ACYL ISOINDOLINE DERIVATIVES AND ACYL ISOQUINOLINE DERIVATIVES AS ANTI-VIRAL AGENTS

Abstract: Anti-viral agents of Formula (I) wherein: R^3 represents aryl or heteroaryl; R^4 represents one or two substituents independently selected from hydrogen, C_1-alkyl, halogen, OR^5, C(O)(NR^6R^7)^5, C(O)R^8, CO_2H, CO_2R^9, NR^6R^7, NR^6C(O)R^8, NR^6CO_2R^9, NR^6C(O)NR^6R^7R^8R^9, NR^6SO_2R^9, SO_2NR^6R^7, SO_3R^9, nitro, cyano, heterocyclyl, heteroaryl, aryl, aralkyl, heteroaryloalkyl or CF_3; R^5 and R^6 independently represent hydrogen, C_1-alkyl, aryl, heteroaryl, aralkyl, aryloalkyl or heteroaryloalkyl; n represents 0 or 1; when n represents 0, R^1 represents C(O)R^5 and R^2 represents C_1-alkyl, heterocyclylalkyl, aryl or heteroaryloalkyl; when n represents 1, either i) R^1 represents C(O)R^5, R^2 represents C_1-alkyl, heterocyclylalkyl, arylalkyl or heteroaryloalkyl; and R^2 and R^3 independently represent hydrogen, C_1-alkyl, aryl, heteroaryl, aralkyl, or heteroaryloalkyl; or ii) R^1 and R^2 independently represent hydrogen, C_1-alkyl, aryl, heteroaryl, aralkyl, or heteroaryloalkyl; R^3 represents C_1-alkyl, heterocyclylalkyl, arylalkyl or heteroaryloalkyl; and R^4 and R^5 together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; R^6 is selected from the group consisting of C_1-alkyl, aryl, heteroaryl, aralkyl, and heteroaryloalkyl; R^7 represents hydrogen, C_1-alkyl, aryl, heteroaryl, aralkyl, or heteroaryloalkyl; or R^7 and R^5 together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; R^8 represents hydroxy or NR^6R^7; and salts, solvates and esters thereof; provided that when R^6 is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloalkyl, or aryl, then R is other than tert-buty1. Processes for their preparation and methods of using them in HCV treatment are provided.
ACYL ISOINDOLINE DERIVATIVES AND ACYL ISOQUINOLINE DERIVATIVES AS ANTI-VIRAL AGENTS

FIELD OF THE INVENTION

The present invention relates to novel acyl isoindoline derivatives and novel acyl tetrahydroisoquinoline derivatives useful as anti-viral agents. Specifically, the present invention involves novel HCV inhibitors.

BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K.L. (1997) Hepatology 26 (suppl 1): 71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of those treated, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon, both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) Science 244:359-362), hepatitis C virus (HCV) is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo, G et al (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the Flaviviridae family. Like the other members of the Flaviviridae, such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and
pestiviruses (e.g. bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo, Q-L. et al (1989) Science 244:359-3; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5′ nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al ‘An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5′ noncoding region’ RNA- A Publication of the RNA Society. 1(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) Virology 2nd Edition, p931-960; Raven Press, N.Y.). Following the termination codon at the end of the long ORF, there is a 3′ NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the “3′ X-tail” (Kolykhlov, A. et al (1996) J. Virology 70:3363-3371; Tanaka, T. et al (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. et al (1996) J. Virology 70:3307-3312; Yamada, N. et al (1996) Virology 223:255-261). The 3′ NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. et al (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhlov et al. (2000) Journal of Virology, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to cure HCV infection.

Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV.
SUMMARY OF THE INVENTION
The present invention involves novel acyl isoindoline compounds and novel acyl tetrahydroisoquinoline compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and use of the compounds in treating viral infection, especially HCV infection.

DETAILED DESCRIPTION OF THE INVENTION
The present invention provides compounds of Formula (I)

\[
\begin{array}{c}
\text{R}^3 \text{ represents aryl or heteroaryl;} \\
\text{R}^4 \text{ represents one or two substituents independently selected from hydrogen, C}_{1-6}\text{alkyl, halo, } \text{OR}^A, \text{C(O)NR}^B\text{R}^C, \text{C(O)R}^D, \text{CO}_2\text{H, CO}_2\text{R}^D, \text{NR}^B\text{R}^C, \text{NR}^E\text{C(O)R}^D, \text{NR}^E\text{CO}_2\text{R}^D, \\
\text{NR}^E\text{C(O)NR}^B\text{R}^G, \text{NR}^E\text{SO}_2\text{R}^D, \text{SO}_2\text{NR}^B\text{R}^G, \text{SO}_2\text{R}^D, \text{nitro, cyano, heterocyclyl, heteroaryl, aryl, arylalkyl heteroarylalkyl or CF}_3; \\
\text{R}^5 \text{ and } \text{R}^6 \text{ independently represent hydrogen, C}_{1-6}\text{alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;} \\
\text{n represents 0 or 1;} \\
\text{when } \text{n represents 0, } \text{R}^1 \text{ represents C(O)R}^H \text{ and } \text{R}^2 \text{ represents C}_{1-6}\text{alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;} \\
\text{when } \text{n represents 1, either} \\
i) \text{R}^1 \text{ represents C(O)R}^H, \text{R}^2 \text{ represents C}_{1-6}\text{alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl}; \text{ and R}^7 \text{ and R}^8 \text{ independently represent hydrogen, C}_{1-6}\text{alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;} \\
or \\
ii) \text{R}^1 \text{ and R}^2 \text{ independently represent hydrogen, C}_{1-6}\text{alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; R}^7 \text{ represents C(O)R}^H, \text{and R}^8 \text{ represents C}_{1-6}\text{alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;} \\
\end{array}
\]

3
R^A represents hydrogen, C_1-alkyl, arylalkyl, heteroaryllalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, C_1-alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^D is selected from the group consisting of C_1-alkyl, aryl, heteroaryl, aryalkyl, and heteroaryllalkyl;

R^E represents hydrogen or C_1-alkyl;

R^F and R^G are independently selected from the group consisting of hydrogen, C_1-alkyl, aryl, heteroaryl, aryalkyl, and heteroaryllalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^H represents hydroxy or NR^B R^C;

and salts, solvates and esters thereof; provided that when R^H is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than tert-butyl.

One embodiment of the invention provides compounds of Formula (I) represented by Formula (Ia)

\[
\begin{align*}
\text{(Ia)} & \\
\end{align*}
\]

wherein:

R^H represents hydroxy or NR^B R^C;

R^2 represents C_1-alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl;

R^3 represents aryl or heteroaryl;

R^4 represents one or two substituents independently selected from hydrogen, C_1-alkyl, halo, OR^A, C(O)NR^B R^C, C(O)R^D, CO_2 R^D, NR^B R^C, NR^E C(O) R^D, NR^E CO_2 R^D, NR^E C(O) NR^F R^G, NR^E SO_2 R^D, SO_2 NR^F R^G, SO_2 R^D, nitro, cyano, heterocyclyl, heteroaryl, aryl, aryalkyl heteroaryllalkyl or CF_3;
R⁵ and R⁶ independently represent hydrogen, C₁₋₇alkyl, aryl, heteroaryl, arylalkyl, or heteroarylmethyalkyl;

R⁷ represents hydrogen, C₁₋₇alkyl, arylalkyl, heteroarylmethyalkyl, aryl or heteroaryl;

R⁸ and R⁹ independently represent hydrogen, C₁₋₇alkyl, aryl or heteroaryl; or R⁸ and R⁹ together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R⁰ is selected from the group consisting of C₁₋₇alkyl, aryl, heteroaryl, arylalkyl, and heteroarylmethyalkyl;

R⁰ represents hydrogen or C₁₋₇alkyl;

R¹ and R² are independently selected from the group consisting of hydrogen, C₁₋₇alkyl, aryl, heteroaryl, arylalkyl, and heteroarylmethyalkyl; or R¹ and R² together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof; provided that when R⁴ is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than tert-butyl.

Another embodiment of the invention provides compounds of Formula (I) represented by Formula (lb)

![Formula (lb)](image)

wherein:

R² represents hydroxy or NR⁸R⁹;

R¹ and R² independently represent hydrogen, C₁₋₇alkyl, aryl, heteroaryl, arylalkyl, or heteroarylmethyalkyl;

R³ represents aryl or heteroaryl;
R^4 represents one or two substituents independently selected from hydrogen, C_1-6 alkyl, halo, OR^5, C(O)NR^6R^7, C(O)R^8, CO_2H, CO_2R^9, NR^6R^9, NR^6C(O)R^8, NR^6CO_2R^9, NR^5C(O)NR^6R^9, NR^5SO_2R^9, SO_2NR^5R^9, SO_2R^9, nitro, cyano, heterocyclyl, heteroaryl, aryl, arylalkyl heteroarylalkyl or CF_3;

R^5 and R^9 independently represent hydrogen, C_1-6 alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

R^8 represents C_1-6 alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

R^A represents hydrogen, C_1-6 alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, C_1-6 alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^D is selected from the group consisting of C_1-6 alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R^E represents hydrogen or C_1-6 alkyl;

R^F and R^G are independently selected from the group consisting of hydrogen, C_1-6 alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof; provided that when R^H is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than tert-butyl.

A further embodiment of the invention provides compounds of Formula (I) represented by Formula (lc)

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\begin{align*}
\text{(lc)}
\end{align*}
\]

wherein:

R^H represents hydroxy or NR^6R^9;
R² represents C₁₋₆alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

R³ represents aryl or heteroaryl;

R⁴ represents one or two substituents independently selected from hydrogen, C₁₋₆alkyl, halo, OR₆, C(O)NR₆R₇, C(O)R₈, CO₂H, CO₂R₉, NR₆R₇, NR₆C(O)R₈, NR₆CO₂R₉, NR₆C(O)NR₆R₇, NR₆SO₂R₉, SO₂NR₆R₇, SO₂R₉, nitro, cyano, heterocyclyl, heteroaryl, aryl, arylalkyl heteroarylalkyl or CF₃;

R⁵ and R⁶ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

R⁷ and R⁸ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

R⁹ represents hydrogen, C₁₋₆alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R¹⁰ and R¹¹ independently represent hydrogen, C₁₋₆alkyl, aryl or heteroaryl; or R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R¹² is selected from the group consisting of C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R¹³ represents hydrogen or C₁₋₆alkyl;

R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof; provided that when R¹ is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than tert-butyl.

There is provided as a further aspect of the present invention a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof for use in human or veterinary medical therapy, particularly in the treatment or prophylaxis of viral infection, particularly HCV infection.

It will be appreciated that reference herein to therapy and/or treatment includes, but is not limited to prevention, retardation, prophylaxis, therapy and cure of the disease. It will
further be appreciated that references herein to treatment or prophylaxis of HCV infection includes treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

According to another aspect of the invention, there is provided the use of a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with viral infection, particularly HCV infection, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof.

It will be appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. All of these racemic compounds, enantiomers and diastereoisomers are contemplated to be within the scope of the present invention.

Preferably, R^3 represents phenyl optionally substituted by halo, C_{1-6}alkyl or C_{1-3}alkoxy; more preferably tert-butylphenyl optionally 3-substituted by halo, C_{1-3}alkyl or C_{1-3}alkoxy; especially preferred is 4-tert-butylphenyl optionally 3-substituted by halo, C_{1-3}alkyl or C_{1-3}alkoxy, especially bromo, chloro, methyl or methoxy; most preferably R^3 is 3-methoxy-4-tert-butylphenyl.

Preferably, when n represents 1, R^4 is positioned on the C6 or C7 positions of the tetrahydroisoquinoline ring. Preferably, R^4 is a single substituent. Preferably, R^4 represents hydrogen, OH, -C(O)OH, -OCH_3, OCH_2Ph, -OCH-1,3-thiazol-4-yl, C(O)NH_2, -CH_2C(O)NH_2, 2-furanyl, -OCH_2-3-pyridinyl or 4-pyridinyl.

Preferably, R^5 and R^6 represent hydrogen.

When n represents 0, R^1 preferably represents C(O)OH and R^2 preferably represents CH_2Ph or 2-methylpropyl.

When n represents 1, either

i) R^1 preferably represents C(O)OH; R^2 preferably represents -CH_2Ph, 2-methylpropyl or 2-methyl-2-propen-1-yl; and R^7 and R^8 preferably each represent hydrogen;
ii) $R^1$ and $R^2$ preferably each represent hydrogen; $R^7$ preferably represents C(O)OH; and $R^8$ preferably represents –CH$_2$Ph, 2-methylpropyl or 2-methyl-2-propen-1-yl.

Preferably, $R^H$ represents hydroxy.

It is to be understood that the present invention covers all combinations of suitable, convenient and preferred groups described herein.

As used herein unless otherwise specified, "alkyl" refers to an optionally substituted hydrocarbon group. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Where the alkyl hydrocarbon group is cyclic, it will be understood that there will be a minimum of 3 carbon atoms in the group. Preferably, the group is saturated. Preferred alkyl moieties are C$_{1-4}$alkyl. Unless otherwise stated, optional substituents include C$_{1-4}$alkyl, halo, OR$^A$, SR$^A$, C(O)NR$^B$R$^C$, C(O)R$^D$, CO$_2$H, CO$_2$R$^D$, NR$^B$R$^C$, NR$^E$C(O)R$^D$, NR$^E$CO$_2$R$^D$, NR$^E$C(O)NR$^F$R$^G$, SO$_2$NR$^F$R$^G$, SO$_2$R$^D$, nitro, cyano, oxo, and heterocyclic.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl and biaryl groups, all of which may be optionally substituted. Preferred "aryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted phenyl. Preferred "aryl" substituents are selected from the group consisting of C$_{1-6}$alkyl, halo, OR$^A$, C(O)NR$^B$R$^C$, C(O)R$^D$, CO$_2$H, CO$_2$R$^D$, NR$^B$R$^C$, NR$^E$C(O)R$^D$, NR$^E$CO$_2$R$^D$, NR$^E$C(O)NR$^F$R$^G$, SO$_2$NR$^F$R$^G$, SO$_2$R$^D$, nitro, cyano, heterocyclic, and CF$_3$.

As used herein, "heteroaryl" refers to an optionally substituted, 5 or 6 membered, aromatic group comprising one to four heteroatoms selected from N, O and S, with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Preferred "heteroaryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted pyridyl and thiazolyl. Preferred "heteroaryl" substituents are selected from the group consisting of C$_{1-6}$alkyl, halo, OR$^A$, C(O)NR$^B$R$^C$, C(O)R$^D$, CO$_2$H, CO$_2$R$^D$, NR$^B$R$^C$, NR$^E$C(O)R$^D$, NR$^E$CO$_2$R$^D$, NR$^E$C(O)NR$^F$R$^G$, SO$_2$NR$^F$R$^G$, SO$_2$R$^D$, nitro, cyano, heterocyclic, CF$_3$.

As used herein, "heterocyclic" and "heterocyclyl" refer to an optionally substituted, 5 or 6 membered, saturated cyclic hydrocarbon group containing 1 or 2 heteroatoms selected from N, optionally substituted by hydrogen, C$_{1-4}$alkyl, C(O)R$^D$, SO$_2$R$^D$, aryl or heteroaryl; O; and S, optionally substituted by one or two oxygen atoms.

Preferred compounds of Formula (I) useful in the present invention are selected from the group consisting of:
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid;

5  2-(3-Methoxy-4-tert-butylbenzoyl)-7-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-7-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-{[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-{[(1,3-thiazol-4-ylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
7-(Aminocarbonyl)-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
15 7-[(2-Amino-2-oxoethyl)oxy]-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-(2-furanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-6-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-6-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-6-{[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
25 2-(3-Methoxy-4-tert-butylbenzoyl)-6-{[(3-pyridinylmethyl)oxy]-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,6-dicarboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-6-(4-pyridinyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-isobutyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(2-methyl-2-propen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
35 2-(3-Methoxy-4-tert-butylbenzoyl)-1-(phenylmethyl)-2,3-dihydro-1H-isindoledi-1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1-(2-methylpropyl)-2,3-dihydro-1H-isindoledi-1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(phenylmethyl) 1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methyl-2-propen-1-yl)-1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methylpropyl)-1-carboxylic acid;
and salts, solvates and esters, and individual enantiomers thereof.

Also included in the present invention are pharmaceutically acceptable salt complexes. The present invention also covers the physiologically acceptable salts of the compounds of Formula (I). Suitable physiologically acceptable salts of the compounds of Formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di-basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, 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 and the like.

The present invention also relates to solvates of the compounds of Formula (I), for example hydrates.

The present invention also relates to pharmaceutically acceptable esters of the compounds of Formula (I), for example carboxylic acid esters -COOR, in which R is selected from straight or branched chain alkyl, for example n-propyl, n-butyl, alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxyethyl), aryl (e.g. phenyl optionally substituted by halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy or amino). Unless otherwise specified, any alkyl moiety present in such esters preferably contains 1 to 18 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group.

It will further be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

Compounds of Formula (I) wherein either R¹ or R⁷ is C(O)R¹⁴ and R⁸H is NR⁸R⁹ may be prepared from a compound of Formula (I) wherein either R¹ or R⁷ is C(O)R¹⁴ and R⁸H is hydroxy using a coupling agent such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and an amine NHR⁸R⁹.

Compounds of Formula (I) wherein either R¹ or R⁷ is C(O)R¹⁴ and R⁸H is hydroxy may be prepared from a compound of Formula (II)
wherein either $R^1$ or $R^7$ is $\text{C(O)R}^H$ and $R^H$ is an alkoxy, benzyloxy or silyloxy group and $n$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I). For example when $R^H$ is methoxy and $n$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I), by treatment with an appropriate base, for example aqueous sodium hydroxide, optionally in a solvent such as methanol, tetrahydrofuran or a mixture thereof. Preferably, the temperature is in the range 25 to 100°C, more preferably 50 to 100°C. Alternatively, when $R^H$ is a methoxy group and $n$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I), by treatment with lithium iodide in a suitable solvent such as pyridine, lutidine or collidine, preferably in the temperature range 100-170°C.

For example when $R^H$ is tert-butoxy, and $n$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I), by treatment with an appropriate acid, for example trifluoroacetic acid. Suitably, the reaction is carried out in a solvent, for example dichloromethane. Preferably, the temperature is in the range 0 to 50°C, more preferably 15 to 30°C.

For example when $R^H$ is silyloxy, and $n$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I), by treatment with a suitable fluoride source for example tetrabutylammonium fluoride. The reaction is carried out in a suitable solvent, for example tetrahydrofuran.

Compounds of Formula (I) wherein either $R^1$ or $R^7$ is $\text{C(O)R}^H$ and $R^H$ is hydroxy or a protected form thereof may also be prepared by reaction of a compound of Formula (III)

![Diagram](attachment:formula_iii.png)

wherein $R^1$ or $R^7$ is $\text{C(O)R}^H$ and $R^H$ is hydroxy or a protected form thereof, and $n$, $R^1$, $R^2$, $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined above for Formula (I); with a suitable acylating agent, for example $R^3$, $\text{C(O)-Y}$, wherein $Y$ is a halo atom, preferably chloro or bromo, and $R^3$ is as defined above for Formula (I). Preferably the reaction is carried out in a suitable solvent, for example triethylamine and thereafter removing any protecting group. Suitable protecting groups
can be found, but are not restricted to, those found in T W Greene and P G M Wuts ‘Protective Groups in Organic Synthesis’, 3rd Ed (1999), J Wiley and Sons.

Compounds of Formula (II) wherein \( n \) is 0 and \( R^1 \) is \( C(O)R^3 \) wherein \( R^3 \) is an alkoxy, benzyloxy or silyloxy group may be prepared from compounds of Formula (IV)

\[
\text{(IV)}
\]

wherein \( R^3 \) is an alkoxy, benzyloxy or silyloxy group, and \( R^3, R^4, R^5 \) and \( R^6 \) are as defined above for Formula (I), by treatment with a suitable base such as lithium bis(trimethylsilyl)amide, lithium disopropylamide, n-butyl lithium, lithium 2,2,6,6-tetramethylpiperidide (LTMP), sodium hydride, and an alkylating agent \( R^2Y \) where \( Y \) is a halo atom such as chloro, bromo or iodo or \( Y \) is a sulphonate leaving group such as mesylate or tosylate, and \( R^2 \) is the same as defined above for Formula (I) when \( n \) is 0, in a suitable solvent such as tetrahydrofuran.

Compounds of Formula (III) wherein \( n \) is 0 and \( R^6 \) is hydrogen may be prepared by reacting compounds of Formula (V)

\[
\text{(V)}
\]

in which \( Y \) is a halo atom such as chloro, bromo or iodo, and \( R^4 \) is as defined above for Formula (I), with compounds of Formula (VI)

\[
\text{(VI)}
\]

in which \( R^3 \) is an alkoxy, benzyloxy or silyloxy group, and \( R^2 \) and \( R^5 \) are as defined above for Formula (I), in the presence of a suitable base such as LTMP (see for example Tetrahedron Letters (2001) 42, 2245].

Compounds of Formula (III) wherein \( n \) is 0 may also be prepared from compounds of Formula (VII)

\[
\text{(VII)}
\]
in which P is a suitable nitrogen protecting group such as benzylloxycarbonyl (CBZ), tert-butyloxycarbonyl (BOC), or benzyl, by treatment with a suitable base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide, n-butyl lithium, lithium 2,2,6,6-tetramethylpiperidine (LTMP), sodium hydride, R^H is a protected hydroxy group, and R^4, R^5 and R^6 are as defined above for Formula (I), and an alkylation agent R^5Y where Y is a halo atom such as chloro, bromo or iodo or Y is a sulphonate leaving group such as mesyfate or tosyfate, and R^2 is the same as defined above for Formula (I) when n is 0, in a suitable solvent such as tetrahydrofuran, and then removing the protecting group P.

Compounds of Formula (IV) may be prepared by reaction of compounds of Formula (VIII)

![VIII](image)

in which R^H is an alkoxy, benzyloxyl or silyloxyl group, and R^4, R^5 and R^6 are as defined above for Formula (I), with a suitable acylating agent, for example R^3-C(O)-hal, wherein hal is a halo atom, preferably chloro or bromo, and R^3 is as defined above for Formula (I). Preferably, the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine.

Compounds of Formula (VI) may be prepared by reaction of a compound of Formula (IX)

![IX](image)

in which R^H is alkoxy, benzyloxyl or silyloxyl and R^2 is defined above for Formula (I) when n is 0, with a compound of Formula R^2-CHO, where R^2 as defined above for Formula (I), in the presence of a suitable base, for example triethylamine, in a suitable solvent, for example dichloromethane.

Compounds of Formula (VII) may be prepared by reacting compounds of Formula (X)

![X](image)

in which R^H is an alkoxy, benzyloxyl or silyloxyl group, Y is a halo atom such as chloro, bromo or iodo, and R^4, R^5 and R^6 are as defined above for Formula (I), with an amine P-NH$_2$ in which P is a suitable protecting group such as benzyl or tert-butyloxycarbonyl.
hydrazide or benzylxoycarbonyl hydrazide (see for example J. Heterocyclic Chem. (1984) 21, 1355).

Compounds of Formula (VIII) may alternatively be prepared by reacting compounds of Formula (X) with ammonia or ammonium hydroxide.

Compounds of Formula (VIII) may alternatively be prepared by deprotection of a compound of Formula (VII)

\[
\text{(VII)}
\]

in which P is a suitable protecting group such as benzyl or tert-butyloxycarbonyl hydrazide or benzylxoycarbonyl hydrazide, \( R^H \) is an alkoxy, benzyloxy or silyloxy group, and \( R^4, R^5 \) and \( R^6 \) are as defined above for Formula (I).

Compounds of Formula (X) may be prepared by reacting compounds of Formula (XI) or Formula (XII), in which \( R^H, R^4, R^5 \) and \( R^6 \) are as defined above for Formula (I), with a suitable halogenating agent such as N-bromosuccinimide or bromine, in a suitable solvent such as acetic acid, carbon tetrachloride or acetonitrile. See for example Synthesis (1975) 252, Gazz. Chim. Ital. (1976) 106, 65, J. Med Chem. (1981) 24, 1003, JCS Perkin Trans. 2, (1983) 12, 1821.

\[
\text{(XI)}
\]

\[
\text{(XII)}
\]

Compounds of Formula (II) in which \( n \) is 0 and \( R^1 \) is \( C(O)R^H \) wherein \( R^H \) is an alkoxy, benzyloxy or silyloxy group may also be prepared from compounds of Formula (XIII)

\[
\text{(XIII)}
\]

in which \( R^H \) is an alkoxy, benzyloxy or silyloxy, \( Y \) is a halo atom such as chloro, bromo or iodo, and \( R^2, R^3, R^4, R^5 \) and \( R^6 \) are as defined above for Formula (I) when \( n \) is 0, using a palladium catalyst such as tris(dibenzylideneacetone)palladium(0) (Pd(“dba)3) and a
ligand such as 2-(diphenylphosphino)-2’-(N,N-dimethylamino)biphenyl, with a base such as lithium tert-butoxide (see for example J. Org. Chem (2002) 67, 465).

Compounds of Formula (XIII) may be prepared from compounds of Formula (XIV)

(IV)

in which \( R^1 \) is an alkoxy, benzyloxy or silyloxy group, \( Y \) is a halo atom such as chloro, bromo or iodo, and \( R^2, R^4, R^5 \) and \( R^6 \) are as defined above for Formula (I) when \( n \) is 0, by reaction with a suitable acylating agent, for example \( R^3-C(O)-\text{hal} \), wherein hal is a halo atom, preferably chloro or bromo, and \( R^5 \) is as defined above for Formula (I). Preferably, the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine.

Compounds of Formula (XIV) may be prepared from compounds of Formula (IX)

(IX)

in which \( R^H \) is an alkoxy, benzyloxy or silyloxy group, \( R^5 \) and \( R^6 \) are hydrogen, and \( R^2 \) is as defined above for Formula (I), by reaction with an appropriate aldehyde (XV)

(XV)

in which \( Y \) is a halo atom such as chloro, bromo or iodo, and \( R^4 \) is as defined above for Formula (I) when \( n \) is 0, and reduction of the resulting imine using for example sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride.

Compounds of Formula (XIV) may also be prepared from compounds of Formula (IX) in which \( R^H \) is an alkoxy, benzyloxy or silyloxy group, and \( R^2 \) is as defined above for Formula (I), and \( R^5 \) and \( R^6 \) are hydrogen, by reaction with compounds of Formula (XVI) in which \( Y \) is a halo atom such as chloro, bromo or iodo and \( R^4 \) is as defined above for Formula (I). Preferably, the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine.

(XVI)
Compounds of Formula (III) in which \( n \) is 1 and \( R^7 \) is C(O)R^H wherein R^H is an alkoxy, benzyloxy or silyloxy group, R^6 represents C_{1-6}alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl, R^1 and R^2 represent hydrogen, and R^4, R^5 and R^8 are as defined above for Formula (I), may be prepared from a compound of Formula (XVII)

\[
\begin{array}{c}
\text{R}^4 \ \text{H} \\
\text{R}^5 \ \text{R}^6 \\
\text{H}_2 \text{N} \\
\text{R}^8 \\
\text{O} \\
\text{R}^H \\
\end{array}
\]  

(XVII)

in which R^H is an alkoxy, benzyloxy or silyloxy group, R^8 represents C_{1-6}alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl and R^4, R^5 and R^6 are as defined above for Formula (I) by reaction with formaldehyde, and an acid such as hydrochloric acid (see for example Bioorg Med Chem Letters (1998) 8, 2447, Chem. Pharm. Bull. (1988) 36, 190).

Compounds of Formula (III) in which \( n \) is 1 and \( R^7 \) is C(O)R^H wherein R^H is an alkoxy, benzyloxy or silyloxy group, R^6 represents C_{1-6}alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl, R^1 represents hydrogen, C_{1-6}alkyl, aryl, heteroaryl, aryalkyl, or heteroaryllalkyl, R^2 represents hydrogen and R^4, R^5 and R^8 are as defined above for Formula (I), may also be prepared by reaction of a compound of Formula (XVIII)

\[
\begin{array}{c}
\text{P} \\
\text{N} \\
\text{COR}^H \\
\text{R}^8 \\
\end{array}
\]  

(XVIII)

in which R^H is an alkoxy, benzyloxy or silyloxy group, P is a protecting group such as p-chlorophenyl, and R^8 represents C_{1-6}alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl, with a compound of Formula (XIX)

\[
\begin{array}{c}
\text{Y} \\
\text{Y} \\
\end{array}
\]  

(XIX)

in which Y is a halo atom such as chloro, bromo or iodo, using a base, such as sodium hydroxide, in a suitable solvent, such as toluene, and with a phase transfer catalyst, such as tetrabutylammonium bromide, followed treatment with an acid, for example hydrochloric acid (see for example Synthesis (2001) 1716).

Compounds of Formula (II) in which \( n \) is 1 and \( R^7 \) is C(O)R^H wherein R^H is an alkoxy, benzyloxy or silyloxy group, R^6 represents C_{1-6}alkyl, heterocyclylalkyl, aryalkyl or heteroaryllalkyl, R^1 and R^2 independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, aryalkyl, or heteroaryllalkyl, may be prepared from a compound of Formula (XX)
in which R\(^H\) is an alkoxy, benzyloxy or silyloxy group, R\(^1\) and R\(^2\) independently represent hydrogen, C\(_{1-6}\)alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and R\(^3\), R\(^4\), R\(^5\) and R\(^6\) are as defined above for Formula (I), by treatment with a suitable base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide, n-butyl lithium, lithium 2,2,6,6-tetramethylpiperidide (LTMP), sodium hydride, and an alkylation agent R\(^3\)Y where Y is a halo atom such as chloro, bromo or iodo and R\(^8\) represents C\(_{1-6}\)alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl, in a suitable solvent such as tetrahydrofuran.

Compounds of Formula (XX) in which R\(^H\) is an alkoxy, benzyloxy or silyloxy group, R\(^1\) and R\(^2\) independently represent hydrogen, C\(_{1-6}\)alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and R\(^3\), R\(^4\), R\(^5\) and R\(^6\) are as defined above for Formula (I); may be prepared from a compound of Formula (XXI)

in which R\(^H\) is an alkoxy, benzyloxy or silyloxy group, R\(^1\) and R\(^2\) independently represent hydrogen, C\(_{1-6}\)alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and R\(^4\), R\(^5\) and R\(^6\) are as defined above for Formula (I), with a suitable acylating agent, for example R\(^3\)-C(O)-Y, wherein Y is a halo atom, preferably chloro or bromo, and R\(^3\) is as defined above for Formula (I). Preferably the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine and thereafter removing any protecting group. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3rd Ed (1999), J Wiley and Sons.

Compounds of Formula (XXI) in which R\(^H\) is an alkoxy, benzyloxy or silyloxy group, R\(^1\) represents hydrogen, C\(_{1-6}\)alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, R\(^2\) is hydrogen and R\(^4\), R\(^5\) and R\(^6\) are as defined above for Formula (I); may be prepared from a compound of Formula (XXII)
in which \( R^H \) is an alkoxy, benzyloxy or silyloxy group, \( R^1 \) represents hydrogen, \( C_{1-6} \)-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^4, R^5, R^6 \) are as defined above for Formula (I), for example using palladium on carbon and hydrogen in a suitable solvent such as ethanol, or by using sodium borohydride in methanol.

Compounds of Formula (XXII) in which \( R^H \) is an alkoxy or benzyloxy group, may be prepared by a Bischler-Napieralski reaction, that is cyclisation of a compound of Formula (XXIII)

in which \( R^H \) is an alkoxy or benzyloxy group \( R^1 \) represents hydrogen, \( C_{1-6} \)-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^4, R^5, R^6 \) are as defined above for Formula (I), using a suitable reagent such as phosphorous oxychloride, examples are given in, but not restricted to, Org React (1951) 6, 74, J. C. S. Perkin Trans 1 (1981) 2830.

Compounds of Formula (XX) in which \( R^H \) is an alkoxy, benzyloxy or silyloxy group, \( R^1 \) and \( R^2 \) independently represent hydrogen, \( C_{1-6} \)-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^3, R^4, R^5, R^6 \) are as defined above for Formula (I), may also be prepared from a compound of Formula (XXIV)

in which \( R^H \) is an alkoxy, benzyloxy or silyloxy group, \( R^1 \) and \( R^2 \) independently represent hydrogen, \( C_{1-6} \)-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^3, R^4, R^5, R^6 \) are as defined above for Formula (I), by heating with a suitable base such as sodium methoxide in a suitable solvent such as methanol.

Compounds of Formula (XXIV) may be prepared from a compound of Formula (XXV)
in which R^1 and R^2 are as defined above for Formula (I), by reaction with a compound of Formula (XIX) in the presence of base such as sodium methoxide in a suitable solvent such as methanol (see for example Synthesis (1992) 1157).

Compounds of Formula (XXI) in which R^1 is an alkox, benzyloxy or silyloxy group, R^3 and R^4 represent hydrogen, and R^5, R^6, R^7 and R^8 are as defined above for Formula (I), may be prepared from a compound of Formula (XXVI)

in which R^1 is an alkox, benzyloxy or silyloxy group and R^4, R^5 and R^6 are as defined above for Formula (I), by reaction with formaldehyde, and an acid such as hydrochloric acid (see for example Bioorg Med Chem Letters (1998) 8, 2447).

Compounds of Formula (III) wherein n is 1 and R^1 represents C(O)R^1; R^2 represents C_{1-6}alkyl, heterocyclylalkyl, arylalkyl or heteroaryllalkyl; R^3 and R^8 independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, or heteroaryllalkyl, and R^4, R^5 and R^6 are as defined above for Formula (I) may be prepared from a compound of Formula (XXVII)

in which R^7 and R^8 independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, or heteroaryllalkyl and R^4, R^5 and R^6 are as defined above for Formula (I) by reaction with a compound of formula R^2COCOR^1 in which R^1 is as defined above for Formula (III) and R^2 represents C_{1-6}alkyl, heterocyclylalkyl, arylalkyl or heteroaryllalkyl (see for example J. Org. Chem. (1976) 41, 443).

Compounds of Formula (II) in which n is 1 and R^1 represents C(O)R^1 wherein R^1 is an alkoxy, benzyloxy or silyloxy group, R^2 represents C_{1-6}alkyl, heterocyclylalkyl, arylalkyl or heteroaryllalkyl; R^7 and R^8 independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, or heteroaryllalkyl, and R^3, R^4, R^5 and R^6 are as defined above for Formula (I), may be prepared from a compound of Formula (XXVIII)
in which $\text{R}^1$ is an alkoxy, benzyloxy or silyloxy group, $\text{R}^7$ and $\text{R}^8$ independently represent hydrogen, $\text{C}_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and $\text{R}^3$, $\text{R}^4$, $\text{R}^5$, and $\text{R}^6$ are as defined above for Formula (I), by treatment with a suitable base, such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide, n-butyl lithium, lithium 2,2,6,6-tetramethylpiperidide (LTMP), or sodium hydride, and an alkylating agent $\text{R}^2\text{Y}$ where $\text{Y}$ is a halo atom such as chloro, bromo or iodo and $\text{R}^2$ represents $\text{C}_{1-6}$alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl, in a suitable solvent such as tetrahydrofuran.

Compounds of Formula (XXVIII) in which $\text{R}^1$ is an alkoxy group may be prepared from a compound of Formula (XXIX)

in which $\text{R}^7$ and $\text{R}^8$ independently represent hydrogen, $\text{C}_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and $\text{R}^3$, $\text{R}^4$, $\text{R}^5$, and $\text{R}^6$ are as defined above for Formula (I), by esterification with an aqueous acid such as hydrochloric acid. The acid may then be esterified using an acid such as hydrochloric acid in the presence of a suitable alcohol such as methanol.

Compounds of Formula (XXIX) in which $\text{R}^7$ represents hydrogen, $\text{C}_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, $\text{R}^6$ and $\text{R}^8$ are hydrogen, and $\text{R}^3$, $\text{R}^4$ and $\text{R}^5$ are as defined above for Formula (I), may be prepared from a compound of Formula (XXX)

in which $\text{R}^7$ represents hydrogen, $\text{C}_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and $\text{R}^3$, $\text{R}^4$ and $\text{R}^5$ are as defined above for Formula (I), for example using palladium on carbon and hydrogen in a suitable solvent such as ethanol, or using sodium borohydride in methanol.

Compounds of Formula (XXX) may be prepared from a compound of Formula (XXXI)
in which \( R^7 \) represents hydrogen, \( \text{C}_{1-6}\text{alkyl} \), aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^4 \) and \( R^5 \) are as defined above for Formula (I), using a cyanide source such as sodium cyanide, potassium cyanide or trimethylsilyl cyanide and a suitable acylating agent, for example \( R^3\text{-C(O)-Y} \), wherein Y is a halo atom, preferably chloro or bromo and \( R^3 \) is as defined above for Formula (I), and optionally with a Lewis acid catalyst such as aluminium trichloride (an example of a Reissert reaction). Examples are given in (but are not restricted to) J. Org. Chem (1992) 57, 750, J. Org. Chem. (1970) 35, 3119.

Compounds of Formula (II) in which \( n = 1 \) and \( R^1 \) represents \( \text{C(O)}R^H \) wherein \( R^H \) is an alkoxy group, \( R^2 \) represents \( \text{C}_{1-6}\text{alkyl} \), heterocyclylalkyl, arylalkyl or heteroarylalkyl; \( R^7 \) and \( R^8 \) independently represent hydrogen, \( \text{C}_{1-6}\text{alkyl} \), aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^3 \), \( R^4 \), \( R^5 \) and \( R^6 \) are as defined above for Formula (I), may also be prepared from a compound of Formula (XXXII)

\[
\begin{align*}
\text{R}^4 & \quad \text{N} \quad \text{O} \\
\text{R}^2 & \quad \text{CN} \\
\text{R}^3 & \quad \text{R}^5 \\
\text{R}^6 & \quad \text{R}^8
\end{align*}
\]

in which \( R^2 \) represents \( \text{C}_{1-6}\text{alkyl} \), heterocyclylalkyl, arylalkyl or heteroarylalkyl; \( R^7 \) and \( R^8 \) independently represent hydrogen, \( \text{C}_{1-6}\text{alkyl} \), aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^3 \), \( R^4 \), \( R^5 \) and \( R^6 \) are as defined above for Formula (I), for example by treatment with an aqueous acid such as hydrochloric acid. The acid may then be esterified using an acid such as hydrochloric acid in the presence of a suitable alcohol such as methanol.

Compounds of Formula (XXXII) may be prepared from a compound of Formula (XXIX) in which in which \( R^7 \) and \( R^8 \) independently represent hydrogen, \( \text{C}_{1-6}\text{alkyl} \), aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and \( R^3 \), \( R^4 \), \( R^5 \) and \( R^6 \) are as defined above for Formula (I), by treatment with a suitable base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide, n-butyl lithium, lithium 2,2,6,6-tetramethylpiperidide (LTMP), sodium hydride, and an alkylating agent \( R^3\text{-Y} \) wherein \( Y \) is a halo atom such as chloro, bromo or iodo and \( R^2 \) represents \( \text{C}_{1-6}\text{alkyl} \), heterocyclylalkyl, arylalkyl or heteroarylalkyl, in a suitable solvent such as tetrahydrofuran.

Compounds of Formula (XXXII) may also be prepared from a compound of Formula (XXXIII)
in which R² represents C₄₋₆-alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl, R⁷ and R⁸ independently represent hydrogen, C₄₋₆-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, and R⁴, R⁵ and R⁶ are as defined above for Formula (I), using a cyanide source such as sodium cyanide, potassium cyanide or trimethylsilyl cyanide and a suitable acylating agent, for example R³⁻C(O)-hal, wherein hal is a halo atom, preferably chloro or bromo and R³ is as defined above for Formula (I), and optionally with a Lewis acid catalyst such as aluminium trichloride (an example of a Reissert reaction). Examples are given in (but are not restricted to) J. Org. Chem. (1992) 57, 750.

Compounds of Formula (XXXIII) may be prepared by a Bischler-Napieralski reaction, that is cyclisation of a compound of Formula (XXXIV)

in which R² represents C₄₋₆-alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl; and R⁷ and R⁸ independently represent hydrogen, C₄₋₆-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl and R⁴, R⁵ and R⁶ are as defined above for Formula (I), using a suitable reagent such as phosphorous oxychloride or phosphorous pentoxide. Examples are given in, but not restricted to, Org React (1951) 6, 74, J. C. S. Perkin Trans 1 (1981) 2830.

Compounds of Formula (XXVII) in which R⁹ is an alkoxy group, R⁷ represents hydrogen, C₄₋₆-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, R⁸ and R⁹ are hydrogen, and R⁴, R⁵ and R⁶ are as defined above for Formula (I), may also be prepared from a compound of Formula (XXXV)

in which R⁹ is an alkoxy group, R⁷ represents hydrogen, C₄₋₆-alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl and R⁴ and R⁵ are as defined above for Formula (I), by reaction with a suitable acylating agent, for example R³⁻C(O)-Y, wherein Y is a halo atom, preferably chloro or bromo, and R³ is as defined above for Formula (I). Preferably the
reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine.

Compounds of Formula (XXXV) in which \( R^1 \) is an alkoxy group may be prepared from a compound of Formula (XXXVI)

\[
\begin{align*}
\text{COR}^H \\
R^4 & \quad \text{(XXXVI)} \\
R^5 & \\
R^7 &
\end{align*}
\]

in which \( R^1 \) is an alkoxy group and \( R^7 \) represents hydrogen, \( C_1-C_6 \text{alkyl, aryl, heteroaryl, a} \text{rylalkyl, or heteroarylalkyl and } R^4 \text{ and } R^5 \text{ are as defined above for Formula (I), by reduction, for example by using hydrogen and a platinum oxide catalyst, see for example Chem. Pharm. Bull. (1997) 45, 1248.}

Compounds of Formula (XXIX) may also be prepared from a compound of Formula (XXXVII)

\[
\begin{align*}
R^4 & \\
R^5 & \quad \text{(XXXVII)} \\
R^7 & \\
R^8 &
\end{align*}
\]

in which \( R^7 \) and \( R^8 \) independently represent hydrogen, \( C_1-C_6 \text{alkyl, aryl, heteroaryl, a} \text{rylalkyl, or heteroarylalkyl and } R^4, R^5 \text{ and } R^6 \text{ are as defined for Formula (I), using a cyanide source such as sodium cyanide, potassium cyanide or trimethylsilyl cyanide and a suitable acylating agent, for example } R^8-C(=O)-Y, \text{ wherein } Y \text{ is a halo atom, preferably chloro or bromo and } R^3 \text{ is as defined above for Formula (I), and optionally with a Lewis acid catalyst such as aluminium trichloride (an example of a Reissert reaction). Examples are given in (but are not restricted to) J. Org. Chem. (1992) 57, 750.}

Compounds of Formula (I) in which \( R^1 \) is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and \( R^4 \) is a carboxylic acid, may be prepared from a compound of Formula (II) in which \( R^4 \) is trifluoromethanesulphonate or a halide such bromide, by treatment with carbon monoxide and water in the presence of a suitable palladium catalyst such as palladium (II) acetate and bis-diphenylphosphinoferrocene or combinations thereof, in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF.
Compounds of Formula (I) in which $\text{R}^{\text{II}}$ is esterified to form $\text{OR}$ wherein $\text{OR}$ is an alkoxy, benzyloxy or silyloxy group, and $\text{R}^{4}$ is an ester ($\text{CO}_{2}\text{R}^{2}$), may be prepared from a compound of Formula (II) in which $\text{R}^{4}$ is is trifluoromethanesulphonate or a halide such bromide, by treatment with carbon monoxide an alcohol $\text{R}^{0}\text{OH}$ in the presence of a suitable palladium catalyst such as palladium (II) acetate and bis-diphenylphosphinoferrocene or combinations thereof, in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF.

Compounds of Formula (I) in which $\text{R}^{\text{II}}$ is esterified to form $\text{OR}$ wherein $\text{OR}$ is an alkoxy, benzyloxy or silyloxy group, and $\text{R}^{4}$ is a substituted vinyl group may be prepared by reaction between a compound of Formula (II) in which $\text{R}^{4}$ is trifluoromethanesulphonate or a halide such bromide, and an appropriate vinyl compound (XXXVIII) (examples include vinyl ester $\text{L} = \text{CO}_{2}\text{R}^{2}$, vinyl sulphone $\text{L} = \text{SO}_{2}\text{R}^{2}$, vinyl ketone $\text{L} = \text{COR}^{1}$ wherein $\text{R}^{1}$ is a vinyl group) in the presence of a suitable palladium catalyst such as palladium (II) acetate and bis-diphenylphosphinoferrocene complexed with dichloromethane in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF.

Compounds of Formula (I) in which $\text{R}^{\text{II}}$ is esterified to form $\text{OR}$ wherein $\text{OR}$ is an alkoxy, benzyloxy or silyloxy group, and $\text{R}^{4}$ is a 2-substituted ethyl group may be prepared by hydrogenation of an appropriately substituted vinyl derivative using a catalyst such as palladium on carbon, in a suitable solvent such as ethanol.

Compounds of Formula (I) in which $\text{R}^{\text{II}}$ is esterified to form $\text{OR}$ wherein $\text{OR}$ is an alkoxy, benzyloxy or silyloxy group, and $\text{R}^{4}$ is trifluoromethanesulphonate, may be prepared from a compound of Formula (II) in which $\text{R}^{4}$ is $\text{OH}$, by treatment with trifluoromethanesulphonic anhydride in the presence of a suitable base such as triethylamine, in a suitable solvent such as dichloromethane.

Compounds of Formula (I) in which $\text{R}^{\text{II}}$ is esterified to form $\text{OR}$ wherein $\text{OR}$ is an alkoxy, benzyloxy or silyloxy group, and $\text{R}^{4}$ is an aryl or heteroaryl group may be prepared by reaction between a compound of Formula (II) in which $\text{R}^{4}$ is trifluoromethanesulphonate or a halide such bromide, and an appropriate aryl or heteroaryl boronic acid derivative ($\text{R}^{4}$-B(OH)$_{2}$), in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0), in the presence of a suitable base such as potassium phosphate in a suitable solvent such as dimethoxymethane. Alternatively the
aryl or heteroaryl group may be in the form an organozinc reagent (R^4-Zn-hal) or an organotin reagent (R^4-Sn(n-alkyl)_3).

Compounds of Formula (I) in which R^I is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and R^4 is OH, may be prepared from a compound of Formula (II) in which R^4 is benzyloxy, by hydrogenation with a suitable catalyst such as palladium on carbon in a suitable solvent such as ethanol.

Compounds of Formula (I) in which R^II is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and R^4 is an optionally substituted ether (OR^A) may be prepared by treatment of a compound in which R^4 is OH with an alkylating agent (hal-(CH_2)_(n-R^A), hal-(CH_2)_(n-het), n= 1-5) in the presence of a suitable base such as sodium hydride or potassium carbonate in a suitable solvent such as DMF.

Compounds of Formula (I) in which R^II is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and the compound of Formula (I) contains an amide group, may be prepared from the corresponding carboxylic acid using an amine or amine equivalent R^B_R^C NH and a coupling agent such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) in a suitable solvent such as DMF.

Compounds of Formula (I) in which R^II is NR^B_R^C may be prepared from compounds of Formula (I) in which R^I is hydroxy, using an amine or amine equivalent R^B_R^C NH and a coupling agent such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) in a suitable solvent such as DMF.

Compounds of Formula (I) in which R^II is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and R^4 is NH_2 may be prepared from compounds of Formula (I) in which R^4 is a halogen such as bromo by treatment with lithium bis(trimethylsilyl)amide and catalyst reagents such as tris(dibenzylideneacetone)dipalladium(0) and 2-(dicyclohexylphosphino)biphenyl or combinations thereof, in a suitable solvent such as tetrahydrofuran.

Compounds of Formula (I) in which R^II is esterified to form OR wherein OR is an alkoxy, benzyloxy or silyloxy group, and R^4 is SO_2_R^D may be prepared from compounds of Formula (I) in which R^4 is a halogen such as bromo by treatment with a sodium salt of an alkylsulfinic acid (eg sodium methylsulfinic acid), in the presence of a copper catalyst (such as copper triflate complexed with toluene) in a suitable solvent such as dimethylsulfoxide, preferably in the temperature range 80-120 °C.

Compounds of Formula (V), (IX), (XI), (XII), (XV), (XVI), (XVII), (XVIII), (XIX), (XXIII), (XXV), (XXVI), (XXVII), (XXIX), (XXXIV), (XXXVI), (XXXVII) and (XXXVIII) are commercially available or well known in the art.
With appropriate manipulation and protection of any chemical functionality, synthesis of
compounds of Formula (I) is accomplished by methods analogous to those above and to
those described in the Experimental section. Suitable protecting groups can be found, but
are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Code</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strata cartridge</td>
<td>Dual action SPE cartridge available from Phenomenex</td>
<td></td>
</tr>
<tr>
<td>SPE</td>
<td>solid phase extraction column</td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DMF</td>
<td>dimethylformamide</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
<td></td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
<td></td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
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</tr>
</tbody>
</table>
| HATU | O-(7-azabenozotriazol-1-yl)-N,N,N',N'-tetramethyluronium-

hexafluorophosphate |
| DME | dimethoxy methane |
| OASIS cartridge | Sample extraction cartridge available from Waters |

EXAMPLES

All Examples and Intermediates are racemic.

**Intermediate 1**

2-[(4-Chloro-benzylidene)-amino]-3-phenyl-propionic acid, tert-butyl ester

![Chemical Structure](image)

Phenylalanine tert-butyl ester hydrochloride (2 g) was dissolved in dichloromethane (20
mL) and treated with 4-chlorobenzaldehyde (1.09 g). Triethylamine (1.08 mL) was added
and the mixture stirred at 50 °C for 4h. The reaction mixture was washed with water (25
mL). The organic phase was collected through a hydrophobic frit and concentrated to give
the title compound.

^1H NMR (CDCl₃): δ 7.94 (s, 1H), 7.69 (d, 2H), 7.41 (d, 2H), 7.32-7.20 (m, 5H), 4.12 (dd, 1H), 3.37 (dd, 1H), 3.15 (dd, 1H) and 1.49 (s, 9H).
Intermediate 2
3-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, tert-butyl ester

Intermediate 1 (343 mg) was dissolved in toluene (4 mL) and the solution cooled to 0°C under nitrogen. α,α’-Dibromo-o-xylene (290 mg) was added and the stirred reaction mixture was treated with caesium hydroxide monohydrate (840 mg) and tetra-n-butyl ammonium bromide (3.2 mg.) After 1h, the mixture was partitioned between diethyl ether (10 mL) and water (10 mL). The organic phase was concentrated to dryness and the residue re-dissolved in tetrahydrofuran (4 mL) then treated with citric acid solution (0.5 M, 10 mL). After stirring for 1h at room temperature, this mixture was extracted with cyclohexane. The aqueous phase was basified by addition of solid sodium hydrogencarbonate and extracted with diethyl ether. The organic extract was dried (Na₂SO₄) and concentrated to give the title compound.

MS calcd for (C₂₁H₂₃NO₂ + H)⁺: 324
MS found (electrospray): (M+H)⁺ = 324

Intermediate 3
2-(3-Methoxy-4-tert-butylbenzoyl)-3-benzyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, tert-butyl ester

Intermediate 2 (162 mg) was dissolved in dichloromethane (4 mL) and treated with 3-methoxy-4-tert-butylbenzoyl chloride⁴ (136 mg.) Triethylamine (92 uL) was added and the solution stirred overnight at room temperature. The reaction mixture was quenched by addition of sodium bicarbonate solution (1 M, 15 mL) and extracted with dichloromethane (15 mL.) The organic extract was concentrated to dryness and purified by silica gel chromatography eluting with ethyl acetate/cyclohexane (1:20, 1:15 then 1:10,) to give the title compound.

*Prepared from 3-methoxy-4-tert-butylbenzoic acid (J. Org. Chem. (1961), 26, 1732.)
MS calcd for (C₉₀H₉₉NO₄ + H)⁺: 514
MS found (electrospray): (M+H)⁺ = 514

Intermediate 4
**2-(3-Methoxy-4-tert-butylbenzoyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester**

7-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester hydrochloride (WO 01/04090) (200 mg) was dissolved in dichloromethane (7 mL) and the solution cooled to around 0°C under nitrogen. The solution was treated dropwise with diisopropylethylamine (127 mg), followed by N-methyl morpholine (109 mg) and stirred for 30 minutes at 0°C. After this time the reaction mixture was treated drop-wise with 3-methoxy-4-butylbenzoylchloride (220 mg) in dichloromethane (1 mL) and warmed to room temperature and stirred for 1.5 hours. The reaction mixture was acidified with dilute hydrochloric acid and extracted three times with ethyl acetate. The organic extracts were combined, dried (Na₂SO₄), filtered, concentrated to dryness and purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,…until 100:0 is reached) to give the title compound.

**Intermediate 5**

**2-(3-Methoxy-4-tert-butylbenzoyl)-7-[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester**

A stirred solution of Intermediate 4 (1 g) in acetone (16.5 mL) under nitrogen was treated with K₂CO₃ (1.1 g) and heated to reflux. The refluxing mixture was treated with benzyl bromide (650 mg) and stirred at reflux for 4 hours. After the reaction mixture had cooled to room temperature it was treated with water (25 mL) and extracted three times with dichloromethane (1x 45 mL, 2x 25 mL). The organic extracts were combined, dried (via a hydrophobic frit), concentrated to dryness and purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,…until 100:0 is reached) to give the title compound.

**MS calc'd** for (C₃₂H₃₃NO₅ + H⁺): 488

**MS found** (electrospray): (M+H)⁺ = 488
**Intermediate 6**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[[phenylmethyl]oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 5 (1 g) was dissolved in tetrahydrofuran (10 mL) and the solution cooled to –78°C under nitrogen. The solution was treated with LHMDS (lithium bis(trimethylsilylamide) (1.06M in THF, 2.3 mL) keeping the temperature of the reaction below –70°C and stirred for 20 minutes. After this time the reaction was treated with benzyl bromide (0.49 mL) and then allowed to warm to room temperature over five hours and stirring continued overnight. The reaction mixture was treated with saturated ammonium chloride (20 mL) and extracted twice with ethyl acetate (2x 30 mL). The organic extracts were combined, washed with brine, dried (Na₂SO₄), filtered, concentrated to dryness and purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85, ..., until 100:0 is reached) to give the **title compound**.

MS calcd for (C₃₇H₃₆NO₁₆ + H)⁺: 578
MS found (electrospray): (M+H)⁺ = 578

**Intermediate 7**

2-(3-Methoxy-4-tert-butylbenzoyl)-7-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

A stirred solution of Intermediate 6 (500 mg) in ethanol (40 mL) was hydrogenated over 10% Pd/C (wet 50% w/w) for 14 hours at room temperature. The reaction mixture was filtered through celite to remove the catalyst. The celite was washed with ethanol (200 mL). The filtrate was concentrated to dryness and purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (1:1 v/v) to give the **title compound**.

MS calcd for (CₙHₙ₅NO₅ + H)⁺: 488
MS found (electrospray): (M+H)⁺ = 488
**Intermediate 8**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-
{( trifluoromethyl)sulfonyl]oxy}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 7 (3 g) was dissolved in dimethylformamide (100 mL) and the solution cooled to 0°C under nitrogen. Triethylamine (2.3 mL) was added and the stirred solution treated with N-phenyltrifluoromethanesulfonamide (4.83 g). After 30 minutes at 0°C the reaction mixture was allowed to reach room temperature and stirred for 72 hours. The reaction mixture was diluted with water (5 mL) and concentrated, treated with water (200 mL) and extracted with ethyl acetate (4x 250 mL). The combined organic extracts were washed with water (2x 250 mL), dried (Na₂SO₄), filtered, concentrated to dryness and purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (5:95, 10:90 then 20:80, v/v) to give the title compound.

MS calcd for (C₃₀H₂₈F₃NO₇S + H)⁺: 620
MS found (electrospray): (M+H)⁺ = 620

**Intermediate 9**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid, dimethyl ester

A solution of Intermediate 8 (3 g) in dimethylformamide (15 mL) and methanol (3.75 mL) was treated with triethylamine (1.34 mL), followed by Pd(OAc)₂ (65 mg) and diphenylphosphinoferrocene (322 mg). The reaction mixture was then purged with carbon monoxide and under an atmosphere of carbon monoxide (balloon pressure) stirred at 60°C for 4 hours and then stirred overnight at room temperature. The reaction mixture was treated with half saturated NaHCO₃ solution (40 mL) and extracted with ethyl acetate (2x 50 mL). The organic extracts were combined, washed with brine, dried (Na₂SO₄),
concentrated to dryness and the residue purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (1:6 v/v) to give the title compound.

MS calcd for (C$_{32}$H$_{35}$NO$_5$ + H)$^+$: 530
MS found (electrospray): (M+H)$^+$ = 530

**Intermediate 10**

2-(3-Methoxy-4-tert-butylbenzoyl)-7-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 7 (238 mg) was dissolved in acetone (7 mL) under nitrogen and was treated with K$_2$CO$_3$ (262 mg) and heated to reflux. The refluxing mixture was treated with methyl iodide (54 uL) and stirred at reflux overnight. After the reaction mixture had cooled to room temperature it was treated with water (7 mL) and extracted three times with dichloromethane (1x 15 mL, 2x 7 mL). The organic extracts were combined, dried (Na$_2$SO$_4$), concentrated to dryness and purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,...until 100:0 is reached) to give the title compound.

MS calcd for (C$_{31}$H$_{33}$NO$_5$ + H)$^+$: 502
MS found (electrospray): (M+H)$^+$ = 502

**Intermediate 11**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[(1,3-thiazol-4-ylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 7 (100 mg) was dissolved in acetone (5 mL) under nitrogen and was treated with K$_2$CO$_3$ (166 mg) and heated to reflux. The refluxing mixture was treated with 4-chloromethyl 2-thiazole (152 mg) and stirred at reflux overnight. After the reaction mixture had cooled to room temperature it was treated with water (10 mL) and extracted three times with dichloromethane (3x 10 mL). The organic extracts were combined, dried (Na$_2$SO$_4$), concentrated to dryness and purified by silica gel chromatography, gradient
elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,... until 100:0 is reached) to give the title compound.

MS calc'd for (C_{33}H_{34}N_{2}O_{6}S + H)^+ : 571
MS found (electrospray): (M+H)^+ = 571

**Intermediate 12**

2-(3-Methoxy-4-tert-butybenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-7-dicarboxylic acid, 3-methyl ester

A solution of Intermediate 9 (1 g) in tetrahydrofuran (20 mL), methanol (20 mL) and water (20 mL) was treated with lithium hydroxide (136 mg) and stirred overnight at room temperature. The reaction mixture was concentrated and the residue partitioned between 2N HCl (100 mL) and ethyl acetate (100 mL). The organic phase was concentrated to give the title compound.

MS calc'd for (C_{31}H_{35}NO_{6} + H)^+ : 516
MS found (electrospray): (M+H)^+ = 516

**Intermediate 13**

7-(Aminocarbonyl)-2-(3-Methoxy-4-tert-butybenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

A solution of Intermediate 12 (600 mg) in thionyl chloride (10 mL), was heated at reflux for 4 hours and then concentrated, dissolved in toluene (6 mL) and concentrated again. A portion of the residue (480 mg) was dissolved in ammonia in ethanol (2M, 10 mL) and stirred for 15 minutes at room temperature. The reaction mixture was partitioned between 2N HCl (20 mL) and dichloromethane (20 mL). The organic phase was dried (via a hydrophobic frit) and concentrated. The residue was purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,... until 100:0 is reached) to give the title compound.
'H NMR (CD3OD): δ 7.60 (1H, d), 7.41 (1H, s), 7.32 (6H, m), 7.21 (1H, d), 6.93 (2H, m), 5.99 (1H, bs), 5.54 (1H, bs), 4.64 (1H, d), 4.20 (1H, d), 3.87 (3H, s), 3.81 (1H, d), 3.57 (3H, s), 3.37 (1H, d), 3.22 (1H, d), 3.06 (1H, d), 1.41 (9H, s)

5 Intermediate 14
7-[(2-Amino-2-oxoethyl)oxy]-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 7 (100 mg) was dissolved in acetone (5 mL) under nitrogen was treated with K2CO3 (84 mg) and heated to reflux. The refluxing mixture was treated with bromoacetamide (85 mg) and stirred at reflux overnight. After the reaction mixture had cooled to room temperature it was diluted with water (40 mL) and extracted twice with ethyl acetate (2x 40 mL). The organic extracts were combined, dried (Na2SO4), filtered, concentrated to dryness and purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,...until 100:0 is reached) to give the title compound.

MS calcd for (C32H38N2O6 + H)\(^+\): 545
MS found (electrospray): (M+H)\(^+\) = 545

20 Intermediate 15
2-(3-Methoxy-4-tert-butylbenzoyl)-7-(2-furanyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

A solution of Intermediate 8 (150 mg) in dimethylformamide (4 mL) was treated with tributyl(2-furanyl) stannane (173 mg), catalytic Pd(PPh3)2Cl2 (15 mg), and lithium chloride (15 mg) and stirred at 100°C under nitrogen for 3 hours. The reaction mixture was cooled to room temperature and filtered through celite, and concentrated. The residue was purified by silica gel chromatography, gradient elution with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85,...until 100:0 is reached) to give the title compound.

MS calcd for (C34H36N2O6 + H)\(^+\): 538
MS found (electrospray): (M+H)^+ = 538

**Intermediate 16**

2-(3-Methoxy-4-tert-butylbenzoyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 16 was prepared from 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester hydrochloride (J. Med Chem., 36, 1993, 3985) using a similar procedure to that described for Intermediate 4.

MS calcd for (C_{23}H_{27}NO_5 + H)^+ = 398
MS found (electrospray): (M+H)^+ = 398

**Intermediate 17**

2-(3-Methoxy-4-tert-butylbenzoyl)-6-{[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 17 was prepared from Intermediate 16 using a similar procedure to that described for Intermediate 5.

MS calcd for (C_{30}H_{36}NO_5 + H)^+ = 488
MS found (electrospray): (M+H)^+ = 488

**Intermediate 18**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-6-{[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

35
Intermediate 18 was prepared from Intermediate 17 using a similar procedure to that described for Intermediate 6.
MS calcd for (C_{37}H_{33}NO_{5} + H)^+ = 578
MS found (electrospray): (M+H)^+ = 578

**Intermediate 19**
2-(3-Methoxy-4-tert-butylbenzoyl)-6-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 19 was prepared from Intermediate 18 using a similar procedure to that described for Intermediate 7.
MS calcd for (C_{39}H_{35}NO_{5} + H)^+ = 488
MS found (electrospray): (M+H)^+ = 488

**Intermediate 20**
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-6-([(trifluoromethyl)sulfonyl]oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 20 was prepared from Intermediate 19 using a similar procedure to that described for Intermediate 7.
MS calcd for (C_{39}H_{34}NO_{5}S + H)^+ = 521
MS found (electrospray): (M+H)^+ = 521
Intermediate 20 was prepared from Intermediate 19 using a similar procedure to that described for Intermediate 8.
MS calcd for $(C_{31}H_{52}F_2NO_7S + H)^+ \approx 620$
MS found (electrospray): $(M+H)^+ = 620$

**Intermediate 21**
2-(3-Methoxy-4-tert-buty1benzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,6-dicarboxylic acid, 3,6-dimethyl ester

Intermediate 21 was prepared from Intermediate 20 using a similar procedure to that described for Intermediate 9.
MS calcd for $(C_{32}H_{38}NO_9 + H)^+ \approx 530$
MS found (electrospray): $(M+H)^+ = 530$

**Intermediate 22**
2-(3-Methoxy-4-tert-buty1benzoyl)-6-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

Intermediate 22 was prepared from Intermediate 19 using a similar procedure to that described for Intermediate 10.
MS calcd for $(C_{31}H_{39}NO_9 + H)^+ \approx 502$
MS found (electrospray): $(M+H)^+ = 502$

**Intermediate 23**
2-(3-Methoxy-4-tert-buty1benzoyl)-6-[[3-pyridinylmethyl]oxy]-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester
Intermediate 23 was prepared from Intermediate 19 using a similar procedure to that described for Intermediate 11.

MS calcd for (C_{36}H_{36}N_{2}O_{6} + H)^+ : 579

MS found (electrospray): (M+H)^+ = 579

**Intermediate 24**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,6-dicarboxylic acid, 3-methyl ester

Intermediate 24 was prepared from Intermediate 21 using a similar procedure to that described for Intermediate 12.

MS calcd for (C_{31}H_{38}NO_{6} + H)^+ : 516

MS found (electrospray): (M+H)^+ = 516

**Intermediate 25**

2-(3-Methoxy-4-tert-butylbenzoyl)-6-(4-pyridinyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester
Intermediate 25 was prepared from Intermediate 20 using a similar procedure to that described for Intermediate 15.

MS calc'd for (C_{39}H_{36}N_{2}O_{4} + H)^+: 549
MS found (electrospray): (M+H)^+ = 549

**Intermedate 26**

3-Isobutyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, tert butyl ester

![Chemical Structure]

To a mixture of 1,1-dimethylethyl -N-[4-chlorophenyl)methylidine]glycinate\(^1\) (0.93 g), tetran-butylammonium bromide (0.010 g, 0.030 mmol) and 1,2-bis(bromomethyl)benzene (0.87 g, 3.30 mmol) in toluene (12 mL) at room temperature was added cesium hydroxide monohydrate (2.25 g, 13.39 mmol) and the resultant mixture was stirred vigorously for 19 hours. Water was added and this mixture was extracted with diethyl ether. The extracts were evaporated to dryness and the residue was dissolved in THF (10 mL). To this solution was added 0.5M citric acid and the resultant mixture was stirred vigorously for 1 hour. The aqueous phase was separated and was successively washed with cyclohexane, basified using solid sodium carbonate and finally extracted with diethyl ether. The extracts were dried and evaporated to give the **title compound**.

MS calc'd for (C_{18}H_{27}NO_{2} + H)^+: 290
MS Found (electrospray): (M+H)^+ = 290.
1) Synlett, 2001, (7), 1185-1187

**Intermediate 27**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-isobutyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, tert butyl ester

![Chemical Structure]

To a stirred solution of Intermediate 26 (0.38 g) in dichloromethane (10 mL) was added triethylamine (0.75 mL, 5.41 mmol) and 3-methoxy-4-tert-butylbenzoyl chloride (1.00 g, 4.41 mmol) and the resultant mixture was stirred at room temperature for 67 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution and
was then dried and evaporated to a solid. A sample of the **title compound** was obtained using chromatography over silica gel eluting with ethyl acetate/cyclohexane (1:9 v/v).

MS calcd for \((C_{29}H_{41}NO_4 + H)^+\): 480

MS found (electrospray) \((M+H)^+ = 480\).

**Intermediate 28**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

![Intermediate 28 chemical structure](image)

To a stirred solution of methyl 1,2,3,4-tetrahydro-3-isoquinolinocarboxylate hydrochloride (4.5 g) in dichloromethane (150 mL) was added triethylamine (6.1 mL) and 3-methoxy-4-tert-butylbenzoyl chloride (5.0 g) and the resultant mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution and was then dried and evaporated to gum. This material was purified using chromatography over silica gel eluting with ethyl acetate/cyclohexane (15:85 v/v). Appropriate fractions were combined and evaporated to give the **title compound**.

MS calcd for \((C_{23}H_{27}NO_4 + H)^+\): 382

MS found (electrospray) \((M+H)^+ = 382\).

**Intermediate 29**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(2-methyl-2-propen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl ester

![Intermediate 29 chemical structure](image)

Intermediate 29 was prepared from Intermediate 28 using a similar procedure to that described for Intermediate 6.

MS calcd for \((C_{27}H_{35}NO_4 + H)^+\): 436

MS found (electrospray): \((M+H)^+ = 436\)
Intermediate 30
1,3-Dihydro-2H-isooindole-1,2-dicarboxylic acid, 2- tert-Butyl ester, 1-methyl ester

To a stirred suspension of potassium carbonate (2.7 g, 0.02 mol) in anhydrous DMF (20 mL) was added a solution of 1,3-dihydro-isooindole-1,2-dicarboxylic acid 1-tert-butyl ester (2.6 g, 0.01 mol) in anhydrous DMF (30 mL) under nitrogen followed by methyl iodide (7.0 g, 0.05 mol) and stirring was continued at ambient temperature for 20 hours. The reaction mixture was then partitioned between ether and water. The organic layer was then washed with water, separated and dried over Na₂SO₄ and evaporated to give the title compound.

MS calc'd for (C₁₅H₁₉NO₄ +H)⁺: 278.
MS found (electrospray) (M+H)⁺ 278.

Intermediate 31
1-Phenylmethyl-1,3-dihydro-2H-isooindole-1,2-dicarboxylic acid, 2- tert-Butyl ester, 1-methyl ester

To a solution of Intermediate 30 (0.5g, 1.8 mmol) in anhydrous tetrahydrofuran (20 mL) at −78°C under nitrogen, was added a 1.0 M solution of LHMDS (lithium bis(trimethylsilylamide) in THF (1.8 mL, 2.16 mmol). After 1 hour, benzyl bromide (0.45 mL, 3.7 mmol) was added to the reaction mixture. The stirred solution was maintained at −78°C for 1 hour, then slowly warmed to room temperature overnight. The reaction mixture was quenched with ammonium chloride solution and extracted twice with ethyl acetate. The combined organics were washed with brine, then dried over sodium sulphate, filtered and evaporated to give the title compound.

MS calc'd for (C₂₂H₂₆NO₄ +H)⁺: 368.
MS found (electrospray) (M+H)⁺ 368.

Intermediate 32
1-(Phenylmethyl)-2,3-dihydro-1H-isooindole-1-carboxylic acid, methyl ester
Intermediate 31 (0.23 g, 0.63 mmol) was dissolved in a 4.0 M solution of hydrogen chloride solution in dioxane (2 mL) and stirred for 2 hours at room temperature. The reaction mixture was then evaporated to an oil which was triturated with diethyl ether to provide a solid which was filtered off to give the title compound.

MS calc'd for (C_{17}H_{17}NO_{2}+H)^+: 268.
MS found (electrospray) (M+H)^+ 268.

**Intermediate 33**

2-[(3-Methoxy-4-tert-butylphenyl]carbonyl]-1-(phenylmethyl)-2,3-dihydro-1H-isooindole-1-carboxylic acid, methyl ester

To a stirred solution of Intermediate 32 (0.14 g, 0.46 mmol) in anhydrous dichloromethane (10 mL) under nitrogen was added triethylamine (0.13 mL, 0.92 mmol) followed by 3-methoxy-4-tert-butylbenzoyl chloride (0.13 g, 0.58 mmol). The resultant mixture was stirred at ambient temperature for 18 hours and then washed with water. The organic phase was separated, washed with water, dried over sodium sulphate and evaporated to give an oily solid. This was purified by chromatography over silica using ethyl acetate/cyclohexane (1:10 v/v) as eluent. The fractions containing the desired product were combined and evaporated to give the title compound.

MS calc'd for (C_{29}H_{35}NO_{4}+H)^+: 458.
MS found (electrospray) (M+H)^+ 458.

**Intermediate 34**

1-(2-Methyl-2-propen-1-yl)-1,3-dihydro-2H-isooindole-1,2-dicarboxylic acid, 1-methyl ester, 2-tert butyl ester
The **title compound** was prepared using a similar procedure to that described for Intermediate 31 using 3-methylbromopropene (0.49 g, 3.6 mmol.) instead of benzyl bromide.

MS calc'd for $(C_{19}H_{25}NO_4+H)^+\,$: 332.
MS found (electrospray) $(M+H)^+\,$ 332.

**Intermediate 35**
1-(2-Methylpropyl)-1,3-dihydro-2H-isindole-1,2- dicarboxylic acid, 1-methyl ester,

**2-tert butyl ester**

To 10\% palladium on carbon (150 mg, wetted) under a nitrogen atmosphere was added Intermediate 34 (0.57g, 0.15 mmol), followed by ethanol (20 mL). The reaction mixture was then placed under an atmosphere of hydrogen with stirring at ambient temperature for 18 hours. After flushing with nitrogen the reaction mixture was filtered through celite and evaporated to yield the **title compound**.

MS calc'd for $(C_{19}H_{27}NO_4+H)^+\,$: 334.
MS found (electrospray) $(M+H)^+\,$ 334.

**Intermediate 36**
1-(2-Methylpropyl)-2,3-dihydro-1H-isindole-1-carboxylic acid, methyl ester
The title compound was prepared using a similar procedure to that described for Intermediate 32 using Intermediate 35.

MS calcd for (C_{14}H_{19}NO_2H)^+: 234.
MS found (electrospray) (M+H)^+ 234.

**Intermediate 37**

2-{3-Methoxy-4-tert-butylyphenyl[carbonyl]-1-(2-methylpropyl)-2,3-dihydro-1H-isooindole-1-carboxylic acid

The title compound was prepared using a similar procedure to that described for Intermediate 4 using Intermediate 36.

MS calcd for (C_{28}H_{33}NO_4H)^+: 424.
MS found (electrospray) (M+H)^+ 424.

**Intermediate 38**

1-Isoquinoline-carboxylic acid, tert-butyl ester

To a stirred suspension of 1-isooquinoline carboxylic acid (10 g, 57.7 mmol) in dry dichloromethane (120 mL) at 0 °C was added 2-methyl-propan-2-ol (12.1 mL, 128 mmol), 4-dimethylaminopyridine (3.53 g, 28.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (12.2 g, 63.5 mmol). The mixture was allowed to attain room temperature and stirred overnight. Water (100 mL) was added, the mixture filtered and the layers separated. The aqueous layer was extracted with dichloromethane (30 mL), the organic fractions combined, dried (MgSO_4) and evaporated to give an oil. Purification by SPE (silica) eluting with cyclohexane, then cyclohexane/ethyl acetate (3:1 v/v) gave the title compound.

MS calcd for (C_{14}H_{15}NO_2H)^+:230.
MS found (electrospray) (M+H)^+ 230.
**Intermediate 39**

1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid, tert butyl ester

![Intermediate 39 structure](image)

To a solution of Intermediate 38 (2.98 g, 13 mmol) in ethanol (24 mL) was added platinum oxide hydrate (295 mg, 1.3 mmol). The mixture was stirred under an atmosphere of hydrogen gas overnight. After flushing with nitrogen gas, the solution was filtered through celite and the filtrate evaporated in vacuo to provide the title compound.

MS calcd for (C_{14}H_{16}NO_{2}H)^+: 234.
MS found (electrospray) (M+H)^+ 234.

**Intermediate 40**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, tert butyl ester

![Intermediate 40 structure](image)

The title compound was prepared using a similar procedure to that described for Intermediate 28 using Intermediate 39 as starting material.

MS calcd for (C_{28}H_{30}NO_{4}H)^+: 424.
MS found (electrospray) (M+H)^+ 424.

**Intermediate 41**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(phenylmethyl) 1-carboxylic acid, tert butyl ester

![Intermediate 41 structure](image)

The title compound was prepared using a similar procedure to that described for Intermediate 31 using Intermediate 40 as starting material.

MS calcd for (C_{33}H_{36}NO_{4}H)^+: 514.
MS found (electrospray) (M+H)^+ 514.
Intermediate 42
2-(3-Methoxy-4-tert-buty]benzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methyl-2-propen-1-yl)-1-carboxylic acid, tert butyl ester

The title compound was prepared using a similar procedure to that described for Intermediate 31 using Intermediate 40 as starting material.
MS calcd for (C_{38}H_{56}NO_{4}+H)^+ 478.
MS found (electrospray) (M+H)^+ 478.

Intermediate 43
2-(3-Methoxy-4-tert-buty]benzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methylpropyl)-1-carboxylic acid, tert butyl ester

The title compound was prepared using a similar procedure to that described for Intermediate 35 using Intermediate 42 as starting material.
MS calcd for (C_{30}H_{41}NO_{4}+H)^+ 480.
MS found (electrospray) (M+H)^+ 480.

Example 1
2-(3-Methoxy-4-tert-buty]benzoyl]-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

A solution of Intermediate 3 (73 mg) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL) and stirred overnight at room temperature. The reaction mixture
was concentrated to dryness and purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (1:15, 1:10, 1:5, 1:2, then 1:0.) to give the title compound.

MS calcd for (C_{30}H_{31}NO_{6} + H)^+ : 458
MS found (electrospray): (M+H)^+ = 458

**Example 2**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid

A solution of Intermediate 9 (52 mg) was dissolved in THF (1 mL) and methanol (1 mL). Sodium hydroxide solution (10N, 1 mL) was added and the mixture heated at 90°C for 18 hours. The THF and methanol were removed *in vacuo* and the residue acidified with 2N aqueous HCl. The mixture was extracted with ethyl acetate and the combined extracts washed with brine, dried (Na_{2}SO_{4}) and concentrated to give a colourless gum which was triturated with ether/cyclohexane to give the title compound.

MS calcd for (C_{30}H_{31}NO_{6} + H)^+ : 502
MS found (electrospray): (M+H)^+ = 502

$^1$H NMR (MeOD): δ 7.88 (1H, s), 7.49 (1H, s), 7.41 (1H, d), 7.36-7.23 (6H, m), 6.93 (1H, d), 6.86 (1H, s), 4.43 (1H, d), 4.17 (1H, d), 3.84 (3H, s), 3.46 (1H, d), 3.41 (1H, d), 3.20 (1H, d), 3.16 (1H, d), 1.40 (9H, s). Carboxylic acid protons assumed to be exchanged with the solvent.

**Example 3**

2-(3-Methoxy-4-tert-butylbenzoyl)-7-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

A solution of Intermediate 7 (146 mg) in pyridine (5 mL) was treated with lithium iodide (100 mg) and stirred at reflux under nitrogen for 72 hours. After the reaction mixture had cooled to room temperature it was diluted with 1M HCl (10 mL) and extracted with dichloromethane (3x 10 mL). The combined organic extracts were combined, washed...
with a mixture of brine and 1M HCl (10:1 ; 3x 2 mL), dried (via a hydrophobic frit) and concentrated. The residue was purified by reverse phase HPLC on a C18 column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents to give the title compound.

MS calcd for (C_{29}H_{31}NO_{5} + H)^+: 474
MS found (electrospray): (M+H)^+ = 474

^1H NMR (CDCl3): δ 7.30 (6H, m), 7.00 (1H, d), 6.94 (1H, s), 6.90 (1H, d), 6.60 (1H, d), 6.36 (1H, s), 4.35 (1H, d), 4.12 (1H, d), 3.61 (3H, s), 3.53 (1H, d), 3.27 (1H, d), 3.18 (1H, d), 3.05 (1H, d), 1.39 (9H, s) Carboxylic acid protons not seen.

**Example 4**

2-(3-Methoxy-4-tert-butylbenzoyl)-7-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

![Chemical Structure](image)

This was prepared from Intermediate 10 using a similar procedure to that described for Example 3.

MS calcd for (C_{30}H_{33}NO_{5} + H)^+: 488
MS found (electrospray): (M+H)^+ = 488

^1H NMR (CDCl3): δ 7.31 (6H, m), 7.13 (1H, d), 6.99 (1H, s), 6.94 (1H, d), 6.77 (1H, d), 6.45 (1H, s), 4.42 (1H, d), 4.10 (1H, d), 3.86 (3H, s), 3.73 (3H, s), 3.66 (1H, d), 3.27 (2H, m), 3.15 (1H, d), 1.41 (9H, s) Carboxylic acid proton not seen.

**Example 5**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

![Chemical Structure](image)

This was prepared from Intermediate 6 using a similar procedure to that described for Example 3.

MS calcd for (C_{36}H_{37}NO_{5} + H)^+: 564
MS found (electrospray): (M+H)^+ = 564

^1H NMR (CDCl_3): δ 7.33 (11H, m), 7.13 (1H, d), 6.99 (1H, s), 6.91 (1H, d), 6.84 (1H, d), 6.53 (1H, s), 4.97 (2H, s), 4.41 (1H, d), 4.09 (1H, d), 3.86 (3H, s), 3.66 (1H, d), 3.26 (2H, m), 3.13 (1H, d), 1.41 (9H, s). Carboxylic acid proton not seen.

**Example 6**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[(1,3-thiazol-4-ylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

![Chemical structure image]

A solution of Intermediate 11 (80 mg) in tetrahydrofuran (1.37 mL) and methanol (1.37 mL) was treated with sodium hydroxide (1.4 mL) and stirred at reflux overnight. The reaction mixture was concentrated and the residue partitioned between 2N HCl (8 mL) and dichloromethane (15 mL). The organic phase was dried (via a hydrophobic frit), concentrated and the residue purified by reverse phase HPLC on a C18 column using a two solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents to give the title compound.

MS calcld for (C_{38}H_{34}N_2O_6S + H)^+: 571

MS found (electrospray): (M+H)^+ = 571

^1H NMR (CD_3OD): δ 8.99 (1H, s), 7.57 (1H, s), 7.37 (1H, d), 7.30 (5H, m), 7.10 (1H, s), 6.88 (3H, m), 6.55 (1H, s), 5.11 (2H, s), 4.36 (1H, d), 4.14 (1H, d), 3.85 (3H, s), 3.47 (1H, d), 3.35 (1H, d) 3.16 (1H, d), 3.06 (1H, d), 1.40 (9H, s) Carboxylic acid proton assumed to be exchanged with the solvent.

**Example 7**

7-(Aminocarbonyl)-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

![Chemical structure image]

This was prepared from Intermediate 13 using a similar procedure to that described for Example 3, except 2,6-dimethylpyridine was used in place of pyridine.

49
MS calcd for \((C_{30}H_{32}N_2O_5 + H)^+\): 501
MS found (electrospray): \((M+H)^+ = 501\)

\(^1H\) NMR (CD\(_3\)OD): \(\delta\) 7.73 (1H, d), 7.35 (8H, m), 6.92 (1H, d), 6.89 (1H, s), 4.48 (1H, d), 4.17 (1H, d), 3.85 (3H, s), 3.48 (2H, m), 3.19 (2H, m), 1.40 (9H, s) Carboxylic acid proton assumed to be exchanged with the solvent.

**Example 8**

7-[(2-Amino-2-oxoethyl)oxy]-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

This was prepared from Intermediate 14 using a similar procedure to that described for Example 3.

MS calcd for \((C_{31}H_{33}N_2O_5 + H)^+\): 531
MS found (electrospray): \((M+H)^+ = 531\)

\(^1H\) NMR (CDCl\(_3\)): \(\delta\) 7.31 (5H, m), 7.13 (1H, d), 6.99 (1H, s), 6.91 (1H, d), 6.76 (1H, d), 6.47 (2H, s), 5.98 (2H, bs), 4.45 (1H, d), 4.40 (2H, s), 4.17 (1H, d), 3.86 (3H, s), 3.64 (1H, d), 3.30 (1H, d), 3.20 (1H, d), 3.11 (1H, d), 1.42 (9H, s) Carboxylic acid proton not seen.

**Example 9**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-(2-furanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

This was prepared from Intermediate 15 using a similar procedure to that described for Example 6.

MS calcd for \((C_{33}H_{36}NO_5 + H)^+\): 524
MS found (electrospray): \((M+H)^+ = 524\)

\(^1H\) NMR (CD\(_3\)OD): \(\delta\) 7.53 (1H, d), 7.47 (1H, s), 7.40(1H, d), 7.34 (5H, m), 7.21 (1H, d), 7.18(1H, d), 6.95 (1H, s), 6.90 (1H, s), 6.65 (1H, d), 6.44 (1H, m), 4.43 (1H, d), 4.18 (1H, d), 3.83 (3H, s), 3.45 (2H, t), 3.19 (1H, d), 3.11 (1H, d), 1.41 (9H, s)
Carboxylic acid proton assumed to be exchanged with the solvent.
Example 10
2-(3-Methoxy-4-tert-butylbenzoyl)-6-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 10 was prepared from Intermediate 19 using a similar procedure to that described for Example 3.
MS calcd for (C_{29}H_{31}NO_{5} + H)^+: 474
MS found (electrospray): (M+H)^+ = 474

1H NMR (d_{5}-MeOD): δ 7.37 (1H, d), 7.34-7.25 (5H, m), 6.91-6.87 (2H, m), 6.67-6.63 (2H, m), 6.53-6.49 (1H, m), 4.29 (1H, d), 4.15 (1H, d), 3.67 (1H, d), 3.37 (1H, d), 3.16 (1H, d), 2.99 (1H, d), 1.39 (9H, s). Carboxylic acid and phenol protons are assumed to be exchanging with the solvent.

Example 11
2-(3-Methoxy-4-tert-butylbenzoyl)-6-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 11 was prepared from Intermediate 22 using a similar procedure to that described for Example 3.
MS calcd for (C_{30}H_{33}NO_{5} + H)^+: 488
MS found (electrospray): (M+H)^+ = 488

1H NMR (CDCl_{3}): δ 7.35-7.27 (6H, m), 7.00 (1H, s), 6.94 (1H, d), 6.81 (1H, s), 6.80-6.78 (2H, m), 6.66 (1H, dd), 4.41 (1H, d), 4.10 (1H, d), 3.85 (3H, s), 3.78 (3H, s), 3.66 (1H, d), 3.31 (1H, d), 3.25 (1H, d), 3.15 (1H, d), 1.41 (9H, s). Carboxylic acid proton is assumed to be exchanging with water in the solvent.

Example 12
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-6-[[phenylmethyl]oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 12 was prepared from Intermediate 18 using a similar procedure to that described for Example 3.
MS calc'd for $\text{C}_{36}\text{H}_{35}\text{NO}_{5} + \text{H}$: 564
MS found (electrospray): (M+H)$^+$ = 564
$^1$H NMR (CDCl$_3$): $\delta$ 7.44-7.27 (11H, m), 7.00 (1H, s), 6.94 (1H, d), 6.87 (1H, s), 6.80 (1H, d), 6.73 (1H, dd), 5.06 (1H, d), 5.01 (1H, d), 4.41 (1H, d), 4.09 (1H, d), 3.85 (3H, s), 3.67 (1H, d), 3.30 (1H, d), 3.25 (1H, d), 3.14 (1H, d), 1.41 (9H, s). Carboxylic acid proton is assumed to be exchanging with water in the solvent.

Example 13
2-(3-Methoxy-4-tert-butylbenzoyl)-6-[[3-pyridinylmethyl]oxy]-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 13 was prepared from Intermediate 23 using a similar procedure to that described for Example 6.
MS calc'd for $\text{C}_{38}\text{H}_{36}\text{N}_2\text{O}_5 + \text{H}$: 565
MS found (electrospray): (M+H)$^+$ = 565
$^1$H NMR (d$_7$-MeOD): $\delta$ 8.60 (1H, s), 8.49 (1H, d), 7.92 (1H, d), 7.47-7.44 (1H, m), 7.37 (1H, d), 7.33-7.22 (5H, m), 6.93-6.87 (3H, m), 6.78-6.73 (2H, m), 5.11 (2H, s), 4.34 (1H, d), 4.16 (1H, d), 3.84 (3H, s), 3.43 (1H, d), 3.39 (1H, d), 3.17 (1H, d), 3.08 (1H, d), 1.41 (9H, s). Carboxylic acid proton is assumed to be exchanging with the solvent.

Example 14
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-6-dicarboxylic acid
Example 14 was prepared from Intermediate 21 using a similar procedure to that described for Example 6.
MS calcld for (C₃₀H₃₁NO₆ + H)⁺: 502
MS found (electrospray): (M+H)⁺ = 502
¹H NMR (d₃-MeOD): δ 7.84 (1H, s), 7.79 (1H, d), 7.40 (1H, d), 7.36-7.24 (5H, m), 6.96 (1H, d), 6.93-6.85 (2H, m), 4.47 (1H, d), 4.16 (1H, d), 3.85 (3H, s), 3.56-3.44 (2H, m), 3.23-3.15 (2H, m), 1.40 (9H, s). Carboxylic acid protons are assumed to be exchanging with the solvent.

Example 15
2-(3-Methoxy-4-tert-butylbenzoyl)-6-(4-pyridinyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 15 was prepared from Intermediate 25 using a similar procedure to that described for Example 6.
MS calcld for (C₃₉H₃₄N₂O₄ + H)⁺: 535
MS found (electrospray): (M+H)⁺ = 535
¹H NMR (CDCl₃): δ 8.61 (2H, d), 7.60 (2H, d), 7.47 (1H, s), 7.44 (1H, d), 7.37-7.27 (6H, m), 7.06 (1H, d), 7.01 (1H, s), 6.96 (1H, d), 4.58 (1H, d), 4.24 (1H, d), 3.87 (3H, s), 3.72 (1H, d), 3.43 (1H, d), 3.30-3.22 (2H, m), 1.42 (9H, s). Carboxylic acid proton is assumed to be exchanging with water in the solvent.

Example 16
2-(3-Methoxy-4-tert-butylbenzoyl)-3-isobutyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
A solution of Intermediate 27 (1.53 g) in trifluoroacetic acid (10 mL) was stirred at room temperature for 1.5 hours. The mixture was evaporated to dryness and the residue was further evaporated from dichloromethane (x2) to give a solid. This material was partially purified by chromatography over silica gel eluting with ethyl acetate/cyclohexane (1:3 v/v) and then further purified using reverse phase HPLC on a C18 column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents to give the title compound.

MS calcd for (C_{26}H_{33}NO_3 + H)^+: 424

MS found (electrospray): (M+H)^+ = 424.

^1H NMR (CDCl_3): δ 7.39 (1H, d), 7.26-7.12 (3H, m), 7.01 (1H, d), 6.99-6.91 (2H, s), 4.68 (1H, d), 4.55 (1H, d), 3.85 (3H, s), 3.37 (1H, d), 3.10 (1H, d), 2.61 (1H, dd), 1.95 (1H, dd), 1.86 (1H, m), 1.40 (9H, s), 1.01 (3H, d) 0.93 (3H, d). Carboxylic acid proton is assumed to be exchanging with the solvent.

**Example 17**

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(2-methyl-2-propen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Example 17 was prepared from Intermediate 29 using a similar procedure to that described for Example 6.

MS calcd for (C_{26}H_{33}NO_3 + H)^+: 422

MS found (electrospray): (M+H)^+ = 422

^1H NMR (CDCl_3): δ 7.35 (1H, d), 7.31-7.19 (3H, m), 7.07-6.97 (3H, m), 5.03 (1H, br s), 4.91 (1H, br s), 4.63 (1H, d), 4.45 (1H, d), 3.87 (3H, s), 3.43 (1H, d), 3.32 (1H, d), 3.17
(1H, d), 2.87 (1H, d), 1.87 (3H, s), 1.42 (9H, s) Carboxylic acid proton is assumed to be exchanging with water in the solvent.

**Example 18**

2-(3-Methoxy-4-tert-butylbenzoyl)-1-(phenylmethyl)-2,3-dihydro-1H-isoinole-1-carboxylic acid

![Chemical structure](image)

A solution of Intermediate 33 (0.07g, 0.15 mmol) in THF (4 mL) and methanol (1 mL) and 2M sodium hydroxide (1 mL) were stirred at 75°C over 18 hours. The reaction mixture was then cooled and evaporated to a gum, then taken up in 2N HCl and extracted twice with ethyl acetate. The organics were then washed with brine and dried over sodium sulphate, filtered and evaporated to give a solid, which was triturated with ether to give the title compound.

MS calcd for (C_{28}H_{26}NO_{4}+H)^+ 444.

MS found (electrospray): (M+H)^+ 444.

^1H NMR (CDCl₃): 812.8 (1H, bs), 7.5 (1H, d), 7.42 (1H, t), 7.3 (2H, m), 7.12 (4H, m), 6.85 (1H, dd), 6.78 (1H, d), 6.72 (2H, dd), 4.45 (1H, d), 3.98 (1H, d), 3.85 (1H, d), 3.80 (3H, s), 3.47 (1H, d), 1.35 (9H, s).

**Example 19**

2-(3-Methoxy-4-tert-butylbenzoyl)-1-(2-methylpropyl)-2,3-dihydro-1H-isoinole-1-carboxylic acid

![Chemical structure](image)

The title compound was prepared from Intermediate 37 using a similar procedure to that described for Example 18.

MS calcd for (C_{28}H_{31}NO_{4}+H)^+ 410.
MS found (electrospray): (M+H)+ 410.

$^1$H NMR (CDCl$_3$): $\delta$ 12.5 (1H, s), 7.33 (4H, m), 7.23 (1H, m), 7.08 (1H, d), 6.99 (1H, s),
5.00 (1H, d), 4.73 (1H, d), 3.87 (3H, s), 2.67 (1H, dd), 2.18 (1H, dd), 1.36 (9H, s), 1.35
(1H,m), 0.88 (3H, d), 0.56 (3H, d).

**Example 20**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(phenylmethyl) 1-
carboxylic acid

To Intermediate 41 (50 mg, 0.097 mmol) in dichloromethane (0.5 mL) was added
triethylsilane (31 ul, 0.195 mmol) followed by trifluoroacetic acid (0.5 mL). The solution
was stirred overnight at room temperature. The solvent was evaporated in vacuo, co-
evaporated 3 times with dichloromethane and the residue triturated with ether to provide the
**title compound**.

MS calcd for (C$_{29}$H$_{33}$NO$_4$+H)$^+$: 458.

MS found (electrospray): (M+H)+ 458.

**Example 21**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methyl—2-
propen-1-yl)-1-carboxylic acid

The **title compound** was prepared using a similar procedure to that described for Example
20 using Intermediate 42 as starting material.

MS calcd for (C$_{29}$H$_{33}$NO$_4$+H)$^+$: 422.

MS found (electrospray) (M+H)$^+$ 422.

**Example 22**

2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methylpropyl)-
1-carboxylic acid
The title compound was prepared using a similar procedure to that described for Example 20 using Intermediate 43 as starting material. MS calcd for \((C_{28}H_{36}NO_4+H)^+\): 424. MS found (electrospray) \((M+H)^+\) 424.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in admixture with one or more physiologically acceptable diluents or carriers.

The compounds of the present invention can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.
The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound (IC\textsubscript{50}, potency, (EC\textsubscript{50}) efficacy, and the biological half-life (of the compound), the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a preferred method of administration of the present compounds.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula(I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.
Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

ASSAY

The potential for compounds of the invention to inhibit NS5B wildtype HCV polymerase activity may be demonstrated, for example, using the following in vitro assay:

**In Vitro Detection of Inhibitors of HCV RNA-dependent RNA Polymerase Activity**

Incorporation of $^{33}$P-GMP into RNA was followed by absorption of the biotin labelled RNA polymer by streptavidin containing SPA beads. A synthetic template consisting of biotinylated 13mer-oligoG hybridised to polyrC was used as a homopolymer substrate.

Reaction Conditions were 0.5 μM $^{33}$P-GTP (0.2 Ci/mMol), 1 mM Dithiothreitol, 20 mM MgCl$_2$, 5mM MnCl$_2$, 20 mM Tris-HCl, pH7.5, 1.6 μg/mL polyC/0.256 μM biotinylated oligoG13, 10% glycerol, 0.01% NP-40, 0.2 μL RNASin and 50 mM NaCl.

HCV RNA Polymerase (Recombinant full-length NS5B (Lohmann et al, J. Virol. 71 (11), 1997, 8416 'Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity') expressed in baculovirus and purified to homogeneity) was added to 10 nM final concentration.

5x concentrated assay buffer mix was prepared using 1M MnCl$_2$ (0.25 mL), glycerol (4mL), 10% NP-40 (0.025 mL) and Water (7.225 mL), Total 10 mL.
2x concentrated enzyme buffer contained 1M-Tris-HCl, pH7.5 (0.4 mL), 5M NaCl (0.2 mL), 1M-MgCl₂ (0.4 mL), glycerol (1 mL), 10% NP-40 (10 mL), 1M DTT (20 μL) and water (7.97 mL), Total 10 mL.

Substrate Mix was prepared using 5x Concentrated assay Buffer mix (4μL), [³²P]-GTP (10 μCi/μL, 0.02μL), 25 μM GTP (0.4 μL), 0.4 u/μL RNasin (0.04 μL), 20 μg/mL polyrC/biotinylated-oligorG (1.6 μL), and Water (3.94 μL), Total 10 μL.

Enzyme Mix was prepared by adding 1mg/ml full-length NS5B polymerase (1.5 μL) to 2.811mL 2x-concentrated enzyme buffer.

The Assay was set up using compound (1μL), Substrate Mix (10 μL), and Enzyme Mix (added last to start reaction) (10 μL), Total 21 μL.

The reaction was performed in a U-bottomed, white, 96-well plate. The reaction was mixed on a plate-shaker, after addition of the Enzyme, and incubated for 1h at 22 ℃. After this time, the reaction was stopped by addition of 40 μL 1.875 mg/ml streptavidin SPA beads in 0.1 M EDTA. The beads were incubated with the reaction mixture for 1h at 22 ℃ after which 120 μL 0.1 M EDTA in PBS was added. The plate was sealed, mixed centrifuged and incorporated radioactivity determined by counting in a Trilux (Wallac) or Topcount (Packard) Scintillation Counter.

After subtraction of background levels without enzyme, any reduction in the amount of radioactivity incorporated in the presence of a compound, compared to that in the absence, was taken as a measure of the level of inhibition. Ten concentrations of compounds were tested in three- or fivefold dilutions. From the counts, percentage of inhibition at highest concentration tested or IC₅₀s for the compounds were calculated using Grafit3 or Grafit4 software packages.

Exemplified compounds have an IC₅₀ of <25 μM in the above described assay. Preferred compounds have an IC₅₀ of <5 μM. Accordingly, the compounds of the invention are of potential therapeutic benefit in the treatment and prophylaxis of HCV.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example immune therapies ((eg. Interferon, such as Interferon alfa-2a (Roferon-A; Hoffmann-La Roche), interferon alpha-2b (Intron-A; Schering-Plough), interferon alfacon-1 (Infergen; Intermune), peginterferon alpha-2b (Peg-Interon; Schering-Plough) or peginterferon alpha-2a (Pegasys; Hoffmann-La Roche))), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarnics, anti-leukotrienes, inhibitors of cell
adhesion (e.g. ICAM antagonists), anti-oxidants (e.g. N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (e.g. ribavirin and amantidine). The compositions according to the invention may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.
Claims

1. Compounds of Formula (I):

wherein:

R³ represents aryl or heteroaryl;

R⁴ represents one or two substituents independently selected from hydrogen, C₁₋₆alkyl, halo, OR⁴, C(O)NR⁵R⁶, C(O)R⁶, CO₂H, CO₂R⁶, NR⁵R⁶, NR⁶C(O)R⁷, NR⁶CO₂R⁷, NR⁶C(O)NR⁵R⁶, NR⁶SO₂R⁷, SO₂NR⁵R⁶, SO₂R⁷, nitro, cyano, heterocyclyl, heteroaryl, aryl, arylalkyl heteroarylalkyl or CF₃;

R⁵ and R⁶ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

n represents 0 or 1;

when n represents 0, R¹ represents C(O)R¹ and R² represents C₁₋₆alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

when n represents 1, either

i) R¹ represents C(O)R¹; R² represents C₁₋₆alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl; and R⁷ and R⁸ independently represent hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl;

or

ii) R¹ and R² independently represent hydrogen, C₁₋₆alkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; R⁷ represents C(O)R¹; and R⁸ represents C₁₋₆alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

R⁴ represents hydrogen, C₁₋₆alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R⁵ and R⁶ independently represent hydrogen, C₁₋₆alkyl, aryl or heteroaryl; or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;
R^0 is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

5 \hspace{1cm} R^E \text{ represents hydrogen or C}_{1-6}\text{alkyl;}

R^F and R^G are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

10 \hspace{1cm} R^H \text{ represents hydroxy or NR}^0R^C;\text{;}

and salts, solvates and esters thereof; provided that when R^H is hydroxy, which is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than tert-butyl.

2. A compound as claimed in claim 1 selected from the group consisting of:

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

20 2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxylic acid;

2-(3-Methoxy-4-tert-butylbenzoyl)-7-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

25 2-(3-Methoxy-4-tert-butylbenzoyl)-7-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-[(1,3-thiazol-4-ylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

30 7-(Aminocarbonyl)-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

7-[(2-Amino-2-oxoethyl)oxy]-2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

35 2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-7-(2-furanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

2-(3-Methoxy-4-tert-butylbenzoyl)-6-hydroxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

2-(3-Methoxy-4-tert-butylbenzoyl)-6-methoxy-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

40 2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-6-[(phenylmethyl)oxy]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-6-[(3-pyridinylmethyl)oxy]-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-dicarboxylic acid;
5
2-(3-Methoxy-4-tert-butylbenzoyl)-6-(4-pyridyl)-3-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-isobutyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-3-(2-methyl-2-propen-1-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;
10
2-(3-Methoxy-4-tert-butylbenzoyl)-1-(phenylmethyl)-2,3-dihydro-1H-isindole-1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1-(2-methylpropyl)-2,3-dihydro-1H-isindole-1-carboxylic acid;
15
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(phenylmethyl) 1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methyl-2-propen-1-yl)-1-carboxylic acid;
2-(3-Methoxy-4-tert-butylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-(2-methylpropyl)-1-carboxylic acid;
20
and salts, solvates and esters, and individual enantiomers thereof.

3. A compound as claimed in claim 1 wherein R^3 represents phenyl optionally substituted by halo, C_{1-4}alkyl or C_{1-3}alkoxy.

25
4. A compound as claimed in claim 3 wherein R^3 represents tert-butylphenyl optionally 3-substituted by halo, C_{1-4}alkyl or C_{1-3}alkoxy.

5. A compound as claimed in claim 1 wherein when n represents 1, R^4 is positioned on the C6 or C7 positions of the tetrahydroisoquinoline ring.

6. A compound as claimed in claim 5 wherein R^4 is a single substituent.

7. A compound as claimed in claim 1 wherein R^5 and R^6 each represent hydrogen.

35
8. A compound as claimed in claim 1 wherein when n represents 0, R^1 represents C(O)OH and R^2 represents CH_3Ph or 2-methylpropyl.

9. A compound as claimed in claim 1 wherein when n represents 1, R^1 represents C(O)OH; R^2 represents -CH_3Ph, 2-methylpropyl or 2-methyl-2-propen-1-yl; and R^7 and R^8 each represent hydrogen.
10. A compound as claimed in claim 1 wherein when n represents 1, R¹ and R² each represent hydrogen; R⁷ represents C(O)OH; and R⁸ preferably represents –CH₂Ph, 2-methylpropyl or 2-methyl-2-propen-1-yl.

11. A method of treating or preventing viral infection which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I) as defined in claim 1.

12. A method as claimed in claim 11 which involves inhibiting HCV.

13. A method as claimed in claim 11 in which the compound is administered in an oral dosage form.

14. A compound of Formula (I) as defined in claim 1 for use in medical therapy.

15. A compound as claimed in claim 14 wherein the medical therapy is the treatment of viral infection.

16. A compound as claimed in claim 15 wherein the viral infection is HCV.

17. Use of a compound of Formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of viral infection.

18. Use as claimed in claim 17, wherein the viral infection is HCV.

19. A pharmaceutical formulation comprising a compound of Formula (I) as defined in claim 1 in conjunction with a pharmaceutically acceptable diluent or carrier.

20. A process for the preparation of a compound of Formula (I) as defined in claim 1, comprising treating with base a compound of Formula (II)

![Chemical Formula](attachment:image)

in which n, R¹ R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined above for Formula (I), except that when R¹ or R⁷ represents C(O)R¹⁰, R¹⁰ is an alkoxy, benzyloxy or silyloxy group.
21. A process for the preparation of a compound of Formula (I) as defined in claim 1, comprising treating with an acylating agent a compound of Formula (III)

```
R^4
\( (CR^7R^8)_n \)
NH
R^1
R^2
```

in which \( n, R^1, R^2, R^3, R^4, R^5, R^6, R^7 \) and \( R^8 \) are as defined above for Formula (I), except that when \( R^1 \) or \( R^7 \) represents \( C(O)R^H \), \( R^H \) is hydroxy or a protected form thereof.
**INTERNATIONAL SEARCH REPORT**

### A. CLASSIFICATION OF SUBJECT MATTER

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<th>IPC</th>
<th>C07D217/26</th>
<th>C07D417/12</th>
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According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Mindestens die nachstehende Klassifikation (classification system followed by classification symbols)

**IPC 7** 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 practical, search terms used)**

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>SHAMMA M ET AL: &quot;DIHYDRO-REISSERT COMPOUNDS&quot; J.ORG.CHEM., vol. 35, no. 9, 1970, pages 3119-3121, XP002289146 page 3120; compounds VIII, IX</td>
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**X** Further documents are listed in the continuation of box C.

**X** Patent family members are listed in annex.

* Special categories of cited documents:
  
  "A" document defining the general state of the art which is not considered to be of particular relevance
  
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**Date of the actual completion of the International search**

21 July 2004

**Date of mailing of the international search report**

06/08/2004

**Name and mailing address of the ISA**

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**Authorized officer**

Stix-Malaun, E

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>A</td>
<td>US 2002/193399 A1 (HAGMANN WILLIAM K ET AL) 19 December 2002 (2002-12-19) abstract examples page 5, right-hand column, last line, paragraph 1 claims 1,5</td>
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<td>A</td>
<td>WO 98/47877 A (DAUGAN ALAIN CLAUDE MARIE; GLAXO GROUP LTD (GB); PIANETTI PASCAL MAUR) 29 October 1998 (1998-10-29) examples claims</td>
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**INTERNATIONAL SEARCH REPORT**

**Box II**  
Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III**  
Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.
<table>
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