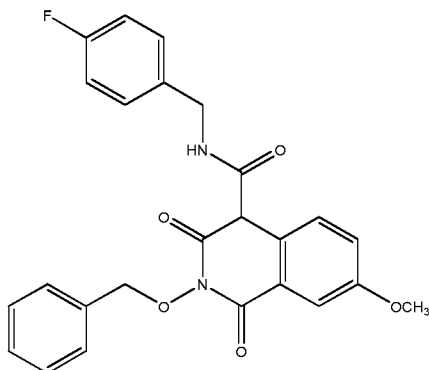
min at -78 °C, temperature was risen to 0 °C and the argon inlet was removed. Solid CO₂ was added portionwise for 1 h. After acidification with 3.0 M HCl, the solution was extracted with ethyl acetate. BOP (2.00 g, 4.6 mmol) and diisopropylethylamine (3.5 mL, 21.0 mmol) were added at -20 °C to the precedent organic solution. After 20 min stirring at
 5 -20 °C, a solution of *O*-benzylhydroxylamine (0.87 g, 5.5 mmol) in ethyl acetate (5.0 mL) was added. After stirring for 1 h at -20 °C and 12 h at room temperature, the mixture was washed with 2.0 M HCl, 1.0 M NaHCO₃ solutions and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. After column chromatography of the residue (eluent: petroleum ether/AcOEt, 70/30), **intermediate 85** was obtained as a yellow oil
 10 (40%); ¹H NMR (300 MHz, CDCl₃): δ = 3.65 (s, 3 H, OCH₃), 3.77 (s, 3 H, OCH₃), 3.78 (s, 3 H, OCH₃), 4.81 (s, 2 H, OCH₂), 5.13 (s, 1 H, CH), 7.03 (dd, 1 H, H₄, ³J_{H-H} = 8.5 Hz and ⁴J_{H-H} = 2.6 Hz), 7.23 (s, 5 H, H_{Ar}), 7.39 (d, 1 H, H₆, ⁴J_{H-H} = 2.6 Hz), 7.50 (d, 1 H, H₃, ³J_{H-H} = 8.5 Hz), 9.49 (s, 1 H, NH); NMR ¹³C (75 MHz, CDCl₃): δ = 52.1 (CH), 52.5 (OCH₃), 52.7 (OCH₃), 55.5 (OCH₃), 77.9 (OCH₂), 115.9 (CH_{Ar}), 118.4 (CH_{Ar}), 126.5 (C_{IV}), 128.4
 15 (2 CH_{Ar}), 128.6 (CH_{Ar}), 129.3 (2 CH_{Ar}), 129.9 (C_{IV}), 133.0 (CH_{Ar}), 135.2 (C_{IV}), 159.0 (C₅), 165.7 (CO), 168.0 (CO), 169.6 (CO); MALDI-TOF: m/z = 388 (M+H)⁺.

A51-f intermediate 86: Methyl 2-(benzyloxy)-7-methoxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate



20 The process followed in this step is the same as described in example A35e. Yellow powder (61%); 100% keto form; mp 115-117 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.70 (s, 3 H, OCH₃), 3.87 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 5.38 (s, 1 H, H₄), 7.37 – 7.43 (m, 6 H, H_{Ar}), 7.55-7.56 (m, 2 H, H_{Ar}); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 54.5 (C₄), 55.6 (OCH₃), 55.8 (OCH₃), 78.3 (OCH₂), 112.0 (CH_{Ar}), 118.1 (CH_{Ar}), 126.1 (C_{IV}), 127.1
 25 (2 CH_{Ar}), 127.6 (CH_{Ar}), 128.9 (2 CH_{Ar}), 130.8 (CH_{Ar}), 133.2 (C_{IV}), 137.1 (C_{IV}), 159.5 (CO), 161.0 (CO), 164.0 (CO), 169.9 (CO); MALDI-TOF: m/z = 356 (M+H)⁺; Anal. (C₁₉H₁₇NO₆) C, H, N.

A51-g intermediate 87: N-(4-fluorobenzyl)-2-(benzyloxy)-7-methoxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

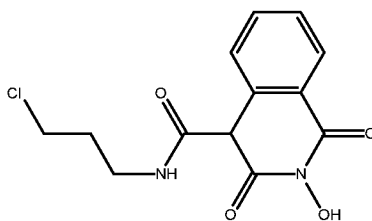


The process followed in this step is the same as described in example A35f. White powder (69%); 100% keto form; mp 194-196 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.86 (s, 3 H, OCH₃), 4.31 (s, 2 H, CH₂), 5.01 (s, 2 H, OCH₂), 5.12 (s, 1 H, H₄), 7.19 – 7.56 (m, 12 H, H_{Ar}), 9.28 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 41.9 (CH₂), 54.9 (C₄), 55.6 (OCH₃), 77.4 (OCH₂), 111.1 (CH_{Ar}), 115.1 (d, C_{3'} and C_{5'}, $^2\text{J}_{\text{C-F}}$ = 20.7 Hz), 121.4 (CH_{Ar}), 126.3 (C_{IV}), 126.6 (C_{IV}), 128.1 (CH_{Ar}), 128.4 (2 CH_{Ar}), 128.9 (CH_{Ar}), 129.2 (d, C_{2'} and C_{6'}, $^3\text{J}_{\text{C-F}}$ = 8.2 Hz), 129.4 (2 CH_{Ar}), 134.4 (C_{IV}), 134.7 (d, C_{1'}, $^4\text{J}_{\text{C-F}}$ = 2.7 Hz), 159.0 (CO), 160.8 (CO), 161.3 (d, C_{4'}, $^1\text{J}_{\text{C-F}}$ = 241.1 Hz), 164.5 (CO), 166.3 (CO); MALDI-TOF: m/z = 449 (M+H)⁺; Anal. (C₂₅H₂₁FN₂O₅) C, H, N.

B FINAL COMPOUNDS

EXAMPLE B1

Compound 1: N-(3-Chloropropyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

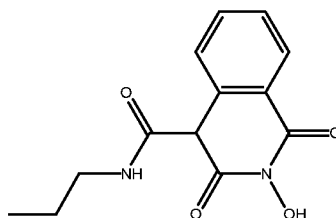


Intermediate 5 (0.387 g, 1.0 mmol) was dissolved in a minimum of CH₂Cl₂ and boron tribromide (1.0 M solution in CH₂Cl₂, 5.0 mL, 5.0 mmol) was added dropwise at room temperature. The solution was stirred for 1 h and water (20 mL) was slowly added. After 15 min stirring, the precipitate was filtered and the aqueous layer was extracted with ethyl acetate. Organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Organic

residues and precipitate were gathered and triturated with ether. Insoluble materials were filtered and dried at room temperature giving **compound 1**. White solid (90%); mp > 180 °C (dec); 94% enol form; 6% keto form; **Keto form**; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.22 (m, 2 H, CH₂), 4.01 (m, 2 H, CH₂), 4.82 (m, 2 H, CH₂), 7.41 (td, 1 H, H_{Ar}, 3J = 7.6 Hz, 4J = 1.6 Hz), 7.70 (td, 1 H, H_{Ar}, 3J = 7.6 Hz, 4J = 1.6 Hz), 8.02 (dd, 1 H, H_{Ar}, 3J = 7.6 Hz, 4J = 1.6 Hz), 8.17 (dd, 1 H, H_{Ar}, 3J = 7.6 Hz, 4J = 1.6 Hz), 10.91 (t, 1 H, NH, 3J = 5.5 Hz); **Enol form**; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.18 (quin, 2 H, CH₂, 3J = 7.0 Hz), 3.59 (t, 2 H, CH₂, 3J = 7.0 Hz), 4.64 (m, 2 H, CH₂), 7.12 (td, 1 H, H_{Ar}, 3J = 8.0 Hz, 4J = 1.2 Hz), 7.49 (td, 1 H, H_{Ar}, 3J = 8.0 Hz, 4J = 1.2 Hz), 8.07 (dd, 1 H, H₅, 3J = 8.0 Hz, 4J = 1.2 Hz), 8.22 (dd, 1 H, H_{Ar}, 3J = 8.0 Hz, 4J = 1.2 Hz), 12.12 (t, 1 H, NH, 3J = 5.5 Hz); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 20.2 (CH₂), 37.8 (CH₂), 67.5 (CH₂), 84.5 (C_{IV}, C₄), 119.7 (C_{IV}), 122.0 (CH), 123.7 (CH), 127.8 (CH), 132.7 (CH), 135.0 (C_{IV}), 159.5 (CO), 162.8 (CO), 166.7 (CO); ESI-MS: m/z = 297 ((M+H)⁺, 100%, ^{35}Cl); 299 ((M+H)⁺, 32%, ^{37}Cl); Anal. (C₁₃H₁₃ClN₂O₄) C, H, N.

EXAMPLE B2

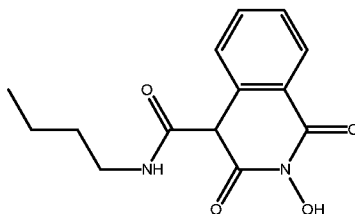
Compound 2: N-Propyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 6 (0.265 g, 0.74 mmol) was dissolved in a mixture of ethyl acetate (10 mL) and methanol (5 mL) and hydrogenated for 4 h at room temperature over Pd/C 5% (20 mg). The catalyst was filtered and the solvent was removed *in vacuo*. Trituration of the residue in ether afforded the deprotected **compound 2** as a white solid (90%); mp 180 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.92 (t, 3 H, CH₃, 3J = 7.1 Hz), 1.51 (sext, 2 H, NH-CH₂-CH₂, 3J = 7.0 Hz), 3.11 (d_{app}, 2 H, NH-CH₂, 3J = 5.6 Hz), 5.13 (s, 1 H, CH), 7.46 (d, 1 H, H_{Ar}, 3J = 7.7 Hz), 7.60 (t, 1 H, H_{Ar}, 3J = 7.2 Hz), 7.76 (t, 1 H, H_{Ar}, 3J = 7.2 Hz), 8.11 (d, 1 H, H₈, 3J = 7.7 Hz), 8.82 (m, 1 H, NH), 10.80 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 11.3 (CH₃), 22.1 (CH₂), 40.9 (CH₂), 55.4 (CH), 125.4 (C_{IV}), 126.6 (CH), 127.9 (CH), 133.8 (CH), 134.7 (C_{IV}), 161.6 (CO), 164.8 (CO), 166.1 (CO); ESI-MS: m/z = 263 (M+H)⁺; Anal. (C₁₃H₁₄N₂O₄) C, H, N.

EXAMPLE B3

Compound 3: *N*-Butyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

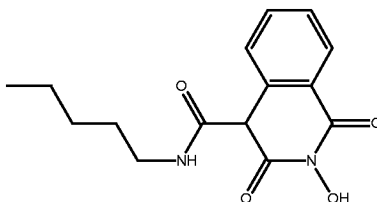


Intermediate 7 was hydrogenated over Pd/C 5% giving **compound 3**. White solid (53%);

mp 180 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.92 (t, 3 H, CH₃, 3J = 7.0 Hz), 1.15-1.36 (m, 4 H, 2 CH₂), 3.25 (q, 2 H, NH-CH₂, 3J = 7.0 Hz), 5.00 (s, 1 H, CH), 7.40 (d, 1 H, H_{Ar}, 3J = 7.7 Hz), 7.69 (t, 1 H, H_{Ar}, 3J = 7.4 Hz), 7.69 (t, 1 H, H_{Ar}, 3J = 7.4 Hz), 8.15 (d, 1 H, H₈, 3J = 8.1 Hz), 8.72 (dapp, 1 H, NH, 3J = 7.0 Hz), 10.45 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 14.0 (CH₃), 19.8 (CH₂), 31.3 (CH₂), 39.2 (CH₂), 55.8 (CH), 125.8 (C_{IV}), 127.0 (CH), 128.3 (CH), 128.6 (CH), 135.1 (C_{IV}), 162.0 (CO), 165.2 (CO), 166.4 (CO); ESI-MS: m/z = 277 (M+H)⁺; Anal. (C₁₄H₁₆N₂O₄) C, H, N.

EXAMPLE B4

Compound 4: *N*-Pentyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

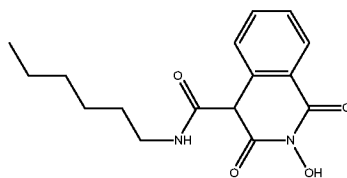


Intermediate 8 was hydrogenated over Pd/C 5% giving **compound 4**. White solid (52%);

mp 130 °C (dec); 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.80 (t, 3 H, CH₃, 3J = 6.6 Hz), 1.21-1.22 (m, 4 H, 2 CH₂), 1.37-1.39 (m, 2 H, CH₂), 3.00 (m, 2 H, NH-CH₂), 4.99 (s, 1 H, CH), 7.33 (d, 1 H, H_{Ar}, 3J = 7.0 Hz), 7.48 (t, 1 H, H_{Ar}, 3J = 7.0 Hz), 7.63 (t, 1 H, H_{Ar}, 3J = 7.0 Hz), 8.00 (d, 1 H, H₈, 3J = 7.5 Hz), 8.68 (m, 1 H, NH), 10.51 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 14.3 (CH₃), 22.2 (CH₂), 28.9 (2 CH₂), 39.5 (CH₂), 55.8 (CH), 125.2 (C_{IV}), 127.0 (CH), 128.3 (CH), 128.6 (CH), 134.1 (CH), 135.3 (C_{IV}), 162.0 (CO), 165.2 (CO), 166.4 (CO); ESI-MS: m/z = 291 (M+H)⁺; Anal. (C₁₅H₁₈N₂O₄) C, H, N.

EXAMPLE B5

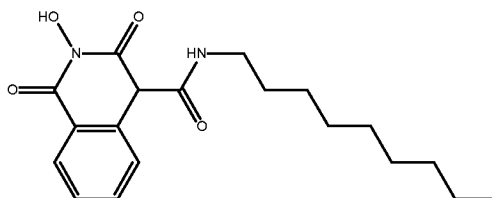
Compound 5: *N*-Hexyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 9 was treated with boron trichloride giving **compound 5**. Light brown solid (79%); mp 137-138 °C; 90% keto form; 10% enol form; **Keto form**; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.89 (t, 3 H, CH₃, 3J = 7.0 Hz), 1.24 (m, 6 H, CH₂), 1.40 (quin, 2 H, CH₂, 3J = 7.0 Hz), 3.05 (m, 2 H, CH₂), 5.05 (s, 1 H, CH), 7.38 (dd, 1 H, H₅, 3J = 8.0 Hz, 4J = 1.5 Hz), 7.54 (td, 1 H, H_{Ar}, 3J = 8.0 Hz, 4J = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, 3J = 8.0 Hz, 4J = 1.5 Hz), 8.05 (dd, 1 H, H₈, 3J = 8.0 Hz, 4J = 1.5 Hz), 8.75 (t, 1 H, NH, 3J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 13.9 (CH₃), 22.0 (CH₂), 25.8 (CH₂), 28.7 (CH₂), 30.8 (CH₂), 40.1 (CH₂), 55.3 (CH), 125.3 (C_{IV}), 126.4 (CH), 127.8 (CH), 128.1 (CH), 133.7 (CH), 134.6 (C_{IV}), 161.5 (CO), 164.7 (CO), 165.9 (CO); **Enol form**; only several peaks could be attributed on the ^1H NMR spectrum; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.73 (t, 3 H, CH₃, 3J = 7.0 Hz), 3.24 (t, 2 H, CH₂, 3J = 7.0 Hz), 7.32 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.2 Hz), 8.15 (dd, 1 H, H₈, 3J = 8.0 Hz, 4J = 1.2 Hz); ESI-MS: m/z = 305 (M+H)⁺; Anal. (C₁₆H₂₀N₂O₄) C, H, N.

EXAMPLE B6

Compound 6: *N*-Nonyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

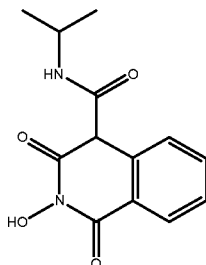


Intermediate 10 was hydrogenated over Pd/C 5% giving **compound 6**. White solid (54%); mp 164 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.70 (t, 3 H, CH₃, 3J = 7.0 Hz), 1.10-1.40 (m, 14 H, 7 CH₂), 3.05 (m, 2 H, NH-CH₂), 5.00 (s, 1 H, CH), 7.35 (d, 1 H, H_{Ar}, 3J = 7.0 Hz), 7.42 (t, 1 H, H_{Ar}, 3J = 7.0 Hz), 7.59 (t, 1 H, H_{Ar}, 3J = 7.0 Hz), 8.04 (d, 1 H, H₈, 3J = 7.5 Hz), 8.72 (m, 1 H, NH), 10.56 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 13.9 (CH₃), 22.0 (CH₂), 26.2 (CH₂), 28.6 (CH₂), 28.7 (CH₂), 28.9 (CH₂), 29.5 (CH₂), 31.2 (CH₂), 39.0 (CH₂), 55.3 (CH), 125.3 (C_{IV}), 126.5 (CH), 127.8

(CH), 128.1 (CH), 133.6 (CH), 134.6 (C_{IV}), 161.5 (CO), 164.7 (CO), 165.9 (CO); ESI-MS: $m/z = 347$ (M+H)⁺; Anal. (C₁₉H₂₆N₂O₄) C, H, N.

EXAMPLE B7

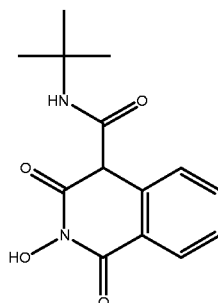
Compound 7: N-Isopropyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 11 was treated with boron trichloride giving **compound 7**. Beige solid (56%); mp 190 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.12 (d, 3 H, CH₃, ³*J* = 6.5 Hz), 1.19 (d, 3 H, CH₃, ³*J* = 6.5 Hz), 3.80 (sext, 1 H, CH, ³*J* = 6.5 Hz), 5.07 (s, 1 H, CH), 7.45 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.60 (t, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.77 (t, 1 H, H_{Ar}, ³*J* = 7.3 Hz), 8.12 (d, 1 H, H₈, ³*J* = 7.5 Hz), 8.75 (d_{app}, 1 H, NH, ³*J* = 7.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 22.1 (2 CH₃), 41.3 (CH), 55.3 (CH), 125.4 (C_{IV}), 126.4 (CH), 127.9 (CH), 128.2 (CH), 133.8 (CH), 134.7 (C_{IV}), 161.6 (CO), 164.8 (CO), 165.1 (CO); ESI-MS: $m/z = 263$ (M+H)⁺; Anal. (C₁₃H₁₄N₂O₄) C, H, N.

EXAMPLE B8

Compound 8: N-Tert-butyl-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide

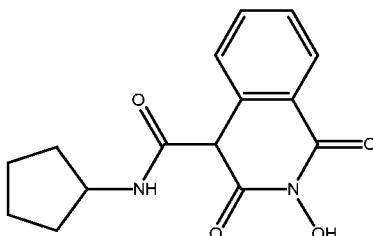


Intermediate 12 was treated with boron trichloride giving **compound 8**. White solid (49%); mp 174 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.25 (s, 9 H, 3 CH₃), 5.09 (s, 1 H, CH), 7.42 (d, 1 H, H_{Ar}, ³*J* = 7.3 Hz), 7.53 (t, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.70 (t, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 8.05 (d, 1 H, H₈, ³*J* = 7.7 Hz), 8.47 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 28.1 (3 CH₃), 50.9 (C_{IV}), 55.7 (CH), 125.3 (C_{IV}), 126.3 (CH),

127.8 (CH), 128.0 (CH), 133.7 (CH), 134.9 (C_{IV}), 161.6 (CO), 164.9 (CO), 165.3 (CO);
ESI-MS: $m/z = 277$ (M+H)⁺; Anal. (C₁₄H₁₆N₂O₄) C, H, N.

EXAMPLE B9

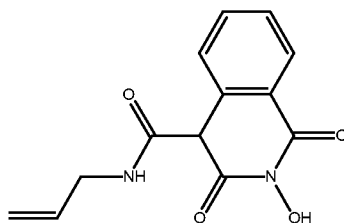
Compound 9: *N*-Cyclopentyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-
carboxamide



Intermediate 13 was hydrogenated over Pd/C 5% giving **compound 9**. Brown solid (64%); mp 160 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.40-1.80 (m, 8 H, 4 CH₂), 3.97 (m, 1 H, CH), 5.09 (s, 1 H, CH), 7.42 (d, 1 H, H_{Ar}, ³*J* = 7.0 Hz), 7.57 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 7.72 (t, 1 H, H_{Ar}, ³*J* = 7.3 Hz), 8.10 (d, 1 H, H₈, ³*J* = 7.6 Hz), 8.81 (d_{app}, 1 H, NH, ³*J* = 6.1 Hz), 10.63 (s, 1 H, OH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 23.41 (CH₂), 23.45 (CH₂), 32.1 (CH₂), 32.2 (CH₂), 50.9 (CH), 55.1 (CH), 125.3 (C_{IV}), 126.3 (CH), 127.8 (CH), 128.1 (CH), 133.7 (CH), 134.7 (C_{IV}), 161.5 (CO), 164.7 (CO), 165.4 (CO); ESI-MS: $m/z = 289$ (M+H)⁺; Anal. (C₁₅H₁₆N₂O₄) C, H, N.

EXAMPLE B10

Compound 10: *N*-Allyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-
carboxamide

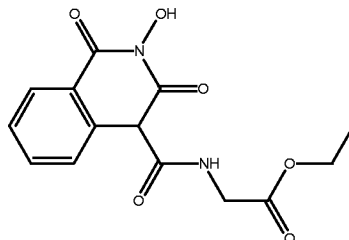


Intermediate 14 was treated with boron trichloride giving **compound 10**. Brown solid (53%); mp 178 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.73 (m, 2 H, CH₂-CH=CH₂), 5.02-5.20 (m, 3 H, C₄H, CH₂-CH=CH₂), 5.80 (m, 1 H, CH₂-CH=CH₂), 7.43 (d, 1 H, H_{Ar}, ³*J* = 7.5 Hz), 7.55 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 7.71 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.07 (d, 1 H, H₈, ³*J* = 7.5 Hz), 9.00 (m, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 41.7 (CH₂-CH=CH₂), 55.7 (CH), 115.9 (CH₂-CH=CH₂), 125.8 (C_{IV}), 127.1 (CH), 128.3

(CH), 128.7 (CH), 134.2 (CH), 134.8 (CH), 135.0 (C_{IV}), 162.0 (CO), 165.2 (CO), 166.5 (CO); ESI-MS: m/z = 261.1 (M+H)⁺; Anal. (C₁₃H₁₂N₂O₄) C, H, N.

EXAMPLE B11

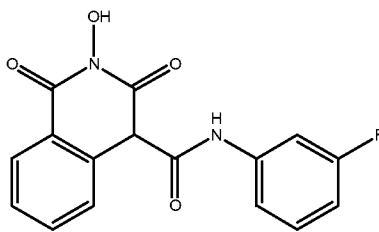
Compound 11: Ethyl 2-[(2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-yl)formamido]acetate



Intermediate 15 was treated with boron trichloride giving **compound 11**. Beige solid (88%); mp 97-98 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 1.20 (t, 3 H, CH₃, ³J = 7.0 Hz), 4.01-4.12 (m, 4 H, CH₂), 5.12 (s, 1 H, CH), 7.48-7.70 (m, 4 H, NH, 3 H_{Ar}), 8.01 (dd, 1 H, H₈, ³J = 8.0 Hz, ⁴J = 1.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.2 (CH₃), 42.1 (CH₂), 55.3 (CH), 61.0 (OCH₂), 127.3 (C_{IV}), 128.1 (CH), 129.0 (CH), 129.1 (CH), 132.8 (C_{IV}), 134.1 (CH), 161.1 (CO), 163.8 (CO), 164.8 (CO), 169.4 (CO); ESI-MS: m/z = 307 (M+H)⁺; Anal. (C₁₄H₁₄N₂O₆) C, H, N.

EXAMPLE B12

Compound 12: *N*-(3-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

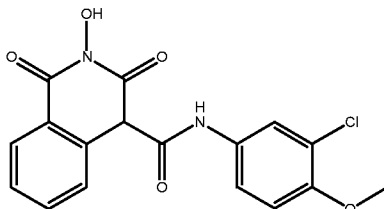


Intermediate 16 was treated with boron trichloride giving **compound 12**. Black solid (68%); mp 170-172 °C; 100% keto form; ¹H NMR (300 MHz, CDCl₃): δ = 4.27 (s, 1 H, CH), 6.82-6.95 (m, 2 H, H_{Ar}), 7.00-7.49 (m, 5 H, NH, 4 H_{Ar}), 7.75 (d, 1 H, H_{Ar}, ³J = 7.5 Hz), 8.23 (dd, 1 H, H₈, ³J = 8.0 Hz, ⁴J = 1.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 55.9 (CH), 108.9 (d, CH, C₂, ²J_{C-F} = 28.0 Hz), 111.2 (d, CH, C₄, ²J_{C-F} = 28.1 Hz), 118.4 (d, CH, C₆, ⁴J_{C-F} = 3.2 Hz), 126.8 (C_{IV}), 127.3 (CH), 128.4 (CH), 128.5 (d, CH, C₅, ³J_{C-F} = 8.4 Hz), 129.1 (CH), 130.3 (CH), 131.4 (C_{IV}), 136.1 (d, C_{IV}, C₁, ³J_{C-F} = 10.0 Hz), 161.1 (d,

C_{IV}, C₃, $^1J_{C-F}$ = 255.6 Hz), 161.4 (CO), 161.8 (CO), 166.2 (CO); ESI-MS: m/z = 315 (M+H)⁺; Anal. (C₁₆H₁₁FN₂O₄) C, H, N.

EXAMPLE B13

Compound 13: *N*-(3-Chloro-4-methoxyphenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 17 was treated with boron trichloride giving **compound 13**. Purple solid

(79%); 33% keto form; 67% enol form; **Keto form**; ^1H NMR (300 MHz, Acetone- d_6): δ =

3.93 (s, 3 H, OCH₃), 5.27 (s, 1 H, CH), 7.04 (d, 1 H, H₅, 3J = 7.5 Hz), 7.35 (dd, 1 H, H_{Ar},

10 3J = 7.5 Hz, 4J = 1.4 Hz), 7.51-7.62 (m, 2 H, H_{Ar}), 7.70 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.4

Hz), 7.78 (d, 1 H, H₂, 4J = 1.4 Hz), 8.11 (dd, 1 H, H₈, 3J = 7.5 Hz, 4J = 1.4 Hz), 9.82 (s, 1

H, NH); ^{13}C NMR (75 MHz, Acetone- d_6): δ = 55.5 (OCH₃), 56.2 (CH), 115.1 (CH), 116.2

(C_{IV}), 120.5 (CH), 120.7 (CH), 127.0 (C_{IV}), 127.1 (CH), 127.8 (CH), 128.2 (CH), 128.3

(C_{IV}), 129.1 (CH), 131.5 (C_{IV}), 148.5 (CO), 161.3 (CO), 161.5 (CO), 164.4 (CO); **Enol**

15 **form**; ^1H NMR (300 MHz, Acetone- d_6): δ = 3.95 (s, 3 H, OCH₃), 7.15 (d, 1 H, H₅, 3J =

7.5 Hz), 7.51-7.62 (m, 3 H, H_{Ar}), 7.71 (td, 1 H, H_{Ar}, 3J = 7.6 Hz, 4J = 1.5 Hz), 7.80 (d, 1 H,

H₂, 4J = 1.5 Hz), 8.18 (dd, 1 H, H₈, 3J = 7.6 Hz, 4J = 1.5 Hz), 10.03 (s, 1 H, NH); ^{13}C

NMR (75 MHz, Acetone- d_6): δ = 56.1 (OCH₃), 84.3 (C_{IV}, C₄), 117.8 (CH), 118.5 (C_{IV}),

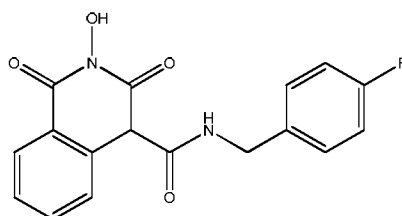
119.2 (CH), 119.5 (CH), 127.6 (CH), 128.4 (CH), 129.2 (C_{IV}), 130.1 (C_{IV}), 131.1 (CH),

20 132.4 (CH), 133.5 (C_{IV}), 148.6 (CO), 160.1 (CO), 160.5 (CO), 162.4 (CO); ESI-MS: m/z =

361 ((M+H)⁺, 100%, ^{35}Cl); 363 ((M+H)⁺, 32%, ^{37}Cl); Anal. (C₁₇H₁₃ClN₂O₅) C, H, N.

EXAMPLE B14

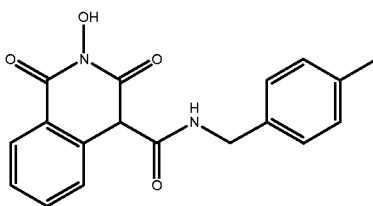
Compound 14: *N*-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 18 was treated with boron trichloride giving **compound 14**. Compound 14: light yellow solid (81%); mp > 155 °C (dec); 100% keto form; ¹H NMR (300 MHz, Acetone-*d*₆): δ = 4.43 (m, 2 H, CH₂), 5.18 (s, 1 H, CH), 7.08 (t, 2 H, H_{3'}, H_{5'}, ³J_{H-H} = ³J_{H-F} = 7.7 Hz), 7.34 (m, 2 H, H_{Ar}), 7.46-7.60 (m, 2 H, H_{Ar}), 7.71 (td, 1 H, H_{Ar}, ³J = 7.5 Hz, ⁴J = 1.5 Hz), 8.15 (dd, 1 H, H₈, ³J = 7.5 Hz, ⁴J = 1.5 Hz), 8.51 (t, 1 H, NH, ³J = 5.0 Hz); ¹³C NMR (75 MHz, Acetone-*d*₆): δ = 42.5 (CH₂), 55.8 (CH), 115.0 (d, 2 CH, C_{3'}, C_{5'}, ²J_{C-F} = 21.4 Hz), 125.2 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.3 (CH), 129.3 (d, 2CH, C_{2'}, C_{6'}, ³J_{C-F} = 8.6 Hz), 133.7 (CH), 133.8 (C_{IV}), 134.2 (d, C_{IV}, C_{1'}, ⁴J_{C-F} = 3.1 Hz), 161.3 (d, C_{IV}, C_{4'}, ¹J_{C-F} = 241.2 Hz), 162.1 (CO), 163.0 (CO), 166.4 (CO); ESI-MS: *m/z* = 329 (M+H)⁺; Anal. (C₁₇H₁₃FN₂O₄) C, H, N.

EXAMPLE B15

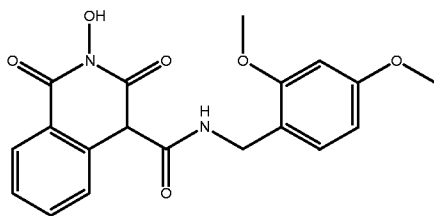
Compound 15: *N*-(4-Methylbenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 19 was treated with boron trichloride giving **compound 15**. Beige solid (88%); mp 171 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.32 (s, 3 H, CH₃), 4.38 (d, 2 H, ³J = 5.3 Hz), 5.27 (s, 1 H, CH), 7.27 (m, 4 H, H_{Ar}), 7.52 (dd, 1 H, H₅, ³J = 7.9 Hz, ⁴J = 1.2 Hz), 7.67 (td, 1 H, H_{Ar}, ³J = 7.9 Hz, ⁴J = 1.2 Hz), 7.82 (td, 1 H, H_{Ar}, ³J = 7.9 Hz, ⁴J = 1.2 Hz), 8.19 (dd, 1 H, H₈, ³J = 7.9 Hz, ⁴J = 1.2 Hz), 9.37 (t, 1 H, NH, ³J = 5.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 21.2 (CH₃), 42.9 (CH₂), 55.8 (CH), 125.9 (C_{IV}), 127.1 (CH), 127.7 (2CH), 128.4 (CH), 128.7 (CH), 129.4 (2CH), 134.3 (CH), 135.0 (C_{IV}), 135.9 (C_{IV}), 136.6 (C_{IV}), 162.1 (CO), 165.2 (CO), 166.6 (CO); ESI-MS: *m/z* = 325 (M+H)⁺; Anal. (C₁₈H₁₆N₂O₄) C, H, N.

EXAMPLE B16

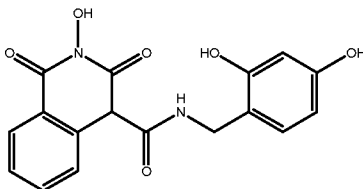
Compound 16: *N*-(2,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 20 was treated with boron trichloride giving **compound 16**. Salmon solid (93%); mp 125-127 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.75 (s, 3 H, OCH₃), 3.79 (s, 3 H, OCH₃), 4.15 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 4.19 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 5.17 (s, 1 H, CH), 6.48 (dd, 1 H, H₅, ³*J* = 7.6 Hz, ⁴*J* = 1.2 Hz), 6.57 (d, 1 H, H₃, ⁴*J* = 1.2 Hz), 7.11 (d, 1 H, H₆, ³*J* = 7.6 Hz), 7.40 (dd, 1 H, H_{Ar}, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 7.54 (td, 1 H, H_{Ar}, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 8.05 (dd, 1 H, H₈, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 9.00 (t, 1 H, NH, ³*J* = 5.1 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 38.2 (CH₂), 55.6 (OCH₃), 55.7 (OCH₃), 55.9 (CH), 98.8 (CH, C₃'), 104.7 (CH, C₅'), 118.3 (C_{IV}, C₁'), 125.8 (C_{IV}), 127.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (CH), 134.2 (CH), 135.0 (C_{IV}), 158.3 (CO), 160.5 (CO), 162.1 (CO), 165.3 (CO), 166.4 (CO); ESI-MS: *m/z* = 371 (M+H)⁺; Anal. (C₁₉H₁₈N₂O₆) C, H, N.

EXAMPLE B17

Compound 17: *N*-(2,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

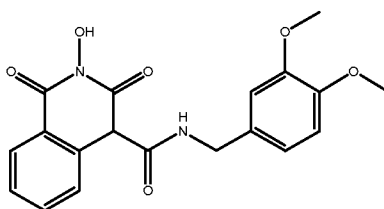


Intermediate 20 was treated with boron tribromide giving **compound 17**. Pink solid (66%); mp > 111 °C (dec); 55% keto form; 45% enol form; **Keto form**; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.10 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 4.12 (dd, 1 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.1 Hz), 5.17 (s, 1 H, CH), 6.28 (dd, 1 H, H₅, ³*J* = 7.6 Hz, ⁴*J* = 1.2 Hz), 6.31 (d, 1 H, H₃, ⁴*J* = 1.2 Hz), 6.88 (d, 1 H, H₆, ³*J* = 7.6 Hz), 7.43 (dd, 1 H, H₅, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 7.52 (td, 1 H, H_{Ar}, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 8.05 (dd, 1 H, H₈, ³*J* = 7.5 Hz, ⁴*J* = 1.5 Hz), 8.90 (t, 1 H, NH, ³*J* = 5.1 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 38.2 (CH₂), 56.0 (CH), 106.3 (CH), 108.3 (C_{IV}), 108.6 (CH), 125.9 (C_{IV}), 126.1 (CH), 128.3 (CH), 128.6 (CH), 129.7 (CH), 134.2 (CH), 135.0 (C_{IV}), 153.2 (CO), 159.3 (CO), 162.1 (CO), 163.3 (CO), 165.7 (CO); **Enol form**; ¹H

NMR (300 MHz, DMSO- d_6): δ = 4.29 (dd, 1 H, CH₂, 2J = 11.9 Hz, 3J = 5.1 Hz), 4.31 (dd, 1 H, CH₂, 2J = 11.9 Hz, 3J = 5.1 Hz), 6.15 (dd, 1 H, H₅, 3J = 7.6 Hz, 4J = 1.2 Hz), 6.26 (d, 1 H, H₃, 4J = 1.2 Hz), 7.01 (d, 1 H, H₆, 3J = 7.6 Hz), 7.19 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 7.51 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 8.05 (dd, 1 H, H₅, 3J = 7.5 Hz, 4J = 1.5 Hz), 8.27 (t, 1 H, NH, 3J = 5.1 Hz), 8.89 (dd, 1 H, H₈, 3J = 7.5 Hz, 4J = 1.5 Hz); ¹³C NMR (75 MHz, DMSO- d_6): δ = 39.2 (CH₂), 84.3 (C_{IV}, C₄), 106.1 (C_{IV}), 106.3 (CH), 108.3 (CH), 126.8 (C_{IV}), 127.9 (CH), 128.3 (CH), 129.2 (CH), 129.7 (CH), 131.2 (CH), 134.5 (C_{IV}), 149.2 (CO), 156.5 (CO), 159.5 (CO), 161.3 (CO), 166.5 (CO); ESI-MS: m/z = 343 (M+H)⁺; Anal. (C₁₇H₁₄N₂O₆) C, H, N.

EXAMPLE B18

Compound 18: N-(3,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

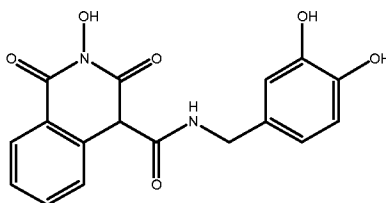


Intermediate 21 was treated with boron trichloride giving **compound 18**. Salmon solid (67%); mp 126-127 °C; 66% keto form; 34% enol form; **Keto form**; ¹H NMR (300 MHz, Acetone- d_6): δ = 3.79 (s, 3 H, OCH₃), 3.80 (s, 3 H, OCH₃), 4.38 (m, 2 H, CH₂), 4.72 (s, 1 H, CH), 6.76-6.90 (m, 3 H, H_{Ar}), 7.36 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 7.56 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 7.69 (dd, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 8.15 (dd, 1 H, H₈, 3J = 7.5 Hz, 4J = 1.5 Hz), 9.82 (t, 1 H, NH, 3J = 5.2 Hz); ¹³C NMR (75 MHz, Acetone- d_6): δ = 46.1 (CH₂), 55.2 (OCH₃), 55.3 (OCH₃), 55.6 (CH), 111.0 (CH), 111.5 (CH), 114.4 (CH), 114.8 (CH), 118.6 (CH), 120.0 (CH), 128.6 (C_{IV}), 128.7 (CH), 131.9 (C_{IV}), 133.1 (C_{IV}), 149.9 (CO), 152.1 (CO), 160.5 (CO), 161.3 (CO), 164.2 (CO); **Enol form**; ¹H NMR (300 MHz, Acetone- d_6): δ = 3.82 (s, 3 H, OCH₃), 3.87 (s, 3 H, OCH₃), 4.34 (m, 2 H, CH₂), 6.76-6.90 (m, 3 H, H_{Ar}), 7.40 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 7.59 (td, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 7.71 (dd, 1 H, H_{Ar}, 3J = 7.5 Hz, 4J = 1.5 Hz), 8.17 (dd, 1 H, H₈, 3J = 7.5 Hz, 4J = 1.5 Hz), 10.35 (t, 1 H, NH, 3J = 5.2 Hz); ¹³C NMR (75 MHz, Acetone- d_6): δ = 42.8 (CH₂), 55.1 (OCH₃), 55.2 (OCH₃), 84.2 (C_{IV}, C₄), 111.1 (CH), 111.7 (CH), 119.4 (CH), 125.8 (C_{IV}), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.9 (C_{IV}), 131.8 (C_{IV}), 133.6

(CH), 149.9 (CO), 151.0 (CO), 157.3 (CO), 161.3 (CO), 162.4 (CO); ESI-MS: $m/z = 371$ (M+H)⁺; Anal. (C₁₉H₁₈N₂O₆) C, H, N.

EXAMPLE B19

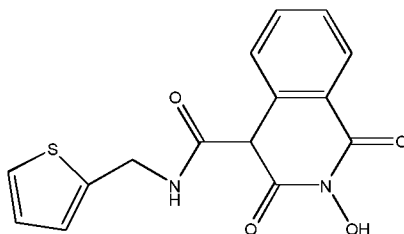
Compound 19: *N*-(3,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide



Intermediate 21 was treated with boron tribromide giving **compound 19**. Salmon solid (95%); mp > 150 °C (dec); 100% keto form; ¹H NMR (300 MHz, Acetone-*d*₆): δ = 4.15 (dd, 2 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.0 Hz), 4.17 (dd, 2 H, CH₂, ²*J* = 11.9 Hz, ³*J* = 5.0 Hz), 5.12 (s, 1 H, CH), 6.52 (d, 1 H, H₅, ³*J* = 7.6 Hz), 6.64-6.73 (m, 2 H, H_{Ar}), 7.39 (dd, 1 H, H₅, ³*J* = 7.6 Hz, ⁴*J* = 1.5 Hz), 7.54 (td, 1 H, H_{Ar}, ³*J* = 7.6 Hz, ⁴*J* = 1.5 Hz), 7.69 (td, 1 H, H_{Ar}, ³*J* = 7.6 Hz, ⁴*J* = 1.5 Hz), 8.06 (dd, 1 H, H₈, ³*J* = 7.6 Hz, ⁴*J* = 1.5 Hz), 9.12 (t, 1 H, NH, ³*J* = 5.2 Hz); ¹³C NMR (75 MHz, Acetone-*d*₆): δ = 42.6 (CH₂), 55.9 (CH), 114.8 (CH), 118.6 (CH), 122.8 (CH), 123.8 (C_{IV}), 127.2 (CH), 128.7 (CH), 129.3 (CH), 131.9 (C_{IV}), 132.4 (CH), 134.9 (C_{IV}), 146.2 (C_{IV}), 151.0 (C_{IV}), 161.5 (CO), 165.0 (CO), 166.4 (CO); ESI-MS: $m/z = 343$ (M+H)⁺; Anal. (C₁₇H₁₄N₂O₆) C, H, N.

EXAMPLE B20

Compound 20 : *N*-((Thiophen-2-yl)methyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

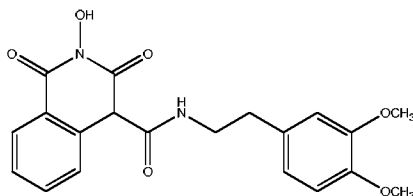


Intermediate 22 was hydrogenated on Pd/C 5% giving **compound 20**. Brown solid (66%); mp > 110 °C (dec); 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.44 (m, 2 H, CH₂), 6.75-6.81 (m, 2 H, CH Thioph), 6.90 (d, 1 H, CH Thioph, ³*J* = 5.0 Hz), 7.41 (d, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 7.69 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 7.78 (t, 1 H, H_{Ar}, ³*J* = 7.2 Hz), 8.11 (d, 1 H, H₈, ³*J* = 7.7 Hz), 9.19 (s, 1 H, NH), 10.8 (s, 1 H, OH); ¹³C NMR (75 MHz,

DMSO- d_6): δ = 38.0 (CH₂), 78.4 (C_{IV}), 125.1 (C_{IV}), 125.5 (CH), 125.8 (CH), 125.85 (CH), 127.0 (CH), 127.9 (CH), 129.7 (CH), 134.3 (CH), 139.5 (C_{IV}), 142.1 (C_{IV}), 161.8 (CO), 168.1 (CO), 168.3 (CO); ESI-MS: m/z = 317 (M+H)⁺; Anal. (C₁₅H₁₂N₂O₄S) C, H, N.

EXAMPLE B21

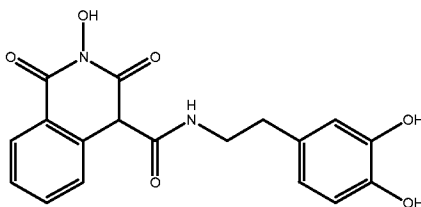
- 5 Compound 21: *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



- Intermediate 23** was treated with boron trichloride giving **compound 21**. Orange solid (95%); mp 112-114 °C; 100% keto form; ¹H NMR (300 MHz, DMSO- d_6): δ = 2.70 (m, 2 H, CH₂), 3.35 (m, 2 H, CH₂), 3.74 (s, 3 H, OCH₃), 3.75 (s, 3 H, OCH₃), 4.72 (s, 1 H, CH), 6.80-6.90 (m, 3 H, H_{Ar}), 7.42 (dd, 1 H, H₅, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 7.67 (td, 1 H, H_{Ar}, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 7.75 (td, 1 H, H_{Ar}, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 8.17 (dd, 1 H, H₈, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 8.76 (t, 1 H, NH, ³ J = 5.2 Hz); ¹³C NMR (75 MHz, DMSO- d_6): δ = 34.5 (CH₂), 41.2 (CH₂), 55.1 (OCH₃), 55.2 (OCH₃), 55.8 (CH), 111.9 (CH), 112.7 (CH), 121.7 (CH), 125.6 (C_{IV}), 127.0 (CH), 128.0 (CH), 128.2 (CH), 131.9 (C_{IV}), 133.6 (CH), 134.5 (C_{IV}), 149.8 (CO), 152.1 (CO), 161.5 (CO), 162.1 (CO), 164.7 (CO); ESI-MS: m/z = 385 (M+H)⁺; Anal. (C₂₀H₂₀N₂O₆) C, H, N.

EXAMPLE B22

- 20 Compound 22: *N*-[2-(3,4-Dihydroxyphenyl)ethyl]-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide



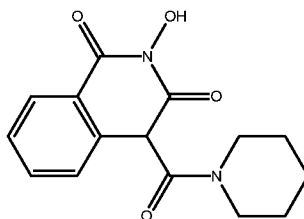
- Intermediate 23** was treated with boron tribromide giving **compound 22**. Orange solid (95%); mp 148-150 °C; 100% keto form; ¹H NMR (300 MHz, DMSO- d_6): δ = 2.34 (m, 2 H, CH₂), 3.47 (m, 2 H, CH₂), 5.07 (s, 1 H, CH), 6.75-6.90 (m, 3 H, H_{Ar}), 7.40-7.55 (m, 2 H, H_{Ar}), 7.67 (dd, 1 H, H_{Ar}, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 8.12 (dd, 1 H, H₈, ³ J = 7.9 Hz, ⁴ J = 1.5 Hz), 8.56 (t, 1 H, NH, ³ J = 5.2 Hz); ¹³C NMR (75 MHz, DMSO- d_6): δ = 35.0 (CH₂),

41.7 (CH₂), 55.9 (CH), 115.0 (CH), 116.1 (CH), 123.5 (CH), 127.7 (CH), 127.8 (C_{IV}), 128.0 (CH), 129.4 (CH), 129.7 (CH), 129.8 (C_{IV}), 131.3 (C_{IV}), 142.8 (CO), 144.0 (CO), 160.5 (CO), 161.4 (CO), 162.7 (CO); ESI-MS: $m/z = 357$ (M+H)⁺; Anal. (C₁₈H₁₆N₂O₆) C, H, N.

5

EXAMPLE B23

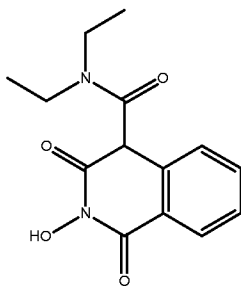
Compound 23: (2-hydroxy-1,3-dioxoisoquinolin-4-yl)(piperidin-1-yl)methanone



Intermediate 24 was hydrogenated on Pd/C 5% giving **compound 23**. Black solid (64%); mp > 128 °C (dec); 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.49-1.64 (m, 6 H, 3 CH₂), 3.35 (t, 2 H, N-CH₂, ³*J* = 5.1 Hz), 3.66 (t, 2 H, N-CH₂, ³*J* = 5.1 Hz), 5.97 (s, 1 H, CH), 7.30 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.61 (t, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.76 (t, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 8.12 (d, 1 H, H₈, ³*J* = 7.7 Hz), 10.8 (s, 1 H, OH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 23.7 (CH₃), 25.1 (CH₂), 26.0 (CH₂), 43.0 (CH₂), 47.4 (CH₂), 50.3 (CH), 125.3 (C_{IV}), 126.7 (CH), 127.7 (CH), 127.9 (CH), 133.7 (CH), 135.0 (C_{IV}), 161.3 (CO), 164.6 (CO), 164.7 (CO); ESI-MS: $m/z = 289$ (M+H)⁺; Anal. (C₁₅H₁₆N₂O₄) C, H, N.

EXAMPLE B24

Compound 24: *N,N*-Diethyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

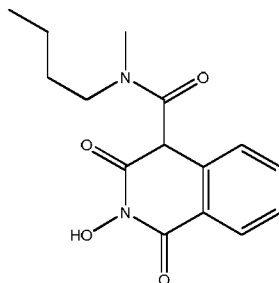


Intermediate 25 was hydrogenated on Pd/C 5% giving **compound 24**. White solid (52%); mp 178 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.21 (t, 3 H, CH₃, ³*J* = 6.4 Hz), 1.28 (t, 3 H, CH₃, ³*J* = 6.6 Hz), 3.21-3.41 (m, 2 H, NH-CH₂), 3.60-3.73 (m, 2 H, NH-CH₂), 5.77 (s, 1 H, CH), 7.22 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.55 (t, 1 H, H_{Ar}, ³*J* = 7.6 Hz), 7.70 (t, 1 H, H_{Ar}, ³*J* = 7.5 Hz), 8.08 (d, 1 H, H₈, ³*J* = 7.7 Hz), 10.50 (s, 1 H, OH); ¹³C NMR

(75 MHz, DMSO- d_6): δ = 12.7 (CH₃), 14.8 (CH₃), 40.4 (CH₂), 42.8 (CH₂), 50.6 (CH), 125.5 (C_{IV}), 126.5 (CH), 127.9 (CH), 128.0 (CH), 133.9 (CH), 135.3 (C_{IV}), 161.5 (CO), 164.8 (CO), 166.0 (CO); ESI-MS: m/z = 277 (M+H)⁺; Anal. (C₁₄H₁₆N₂O₄) C, H, N.

EXAMPLE B25

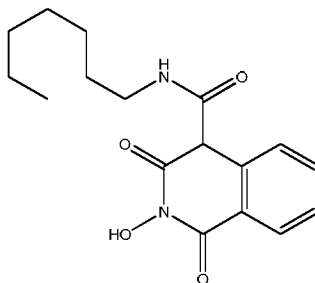
- 5 Compound 25: *N*-Butyl-*N*-methyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 26 was hydrogenated on Pd/C 5% giving **compound 25**. Brown solid (62%); mp 120-124 °C; 100% keto form; ¹H NMR (300 MHz, DMSO- d_6): δ = 0.92 (t, 3 H, CH₃, ³ J = 8.4 Hz), 1.27-1.70 (m, 4 H, 2 CH₂), 2.95 (s, 3 H, NH-CH₃), 3.34 (m, 2 H, NH-CH₂), 5.90 (s, 1 H, CH), 7.32 (d, 1 H, H_{Ar}, ³ J = 7.5 Hz), 7.61 (t, 1 H, H_{Ar}, ³ J = 7.5 Hz), 7.76 (d, 1 H, H_{Ar}, ³ J = 7.5 Hz), 8.12 (d, 1 H, H₈, ³ J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 14.2 (CH₃), 19.8 (CH₂), 29.0 (CH₂), 31.0 (CH₂), 34.2 (NHCH₃), 36.7 (NHCH₃), 47.7 (NHCH₂), 50.7 (NHCH₂), 51.0 (CH), 51.5 (CH), 126.0 (C_{IV}), 127.3 (CH), 128.3 (CH), 128.6 (CH), 134.3 (CH), 135.6 (C_{IV}), 161.9 (CO), 165.2 (CO), 167.3 (CO); ESI-MS: m/z = 291 (M+H)⁺; Anal. (C₁₅H₁₈N₂O₄) C, H, N.

EXAMPLE B26

Compound 26: *N*-Heptyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

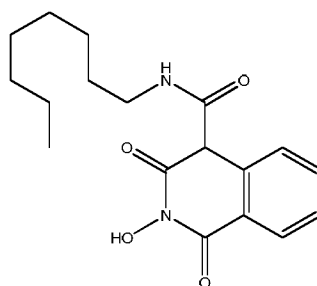


Intermediate 27 was hydrogenated on Pd/C 5% giving **compound 26**. Grey solid (74%); mp 120-130 °C; 100% keto form; ¹H NMR (300 MHz, DMSO- d_6): δ = 0.90 (t, 3 H, CH₃, ³ J = 7.0 Hz), 1.23-1.25 (m, 8 H, 4 CH₂), 1.40-1.42 (m, 2 H, CH₂), 3.07 (q, 2 H, NH-CH₂, ³ J

= 7.1 Hz), 5.08 (s, 1 H, CH), 7.40 (d, 1 H, H_{Ar} , $^3J = 7.2$ Hz), 7.55 (t, 1 H, H_{Ar} , $^3J = 7.5$ Hz), 7.70 (t, 1 H, H_{Ar} , $^3J = 7.5$ Hz), 8.11 (d, 1 H, H_8 , $^3J = 7.5$ Hz), 8.82 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 13.9 (CH₃), 22.0 (CH₂), 26.1 (CH₂), 28.3 (CH₂), 28.8 (CH₂), 31.2 (CH₂), 38.7 (CH₂), 55.3 (CH), 125.3 (C_{IV}), 126.4 (CH), 127.8 (CH), 128.1 (CH), 133.6 (CH), 134.6 (C_{IV}), 161.5 (CO), 164.7 (CO), 165.9 (CO); ESI-MS: m/z = 319 (M+H)⁺; Anal. (C₁₇H₂₂N₂O₄) C, H, N.

EXAMPLE B27

Compound 27: N-Octyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



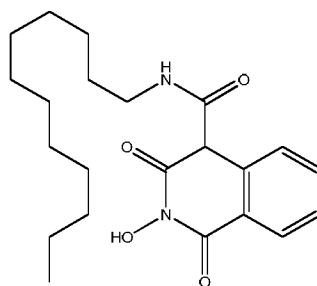
10

Intermediate 28 was hydrogenated on Pd/C 5% giving **compound 27**. Beige solid (67%); mp 92-96 °C; 100% keto form; 1H NMR (300 MHz, DMSO- d_6): δ = 0.92 (t, 3 H, CH₃, $^3J = 7.3$ Hz), 1.29-1.31 (m, 10 H, 5 CH₂), 1.47-1.49 (m, 2 H, CH₂), 5.11 (s, 1 H, CH), 7.44 (d, 1 H, H_{Ar} , $^3J = 7.3$ Hz), 7.60 (t, 1 H, H_{Ar} , $^3J = 7.0$ Hz), 7.75 (t, 1 H, H_{Ar} , $^3J = 7.0$ Hz), 8.11 (d, 1 H, H_8 , $^3J = 7.3$ Hz), 8.80 (s, 1 H, NH), 10.63 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 13.9 (CH₃), 22.0 (CH₂), 26.2 (CH₂), 28.6 (2 CH₂), 28.7 (CH₂), 31.1 (CH₂), 39.0 (CH₂), 55.3 (CH), 125.3 (C_{IV}), 126.5 (CH), 127.8 (CH), 128.1 (CH), 133.6 (CH), 134.6 (C_{IV}), 161.5 (CO), 164.7 (CO), 165.9 (CO); ESI-MS: m/z = 333 (M+H)⁺; Anal. (C₁₈H₂₄N₂O₄) C, H, N.

20

EXAMPLE B28

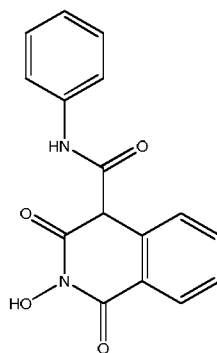
Compound 28: N-Dodecyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 29 was hydrogenated on Pd/C 5% giving **compound 28**. Grey solid (52%); mp 132-144 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 0.86 (t, 3 H, CH_3 , 3J = 6.6 Hz), 1.20-1.26 (m, 18 H, 9 CH_2), 1.39-1.41 (m, 2 H, CH_2), 3.06 (m, 2 H, CH_2), 5.08 (s, 1 H, CH), 7.39 (d, 1 H, H_{Ar} , 3J = 7.2 Hz), 7.54 (t, 1 H, H_{Ar} , 3J = 8.0 Hz), 7.68 (t, 1 H, H_{Ar} , 3J = 8.0 Hz), 8.05 (d, 1 H, H_8 , 3J = 8.0 Hz), 8.75 (s, 1 H, NH), 10.57 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 14.4 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 29.1 (CH_2), 29.2 (2 CH_2), 29.5 (4 CH_2), 31.8 (CH_2), 39.5 (CH_2), 55.8 (CH), 125.8 (C_{IV}), 127.0 (CH), 128.3 (CH), 128.6 (CH), 134.1 (CH), 135.2 (C_{IV}), 162.0 (CO), 165.2 (CO), 166.4 (CO); ESI-MS: m/z = 389 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_4$) C, H, N.

EXAMPLE B29

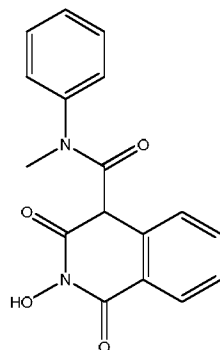
Compound 29: *N*-Phenyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 30 was treated with boron trichloride giving **compound 29**. Grey solid (73%); mp 170-175 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): δ = 5.33 (s, 1 H, CH), 7.11 (t, 1 H, H_{Ar} , 3J = 7.0 Hz), 7.34 (t, 2 H, H_{Ar} , 3J = 7.5 Hz), 7.52 (t, 1 H, H_{Ar} , 3J = 7.2 Hz), 7.57-7.61 (m, 3 H, H_{Ar}), 7.69 (t, 1 H, H_{Ar} , 3J = 7.0 Hz), 8.10 (d, 1 H, H_{Ar} , 3J = 7.7 Hz), 10.94 (s, 1 H, NH); ^{13}C NMR (75 MHz, DMSO- d_6): δ = 56.1 (CH), 119.4 (2 CH), 124.2 (CH), 125.4 (C_{IV}), 126.7 (CH), 128.0 (CH), 128.4 (CH), 128.9 (2 CH), 133.9 (CH), 134.3 (C_{IV}), 138.2 (C_{IV}), 161.5 (CO), 164.6 (CO), 164.8 (CO); ESI-MS: m/z = 297 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4$) C, H, N.

EXAMPLE B30

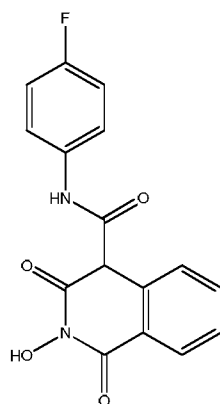
Compound 30: *N*-Methyl-*N*-phenyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 31 was hydrogenated on Pd/C 5% giving **compound 30**. Brown solid (40%); mp 130-135 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.25 (s, 3 H, CH₃), 5.23 (s, 1 H, CH), 7.16 (d, 1 H, H_{Ar}, ³*J* = 5.7 Hz), 7.22 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 7.43 (t, 1 H, H_{Ar}, ³*J* = 7.3 Hz), 7.48-7.55 (m, 4 H, H_{Ar}), 7.67 (t, 1 H, H_{Ar}, ³*J* = 7.3 Hz), 8.00 (d, 1 H, H_{Ar}, ³*J* = 7.3 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 38.1 (CH₃), 51.8 (CH), 125.8 (C_{IV}), 125.9 (CH), 126.8 (CH), 128.4 (2 CH), 128.6 (CH), 128.9 (CH), 130.5 (2 CH), 134.3 (2 CH), 135.1 (C_{IV}), 143.3 (C_{IV}), 161.6 (CO), 165.0 (CO), 166.8 (CO); ESI-MS: *m/z* = 311 (M+H)⁺; Anal. (C₁₇H₁₄N₂O₄) C, H, N.

EXAMPLE B31

Compound 31: N-(4-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

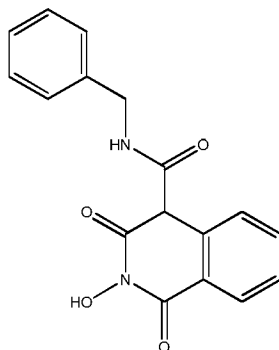


Intermediate 32 was treated with boron trichloride giving **compound 31**. Beige solid (76%); mp 172-180 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 5.29 (s, 1 H, CH), 7.19 (t, 2 H, H_{Ar}, ³*J* = 8.6 Hz), 7.48 (d, 1 H, H_{Ar}, ³*J* = 7.5 Hz), 7.54-7.63 (m, 4 H, H_{Ar}), 7.71 (t, 1 H, H_{Ar}, ³*J* = 7.0 Hz), 8.11 (d, 1 H, H_{Ar}, ³*J* = 7.7 Hz), 10.94 (s, 1 H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 56.3 (CH), 116.0 (d, 2 CH, C_{3''}, C_{5''}, ²*J*_{C-F} = 22.5 Hz), 121.8 (d, 2 CH, C_{2''}, C_{6''}, ³*J*_{C-F} = 9.0 Hz), 125.9 (C_{IV}), 127.1 (CH), 128.5 (CH), 128.9

(CH), 134.4 (CH), 134.7 (C_{IV}), 135.1 (C_{IV}), 158.9 (d, C_{IV}, C_{4'}, $^1J_{C-F} = 239.2$ Hz), 161.9 (CO), 165.0 (CO), 165.3 (CO); ESI-MS: $m/z = 315$ (M+H)⁺; Anal. (C₁₆H₁₁FN₂O₄) C, H, N.

EXAMPLE B32

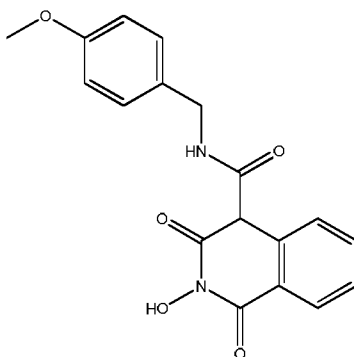
Compound 32: N-Benzyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 33 was hydrogenated on Pd/C 5% giving **compound 32**. Beige solid (69%); mp 152-155 °C; 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): $\delta = 4.32$ (s, 2 H, CH₂), 5.17 (s, 1 H, CH), 7.28-7.33 (m, 5 H, H_{Ar}), 7.42 (m, 1 H, H_{Ar}), 7.55 (m, 1 H, H_{Ar}), 7.70 (m, 1 H, H_{Ar}), 8.07 (d, 1 H, H_{Ar}, $^3J = 7.7$ Hz), 9.31 (s, 1 H, NH), 10.62 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 42.6$ (CH₂), 55.2 (CH), 125.3 (C_{IV}), 126.6 (CH), 127.0 (CH), 127.2 (2 CH), 128.0 (CH), 128.2 (CH), 128.4 (2 CH), 133.7 (CH), 134.4 (C_{IV}), 138.5 (C_{IV}), 161.5 (CO), 164.7 (CO), 166.2 (CO); ESI-MS: $m/z = 311$ (M+H)⁺; Anal. (C₁₇H₁₄N₂O₄) C, H, N.

EXAMPLE B33

Compound 33: N-(4-Methoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

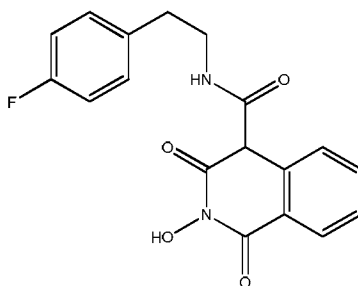


Intermediate 34 was treated with boron trichloride giving **compound 33**. Brown solid (45%); mp > 170 °C (dec); 100% keto form; ^1H NMR (300 MHz, DMSO- d_6): $\delta = 3.74$ (s, 3 H, OCH₃), 4.24 (dd, 1 H, CH₂, $^2J = 14.7$ Hz, $^3J = 5.6$ Hz), 4.29 (dd, 1 H, CH₂, $^2J = 14.7$

Hz, $^3J = 5.6$ Hz), 5.14 (s, 1 H, CH), 6.90 (d, 2 H, H_{Ar}, $^3J = 8.2$ Hz), 7.19 (d, 2 H, H_{Ar}, $^3J = 8.2$ Hz), 7.39 (d, 1 H, H_{Ar}, $^3J = 7.5$ Hz), 7.55 (t, 1 H, H_{Ar}, $^3J = 7.3$ Hz), 7.70 (t, 1 H, H_{Ar}, $^3J = 6.9$ Hz), 8.06 (d, 1 H, H₈, $^3J = 7.6$ Hz), 9.21 (t, 1 H, NH, $^3J = 5.3$ Hz), 10.59 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-*d*₆): $\delta = 42.1$ (CH₂), 55.0 (OCH₃), 55.2 (CH), 113.7 (2 CH), 125.3 (C_{IV}), 126.6 (CH), 127.9 (CH), 128.2 (CH), 128.6 (2 CH), 130.3 (C_{IV}), 133.7 (CH), 134.5 (C_{IV}), 158.4 (CO), 161.5 (CO), 164.7 (CO), 166.0 (CO); ESI-MS: $m/z = 341$ (M+H)⁺; Anal. (C₁₈H₁₆N₂O₅) C, H, N.

EXAMPLE B34

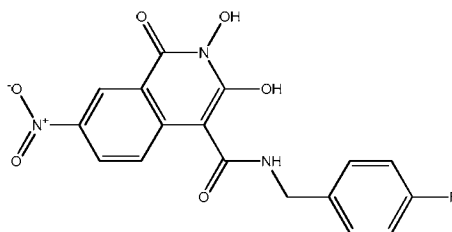
Compound 34: *N*-(4-Fluorophenethyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 35 was hydrogenated on Pd/C 5% giving **compound 34**. Grey solid (60%); mp 100-110 °C; 100% keto form; ^1H NMR (300 MHz, DMSO-*d*₆): $\delta = 2.73$ (t, 2 H, CH₂, $^3J = 5.0$ Hz), 3.37 (m, 2 H, CH₂), 5.03 (s, 1 H, CH), 7.12-7.24 (m, 5 H, H_{Ar}), 7.53 (t, 1 H, H_{Ar}, $^3J = 7.3$ Hz), 7.63 (t, 1 H, H_{Ar}, $^3J = 6.8$ Hz), 8.04 (d, 1 H, H_{Ar}, $^3J = 8.1$ Hz), 8.83 (m, 1 H, NH), 10.58 (s, 1 H, OH); ^{13}C NMR (75 MHz, DMSO-*d*₆): $\delta = 33.8$ (CH₂), 40.7 (CH₂), 55.2 (CH), 114.9 (d, 2 CH, C_{3''}, C_{5''}, $^2J_{\text{C-F}} = 20.9$ Hz), 125.3 (C_{IV}), 126.6 (CH), 127.8 (CH), 128.1 (CH), 130.6 (d, 2 CH, C_{2''}, C_{6''}, $^3J_{\text{C-F}} = 8.2$ Hz), 133.6 (CH), 134.4 (C_{IV}), 135.2 (C_{IV}), 160.9 (d, C_{IV}, C_{4''}, $^1J_{\text{C-F}} = 241.5$ Hz), 161.5 (CO), 164.7 (CO), 166.0 (CO); ESI-MS: $m/z = 343$ (M+H)⁺; Anal. (C₁₈H₁₅FN₂O₄) C, H, N.

EXAMPLE B35

Compound 35: *N*-(4-Fluorobenzyl)-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide

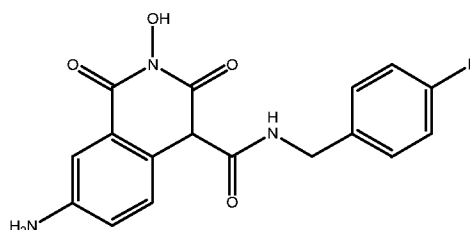


Intermediate 41 (0.46 g, 1.0 mmol) was dissolved in a minimum of CH_2Cl_2 at -78°C and boron trichloride (1.0 M solution in CH_2Cl_2 , 5.0 mL, 5.0 mmol) was added dropwise. The solution was stirred for 1 h at -78°C and the reaction mixture was allowed to reach 0°C .

- 5 Then water (5.0 mL) was added. The first precipitate (impure fraction) was filtered and the filtrate was kept several hours at room temperature. The second precipitate was filtrated and triturated with ether. Orange solid (15%); mp $159\text{--}162^\circ\text{C}$; 100% enol form; ^1H NMR (300 MHz, $\text{DMSO-}d_6$): $\delta = 4.46$ (d, 2 H, NHCH_2 , $^3J = 5.0$ Hz), 7.14 (t, 2 H, H_{Ar} , $^3J_{\text{H-H}} = ^3J_{\text{H-F}} = 8.6$ Hz), 7.36 (dd, 2 H, H_{Ar} , $^3J_{\text{H-H}} = 8.8$ Hz, $^4J_{\text{H-F}} = 5.7$ Hz), 7.98 (dd, 1 H, H_6 , $^3J = 9.6$ Hz, $^4J = 2.6$ Hz), 8.75 (d, 1 H, H_8 , $^4J = 2.3$ Hz), 9.38 (d, 1 H, H_5 , $^3J = 9.7$ Hz), 10.07 (s, 1 H, OH), 10.28 (t, 1 H, NH, $^3J = 5.0$ Hz); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$): $\delta = 41.4$ (NHCH_2), 89.7 (C_4), 115.0 (d, 2 CH, $^2J_{\text{C-F}} = 21.3$ Hz), 116.0 (C_{IV}), 123.7 (CH), 123.8 (CH), 124.2 (CH), 129.2 (d, 2 CH, $^3J_{\text{C-F}} = 8.2$ Hz), 136.7 (C_{IV}), 138.3 (C_{IV}), 143.0 (C_7), 157.5 (CO), 159.5 (CO), 161.1 (d, C_{IV} , $^1J_{\text{C-F}} = 241.0$ Hz), 167.6 (CO); ESI-MS: $m/z = 374$ ($\text{M}+\text{H}$) $^+$; Anal. (C₁₇H₁₂FN₃O₆) C, H, N.

EXAMPLE B36

Compound 36: *N*-(4-Fluorobenzyl)-7-amino-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

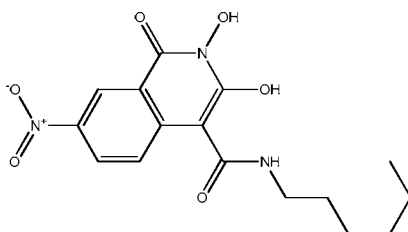


- 20 **Intermediate 41** (0.46 g, 1.0 mmol) was dissolved in a mixture of ethyl acetate (10 mL) and methanol (5 mL) and hydrogenated for 4 h at room temperature over Pd/C 5% (50.0 mg). The catalyst was filtered and the solvent was removed *in vacuo*. Trituration of the residue in ether afforded the deprotected compound as a green solid. Yield: 70%; mp $212\text{--}216^\circ\text{C}$; 100% keto form; ^1H NMR (300 MHz, $\text{DMSO-}d_6$): $\delta = 4.25$ (dd, 1 H, NHCH_2 , $^2J = 15.3$ Hz, $^3J = 5.5$ Hz), 4.32 (dd, 1 H, NHCH_2 , $^2J = 15.3$ Hz, $^3J = 5.5$ Hz), 4.90 (s, 1 H, CH),

5.60 (s, 2 H, NH₂), 6.85 (dd, 1 H, H₆, ³J = 8.2 Hz, ⁴J = 2.0 Hz), 7.02 (d, 1 H, H₅, ³J = 8.2 Hz), 7.17 (t, 2 H, ³J_{H-H} = ³J_{H-F} = 8.6 Hz), 7.25 (d, 1H, H₈, ⁴J = 2.0 Hz), 7.30 (dd, 2 H, ³J_{H-H} = 8.4 Hz, ³J_{H-F} = 5.7 Hz), 9.15 (t, 1H, NH, ³J = 5.1 Hz), 10.46 (s, 1 H, OH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 42.9 (NHCH₂), 55.4 (CH), 112.3 (CH), 116.1 (d, 2 CH, ²J_{C-F} = 21.3 Hz), 120.6 (CH), 121.7 (C_{IV}), 126.7 (C_{IV}), 128.2 (CH), 130.2 (d, 2 CH, ³J_{C-F} = 8.2 Hz), 135.9 (d, 2 CH, ⁴J_{C-F} = 2.7 Hz), 149.7 (C₇), 162.3 (d, C_{IV}, ¹J_{C-F} = 241.0 Hz), 163.0 (CO), 166.2 (CO), 168.0 (CO); ESI-MS: *m/z* = 344 (M+H)⁺; Anal. (C₁₇H₁₄FN₃O₄) C, H, N.

EXAMPLE B37

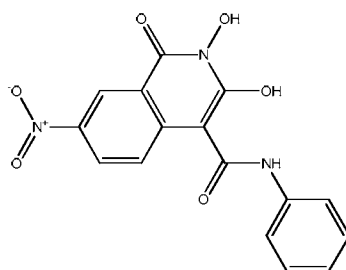
Compound 37: *N*-Hexyl-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 42 was treated with boron trichloride according to example B35. Yellow powder (20%); mp 114-116 °C; 100% enol form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 0.87 (m, 3 H, CH₃), 1.30 (m, 6 H, CH₂), 1.48 (m, 2 H, CH₂), 3.24 (t, 2 H, CH₂, ³J = 5.1 Hz), 7.99 (d, 1 H, H₆, ³J = 9.5 Hz), 8.74 (s, 1 H, H₈), 9.23 (d, 1 H, H₅, ³J = 9.5 Hz); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 14.4 (CH₃), 22.6 (CH₂), 26.8 (CH₂), 29.8 (CH₂), 31.5 (CH₂), 38.8 (CH₂), 90.3 (C₄), 116.4 (C_{IV}), 124.1 (CH_{Ar}), 124.3 (CH_{Ar}), 124.6 (CH_{Ar}), 138.7 (C_{IV}), 143.2 (C_{IV}), 157.9 (CO), 161.0 (CO), 167.9 (CO); MALDI-TOF: *m/z* = 350 (M+H)⁺; Anal. (C₁₆H₁₉N₃O₆) C, H, N.

EXAMPLE B38

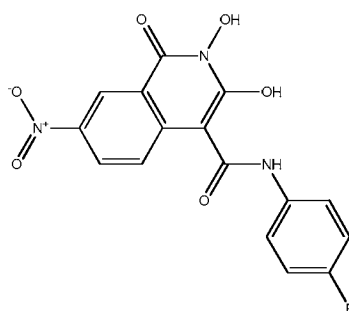
Compound 38: *N*-Phenyl-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 43 was treated with boron trichloride according to example B35. Yellow powder (32%); mp 162-165 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 6.98 (t, 1 H, H_4 , $^3J = 7.4$ Hz), 7.29 (t, 2 H, H_3 and H_5 , $^3J = 7.6$ Hz), 7.65 (d, 2 H, H_2 and H_6 , $^3J = 7.8$ Hz), 8.07 (d, 1 H, H_6 , $^3J = 9.8$ Hz), 8.79 (s, 1 H, H_8), 9.40 (d, 1 H, H_5 , $^3J = 9.8$ Hz), 12.43 (s, 1 H, OH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 90.3 (C_4), 116.9 (C_1), 119.6 (2 CH_{Ar}), 119.6 (CH_{Ar}), 124.2 (2 CH_{Ar}), 125.0 (CH_{Ar}), 129.2 (2 CH_{Ar}), 139.1 (C_{IV}), 140.7 (C_{IV}), 143.6 (C_7), 158.3 (CO), 161.6 (CO), 166.3 (CO); MALDI-TOF: m/z = 342 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_6$) C, H, N.

EXAMPLE B39

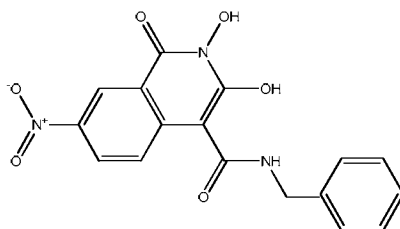
10 Compound 39: *N*-(4-Fluorophenyl)-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 43 was treated with boron trichloride according to example B35. Brown powder (40%); mp 178-180 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 7.13 (t, 2 H, H_3 and H_5 , $^3J_{\text{H-H}} = ^3J_{\text{H-F}} = 8.3$ Hz), 7.66 (dd, 2 H, H_2 and H_6 , $^3J_{\text{H-H}} = 8.3$ Hz and $^4J_{\text{H-F}} = 5.3$ Hz), 8.06 (d, 1 H, H_6 , $^3J = 9.8$ Hz), 8.78 (s, 1 H, H_8), 9.40 (d, 1 H, H_5 , $^3J = 9.8$ Hz), 12.46 (s, 1 H, OH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 90.1 (C_4), 115.7 (d, C_3 and C_5 , $^2J_{\text{C-F}} = 21.8$ Hz), 116.9 (C_{IV}), 121.2 (d, C_2 and C_6 , $^3J_{\text{C-F}} = 6.5$ Hz), 124.2 (2 CH_{Ar}), 125.0 (CH_{Ar}), 137.1 (C_{IV}), 139.0 (C_{IV}), 143.6 (C_7), 156.2 (CO), 159.3 (CO), 160.1 (d, C_4 , $^1J_{\text{C-F}} = 259.0$ Hz), 166.3 (CO); MALDI-TOF: m/z = 360 ($\text{M}+\text{H}$) $^+$; Anal. ($\text{C}_{16}\text{H}_{10}\text{FN}_3\text{O}_6$) C, H, N.

EXAMPLE B40

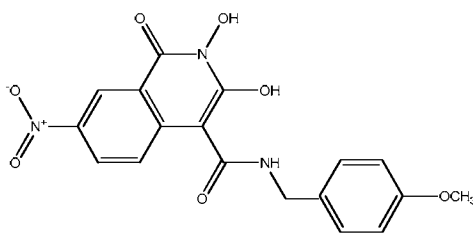
Compound 40: *N*-Benzyl-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 45 was treated with boron trichloride according to example B35. Yellow powder (25%); mp 164-166 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 4.49 (s, 2 H, CH₂), 7.25-7.34 (m, 5 H, H_{Ar}), 8.02 (d, 1H, H₆, 3J = 9.1 Hz), 8.76 (s, 1 H, H₈), 9.24 (d, 1 H, H₅, 3J = 9.1 Hz); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 42.6 (CH₂), 90.2 (C₄), 116.5 (C_{IV}), 124.1 (CH_{Ar}), 124.2 (CH_{Ar}), 124.7 (CH_{Ar}), 127.0 (CH_{Ar}), 127.7 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 138.7 (C_{IV}), 140.9 (C_{IV}), 143.4 (C₇), 158.0 (CO), 161.1 (CO), 167.9 (CO); MALDI-TOF: m/z = 356 (M+H)⁺; Anal. (C₁₇H₁₃N₃O₆) C, H, N.

EXAMPLE B41

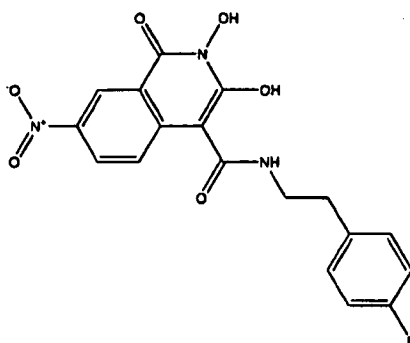
10 Compound 41: *N*-(4-Methoxybenzyl)-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 46 was treated with boron trichloride according to example B35. Orange powder (40%); mp 137 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 3.73 (s, 3 H, OCH₃), 4.40 (s, 2 H, CH₂), 6.89 (d, 2 H, H_{Ar}, 3J = 8.1 Hz), 7.26 (d, 2 H, H_{Ar}, 3J = 8.1 Hz), 8.00 (d, 1 H, H₆, 3J = 9.2 Hz), 8.75 (s, 1 H, H₈), 9.28 (d, 1 H, H₅, 3J = 9.2 Hz), NMR ^{13}C (75 MHz, DMSO- d_6): δ = 42.1 (CH₂), 55.5 (OCH₃), 90.2 (C₄), 114.2 (C_{3'} and C_{5'}), 116.6 (C_{IV}), 124.1 (CH_{Ar}), 124.2 (CH_{Ar}), 124.7 (CH_{Ar}), 129.1 (C_{2'} and C_{6'}), 132.6 (C_{IV}), 138.8 (C_{IV}), 143.2 (C_{IV}), 158.0 (CO), 158.5 (CO), 160.9 (CO), 167.8 (CO); MALDI-TOF: m/z = 386 (M+H)⁺; Anal. (C₁₈H₁₅N₃O₇) C, H, N.

EXAMPLE B42

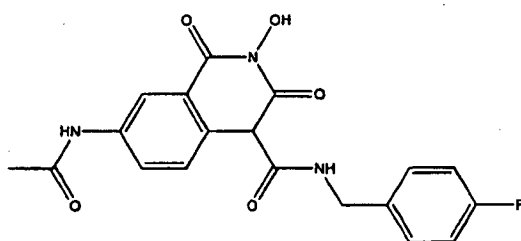
Compound 42: *N*-(4-Fluorophenethyl)-2,3-dihydroxy-7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide



Intermediate 47 was treated with boron trichloride according to example B35. Yellow powder (18%); mp 153 °C; 100% enol form; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.79 (t, 2 H, CH₂, 3J = 7.3 Hz), 3.48 (t, 2 H, CH₂, 3J = 7.3 Hz), 7.11 (t, 2 H, H₃ and H₅, $^3J_{\text{H-H}} = ^3J_{\text{H-F}} = 7.5$ Hz), 7.30 (dd, 2 H, H₂ and H₆, $^3J_{\text{H-H}} = 7.3$ Hz and $^4J_{\text{H-F}} = 6.0$ Hz), 7.97 (d, 1 H, H₆, 3J = 9.8 Hz), 8.73 (s, 1 H, H₈), 9.35 (d, 1 H, H₅, 3J = 9.8 Hz); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 34.9 (CH₂), 40.7 (CH₂), 89.9 (C₄), 115.2 (d, C₃ and C₅, $^2J_{\text{C-F}} = 20.7$ Hz), 116.3 (C_{IV}), 124.0 (CH_{Ar}), 124.6 (CH_{Ar}), 128.2 (CH_{Ar}), 130.4 (d, C₂ and C₆, $^3J_{\text{C-F}} = 7.6$ Hz), 136.2 (C_{IV}), 136.5 (C_{IV}), 142.8 (C₇), 157.9 (CO), 160.4 (CO), 160.9 (d, C₄, $^1J_{\text{C-F}} = 242.7$ Hz), 167.7 (CO); MALDI-TOF: m/z = 388 (M+H)⁺; Anal. (C₁₈H₁₄FN₃O₆) C, H, N.

EXAMPLE B43

Compound 43: *N*-(4-Fluorobenzyl)-7-acetamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



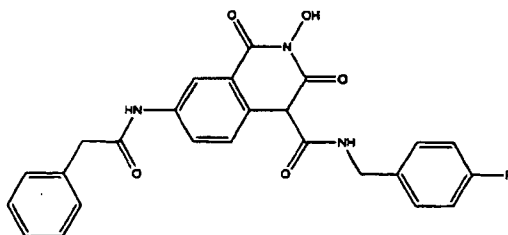
Intermediate 52 (1.0 mmol) was dissolved in a minimum of CH₂Cl₂ and boron trichloride (1.0 M solution in CH₂Cl₂, 6.0 mL, 6.0 mmol) was added dropwise at -78 °C. The solution was stirred for 1 h at -78 °C and water (20 mL) was slowly added. After 15 min stirring, the precipitate was filtered and triturated with ether. Beige solid (43%); 100% keto form; mp 227-230 °C; ^1H NMR (300 MHz, DMSO- d_6): δ = 2.08 (s, 3 H, CH₃), 4.29 (dd, 1 H, CH₂, 2J = 15.5 Hz and 3J = 5.6 Hz), 4.30 (dd, 1 H, CH₂, 2J = 15.5 Hz and 3J = 5.6 Hz), 5.08 (s, 1 H, H₄), 7.17 (t, 2 H, H₃ and H₅, $^3J_{\text{H-H}} = ^3J_{\text{H-F}} = 8.9$ Hz), 7.28-7.32 (m, 3 H, H₅, H₂ and H₆), 7.84 (dd, 1 H, H₆, 3J = 8.5 Hz and 4J = 2.2 Hz), 8.32 (d, 1 H, H₈, 4J = 2.2 Hz), 9.27 (t, 1 H, NH, 3J = 5.6 Hz), 10.27 (s, 1 H, NH); NMR ^{13}C (75 MHz, DMSO- d_6): δ = 24.5 (CH₃),

42.4 (CH₂), 55.2 (C₄), 115.6 (d, C_{3'} and C_{5'}, ²J_{C-F} = 21.3 Hz), 117.9 (CH_{Ar}), 124.7 (CH_{Ar}), 126.2 (C_{IV}), 127.6 (CH_{Ar}), 129.1 (C_{IV}), 129.7 (d, C_{2'} and C_{6'}, ³J_{C-F} = 8.7 Hz), 135.2 (d, C_{1'}, ⁴J_{C-F} = 2.2 Hz), 139.7 (C₇), 161.7 (C_{4'}, ¹J_{C-F} = 241.6 Hz), 161.9 (CO), 165.2 (CO), 166.8 (CO), 169.3 (CO); MALDI-TOF: m/z = 386 (M+H)⁺; Anal. (C₁₉H₁₆FN₃O₅) C, H, N.

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EXAMPLE B44

Compound 44: N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-phenylacetamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

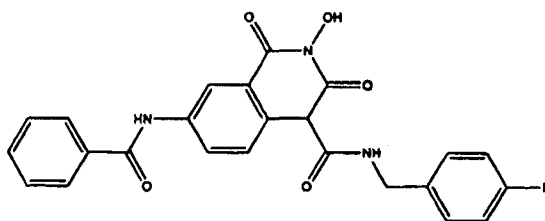


Intermediate 56 (0.10 g) was dissolved in a mixture of *N,N*-dimethylformamide (10 mL) and methanol (10 mL) and hydrogenated for 3 h at room temperature over Pd/C 5% (10 mg). The catalyst was filtered and the solvent was removed *in vacuo*. Trituration of the residue in ether afforded the deprotected **compound 44** as a grey solid (83%); mp 203-204 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.67 (s, 2 H, CH₂), 4.29 (d, 2 H, CH₂, ³J = 5.8 Hz), 5.08 (s, 1 H, H₄), 7.17 (t, 2 H, H_{3''} and H_{5''}, ³J_{H-H} = ³J_{H-F} = 8.8 Hz), 7.25-7.35 (m, 8 H, H_{Ar}, H₅, H_{2''} and H_{6''}), 7.87 (dd, 1 H, H₆, ³J = 8.4 Hz and ⁴J = 2.2 Hz), 8.33 (d, 1 H, H₈, ⁴J = 2.2 Hz), 9.25 (t, 1 H, NH, ³J = 5.8 Hz), 10.51 (s, 1 H, NH), 10.61 (s, 1 H, NOH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.4 (CH₂), 43.7 (CH₂), 55.2 (C₄), 115.6 (d, C_{3''} and C_{5''}, ²J_{C-F} = 20.7 Hz), 118.1 (CH_{Ar}), 124.8 (CH_{Ar}), 126.2 (C_{IV}), 127.1 (CH_{Ar}), 127.7 (CH_{Ar}), 128.8 (2 CH_{Ar}), 129.3 (C_{IV}), 129.6 (2 CH_{Ar}), 129.7 (d, C_{2''} and C_{6''}, ³J_{C-F} = 8.2 Hz), 135.2 (d, C_{1''}, ⁴J_{C-F} = 2.7 Hz), 136.1 (C_{IV}), 139.6 (C_{IV}), 161.7 (d, C_{4''}, ¹J_{C-F} = 241.1 Hz), 161.8 (CO), 165.2 (CO), 166.8 (CO), 170.0 (CO); MALDI-TOF: m/z = 462 (M+H)⁺; Anal. (C₂₅H₂₀FN₃O₅) C, H, N.

EXAMPLE B45

Compound 45: N-(4-Fluorobenzyl)-7-benzamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide

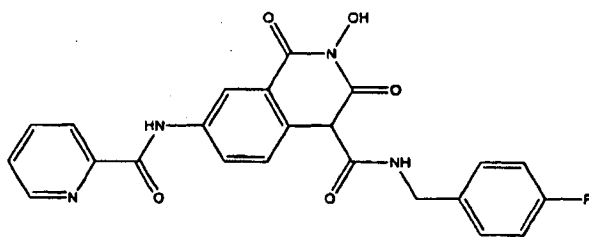
25



Intermediate 60 was hydrogenated over Pd/C 5% according to example B44. Grey powder (89%); mp 196-198 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.32 (d, 1 H, CH₂, ²*J*=15.2 Hz and ³*J*= 5.7 Hz), 4.33 (d, 1 H, CH₂, ²*J*=15.2 Hz and ³*J*= 5.7 Hz), 5.12 (s, 1 H, H₄), 7.18 (t, 2 H, H_{3''} and H_{5''}, ³*J*_{H-H}= ³*J*_{H-F}= 8.9 Hz), 7.32 (dd, 2 H, H_{2''} and H_{6''}, ³*J*_{H-H}= 8.9 Hz and ⁴*J*_{H-F}= 5.6 Hz), 7.37 (d, 1 H, H₅, ³*J*= 8.5 Hz), 7.56-7.62 (m, 3 H, H_{Ar}), 7.99-8.01 (m, 2 H, H_{Ar}), 8.11 (dd, 1H, H₆, ³*J*= 8.5 Hz and ⁴*J*= 2.2 Hz), 8.53 (d, 1 H, H₈, ⁴*J*= 2.2 Hz), 9.29 (t, 1 H, NH, ³*J*= 5.7 Hz), 10.56 (s, 1 H, NH), 10.63 (s, 1 H, NOH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.4 (CH₂), 55.3 (C₄), 115.6 (d, C_{3''} and C_{5''}, ²*J*_{C-F}= 21.3 Hz), 119.4 (CH_{Ar}), 126.0 (CH_{Ar}), 126.2 (C_{IV}), 127.5 (CH_{Ar}), 128.2 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 129.7 (d, C_{2''} and C_{6''}, ³*J*_{C-F}= 8.2 Hz), 132.4 (CH_{Ar}), 134.1 (C_{IV}), 134.8 (C_{IV}), 135.2 (C_{IV}), 139.6 (C₇), 161.8 (C_{4''}, ¹*J*_{C-F}= 241.0 Hz), 161.9 (CO), 165.3 (CO), 166.2 (CO), 166.8 (CO); MALDI-TOF: *m/z* = 448 (M+H)⁺; Anal. (C₂₄H₁₈FN₃O₅) C, H, N.

EXAMPLE B46

Compound 46: *N*-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-picolinamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 64 was treated with boron trichloride according to example B43. Yellow powder (33%); mp 211-212 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ =

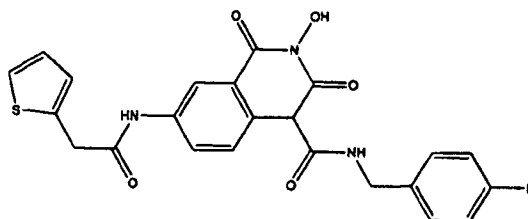
4.31 (dd, 1 H, CH₂, ²*J*= 15.6 Hz and ³*J*= 5.6 Hz), 4.32 (dd, 1 H, CH₂, ²*J*= 15.6 Hz and ³*J*= 5.6 Hz), 5.14 (s, 1 H, C₄), 7.18 (t, 2 H, C_{3''} and C_{5''}, ³*J*_{H-H}= ³*J*_{H-F}= 8.6 Hz), 7.31 (dd, 2 H, H_{2''} and H_{6''}, ³*J*_{H-H}= 8.6 Hz and ⁴*J*_{H-F}= 5.7 Hz), 7.38 (d, 1 H, ³*J*= 8.3 Hz, H_{Ar}), 7.69-7.73 (m, 1 H, H_{Ar}), 8.07-8.20 (m, 3 H, H_{Ar}), 8.74-8.78 (m, 2 H, H_{Ar}), 9.32 (t, 1 H, NH, ³*J*= 5.6 Hz), 11.02 (s, 1 H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.4 (CH₂), 55.3 (C₄), 115.6 (d, C_{3''} and C_{5''}, ²*J*_{C-F}= 21.3 Hz), 119.6 (CH_{Ar}), 123.1 (CH_{Ar}), 126.2 (C_{IV}), 126.4 (CH_{Ar}),

127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 129.7 (d, C_{2''} and C_{6''}, ³J_{C-F} = 85 Hz), 130.1 (C_{IV}), 135.3 (d, C_{1''}, ⁴J_{C-F} = 3.3 Hz), 138.7 (CH_{Ar}), 138.8 (C₇), 149.0 (CH_{Ar}), 150.0 (C_I), 161.7 (d, C_{4''}, ¹J_{C-F} = 241.0 Hz), 161.9 (CO), 163.4 (CO), 165.2 (CO), 166.8 (CO); MALDI-TOF: m/z = 449 (M+H)⁺; Anal. (C₂₃H₁₇FN₄O₅) C, H, N.

5

EXAMPLE B47

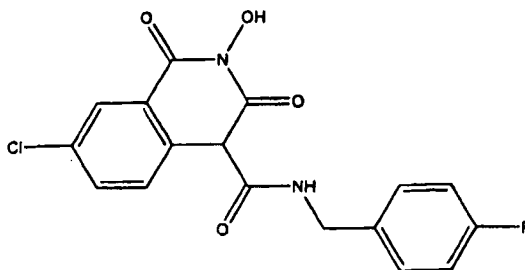
Compound 47: *N*-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-(2-(thiophen-2-yl)acetamido)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 68 was treated with boron trichloride according to example B43. Green powder (61%); mp 183-186 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.91 (s, 2 H, CH₂), 4.30 (dd, 1 H, CH₂, ²J = 15.6 Hz and ³J = 5.7 Hz), 4.31 (dd, 1 H, CH₂, ²J = 15.6 Hz and ³J = 5.7 Hz), 5.09 (s, 1 H, C₄), 6.99-7.00 (m, 2 H, H_{Ar}), 7.17 (t, 2 H, H_{3''} and H_{5''}, ³J_{H-H} = ³J_{H-F} = 8.8 Hz), 7.31 (dd, 2 H, H_{2''} and H_{6''}, ³J_{H-H} = 8.6 Hz and ⁴J_{H-F} = 5.1 Hz), 7.41-7.42 (m, 2 H, H_{Ar}), 7.86 (d, 1 H, H_{Ar}, ³J = 8.6 Hz), 8.34 (s, 1 H, H₈), 9.27 (t, 1 H, NH, ³J = 5.7 Hz), 10.56 (s, 1 H, NH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 38.0 (CH₂), 42.4 (CH₂), 55.2 (C₄), 115.5 (d, C_{3''} and C_{5''}, ²J_{C-F} = 21.3 Hz), 118.1 (CH_{Ar}), 124.9 (CH_{Ar}), 125.7 (CH_{Ar}), 126.2 (C_{IV}), 127.0 (CH_{Ar}), 127.2 (CH_{Ar}), 128.9 (CH_{Ar}), 129.5 (C_{IV}), 129.7 (d, C_{2''} and C_{6''}, ³J_{C-F} = 8.2 Hz), 135.2 (d, C_{1''}, ⁴J_{C-F} = 2.7 Hz), 137.2 (C_{IV}), 139.4 (C_{IV}), 1613.7 (d, C_{4''}, ¹J_{C-F} = 240.5 Hz), 161.8 (CO), 165.2 (CO), 166.8 (CO), 168.9 (CO); MALDI-TOF: m/z = 468 (M+H)⁺; Anal. (C₂₃H₁₈FN₃O₅S) C, H, N.

EXAMPLE B48

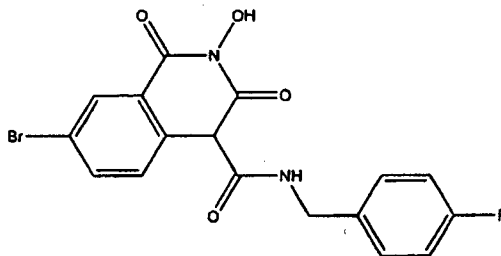
Compound 48: *N*-(4-Fluorobenzyl)-7-chloro-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 72 was treated with boron trichloride according to example B43. Beige powder (69%); mp 168-169 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.28 (dd, 1 H, CH₂, ²*J* = 15.5 Hz and ³*J* = 6.2 Hz), 4.29 (dd, 1 H, CH₂, ²*J* = 15.5 Hz and ³*J* = 6.2 Hz), 5.16 (s, 1 H, H₄), 7.18 (t, 2 H, H₃ and H₅, ³*J*_{H-H} = ³*J*_{H-F} = 9.0 Hz), 7.30 (dd, 2 H, H₂ and H₆, ³*J*_{H-H} = 9.0 Hz and ³*J*_{H-F} = 5.6 Hz), 7.41 (d, 1 H, H_{Ar}, ³*J* = 8.2 Hz), 7.79 (d, 1 H, H_{Ar}, ³*J* = 8.2 Hz), 8.02 (s, 1H, H₈), 9.34 (t, 1 H, NH, ³*J* = 6.2 Hz); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.5 (CH₂), 55.3 (C₄), 115.6 (d, C₃ and C₅, ²*J*_{C-F} = 21.3 Hz), 127.5 (CH_{Ar}), 127.7 (C_{IV}), 129.2 (CH_{Ar}), 129.7 (d, C₂ and C₆, ³*J*_{C-F} = 8.2 Hz), 133.5 (C_{IV}), 133.8 (C_{IV}), 134.1 (CH_{Ar}), 135.1 (C_{IV}), 161.0 (CO), 161.8 (d, C₄, ¹*J*_{C-F} = 240.6 Hz), 164.9 (CO), 166.4 (CO); MALDI-TOF: *m/z* = 363 and 365 (M+H)⁺; Anal. (C₁₇H₁₂ClFN₂O₄) C, H, N.

EXAMPLE B49

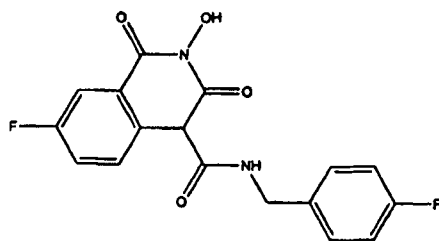
Compound 49: *N*-(4-Fluorobenzyl)-7-bromo-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 76 was treated with boron trichloride according to example B43. Pink powder (45%); mp 170-171 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.28 (dd, 1 H, CH₂, ²*J*_{H-H} = 15.3 Hz and ³*J*_{H-F} = 5.1 Hz), 4.29 (dd, 1 H, CH₂, ²*J*_{H-H} = 15.3 Hz and ³*J*_{H-F} = 5.1 Hz), 5.14 (s, 1 H, H₄), 7.18 (t, 2 H, H₃ and H₅, ³*J*_{H-H} = ³*J*_{H-F} = 8.6 Hz), 7.28-7.36 (m, 3 H, H_{Ar}), 8.06 (d, 1 H, H_{Ar}, ³*J* = 8.2 Hz), 8.14 (s, 1 H, H₈), 9.33 (t, 1 H, NH, ³*J* = 5.1 Hz); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.5 (CH₂), 55.4 (C₄), 115.6 (d, C₃ and C₅, ²*J*_{C-F} = 21.3 Hz), 121.6 (C₇), 127.9 (C_{IV}), 129.4 (CH_{Ar}), 129.7 (d, C₂ and C₆, ³*J*_{C-F} = 8.2 Hz), 130.5 (CH_{Ar}), 134.2 (C_{IV}), 135.1 (d, C₁, ⁴*J*_{C-F} = 2.2 Hz), 136.9 (CH_{Ar}), 160.9 (CO), 161.8 (d, C₄, ¹*J*_{C-F} = 240.6 Hz), 164.9 (CO), 166.3 (CO); MALDI-TOF: *m/z* = 407 and 409(M+H)⁺; Anal. (C₁₇H₁₂BrFN₂O₄) C, H, N.

EXAMPLE B50

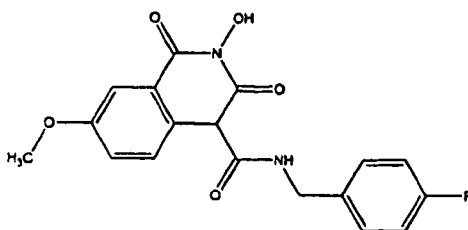
Compound 50: *N*-(4-Fluorobenzyl)-7-fluoro-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 80 was treated with boron trichloride according to example B43. Pink powder (55%); mp 179-180 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 4.30 (dd, 1 H, CH₂, ²*J* = 15.6 Hz and ³*J* = 5.3 Hz), 4.31 (dd, 1 H, CH₂, ²*J* = 15.6 Hz and ³*J* = 5.3 Hz), 5.15 (s, 1 H, H₄), 7.17 (t, 2 H, H₃' and H₅', ³*J*_{H-H} = ³*J*_{H-F} = 8.6 Hz), 7.30 (dd, 2 H, H₂' and H₆', ³*J*_{H-H} = 8.6 Hz and ⁴*J*_{H-F} = 5.7 Hz), 7.44 (dd, 1 H, H₅', ³*J*_{H-H} = 8.0 Hz and ⁴*J*_{H-F} = 5.1 Hz), 7.60 (td, 1H, H₆', ³*J*_{H-H} = ³*J*_{H-F} = 8.0 Hz and ⁴*J*_{H-H} = 1.9 Hz), 7.79 (dd, 1 H, H₈', ³*J*_{H-F} = 9.1 Hz and ⁴*J*_{H-H} = 1.9 Hz), 9.33 (t, 1 H, NH, ³*J* = 5.3 Hz); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 42.4 (CH₂), 55.2 (C₄), 114.3 (d, CH_{Ar}, ²*J*_{C-F} = 23.5 Hz), 115.6 (d, C₃' and C₅', ²*J*_{C-F} = 21.3 Hz), 121.7 (d, CH_{Ar}, ²*J*_{C-F} = 22.4 Hz), 127.9 (d, C_{8a}', ³*J*_{C-F} = 8.2 Hz), 129.6 (d, 1H, C₅', ³*J*_{C-F} = 8.2 Hz), 129.7 (d, C₂' and C₆', ³*J*_{C-F} = 8.2 Hz), 131.2 (d, C_{4a}', ⁴*J*_{C-F} = 3.3 Hz), 135.1 (d, C₁', ⁴*J*_{C-F} = 3.3 Hz), 161.1 (d, C₁', ⁴*J*_{C-F} = 2.2 Hz), 161.7 (d, C₇', ¹*J*_{C-F} = 241.1 Hz), 162.0 (C₄', ¹*J*_{C-F} = 244.4 Hz), 165.0 (CO), 166.5 (CO); MALDI-TOF: *m/z* = 347 (M+H)⁺; Anal. (C₁₇H₁₂F₂N₂O₄) C, H, N.

EXAMPLE B51

Compound 51: *N*-(4-Fluorobenzyl)-2-hydroxy-7-methoxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide



Intermediate 87 was hydrogenated over Pd/C 5% according to example B44. White powder (86%); mp 174-177 °C; 100% keto form; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.85 (s, 3 H, OCH₃), 4.29 (dd, 1 H, CH₂, ²*J* = 14.6 Hz, ³*J* = 5.0 Hz), 4.30 (dd, 1 H, CH₂, ²*J* = 14.6 Hz, ³*J* = 5.0 Hz), 5.06 (s, 1 H, H₄), 7.17 (t, 2 H, H₃' and H₅', ³*J*_{H-H} = ³*J*_{H-F} = 8.9 Hz), 7.26-7.32 (m, 4 H, H_{Ar}), 7.52 (d, 1 H, H₈', ⁴*J* = 2.3 Hz), 9.25 (t, 1 H, NH, ³*J* = 5.1 Hz), 10.61 (s, 1 H, NOH); NMR ¹³C (75 MHz, DMSO-*d*₆): δ = 41.9 (CH₂), 54.5 (C₄), 55.5 (OCH₃), 110.9 (CH_{Ar}), 115.1 (d, C₃' and C₅', ²*J*_{C-F} = 21.3 Hz), 121.0 (CH_{Ar}), 126.4 (C_{IV}), 126.5

(C_{IV}), 128.0 (CH_{Ar}), 129.1 (d, C₂ and C₆, ³J_{C-F} = 8.2 Hz), 134.7 (d, C₁, ⁴J_{C-F} = 2.7 Hz), 158.9 (CO), 161.2 (d, C₄, ¹J_{C-F} = 240.6 Hz), 161.4 (CO), 164.8 (CO), 166.4 (CO); MALDI-TOF: m/z = 359 (M+H)⁺; Anal. (C₁₈H₁₅FN₂O₅) C, H, N.

5 C BIOLOGICAL EXAMPLES

EXAMPLE C1: Integrase assays.

The enzymatic integration reactions were carried out with minor modifications as described previously (Christ et al., Debyser et al.). To determine the susceptibility of the HIV-1 IN enzyme to different compounds, we used an enzyme-linked immunosorbent assay (ELISA) (adapted from Hwang et al.). The overall integration assay uses an oligonucleotide substrate for which one oligonucleotide (5'-ACTGCTAGAGATTTTCCACACTGACTAAAAGGGTC-3' (SEQ ID NO 1)) is labeled with biotin at the 3' end and the other oligonucleotide (5'-GACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGT-3' (SEQ ID NO 2)) is labeled with digoxigenin at the 5' end. For the strand transfer assay, a precleaved oligonucleotide substrate (the second oligonucleotide lacks GT [underlined] at the 3' end) was used. The IN enzyme was diluted in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol, and 1 mM β-mercaptoethanol. To perform the reaction, 4 μl of diluted IN (corresponding to a concentration of 1.6 μM) and 4 μl of annealed oligonucleotides (7 nM) were added in a final reaction volume of 40 μl containing 10 mM MgCl₂, 5 mM dithiothreitol, 20 mM HEPES (pH 7.5), 5% polyethylene glycol, and 15% dimethyl sulfoxide. As such, the final concentration of IN in this assay was 160 nM. The reaction was carried out for 1 h at 37°C. Reaction products were denatured with 30 mM NaOH and detected by ELISA on avidin-coated plates. For determining the effect of compounds on the 3' processing activity a classical cleavage assay with detection of products by denaturing gel electrophoresis was performed as described previously (Christ et al. Debyser et al.). Briefly, 0.2 pmol of the radioactive labeled oligonucleotide substrate (INT1, ³²P-5' TGTGGAAAATCTCTAGCAGT 3' (SEQ ID NO 3); INT2, 5'ACTGCTAGAGATTTTCCACA 3' (SEQ ID NO 4)) and 10 nmol IN in a final volume of 10 μl was incubated for 1 h at 37°C. The final reaction mixture contained 20 mM HEPES pH 7.5), 5 mM dithiothreitol (DTT), 10 mM MgCl₂, 0.5% (v/v) polyethylene glycol 8000, 15% DMSO,. IN was diluted previously in 750 mM NaCl, 10 mM Tris (pH

7.6), 10% glycerol and 1 mM β -mercaptoethanol. The reactions were stopped by the addition of formamide loading buffer (95% formamide, 0.1% xylene cyanol, 0.1% xylene cyanol, 0.1% bromophenol blue and 0.1% sodium dodecyl sulfate). Samples were loaded on a 15% denaturing polyacrylamide/ureum gel. The extent of 3'-processing or DNA strand transfer was based on measuring the respective amounts of -2 bands or strand transfer products relative to the intensity of the total radioactivity present in the lane. These data were determined using the OptiQuant Acquisition and Analysis software (Perkin Elmer Corporate, Fremont, CA). The results are shown in table 1.

EXAMPLE C2: Drug susceptibility assay.

The inhibitory effect of antiviral drugs on the HIV-induced cytopathic effect (CPE) in MT-4 cell culture was determined by the MTT-assay (Pauwels et al.). This assay is based on the reduction of the yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase of metabolically active cells to a blue formazan derivative, which can be measured spectrophotometrically. The 50% cell culture infective dose of the HIV strains was determined by titration of the virus stock using MT-4 cells. For the drug susceptibility assays, MT-4 cells were infected with 100 to 300 50% cell culture infective doses of the HIV strains in the presence of fivefold serial dilutions of the antiviral drugs. The concentration of the compound achieving 50% protection against the CPE of HIV, which is defined as the 50% effective concentration (IC_{50}), was determined. The concentration of the compound destroying 50% of the MT-4 cells, which is defined as the 50% cytotoxic concentration (CC_{50}), was determined as well. The results are shown in table 1.

References

- Hwang, Y., D. Rhodes, and F. Bushman. 2000. Rapid microtiter assays for poxvirus topoisomerase, mammalian type IB topoisomerase and HIV-1 integrase: application to inhibitor isolation. *Nucleic Acids Res.* 28:4884-4892.
- Pauwels, R., J. Balzarini, M. Baba, R. Snoeck, D. Schols, P. Herdewijn, J. Desmyter, and E. De Clercq. 1988. Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. *J Virol Methods* 20:309-21.

Debyser, Z., et al., Assays for the evaluation of HIV-1 integrase inhibitors., in Methods in Molecular Biology., C.H. Schein, Editor. 2001, Humana Press Inc.: Totowa, NJ. p. 139-155.

- 5 Christ, F., Busschots, K., Hendrix, J., Engelborghs, Y., Debyser, Z., Assays for the evaluation of HIV-1 integrase enzymatic activity, DNA-binding and co-factor interaction. In Integrase Ed. N. Neamati To be published 2009.

TABLE 1

Compound number	Integrase enzymatic activity			Activity in MT-4 cells	
	Overall enzymatic activity IC ₅₀ in μ M	Strand transfer enzymatic activity IC ₅₀ in μ M	3' processing activity IC ₅₀ in μ M	HIV-1 EC ₅₀ in μ M	Cytotoxicity CC ₅₀ in μ M
1	0.035 $\pm$ 0.007	0.187 $\pm$ 0.007	-	>0.51	0.51
2	1.82 $\pm$ 1.14	1.99 $\pm$ 1.28	-	27.98 $\pm$ 5.12	131 $\pm$ 13
3	0.66 $\pm$ 0.03	0.48 $\pm$ 0.01	-	9.18 $\pm$ 0.95	128 $\pm$ 8
4	0.65 $\pm$ 0.02	0.53 $\pm$ 0.01	-	10.72 $\pm$ 2.96	130 $\pm$ 3
5	0.003 $\pm$ 0	0.195 $\pm$ 0.019	0.51 $\pm$ 0.17	2.72 $\pm$ 0.42	57.7 $\pm$ 2.1
6	6.65 $\pm$ 0.58	6.67 $\pm$ 0	-	29.03 $\pm$ 0	88.5 $\pm$ 2.5
7	4.43 $\pm$ 0.74	5.05 $\pm$ 0.71	-	30.18 $\pm$ 2.1	162.5 $\pm$ 31.5
8	4.45 $\pm$ 0.79	4.46 $\pm$ 0.26	-	>142	142
9	2.29 $\pm$ 1.16	2.86 $\pm$ 0.99	-	27.56 $\pm$ 0.38	128.5 $\pm$ 1
10	54.00 $\pm$ 20.00	50.00 $\pm$ 9.00	-	>129	129
11	0.623 $\pm$ 0.04	0.901 $\pm$ 0.21	-	51.85 $\pm$ 6.87	>125
12	0.01 $\pm$ 0.00	0.11 $\pm$ 0.017	-	2.47 $\pm$ 1.06	64.03 $\pm$ 3.8
13	0.02 $\pm$ 0.00	0.277 $\pm$ 0.126	1.58 $\pm$ 0.15	3.34 $\pm$ 1.55	12.3 $\pm$ 0.4
14	0.056 $\pm$ 0.021	0.099 $\pm$ 0.041	0.066 $\pm$ 0.016	2.34 $\pm$ 0.24	>125
15	2.51 $\pm$ 0.02	2.55 $\pm$ 0.07	-	2.54 $\pm$ 0.079	127
16	0.035 $\pm$ 0.021	0.254 $\pm$ 0.115	-	9.24 $\pm$ 0.68	60.4 $\pm$ 5.13
17	0.035 $\pm$ 0.007	0.572 $\pm$ 0.339	2.35 $\pm$ 0.25	7.94 $\pm$ 4.84	>128

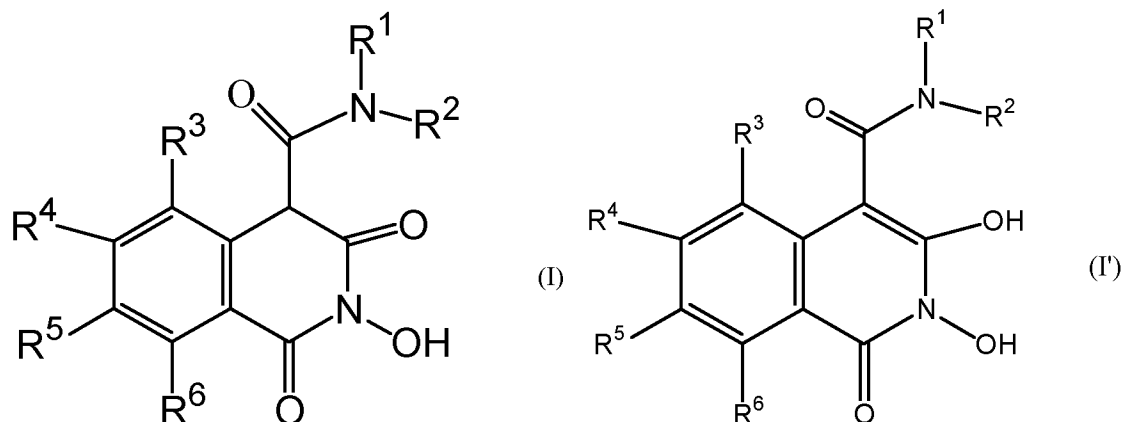
Compound number	Integrase enzymatic activity			Activity in MT-4 cells	
	Overall enzymatic activity IC ₅₀ in μ M	Strand transfer enzymatic activity IC ₅₀ in μ M	3' processing activity IC ₅₀ in μ M	HIV-1 EC ₅₀ in μ M	Cytotoxicity CC ₅₀ in μ M
18	0.235±0.007	0.307±0.072	-	>125	125
19	0.205±0.035	0.258±0.184	-	>11	11
20	4.5±0.02	3.49±2.57	-	>175	175
21	0.495±0.078	0.126±0.008	-	70.77±9.34	>125
22	0.673±0.538	0.296±0.196	-	>63	63
23	8.12±1.61	9.1±1.85	-	>120	120
24	123±58	206±17	-	>28	28
25	8.66±1.27	8.7±0.49	-	>63.76	63.76
26	0.86±0.03	1.05±0.13	-	32.53±13.91	109.5±1.5
27	9.05±0.28	9.13	-	27.96	98.5±6.5
28	17.46±0.66	20.73±5.08	-	>18.55	18.55
29	0.31±0.13	0.73±0.33	-	4.95	105.5±5.5
30	5.21±0.51	5.6±0.19	-	>107.2	107.2
31	0.8±0.3	1.12±0.78	-	1.75	114.5±2.5
32	0.08±0.01	0.03±0.01	-	3.12	130±10
33	1.19±0.47	1.03±0.4	-	17.63	118.5±8.5
34	0.16±0.13	0.37±0.18	-	9.39±4.75	134±22
35	0.0106±0.0013	0.0145±0.0000 2	-	0.103±0.027	121.5±3.5
36	0.3±0.014	0.382±0.282	-	23.29±3.58	217
37 VS47	0.9±0.12	1.64±0.01		4.21±0.69	>250
38 VS52	0.02±0.01	0.03±0.01		0.17	115.5±18.5

Compound number	Integrase enzymatic activity			Activity in MT-4 cells	
	Overall enzymatic activity IC ₅₀ in μ M	Strand transfer enzymatic activity IC ₅₀ in μ M	3' processing activity IC ₅₀ in μ M	HIV-1 EC ₅₀ in μ M	Cytotoxicity CC ₅₀ in μ M
39 VS49	0.03 $\pm$ 0	0.01 $\pm$ 0		0.19	186.5 $\pm$ 7.5
40 VS53	0.01 $\pm$ 0	0.003 $\pm$ 0		0.21	118.5 $\pm$ 8.5
41 VS51	0.04 $\pm$ 0.01	0.01 $\pm$ 0		2.97	>250
42 VS50	0.06 $\pm$ 0.01	0.03 $\pm$ 0		0.95	>250
43 VS41	0.1 $\pm$ 0.02	0.06 $\pm$ 0		29.28 $\pm$ 4.46	149 $\pm$ 149
44 VS43	0.43 $\pm$ 0.28	0.27 $\pm$ 0.18		>31.86	31
45 VS42	0.31 $\pm$ 0.15	0.21 $\pm$ 0.04		>21.06	21
46 VS44	0.16 $\pm$ 0	0.77 $\pm$ 0.01		>1.17	1
47 VS46	0.26 $\pm$ 0.16	0.27 $\pm$ 0.0		>41.09	41
48 VS55	0.51 $\pm$ 0.18	0.26 $\pm$ 0.01		1.19	105.5 $\pm$ 4.5
49 VS54	0.43 $\pm$ 0.06	0.21 $\pm$ 0.05		2.99	99.5 $\pm$ 7.5
50 VS56	0.73 $\pm$ 0.03	0.5 $\pm$ 0.01		0.72	116.5 $\pm$ 2.5

Compound number	Integrase enzymatic activity			Activity in MT-4 cells	
	Overall enzymatic activity IC ₅₀ in μ M	Strand transfer enzymatic activity IC ₅₀ in μ M	3' processing activity IC ₅₀ in μ M	HIV-1 EC ₅₀ in μ M	Cytotoxicity CC ₅₀ in μ M
51 VS45	0.35±0.03	0.62±0.02		6.5±1.45	21±0

CLAIMS

1. A compound of formula (I),



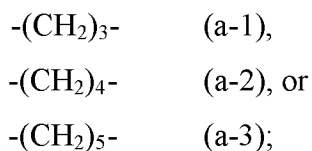
5 or a tautomer (I') thereof, or a pharmaceutically acceptable salt or solvate or prodrug of said compound or tautomer thereof,

wherein

R¹ and R² are each independently selected from:

- 10 hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹; C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;
- 15 C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;
- Ar¹;
- Het¹; or

20 R¹ and R² together form a bivalent radical of formula



25 R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;
 C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,
 -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;
 C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio;
 5 C₃₋₆cycloalkyl;
 -NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;
 -NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted
 10 with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or
 Het³; or C(=O)R¹²;

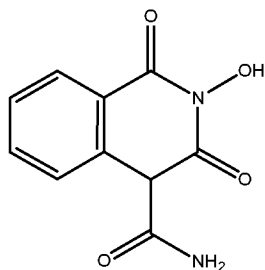
each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂,
 -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or
 Het⁴;

15 each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally
 substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H,
 C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

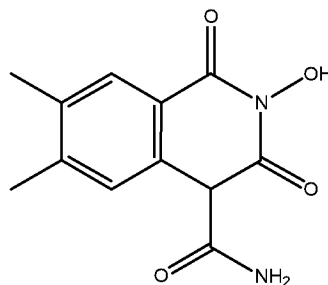
each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally
 20 substituted with 1 to 5 substituents independently selected from halo, C₁₋₆alkyl, OH,
 C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring
 system containing 1, 2, 3, or 4 heteroatoms independently selected from the group
 25 consisting of O, N, and S, and said heterocyclic ring system is optionally
 substituted with 1 to 4 substituents independently selected from halo, C₁₋₆alkyl, OH,
 C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃.

provided that the following compounds are excluded:



2-Hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



2-Hydroxy-6,7-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide.

5

2. The compound as claimed in claim 1 wherein

R^1 is hydrogen; C_{1-12} alkyl or C_{2-12} alkenyl, which are each optionally substituted with one or more substituents selected from halo, $C(=O)R^9$, Ar^3 , and Het^3 ; C_{3-10} cycloalkyl; or Ar^1 ;

10 R^2 is hydrogen or C_{1-6} alkyl; or

R^1 and R^2 together form the bivalent radical of formula (a-3);

R^3 , R^4 , R^5 and R^6 are each, independently, hydrogen, NO_2 , $-NR^7R^8$, C_{1-6} alkoxy, $-NHC(=O)C_{1-6}$ alkyl optionally substituted with $-C(=O)OC_{1-6}$ alkyl or Ar^3 , $-NHC(=O)Ar^2$, or $-NHC(=O)Het^2$;

15 R^7 and R^8 are each, independently, hydrogen or C_{1-6} alkyl;

R^9 is C_{1-6} alkoxy; and

Ar^1 and Ar^3 are each optionally substituted with 1 or 2 substituents independently selected from halo, C_{1-6} alkyl, OH, and C_{1-6} alkyloxy;

Het^2 is pyridinyl; and

20 Het^3 is thienyl.

3. The compound as claimed in any one of claims 1 or 2 wherein

R¹ is hydrogen; C₁₋₁₂alkyl or C₂₋₁₂alkenyl, which are each optionally substituted with one or more substituents selected from halo, -C(=O)OC₂H₅, phenyl, and thienyl; C₅cycloalkyl; or phenyl;

R² is hydrogen, methyl, or ethyl; or

5 R¹ and R² together form the bivalent radical of formula (a-3);

R³, R⁴, R⁵ and R⁶ are each, independently, hydrogen, NO₂, or NH₂, methyloxy, -NHCOCH₃, -NHCOCH₂phenyl, -NHCOphenyl, -NHCOpyridinyl, or -NHCOCH₂thienyl; and

10 each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, and methyloxy.

4. The compound as claimed in any one of claims 1 to 3, wherein

R¹ is hydrogen, C₁₋₁₂alkyl, phenylmethyl, phenylethyl, or phenyl;

R² is hydrogen; and

15 R⁵ is hydrogen, methyloxy, -NHCOCH₂phenyl, -NHCOphenyl, -NHCOpyridinyl, or -NHCOCH₂thienyl; and

each phenyl is optionally substituted with 1 or 2 substituents independently selected from halo, methyl, OH, and methyloxy.

20 5. The compound as claimed in any one of claims 1 to 4 wherein the compound is

N-(3-Chloropropyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-Hexyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

25 *N*-(3-Fluorophenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(3-Chloro-4-methoxyphenyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

30 *N*-(2,4-Dimethoxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(2,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(3,4-Dihydroxybenzyl)-2-hydroxy-1,3-dioxoisoquinoline-4-carboxamide,

N-Dodecyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

5 *N*-Benzyl-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-2,3-dihydroxy -7-nitro-1-oxo-1,2-dihydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-7-amino-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,

10 *N*-Phenyl-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,

N-(4-Fluorophenyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,

N-Benzyl-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,

N-(4-Methoxybenzyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-

15 carboxamide,

N-(4-Fluorophenethyl)-2,3-dihydroxy -7-nitro -1-oxo-1,2-dihydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)-7-acetamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

20 *N*-(4-Fluorobenzyl)-2-hydroxy-1,3-dioxo-7-phenylacetamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)- 7-benzamido-2-hydroxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)- 2-hydroxy-1,3-dioxo-7-picolinamido-1,2,3,4-

25 tetrahydroisoquinoline-4-carboxamide,

N-(4-Fluorobenzyl)- 2-hydroxy-1,3-dioxo-7-(2-(thiophen-2-yl)acetamido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, or

N-(4-Fluorobenzyl)-2-hydroxy-7-methoxy-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide.

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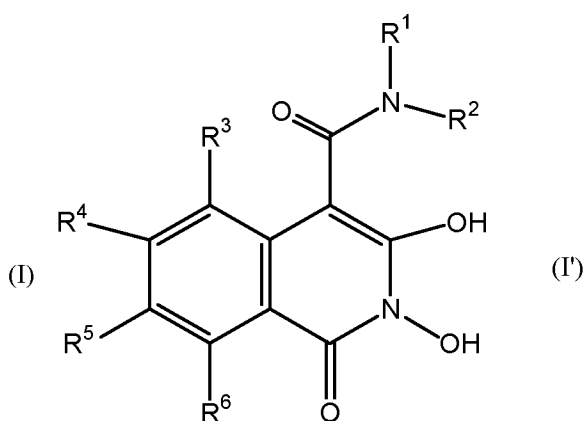
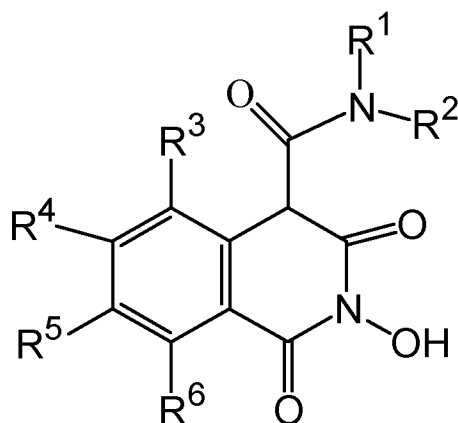
6. The compound as claimed in any one of claims 1 to 5 for use as a medicine.

7. A pharmaceutical composition comprising an effective amount of a compound as claimed in any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

8. The pharmaceutical composition as claimed in claim 7, further comprising a therapeutically effective amount of an HIV/AIDS treatment agent selected from the group consisting of: an HIV/AIDS antiviral agent; an anti-infective agent; and an immunomodulator.

9. The compound as claimed in any one of claim 1 to 5, or the pharmaceutical composition as claimed in claims 7 or 8 for use as a treatment of infection by HIV, or for treating AIDS.

10. A compound of formula (I),



or a tautomer (I') thereof, or a pharmaceutically acceptable salt or solvate of said compound or tautomer thereof,

wherein

R¹ and R² are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₁₂alkyl, C₂₋₁₂alkenyl, or C₂₋₁₂alkynyl, which are each optionally substituted with one or more substituents selected from halo, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, and Het³;

C₃₋₁₀cycloalkyl or C₃₋₁₀cycloalkenyl, which are each optionally substituted with one or more substituents selected from halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, and Ar³;

Ar¹;

Het¹; or

R¹ and R² together form a bivalent radical of formula

-(CH₂)₃- (a-1),

-(CH₂)₄- (a-2), or

-(CH₂)₅- (a-3);

R³, R⁴, R⁵ and R⁶ are each independently selected from:

hydrogen; halo; -OH; -SH; -CN; -NO₂; -NR⁷R⁸; -OCF₃; CF₃; C(=O)R⁹; C(=S)R⁹;

C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂,

-NR⁷R⁸, -OCF₃, C(=O)R⁹, C(=S)R⁹, Ar³, or Het³;

C₁₋₆alkyloxy; C₁₋₆alkylthio; Ar²; Ar²oxy; Ar²thio; Het²; Het²oxy; Het²thio;

C₃₋₆cycloalkyl;

-NHC(=O)C₁₋₆alkyl optionally substituted with halogen, -C(=O)OC₁₋₆alkyl, or Ar³;

-NHC(=O)Ar²; or -NHC(=O)Het²;

each R⁷ and R⁸ is independently selected from hydrogen; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; or C(=O)R¹²;

each R⁹ is hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, -OH, -SH, -CN, -NO₂, -NR¹⁰R¹¹, -OCF₃, C(=O)R¹², C(=S)R¹², Ar³, or Het³; C₁₋₆alkoxy; -NR¹⁰R¹¹; Ar⁴; or Het⁴;

each R¹⁰, R¹¹, and R¹² is independently selected from hydrogen; OH; C₁₋₆alkyl optionally substituted with halo, C₁₋₆alkyl, -OH, -SH, -CN, -NO₂, -NH₂, -OCF₃, C(=O)H, C(=S)H, Ar³, or Het³; C₁₋₆alkoxy; Ar⁴; or Het⁴;

each of Ar¹, Ar², Ar³, and Ar⁴, is independently phenyl or naphthyl, and is optionally substituted with 1 to 5 substituents independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and CF₃;

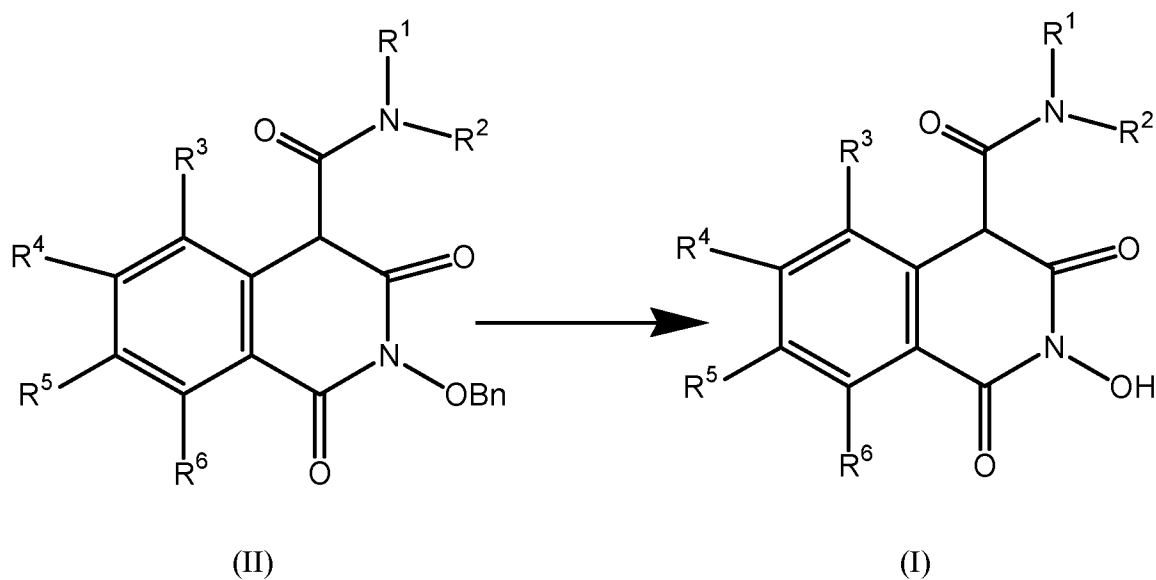
- 5 each of Het¹, Het², Het³, and Het⁴, is independently a mono- or bicyclic heterocyclic ring system containing 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of O, N, and S, and said heterocyclic ring system is optionally substituted with 1 to 4 substituents independently selected from halo, C₁₋₆alkyl, OH, C₁₋₆alkyloxy, NO₂, -OCF₃, and -CF₃;

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for use as an antiviral agent or for treating AIDS.

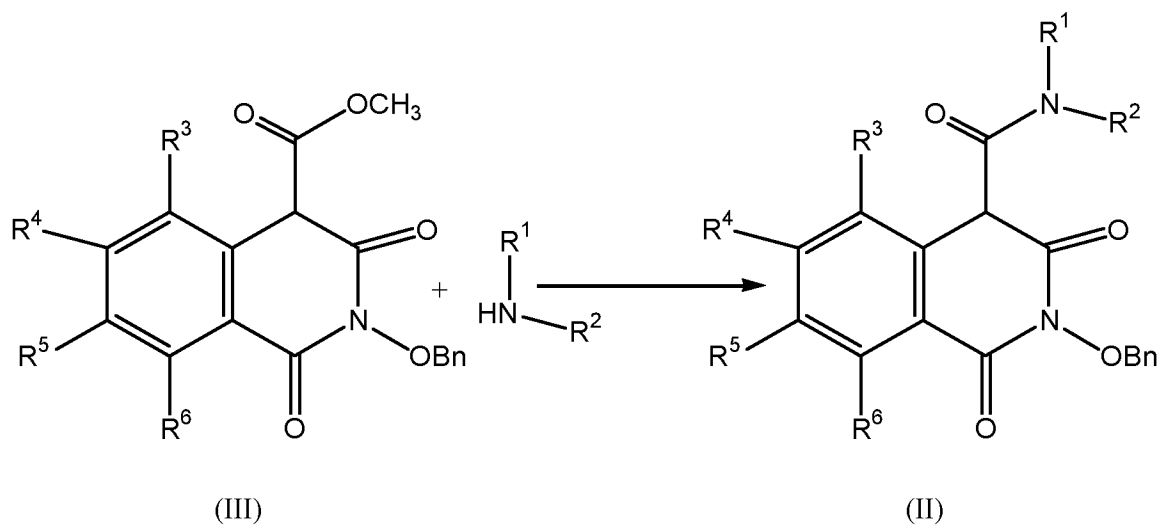
11. . A process for making a compound as claimed in any one of claims 1 to 5 wherein

- a) the intermediate of formula (II) is reacted with a boron halide or is deprotected by
15 catalytic dehydrogenation with the formation of a compound of formula (I)

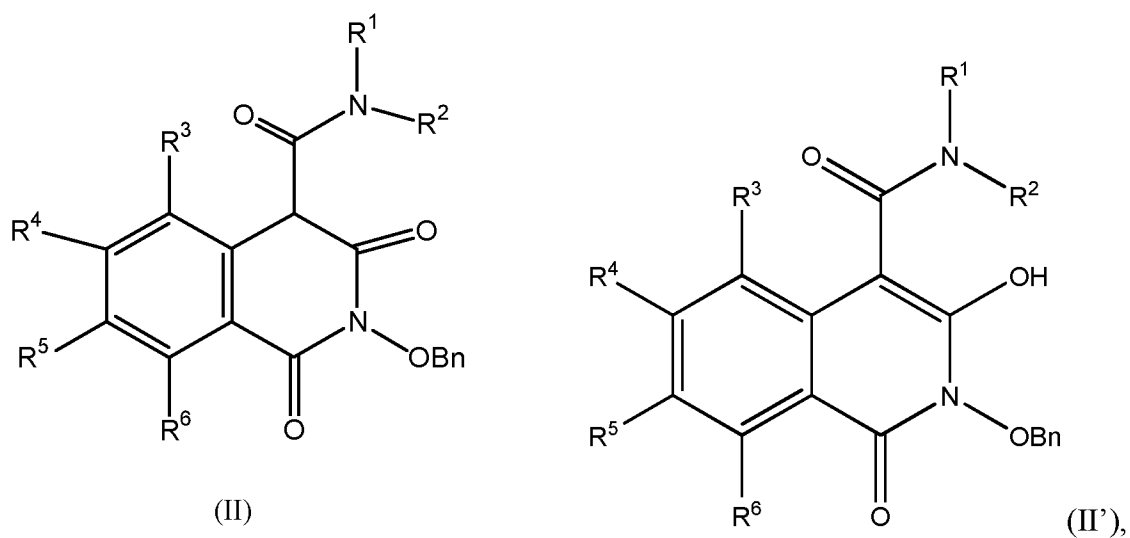


12. The process for making a compound according to claim 11 wherein

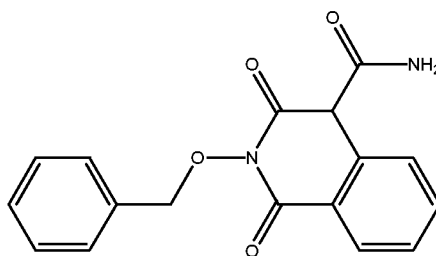
- a) the intermediate of formula (II) is obtained by reacting intermediate of formula (III) with
20 a suitable amine



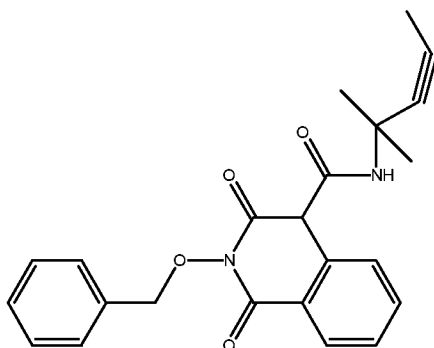
13. An intermediate of formula (II) or (II') wherein the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^6 , are as defined in any one of claims 1 to 5



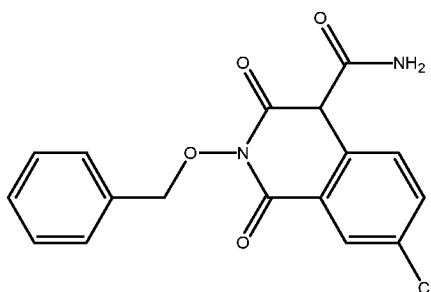
5 provided that the following compounds are excluded:



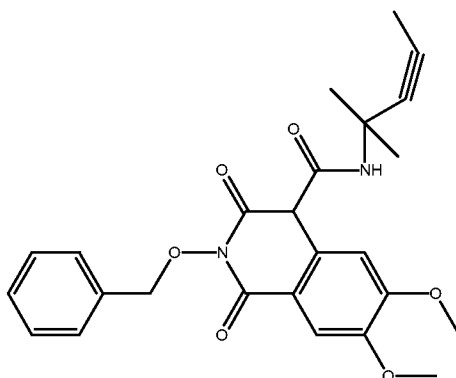
2-Benzyloxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



2-Benzyloxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-(1,1-dimethyl-but-2-ynyl)-carboxamide,



5 2-Benzyloxy-7-chloro-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-carboxamide,



2-Benzyloxy-6,7-dimethoxy-1,3-dioxo-1,2,3,4-tetrahydro-isoquinoline-4-(1,1-dimethyl-but-2-ynyl)-carboxamide.

- 10 14. An intermediate as claimed in claim 13 for use as medicine.
15. An intermediate as claimed in claim 14 for use as an antiviral agent.
16. A process for preparing a pharmaceutical composition as claimed in claim 7 or 8 wherein a therapeutically effective amount of a compound as claimed in any one of
- 15 claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

17. The process for preparing a pharmaceutical composition as claimed in claim 9 wherein a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 and a therapeutically effective amount of an HIV/AIDS treatment agent as claimed in claim 8 are intimately mixed with a pharmaceutically acceptable carrier.

5

18. The use of a compound of formula (I) as defined in claim 10 for the manufacture of a medicament for the prevention or treatment of viral infections in mammals.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/073480

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D217/26 C07D409/12 A61K31/472 A61P31/18
ADD.

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)

C07D A61K A61P

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)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 886 163 A (KADIN SAUL B) 27 May 1975 (1975-05-27) cited in the application column 1, line 60 column 3, line 45 column 11, line 15 - line 19; example VIII second entry; column 19 - column 20; example XXIV entries 13 and 14; column 27; example XXXI second entry; column 35; example XLIV ----- -/-	1-4,6,7, 11-14,16



Further documents are listed in the continuation of Box C.



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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 2012

Date of mailing of the international search report

16/05/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/073480

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BILLAMBOZ M ET AL: "Design, synthesis, and biological evaluation of a series of 2-hydroxyisoquinoline-1,3(2H,4H)-diones as dual inhibitors of human immunodeficiency virus type 1 integrase and the reverse transcriptase RNase H domain", JOURNAL OF MEDICINAL CHEMISTRY 20081225 US LNKD- DOI:10.1021/JM8007085, vol. 51, no. 24, 25 December 2008 (2008-12-25), pages 7717-7730, XP002636354, ISSN: 0022-2623 table 1 scheme 1 -----	1-18
A	BILLAMBOZ M ET AL: "2-Hydroxyisoquinoline-1,3(2H,4H)-diones as inhibitors of HIV-1 integrase and reverse transcriptase RNase H domain: Influence of the alkylation of position 4", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY 2011 ELSEVIER MASSON SAS FRA LNKD- DOI:10.1016/J.EJMECH.2010.11.033, vol. 46, no. 2, 27 November 2010 (2010-11-27), pages 535-546, XP002636355, ISSN: 0223-5234 table 1 -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/073480

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3886163	A	27-05-1975	NONE
