BENZODIAZEPINES AS HCV INHIBITORS

The present invention relates to the use of benzodiazepines as inhibitors of HCV replication as well as their use in pharmaceutical compositions aimed to treat or combat HCV infections. In addition, the present invention relates to compounds per se. The present invention also concerns processes for the preparation of such compounds, pharmaceutical compositions comprising them, and combinations of said compounds with other anti-HCV agents.

Following its discovery in 1989 as the agent implicated in the majority of viral non-A, non-B hepatitis (Choo et al., *Science* 244, 359-362, 1989), hepatitis C virus (HCV) has become a focus of considerable medical research (Lauer, G.M and Walker, B.D., *New Eng. J Med.* 345, 41-52, 2001). HCV is a member of the *Flaviviridae* family of viruses in the *hepacivirus* genus, and is closely related to the *flavivirus* genus, which includes a number of viruses implicated in human disease, such as dengue virus and yellow fever virus, and to the animal *pestivirus* family, which includes bovine viral diarrhea virus (BVDV). HCV is a positive-sense, single-stranded RNA virus, with a genome of around 9,600 bases. The genome comprises both 5' and 3' untranslated regions which adopt RNA secondary structures, and a central open reading frame that encodes a single polyprotein of around 3,010-3,030 amino acids. The polyprotein encodes ten gene products which are generated from the precursor polyprotein by an orchestrated series of co- and posttranslational endoproteolytic cleavages mediated by both host and viral proteases. The viral structural proteins include the core nucleocapsid protein, and two envelope glycoproteins E1 and E2. The non-structural (NS) proteins encode some essential viral enzymatic functions (helicase, polymerase, protease), as well as proteins of unknown function. Replication of the viral genome is mediated by an RNA-dependent RNA polymerase, encoded by non-structural protein 5b (NS5b). In addition to the polymerase, the viral helicase and protease functions, both encoded in the bifunctional NS3 protein, have been shown to be essential for replication of HCV RNA in chimpanzee models of infection (Kolykhalov, A.A., Mihalik, K., Feinstone, S.M., and Rice, C.M. *J Virol.* 74, 2046-2051, 2000). In addition to the NS3 serine protease, HCV also encodes a metalloproteinase in the NS2 region.

HCV replicates preferentially in hepatocytes but is not directly cytopathic, leading to persistent infection. In particular, the lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. There are 6 major HCV genotypes and more than 50 subtypes, which are differently distributed geographically. HCV type 1 is the predominant genotype in the

US and Europe. For instance, HCV type 1 accounts for 70 to 75 percent of all HCV infections in the United States. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy. An estimated 170 million persons worldwide are infected with hepatitis C virus (HCV). Following the initial acute infection, a majority of infected individuals develop chronic hepatitis, which can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma) (National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C. *Hepatology*, 36, 5 Suppl. S3-S20, 2002). Liver cirrhosis due to HCV infection is responsible for about 10,000 deaths per year in the U.S.A. alone, and is the leading cause for liver transplantations. Transmission of HCV can occur through contact with contaminated blood or blood products, for example following blood transfusion or intravenous drug use. The introduction of diagnostic tests used in blood screening has led to a downward trend in post-transfusion HCV incidence. However, given the slow progression to the end-stage liver disease, the existing infections will continue to present a serious medical and economic burden for decades (Kim, W.R. *Hepatology*, 36, 5 Suppl. S30-S34, 2002).

The treatment of this chronic disease is an unmet clinical need, since current therapy is only partially effective and limited by undesirable side effects.
Current HCV therapies are based on (pegylated) interferon-alpha (IFN-α) in combination with ribavirin. This combination therapy yields a sustained virologic response in more than 40% of patients infected by genotype 1 viruses and about 80% of those infected by genotypes 2 and 3. Beside the limited efficacy on HCV type 1, combination therapy has significant side effects and is poorly tolerated in many patients. For instance, in registration trials of pegylated interferon and ribavirin, significant side effects resulted in discontinuation of treatment in approximately 10 to 14 percent of patients. Major side effects of combination therapy include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. The development of more effective, convenient and tolerated treatments is a major public health objective.

One area of particular focus has been the search for inhibitors of the NS5b RNA-dependent RNA polymerase referred to above as close structural homologs of this polymerase do not exist within the uninfected host cell and such inhibitors will provide a more specific mode of action. Inhibitors which are currently under investigation can be classified as either nucleoside inhibitors (NIs) or non-nucleoside inhibitors (NNIs). NIs directly compete with nucleotide substrates for binding to highly conserved active

sites. Greater specificity may be achieved by NNIs, which may interact outside of the highly conserved active site at a unique allosteric site common only to structurally related polymerases. Preliminary clinical trials have resulted in a high failure rate, thereby highlighting the need to pursue the search for novel NS5b inhibitors.

Thus, there is a high medical need for low molecular weight compounds that lead to an inhibition of HCV replication.

It has been surprisingly found that certain benzodiazepine derivatives exhibit antiviral activity in mammals infected with HCV. These compounds are therefore useful in treating or combating HCV infections.

WO00/66106 discloses 1,4-benzodiazepine-2-one and 1,4-benzodiazepine-2,5-dione compounds, enantiomers, pharmaceutically acceptable salts, prodrugs or derivatives of the benzodiazepine compounds. These benzodiazepine compounds can be used to treat a variety of dysregulatory disorders related to cellular death, such as autoimmune disorders, inflammatory conditions, hyperproliferative conditions, viral infections, and atherosclerosis.

WO99/58117 relates to the use of compounds for reducing apoptosis. Said compounds are ligands of benzodiazepine peripheral receptor.

WO00/12547 relates to 1,4-benzodiazepines or 1,4- benzothiazepines derivatized with a peptide that can inhibit the interaction between annexin and annexin binding proteins, in particular, the interaction between annexin and viral proteins that bind annexins such as the HBsAg protein of HBV, glycoprotein B of the cytomegalovirus or any annexin binding protein from the influenza virus. These 1,4-benzodiazepines or 1,4-benzo-thiazepines derivatives can be used to prevent or treat diseases in which interactions between annexin family members and annexin binding proteins are involved such as HBV and/or HDV infections, cytomegalovirus infections or influenza virus infections.

EP0574781 discloses 2-amino-5-heterocyclic-substituted-1,4-benzodiazepines and their use in the treatment of AIDS and AIDS-related diseases.

Cortés E C et al.: "Efficient synthesis and spectral determination of 11-[(o-; m-; and p-substituted)-phenyl]-8-chloro-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones". Journal of Heterocyclic Chemistry 2004, 41(2), 277-280. This publication discloses the synthesis of 11-aryl-8-chloro-3,3-dimethyl-2,3,4,5,10,11-

hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones, with possible pharmacological activity in the central nervous system.

Cortés Cortés E et al.: "Synthesis and spectral properties of 11-[(o-; and p-substituted)-phenyl]-8-[(o-; m-; p-methoxy)phenylthio]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones". Journal of Heterocyclic Chemistry 2002, 39(1), 55-59. This publication discloses the preparation of twelve 2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones which have potentially useful pharmacological properties; by condensation and cyclization between 3-{[4-(o-; m-; p-methoxy)-phenylthio]-1,2-phenylenediamine}-5,5-dimethyl-2-cyclohexenone with (o-; and p-substituted)benzaldehyde.

Matsuo K et al.: "Synthesis and reactions of 11-substituted 3,3-dimethyl-2,3,4,5-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones". Chemical & Pharmaceutical Bulletin 1985, 33(9), 4057-62. This publication discloses 11-substituted 3,3-dimethyl-2,3,4,5-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-1-ones which are prepared by dehydrative cyclization of 3-(2-acylaminoanilino)-5,5-dimethyl-2-cyclohexen-1-ones with polyphosphoric acid, showing moderate analgesic activity in mice at 50 mg/kg.

WO 04/001058 describes certain 2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo-[b,e][1,4]diazepin-1-one derivatives as transcription modulating agents useful as anti-infective agents.

US 2005/123906 describes certain 2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]-diazepin-1-one derivatives as protein modulating agents.

WO 05/007141 describes certain 2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo-[b,e][1,4]diazepin-1-one derivatives as inhibitors of RING domain ubiquitin ligases.

US 2003/229065 describes certain 2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo-[b,e][1,4]diazepin-1-one derivatives as transcription modulating agents useful as anti-infective agents.

Other 2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one derivatives are described in the following references, generally without reference to any specific pharmaceutical utility:

Chemistry of Heterocyclic Compounds (New York, NY, United States)(Translation of Khimiya Geterotsiklicheskikh Soedinenii) (2004), 40(7), 949-955;

Journal of Heterocyclic Chemistry (2004), 41(2), 277-280; Rigas Tehniskas Universitates Zinatniskie Raksti, Serija 1:

Materialzinatne un Lietiska Kimija (2002), 4, 84-88; Rigas Tehniskas Universitates Zinatniskie Raksti, Serija 1:

Materialzinatne un Lietiska Kimija (2001), (3), 24-27;

Journal of Heterocyclic Chemistry (2002), 39(1), 55-59;

THEOCHEM (1999), 489(1), 7-17;

Heterocyclic Communications (1996), 2(1), 47-50;

Alexandria Journal of Pharmaceutical Sciences (1993), 7(2), 137-9;

Journal of the Chinese Chemical Society (Taipei, Taiwan) (1993), 40(2), 189-94 ;

Journal of the Indian Chemical Society (1992), 69(9), 596-8;

Bulletin des Societes Chimiques Belges (1992), 101(9), 801-6;

Chemistry Express (1992), 7(2), 133-6;

Journal of the Indian Chemical Society (1990), 67(7), 609-10;

Acta Crystallographica, Section C: Crystal Structure Communications (1987), C43(6), 1161-3;

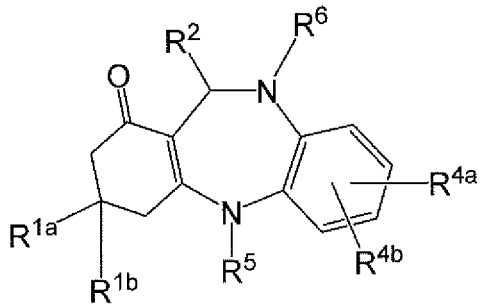
Chemical & Pharmaceutical Bulletin (1985), 33(9), 4057-62;

Journal of Heterocyclic Chemistry (1982), 19(2), 321-6;

JP 47029385; and

Chemical & Pharmaceutical Bulletin (1972), 20(7), 1588-9.

The present invention thus relates to the use of the compounds of the formula (I) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being benzodiazepines of the formula (I):



(I)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

$aryl^2$; or

Het^2;

R^6 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, Het-C_{1-6}alkylaminocarbonyl;

–C(=O)-C_{1-7}alkyl, the C_{1-7}alkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, and carboxyl;

–C(=O)-C_{2-6}alkenyl;

–C(=O)-C_{3-7}cycloalkyl, the C_{3-7}cycloalkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

–C(=O)-aryl;

–C(=O)-Het;

–C(=O)-$NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

–C(=O)-OR^{13a},

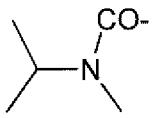
in which R^{13} is hydrogen, C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

–C(=O)-C_{1-6}alkyloxycarbonylC_{1-6}alkyl;

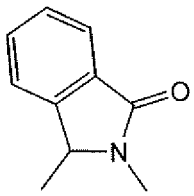
–C(=O)-Het-thioC_{1-6}alkyl; or

–C(=O)-Het-oxyC_{1-6}alkyl; or

R^2 and R^6, together with the intervening grouping in formula (I) of sub-formula:



form a ring of formula:



R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; arylcarbonyl; $-NR^{14a}R^{14b}$; or –C(=O)-$NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, mono- or diC_{1-6}alkylamino, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy,

polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, aminocarbonyl, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

aryl^2 as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

(a) halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl, morpholinyl; phenyl- or napthyl-alkoxy optionally substituted with halogen; phenyl- or naphthyl-carbonyloxy optionally substituted with halogen, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl, morpholinyl; or

(b) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -CO-NR^{20}-, -NR^{20}-CO-, -NR^{20}-SO_2-, -SO_2-NR^{20}-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

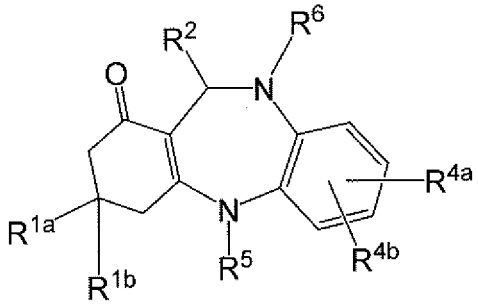
in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, *oxo*, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and

X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, or -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In one embodiment, the invention relates to the use of the compounds of formula (I) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being benzodiazepines of the formula (I):



(I)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

$aryl^2$; or

Het^2;

R^6 is hydrogen;

C_{1-6}alkyl;

–C(=O)-C_{1-7}alkyl, the C_{1-7}alkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, and carboxyl;

–C(=O)-C_{3-7}cycloalkyl, the C_{3-7}cycloalkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

–C(=O)-aryl;

–C(=O)-Het;

–C(=O)-$NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

–C(=O)-OR^{13a},

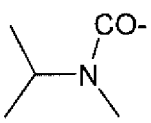
in which R^{13} is hydrogen, C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

–C(=O)-C_{1-6}alkyloxycarbonylC_{1-6}alkyl;

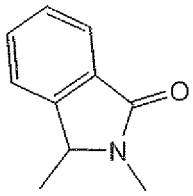
–C(=O)-Het-thioC_{1-6}alkyl; or

–C(=O)-Het-oxyC_{1-6}alkyl; or

R^2 and R^6, together with the intervening grouping in formula (I) of sub-formula:



form a ring of formula:



R^{4a} and R^{4b} are independently hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, arylcarbonyl or $-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhalo-C_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl,

piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

aryl^2 as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with

(c) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl, morpholinyl; phenyl- or napthyl-alkoxy optionally substituted with halogen; phenyl- or naphthyl-carbonyloxy optionally substituted with halogen, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or

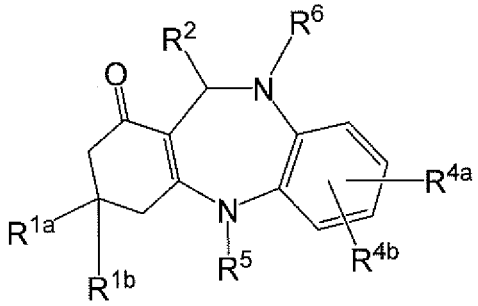
(d) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, *oxo*, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, or -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In a further embodiment, the present invention relates to the following novel compounds of formula (I) *per se*,



(I)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, Het, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

$aryl^2$; or

Het^2;

R^6 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, Het-C_{1-6}alkylaminocarbonyl;

–C(=O)-C_{1-7}alkyl, the C_{1-7}alkyl being optionally substituted independently with one, two or three substituents selected from halo, aryl, and cyano;

–C(=O)-C_{2-6}alkenyl;

–C(=O)-aryl;

–C(=O)-Het;

–C(=O)-$NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, aryl, or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from aryl and Het;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $–OR^{14a}$, or $–NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; $–NR^{14a}R^{14b}$; or -C(=O)-$NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from mono- or diC_{1-6}alkylamino, and Het;

R^5 is hydrogen; or C_{1-6}alkyl optionally substituted with aryl;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, mono- or diC_{1-6}alkylamino; or

(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of C_{1-6}alkyl, and aminocarbonyl;

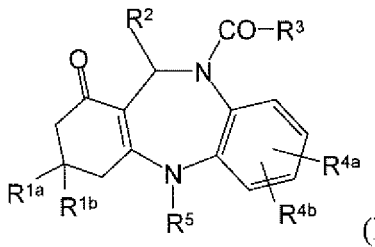
$aryl^2$ as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

(a) halo, C_{1-6}alkyl, hydroxy, trifluoromethyl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, carboxyl, nitro, mono- or diC_{1-6}alkylamino; or

(b) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 1 and X is -O-, -CO-NH-, -NH-CO-, -NH-SO_2-, -SO_2-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, aryl, and nitro.

In one embodiment, the invention relates to the use of the compounds of formula (Ia) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being acylated benzodiazepines of the formula (Ia):



(Ia)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

$aryl^2$; or

Het^2;

R^3 is C_{1-7}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, and Het; or with a cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl or carboxyl;

–C(=O)-C_{2-6}alkenyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl,

aryl;

Het;

-$NR^{12a}R^{12b}$, OR^{13a};

in which each R^{12a} and R^{12b} is, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

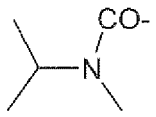
R^{13} is hydrogen, C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

C_{1-6}alkyloxycarbonylC_{1-6}alkyl;

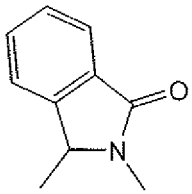
Het-thioC_{1-6}alkyl; or

Het-oxyC_{1-6}alkyl; or

R^2 and R^3, together with the intervening grouping in formula (I) of sub-formula:



form a ring of formula:



R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; arylcarbonyl; $-NR^{14a}R^{14b}$; or $-C(=O)-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, mono- or diC_{1-6}alkylamino, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cyclo-alkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or 2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, aminocarbonyl, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

$aryl^2$ as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, phenyl- or napthyl-alkoxy optionally substituted with halogen; mono- or di-alkylamino; C_{1-6}alkylcarbonyloxy; nitro; polyhaloC_{1-6}alkoxy; phenyl- or naphthyl-carbonyloxy optionally substituted with halogen, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, mono or dialkylamino, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or $aryl^2$ is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and

X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -CO-NR^{20}-, -NR^{20}-CO-,

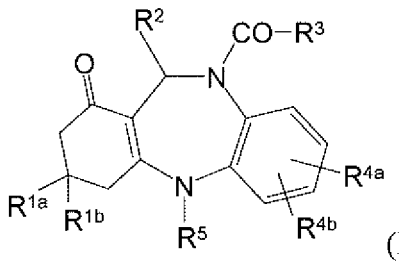
-NR^{20}-SO_2-, -SO_2-NR^{20}-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula –$(X)_n$-aryl or –$(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, –NR^{21}-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In one embodiment, the invention relates to the use of the compounds of formula (Ia) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being acylated benzodiazepines of the formula (Ia):



(Ia)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected

from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

$aryl^2$; or

Het^2;

R^3 is C_{1-7}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, and Het; or with a cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl or carboxyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl,

aryl;

Het;

$-NR^{12a}R^{12b}$, OR^{13a};

in which each R^{12a} and R^{12b} is, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted independently with one, two or three

substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

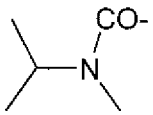
R^{13} is hydrogen, C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

C_{1-6}alkyloxycarbonylC_{1-6}alkyl;

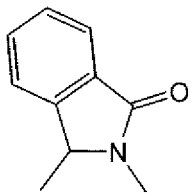
Het-thioC_{1-6}alkyl; or

Het-oxyC_{1-6}alkyl; or

R^2 and R^3, together with the intervening grouping in formula (I) of sub-formula:



form a ring of formula:



R^{4a} and R^{4b} are independently hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, arylcarbonyl or $-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhalo-C_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

$aryl^2$ as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, phenyl- or napthyl-alkoxy optionally substituted with halogen; mono- or di-alkylamino; phenyl- or naphthyl-carbonyloxy optionally substituted with halogen, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, mono or dialkylamino, cyano, nitro, amino, mono- or diC_{1-6}alkyl-amino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or $aryl^2$ is

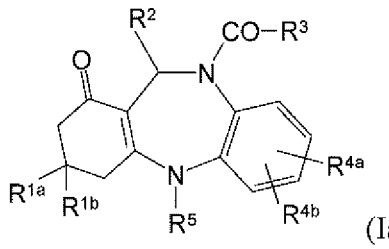
substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In a further embodiment, the present invention relates to the following novel compounds of formula (Ia) *per se*,



(Ia)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, Het, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

aryl^2; or

Het^2;

R^3 is C_{1-7}alkyl optionally substituted independently with one, two or three substituents selected from halo, aryl, and cyano;

C_{2-6}alkenyl;

aryl;

Het;

$-NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, aryl, or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from aryl and Het;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; $-NR^{14a}R^{14b}$; or $-C(=O)-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from mono- or diC_{1-6}alkylamino, and Het;

R^5 is hydrogen; or C_{1-6}alkyl optionally substituted with aryl;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, mono- or diC_{1-6}alkylamino; or

(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of C_{1-6}alkyl, and aminocarbonyl;

aryl^2 as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

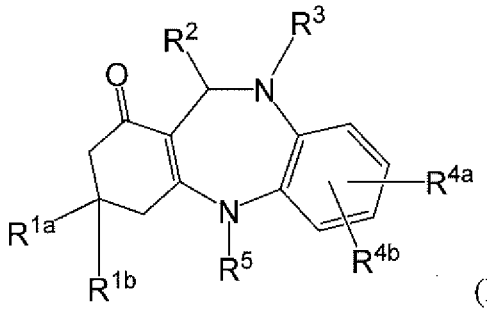
(c) halo, C_{1-6}alkyl, hydroxy, trifluoromethyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, polyhaloC_{1-6}alkoxy, nitro, mono- or diC_{1-6}alkylamino; or

(d) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 1 and X is -O-, -CO-NH-, -NH-CO-, -NH-SO_2-, -SO_2-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, aryl, and nitro.

In a further embodiment, the present invention relates to the following novel compounds of formula (Ia) *per se*, namely Compound Nos. 101, 128, 129, 131, 132, 134, 210, 223 and 224, referred to in the Tables below, and the salts, stereoisomeric forms, and racemic mixtures thereof.

In one embodiment, the invention relates to the use of the compounds of formula (Ib) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being benzodiazepines of the formula (Ib):



(Ib)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

aryl^2; or

Het^2;

R^3 is hydrogen; or C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, or Het-C_{1-6}alkylaminocarbonyl;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy; carboxyl; C_{1-6}alkoxycarbonyl; arylcarbonyl; or $-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhalo-C_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$

in which

p is 0, 1 or 2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

aryl^2 as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

(e) halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl and morpholinyl; or

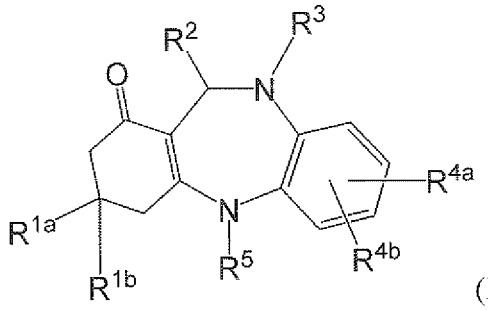
(f) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -CO-NR^{20}-, -SO_2-NR^{20}-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, *oxo*, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, or -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In one embodiment, the invention relates to the use of the compounds of formula (Ib) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compounds being benzodiazepines of the formula (Ib):



(Ib)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

$aryl^2$; or

Het^2;

R^3 is hydrogen or C_{1-6}alkyl;

R^{4a} and R^{4b} are independently hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, arylcarbonyl or $-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhalo-C_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cyclo-alkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

aryl^2 as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally independently substituted with

(g) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl and morpholinyl; or

(h) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-

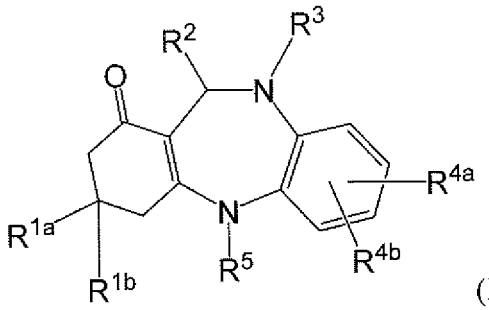
in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, *oxo*, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-,

-NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, or -S-C_{1-6}alkanediyl-

in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

In a further embodiment, the present invention relates to the following novel compounds of formula (Ib) *per se*,



(Ib)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

aryl^2; or

Het^2;

R^3 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, Het-C_{1-6}alkylaminocarbonyl;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with C_{1-6}alkoxy; carboxyl; or $-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl;

R^5 is hydrogen;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, and C_{1-6}alkoxy; or

(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings;

aryl^2 as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

a) halo, hydroxy, polyhalo-C_{1-6}alkoxy, carboxyl, nitro; or

b) a radical of formula $-(X)_n$-aryl in which n is 1 and
X is -O-, -CO-NH-, -SO_2-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three halo.

In a further embodiment, the present invention relates to the following novel compounds of formula (Ib) *per se*, namely Compound Nos. 94, 95, 96, 97, 98, 124, 154, 156, 157, 158 and 159, referred to in the Tables below, and the salts, stereoisomeric forms, and racemic mixtures thereof.

The term "C_{1-6}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example methyl, ethyl, propyl, butyl, 2-methyl-propyl, pentyl, 2-methylbutyl, hexyl, 3-methylpentyl and the like.

The term "C_{1-7}alkyl" as a group or part of a group defines straight and branched chained saturated hydrocarbon radicals having from 1 to 7 carbon atoms, such as, for example methyl, ethyl, propyl, butyl, 2-methyl-propyl, pentyl, 2-methylbutyl, hexyl, 3-methylpentyl, heptyl and the like.

The term "C_{1-6}alkoxy" means C_{1-6}alkyloxy wherein C_{1-6}alkyl is as defined above.

The term "C_{3-7}cycloalkyl" as a group or part of a group defines cyclic saturated hydrocarbon radicals having from 3 to 7 carbon atoms, such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "C_{2-6}alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having at least one double bond, and from 2 to 6 carbon atoms, such as, for example, ethenyl, prop-1-enyl, but-1-enyl, but-2-enyl, pent-1-enyl, pent-2-enyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, 1-methyl-pent-2-enyl and the like. Preferred are C_{2-6}alkenyls having one double bond.

The term "C_{4-8}cycloalkenyl" as a group or part of a group defines cyclic hydrocarbon radicals having at least one double bond, and from 4 to 8 carbon atoms, such as, for example cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl and the like, and including alkyl substitution on the ring, such as for example 2,2-dimethyl-3-methyl-cyclopent-3-enyl. Preferred are C_{4-8}cycloalkenyls having one double bond.

The term "C_{1-6}alkanediyl" as a group or part of a group defines bivalent straight and branched chained hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methanediyl, 1,2-ethanediyl, or 1,1-ethanediyl, 1,3-propanediyl, 1,3-butanediyl, 1, 4-butanediyl, 1,3 -pentanediyl, 1,5-pentanediyl, 1,4-hexanediyl, 1,6-hexanediyl, and the like.

The term "halo" is generic to fluoro, chloro, bromo or iodo.

As used in the foregoing and hereinafter "polyhaloC_{1-6}alkyl" as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, for example, 1,1,1-trifluoroethyl, 1,1-difluoro-ethyl, the polyhalomethyl groups mentioned hereinafter, and the like. A preferred subgroup of polyhaloC_{1-6}alkyl is polyhalomethyl, wherein the latter as a group or part of a group is defined as mono- or polyhalo-substituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atom is attached to an alkyl group within the definition of polyhalomethyl or polyhaloC_{1-4}alkyl, they may be the same or different.

It should also be noted that the radical positions on any molecular moiety used in the definitions, unless indicated otherwise, may be anywhere on such moiety as long as it is chemically stable. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable (*e.g.* halogen or C_{1-4}alkyl) occurs more than one time in any constituent, each definition is independent.

The *N*-oxide forms of the present compounds are meant to comprise any one of the compounds of the present invention wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

For therapeutic use, the salts of the compounds of the present invention are those wherein the counter-ion is pharmaceutically or physiologically acceptable. However, salts having a pharmaceutically unacceptable counter-ion may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound of formula (I). All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable or physiologically tolerable addition salt forms which the compounds of the present invention are able to form can conveniently be prepared using the appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, hemisulphuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, aspartic, dodecyl-sulphuric, heptanoic, hexanoic, benzoic, nicotinic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methane-sulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

Conversely said acid addition salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition base salt form by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, *e.g.* the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Alternatively, when a carboxyl moiety is present on the compound of formula (I), the compound may also be supplied as a salt with a pharmaceutically acceptable cation.

Conversely said base addition salt forms can be converted by treatment with an appropriate acid into the free acid form.

The term "salts" also comprises the hydrates and the solvent addition forms that the compounds of the present invention are able to form. Examples of such forms are *e.g.* hydrates, alcoholates and the like.

In the event that any of the substituents of formula (I) contain chiral centers, as some, indeed, do, the compounds of formulas (I) include all stereoisomeric forms thereof, both as isolated stereoisomers and mixtures of these stereoisomeric forms.

The term stereochemically isomeric forms of compounds of the present invention, as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

Pure stereoisomeric forms of the compounds of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyl-tartaric acid,

ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

The present compounds may also exist in their tautomeric forms. Such forms, although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, within the definition of Het, for example an 1,2,4-oxadiazole may be substituted with a hydroxy group in the 5-position, thus being in equilibrium with its respective tautomeric form as depicted below.



The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13–15) describing prodrugs generally is hereby incorporated. Prodrugs of a compound of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either by routine manipulation or in vivo, to the parent compound. For example, a substituent containing sulfhydryl could be coupled to a carrier which renders the compound biologically inactive until removed by endogenous enzymes or, for example, by enzymes targeted to a particular receptor or location in the subject.

Prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

Whenever used hereinafter, the term "compounds of formula (I)", or similar term is meant to include the compounds of general formula (I), (Ia), (Ib), their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs and esters. An interesting subgroup of the compounds of the present invention or any subgroup thereof are the *N*-oxides, salts and all the stereoisomeric forms thereof.

Examples of compounds of formula (I) include those wherein the aryl or aryl^{2}group is phenyl or naphthyl optionally substituted with halogen; alkoxy; phenyl- or naphthyl-oxy optionally substituted with halo; mono- or di C_{1-6}alkylamino; nitro; hydroxy; or phenyl- or naphthyl-carbonyloxy optionally substituted with halo. Especially preferred substituents include halo such as fluoro, chloro, bromo; alkoxy such as methoxy, ethoxy, isopropoxy, n-butoxy or n-pentoxy; and mono- or di C_{1-6}alkylamino such as dimethylamino or diethylamino.

Examples of compounds of formula (I) include those wherein the Het or Het^2 group is a 5 or 6 membered heterocyclic ring containing 1, 2 or 3, preferably 1 or 2 heteroatoms selected from nitrogen, oxygen and sulphur, for example, furanyl, thienyl, pyrrolyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, triazinyl, and the like. Such Het or Het^2 groups may be optionally substituted with halogen, C_{1-6}alkyl, nitro or aryl optionally substituted with halo. In the compounds of formula (Ib), such heterocyclic groups may be optionally condensed with one or two benzene rings to form for example a carbazolyl, indolyl or cromenyl group.

The above groups which may be optionally substituted with one, two or three substituents are generally preferably either unsubstituted or substituted with one or two substituents.

Further embodiments of the present invention include compounds of formula (I) or any subgroup thereof, wherein at least one of R^{1a} and R^{1b} is hydrogen, halo, C_{1-6}alkyl, aryl

or Het. In a preferred embodiment, both R^{1a} and R^{1b} are methyl. In another preferred embodiment, R^{1a} is hydrogen and R^{1b} is aryl substituted with one or two substituents selected from C_{1-6}alkoxy and phenylC_{1-6}alkoxy. In particular, R^{1a} is hydrogen and R^{1b} is phenyl substituted with one or two substituents selected from methoxy, ethoxy, and phenylmethoxy.

Further embodiments of the present invention include compounds of formula (I) or any subgroup thereof, wherein R^2 is hydrogen; C_{2-6}alkenyl optionally substituted with aryl or halo; C_{4-8}cycloalkenylC_{1-6}alkyl; $aryl^2$; or Het^2. In a preferred embodiment, R^2 is $aryl^2$ substituted with one or two substituents selected from halo, C_{1-6}alkoxy, and $-(X)_n$-aryl, wherein n is 1 and X is –O-C_{1-6}alkanediyl. In particular, R^2 is phenyl substituted with two substituents selected from halo, methoxy, 1-methyl-propoxy, and $-(X)_n$-phenyl, wherein n is 1 and X is –O-methanediyl. In another preferred embodiment, R^2 is C_{2-6}alkenyl substituted with aryl and halo, in particular ethenyl substituted with halo and phenyl.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein R^3 is C_{1-7}alkyl optionally substituted with halo, aryl or carboxyl; C_{3-7}cycloalkyl; aryl; Het; Het-thioC_{1-6}alkyl; or $-NR^{12a}R^{12b}$. In a preferred embodiment of the compounds of formula (Ia) or any subgroup thereof, R^3 is C_{1-6}alkyl or polyhaloC_{1-6}alkyl, in particular methyl, pentyl, or trifluoromethyl.

Further embodiments of the present invention include compounds of formula (Ib) or any subgroup thereof, wherein R^3 is hydrogen. In a preferred embodiment of the compounds of formula (Ib) or any subgroup thereof, R^3 is hydrogen or C_{1-6}alkyl, in particular propyl.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein at least one of R^{4a} and R^{4b} is hydrogen or arylcarbonyl.

Further embodiments of the present invention include compounds of formula (Ib) or any subgroup thereof, wherein at least one of R^{4a} and R^{4b} is hydrogen, halo, C_{1-6}alkyl or arylcarbonyl. In a preferred embodiment, both R^{4a} and R^{4b} are hydrogen.

Further embodiments of the present invention include compounds of formula (I) or any subgroup thereof, wherein R^5 is hydrogen.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein at least one of R^{1a} and R^{1b} is hydrogen, chloro; methyl; phenyl optionally substituted with halo, C_{1-6}alkoxy (for example methoxy, ethoxy or n-propoxy), nitro or mono- or di- C_{1-6}alkylamino; or at least one of R^{1a} and R^{1b} is furanyl or thienyl.

Further embodiments of the present invention include compounds of formula (Ib) or any subgroup thereof, wherein at least one of R^{1a} and R^{1b} is hydrogen, chloro; methyl; phenyl optionally substituted with halo, alkylenedioxy, C_{1-6}alkoxy (for example methoxy, ethoxy or n-propoxy), nitro, mono- or di- C_{1-6}alkylamino or benzyloxy; or at least one of R^{1a} and R^{1b} is furanyl or thienyl.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein both of R^{1a} and R^{1b} are hydrogen.

Further embodiments of the present invention include compounds of formula (Ib) or any subgroup thereof, wherein both of R^{1a} and R^{1b} are hydrogen or both are methyl.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein R^2 is hydrogen, phenyl optionally substituted with halo, C_{1-6}alkyl, polyhalo-C_{1-6}alkyl, C_{1-6}alkoxy, alkylenedioxy, nitro, hydroxy, mono- or di C_{1-6}alkylamino or with benzyloxy optionally substituted with halo (for example fluoro), or R^2 is phenyl optionally substituted with benzoyloxy optionally substituted with halo (for example chloro), or R^2 is furanyl, thienyl or pyrrolyl optionally substituted with halo, C_{1-6}alkyl, nitro, or R^2 is C_{2-6}alkenyl optionally substituted with aryl especially phenyl, or with aryl, especially phenyl, and halogen, especially bromo; or R^2 is cyclopentenylmethyl optionally substituted on the cyclopentenyl ring with C_{1-6} alkyl for example methyl, especially cyclopent-3-enyl, substituted for example with 1, 2 or 3 methyl groups especially 2,2,3-trimethyl.

Further embodiments of the present invention include compounds of formula (Ib) or any subgroup thereof, wherein R^2 is hydrogen, phenyl optionally substituted with halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, alkylenedioxy, nitro, hydroxy, mono- or di-C_{1-6}alkylamino or with benzyloxy optionally substituted with halo (for example fluoro), or R^2 is phenyl or naphthyl, each optionally substituted with benzoyloxy optionally substituted with halo (for example chloro), or R^2 is pyridyl, thienyl, carbazoyl, indolyl or cromenyl, each optionally substituted with C_{1-6}alkyl; or

R^2 is C_{2-6}alkenyl optionally substituted with aryl especially phenyl, or with aryl, especially phenyl, and halogen, especially bromo.

Further embodiments of the present invention include compounds of formula (Ia) or any subgroup thereof, wherein R^3 is methyl, ethyl, isopropyl, n-butyl, sec-butyl, pentyl, heptyl; polyhalomethyl; cyclopropyl; phenyl optionally substituted with halo for example fluoro or with carboxy; benzyl optionally substituted with halo for example fluoro; or R^3 is arylamino for example dichlorophenylamino; or benzothiazolylthio-alkyl (for example -methyl) optionally substituted with C_{1-6}alkoxy for example methoxy.

Further embodiments of the present invention include compounds of formula (I) or any subgroup thereof, wherein at least one of R^{4a} and R^{4b} is hydrogen, for example wherein R^{4a} and R^{4b} are both hydrogen.

Further embodiments of the invention include compounds of formula (Ia) or any subgroup thereof, containing one of more of the following groups:

R^{1a} and R^{1b} are both methyl;
R^2 is 2,4-dichlorophenyl, 3-methoxy-4- benzyloxy-phenyl or 1-bromo-2-phenylethenyl;
R^3 is methyl, phenyl, trifluoromethyl or cyclopropyl;
R^{4a} and R^{4b} are both hydrogen; and
R^5 is hydrogen.

Further embodiments of the invention include compounds of formula (Ib) or any subgroup thereof, containing one of more of the following groups:

R^{1a} and R^{1b} are both methyl or one of R^{1a} and R^{1b} is hydrogen and the other is phenyl substituted with one or two C_{1-6}alkoxy substituents or by a benzyloxy substituent;
R^2 is phenyl substituted with one or two halo or C_{1-6}alkoxy substituents or with a nitro or benzyloxy substituent;
R^3 is hydrogen;
R^{4a} and R^{4b} are both hydrogen or one of R^{4a} and R^{4b} is hydrogen and the other is benzoyl; and
R^5 is hydrogen.

Examples of specific compounds of formula (Ia) in accordance with the invention include Compound Nos. 35, 38, 42, 45, 48, 51, 53 and 193, referred to in the Tables below, and the salts, stereoisomeric forms, and racemic mixtures thereof.

Examples of specific compounds of formula (Ib) in accordance with the invention include Compound Nos.78, 97, 108, 116, 156 and 157 referred to in the Tables below, and the salts, stereoisomeric forms, and racemic mixtures thereof.

Pharmacology

Due to their favorable antiviral properties, as will be apparent from the examples, the compounds of the present invention are useful in the treatment of individuals infected by HCV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with flaviviruses. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HCV and other pathogenic flaviviruses, such as Yellow fever, Dengue fever (types 1-4), St. Louis encephalitis, Japanese encephalitis, Murray valley encephalitis, West Nile virus and Kunjin virus. The conditions associated with HCV include progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and HCC; and for the other pathogenic flaviruses the conditions include yellow fever, dengue fever, hemorrhagic fever and encephalitis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against the above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HCV-infected subjects of an amount effective to combat the conditions associated with HCV and other pathogenic flaviviruses. Consequently, the compounds of the present invention can be used in the manufacture of a medicament useful for treating conditions associated with HCV and other pathogenic flaviviruses.

In an embodiment, the invention relates to the use of a compound of formula (I) or any subgroup thereof as defined herein in the manufacture of a medicament for treating or combating infection or disease associated with HCV infection in a mammal. The invention also relates to a method of treating a flaviviral infection, in particular an HCV infection, or a disease associated with flavivirus infection comprising administering to a mammal in need thereof an effective amount of a compound of formula (I) or a subgroup thereof as defined herein.

In another embodiment, the present invention relates to the use of formula (I) or any subgroup thereof as defined herein for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with flaviviruses, in particular HCV.

In another embodiment, the present invention relates to the use of formula (I) or any subgroup thereof as defined herein for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with flaviviruses, wherein said HCV is inhibited in its replication.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a novel compound of formula (I) as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylactically act against, to stabilize or to reduce viral infection, and in particular HCV viral infection, in infected subjects or subjects being at risk of being infected. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a said compound of formula (I), as specified herein.

Therefore, the compounds of the present invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The dosages of the compounds of the invention will depend on a number of factors which will vary from patient to patient. However, it is believed that generally, the daily oral dosage will utilize 0.001-100 mg/kg total body weight, preferably from 0.01-50 mg/kg and more preferably about 0.01 mg/kg-10 mg/kg. The dose regimen

will vary, however, depending on the conditions being treated and the judgment of the practitioner.

It should be noted that the compounds of the invention can be administered as individual active ingredients, or as mixtures of several embodiments of this formula. In addition, the compounds of the invention may be used as single therapeutic agents or in combination with other therapeutic agents.

Also, the combination of previously known anti-HCV compound, such as, for instance, interferon-α (IFN-α), pegylated interferon-α and/or ribavirin, and a compound of the present invention can be used as a medicine in a combination therapy. The term "combination therapy" relates to a product containing mandatory (a) a compound of the present invention, and (b) optionally another anti-HCV compound, as a combined preparation for simultaneous, separate or sequential use in treatment of HCV infections, in particular, in the treatment of infections with HCV type 1. Thus, to combat or treat HCV infections, the compounds of this invention may be co-administered in combination with for instance, interferon-α (IFN-α), pegylated interferon-α and/or ribavirin, as well as therapeutics based on antibodies targeted against HCV epitopes, small interfering RNA (Si RNA), ribozymes, DNAzymes, antisense RNA, small molecule antagonists of for instance NS3 protease, NS3 helicase and NS5B polymerase.

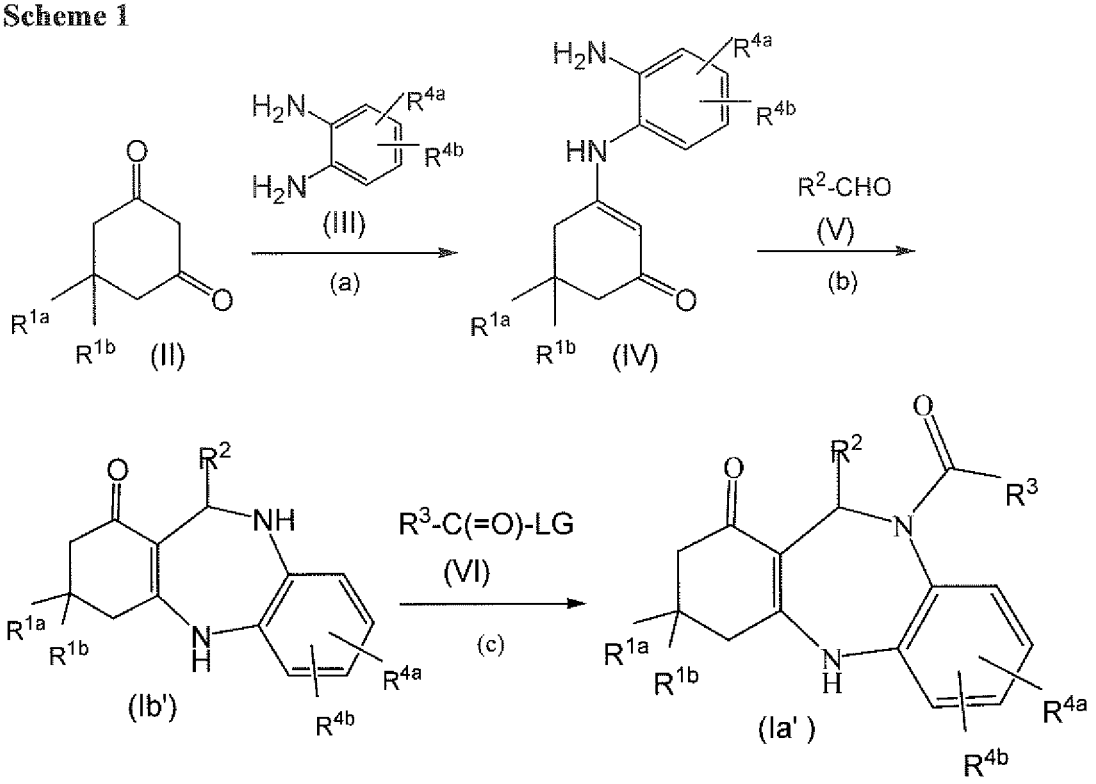
Accordingly, the present invention relates to the use of a compound of formula (I) or any subgroup thereof as defined above for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV viruses, wherein said medicament is used in a combination therapy, said combination therapy preferably comprising a compound of formula (I) and (pegylated) IFN-α and/or ribavirin.

Preparation

The compounds according to the invention are either commercially available or can be prepared in accordance with conventional procedures for example as described in the patent and literature references identified above or in accordance with the synthetic routes described below.

Compounds of formulae (Ia) and (Ib) in which R^5 is hydrogen, represented by formulae (Ia') and (Ib') below, can be prepared in accordance with the synthetic route set out in Scheme 1 below:

Scheme 1



Step (a) a cyclohexane-1,3-dione of formula (II) is reacted with an *o*-phenylene-diamine of formula (III), to give an adduct of formula (IV); the reaction being generally effected in an organic solvent for example toluene for example at reflux.

Step (b): an adduct of formula (IV) is reacted with an aldehyde of formula (V) for example in an anhydrous organic solvent such as ethanol under acid conditions for example in the presence of acetic acid, advantageously at an elevated temperature for example 40°C to 130°C preferably at 75°C for about 5 hours.

Step (c): a compound of formula (Ib') is reacted with an acylating agent of formula (VI), namely R^3-C(=O)-LG, in which LG represent a leaving group; examples of such acylating agents include acyl halides for example acyl chlorides and acyl anhydrides, the acylating reaction being effected in a basic organic solvent such as pyridine for example at a temperature of –20°C to 50°C preferably about 0°C.

Compounds of formula (Ia') in which R^5 is other than hydrogen can be prepared by reacting a corresponding compound of formula (Ia') in which R^5 is hydrogen with a compound of formula R^{5a}-LG^1 in which R^{5a} is as defined for R^5 other than hydrogen and LG^1 is a leaving group, such as an halogen atom, the reaction being generally

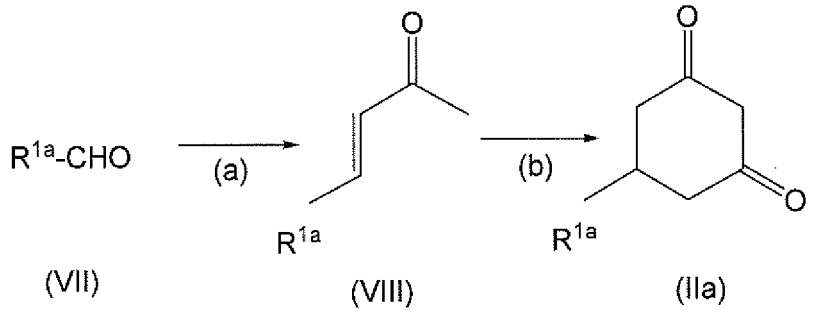
effected in the presence of a base such sodium hydride, and in an appropriate organic solvent for example tetrahydrofuran or dimethylformamide.

Compounds of formula (Ib) in which R^3 is C_{1-6}alkyl may be prepared from a corresponding compound of formula (Ib) in which R^3 is hydrogen by treatment with an alkylating agent for example a C_{1-6}alkyl halide for example an iodide, generally in the presence of a base such as potassium carbonate, and in an appropriate solvent such as acetone, conveniently at room temperature.

Compounds of formula (I) in which R^5 is other than hydrogen can be prepared by reacting a corresponding compound of formula (I), (Ia) or (Ib) in which R^5 is hydrogen with a compound of formula R^{5a}-LG^1 in which R^{5a} is as defined for R^5 other than hydrogen and LG^1 is a leaving group, such as an halogen atom, the reaction being generally effected in the presence of a base such sodium hydride, and in an appropriate organic solvent for example tetrahydrofuran or dimethylformamide.

The starting materials of formula (II) are either commercially available or can be prepared in accordance with conventional procedures. For example compounds of Formula (II) in which R^{1b} is H, represented by formula (IIa) below can be prepared in accordance with the synthetic route set out in Scheme 2 below:

Scheme 2



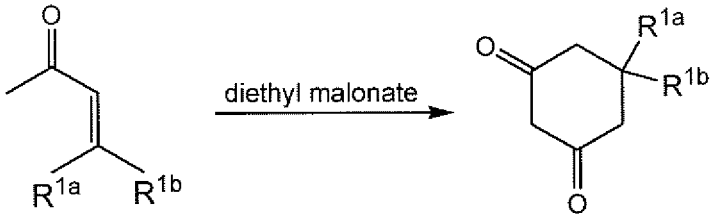
Step a): an aldehyde of formula (VII) is reacted with acetone, in presence of a base such as aqueous sodium hydroxide, to give a ketone of formula (VIII);

Step b): a ketone of formula (VIII) is cyclized to the corresponding cyclohexane-1,3-dione of formula (IIa) by reaction with diethyl malonate in presence of a base, such as potassium *tert*-butoxide in an appropriate solvent such as ethanol.

Other starting materials of formula (II) are commercially available for example the compound of formula (II) in which R^{1a} and R^{1b} are both methyl is widely available under the name of dimedone.

Alternatively compounds of formula (II) can be prepared from an alpha alkene ketone of Formula (IX) by condensation with diethyl malonate in accordance with Scheme 3 below:

Scheme 3



(IX) (II)

Accordingly, a ketone of Formula (IX) can react with one equivalent or an excess of diethylmalonate, optionally in presence of a solvent such as ethanol or isopropanol.

The present invention further includes the novel compounds of formula (IV) and (Ib') for example for use as intermediates in the preparation of the compounds of formula (Ia). The present invention further includes the novel compounds of formula (IV) for example for use as intermediates in the preparation of the compounds of formula (Ib).

EXAMPLES

The following Examples are intended to illustrate, but not to limit, the present invention.

Some of the compounds prepared in the Examples have been analysed by LC/MS on one of the following equipments:

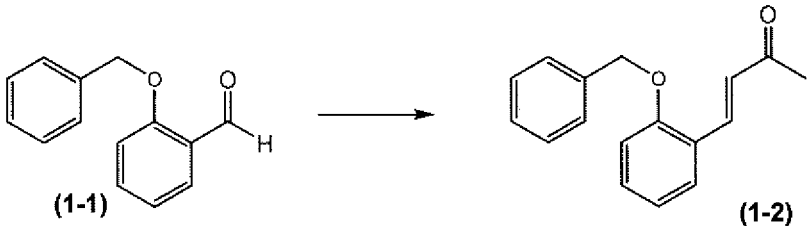
- **LCT**: method XterragradPOS@V1002V1003.olp electrospray ionisation in positive mode, scanning mode from 100 to 900 amu Xterra MS C18 (Waters, Milford, MA) 5 µm, 3.9 x 150 mm); Flow rate 1 ml/min. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile; mobile phase B: 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient from 100 % A for 3 min to 100% B in 5 min., 100% B for 6 min to 100 % A in 3 min, and equilibrate again with 100 % A for 3 min).

- ZQ: method Xterra_15cm@V2001V2001.olp
  electrospray ionisation in both positive and negative (pulsed) mode scanning from 100 to 1000 amu
  Xterra RP C18 (Waters, Milford, MA) 5 µm, 3.9 x 150 mm); Flow rate 1 ml/min. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile; mobile phase B: 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient condition from 100 % A for 3 min to 100% B in 5 min., 100% B for 6 min to 100 % A in 3 min, and equilibrate again with 100 % A for 3 min).

In the Examples the following abbreviations are used:
$(M+H)^+$: molecular ion: Å: Angstrom (10^{-10} m); Ac_2O: acetic acid anhydride; AcOH: acetic acid; Et_2O: diethyl ether; EtOAc: ethyl acetate; EtOH: ethanol; *i*-Pr_2O: diisopropyl ether; M: molar; mol•L^{-1}; *m/z*: mass to charge ratio; MeOH: methanol; N: normal; TLC: Thin Layer Chromatography; DIPE: diisopropyl ether; THF: tetrahydrofuran; DMAP: 4-dimethylamino pyridine; DMF: dimethylformamide; EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBT: 1-hydroxy-benzotriazole; DMA: N,N-dimethylaniline.

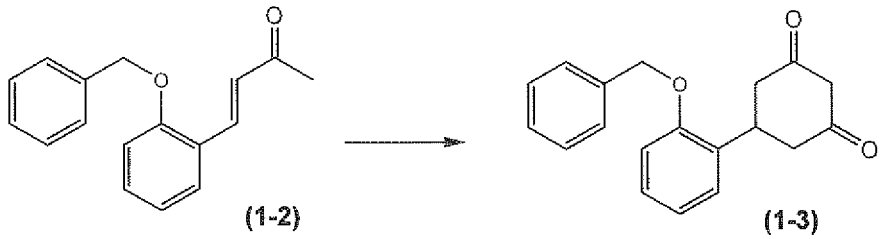
Example 1:
10-Acetyl-3-(2-benzyloxyphenyl)-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 186** diastereomer A

Step A



2-Benzyloxybenzaldehyde (30 g, 141.3 mmol) (Intermediate (**1-1**)) was stirred for 1 week in a mixture of 80 mL acetone and 500 mL of an aqueous NaOH 5% solution. The white precipitate was filtered off, thoroughly washed with water and dried, yielding 35.2 gram (98.9%) of Intermediate (**1-2**): *m/z* = 253 $(M+H)^+$.

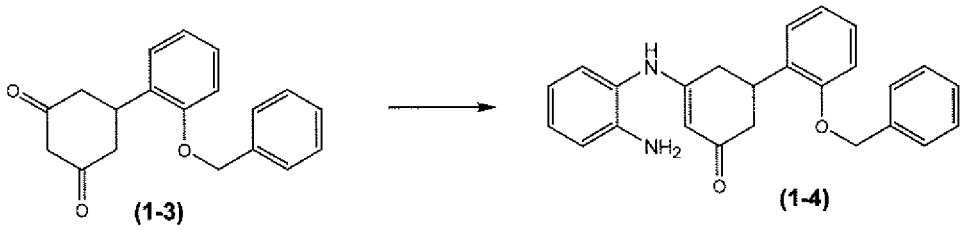
Step B



(1-2) (1-3)

Potassium *tert*-butoxide (2.22 g, 19.8 mmol) and diethyl malonate (3.01 mL, 19.8 mmol) were added to 50 mL EtOH (dried on 3 Å molecular sieves). To this mixture, Intermediate (**1-2**) (5 g, 19.8 mmol) and another 10 mL of dry EtOH was added. The reaction mixture was refluxed overnight. The EtOH was evaporated, and the residue was refluxed in 100 mL 2M NaOH for 2h. The solution was cooled in an ice-bath, 100 mL 5M H_2SO_4 were added, and the mixture was refluxed for 4h. Two layers were formed, and the aqueous layer was decanted from the oily layer. The oil solidified after cooling to room temperature and was extracted with Et_2O. The Et_2O layer was dried (Na_2SO_4) and evaporated to give 4.21 g (72.2%) of Intermediate (**1-3**): $m/z = 295$ $(M+H)^+$.

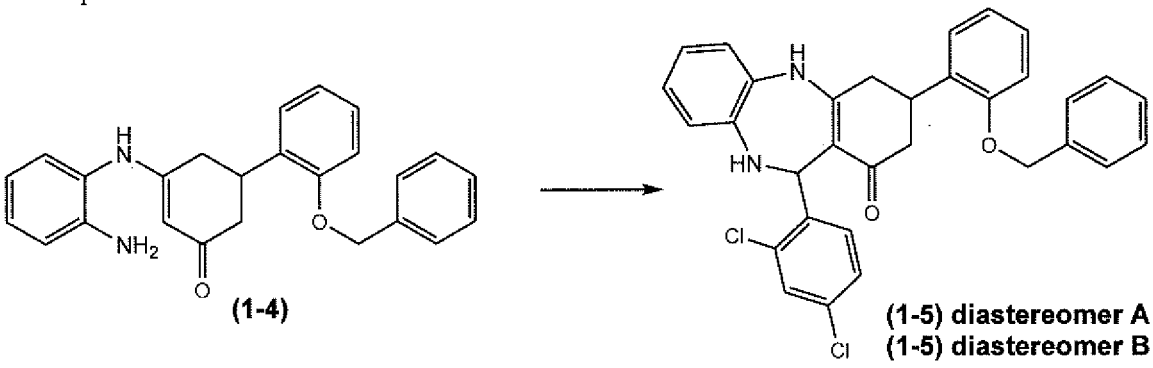
Step C



(1-3) (1-4)

A mixture of Intermediate (**1-3**) (3.47 g, 11.78 mmol) and *o*-phenylenediamine (1.27 g, 11.74 mmol) in 100 mL of dry toluene was reacted in a Dean-Stark apparatus overnight. The reaction was cooled to room temperature and the toluene was evaporated. The residue was stirred in *i*-Pr_2O and filtered off to yield 4.26 g (77.6%) of Intermediate (**1-4**).

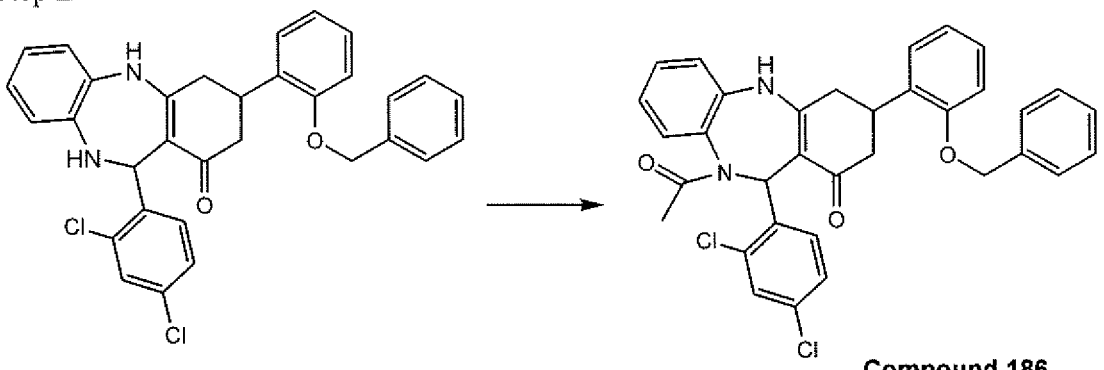
Step D



(1-4) (1-5) diastereomer A
(1-5) diastereomer B

A solution of Intermediate (**1-4**) (200 mg, 0.520 mmol) and 2,4-dichlorobenzaldehyde (91 mg, 0.520 mmol) in 10 mL dry EtOH and 1 mL AcOH was heated at 75 °C for 5h. Solvents were evaporated. The residue was dissolved in EtOAc and stirred for 1.5 h with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). Two diastereomers were obtained, and purified by silica flash column chromatography (gradient elution from heptane / EtOAc 4:1 to 2:1) to give Intermediate (**1-5**) diastereomer **A**, (yield: 118 mg, 41.1%): *m/z* = 542 $(M+H)^+$, and Intermediate (**1-5**) diastereomer **B** (yield: 57 mg, 20.2%):*m/z* = 542 $(M+H)^+$.

Step E



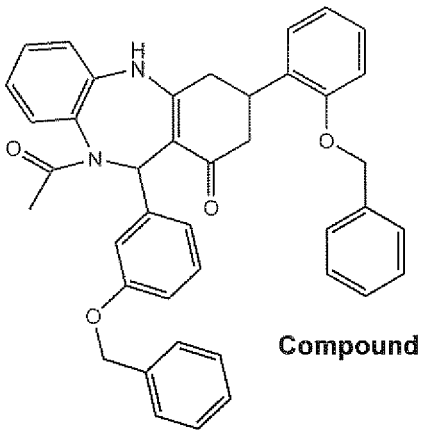
(1-5) diastereomer A **Compound 186**

Acetic anhydride (211 µL) was added at 0°C to a solution of Intermediate **(1-5)** diastereomer **A** (52 mg, 0.096 mmol) in pyridine (3 mL). The mixture was stirred at 0°C during 3 days. Then, water was added to the reaction mixture and the solid was filtered off and washed with water. Purification by preparative TLC (Gradient EtOAc/Heptane 2:1 to 3:1; followed by CH_2Cl_2/MeOH 9:1) provided 41 mg (73.2%) of the final **Compound No. 186**: *m/z* = 583 $(M+H)^+$.

Example 2:
10-Acetyl-3-(2-benzyloxyphenyl)-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 187** diastereomer B .

The title product was prepared from Intermediate **(1-5)** diastereomer B (52 mg, 0.096 mmol) following the procedure described in Example 1.

Example 3
10-Acetyl-3,11-*bis*-(2-benzyloxyphenyl)-11-(3-benzyloxyphenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No.189** diastereomer A



Compound 189

The title product was prepared from Intermediate **(1-4)** (300 mg, 0.780 mmol) and 3-benzyloxybenzaldehyde (199 mg, 0.938 mmol) following the procedure described in Example 1.

Example 4

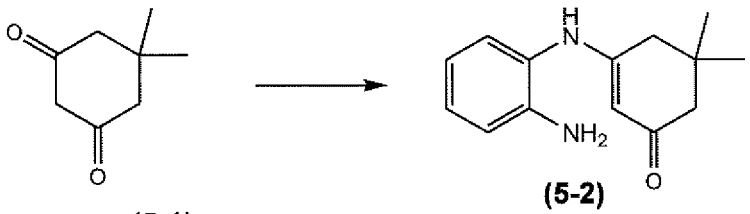
10-Acetyl-3,11-*bis*-(2-benzyloxyphenyl)-11-(3-benzyloxyphenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound 190** diastereomer B.

The title product was prepared from Intermediate (**1-4**) and 3-benzyloxybenzaldehyde following the procedure described in Example 1.

Example 5

10-Acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 38** and enantiomer A **Compound No.36** and enantiomer B **Compound No. 35**

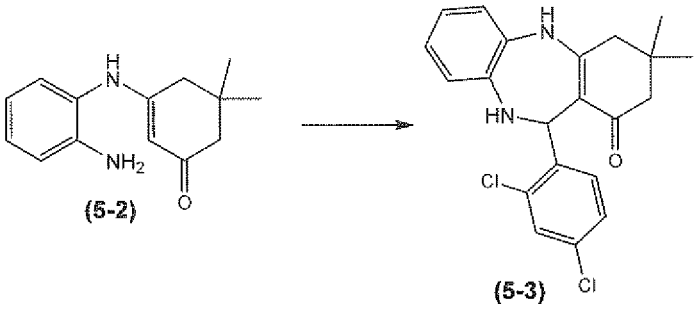
Step A



(5-1) **(5-2)**

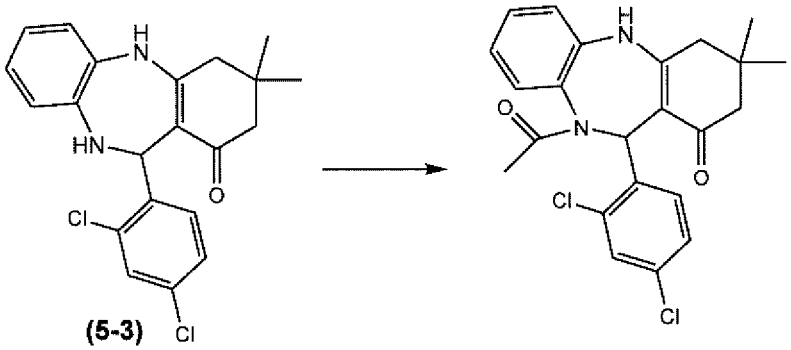
A solution of dimedone (Intermediate (**5-1**)), 5.0 g, 35.67 mmol) and *o*-phenylene-diamine (3.86 g, 35.69 mmol) in 150 mL dry toluene were refluxed overnight in a Dean-Stark trap. After 24h, the solvent was evaporated to give Intermediate (**5-2**) as an orange foam which was used without further purification in the next step.

Step B



A solution of Intermediate (**5-2**) (35.7 mmol) and 2,4-dichlorobenzaldehyde (6.24 g, 35.65 mmol) in a mixture of 100 mL dry EtOH and 10 mL AcOH was heated at 75°C overnight. The reaction mixture was cooled to room temperature and the solvents evaporated. The residue was dissolved in EtOAc and stirred with saturated aqueous $NaHCO_3$ for 1.5 h. Then, the water layer was removed in a separating funnel and the organic layer was filtered off, the filtrate was washed twice with EtOAc. Organic layers were dried (Na_2SO_4), evaporated and the residue dried under high vacuum, yielding 9.45 g (68.4%) of Intermediate (**5-3**): *m/z* = 387 $(M+H)^+$.

Step C



Compound 36 (enantiomer A)
Compound 35 (enantiomer B)

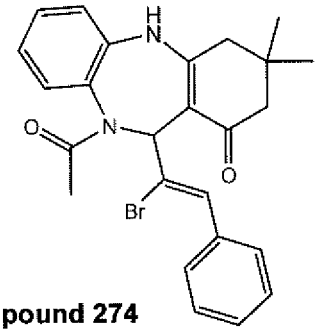
Intermediate (5-3) (1.0 g, 2.582 mmol) was dissolved in 25 mL Pyridine, cooled to 0°C, and 1 mL acetic anhydride was added. The temperature was allowed to warm to room temperature. After 12h, the reaction mixture was cooled to 0°C, and another 1 mL of acetic anhydride was added. After 12h, the reaction mixture was filtered off, washed with water and dried overnight at 40°C under high vacuum. Then, the material was stirred for 1 h in 0.5 N $KHSO_4$ and extracted with CH_2Cl_2. The organic layer was washed with 0.5 N $KHSO_4$, dried (Na_2SO_4) and evaporated. The product was finally sonicated in *i*-Pr_2O, filtered off and dried to give 834 mg (75.2%) of **Compound No. 38** as mixture of **Compound No. 36** enantiomer A and **Compound No. 35** enantiomer B.

Step D: Separation of **Compound No. 36** enantiomer A and **Compound No. 35** enantiomer B.

Compound No. 36 enantiomer A and **Compound No. 35** enantiomer B obtained above in admixture were separated by chiral HPLC using a Berger Minigram SFC, Knauer K2501 UV detector apparatus equipped with a Daicel AD-H 4.6x250mm column. The mobile phase was 80%CO_2/20%MeOH, the flow of 5mL/min and the pressure 100 bars. Detection was performed at 220 nm. Several 100 microL injections of a 5 mg/mL solution were performed. **Compound No. 36** enantiomer A or the "front enantiomer" is the enantiomer which was eluted from the column first followed by **Compound No. 35** enantiomer B or the "back enantiomer", which was the enantiomer which was eluted from the column second: *m/z* = 430 $(M+H)^+$.

Example 6:

10-Acetyl-11-(1-bromo-2-phenylvinyl)-3,3-dimethyl-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No 274**.

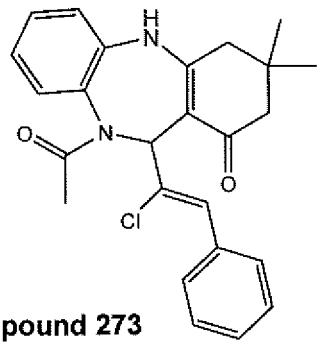


Compound 274

The title compound was prepared from Intermediate **(5-2)** and 2-bromo-3-phenyl-acroleine following the procedure described in Example 5 *m/z* = 466 $(M+H)^+$.

Example 7

10-Acetyl-11-(1-chloro-2-phenylvinyl)-3,3-dimethyl-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No.273**

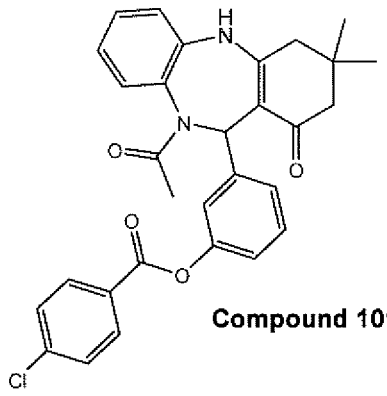


Compound 273

The title compound was prepared from Intermediate (**5-2**) and 2-chloro-3-phenyl-acroleine following the procedure described in Example 5 *m/z* = 421 $(M+H)^+$.

Example 8

10-Acetyl-3,3-dimethyl-11-[3-(4-chlorobenzoyloxy)phenyl]-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 101**

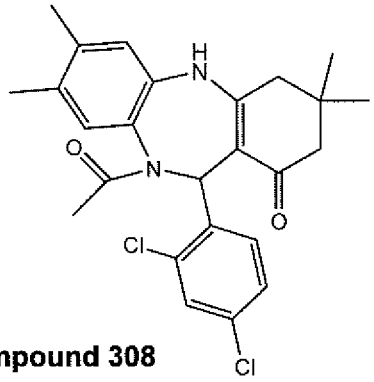


Compound 101

The title compound was prepared from Intermediate (**5-2**) and 3-[(4-chlorobenzoyl)-oxy]benzaldehyde following the described in Example 5: *m/z* = 515 $(M+H)^+$.

Example 9

10-Acetyl-11-(2,4-dichlorophenyl)-3,3,7,8-tetramethyl-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 308**.

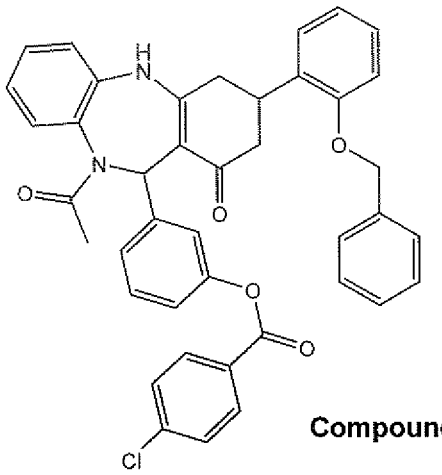


Compound 308

The title compound was prepared from 4,5-dimethyl-*o*-phenylenediamine and 2,4-dichlorobenzaldehyde following the procedure described in Example 5 *m/z* = 457 $(M+H)^+$.

Example 10

10-Acetyl-3-(2-benzyloxyphenyl)-11-[3-(4-chlorobenzoyloxy)phenyl]-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 192** diastereomer A



Compound 192

The title compound was prepared from Intermediate (**1-4**) and 3-[(4-chlorobenzoyl)-oxy]benzaldehyde following the procedure described in Example 1: *m/z* = 669 (M+H)+.

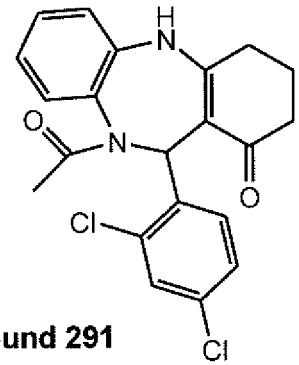
Example 11

10-Acetyl-3-(2-benzyloxyphenyl)-11-[3-(4-chlorobenzoyloxy)phenyl]-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one –**Compound No. 191** diastereomer B

The title compound was prepared from Intermediate (**1-4**) and 3-[(4-chlorobenzoyl)oxy]benzaldehyde following the procedure described in Example 2 *m/z* = 669 $(M+H)^+$.

Example 12

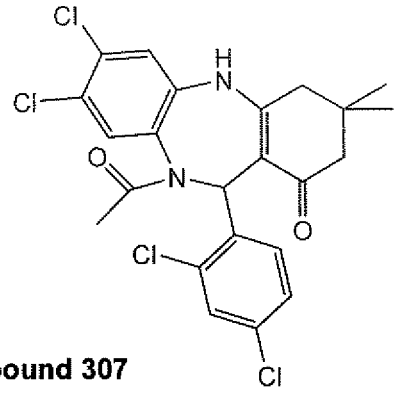
10-Acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]-diazepin-1-one **Compound No. 291** .



Compound 291

The title compound was prepared from cyclohexan-1,3-dianone, *o*-phenylenediamine and 2,4-dichlorobenzaldehyde following the procedure described in Example 5: *m/z* = 401 $(M+H)^+$.

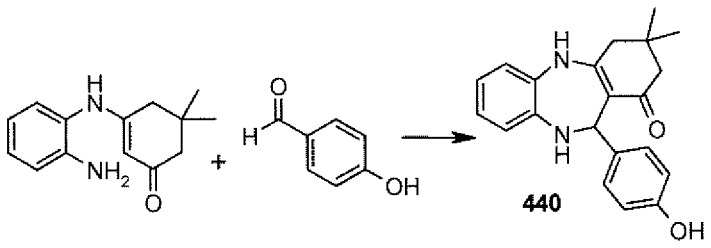
Example 13:
10-Acetyl-7,8-dichloro-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 307** .



Compound 307

The title compound was prepared from 4,5-dichloro-*o*-phenylenediamine and 2,4-dichlorobenzaldehyde following the procedure described in Example 5 *m/z* = 497 $(M+H)^+$.

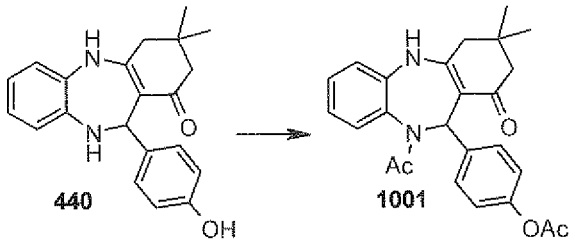
Example 14: 3,3-dimethyl-11-(4-hydroxyphenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 440** .



440

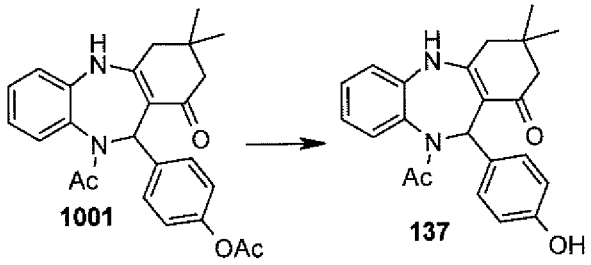
The title compound was prepared from intermediate **5-2** and 4-hydroxybenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 335 $(M+H)^+$.

Example 15: 11-(4-acetoxyphenyl)-10-acetyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 1001**.



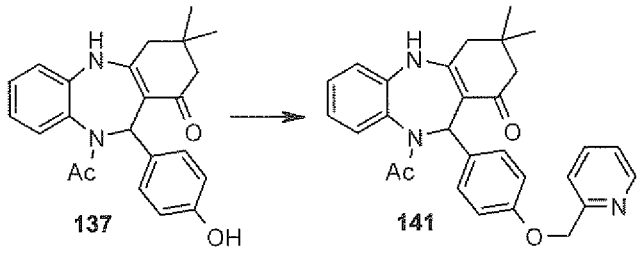
Ac_2O (5 mL) was added at 0 °C to a solution of 3,3-dimethyl-11-(4-hydroxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one **440** in pyridine (50 mL). After 7 days, the reaction mixture was quenched with water (250 mL). Then, the solid was filtered off and washed with water. The solid was successively re-dissolved in CH_2Cl_2, washed with 0.5 N $KHSO_4$ (twice), dried (Na_2SO_4) and evaporated. The residue was sonicated in Et_2O and filtered off to give 4.36 g (71 %) of the target compound **1001**: *m/z* = 419 (M+H)+.

Example 16: 10-acetyl-11-(4-hydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 137 ..**



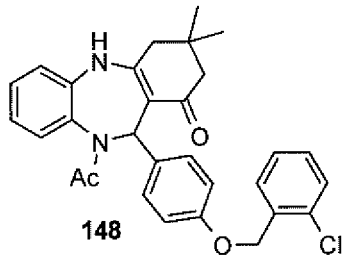
A solution of lithium hydroxide hydrate (672 mg) in water (5 mL) was added to a stirred suspension of 11-(4-acetoxyphenyl)-10-acetyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1001** (4.26 g, 10.2 mmol) in MeOH/THF/H_2O 2.5:0.5:1 (70 mL). After 30 minutes, 1N HCl (20 mL) was added. Then, the reaction mixture was diluted with water (100 mL) and concentrated under reduced pressure. The precipitate was succesively filtered off, washed with water and dried to give 3.70 g (97 %) of the title product **137** as a white powder: *m/z* = 377 (M+H)+.

Example 17: 10-acetyl-3,3-dimethyl-11-[4-(2-pyridylmethoxy)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 141 ..**



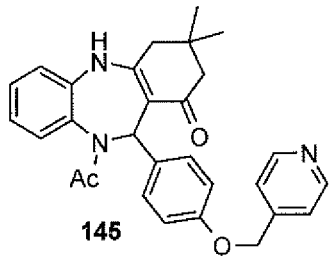
A mixture of 10-acetyl-3,3-dimethyl-11-(4-hydroxyphenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **137** (250 mg, 0.664 mmol), 2-picolylchloride hydrochloride (109 mg, 1eq.), cesium carbonate (476 mg, 2.2 eq.) in dry DMF (10 mL) were stirred at room temperature for 78 h. Then, the reaction mixture was diluted with water (300 mL) and the precipitate was successively filtered off, washed with water, dried and triturated in isopropylether to give 79 mg of the target product **141**: *m/z* = 468 $(M + H)^+$.

Example 18: 10-acetyl-11-[4-(2-chlorobenzyloxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 148** .



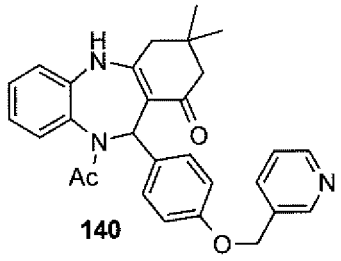
The title compound was prepared from 10-acetyl-11-(4-hydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **137** and 2-chlorobenzyl-bromide following the procedure described for example 17: m/z = 501 $(M+H)^+$.

Example 19: 10-acetyl-3,3-dimethyl-11-[4-(4-pyridylmethoxy)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 145** .



The title compound was prepared from 10-acetyl-11-(4-hydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **137** and 4-picolyl-chloride hydrochloride following the procedure described for example 17: m/z = 468 $(M+H)^+$.

Example 20: 10-acetyl-3,3-dimethyl-11-[4-(3-pyridylmethoxy)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 140 .**

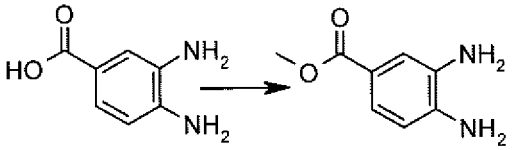


140

The title compound was prepared from 10-acetyl-11-(4-hydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **137** and 3-picolyl-chloride hydrochloride following the procedure described for example 17: m/z = 468 $(M+H)^+$.

Example 21: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid methyl ester **Compound no. 520**

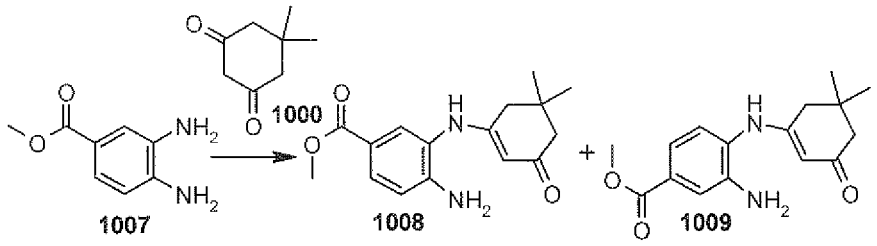
Step A.



1007

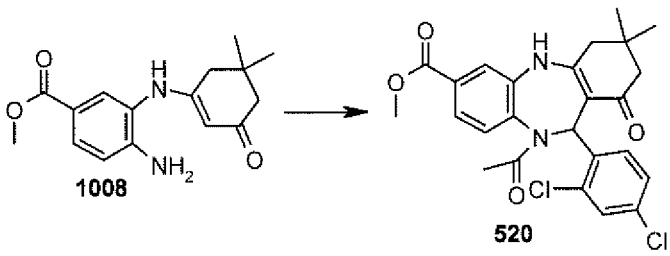
Thionyl chloride (16.0 mL, 220 mmol) was added to a suspension of 3,4-diamino-benzoic acid (16.8 g, 110 mmol) in dry MeOH (200 mL). The resulting mixture was heated at reflux. After 12h, the solution was successively cooled down to room temperature and concentrated under reduced pressure. The residue was triturated in diluted $NaHCO_3$. Then, the precipitate was filtered off and dried to give 10.1 g (55 %) of the target compound **1007**.

Step B.



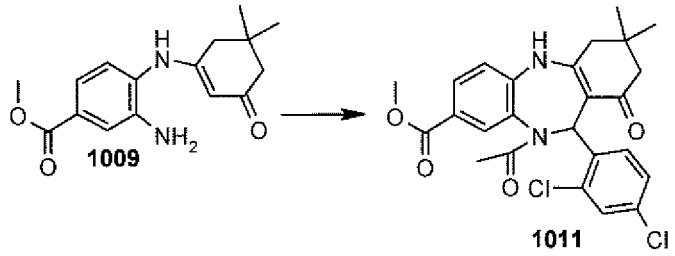
The intermediates **1008** and **1009** were prepared from 3,4-diaminobenzoic acid methyl ester **1007** and dimedone **1000** following the procedure (Step A) described for the synthesis of 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38).

Step C.



The title compound **520** was prepared from **1008** and 2,4-dichlorobenzaldehyde following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): m/z = 487 $(M+H)^+$.

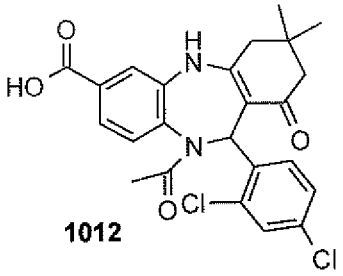
Example 22: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-8-carboxylic acid methyl ester **Compound no. 521 .**



The title compound **521** was prepared from **1009** and 2,4-dichlorobenzaldehyde following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-

hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 487 $(M+H)^+$.

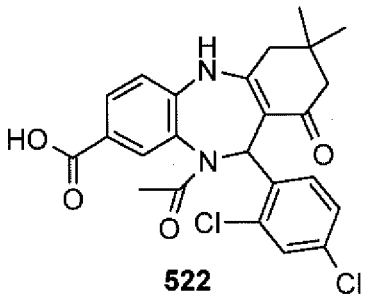
Example 23: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **Compound no. 1012.**



1012

A solution of lithium hydroxide hydrate (354 mg, 8.2 mmol) was added to a suspension of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid methyl ester **520** (2.0 g, 4.10 mmol) in water (25 mL) and THF (25 mL). After 12 h, the pH of the reaction mixture was adjusted to 3 with 1 N HCl. The precipitate was collected by filtration, the washed with water and dried to afford 1.87 g (96.4 %) of the title product **1012**: *m/z* = 473 $(M+H)^+$.

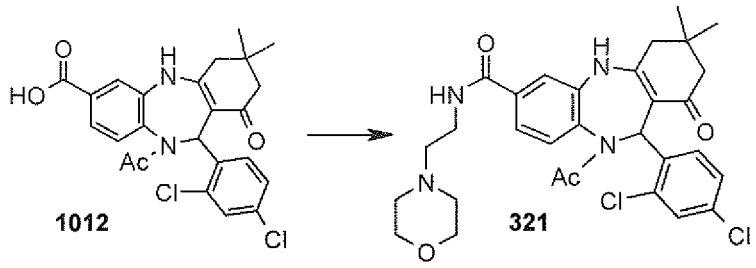
Example 24: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-8-carboxylic acid **Compound no. 522 .**



522

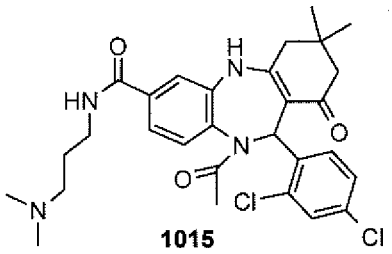
The title compound **522** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepine-8-carboxylic acid methyl ester **521** following the procedure described for the preparation of 10 acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012:** *m/z* = 473 $(M+H)^+$.

Example 25: 10-acetyl-*N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 321 .**



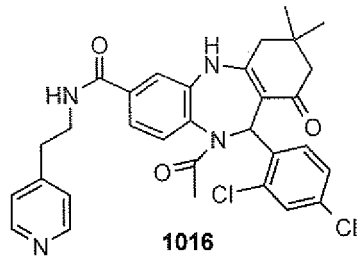
A solution of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** (250 mg, 0.53 mmol), 4-(2-aminoethyl)morpholine, EDCI.HCl (203 mg, 1.06 mmol), HOAT (144 mg, 1.06 mmol), and DIPEA (185 µL, 1.06 mmol) in dry DMF (5 mL) was stirred overnight at room temperature. Then, the reaction mixture was diluted with water (75 mL), and the precipitate formed was collected by filtration, then washed with water and dried to give 120 mg (39%) of the title product **321**: *m/z* = 585 $(M+H)^+$.

Example 26: 10-acetyl-*N*-(*N,N*-dimethylaminopropyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 1015.**



The title compound **1015** was prepared in 73% yield from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** and 3-(*N,N*-dimethylamino)propylamine following the procedure reported for the preparation of *N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **321:** *m/z* = 557 $(M+H)^+$.

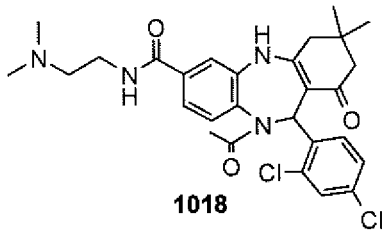
Example 27: 10-acetyl-*N*-(4-pyridylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 1016.**



1016

The title compound **1016** was prepared in 53% yield from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** and 4-pyridylethylamine following the procedure reported for the preparation of 10-acetyl-*N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **321:** *m/z* = 577 $(M+H)^+$.

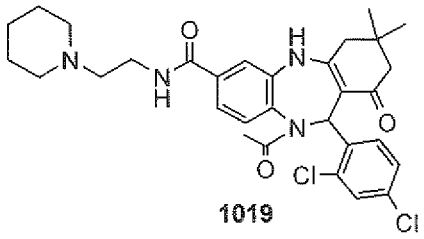
Example 28: 10-acetyl-*N*-(*N,N*-dimethylaminoethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 1018.**



1018

The title compound **1018** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** and 2-(*N,N*-dimethylamino)ethylamine following the procedure reported for the preparation of 10-acetyl-*N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **321:** *m/z* = 543 $(M+H)^+$.

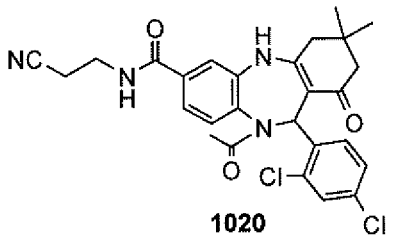
Example 29: 10-acetyl-*N*-(2-piperidin-1-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 1019.**



1019

The title compound **1019** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** and 2-(piperidin-1-yl)ethylamine following the procedure reported for the preparation of 10-acetyl-*N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **321:** *m/z* = 583 $(M+H)^+$.

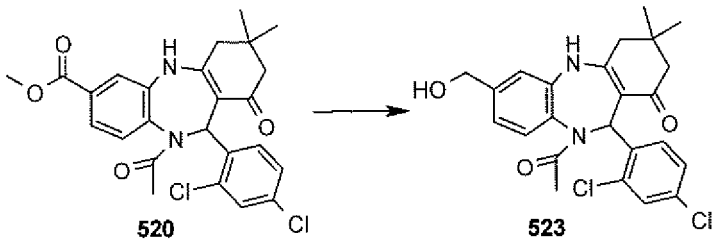
Example 30: 10-acetyl-*N*-(2-cyanoethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **Compound no. 1020.**



1020

The title compound **1020** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid **1012** and 2-cyanoethylamine following the procedure reported for the preparation of 10-acetyl-*N*-(morpholin-4-ylethyl)-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxamide **321:** *m/z* = 525 $(M+H)^+$.

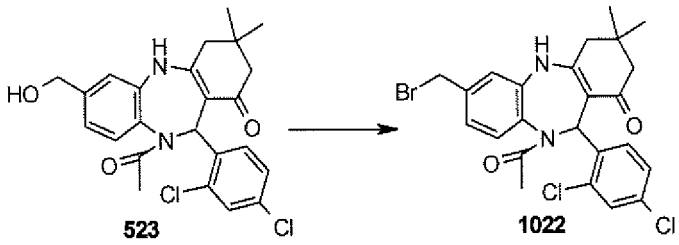
Example 31: 10-acetyl-11-(2,4-dichlorophenyl)-7-hydroxymethyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 523**



520 523

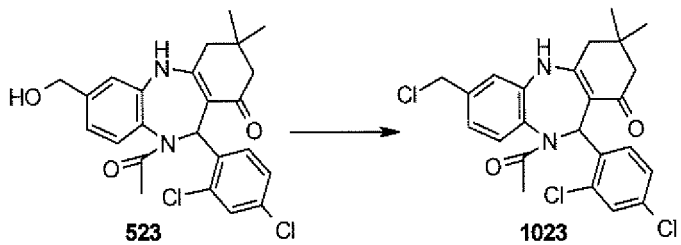
Sodium borohydride (824 mg, 21.8 mmol) was added portion wise to a solution of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxylic acid methyl ester **520** (5.3 g, 10.9 mmol) in absolute ethanol (100 mL). After 24 h, sodium borohydride (824 mg, 21.8 mmol) was added to the reaction mixture. This operation was repeated 3 times (total: 14 eq. of $NaBH_4$ were used). The reaction mixture was added dropwise to a solution of 2N HCl (500 mL). The precipitate was collected by filtration, washed with water and dried to give 3.83 g (77%) of the title product **523** as a white powder: *m/z* = 459 $(M+H)^+$.

Example 32: 10-acetyl-7-bromomethyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1022.**



Phosphorous tribromide (118 µL, 1.25 mmol) was gradually added under nitrogen at 0°C to a stirred solution of 10-acetyl-11-(2,4-dichlorophenyl)-7-hydroxymethyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **523** in DCE (2 mL). The resulting solution was stirred at room temperature for 1h. Then, a diluted aqueous solution of sodium bicarbonate was added. The reaction mixture was extracted with AcOEt, dried (Na_2SO_4) and evaporated to give 157 mg (68 %) of the title product **1022**: *m/z* = 522 $(M+H)^+$.

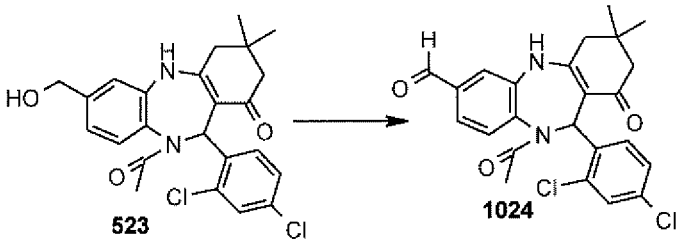
Example 33: 10-acetyl-7-chloromethyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1023.**



Thionylchloride (238 µL, 3.26 mmol) was added dropwise under nitrogen at 0°C to a stirred solution of 10-acetyl-11-(2,4-dichlorophenyl)-7-hydroxymethyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **523** (500 mg, 1.09 mmol)

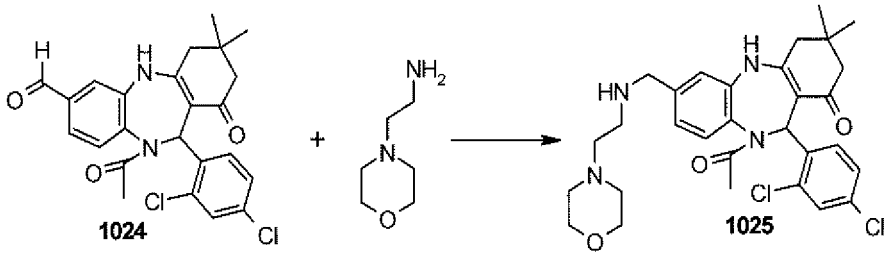
in DCE (10 mL). The resulting solution was stirred at room temperature for 2h. Then, ice-cold water was added. The reaction mixture was extracted with DCM, dried (Na_2SO_4) and evaporated to give 410 mg (79 %) of the title product **1023**: *m/z* = 477 $(M+H)^+$.

Example 34: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **Compound no. 1024.**



Manganese (IV) oxide was added to a stirred solution of 10-acetyl-11-(2,4-dichlorophenyl)-7-hydroxymethyl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **523** in acetone (10 mL). The resulting solution was heated to reflux. After 2 days, the reaction mixture was cooled down to room temperature, filtered over kieselguhr, and evaporated to give 400 mg (40 %) of the title product **1024**: *m/z* = 457 $(M+H)^+$.

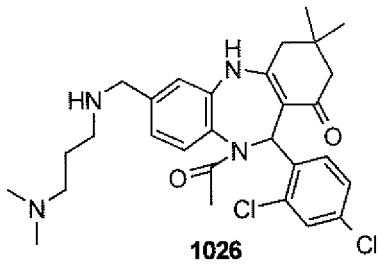
Example 35: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1025.**



A solution of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** (200 mg, 0.44 mmol) and 4-(2-aminoethyl)morpholine (53 µL, 0.40 mmol) in DCM (5 mL) was stirred at room temperature for 30 minutes. Then, $NaBH(OAc)_3$ (122 mg, 0.57 mmol) and acetic acid (26.3 µL, 1.2 eq.) were added. The resulting reaction mixture was stirred overnight at room temperature, then quenched with a saturated solution of

sodiumbicarbonate, extracted with AcOEt, dried (Na_2SO_4) and evaporated to give 190 mg (87%) of the title product **1025**: *m/z* = 571 $(M+H)^+$.

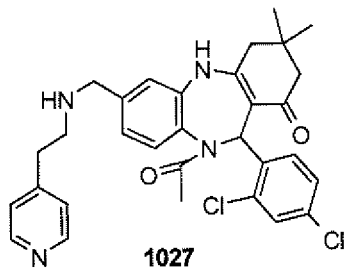
Example 36: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[3-(*N,N*-dimethyl-amino)propylaminomethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1026.**



1026

The title compound **1026** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 3-(*N,N*-dimethylaminopropylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4] diazepin-1-one **1025**: *m/z* = 543 $(M+H)^+$.

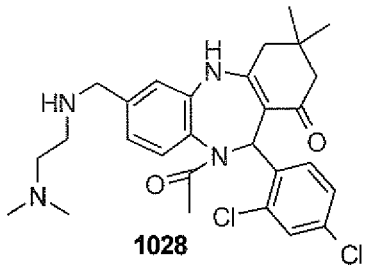
Example 37: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[2-(4-pyridyl)ethyl-aminomethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1027.**



1027

The title compound **1027** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 4-pyridylethylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-yl-ethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 563 $(M+H)^+$.

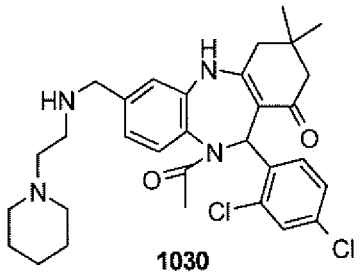
Example 38: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[2-(*N,N*-dimethyl-amino)ethylaminomethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1028.**



1028

The title compound **1028** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 2-(N,N-dimethylamino)ethylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4] diazepin-1-one **1025**: *m/z* = 529 $(M+H)^+$.

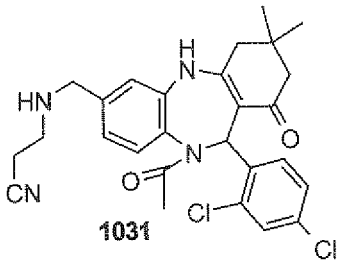
Example 39: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[2-(piperidin-1-yl)-ethylaminomethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1030.**



1030

The title compound **1030** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 2-(piperidin-1-yl)ethylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4] diazepin-1-one **1025**: *m/z* = 569 $(M+H)^+$.

Example 40: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-cyanoethylamino-methyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1031.**

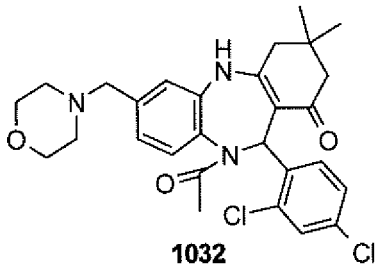


1031

The title compound **1031** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 2-cyanoethylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 511 $(M+H)^+$.

Example 41: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(morpholin-4-ylmethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one

Compound no. 1032.

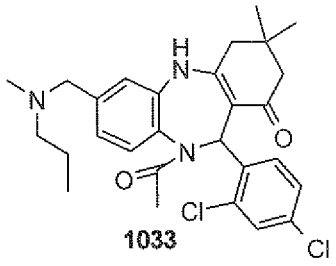


1032

The title compound **1032** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and morpholine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 528 $(M+H)^+$.

Example 42: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(*N*-methyl-*N*-propyl-aminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one

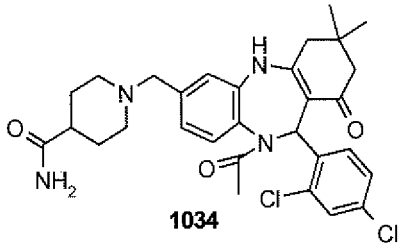
Compound no. 1033.



1033

The title compound **1033** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and *N*-methylpropylamine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: m/z = 514 $(M+H)^+$.

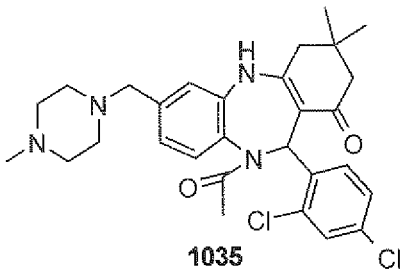
Example 43: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[4-(aminocarbonyl)-piperidin-1-ylmethyl]-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1034.**



1034

The title compound **1034** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 4-(aminocarbonyl)piperidine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]-diazepin-1-one **1025**: m/z = 569 $(M+H)^+$.

Example 44: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(4-methylpiperazin-1-ylmethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1035.**

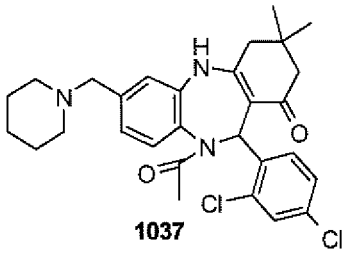


1035

The title compound **1035** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and 4-methylpiperazine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 541 $(M+H)^+$.

Example 45: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(piperidin-1-ylmethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one

Compound no. 1037.

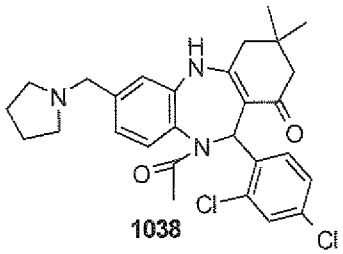


1037

The title compound **1037** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and piperidine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 526 $(M+H)^+$.

Example 46: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(pyrrolidin-1-yl-methyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one

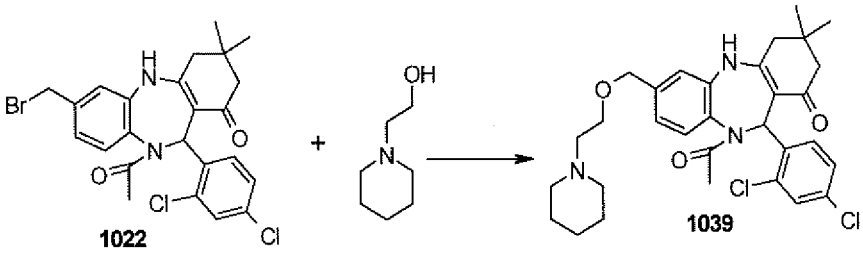
Compound no. 1038.



1038

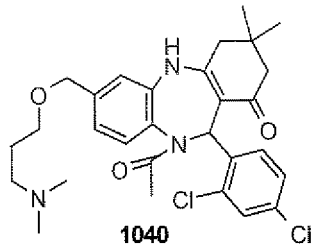
The title compound **1038** was prepared from 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepine-7-carboxaldehyde **1024** and pyrrolidine following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-(2-morpholin-4-ylethylaminomethyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1025**: *m/z* = 512 $(M+H)^+$.

Example 47: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[2-(piperidin-1-yl)-ethoxymethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1039.**



Sodium hydride (17 mg, 60% in mineral oil, 0.42 mmol) was added at 0 °C under argon to a solution of *N*-piperidineethanol (53 µL, 0.4 mmol) in dry DMF (4 mL). The resulting solution was added at 0 °C under argon to a solution of 10-acetyl-7-bromomethyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo-[b,e][1,4]diazepin-1-one **1022** (200 mg, 0.38 mmol) in dry DMF (2 mL). After 2h, the reaction mixture was diluted with ice-cold water (70 mL). The pH of the resulting solution was adjusted to 7 with 2N aqueous NaOH. Then, the reaction mixture was successively extracted with AcOEt (3 times), THF (3 times). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was triturated in toluene, the evaporated. The residue was triturated in DCM and methanol, filtered and concentrated under vacuum. The residue was purified by column chromatography on alumina (CH_2Cl_2/MeOH, gradient 1:0 to 92:8) to give 85 mg (39%) of the target compound **1039**: *m/z* = 570 $(M+H)^+$.

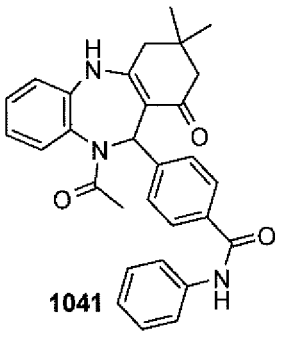
Example 48: 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[3-(*N,N*-dimethyl-amino)propoxymethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1040.**



1040

The title compound **1040** was prepared from 10-acetyl-7-bromomethyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1022** and 3-(*N,N*-dimethylamino)propanol following the procedure reported for the preparation of 10-acetyl-11-(2,4-dichlorophenyl)-3,3-dimethyl-7-[2-(piperidin-1-yl)ethoxymethyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1039**: *m/z* = 544 $(M+H)^+$.

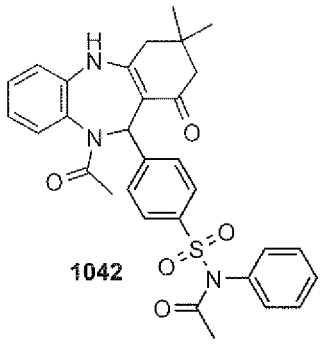
Example 49: 10-acetyl-11-[4-(phenylaminocarbonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1041.**



1041

The title compound **1041** was prepared from 4-(phenylaminocarbonyl)benzaldehyde following the procedure reported for the synthesis of 10-acetyl-11-(2,4-dichloro-phenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 480 $(M+H)^+$.

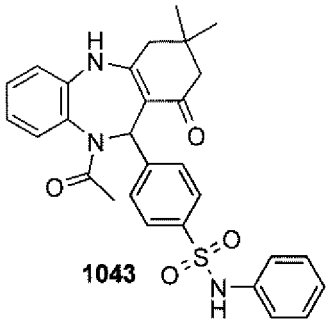
Example 50: 10-acetyl-11-[4-(*N*-acetyl-*N*-phenylaminosulfonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1042.**



1042

The title compound **1042** was prepared from 4-(*N*-phenylaminosulfonyl)benzaldehyde following the procedure reported for the synthesis of 10-acetyl-11-(2,4-dichloro-phenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 558 $(M+H)^+$.

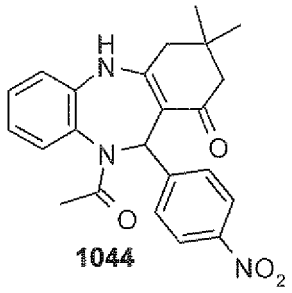
Example 51: 10-acetyl-11-[4-(*N*-phenylaminosulfonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1043.**



1043

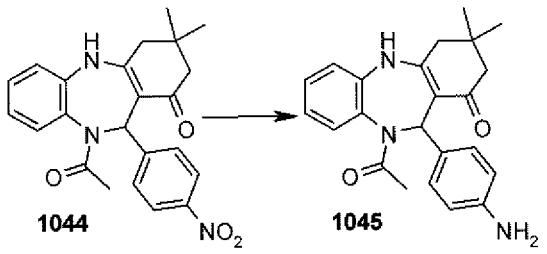
A solution of lithium hydroxide hydrate (11 mg, 0.26 mmol) in water (0.5 mL) was added at 0 °C to a stirred solution of 10-acetyl-11-[4-(*N*-acetyl-*N*-phenylamino-sulfonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1042** (133 mg, 0.26 mmol). After 12 h at room temperature, the reaction mixture was diluted with a saturated solution of ammonium chloride, extracted twice with AcOEt, washed with brine, dried (Na_2SO_4) and evaporated to give 100 mg of the title product: *m/z* = 516 $(M+H)^+$.

Example 52: 10-acetyl-11-(4-nitrophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1044.**



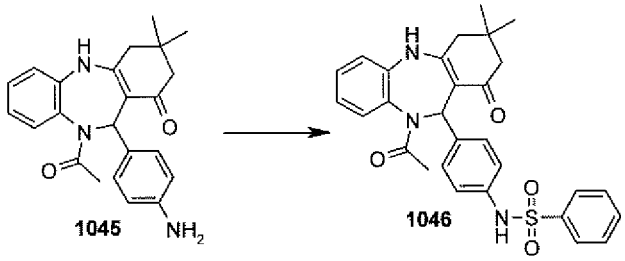
The title compound **1044** was prepared from intermediate **5-2** and 4-nitrobenzaldehyde following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 406 $(M+H)^+$.

Example 53: 10-acetyl-11-(4-aminophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1045.**



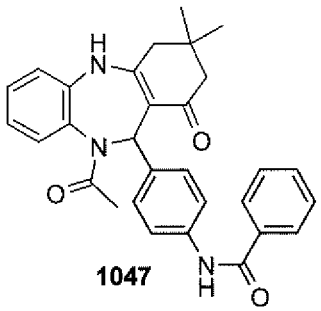
A solution of 10-acetyl-11-(4-nitrophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1044** (862 mg, 2.13 mmol) in MeOH (3 mL) and THF (3 mL) was added to a suspension of iron (476 mg, 8.52 mmol) and ammonium chloride (460 mg, 8.52 mmol) in water (3 mL). The resulting mixture was heated at 70 °C. After 2h, the reaction mixture was filtered on kieselguhr and extensively washed with AcOEt. The combine organic extracts were washed with brine, the dried (Na_2SO_4) and evaporated to give 272 mg (35%) of the title product **1045**: *m/z* = 376 $(M+H)^+$.

Example 54: 10-acetyl-11-[4-(phenylsulfonylamino)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no.1046.**



A solution of 10-acetyl-11-(4-aminophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1045** (127 mg, 0.34 mmol), benzensulfonyl chloride (45.5 µL, 0.36 mmol) in pyridine (2 mL) was stirred at room temperature for 12h. The reaction mixture was successively added dropwise to 10 mL of water, extracted with AcOEt, washed with brine, dried (Na_2SO_4) and evaporated to afford 78 mg of the title product **1046**: *m/z* = 516 $(M+H)^+$.

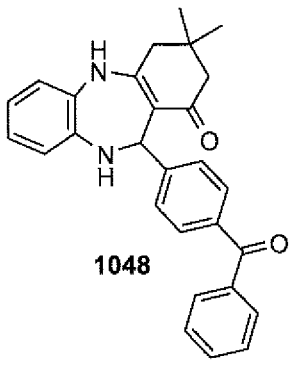
Example 55: 10-acetyl-11-[4-(phenylcarbonylamino)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1047.**



1047

The title compound **1047** was prepared from 10-acetyl-11-(4-aminophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1045** and benzoyl chloride following the procedure described for 10-acetyl-11-[4-(phenylsulfonylamino)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1046**: *m/z* = 480 $(M+H)^+$.

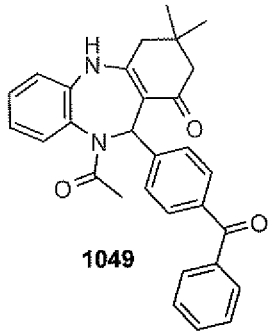
Example 56: 11-[4-(phenylcarbonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1048.**



1048

The title compound was prepared from intermediate **5-2** and 4-(phenylcarbonyl)-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 423 $(M+H)^+$.

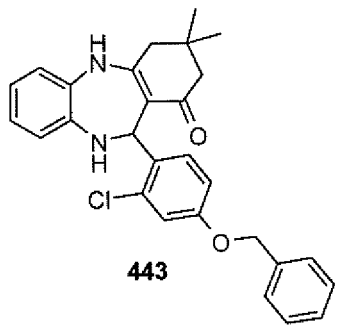
Example 57: 10-acetyl-11-[4-(phenylcarbonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1049.**



1049

The title compound **1049** was prepared from 11-[4-(phenylcarbonyl)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **1048** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 465 $(M+H)^+$.

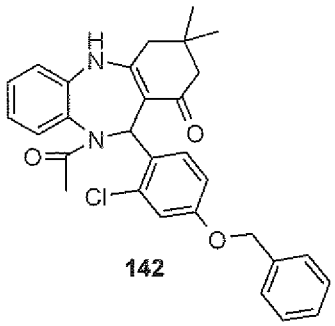
Example 58: 11-[4-benzyloxycarbonyl-2-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 443 .**



443

The title compound **443** was prepared from intermediate **5-2** and 4-benzyloxy-2-chlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 459 $(M+H)^+$.

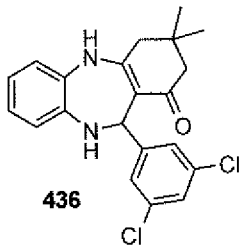
Example 59: 10-acetyl-11-[4-benzyloxycarbonyl-2-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 142 .**



142

The title compound **142** was prepared from 11-[4-benzyloxycarbonyl-2-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **443** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 501 $(M+H)^+$.

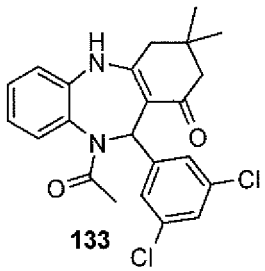
Example 60: 11-[3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 436 .**



436

The title compound **436** was prepared from intermediate **5-2** and 2,5-dichloro-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 387 $(M+H)^+$.

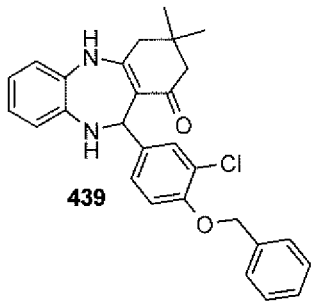
Example 61: 10-acetyl-11-[3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 133 .**



133

The title compound **133** was prepared from 11-[3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **436** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): m/z = 429 $(M+H)^+$.

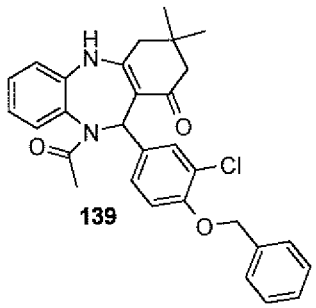
Example 62: 11-[4-benzyloxy-3-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 439 .**



439

The title compound **439** was prepared from intermediate **5-2** and 3-chloro-4-benzyloxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 459 $(M+H)^+$.

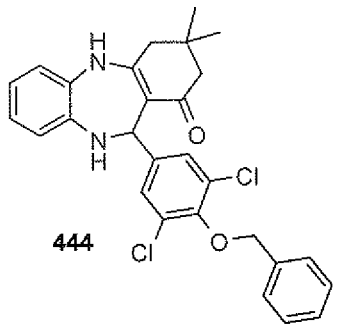
Example 63: 10-acetyl-11-[4-benzyloxy-3-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 139 .**



139

The title compound **139** was prepared from 11-[4-benzyloxy-3-chlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **439** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 501 $(M+H)^+$.

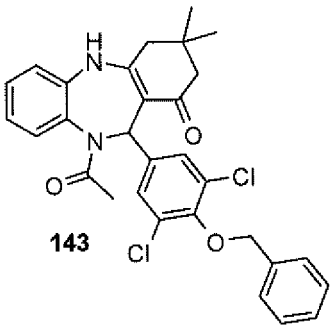
Example 64: 11-[4-benzyloxy-3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 444 .**



444

The title compound **444** was prepared from intermediate **5-2** and 3,5-dichloro-4-benzyloxybenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 493 $(M+H)^+$.

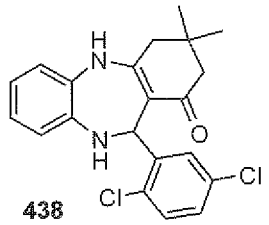
Example 65: 10-acetyl-11-[4-benzyloxy-3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 143**



143

The title compound **143** was prepared from 11-[4-benzyloxy-3,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **444** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 535 $(M+H)^+$.

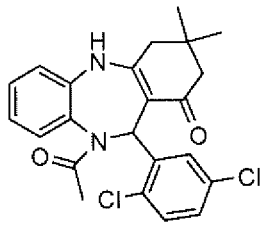
Example 66: 11-[2,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 438 .**



438

The title compound **438** was prepared from intermediate **5-2** and 2,5-dichlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 387 $(M+H)^+$.

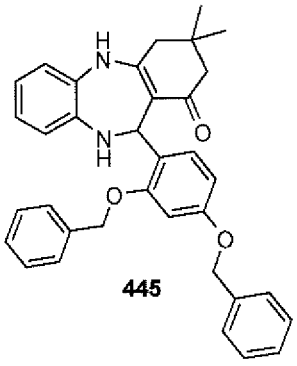
Example 67: 10-acetyl-11-[2,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 138 .**



138

The title compound **138** was prepared from 11-[2,5-dichlorophenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **438** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 429 $(M+H)^+$.

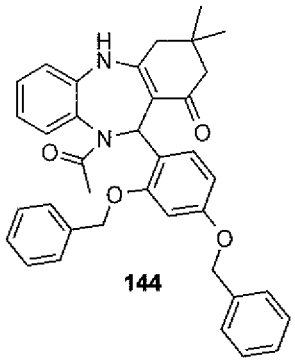
Example 68: 11-[2,4-dibenzyloxyphenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 445 .**



445

The title compound **445** was prepared from intermediate **5-2** and 2,4-dibenzyloxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 531 $(M+H)^+$.

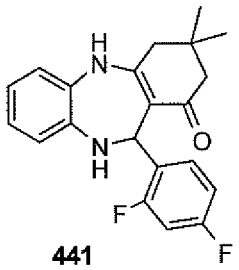
Example 69: 10-acetyl-11-[2,4-dibenzyloxyphenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 144 .**



144

The title compound **144** was prepared from 11-[2,4-dibenzyloxyphenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **445** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 573 $(M+H)^+$.

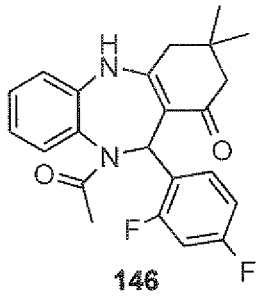
Example 70: 11-(2,4-difluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 441 .**



441

The title compound **441** was prepared from intermediate **5-2** and 2,4-difluoro-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 355 $(M+H)^+$.

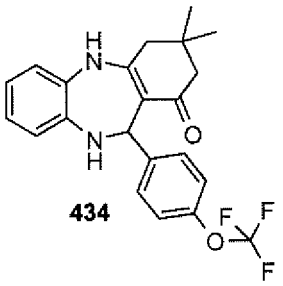
Example 71: 10-acetyl-11-(2,4-difluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 146 .**



146

The title compound **146** was prepared from 11-(2,4-difluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **441** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 397 $(M+H)^+$.

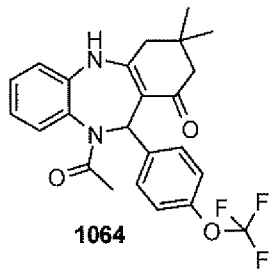
Example 72: 11-(4-trifluoromethyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 434 .**



434

The title compound **434** was prepared from intermediate **5-2** and 4-trifluoromethyloxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 403 $(M+H)^+$.

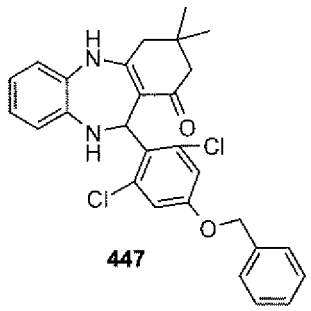
Example 73: 10-acetyl-11-(4-trifluoromethyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 1064.**



1064

The title compound **1064** was prepared from 11-(4-trifluoromethyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **434** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 445 $(M+H)^+$.

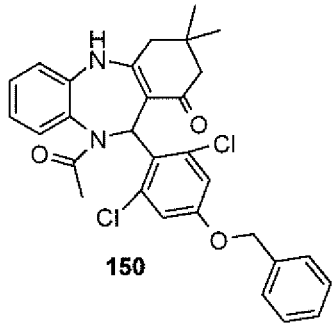
Example 74: 11-(4-benzyloxy-2,6-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 447 .**



447

The title compound **447** was prepared from intermediate **5-2** and 4-benzyloxy-2,6-dichlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 493 $(M+H)^+$.

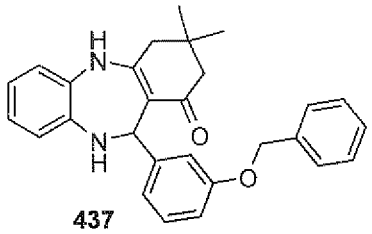
Example 75: 10-acetyl-11-(4-benzyloxy-2,6-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 150 .**



150

The title compound **150** was prepared from 11-(4-benzyloxy-2,6-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **447** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 535 $(M+H)^+$.

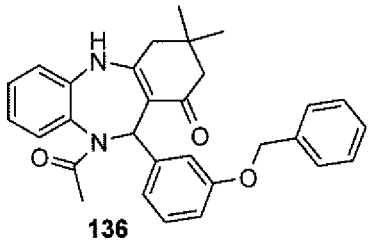
Example 76: 11-(3-benzyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 437 .**



437

The title compound **437** was prepared from intermediate **5-2** and 3-benzyloxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 425 $(M+H)^+$.

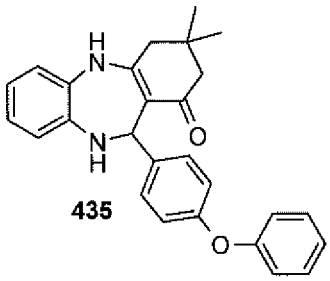
Example 77: 10-acetyl-11-(3-benzyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 136 .**



136

The title compound **136** was prepared from 11-(3-benzyloxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **437** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 467 $(M+H)^+$.

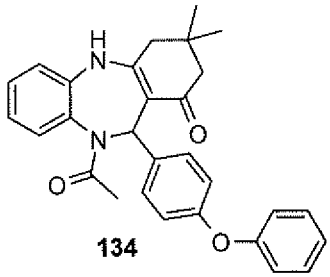
Example 78: 11-(4-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 435 .**



435

The title compound **435** was prepared from intermediate **5-2** and 4-phenoxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 411 $(M+H)^+$.

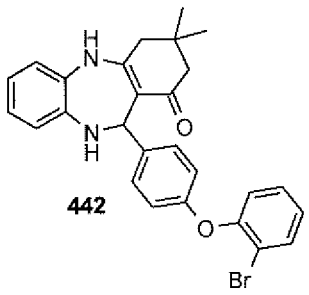
Example 79: 10-acetyl-11-(4-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 134 .**



134

The title compound **134** was prepared from 11-(4-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **435** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 453 $(M+H)^+$.

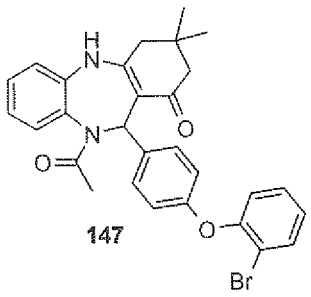
Example 80: 11-[4-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 442 .**



442

The title compound **442** was prepared from intermediate **5-2** and 4-(2-bromophenoxy)-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 490 $(M+H)^+$.

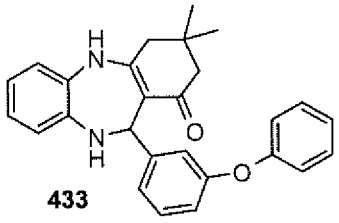
Example 81: 10-acetyl-11-[4-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 147 .**



147

The title compound **147** was prepared from 11-[4-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **442** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 532 $(M+H)^+$.

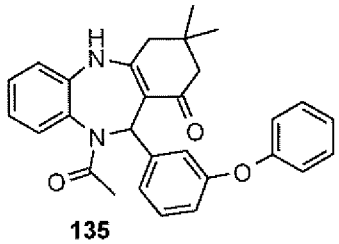
Example 82: 11-(3-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 433 .**



433

The title compound **433** was prepared from intermediate **5-2** and 3-phenoxy-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 411 $(M+H)^+$.

Example 83: 11-(3-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 135 .**

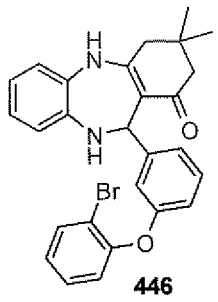


135

The title compound **135** was prepared from 11-(3-phenoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **433** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-

3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 453 $(M+H)^+$.

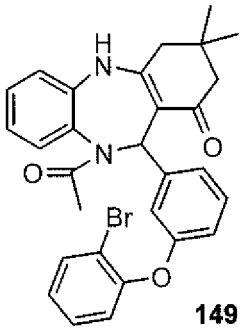
Example 84: 11-[3-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 446 .**



446

The title compound **446** was prepared from intermediate **5-2** and 3-(2-bromophenoxy)-benzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 490 $(M+H)^+$.

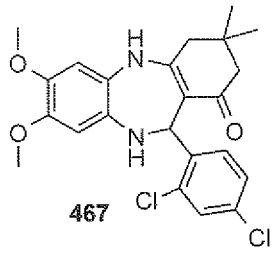
Example 85: 10-acetyl-11-[3-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 149 .**



149

The title compound **149** was prepared from 11-[3-(2-bromophenoxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **446** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 532 $(M+H)^+$.

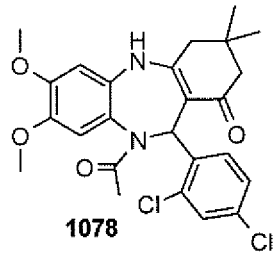
Example 86: 7,8-dimethoxy-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 467 .**



467

The title compound **467** was prepared from 2,4-dichlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 447 $(M+H)^+$.

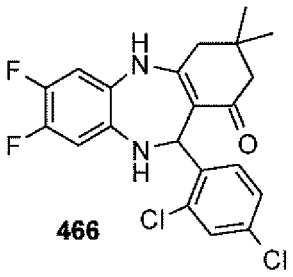
Example 87: 10-acetyl-7,8-dimethoxy-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 309 .**



1078

The title compound **309** was prepared from 7,8-dimethoxy-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **467** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 489 $(M+H)^+$.

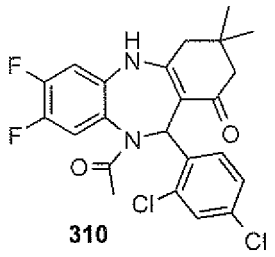
Example 88: 7,8-difluoro-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 466 .**



466

The title compound **466** was prepared from 2,4-dichlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 423 $(M+H)^+$.

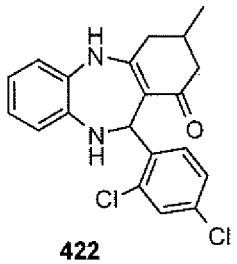
Example 89: 10-acetyl-7,8-difluoro-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 310 .**



310

The title compound **310** was prepared from 7,8-difluoro-11-(2,4-dichlorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **466** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 465 $(M+H)^+$.

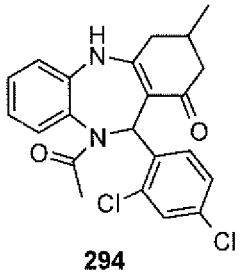
Example 90: 11-(2,4-dichlorophenyl)-3-methyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 422 .**



422

The title compound **422** was prepared from 2,4-dichlorobenzaldehyde following the procedure described for 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **5-3**: *m/z* = 373 $(M+H)^+$.

Example 91: 10-acetyl-11-(2,4-dichlorophenyl)-3-methyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound no. 294**

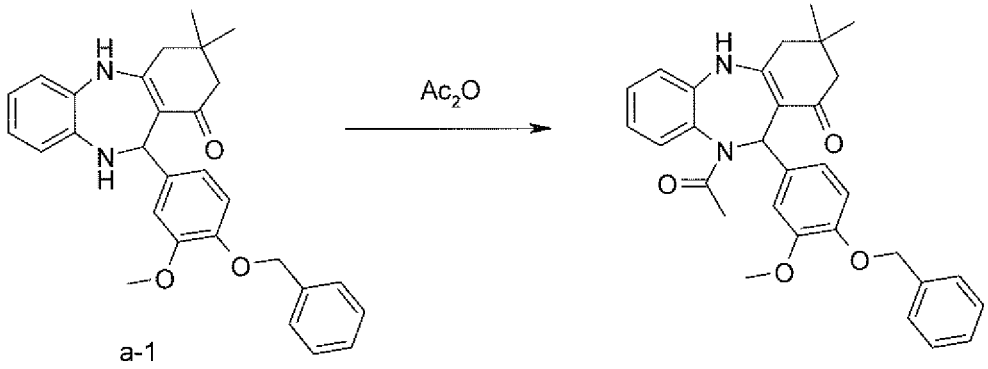


294

The title compound **294** was prepared from 11-(2,4-dichlorophenyl)-3-methyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[b,e][1,4]diazepin-1-one **442** following the procedure described for 10-acetyl-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one (compound no. 38): *m/z* = 415 $(M+H)^+$.

Example 92

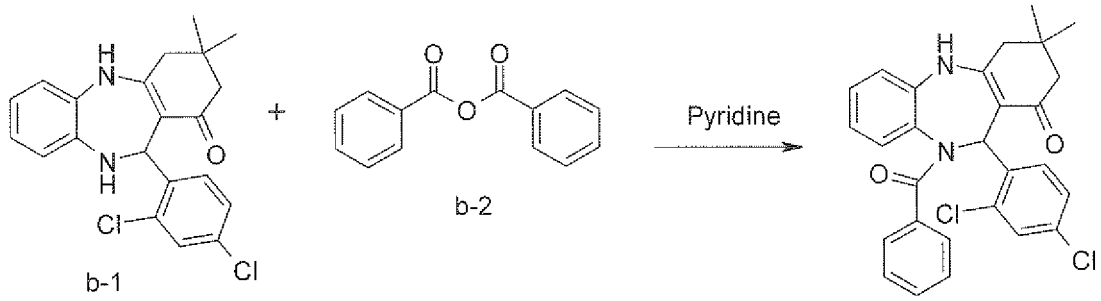
Scheme A



Compound no. 48

A mixture of a-1 (0.0022 mol) in Ac_2O (10 ml) was stirred and refluxed for 1 hour. A tip spat of DMAP was added. The mixture was stirred for 1 hour. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.05). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone (few)/diethyl ether/EtOH. The precipitate was filtered off and dried, yielding: 0.352 g of **Compound no. 48** (melting point: 216°C).

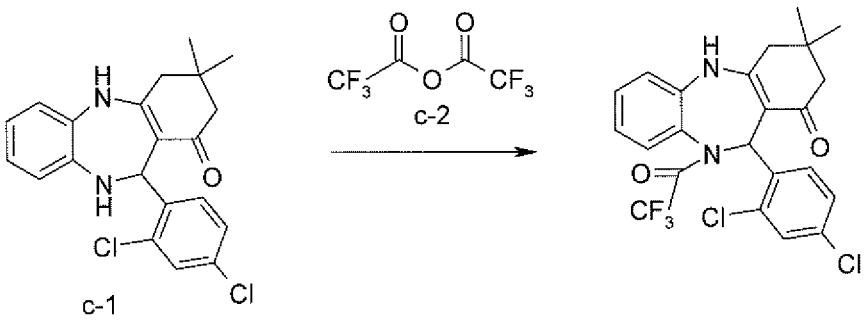
Scheme B



Compound no. 45

b-2 (0.024 mol, 0.54 g) was added at 0°C to a solution of b-1 (0.0006 mol) in pyridine (6 ml). The mixture was stirred at room temperature for 12 h. b-2 (0.0024 mol, 0.54 g) was added again at 0°C. The mixture was stirred for 24 h, then evaporated until dryness. The residue was taken up in CH_2Cl_2. The organic layer was washed with H_2O, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried, yielding: 0.089 g of **compound no. 45** (melting point > 250°C).

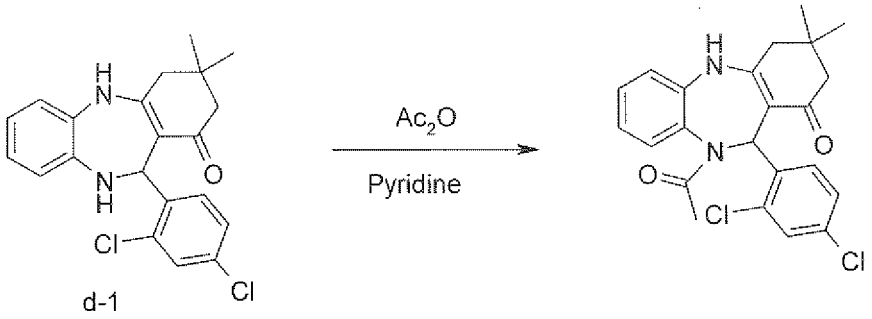
Scheme C



Compound no. 107

A mixture of c-1 (0.0003 mol) in c-2 (5 ml) was stirred at room temperature for 12 h, then cooled with an ice bath. H_2O was added drop wise. The mixture was taken up in CH_2Cl_2. The organic layer was separated, dried (over MgSO4), filtered and the solvent was evaporated until dryness. The residue (0.165 g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 0.089 g of **Compound no. 107** (74%) (melting point > 260°C).

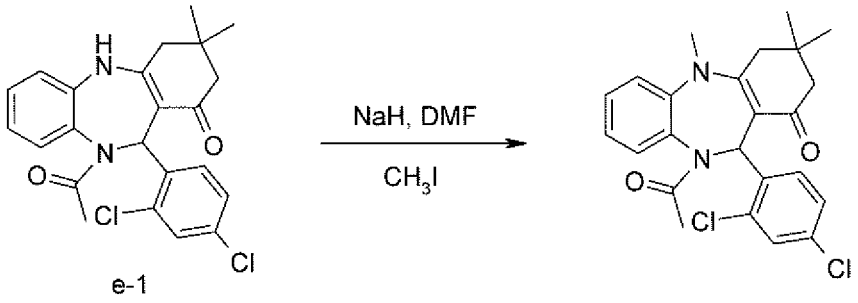
Scheme D



Compound no. 38

Ac_2O (2 ml) was added drop wise at 0°C to a solution of d-1 (0.0052 mol) in Pyridine (50 ml). The mixture was stirred at room temperature for 12 h. Ac_2O (2 ml) was added again at 0°C. The mixture was stirred at room temperature for 12 h. The precipitate was filtered, washed with H_2O and dried, yielding: 1.67 g of **Compound no. 38** (75%)(melting point > 260°C).

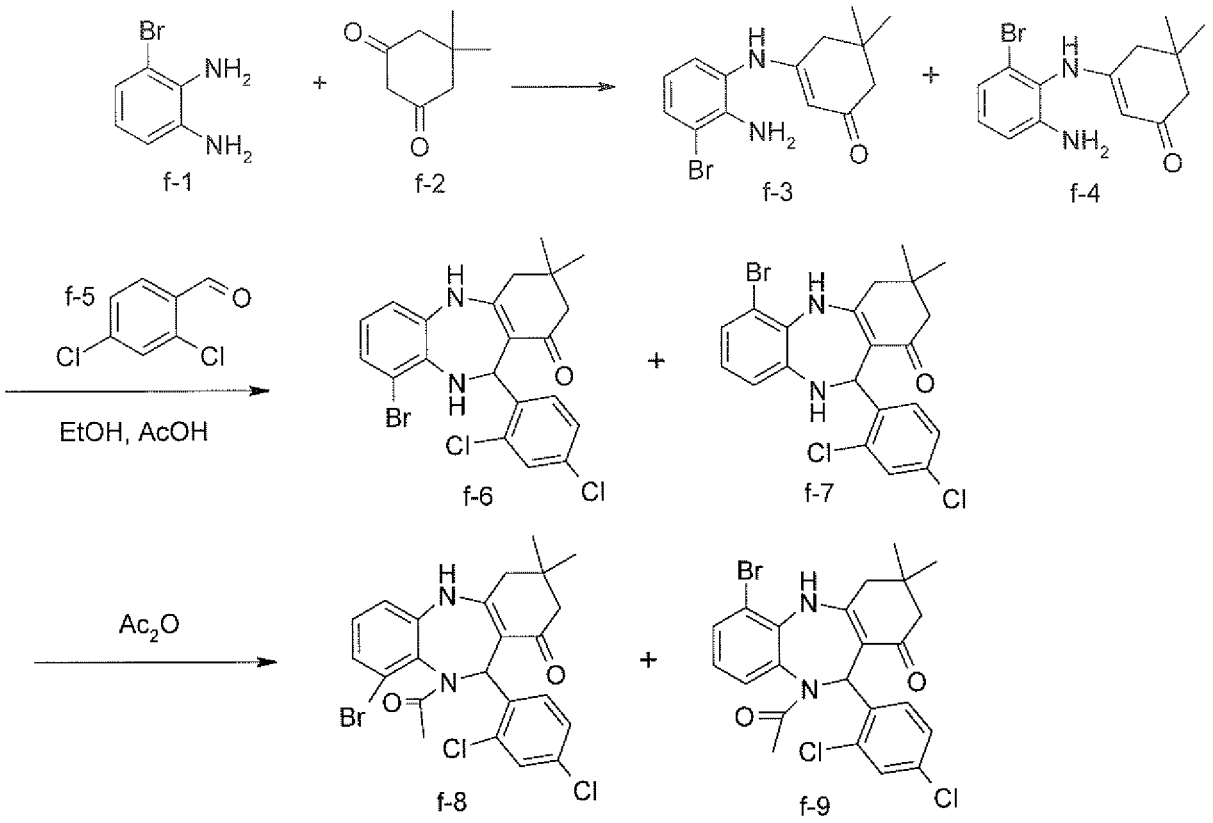
Scheme E



Compound no. 322 (TMC430057)

A mixture of e-1 (0.0004 mol) and NaH (0.0004 mol) in DMF (2 ml) was stirred for 10 minutes. CH_3I (0.0004 mol) was then added. The mixture was stirred at room temperature for 12 h and evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried, yielding: 0.037 g of **Compound no. 322** (20%) (melting point: 145°C).

Scheme F

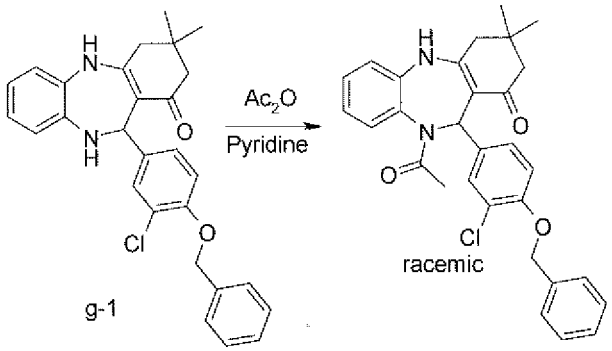


A mixture of f-1 (0.0057 mol) and f-2 (0.0057 mol) in toluene (20 ml) was stirred and refluxed for 12 h, then concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.2). Two fractions were collected and the solvent was evaporated until dryness, yielding a mixture of f-3 and f-4 (71%).

A mixture of f-3 + f-4 (0.004 mol) and f-5 (0.004 mol) in EtOH (10 ml) and AcOH (10 ml) was stirred at 75°C for 12 h, then evaporated until dryness. The residue was taken up in EtOAc. Saturated $NaHCO_3$ was added. The mixture was stirred for 1 hour and 30 minutes, then filtered and extracted with EtOAc. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5). Three fractions were collected and the solvent was evaporated, yielding: 0.2 g of f-7, 1 g of a mixture f-6 + f-7 and 0.1 g of f-6 (melting point: 170°C).

A mixture of f-6 + f-7 (0.0004 mol) in Ac_2O (5 ml) was stirred and refluxed for 4 hours, then concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1). Two fractions were collected and the solvent was evaporated, yielding: 0.065 g of f-9 and 0.09 g of f-8. A part of f-8 was crystallized from diethyl ether/2-propanone. The precipitate was filtered off and dried, yielding: 0.03 g (melting point > 260°C).

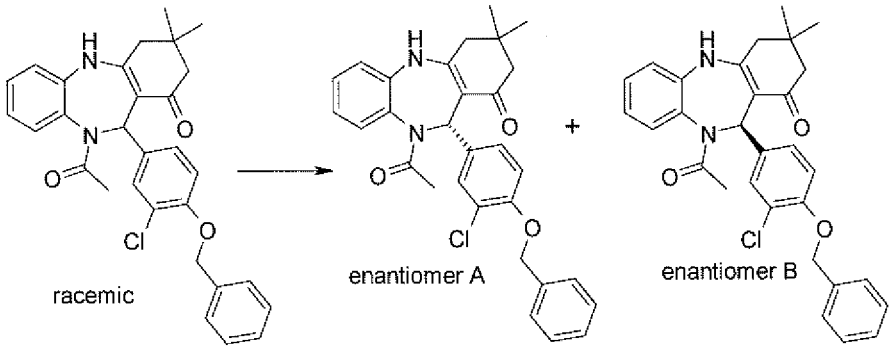
Scheme G



Compound no. 139

The title **compound no. 139** was prepared from Intermediate (**5-2**) and 4-benzyloxy-3-chlorobenzaldehyde following the procedure described in Example 5: *m/z* = 501 $(M+H)^+$.

Separation of the (R)- and (S)- enatiomers of **compound no. 139**.

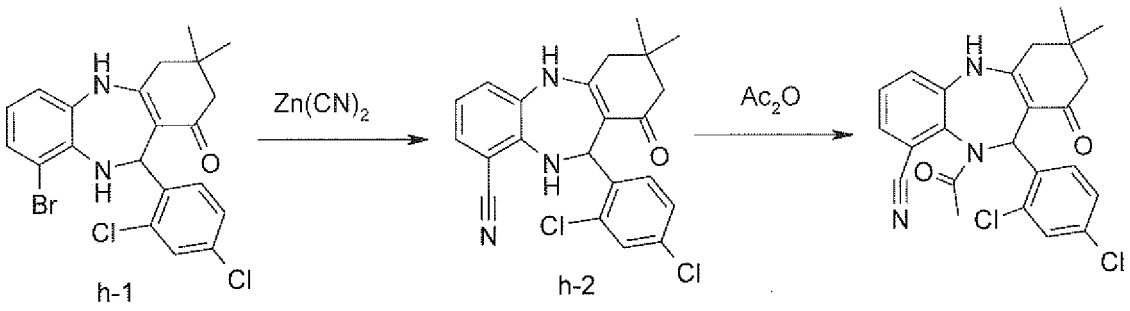


Compound no. 139 **Compound no. 303** **Compound no. 304**

The two enantiomers were separated by SFC with a chiral column (eluent: CO_2/CH_3OH 40/60). Two fractions were collected and the solvent was evaporated, yielding: 0.085 g of enantiomer A and 0.085 g of enantiomer B. Both fractions were crystallized from DIPE/2-propanone. The precipitate was filtered off and dried, yielding: 0.042 g of

Compound no. 303 (enantiomer A) (melting point: 130°C) and 0.055 g of Compound no. 304 (enantiomer B) (melting point: 130°C).

Scheme H

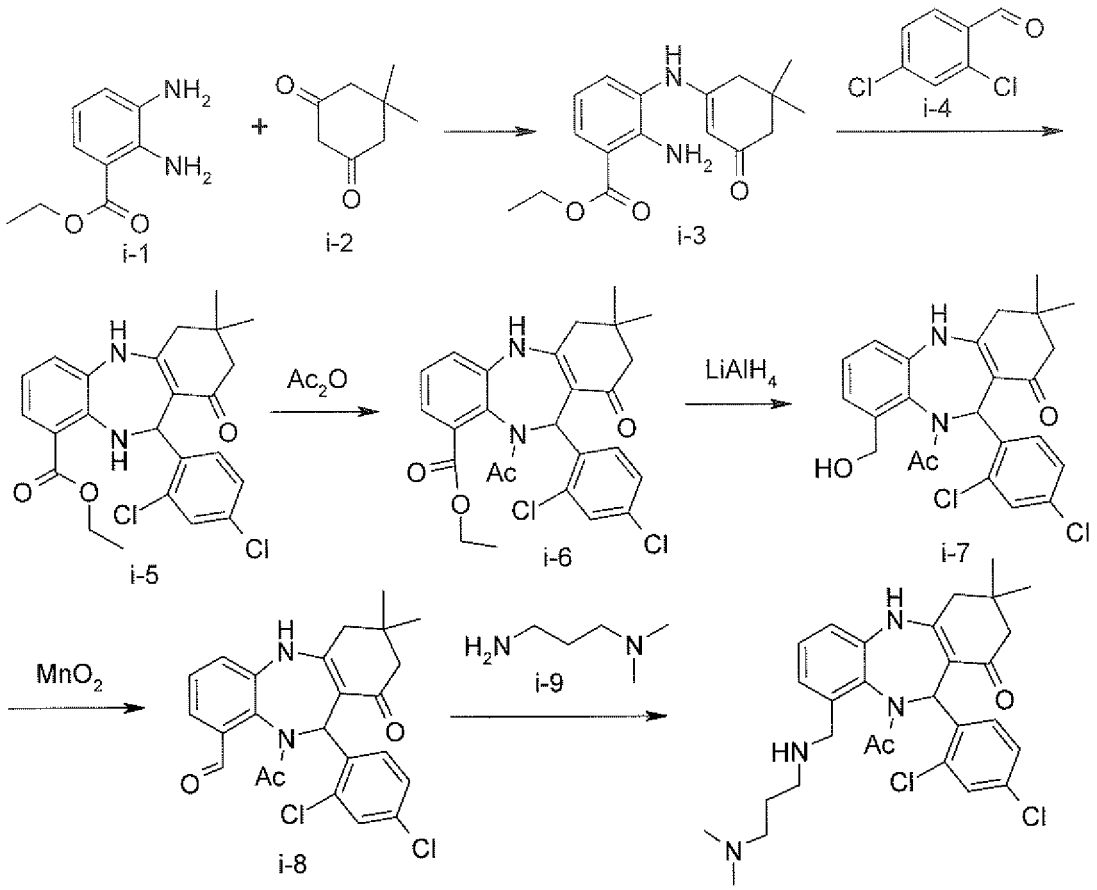


Compound no. 313

A mixture of h-1 (0.0004 mol), $Zn(CN)_2$ (0.0007 mol), Pd_2dba_3 (0.022 g), dppf (0.033 g), Zn (0.0002 mol) and $Zn(OAc)_2$ (0.0002 mol) in DMA (2 ml) was stirred at 130°C in a microwave oven for 30 minutes, then poured into H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 95/5). The pure fractions were collected and the solvent was evaporated. The residue (0.14 g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 0.06 g of h-2 (melting point: 225°C).

A mixture of h-2 (0.0002 mol) in Ac_2O (4 ml) was stirred and refluxed for 12 hours and then evaporated until dryness. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue (0.07 g) was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.025 g of Compound no. 313 (melting point: 248°C).

Scheme I



Compound no. 514

A mixture of i-1 (0.0094 mol) and i-2 (0.0094 mol) in toluene (50 ml) was stirred and refluxed for 12 h in a Dean Stark apparatus, then cooled down to room temperature. The precipitate was filtered off and dried, yielding: 2.3 g of i-3 (76%).

A mixture of i-3 (0.0044 mol) and i-4 (0.0044 mol) in EtOH (12.44 ml) and AcOH (1.23 ml) was stirred at 75°C for 12 h, then evaporated until dryness. The residue was taken up in EtOAc/NaHCO3 10% aq. The mixture was stirred at room temperature for 1 hour and 30 minutes, then filtered off and dried. The residue (0.4 g) was washed with EtOAc, dried (over MgSO4), filtered and the solvent was evaporated until dryness. The residue (1.77 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98.5/1.5/0.1). The pure fractions were collected and the solvent was evaporated, yielding: 1 g of I-5 (52%). A small fraction was crystallized from CH3CN/DIPE (melting point: 208°C). The remaining fraction of i-5 was used in the next reaction step.

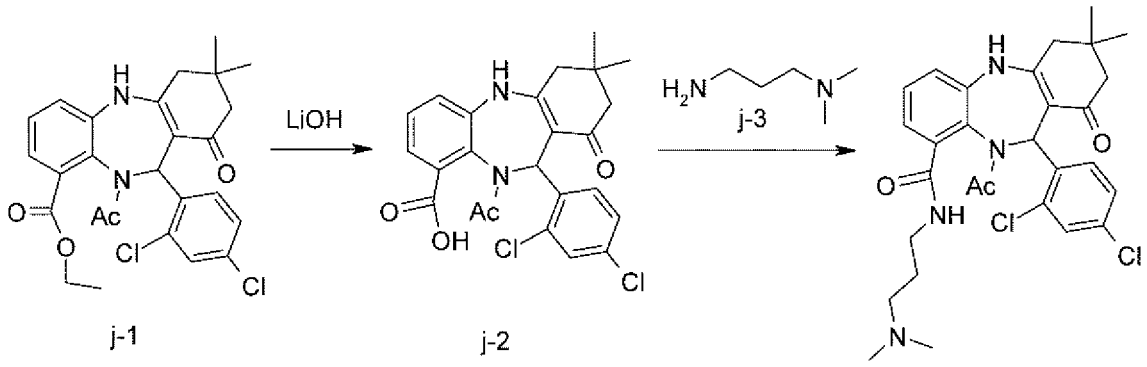
A mixture of i-5 (0.0008 mol) in Ac_2O (60 ml) was stirred and refluxed for 4 hours, then evaporated until dryness, yielding: 0.46 g of i-6 (100%).

i-6 (0.0059 mol) was added at 0°C to a suspension of $LiAlH_4$ (0.0018 mol) in THF (4 ml) under N_2 flow. The mixture was stirred at 0°C for 3 hours. EtOAc then ice were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (over MgSO4), filtered and the solvent was evaporated until dryness. The residue (0.175 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 95/5/0.5 to 93/7/0.7). The pure fractions were collected and the solvent was evaporated, yielding: 0.032 g of i-7 (12%) (melting point 200°C).

A mixture of i-7 (0.0005 mol) and MnO_2 (1.5 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 3 hours, then filtered over celite and washed with CH_2Cl_2. The filtrate was evaporated until dryness. The residue was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding: 0.12 g of i-8 (48%).

A mixture of i-8 (0.0001 mol), i-9 (0.0001 mol), BH_3CN- on solid support (0.0001 mol) and AcOH (5 drops) in CH_3OH (5 ml) was stirred at room temperature for 5 hours. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 94/6/0.6 to 82/18/1.8). The pure fractions were collected and the solvent was evaporated. The residue (0.035 g) was crystallized from CH_3CN. The precipitate was filtered off and dried. Yielding: 0.022 g of Compound no. 514 (31%) (melting point: 258°C).

Scheme J

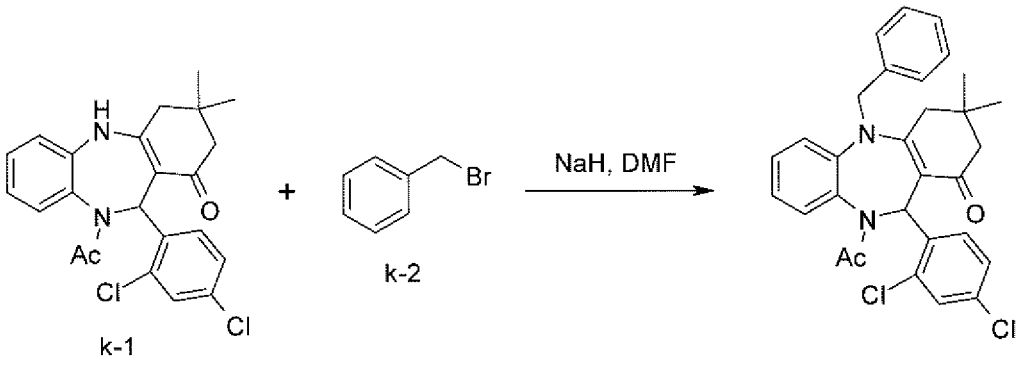


Compound no. 515

A mixture of j-1 (0.0004 mol) and LiOH (0.0009 mol) in THF (20 ml) and H_2O (20 ml) was stirred at 50°C for 36 hours. THF was evaporated. The mixture was acidified with HCl 1N until pH was set to 7. The precipitate was filtered. The filtrate was basified with K_2CO_3 10%. The aqueous layer was acidified with HCl 1N. The precipitate was filtered off and dried, yielding: 0.092 g of j-2 (60%).

A mixture of j-2 (0.0001 mol), j-3 (0.0003 mol), EDCI (0.0003 mol) and HOBT (0.0003 mol) in CH_2Cl_2 (4 ml) and THF (2 ml) was stirred at room temperature for 6 hours, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue (0.1 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 92/8/0.8 to 78/20/2). The pure fractions were collected and the solvent was evaporated. The residue (0.054 g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding: 0.048 g of Compound no. 515 (melting point: 226°C).

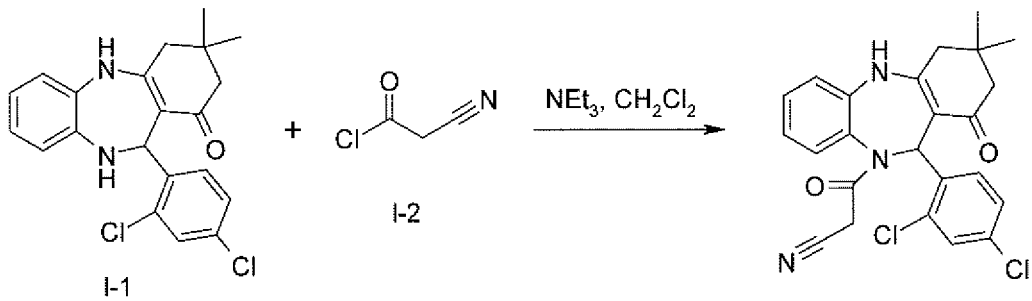
Scheme K



Compound no. 323

NaH (0.0001 mol) was added to a solution of k-1 (0.0005 mol) in DMF (2.5 ml). The mixture was stirred for 10 minutes. k-2 (0.0001 mol) was added. The mixture was stirred at room temperature for 12 h, then evaporated until dryness. The residue (0.45 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. The residue (0.2 g) was crystallized from 2-propanone. The precipitate was filtered off and dried, yielding: 0.043 g of Compound no. 323 (melting point: 235°C).

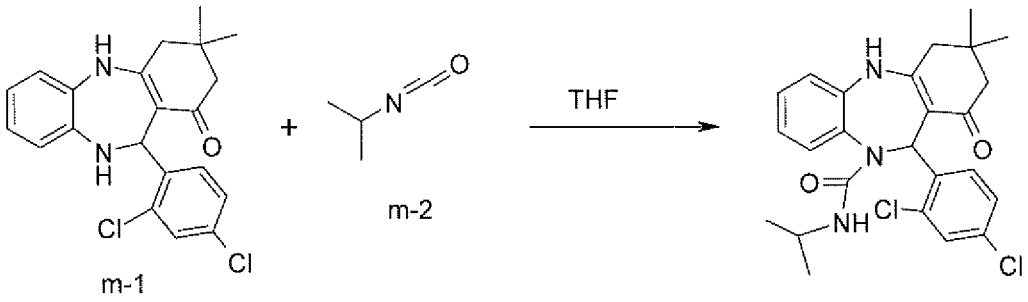
Scheme L



Compound no. 151

A mixture of l-1 (0.0003 mol), l-2 (0.0004 mol) and NEt_3 (0.065 ml) in CH_2Cl_2 (4 ml) was stirred at room temperature for 48 hours. The mixture was stirred at room temperature for 12 h, then poured into H_2O/CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (0.13 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.1 to 94/6/0.6). The pure fractions were collected and the solvent was evaporated. The residue (0.05 g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding: 0.041 g of Compound no. 151 (23%) (melting point > 260°C).

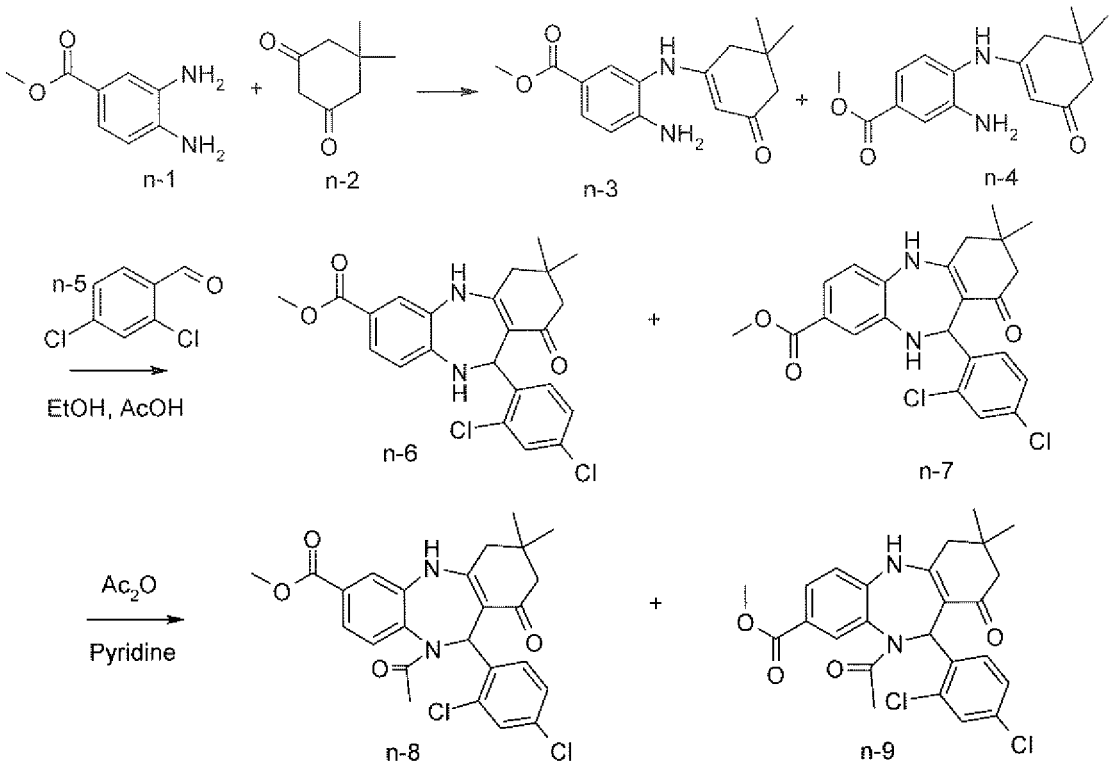
Scheme M



Compound no. 156

A mixture of m-1 (0.0002 mol) and m-2 (0.0003 mol) in THF (5 ml) was stirred and refluxed for 1 hour and 30 minutes, then taken up in H_2O/CH_2Cl_2 and extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was crystallized from CH_3CN/DIPE (few). The precipitate was filtered off and dried, yielding: 0.064 g of Compound no. 156 (53%) (melting point > 260°C).

Scheme N



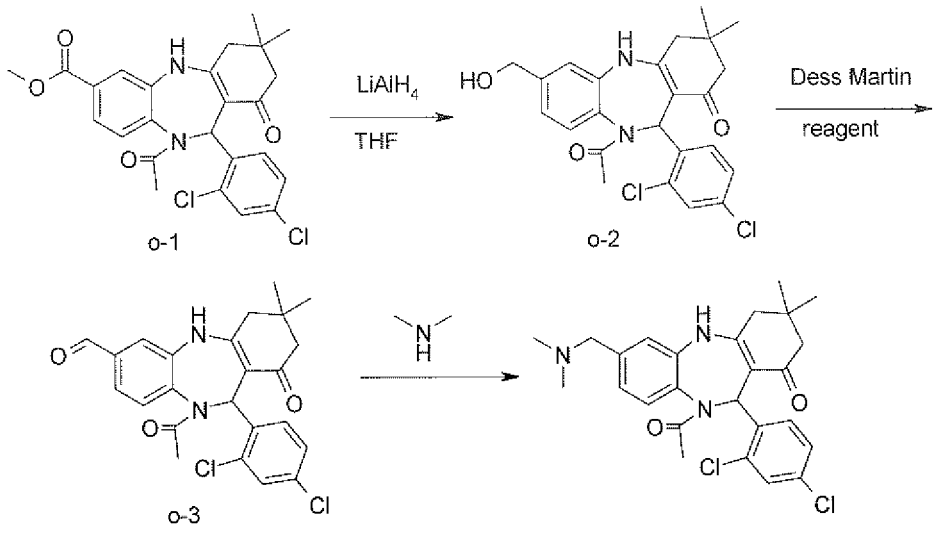
A mixture of n-1 (0.01 mol) and n-2 (0.01 mol) in toluene (20 ml) was stirred and refluxed in a Dean Stark apparatus for 12 h, then evaporated until dryness, yielding: 3 g of n-3 + n-4. This mixture of product was used directly in the next reaction step.

A mixture of n-3 + n-4 (0.01 mol) and n-5 (0.01 mol) in EtOH (25 ml) and AcOH (25 ml) was stirred at 75°C for 12 h, then evaporated until dryness. The residue was taken up in EtOAc and saturated solution of $NaHCO_3$. The mixture was stirred for 1 hour and 30 minutes, and then filtered. The aqueous layer was extracted with EtOAc. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2 100). The pure fractions were collected and the solvent was evaporated, yielding: 1.25 g of n-6 + n-7.

Ac_2O (1 ml) was added to a solution of n-6 + n-7 (0.0012 mol) in pyridine (10 ml). The mixture was stirred at room temperature for 12 h, then evaporated until dryness. The residue (0.54 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.2 to 92/8/0.8). Two fractions were collected and the solvent was evaporated, yielding: 0.14 g F1 (24%) and 0.15 g F2 (25%). Each fraction

was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: n-8 (melting point > 250°C) and n-9 (melting point > 250°C).

Scheme O



Compound no. 516

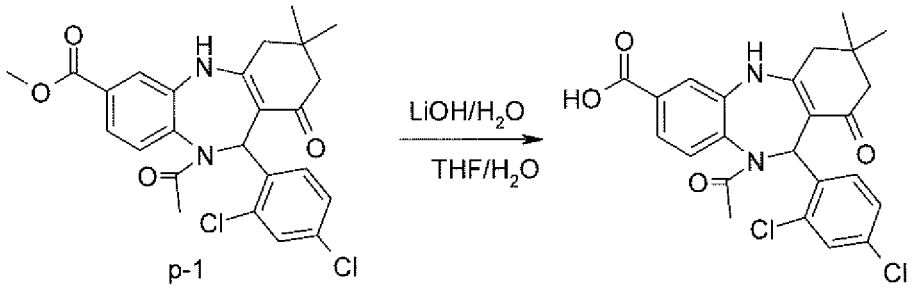
A mixture of o-1 (0.003 mol) and $LiAlH_4$ (0.012 mol) in THF (60 ml) was stirred at room temperature for 2 hours. H_2O and NaOH 3M were the added carefully. The mixture was stirred for 1 h. The mixture was extracted with CH_2Cl_2/CH_3OH (few). The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was washed with H2O and dried, yielding: 1.54 g o-2 (100%). A small part (0.07 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.2 to 92/8/0.8). The pure fractions were collected and the solvent was evaporated, yielding: 0.022 g. The remaining product was used in the next reaction step.

Dess Martin reagent (13.34 ml) was added at room temperature of o-2 (0.0031 mol) in CH_2Cl_2 (11.6 ml). The mixture was stirred at room temperature for 1 hour. Saturated $NaHCO_3$ and $Na_2S_2O_4$ were added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated until dryness. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 1.3 g of o-3.

A mixture of o-3 (0.0002 mol), dimethylamine (0.0006 mol), BH_3CN- on solid support (0.0006 mol) and AcOH (4 drops) in CH_3OH (5 ml) was stirred at room temperature for 12 h. Dimethylamine (0.5 eq) and BH_3CN- on solid support (0.5eq) were added again. The mixture was stirred at room temperature for 12 h, then filtered. The filtrate

was evaporated. The mixture was taken up in CH_2Cl_2/H_2O. The organic layer was separated, dried (over MgSO4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.5). The pure fractions were collected and the solvent was evaporated. The residue (0.085 g) was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding: 0.056 g of Compound no. 516 (52%) (melting point > 260°C).

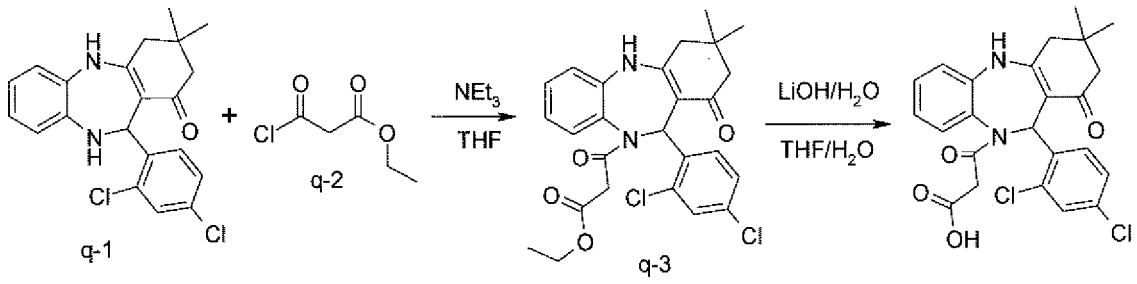
Scheme P



Compound no. 517

A mixture of p-1 (0.0001 mol) and $LiOH/H_2O$ (0.0004 mol) in THF/H_2O (1/1) (10 ml) was stirred at room temperature for 12 h, and then concentrated under reduced pressure. The aqueous layer was washed with diethyl ether, made acidic with HCl 1N and filtered. The precipitate was dried, yielding: 0.045 g of Compound no. 517 (melting point > 250°C).

Scheme Q



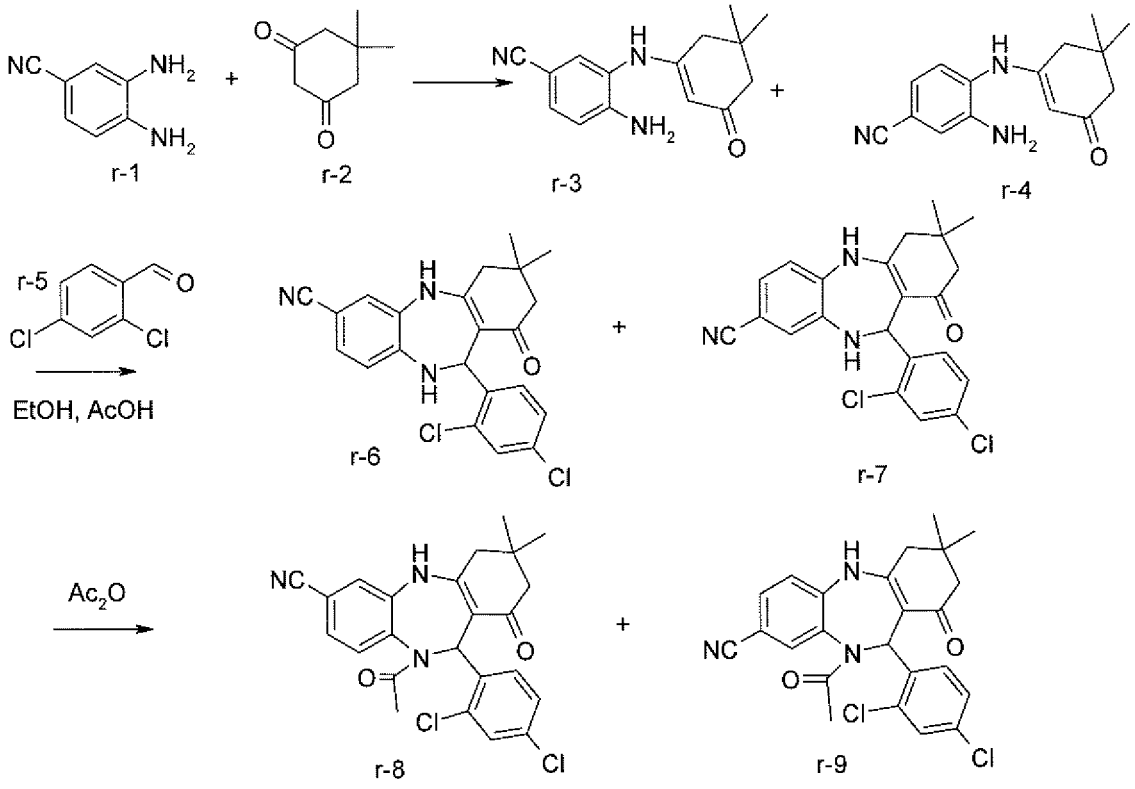
Compound no. 518

q-2 (0.0012 mol) was added drop wise to a mixture of q-1 (0.001 mol) and NEt_3 (0.0012 mol) in THF (5 ml). The mixture was stirred and refluxed for 12 h, then cooled down to room temperature. The precipitate was filtered, washed with THF. The filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.2, 93/7/0.7 then 94/6/0.6). The pure fractions were collected and the solvent was evaporated. The residue (0.09 g, 18%)

was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: q-3 (melting point: 190°C).

A mixture of q-3 (0.0001 mol) and $LiOH/H_2O$ (0.0002 mol) in THF (5 ml) and H_2O (5 ml) was stirred at room temperature for 3 hours. THF was evaporated. The residue was extracted with CH_2Cl_2. The aqueous layer was made acidic with HCl 3N. The mixture was filtered off and dried, yielding: 0.055 g of Compound no. 518 (83%) (melting point: 200°C).

Scheme R



Compound no. 319 **Compound no. 318**

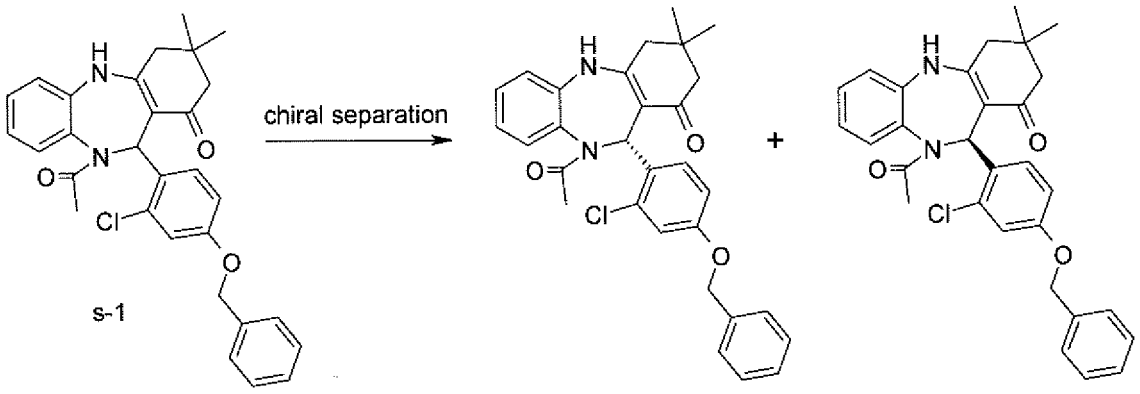
A mixture of r-1 (0.02 mol) and r-2 (0.02 mol) in toluene (100 ml) was stirred and refluxed for 12 h in a Dean Stark apparatus. The solution was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.5). The pure fractions were collected and the solvent was evaporated, yielding 2.04 g of the mixture r-3 + r-4.

A mixture of r-3 + r-4 (0.0063 mol) and r-5 (0.0035 mol) in EtOH (30 ml) and AcOH (3 ml) was stirred at 75°C for 12 h, then evaporated until dryness. The residue was taken up in EtOAc and saturated solution of $NaHCO_3$. The mixture was stirred for

1 hour and 30 minutes, filtered and extracted with EtOAc. The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98.5/1.5/0.1). The pure fractions fractions were collected and the solvent was evaporated, yielding 0.072 g of the mixture r-6 + r-7.

A mixture of r-6 + r-7 (0.0004 mol) in C (5 ml) was stirred and refluxed for 2 hours, then evaporated until dryness. The residue (0.2 g) was purified by column chromatography over silica gel (eluent: toluene/iPrOH/NH_4OH 90/10/0.5). Two fractions were collected and the solvent was evaporated. Yielding: 0.125 g F1 and 0.037 g F2. Each fraction was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried, yielding: 0.034 g of Compound no. 319 (r-8) (melting point > 250°C) and 0.008 g of Compound no. 318 (r-9) (melting point > 250°C).

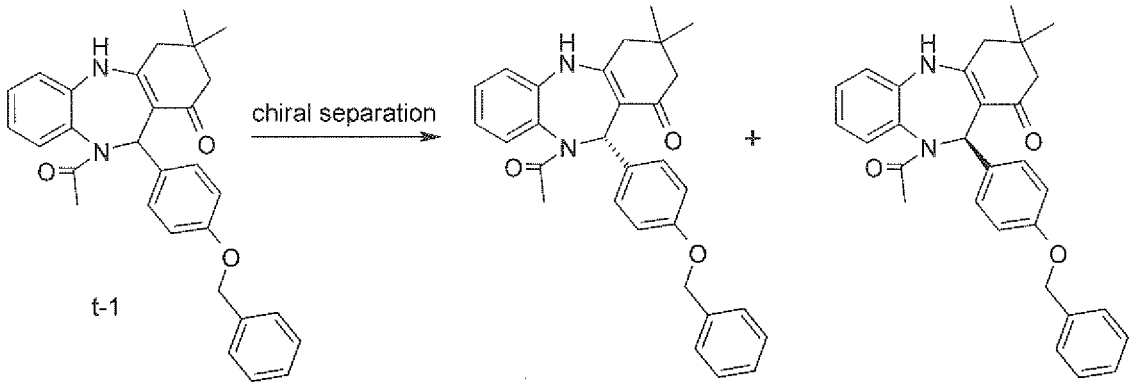
Scheme S



Compound no. 306 **Compound no. 305**

s-1 (0.0001 mol) was purified by SFC with a chiral column (eluent: CO_2/iPrOH 65/35). Two fractions were collected and the solvent was evaporated, yielding: 0.02 g of Compound no. 306 (enantiomer A) and 0.018 g of Compound no. 305 (enantiomer B).

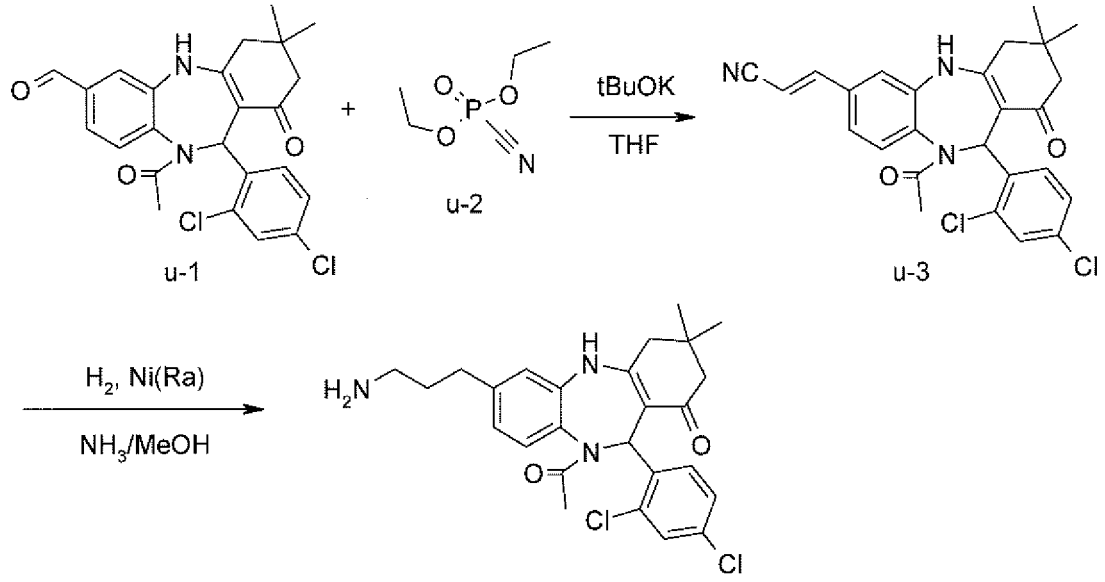
Scheme T



Compound no. 302 **Compound no. 301**

t-1 (0.1 g) was purified by column chromatography over Chiracel pack OD (eluent: EtOH/2-propanol 50/50), yielding 0.054 g of Compound no. 302 (enantiomer A) and 0.044 g of Compound no. 301 (enantiomer B).

Scheme U

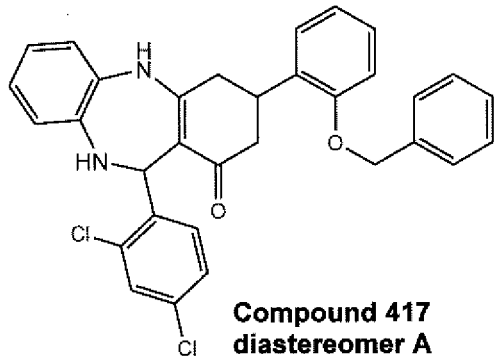


Compound no. 519

tBuOK (0.00044 mol) was added portion wise to a solution of u-2 (0.00044 mol) in THF (5 ml) at 0°C. The mixture was stirred at this temperature for 15 min and u-1 (0.00022 mol) was then added. The reaction was stirred at room temperature for 2 h and poured into water. The solution was acidified using HCl 3N and extracted with CH_2Cl_2. The organic layer was dried (over $MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.5). The pure fractions were collected and the solvent was evaporated, yielding 0.1 g of u-3 (95%).

A mixture of u-3 (0.1 g), Raney Nickel (0.1 g) in a solution of NH_3/MeOH 7 N (10 ml) was hydrogenated under a 3 bars pressure at room temperature for 8 h. The solution was then filtered through a pad of celite using MeOH and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1). The pure fractions were collected and the solvent was evaporated, yielding 0.024 g. The residue was crystallized from CH_3CN/DIPE, yielding 0.013 g of Compound no. 519(TMC533774) (13%) (melting point 242°C).

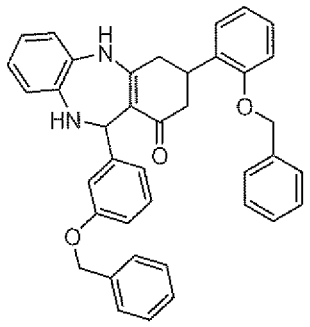
Example 93: 3-(2-Benzyloxyphenyl)-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one: **Compound 417** (diastereomer A) and **Compound 419** (diastereomer B)



Compound 417
diastereomer A
Compound 419
diastereomer B

A solution of Intermediate (**1-4**) (200 mg, 0.520 mmol) and 2,4-dichlorobenzaldehyde (91 mg, 0.520 mmol) in 10 mL dry EtOH and 1 mL AcOH was heated at 75 °C for 5h. Solvents were evaporated. The residue was dissolved in EtOAc and stirred for 1.5 h with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). Two diastereomers were obtained, and purified by silica flash column chromatography (gradient elution from heptane / EtOAc 4:1 to 2:1) to give final **Compound No. 417** diastereomer A, (yield: 118 mg, 41.1%): *m/z* = 542 $(M+H)^+$, and final **Compound No. 419** diastereomer B (yield: 57 mg, 20.2%):*m/z* = 542 $(M+H)^+$.

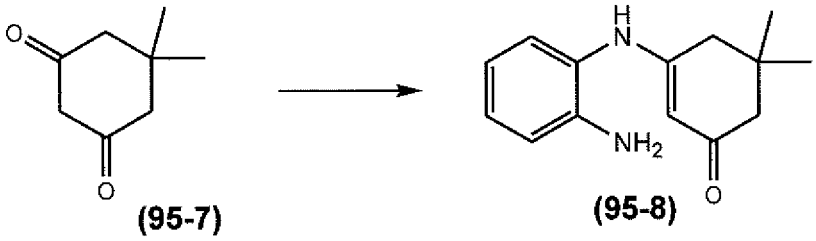
Example 94: 3-(2-Benzyloxyphenyl)-11-(3-benzyloxyphenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 418** (diastereomer A) and **Compound No. 420** (diastereomer B.



The title compounds were prepared and separated from Intermediate (**1-4**) and 3-benzyloxybenzaldehyde following the procedure reported for Compounds Nos. 417 and 419: m/z = 580 $(M+H)^+$.

Example 95: 11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 423**.

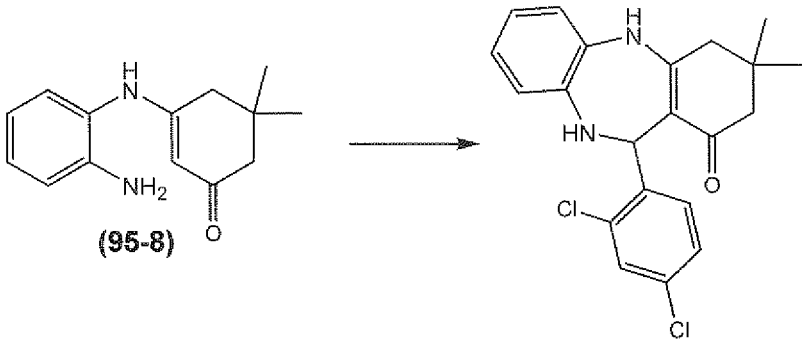
Step A.



(95-7) **(95-8)**

A solution of dimedone (**95-7**, 5.0 g, 35.67 mmol) and *o*-phenylenediamine (3.86 g, 35.69 mmol) in 150 mL dry toluene were refluxed overnight in a Dean-Stark trap. After 24h, the solvent was evaporated to give Intermediate (**95-8**) as an orange foam which was used without further purification in the next step.

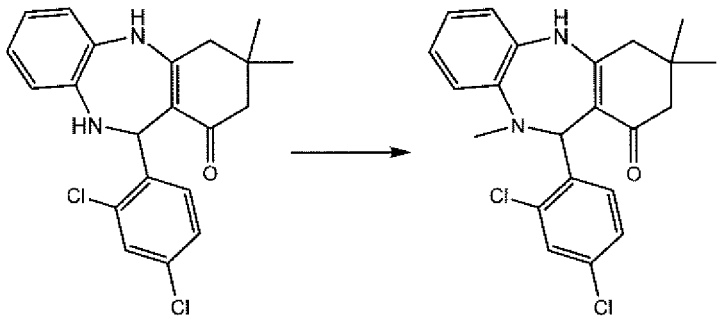
Step B.



Compound 423

A solution of Intermediate (**95-8**) (35.7 mmol) and 2,4-dichlorobenzaldehyde (6.24 g, 35.65 mmol) in a mixture of 100 mL dry EtOH and 10 mL AcOH was heated at 75°C overnight. The reaction mixture was cooled to room temperature and the solvents evaporated. The residue was dissolved in EtOAc and stirred with saturated aqueous $NaHCO_3$ for 1.5 h. Then, the water layer was removed in a separating funnel and the organic layer was filtered off, the filtrate was washed twice with EtOAc. Organic layers were dried (Na_2SO_4), evaporated and the residue dried under high vacuum, yielding 9.45 g (68.4%) of the final **Compound No. 423**: $m/z = 387$ $(M+H)^+$.

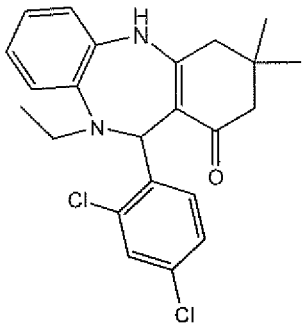
Example 96: 11-(2,4-Dichlorophenyl)-2,3,4,5,10,11-*hexahydro*-3,3,10-trimethyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 507**.



Compound 423 **Compound 507**

Methyl iodide (97 µL, 1.555 mmol) was added to a solution of **Compound No. 423** (0.50 g, 1.291 mmol) and K_2CO_3 (214 mg, 1.55 mmol) in acetone. The tube was sealed and stirred at room temperature overnight. Additional methyl iodide (146 µL, 2.34 mmol) was added and the sealed tube was stirred for 2 days. The reaction mixture was dropped onto water and the solid was filtered off and dried. Purification by preparative TLC (EtOAc / heptane 1:1) followed by sonication in *i*-Pr_2O and filtration afforded final **Compound No. 507**: $m/z = 401$ $(M+H)^+$.

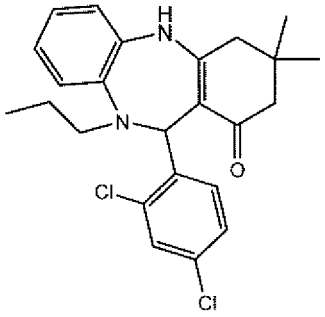
Example 97: 11-(2,4-dichlorophenyl)-10-ethyl-2,3,4,5,10,11-*hexahydro*-3,3-dimethyl1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 508 .**



Compound 508

The title compound was prepared from **Compound No. 423** and ethyl iodide (1 mL, 12.5 mmol) following the procedure reported for **Compound No. 507** *m/z* = 415 $(M+H)^+$.

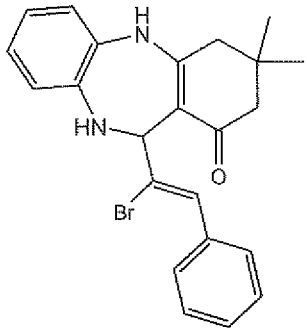
Example 98:11-(2,4-Dichlorophenyl)-2,3,4,5,10,11-*hexahydro*-3,3-dimethyl-10-propyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 509.**



Compound 509

The title compound was prepared from **Compound No. 423** and propyl iodide (1.26 mL, 12.9 mmol) following the procedure reported for **Compound No. 507** *m/z* = 429 $(M+H)^+$.

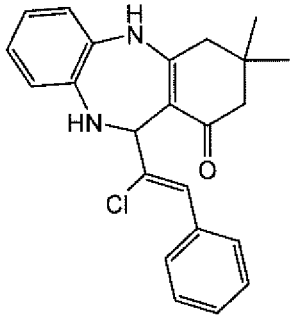
Example 99: 11-(1-Bromo-2-phenylvinyl)-3,3-dimethyl-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 500**



Compound 500

The title compound was prepared from Intermediate (**95-8)** (11.9 mmol) and 2-bromo-3-phenylacroleine (2.51 g, 11.9 mmol) following the procedure reported for **Compound No. 423**: *m/z* = 424 $(M+H)^+$.

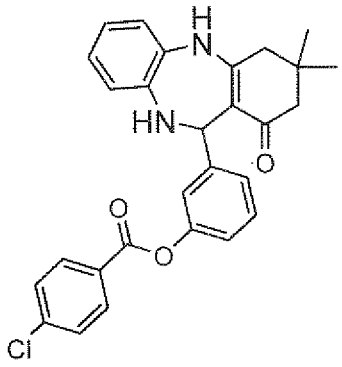
Example 100: 11-(1-Chloro-2-phenylvinyl)-3,3-dimethyl-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 506**



Compound 506

The title compound was prepared from Intermediate (**95-8)** (11.9 mmol) and 2-chloro-3-phenylacroleine (1.98 g, 11,88 mmol) following the procedure reported for **Compound No. 423**: *m/z* = 380 $(M+H)^+$.

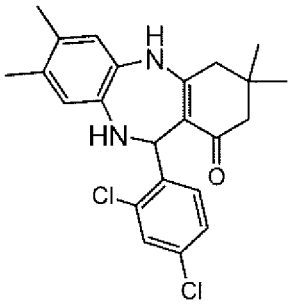
Example 101: 11-[3-(4-Chlorobenzoyloxy)phenyl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 431**.



Compound 431

The title compound was prepared from Intermediate **(95-8)** (3.9 mmol) and 3-[(4-chlorobenzoyl)oxy]benzaldehyde (1.03 g, 3.95 mmol) following the procedure reported for **Compound No. 423**: *m/z* = 474 $(M+H)^+$.

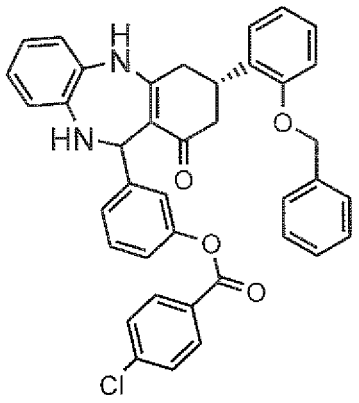
Example 102: 11-(2,4-Dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3,7,8-tetramethyl-1*H*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 464**.



Compound 464

The title compound was prepared from 4,5-dimethyl-*o*-phenylenediamine (2.48 g, 18.21 mmol), and 2,4-dichlorobenzaldehyde (3.19 g, 18.23 mmol) following the procedure reported for **Compound No. 423**: *m/z* = 416 $(M+H)^+$.

Example 103: 11-[3-(4-Chlorobenzoyloxy)phenyl]-3-(2-benzyloxyphenyl)-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 512** diastereomer A



Compound 512
diastereomer A

The compound was prepared from Intermediate **(93-4)** (300 mg, 0.780 mmol) and 3-[(4-chlorobenzoyl)oxy]benzaldehyde (244 mg, 0.936 mmol) following the procedure reported for **Compound No. 417** : *m/z* = 628 $(M+H)^+$.

Example 104: 3-(2-benzyloxyphenyl)-11-[3-(4-chlorobenzoyloxy)phenyl]-2,3,4,5,10,11-*hexahydro*-dibenzo[b,e][1,4]diazepin-1-one –**Compound No. 513** diastereomer B

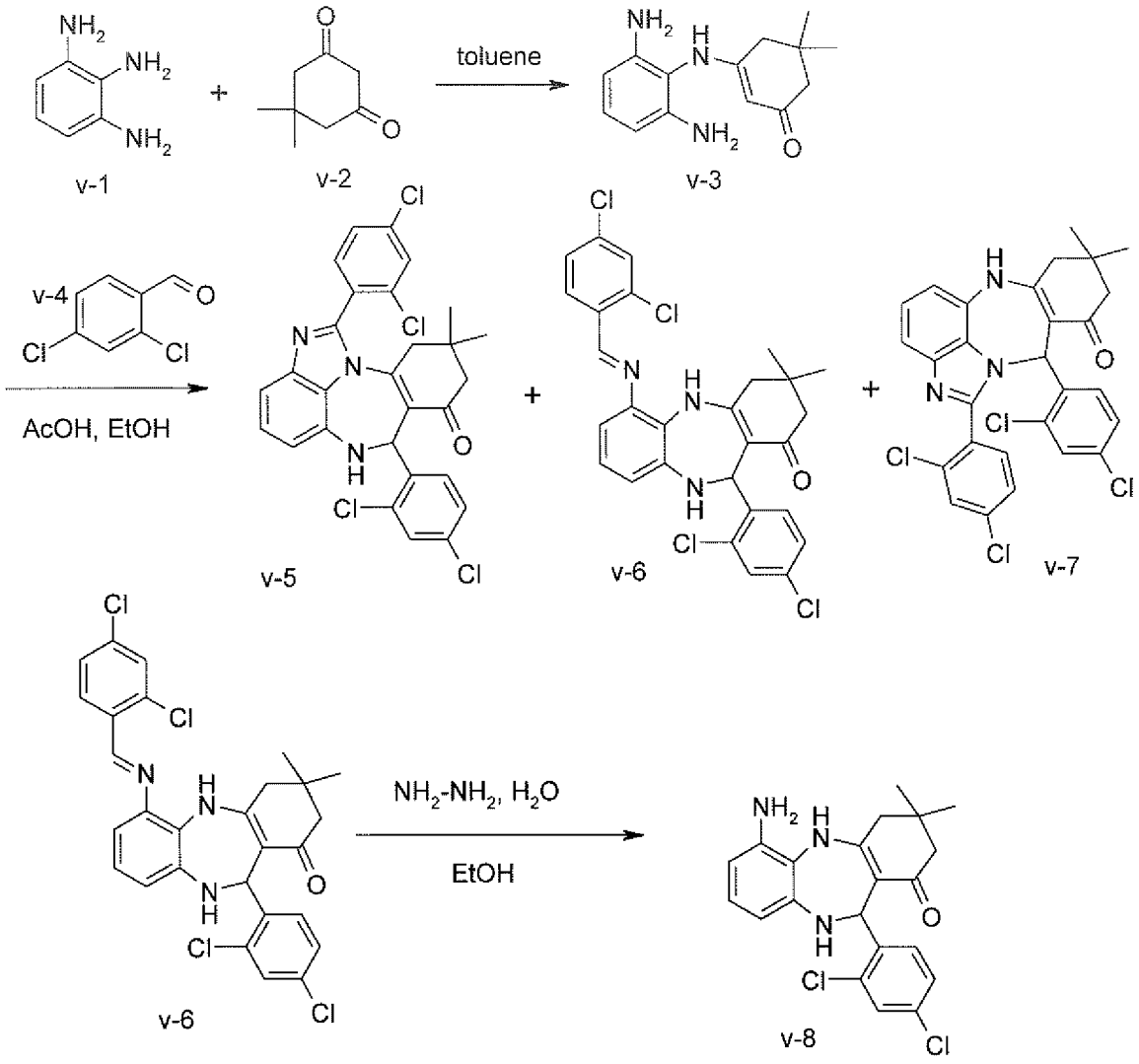
The compound was prepared from Intermediate **(93-4)** (300 mg, 0.780 mmol) and 3-[(4-chlorobenzoyl)oxy]benzaldehyde (244 mg, 0.936 mmol) following the procedure reported for **Compound No. 419**: *m/z* = 628 $(M+H)^+$.

Example 105: 7,8-Dichloro-11-(2,4-dichlorophenyl)-2,3,4,5,10,11-hexahydro-3,3-dimethyl-1H-dibenzo[b,e][1,4]diazepin-1-one **Compound No. 465**

The title compound was prepared from 4,5-dichloro-o-phenylenediamine, and 2,4-dichlorobenzaldehyde following the procedure reported for **Compound No. 423**: m/z = 455 (M+H)+.

Example 106

Scheme V



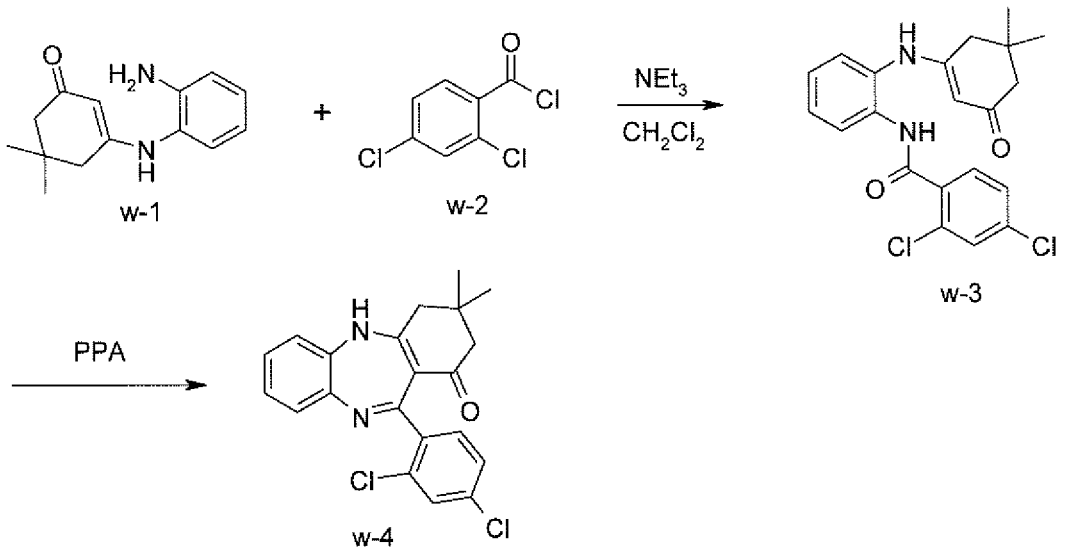
A mixture of v-1 (0.0089 mol) and v-2 (0.0089 mol) in toluene (50 ml) was stirred and refluxed for 12 h in a Dean Starck apparatus, then cooled to room temperature. The precipitate was filtered, washed with diethyl ether and dried, yielding: 2 g of v-3 (100%).

A mixture of v-3 (0.0106 mol) and v-4 (0.0106 mol) in AcOH (2.6 ml) and EtOH (50 ml) was stirred at 75°C for 24 hours, then cooled to room temperature and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2. The organic layer was washed with K_2CO_3 10%, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (5.7 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 100/0/0 to 99/1/0.1). Three fractions were collected and the

solvent was evaporated, yielding: 0.27 g of v-5 (4.5%) (melting point > 260°C), 0.4 g of v-6 (6.7%) and 0.34 g of v-7 (5.7%) (melting point > 260°C).

A mixture of v-6 (0.0006 mol) and NH_2-NH_2/H_2O (0.003 mol) in EtOH (20 ml) was stirred and refluxed for 6 hours, then concentrated under reduced pressure. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 0.12 g (50%). Part of this fraction (0.04 g) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding: 0.03 g of v-8 (melting point: 248°C).

Scheme W



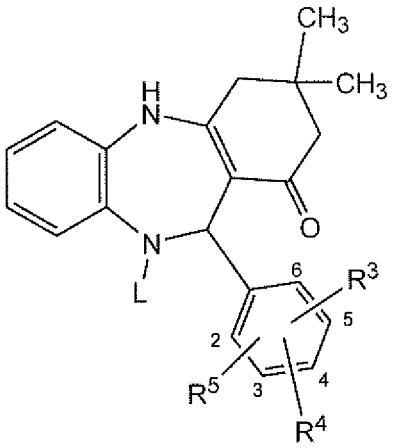
w-2 (0.0024 mol) was added at 5°C to a solution of w-1 (0.0021 mol) and NEt_3 (0.0032 mol) in CH_2Cl_2 (15 ml). The mixture was stirred at 5°C for 2 hours, then stirred at room temperature for 2 hours. The precipitate was filtered, washed with CH_2Cl_2 and dried, yielding: 0.15 g of w-3 (17%) (melting point: 240°C).

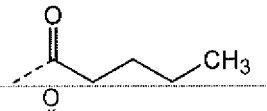
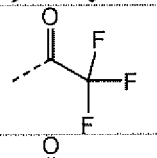
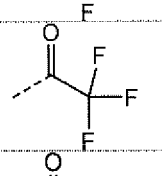
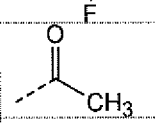
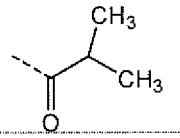
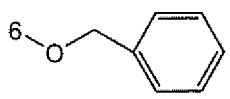
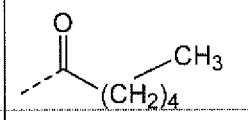
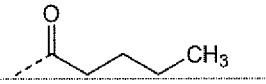
A mixture of w-3 (0.0001 mol) and PPA (1.4 g) was stirred at 130°C for 3 hours, then cooled to room temperature and taken up in K_2CO_3 10%. The precipitate was filtered, washed with H_2O and taken up in CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered, washed with H_2O and the solvent was evaporated until dryness. The residue was crystallized from CH_3CN/DIPE. The precipitate was filtered off and dried, yielding: 0.032 g of w-4 (44%) (melting point: 252°C).

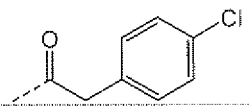
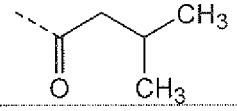
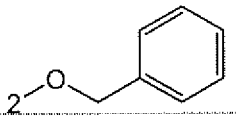
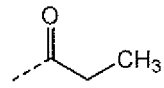
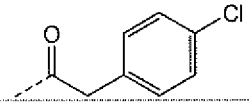
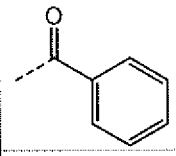
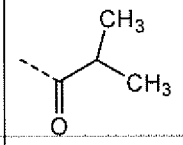
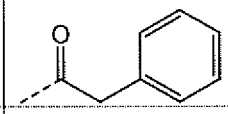
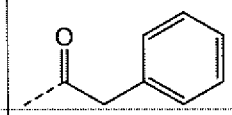
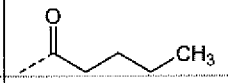
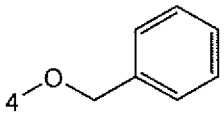
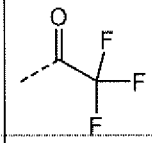
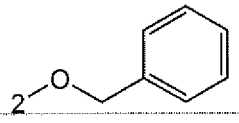
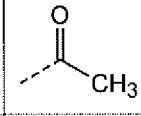
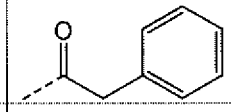
Compounds according to the invention are listed in the Tables below including the compounds that were prepared in accordance with Examples 1-106 above. The remaining compounds listed in the Table may be prepared in an analogous manner to

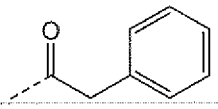
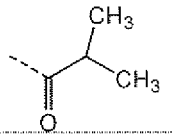
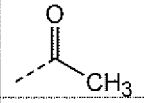
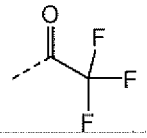
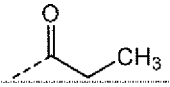
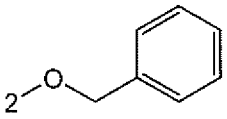
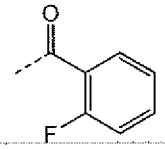
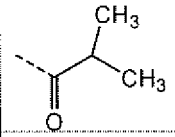
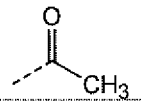
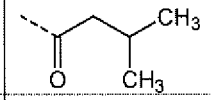
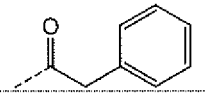
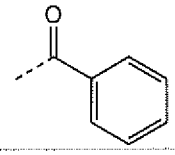
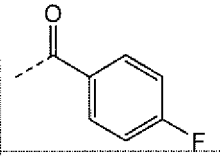
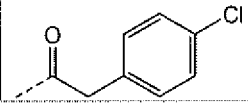
that described in the Examples. In these Tables the suffix A against a compound number denotes a diastereomer A, namely the diastereomer which was eluted first from the chromatography system; the suffix B against a compound number denotes a diastereomer B, namely the diastereomer which was eluted second from the chromatography system. Otherwise the compounds are mixtures of stereoisomeric forms.

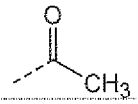
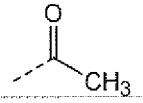
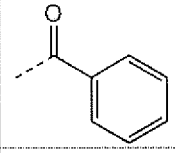
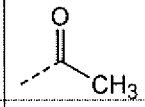
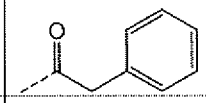
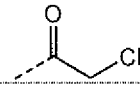
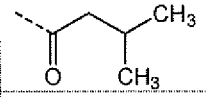
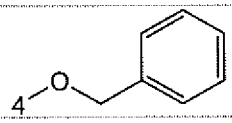
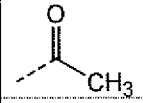
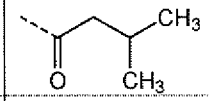
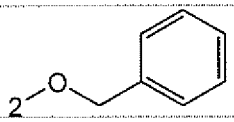
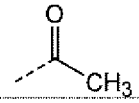
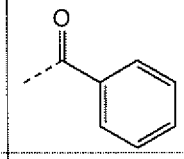
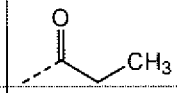
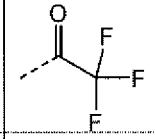
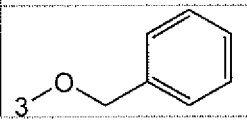
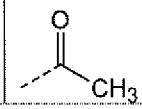
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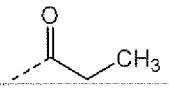
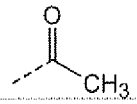
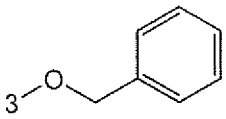
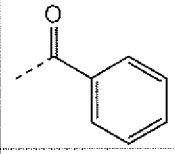
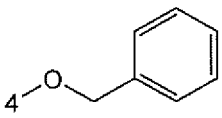
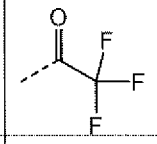
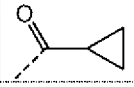
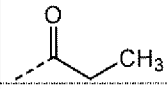
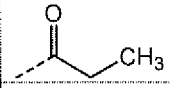
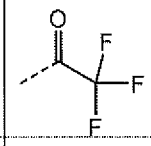
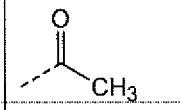
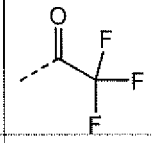
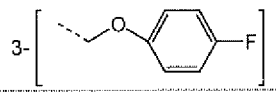
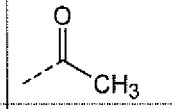
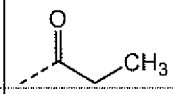
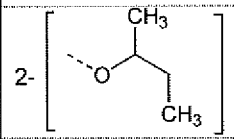
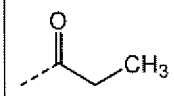
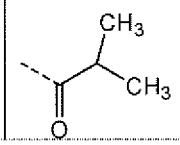


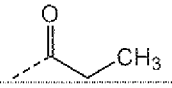
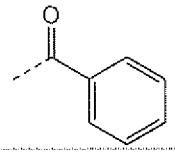
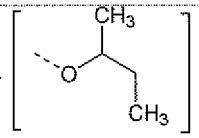
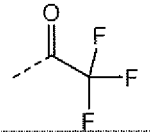
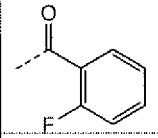
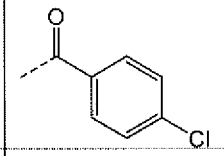
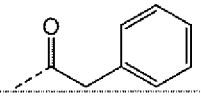
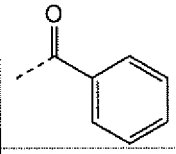
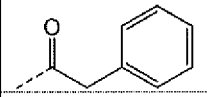
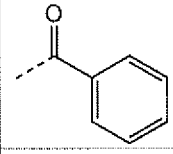
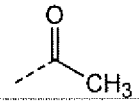
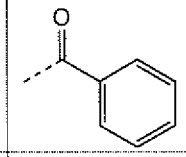
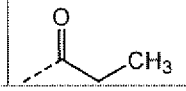
Comp. No.	R^3	R^4	R^5	L
1	2-OCH_3	4-OCH_3	H	
2	4-[-O-CH_2-CH_3]	H	H	
3	2-OCH_3	5-OCH_3	H	
4	4-F	H	H	
5	4-CF_3	H	H	
6		H	H	
7	4-Cl	H	H	

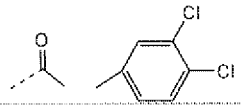
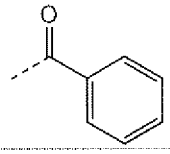
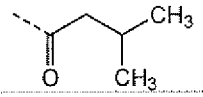
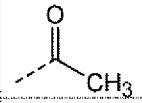
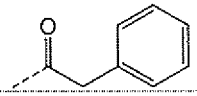
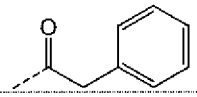
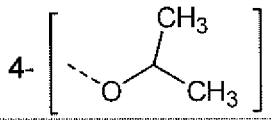
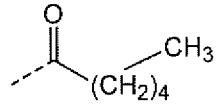
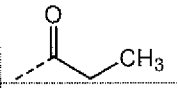
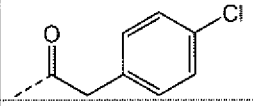
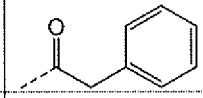
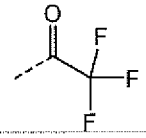
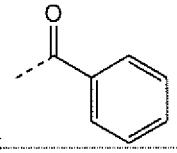
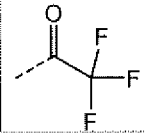
Comp. No.	R^3	R^4	R^5	L
8	4-[$N(CH_3)_2$]	H	H	
9	4-Cl	H	H	
10	4-F	H	H	
11		H	H	
12	4-OCH_3	H	H	
13	4-NO_2	H	H	
14	4-[-O-$(CH_2)_3$-CH_3]	H	H	
15	2-OCH_3	3-Cl	5-Cl	
16	2-Cl	6-Cl	H	
17	2-Cl	4-Cl	H	
18		H	H	
19		H	H	
20	4-Cl	H	H	
21	4-OCH_3	H	H	

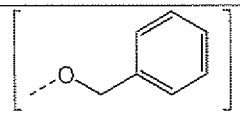
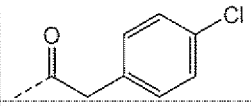
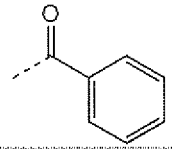
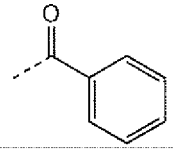
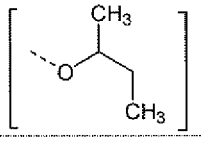
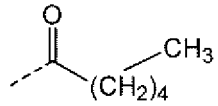
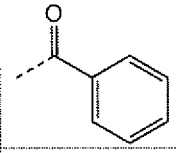
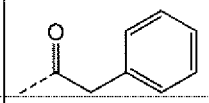
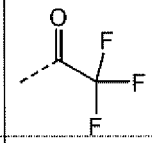
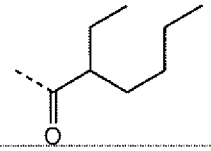
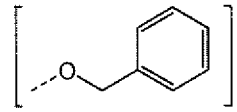
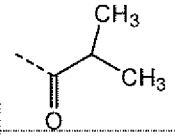
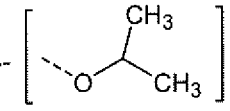
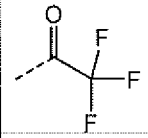
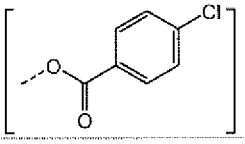
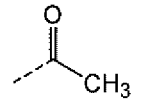
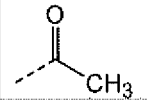
Comp. No.	R^3	R^4	R^5	L
22	2-OCH_3	5-OCH_3	H	
23	2-F	H	H	
24	2-Cl	6-F	H	
25	2-Cl	3-Cl	H	
26	2-OCH_3	3-Cl	5-Cl	
27		H	H	
28	2-Cl	4-Cl	H	
29	2-Cl	3-Cl	H	
30	2-OCH_3	4-OCH_3	H	
31	3-Cl	H	H	
32	4-Cl	H	H	
33	4-OCH_3	H	H	
34	3-OCH_3	H	H	

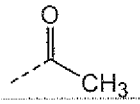
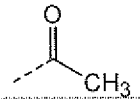
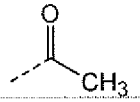
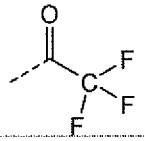
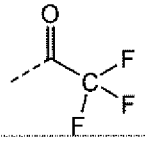
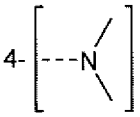
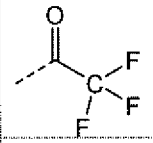
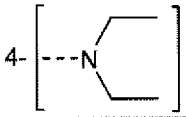
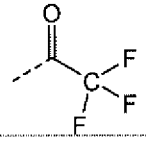
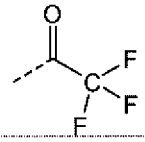
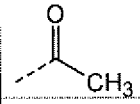
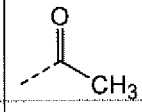
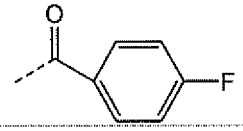
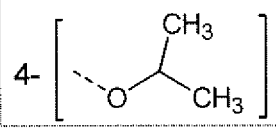
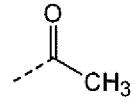
Comp. No.	R^3	R^4	R^5	L
36	2-Cl	4-Cl	H	
35	2-Cl	4-Cl	H	
37	2-Cl	6-F	H	
38	2-Cl	4-Cl	H	
39	3-OH	H	H	
40	2-Cl	3-Cl	H	
41	4-OCH_3	H	H	
42		H	H	
43	2-Cl	6-F	H	
44		H	H	
45	2-Cl	4-Cl	H	
46	2-Cl	6-Cl	H	
47	3-NO_2	H	H	
48		4-OCH_3	H	

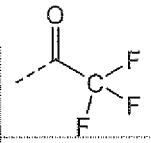
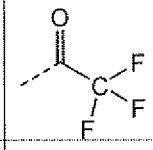
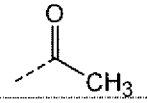
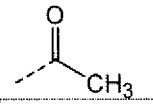
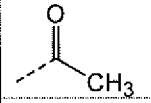
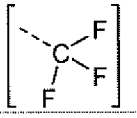
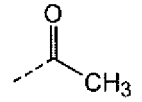
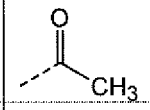
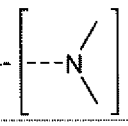
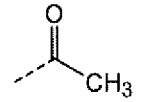
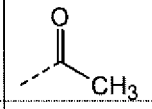
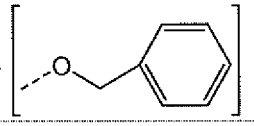
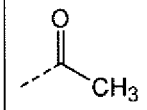
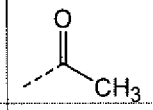
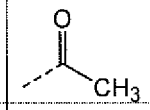
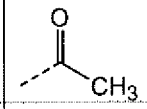
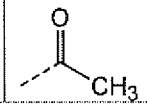
Comp. No.	R^3	R^4	R^5	L
49	4-F	H	H	
50	2-Cl	6-Cl	H	
51		4-OCH_3	H	
52		H	H	
53	2-Cl	4-Cl	H	
54	4-Cl	H	H	
55	4-CF_3	H	H	
56	4-Cl	H	H	
57	4-[-O-CH_2-CH_3]	H	H	
58	2-OCH_3	4-OCH_3	H	
59		4-OCH_3	H	
60	2-OCH_3	5-OCH_3	H	
61		H	H	
62	2-OCH_3	3-Cl	5-Cl	

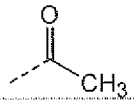
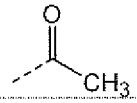
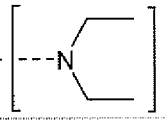
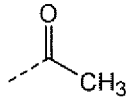
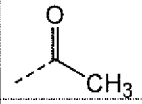
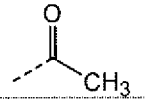
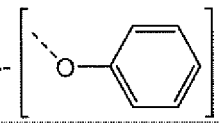
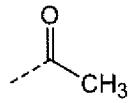
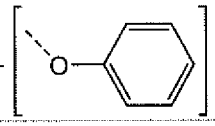
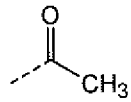
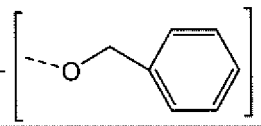
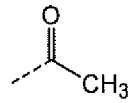
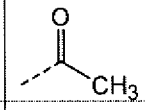
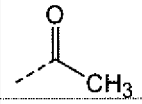
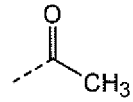
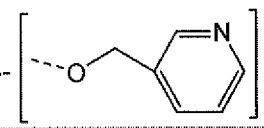
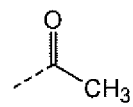
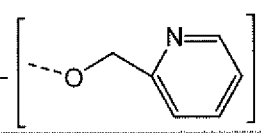
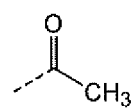
Comp. No.	R^3	R^4	R^5	L
63	2-[-O-$(CH_2)_2$-CH_3]	H	H	
64	3-[-O-CH_2-CH_3]	4-OH	H	
65	2-	H	H	
66	2-Cl	H	H	
67	4-[-O-$(CH_2)_4$-CH_3]	H	H	
68	3-OCH_3	4-OCH_3	H	
69	2-Cl	6-F	H	
70	2-Cl	H	H	
71	2-OCH_3	5-OCH_3	H	
72	2-OCH_3	5-OCH_3	H	
73	3-Cl	5-Cl	6-OCH_3	
74	4-Br	H	H	
75	2-OCH_3	4-OCH_3	H	

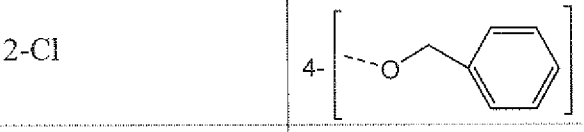
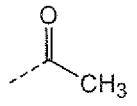
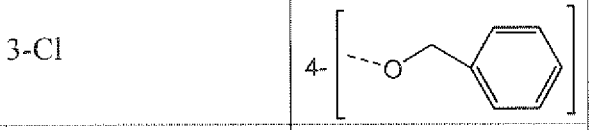
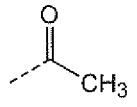
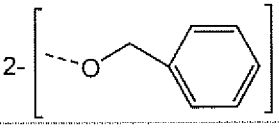
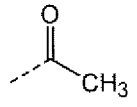
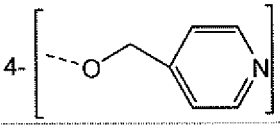
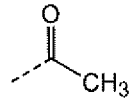
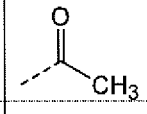
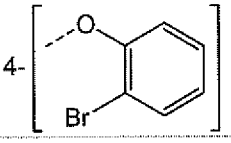
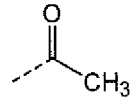
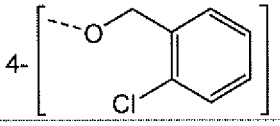
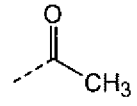
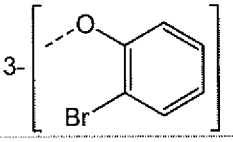
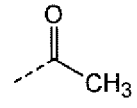
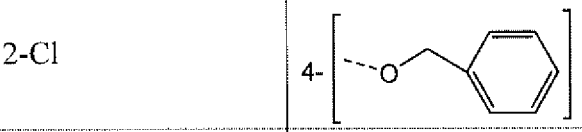
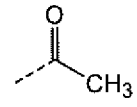
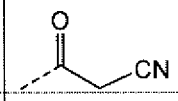
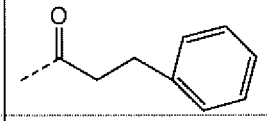
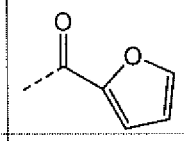
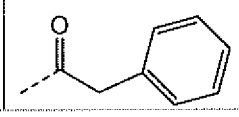
Comp. No.	R^3	R^4	R^5	L
76	4-[-$N(CH_3)_2$]	H	H	
77	4-F	H	H	
78	3-Cl	4-Cl	H	
79	3-[-O-$(CH_2)_3$-CH_3]	H	H	
80	3-OCH_3	4-OCH_3	H	
81	2-OCH_3	H	H	
82	3-OCH_3	H	H	
83	4- 	H	H	
84	3-OCH_3	4-OCH_3	H	
85	4-[-O-CH_2-CH_3]	H	H	
86	4-[-O-CH_2-CH_3]	H	H	
87	2-Cl	H	H	
88	4-Cl	H	H	
89	4-NO_2	H	H	

Comp. No.	R^3	R^4	R^5	L
90	4-	H	H	
91	4-[-O-$(CH_2)_3$-CH_3]	H	H	
92	H	H	H	
93	2-	H	H	
94	2-F	H	H	
95	4-Br	H	H	
96	2-Br	3-OCH_3	6-OCH_3	
98	4-[-O-$(CH_2)_2$-CH_3]	3-OCH_3	H	
99	4-	H	H	
100	4-	H	H	
101	3-	H	H	
102	4-[-O-$(CH_2)_4$-CH_3]	H	H	

Comp. No.	R^3	R^4	R^5	L
103	3-NO_2	H	H	
104	3-F	H	H	
105	3-O-CH_3	H	H	
106	3-O-CH_3	4-O-CH_3	H	
107	2-Cl	4-Cl	H	
108	4- 	H	H	
109	4- 	H	H	
110	4-O-CH_3	H	H	
111	4-Cl	H	H	
112	2-Cl	H	H	
113	4-Br	H	H	
114	4- 	H	H	

Comp. No.	R^3	R^4	R^5	L
115	4-[-O-$(CH_2)_3$-CH_3]	H	H	
116	2-O-CH_3	3-Cl	5-Cl	
117	3-OH	H	H	
118	2-O-CH_3	5-O-CH_3	H	
119	3-O-CH_3	4-O-CH_3	H	
120	4-	H	H	
121	3-O-CH_2-CH_3	4-OH	H	
122	4-	H	H	
123	3-O-$(CH_2)_2$-CH_3	H	H	
124	3-O-CH_3	4-	H	
125	2-O-CH_2-CH_3	H	H	
126	3-Cl	H	H	
127	4-O-$(CH_2)_3$-CH_3	H	H	
128	2-O-CH_3	H	H	

Comp. No.	R^3	R^4	R^5	L
129	3-O-CH_3	4-O-$(CH_2)_2$-CH_3	H	
130	2-O-$(CH_2)_2$-CH_3	H	H	
131		H	H	
132	2-O-CH_3	4-O-CH_3	H	
133	3-Cl	5-Cl	H	
134		H	H	
135		H	H	
136		H	H	
137	4-OH	H	H	
138	2-Cl	5-Cl	H	
139	3-Cl		H	
140		H	H	
141		H	H	

Comp. No.	R^3	R^4	R^5	L
142	2-Cl		H	
143	3-Cl		5-Cl	
144			H	
145		H	H	
146	2-F	4-F	H	
147		H	H	
148		H	H	
149		H	H	
150	2-Cl		6-Cl	
151	2-Cl	4-Cl	H	
152	2-Cl	4-Cl	H	
153	2-Cl	4-Cl	H	
154	2-Cl	4-Cl	H	

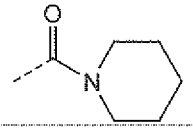
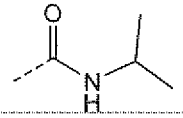
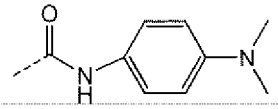
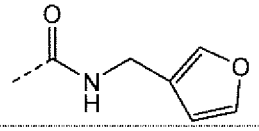
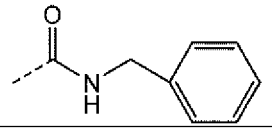
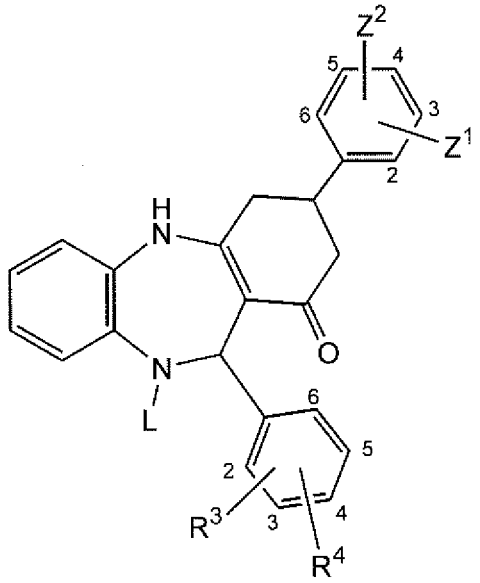
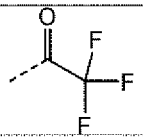
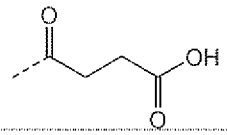
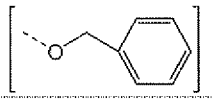
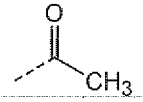
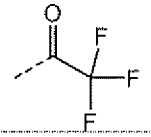
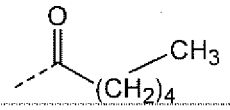
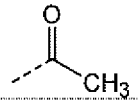
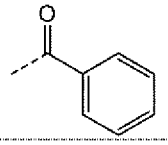
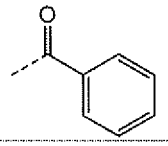
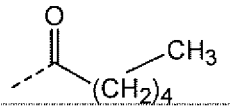
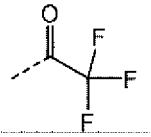
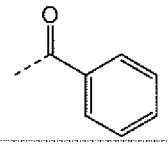
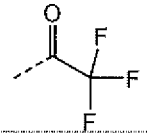
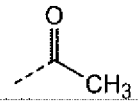
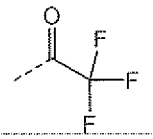
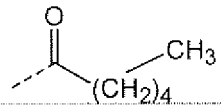
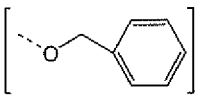
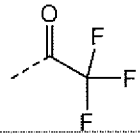
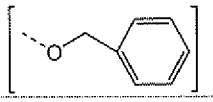
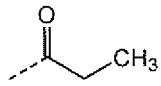
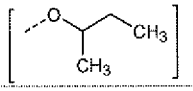
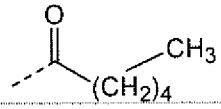
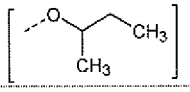
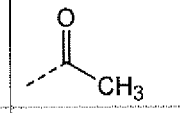
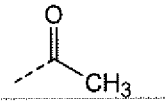
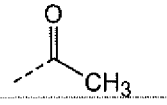
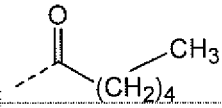
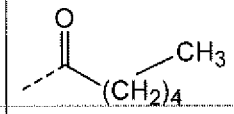
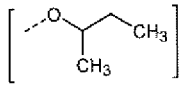
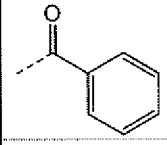
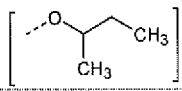
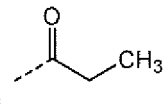
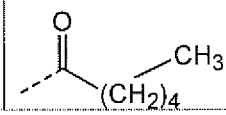
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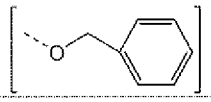
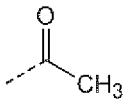
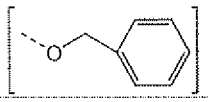
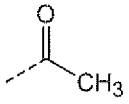
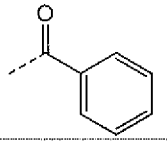
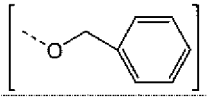
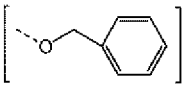
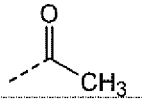
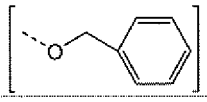
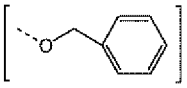
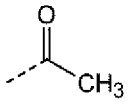
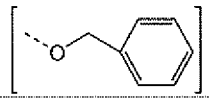
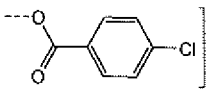
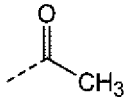
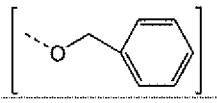
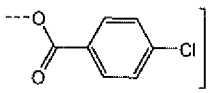
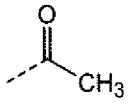
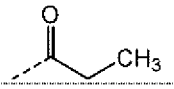
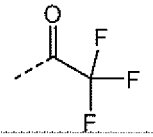
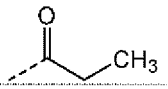
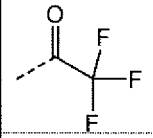
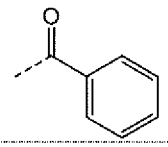
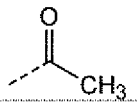
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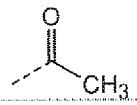
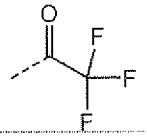
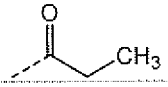
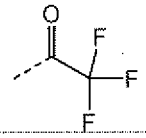
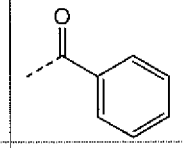
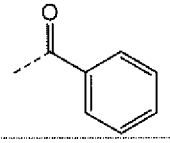
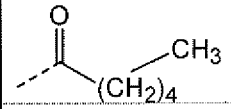
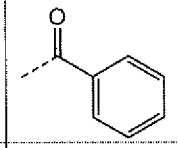
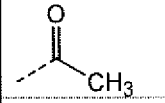
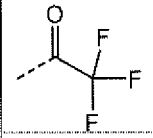
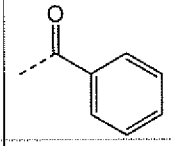
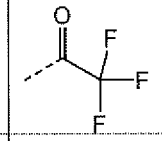
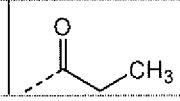


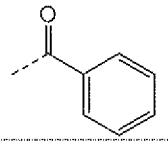
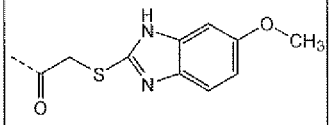
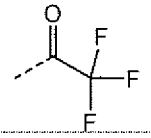
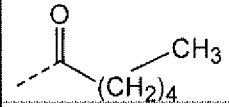
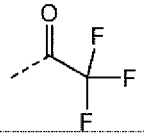
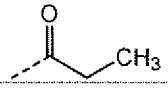
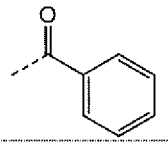
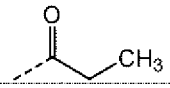
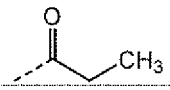
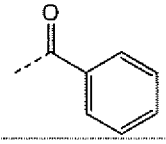
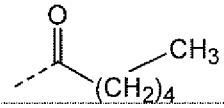
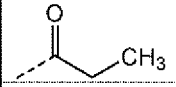
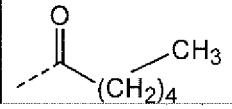
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160	4-Cl	H	4-CH_3	H	

Comp .No.	Z^1	Z^2	R^3	R^4	L
161	4-CH_3	H	4-CH_3	H	
162	2- 	H	H	H	
163	2-[-O-$(CH_2)_2$-CH_3]		4-OCH_3	H	
164	4-Cl	H	4-Cl	H	
165	4-OCH_3	H	4-Cl	H	
166	2-F	H	4-CH_3	H	
167	4-[-O-$(CH_2)_3$-CH_3]	H	H	H	
168	3-NO_2	H	4-OCH_3	H	
169	4-CH_3	H	2-Cl	H	
170	3-OCH_3	4-OCH_3	4-CH_3	H	
171	4-[-O-$(CH_2)_3$-CH_3]	H	H	H	
172	3-OCH_3	4-OCH_3	3-NO_2	H	

Comp .No.	Z^1	Z^2	R^3	R^4	L
173	2-[-O-CH_2-CH_3]	H	4-OCH_3	H	
174	3-NO_2	H	3-OCH_3	4-OCH_3	
175	2- 	H	H	H	
176	2- 	H	H	H	
177	3-OCH_3	4-OCH_3	2- 	H	
178	3-OCH_3	4-OCH_3	2- 	H	
179	4-OCH_3	H	2-[-O-CH_2-CH_3]	H	
180	3-NO_2	H	3-OCH_3	4-OCH_3	
181	3-OCH_3	4-OCH_3	3-NO_2	H	
182	4-CH_3	H	2-Cl	H	
183	3-OCH_3	4-OCH_3	2- 	H	
184	4-OCH_3	5-OCH_3	2- 	H	
185	3-OCH_3	4-OCH_3	4-Cl	H	

Comp .No.	Z^1	Z^2	R^3	R^4	L
186	2-	H	2-Cl	4-Cl	
187	2-	H	2-Cl	4-Cl	
188	4-CH_3	H	4-OCH_3	H	
189	2-	H	3-	H	
190	2-	H	3-	H	
191	2-	H	3-	H	
192	2-	H	3-	H	
193	4-OCH_3	5-OCH_3	3-Cl	H	
194	4-CH_3	H	4-OCH_3	H	
195	4-CH_3	H	3-Cl	H	
196	4-OCH_3	H	4-CH_3	H	
197	4-CH_3	H	3-OCH_3	4-OCH_3	
198	3-OCH_3	4-OCH_3	3-Cl	H	

Comp .No.	Z^1	Z^2	R^3	R^4	L
199	H	H	4-CH_3	H	
200	4-Cl	H	4-OCH_3	H	
201	4-CH_3	H	4-CH_3	H	
202	4-Cl	H	3-NO_2	H	
203	4-Cl	H	3-Cl	H	
204	4-CH_3	H	3-Cl	H	
205	3-OCH_3	4-OCH_3	3-Cl	H	
206	4-OCH_3	H	4-CH_3	H	
207	3-NO_2	H	3-OCH_3	4-OCH_3	
208	4-Cl	H	3-Cl	H	
209	4-CH_3	H	H	H	
210	4-OCH_3	H	4-Cl	H	
211	3-NO_2	H	4-Cl	H	

Comp .No.	Z^1	Z^2	R^3	R^4	L
212	3-NO_2	H	4-CH_3	H	
213	4-F	H	3-OCH_3	H	
214	3-NO_2	H	4-Cl	H	
215	4-Cl	H	4-OCH_3	H	
216	4-OCH_3	H	2-[-O-CH_2-CH_3]	H	
217	4-[-O-$(CH_2)_3$-CH_3]	H	H	H	
218	3-OCH_3	4-OCH_3	4-Cl	H	
219	2-[-O-CH_2-CH_3]	H	4-OCH_3	H	
220	2-[-O-$(CH_2)_2$-CH_3]	H	4-OCH_3	H	
221	3-NO_2	H	4-OCH_3	H	
222	2-[-O-$(CH_2)_2$-CH_3]	H	4-OCH_3	H	
223	4-OCH_3	H	4-OCH_3	H	
224	H	H	2-F	H	

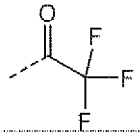
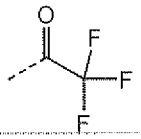
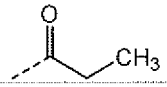
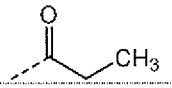
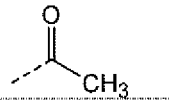
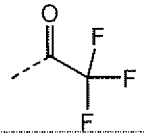
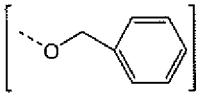
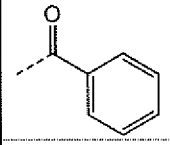
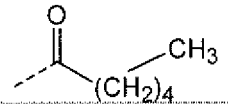
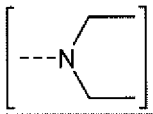
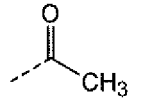
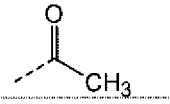
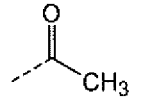
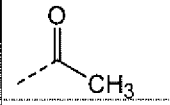
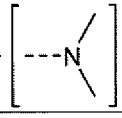
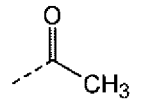
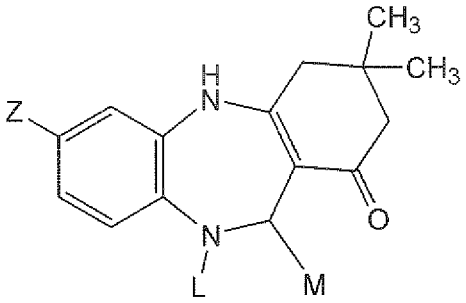
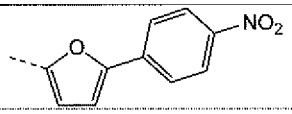
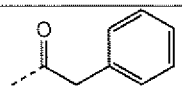
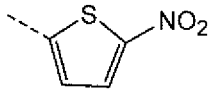
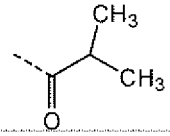
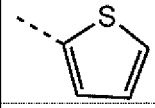
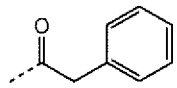
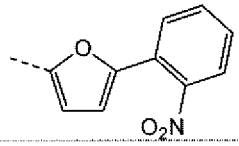
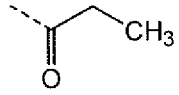
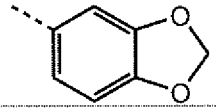
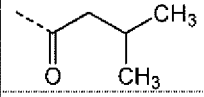
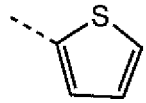
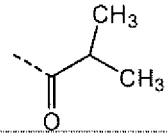
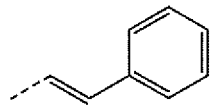
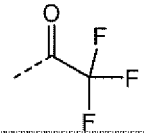
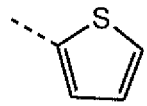
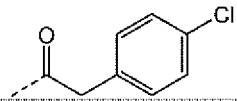
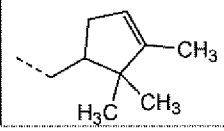
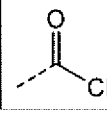
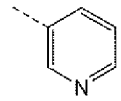
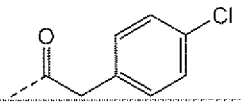
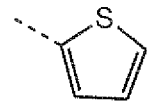
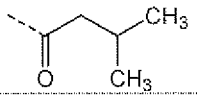
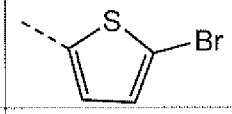
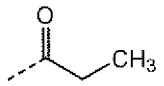
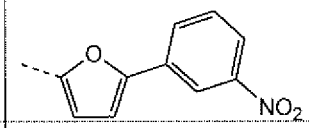
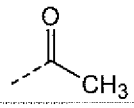
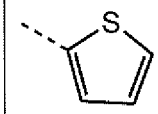
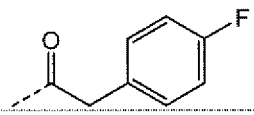
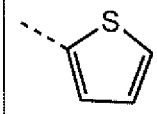
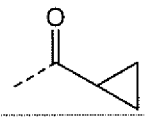
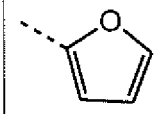
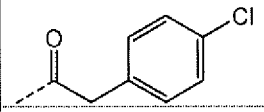
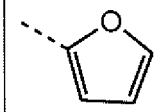
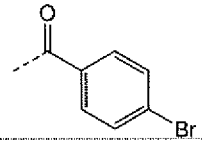
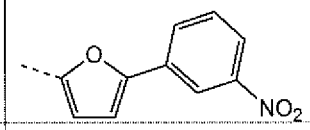
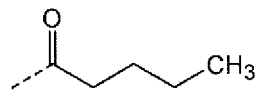
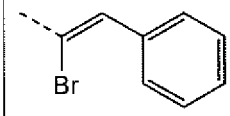
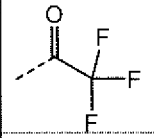
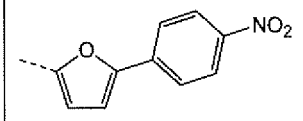
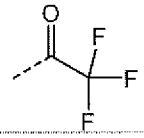
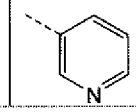
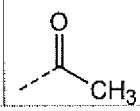
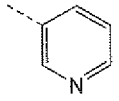
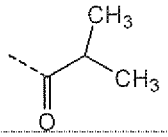
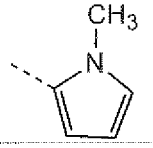
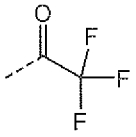
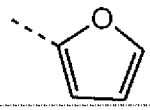
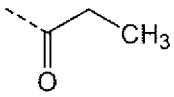
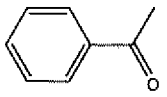
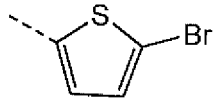
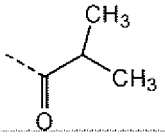
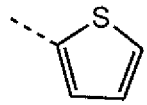
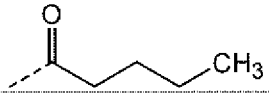
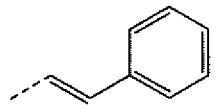
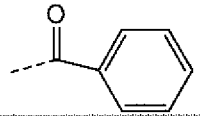
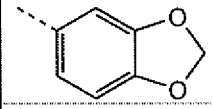
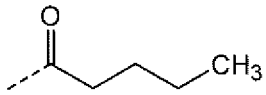
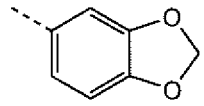
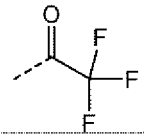
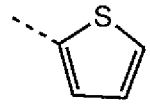
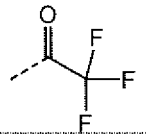
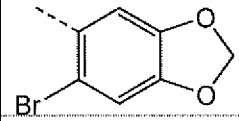
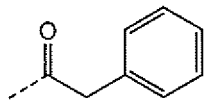
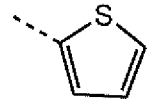
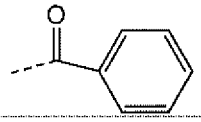
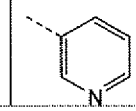
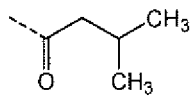
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226	3-OCH_3	4-OCH_3	4-Cl	H	
227	4-OCH_3	H	4-Cl	H	
228	3-OCH_3	4-OCH_3	4-Cl	H	
229	2-Cl	H	4-CH_3	H	
230	4-CH_3	H	3-Cl	H	
231	2-	H	H	H	
232	4-OCH_3	H	4-Cl	H	
233	4-	H	4-O-CH_3	H	
234	3-NO_2	H	H	H	
235	4-	H	H	H	
236	2-F	H	H	H	
237	4-	H	H	H	

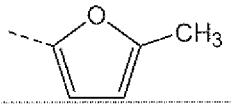
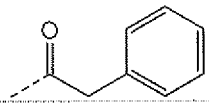
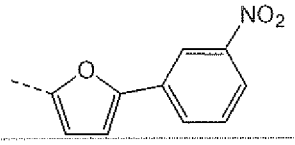
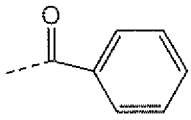
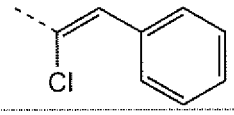
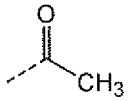
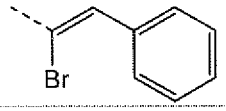
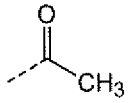
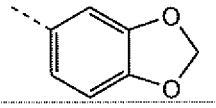
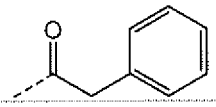
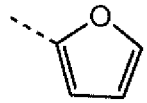
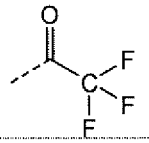
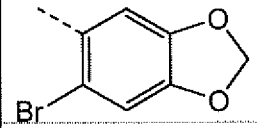
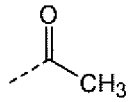
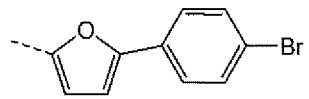
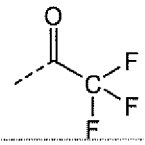
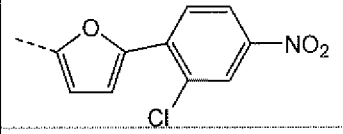
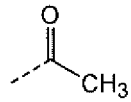
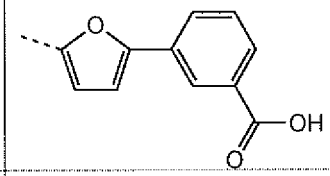
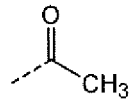
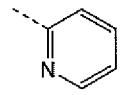
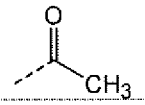
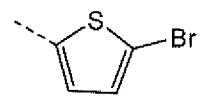
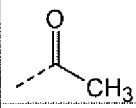
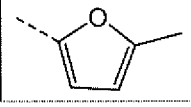
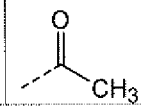
Table 3



Comp. No.	M	L	Z
238			H
239			H
240			H
241			H
242			H
243			H
244			H
245			H
246			H

Comp. No.	M	L	Z
247			H
248			H
249			H
250			H
251			H
252			H
253			H
254			H
255			H
256			H
257			H
258			H

Comp. No.	M	L	Z
259			H
260			H
261			
262			H
263			H
264			H
265			H
266			H
267			H
268			H
269			H
270			H

Comp. No.	M	L	Z
271			H
272			H
273			H
274			H
275			H
276			H
277			H
278			H
279			H
280			H
281			H
282			H
283			H

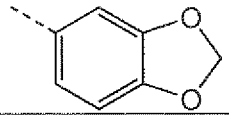
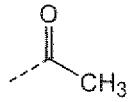
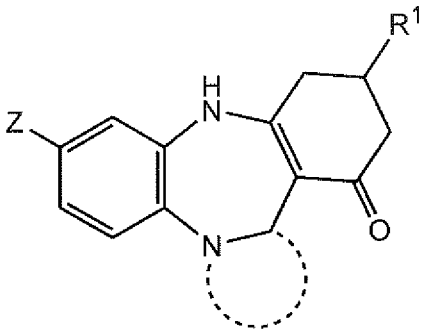
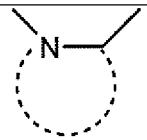
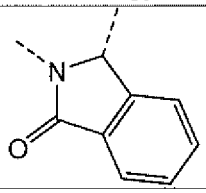
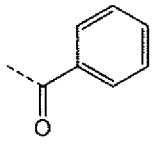
Comp. No.	M	L	Z
284			H

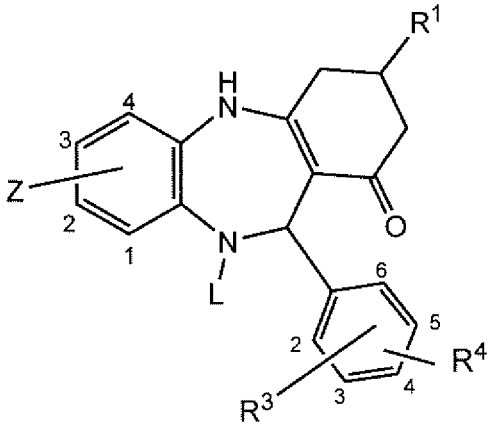
Table 4



Comp. No.	R^1		Z
285	phenyl		

5

Table 5



Comp. No.	R^1	R^3	R^4	L	Z

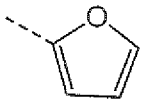
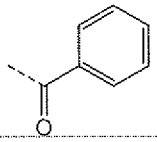
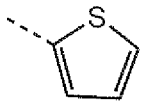
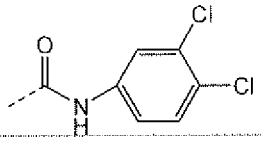
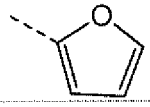
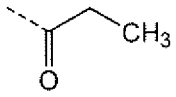
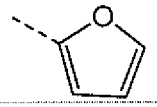
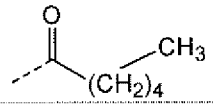
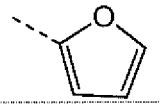
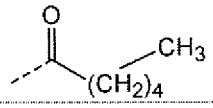
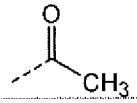
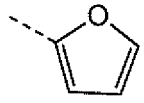
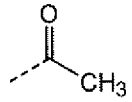
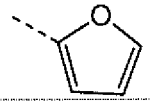
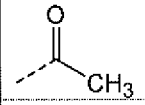
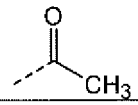
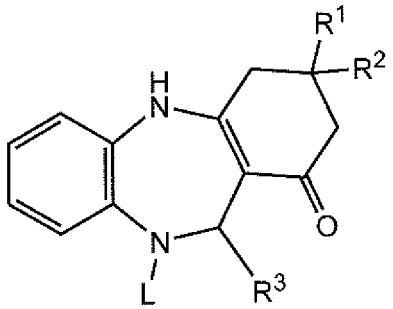
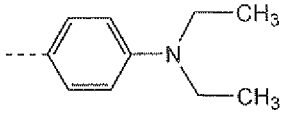
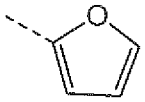
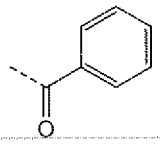
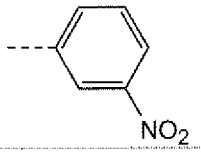
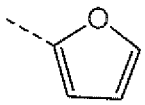
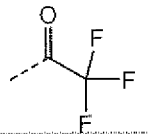
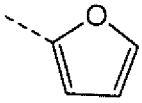
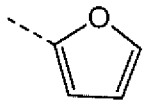
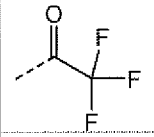
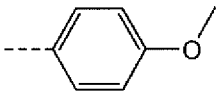
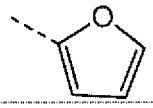
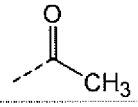
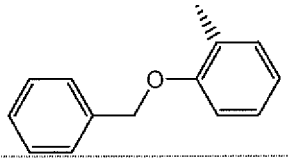
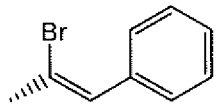
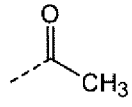
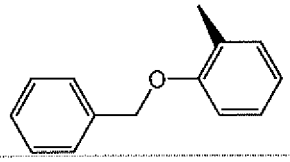
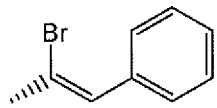
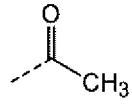
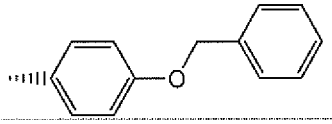
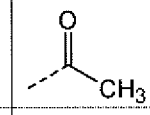
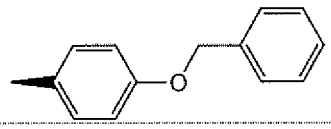
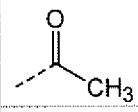
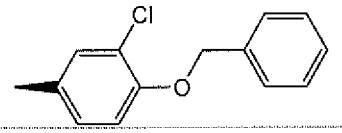
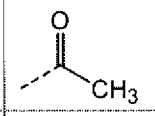
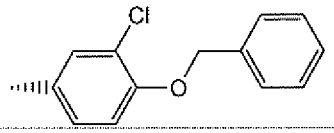
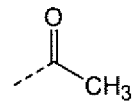
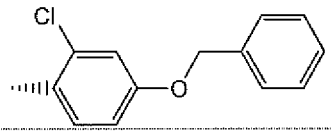
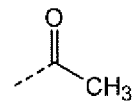
Comp. No.	R^1	R^3	R^4	L	Z
286		3-NO_2	H		H
287		4-OCH_3	H		H
288		3-NO_2	H		H
289		4-Cl	H		H
290		3-NO_2	H		H
291	H	2-Cl	4-Cl		H
292		4-	H		H
293		3-O-CH_3	4-O-CH_3		H
294	CH_3	2-Cl	4-Cl		H

Table 6



Comp .No.	R^1	R^2	R^3	L

Comp .No.	R^1	R^2	R^3	L
295		H		
296		H		
297		H		
298		H		
299		H		
300		H		
302	CH_3	CH_3		
301	CH_3	CH_3		
304	CH_3	CH_3		
303	CH_3	CH_3		
306	CH_3	CH_3		

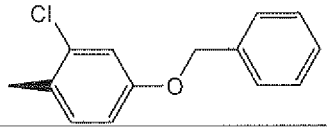
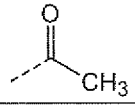
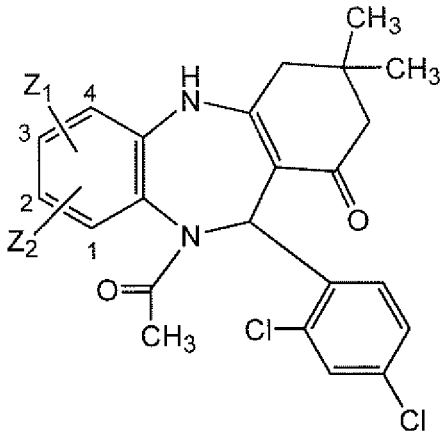
Comp .No.	R^1	R^2	R^3	L
305	CH_3	CH_3		

Table 7



Comp. No.	Z^1	Z^2
307	2-Cl	3-Cl
308	2-CH_3	3-CH_3
309	2-O-CH_3	3-O-CH_3
310	2-F	3-F
311	1-Br	H
312	4-Br	H
313	1-CN	H
314	1-CH_3	H
315	4-CH_3	H
316	4-CN	H
317	4-O-$(CH_2)_3$-CH_3	H
318	2-CN	H
319	3-CN	H
320	4-O-CH_3	H

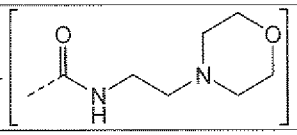
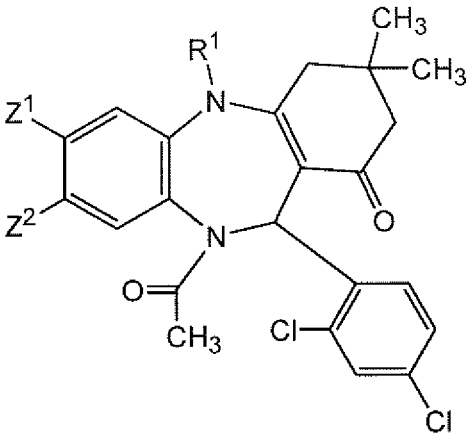
Comp. No.	Z^1	Z^2
321	1-	H

Table 8



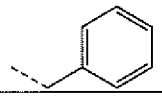
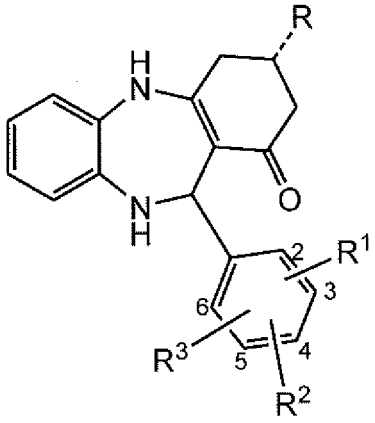
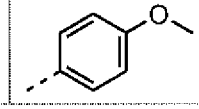
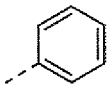
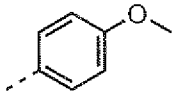
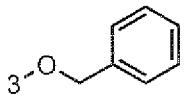
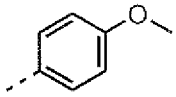
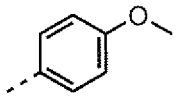
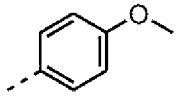
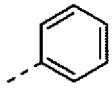
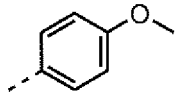
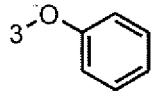
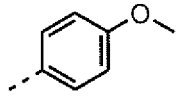
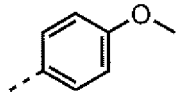
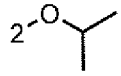
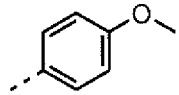
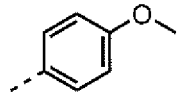
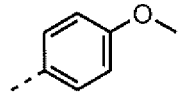
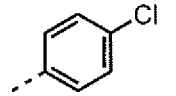
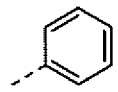
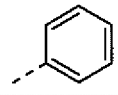
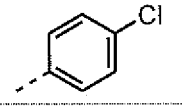
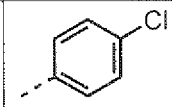
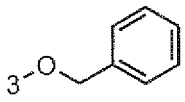
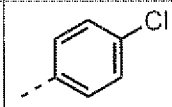
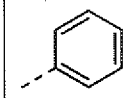
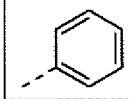
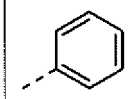
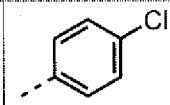
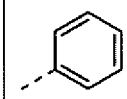
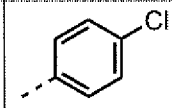
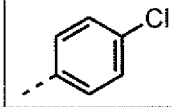
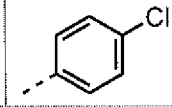
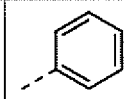
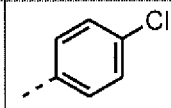
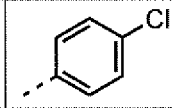
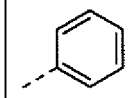
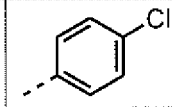
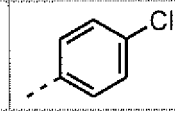
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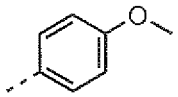
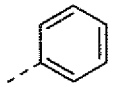
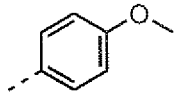
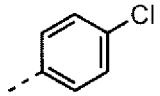
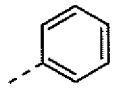
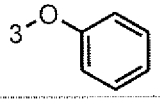
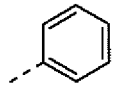
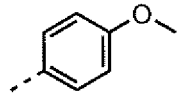
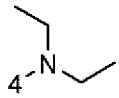
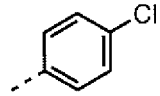
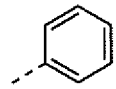
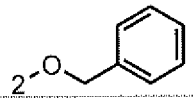
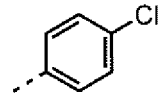
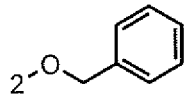
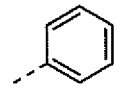
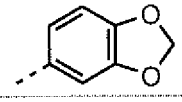
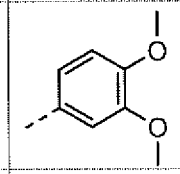
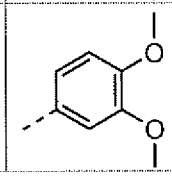
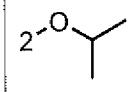
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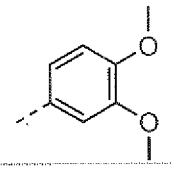
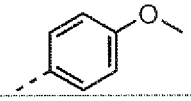
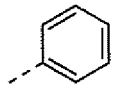
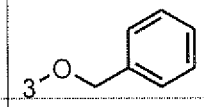
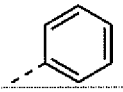
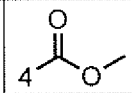
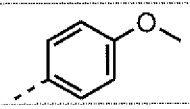
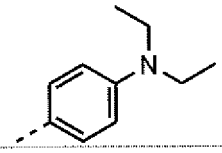
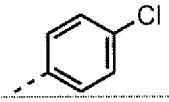
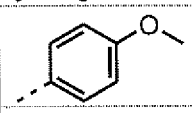
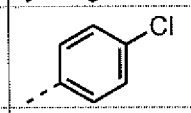
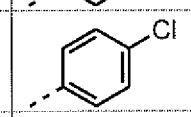
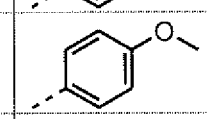
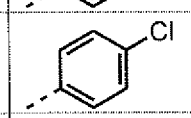
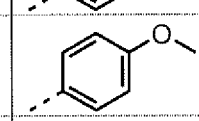
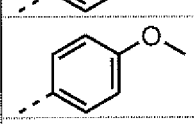
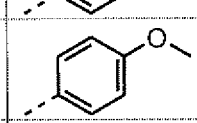
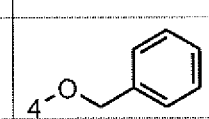
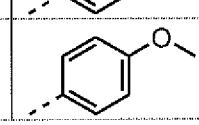
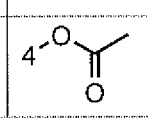


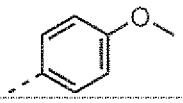
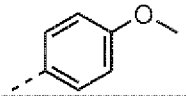
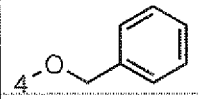
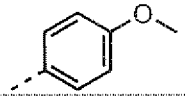
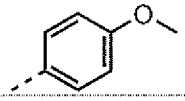
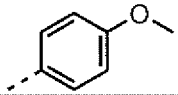
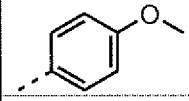
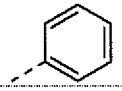
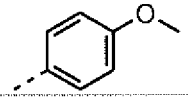
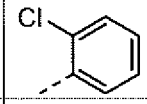
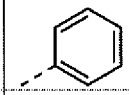
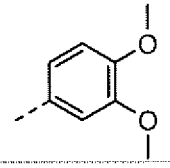
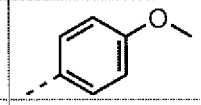
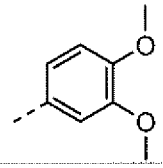
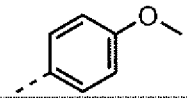
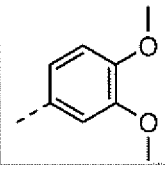
Comp. No	R	R^1	R^2	R^3
324		2-CF_3	H	H

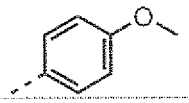
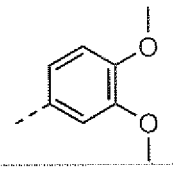
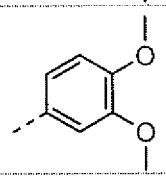
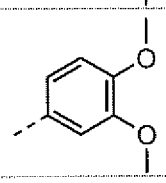
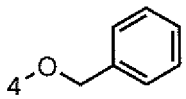
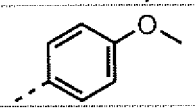
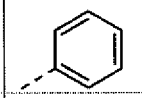
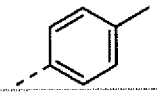
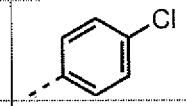
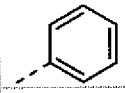
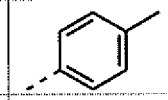
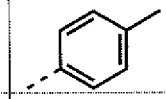
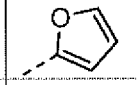
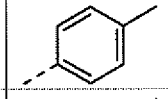
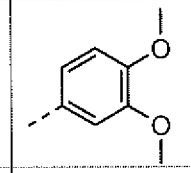
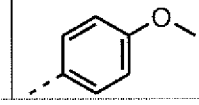
Comp. No	R	R^1	R^2	R^3
325		4-Cl	H	H
326			H	H
327		3-F	H	H
328			H	H
329		4-CF_3	H	H
330		3-O-CH_3	H	H
331			H	H
332		4-O-CH_2-CH_3	H	H
333			H	H
334		2-Cl	6-F	H
335		2-O-CH_3	5-Br	H
336		2-O-CH_3	5-O-CH_3	H
337		3-NO_2	H	H
338		2-O-$(CH_2)_3$-CH_3	H	H
339		3-O-CH_3	4-O-CH_3	5-O-CH_3
340		2-Cl	H	H

Comp. No	R	R^1	R^2	R^3
341			H	H
342		3-Br	4-OH	5-O-CH_3
343		4-CF_3	H	H
344		4-CH_3	H	H
345		2-Br	H	H
346		2-Cl	3-Cl	H
347		2-O-CH_3	3-O-CH_3	H
348		2-O-CH_3	3-O-CH_3	H
349		2-CF_3	H	H
350		3-Cl	H	H
351		2-O-CH_3	5-O-CH_3	H
352		3-O-CH_3	4-O-CH_3	H
353		3-Br	4-OH	5-O-CH_2-CH_3
354		3-CH_3	H	H
355		3-Cl	4-Cl	H
356		2-O-CH_3	5-O-CH_3	H

Comp. No	R	R^1	R^2	R^3
357		2-Cl	3-Cl	H
358		3-NO_2	4-CH_3	H
359		3-NO_2	4-CH_3	H
360		3-O-CH_3	H	H
361			H	H
362		4-S-CH_3	H	H
363			H	H
364			H	H
365			H	H
366			H	H
367			H	H
368		4-S-CH_3	H	H
369		2-O-CH_3	H	H
370			H	H

Comp. No	R	R^1	R^2	R^3
371		2-O-CH_3	5-O-CH_3	H
372		2-O-CH_3	4-O-CH_3	H
373			H	H
374			H	H
375		2-Cl	5-NO_2	H
376		H	H	H
377		4-CF_3	H	H
378		3-Br	4-OH	5-O-CH_2-CH_3
379		3-O-CH_2-CH_3	H	H
380		3-F	H	H
381		2-CH_3	H	H
382		4-S-CH_3	H	H
383		2-Cl	H	H
384		4-CH_3	H	H
385			3-O-CH_3	H
386		3-O-CH_2-CH_3		H

Comp. No	R	R^1	R^2	R^3
387		4-NO_2	H	H
388			H	H
389		3-NO_2	4-Cl	H
390		2-Br	H	H
391		3-CH_3	H	H
392		3-OH	H	H
393		2-O-CH_2-CH_3	H	H
394		3-O-CH_3	4-O-$(CH_2)_2$-CH_3	H
395		4-CH_3	H	H
396		2-NO_2	H	H
397		3-Br	4-OH	5-O-CH_3
398		2-O-CH_3	4-O-CH_3	5-O-CH_3
399		3-Br	4-OH	5-O-CH_2-CH_3
400		2-Br	4-O-CH_3	5-O-CH_3
401		2-O-CH_3	3-O-CH_3	H

Comp. No	R	R^1	R^2	R^3
402		3-Br	4-O-CH_3	5-O-CH_3
403		2-O-CH_3	4-O-CH_3	5-O-CH_3
404		2-O-CH_3	5-Br	H
405			3-O-CH_3	H
406		3-Br	4-O-CH_3	5-O-CH_2-CH_3
407		2-CF_3	H	H
408		4-CH_3	H	H
409		4-CH_3	H	H
410		3-O-CH_2CH_3	H	H
411		2-Cl	H	H
412		2-F	H	H
413		4-Cl	H	H
414		H	H	H
415		4-Cl	H	H
416		4-Cl	H	H

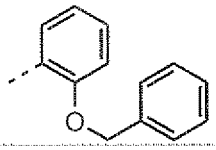
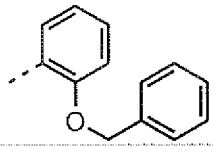
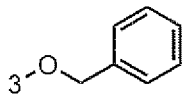
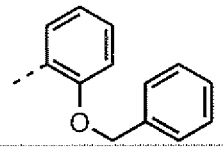
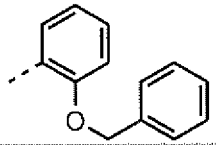
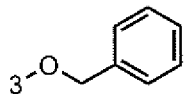
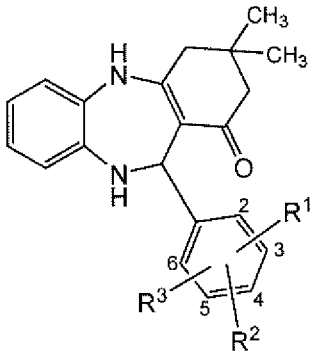
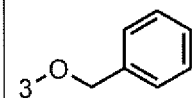
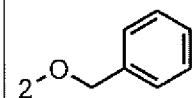
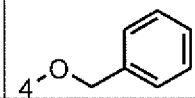
Comp. No	R	R^1	R^2	R^3
417		2-Cl	4-Cl	H
418			H	H
419		2-Cl	4-Cl	H
420			H	H
421	H	2-Cl	4-Cl	H
422	CH_3	2-Cl	4-Cl	H

Table 10



Comp. No	R^1	R^2	R^3
423	2-Cl	4-Cl	H
424		4-O-CH_3	H
425		H	H
426		H	H
427	2-Cl	3-Cl	H
428	2-Cl	6-F	H

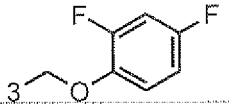
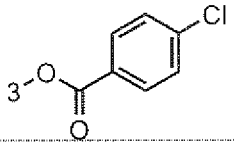
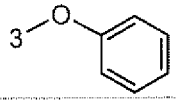
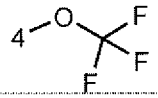
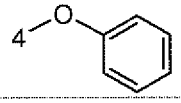
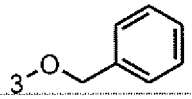
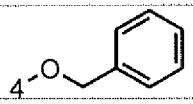
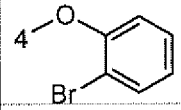
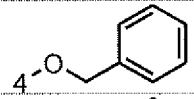
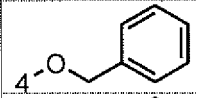
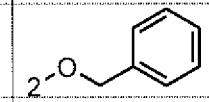
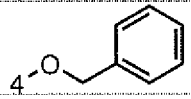
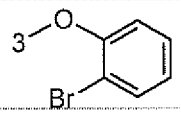
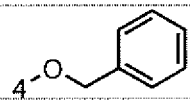
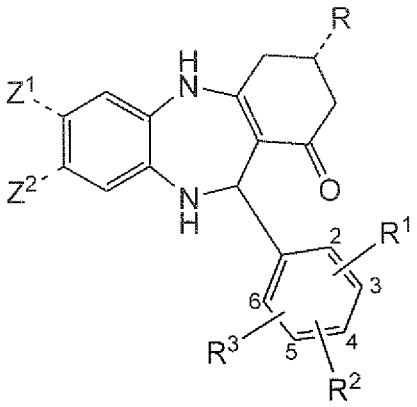
Comp. No	R^1	R^2	R^3
429	4-CF_3	H	H
430		4-O-CH_3	H
431		H	H
432	2-COOH	H	H
433		H	H
434		H	H
435		H	H
436	3-Cl	5-Cl	H
437		H	H
438	2-Cl	5-Cl	H
439	3-Cl		H
440	4-OH	H	H
441	2-F	4-F	H
442		H	H
443	2-Cl		H
444	3-Cl		5-Cl
445			H
446		H	H
447	2-Cl		6-Cl
448	4-NO_2	H	H

Table 11



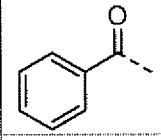
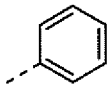
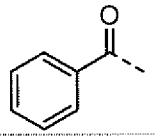
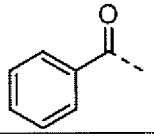
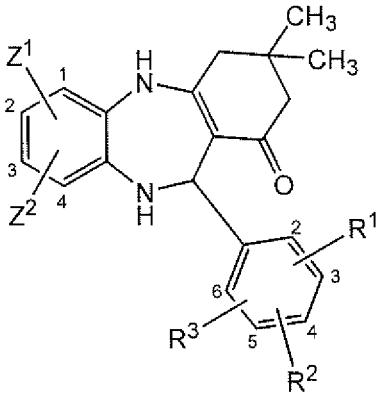
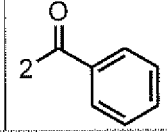
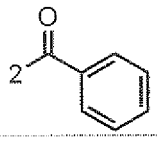
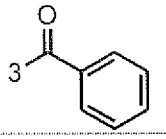
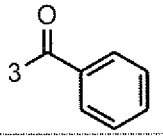
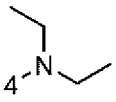
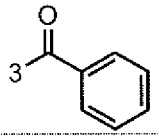
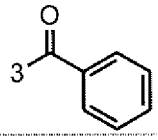
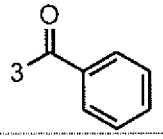
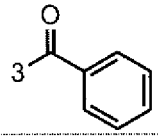
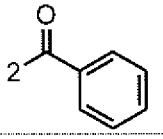
Comp. No	R	R^1	R^2	R^3	Z^1	Z^2
449	H	3-NO_2	H	H	H	
450		4-Cl	H	H		H
451	H	2-O-CH_3	5-O-CH_3	H		H

Table 12

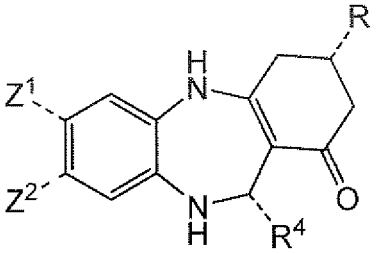


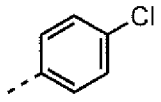
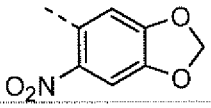
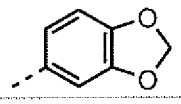
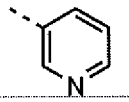
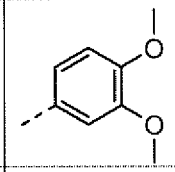
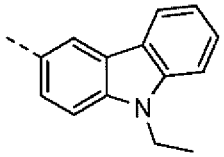
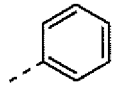
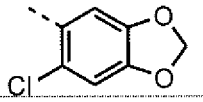
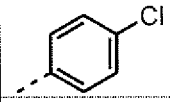
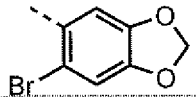
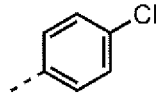
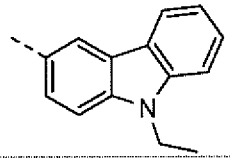
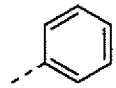
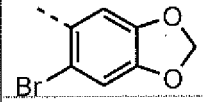
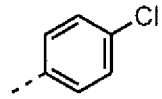
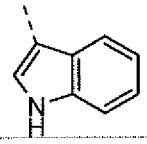
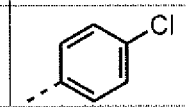
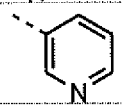
Comp. No	R^1	R^2	R^3	Z^1	Z^2
452	3-NO_2	4-Cl	H	2-CH_3	3-CH_3
453	3-O-CH_3	4-O-CH_3	H		H

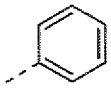
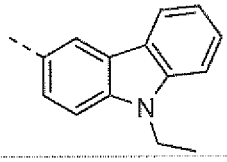
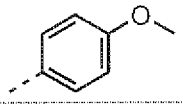
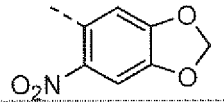
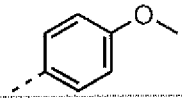
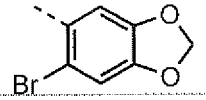
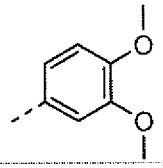
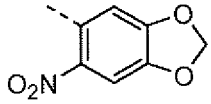
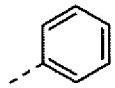
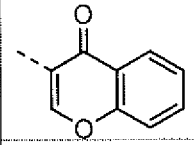
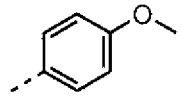
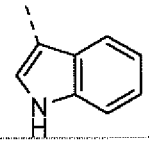
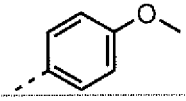
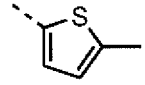
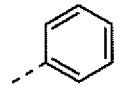
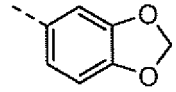
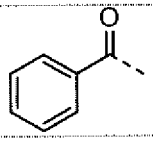
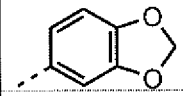
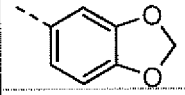
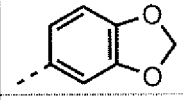
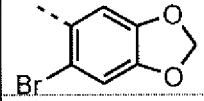
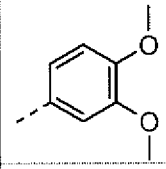
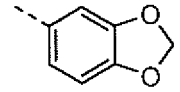
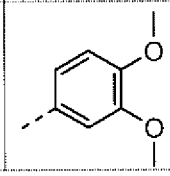
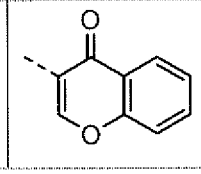
Comp. No	R^1	R^2	R^3	Z^1	Z^2
454	2-F	6-F	H	2-CH_3	3-CH_3
455	3-NO_2	H	H		H
456	3-O-CH_3	4-O-CH_3	H	H	
457	2-Cl	H	H	H	
458		H	H	H	
459	4-Cl	H	H	H	
460	3-Cl	H	H	H	
461	4-F	H	H	H	
462		H	H	H	3-CH_3
463	2-Cl	H	H		H
464	2-Cl	4-Cl	H	2-CH_3	3-CH_3
465	2-Cl	4-Cl	H	2-Cl	3-Cl
466	2-Cl	4-Cl	H	2-F	3-F
467	2-Cl	4-Cl	H	2-O-CH_3	3-O-CH_3
468	2-Cl	4-Cl	H	4-Br	H
469	2-Cl	4-Cl	H	4-CH_3	H
470	2-Cl	4-Cl	H	4-CN	H
471	2-Cl	4-Cl	H	1-CH_3	H
472	2-Cl	4-Cl	H	2-CN	H
473	2-Cl	4-Cl	H	3-CN	H

Comp. No	R^1	R^2	R^3	Z^1	Z^2
474	2-Cl	4-Cl	H	1-NH_2	H

Table 13



Comp. No	R	R^4	Z^1	Z^2
475			H	H
476			H	H
477			H	H
478			H	H
479			H	H
480			H	H
481			H	H
482			H	H
483			H	H

Comp. No	R	R^4	Z^1	Z^2
484			H	H
485			H	H
486			H	H
487			H	H
488			H	H
489			H	H
490			H	H
491				H
492			H	H
493			H	H
494			H	H
495			H	H

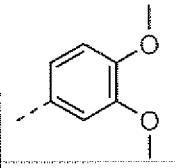
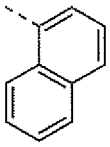
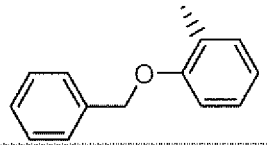
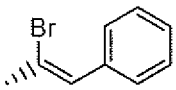
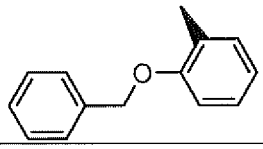
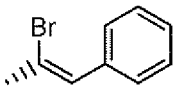
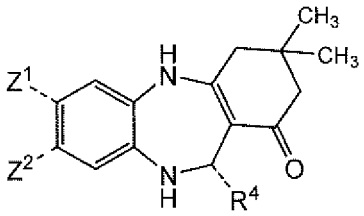
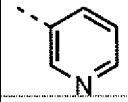
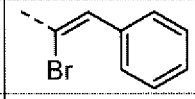
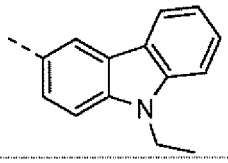
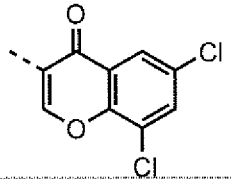
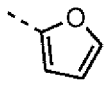
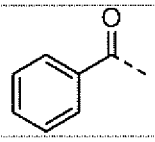
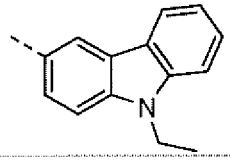
Comp. No	R	R^4	Z^1	Z^2
496			H	H
497			H	H
498			H	H

Table 14



Comp. No	R^4	Z^1	Z^2
499		H	H
500		H	H
501		H	H
502		H	H
503	 		H
504		CH_3	CH_3

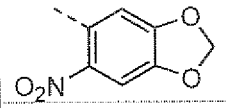
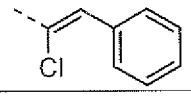
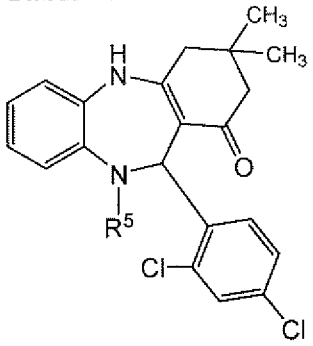
Comp. No	R^4	Z^1	Z^2
505		H	H
506		H	H

Table 15



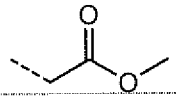
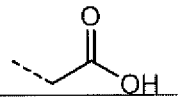
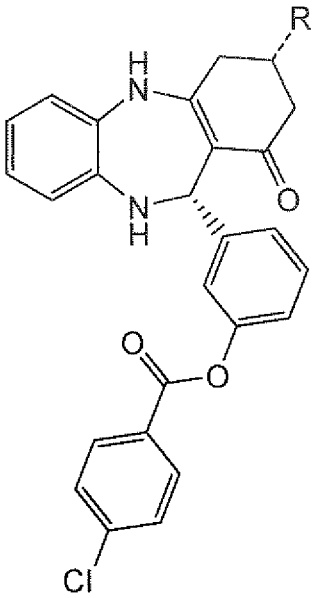
Comp. No	R^5
507	CH_3
508	CH_2-CH_3
509	CH_2-CH_2-CH_3
510	
511	

Table 16



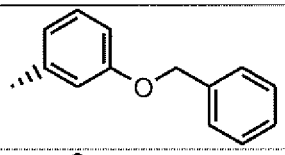
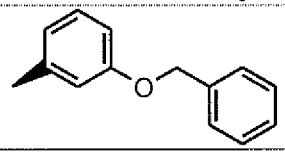
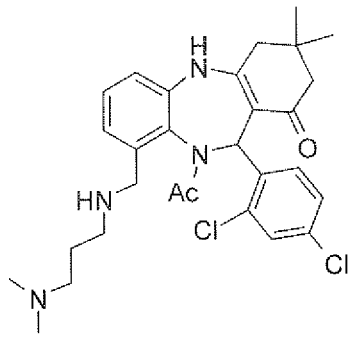
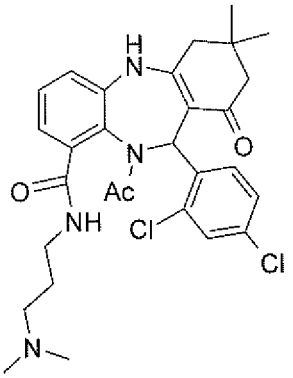
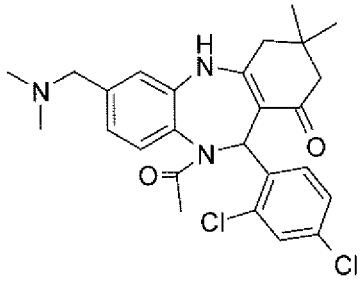
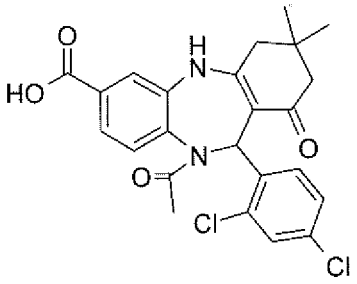
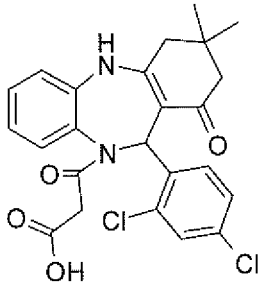
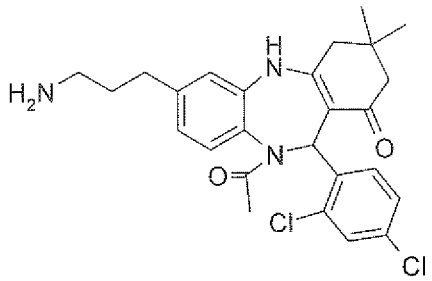
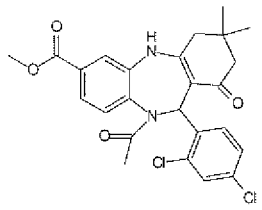
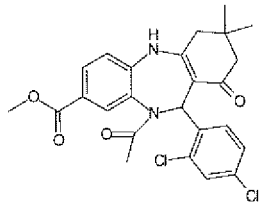
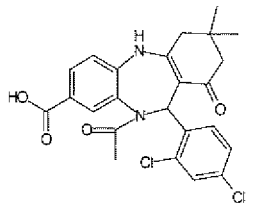
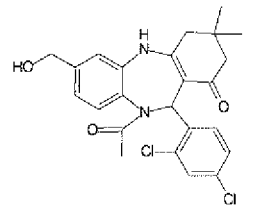
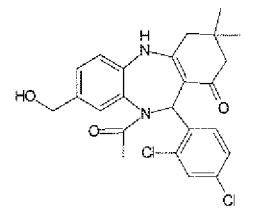
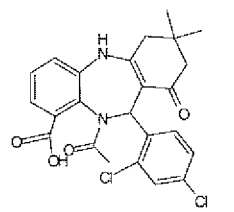
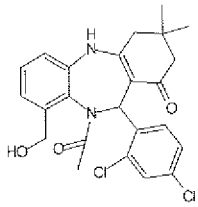
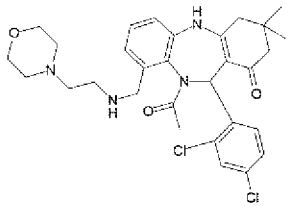
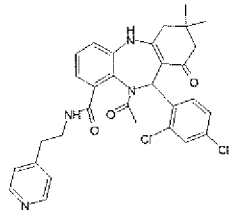
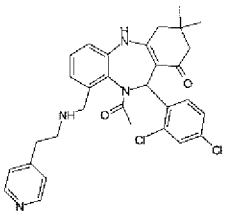
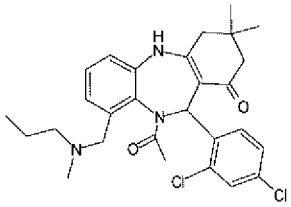
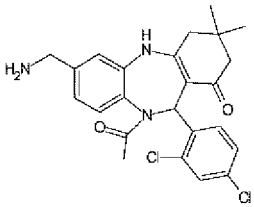
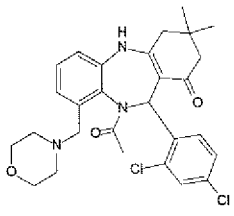
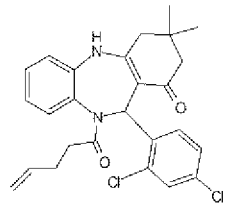
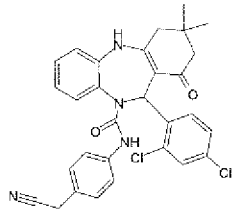
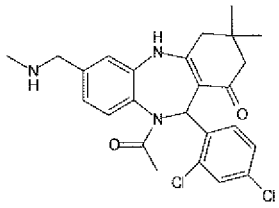
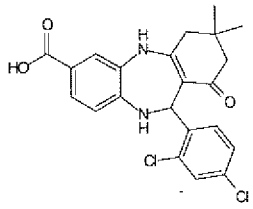
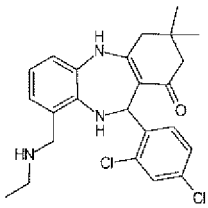
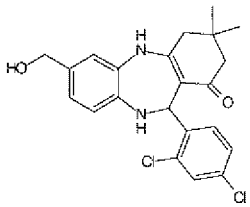
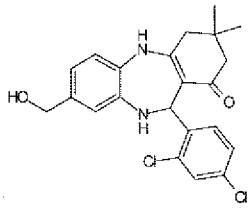
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513	

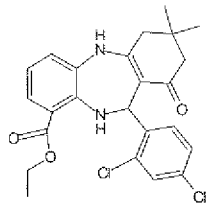
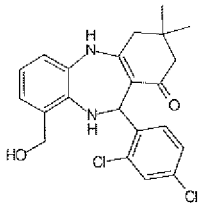
Table 17

Comp. No	Structure
514	
515	
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Comp. No	Structure
519	
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525	

Comp. No	Structure
526	
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528	
529	
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531	
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Comp. No	Structure
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537	
538	
539	

Comp. No	Structure
540	
541	

Antiviral Testing

The compounds of formula (I) were tested for anti-HCV activity in an assay determining their activity against NS5b polymerase and in an HCV replicon assay

A) NS5b Polymerase Assay

a) Protein purification

The cDNA encoding NS5B amino acid 1-570 (HC-J4, genotype 1b, pCV-J4L6S, genebank accession number AF054247) was subcloned into the Nhe I and Xho I restriction sites of pET-21b. Expression of the subsequent His-tagged C-terminal 21 amino acid deleted NS5B was performed as follows:

Following transformation in BL21(DE3) competent cells, bacterial cells were grown in 22 liter LB/Amp media until to reach OD_{600}=0.4-0.6. Protein expression was induced by addition of IPTG 0.4 mM, supplemented with 10 µM $MgCl_2$, and incubated for 14-16 hrs at 20°C. Cells were harvested, resuspended in lysis buffer (20 mM Tris-HCl pH=7.5, 0.3 M NaCl, 10% glycerol, 0.1% NP40, 4 mM $MgCl_2$, 14 mM beta-mercaptoethanol, with tablet of EDTA-free protease coktail inhibitors) and lysed by sonification. The cell lysate was cleared by high-speed centrifugation (20K x *g* for 30 min), captured on Ni-NTA beads for 70 min at 4°C, and eluted with 25 mM Hepes pH 7.5, 0.5 M NaCl, 10% glycerol, 14 mM BME, 500 mM imidazole. The eluent was dialysed against 25 mM Hepes pH 7.5, 10% glycerol, 50 mM NaCl, 14 mM BME, after which the protein was further purified by heparin chromatography using the same buffer with 1 M NaCl for elution. Fractions containing pure protein were collected, dialyzed against storage buffer 25 mM Hepes pH=7.5, 300 mM NaCl, 10% glycerol, 14mM BME), and flash-freezed in liquid nitrogen. This procedure yielded

approximately 40 mg of protein. The protein was judged to be at least 90% pure by SDS PAGE Coomassie staining.

b) Protein Sequence

PDB: 1nb4, Apo form

M A S S M S Y T W T G A L I T P C A A E E S K L P I N P L S N S L L R H H N M
V Y A T T S R S A S L R Q K K V T F D R L Q V L D D H Y R D V L K E M K A K
A S T V K A K L L S I E E A C K L T P P H S A K S K F G Y G A K D V R N L S S
R A V N H I R S V W E D L L E D T E T P I D T T I M A K S E V F C V Q P E K G
G R K P A R L I V F P D L G V R V C E K M A L Y D V V S T L P Q A V M G S S
Y G F Q Y S P K Q R V E F L V N T W K S K K C P M G F S Y D T R C F D S T V
T E S D I R V E E S I Y Q C C D L A P E A R Q A I R S L T E R L Y I G G P L T N
S K G Q N C G Y R R C R A S G V L T T S C G N T L T C Y L K A T A A C R A A
K L Q D C T M L V N G D D L V V I C E S A G T Q E D A A A L R A F T E A M T
R Y S A P P G D P P Q P E Y D L E L I T S C S S N V S V A H D A S G K R V Y Y
L T R D P T T P L A R A A W E T A R H T P I N S W L G N I I M Y A P T L W A R
M I L M T H F F S I L L A Q E Q L E K A L D C Q I Y G A C Y S I E P L D L P Q I
I E R L H G L S A F T L H S Y S P G E I N R V A S C L R K L G V P P L R T W R
H R A R S V R A K L L S Q G G R A A T C G R Y L F N W A V R T K L K L T P I
P A A S Q L D L S G W F V A G Y S G G D I Y H S L S R A R P R A A A L E H H
H H H H H

Calc. Mol. Properties 64941.4 g/mol

c) Biochemical RdRp assay

Measurement of HCV NS5B polymerization activity was performed by evaluating the amount of radiolabeled GTP incorporated by the enzyme in a newly synthesized RNA using heteropolymeric RNA template/primer. The highthroughput RdRp assay was carried out in 384-well plates using 200 nM enzyme, 0.1 µCi of ^{3}H GTP, 5 mM $MgCl_2$, 600 nM GTP, 30 nM PolyC, 300 nM 5' -biotinylated oligo(rG13)/poly(rC) in 20 mM Tris pH 7.5, 21 mM KCl, 2.5 mM DTT, 16.7 mM NaCl and 0.17 mM EDTA. Test compounds were dissolved in dimethylsulfoxide. The test compounds were added to the preformed polymerase-template complex, and incubated at room temperature (RT) for 15 min before the addition of NTPs. The 30-µl reaction was terminated after 2 h at 25°C upon addition of 30-µl PVT-SPA beads (Amersham Biosciences RPNQ0009, 5 mg/ml in 0.5 M EDTA). After incubation at 25°C for 30 min, the plate was counted using a Packard TopCount microplate reader (30 sec/well, 1 min count delay) and EC50 values were calculated.

B) Replicon assay

a) Stable replicon cell reporter assays:

The compounds of the present invention were examined for activity in the inhibition of HCV RNA replication in a cellular assay. The assay demonstrated that the present compounds exhibit activity against HCV replicons functional in a cell culture. The cellular assay was based on a bicistronic expression construct, as described by Lohmann et al. (1999) Science vol. 285 pp. 110-113 with modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624, in a multi-target screening strategy. In essence, the method was as follows.

The assay utilized the stably transfected cell line Huh-7 luc/neo (hereafter referred to as Huh-Luc). This cell line harbored an RNA encoding a bicistronic expression construct comprising the wild type NS3-NS5B regions of HCV type 1b translated from an Internal Ribosome Entry Site (IRES) from encephalomyocarditis virus (EMCV), preceded by a reporter portion (FfL-luciferase), and a selectable marker portion (neo^R, neomycine phosphotransferase). The construct was bordered by 5' and 3' NTRs (non-translated regions) from HCV type 1b. Continued culture of the replicon cells in the presence of G418 (neo^R) was dependent on the replication of the HCV RNA. The stably transfected replicon cells that expressed HCV RNA, which replicated autonomously and to high levels, encoding *inter alia* luciferase, were used for screening the antiviral compounds.

b) Cellular Assay Experimental Method:

The replicon cells were plated in 384 well plates in the presence of the test and control compounds which were added in various concentrations. Following an incubation of three days, HCV replication was measured by assaying luciferase activity (using standard luciferase assay substrates and reagents and a Perkin Elmer ViewLux^{Tm} ultraHTS microplate imager). Replicon cells in the control cultures had high luciferase expression in the absence of any inhibitor. The inhibitory activity of the compound on luciferase activity was monitored on the Huh-Luc cells, enabling a dose-response curve for each test compound. IC50 values were then calculated, which value represents the amount of the compound required to decrease by 50% the level of detected luciferase activity, or more specifically, the ability of the genetically linked HCV replicon RNA to replicate.

The activities of the compounds tested in the above assays are given below. A strip, i.e. -, indicates that no result is available.

Table 18

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
245	>	42.612	=	3.506
33	>	42.612	=	24.740
254	>	42.612	=	15.302
251	>	42.612	=	9.884
250	>	42.612	=	7.950
22	>	42.612	=	10.824
40	>	42.667	>	24.713
26	>	42.612	=	17.830
48	=	15.915	=	16.717
30	>	42.612	=	23.008
13	>	42.660	=	20.373
88	=	18.467	=	6.096
45	=	4.826	=	6.794
74	>	42.656	>	26.654
20	>	42.612	=	6.576
248	>	42.612	=	7.236
95	>	33.333		-
275	>	42.658	=	10.085
84	>	42.677	=	20.852
259	=	29.507	>	33.046
8	>	42.666	=	5.652
263	>	42.670	=	10.392
1	>	42.659	=	8.527
85	>	42.671	=	21.418
5	>	42.661	=	19.866
262	>	42.667	=	5.538
29	>	42.662	=	6.795
50	>	42.662	>	31.996
82	>	42.675	=	6.804
52	>	42.667	=	7.444
25	>	42.674	=	24.634
100	>	42.663	=	3.595
56	>	42.663	=	25.337

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
266	>	42.663	=	23.975
58	>	42.661	=	8.783
87	>	42.663	>	31.997
89	>	42.662	=	5.323
47	>	42.662	=	16.405
268	>	42.660	=	9.041
243	>	33.333	=	25.540
257	>	42.659	=	22.403
55	=	33.253	>	32.007
75	>	42.677	=	20.485
54	>	42.659	=	22.348
10	>	33.333	=	19.511
265	>	42.674	=	11.344
83	>	42.676	=	4.161
19	>	42.669	>	32.001
11	>	42.672	=	14.661
6	>	42.664	=	7.321
267	>	42.678	=	9.391
2	>	42.659	=	26.500
66	>	42.667	=	23.012
86	>	42.678	=	9.693
255	>	42.663	=	21.784
73	>	42.667	=	19.936
81	>	42.675	=	6.720
64	>	42.664	=	22.852
3	>	42.661	>	31.996
99	>	42.658	=	3.690
90	>	42.667	>	32.000
98	>	42.674	=	7.333
264	>	42.673	=	8.865
9	>	42.667	=	3.614
15	>	42.667	=	3.094
31	>	42.667	=	6.364
247	>	33.333	=	17.296
28	>	42.667	=	5.524

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
23	>	42.667	=	20.314
240	>	42.667	=	7.729
94	>	42.667	=	3.395
49	>	42.667	=	11.194
21	>	42.667	=	14.234
38	=	2.844	=	23.797
253	>	42.667	=	8.698
68	>	42.667	=	23.134
260	>	42.667	=	22.501
72	>	42.667	=	23.610
91	>	42.667	=	8.139
46	>	42.667	=	11.148
16	>	42.667	=	10.570
24	>	42.667	=	12.961
60	>	42.667	=	17.884
14	>	33.333	=	10.584
62	>	42.667	=	22.629
34	>	42.667	=	6.810
246	>	42.667	=	1.876
242	>	42.667	=	1.766
41	>	42.667	=	8.444
92	>	42.667	=	17.569
17	>	42.667	=	6.595
39	>	42.667	=	7.420
7	>	42.667	=	8.310
37	>	42.667	=	6.928
12	>	42.667	=	3.110
170	>	42.667	=	3.748
252	>	42.667	=	4.759
271	>	33.333	=	22.883
258	>	42.667	>	32.000
239	>	42.667		-
69	>	42.667	=	4.585
241	>	42.667	=	17.066
290	>	42.667		-

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
288	>	42.667	=	24.997
172	>	42.667	=	11.320
176	=	30.838	=	10.320
163	>	42.667	=	1.763
212	>	42.667	=	23.885
167	>	42.667	=	3.246
295	>	42.667	=	21.566
219	>	42.667	=	2.264
211	>	42.667		-
214	>	42.667		-
231	>	42.667		-
217	>	42.667	=	20.287
296	>	42.667	=	18.259
168	>	42.667	=	3.611
175	>	36.173	=	3.894
173	>	42.667	=	0.208
221	>	42.667	=	23.217
174	>	42.667	=	1.854
222	>	42.667	=	7.730
199	>	42.667	=	11.460
171	>	42.667	=	4.541
162	>	42.667	>	32.000
220	>	42.667	=	3.082
244	>	33.333	=	15.928
77	>	42.667	=	21.246
249	>	42.667	=	3.663
166	>	42.667	=	3.983
43	>	42.667	=	9.171
53	=	19.720	>	32.000
57	>	42.667	=	4.473
42	=	5.679	=	6.393
79	>	42.667	=	31.261
59	>	42.667	=	5.740
61	>	42.667	=	9.452
63	>	42.667	=	4.996

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
223	>	42.667	=	25.025
297	>	42.667	=	23.598
179	>	42.667	=	8.544
65	>	42.667	=	2.480
44	>	42.667	=	9.544
67	>	42.667	=	5.672
93	>	42.667	=	4.050
286	>	42.667	=	19.241
229	>	42.667	=	10.947
225	>	42.667		-
261	>	42.667	=	9.304
70	>	42.667	=	14.626
96	>	42.667	=	11.418
238	>	42.667		-
272	>	42.667		-
27	>	42.667	=	20.667
216	>	42.667	=	25.257
180	>	42.667	=	11.778
4	>	42.667	>	32.000
76	>	33.333	=	6.266
270	>	33.333	=	25.531
161	=	29.915	>	25.000
160	>	33.333	>	25.000
165	>	33.333	=	18.632
177	>	33.333	=	0.767
164	>	33.333	=	18.510
285	>	33.333	=	10.996
80	>	33.333	=	9.532
195	>	33.333	=	6.900
287	>	33.333	=	5.013
205	>	33.333	=	9.962
181	>	33.333	=	2.405
269	>	33.333	=	19.617
227	>	33.333	=	17.008
178	>	42.667	=	0.599

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
215	>	33.333	=	14.135
185	>	33.333	=	4.787
232	>	33.333	=	22.568
188	>	33.333	=	5.161
182	>	42.667	=	1.817
197	>	33.333	=	8.971
256		-	=	3.982
202	>	33.333	=	9.684
218	>	33.333	=	14.826
200	>	33.333	=	9.573
169	>	33.333	=	17.687
224	>	33.333	=	16.077
213	>	33.333	=	12.842
184	>	33.333	=	4.780
210	>	33.333	=	12.148
201	>	33.333	=	9.618
183	>	42.667	=	1.319
289	>	33.333	=	15.375
193	>	33.333	=	5.917
203	>	33.333	=	9.939
196	>	33.333	=	7.322
208	>	33.333	=	11.148
206	>	33.333	=	10.917
228	>	33.333	=	17.242
198	>	33.333	=	9.223
209	>	33.333	=	11.802
204	>	33.333	=	9.959
230	>	33.333	=	19.583
194	>	33.333	=	5.222
51		-	=	7.658
78	>	33.333	=	22.168
226	>	33.333	=	16.342
186	=	40.853	=	2.027
36	>	41.341	=	17.039
35	=	1.283	=	20.495

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
189	>	42.667	=	3.991
191	>	42.667	=	2.875
190	>	42.667	=	1.094
192	>	42.667	=	4.869
102	>	42.676	>	32.007
103	>	42.668	>	32.001
104	>	42.675	>	32.006
105	>	42.661	>	31.996
106	>	42.661	>	31.996
107	>	133.334	=	11.546
108	>	42.660	>	31.995
109	>	42.667	>	32.000
110	>	42.674	=	8.112
111	>	42.669	>	32.001
112	>	42.669	>	32.001
113	>	42.660	>	31.996
114	>	42.669	>	32.001
115	>	42.666	=	14.369
116	>	42.662	>	31.996
117	>	42.657	>	31.993
118	>	42.667	>	32.000
119	>	42.667	>	32.000
120	>	133.334	=	31.781
121	>	42.667	>	32.000
122	>	42.667	>	32.000
123	>	42.667	>	32.000
124	=	8.563	=	28.867
125	>	42.667	>	32.000
126	>	42.667	>	32.000
127	>	42.667	=	11.472
128	>	42.667	>	32.000
129	>	42.667	>	32.000
130	>	42.667	>	32.000
131	>	42.667	>	32.000
132	>	42.667	=	12.754

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
133	>	133.334	=	10.960
134	=	47.268	=	4.636
135	=	54.699	=	2.470
136	>	133.334	=	9.505
137	>	133.334	>	100
138	>	133.334	=	26.739
139	=	1.013	=	2.902
140	=	19.094	=	7.229
141	=	7.906	=	16.310
142	=	0.187	=	4.681
143	=	16.033	=	6.300
144	=	23.014	=	3.095
145	=	23.123	=	5.921
146	=	2.021	=	23.938
147	=	1.971	=	4.219
148	=	83.670	=	3.226
149	=	30.388	=	1.777
150	>	133.334	=	1.686
151	=	1.247	=	18.369
152	=	24.121	=	2.505
153	=	4.054	=	18.647
154	=	122.580	=	5.461
155	>	133.334		-
156	=	5.153	=	6.688
157	=	29.513	=	1.946
158		-	=	31.083
159		-	=	9.593
233	>	42.667	>	32.000
234	>	36.173	=	3.894
235	>	42.667	>	32.000
236	>	42.667	=	11.765
237	>	42.667	=	18.189
276	>	42.657	>	31.993
277	>	42.670	=	13.631
278	>	42.666	=	13.300

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50}(μM)	
279	>	42.675	=	9.266
280	>	42.667	>	32.000
281	>	42.667	>	32.000
282	>	42.667	=	17.042
283	>	42.667	>	32.000
284	>	42.667	=	30.898
291	>	42.667	>	32.000
293	>	42.667	>	32.000
294	=	10.424	=	41.974
298	>	42.667	>	32.000
299	>	133.334	=	2.362
300	>	133.334	=	0.706
302	=	92.472	=	1.870
301	=	1.517	=	15.257
304	=	0.460	=	7.589
303	=	31.530		-
306	=	83.119	=	3.921
305	=	0.035	=	7.739
309	>	133.334	=	39.644
310	=	14.520	=	16.441
311	=	13.328	=	4.028
312	=	6.115	=	7.809
313	=	6.043	=	27.481
314	=	4.432	=	3.004
315	=	4.776	=	14.636
316	=	6.973	=	15.385
317	>	133.334	=	5.752
318	=	67.086		-
319	=	12.687	=	32.428
320	=	6.767	=	33.022
321	>	133.334	=	72.172
322		-	=	44.085
323	=	53.800	=	1.650

Table 19

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
324	>	42.612	=	18.527
325	>	42.612	=	16.290
326	>	33.333	=	4.692
327	>	33.333	=	12.494
328	>	42.670	=	22.713
329	>	33.333	=	11.085
330	>	42.680	=	23.202
331	>	42.663	=	7.441
332	>	42.675	=	9.740
333	>	42.678		-
334	>	42.670		-
335	>	42.672	=	11.929
336	>	42.664	=	13.762
337	>	42.660	=	17.547
338	>	42.664	=	16.895
339	>	42.664	=	9.154
340	>	42.673	=	5.094
341	>	42.667	=	3.926
342	>	42.663	=	4.193
343	>	42.658	=	10.962
344	>	42.664	=	21.600
345	>	42.662	=	21.008
346	>	42.666	=	24.584
347	>	42.672	=	20.700
348	=	29.574	=	4.476
349	>	42.677	=	2.863
350	=	25.136	=	5.213
351	>	42.672		-
352	>	42.665	=	9.608
353	>	42.667	=	5.304
354	>	42.664	=	20.534
355	>	42.666	=	5.483
356	>	42.665	=	16.095

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
357	>	42.666	=	7.006
358	>	42.670	=	20.435
359	>	42.663	=	7.332
360	>	42.667	=	11.225
361	>	42.667	=	6.650
362	=	30.574	=	19.271
363	>	42.667	=	25.826
364	>	42.667	=	20.793
365	=	27.340	=	5.240
366	>	42.667	=	5.308
367	>	42.667	=	24.606
368	>	42.667	=	14.940
369	>	42.667	=	10.001
370	>	42.667	=	3.425
371	>	42.667	=	3.737
372	>	42.667	=	1.944
373	>	42.667	=	9.415
374	>	42.667	=	10.106
375	>	42.667	=	19.933
376	>	42.667	=	9.450
377	>	42.667	=	4.463
378	>	42.667	=	5.944
379	>	42.667	=	6.789
380	>	42.667	=	8.626
381	>	42.667	=	4.766
382	>	42.667	=	16.660
383	>	42.667	=	17.252
384	=	4.582	=	15.911
385	>	42.667	=	3.535
386	>	42.667	>	29.590
387	>	42.667	=	5.558
388	>	42.667	=	6.350
389	>	42.667	=	5.577
390	>	42.667	=	9.067
391	>	42.667	=	18.488

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
392	>	42.667	=	22.649
393	>	33.333	=	6.844
394	>	42.667	=	14.075
395	>	42.667	=	9.906
396	>	42.667	=	11.306
397	>	42.667	=	6.131
398	>	42.667	=	10.911
399	>	42.667	=	19.434
400	>	42.667	=	3.278
401	>	42.667	=	2.880
402	>	42.667	=	8.593
403	>	42.667	=	7.115
404	>	42.667	=	3.242
405	>	42.667	=	5.344
406	>	42.667	=	7.290
407	>	33.333	=	15.646
408	>	33.333	=	14.159
409	>	33.333	=	14.892
410	>	33.333	=	22.575
411	>	33.333	=	17.869
412	>	33.333	=	16.678
413	>	33.333	=	12.031
414	>	33.333	=	13.640
415	>	33.333	=	14.666
416	>	33.333	=	11.166
417	>	42.667	=	8.328
418	>	42.667	=	2.162
419	>	42.667	=	4.815
420	>	42.667	=	3.235
421	>	133.334	=	51.929
423	=	37.863	=	26.399
424	=	11.606	=	12.534
425	>	42.674	=	13.245
426	=	30.781	=	7.306
427	>	42.667	=	20.672

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
428	>	42.667	=	15.991
429	>	42.667	>	30.966
430	>	33.333	=	10.832
431	=	82.880	>	100
449	>	42.667	=	1.211
450	>	42.667	=	4.517
451	>	33.333	=	11.324
452	>	42.680	=	19.688
453	>	42.664	=	19.174
454	>	42.667	=	3.435
455	>	42.667	=	5.070
456	>	42.667	=	17.759
457	>	42.667	=	2.636
458	>	42.667	=	22.916
459	>	42.667		-
460	>	42.667	=	15.648
461	>	42.667	=	24.525
462	=	30.855	>	25.000
463	>	33.333	=	7.432
464	>	133.334	=	82.697
475	>	42.661		-
465	=	59.958	=	3.838
476	>	42.667	=	22.889
477	>	42.667	=	4.492
478	>	42.667	=	2.405
479	>	42.667		-
480	>	42.667	=	5.695
481	>	42.667	=	1.609
482	>	42.667	=	27.029
483	>	42.667	=	15.517
484	>	42.667	=	6.647
485	>	42.667	=	3.388
486	>	42.667	=	3.305
487	>	42.667	=	3.149
488	>	42.667	=	17.821

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
489	>	42.667	=	5.905
490	>	42.667	=	24.862
491	>	42.667	=	12.070
492	>	42.667	=	11.024
493	>	42.667	=	1.302
494	>	42.667	=	21.678
495	>	42.667	=	3.692
496	>	42.667	=	22.875
499	>	42.667	>	31.959
500	>	133.334	=	26.452
501	>	42.678	=	19.781
502	>	42.678	=	13.195
503	>	42.668	=	22.390
504	=	39.062	=	17.106
505	>	42.667	=	13.457
506	>	42.667	=	56.654
507	>	42.667	=	4.632
508	>	42.667	=	1.366
509	>	42.667	=	0.894
512	=	84.493	=	8.418
513	=	70.082	=	3.672
422	>	133.334	>	100
432	>	42.667	=	17.691
433	>	133.334	=	3.811
434	>	133.334	=	22.924
435	>	133.334	=	6.699
436	>	133.334	=	19.689
437	=	32.922	=	6.350
438	>	133.334	=	15.402
439	=	3.631	=	4.332
440	>	133.334	>	100
441	>	133.334	>	100
442	>	133.334	=	2.706
443	=	0.312	=	1.778
444	=	33.230	=	4.449

Compound No.	NS5B Polymerase Assay IC_{50} (μM)		Replicon Assay EC_{50} (μM)	
445	>	133.334	=	1.984
446	>	133.334	=	4.125
447	>	133.334	=	2.518
448	>	133.334	>	100
466	=	68.053	=	6.808
467	>	133.334	=	30.030
468	=	25.627	=	5.175
469	=	32.310	=	8.242
470	=	23.314	=	16.518
471	>	133.334	=	14.691
472	=	9.354	=	16.965
473	=	49.962	=	19.998
474	=	1.721	=	34.082
497	>	133.334	=	3.786
498	>	133.334	=	2.922
510	>	133.334	=	4.563
511	=	1.902	>	100

In the following Table 20 there is listed the Mass spectroscopy (MH+) and melting point values for some of the compounds of the invention. An indication of the procedure employed for the preparation of these compounds is also provided.

Table 20

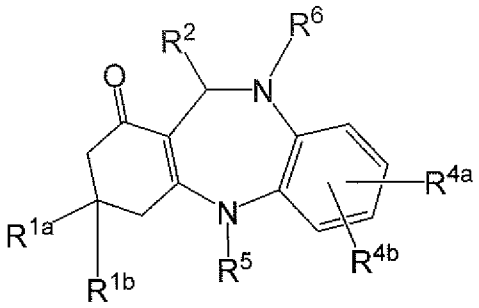
Comp. No.	MH+	Melting point	prepared according to
48	497	216	Scheme A of Example 92
45	491-495	> 250	Scheme B of Example 92
107	483-487	> 260	Scheme C of Example 92
38	429-433	> 250	Scheme D of Example 92
120	429	> 250	Scheme D of Example 92
124	497	215	Scheme D of Example 92
42	467	170	Scheme D of Example 92
273	421-423	258	-
322	443-447	145	Scheme E of Example 92
302	467	-	Scheme T of Example 92

Comp. No.	MH+	Melting point	prepared according to
301	467	-	Scheme T of Example 92
311	507-513	> 260	Scheme F of Example 92
312	507-513	-	Scheme F of Example 92
139	501-503	197	Scheme G of Example 92
313	454-458	248	Scheme H of Example 92
314	443-447	-	Scheme F of Example 92
315	443-447	> 260	Scheme F of Example 92
316	454-458	-	Scheme H of Example 92
520	487-491	> 250	Scheme N of Example 92
521	487-491	> 250	Scheme N of Example 92
517	473-477	> 250	Scheme P of Example 92
522	473-477	-	Scheme P of Example 92
523	459-463	-	Scheme O of Example 92
524	459-463	-	Scheme O of Example 92
518	473-477	200	Scheme Q of Example 92
525	473-477	> 260	Scheme P of Example 92
526	459-463	200	Scheme O of Example 92
304	501-503	130	Scheme G of Example 92
303	501-503	130	Scheme G of Example 92
318	454-458	> 250	Scheme R of Example 92
319	454-458	> 250	Scheme R of Example 92
527	571-575	236	Scheme I of Example 92
306	501-503	-	Scheme S of Example 92
305	501-503	-	Scheme S of Example 92
515	557-561	226	Scheme J of Example 92
321	585-589	> 260	Scheme J of Example 92
528	577-581	> 260	Scheme J of Example 92
514	543-547	258	Scheme I of Example 92
529	563-567	212	Scheme I of Example 92
323	519-523	235	Scheme K of Example 92
530	514-518	> 260	Scheme I of Example 92
531	458-462	> 260	Scheme O of Example 92
532	528-532	> 260	Scheme I of Example 92
151	454-458	> 260	Scheme L of Example 92
152	519-523	242	Scheme L of Example 92

Comp. No.	MH+	Melting point	prepared according to
153	481-485	> 260	Scheme L of Example 92
533	469-473	200	Scheme L of Example 92
154	505-509	> 260	Scheme L of Example 92
155	498-502	> 260	Scheme L of Example 92
156	472-476	> 260	Scheme M of Example 92
516	486-490	> 260	Scheme O of Example 92
534	546-550	220	Scheme M of Example 92
535	472-476	> 260	Scheme O of Example 92
157	549-553	238	Scheme M of Example 92
158	510-514	> 260	Scheme M of Example 92
159	520-524	> 260	Scheme O of Example 92
519	486-490	242	Scheme U of Example 92
468	465-471	170	Scheme F of Example 92
469	401-405	235	Scheme F of Example 92
470	412-416	225	Scheme H of Example 92
471	401-405	225	Scheme F of Example 92
536	431-434	> 250	Scheme P of Example 92
537	444-448	-	Scheme I of Example 92
538	417-421	160	Scheme O of Example 92
539	417-421	168	Scheme O of Example 92
472	412-416	> 250	Scheme R of Example 92
473	412-416	-	Scheme R of Example 92
474	402-406	248	Scheme V of Example 106
540	459-463	208	Scheme I of Example 92
541	417-421	> 260	Scheme I of Example 92

Claims

1. The use of a compound of the formula (I) for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV, said compound being acylated benzodiazepines of the formula (I):



(I)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^2 is hydrogen;

C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{3-7}cycloalkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl,

C_{3-7}cycloalkylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{2-6}alkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-7}cycloalkenyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

C_{4-8}cycloalkenylC_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

aryl^2; or

Het^2;

R^6 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, Het-C_{1-6}alkylaminocarbonyl;

–C(=O)-C_{1-7}alkyl, the C_{1-7}alkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, and carboxyl;

–C(=O)-C_{2-6}alkenyl;

–C(=O)-C_{3-7}cycloalkyl, the C_{3-7}cycloalkyl being optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

–C(=O)-aryl;

–C(=O)-Het;

–C(=O)-$NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

–C(=O)-OR^{13a},

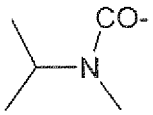
in which R^{13} is hydrogen, C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

–C(=O)-C_{1-6}alkyloxycarbonylC_{1-6}alkyl;

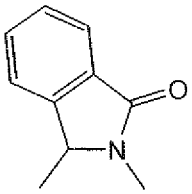
–C(=O)-Het-thioC_{1-6}alkyl; or

–C(=O)-Het-oxyC_{1-6}alkyl; or

R^2 and R^6, together with the intervening grouping in formula (I) of sub-formula:



form a ring of formula:



R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; arylcarbonyl; $-NR^{14a}R^{14b}$; or $-C(=O)-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, mono- or diC_{1-6}alkylamino, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

R^5 is hydrogen; C_{3-7}cycloalkyl; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{15a}R^{15b}$, $-NR^{15a}R^{15b}$, $-C(=O)R^{17}$, $-NR^{15a}C(=O)R^{17}$, $-NR^{15a}SO_pR^{18}$, $-SO_pR^{18}$, $-SO_pNR^{15a}R^{15b}$, $-C(=O)OR^{16}$, or $-NR^{15a}C(=O)OR^{16a}$ in which

p is 0, 1 or2;

each R^{15a} and R^{15b} is, independently, hydrogen; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl;

R^{16} is hydrogen; C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{16a} is C_{2-6}alkenyl; C_{3-7}cycloalkyl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl or Het;

R^{17} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl or aryl;

R^{18} is hydrogen; polyhaloC_{1-6}alkyl; C_{3-7}cycloalkyl; aryl; Het; or C_{1-6}alkyl optionally substituted with a C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; or

(b) phenyl- or naphthyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above; or

(c) phenyl- or naphthyl-carbonyloxy optionally substituted with one, two or three substituents defined for (a) above; and

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, aminocarbonyl, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl;

aryl^2 as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

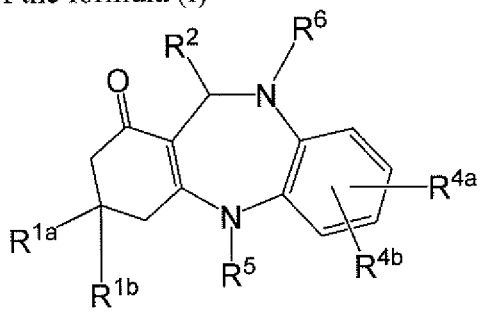
(a) halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, trifluoromethyl, alkylenedioxy, C_{1-6}alkoxy, C_{1-6}alkylthio, polyhalo-C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl, morpholinyl; phenyl- or napthyl-alkoxy optionally substituted with halogen; phenyl- or naphthyl-carbonyloxy optionally substituted with halogen, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, azido, mercapto, C_{3-7}cycloalkyl,

pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkyl-carbonyl-piperazinyl, morpholinyl; or

(b) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{20}$-, -NR^{20}-C_{1-6}alkanediyl-, -NR^{20}-CO-C_{1-6}alkanediyl-, -CO-NR^{20}-C_{1-6}alkanediyl-, -O-, -CO-NR^{20}-, -NR^{20}-CO-, -NR^{20}-SO_2-, -SO_2-NR^{20}-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-, -O-CO-C_{1-6}alkanediyl-, -S- or -S-C_{1-6}alkanediyl-
in which R^{20} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxy, aryl, Het, cyano, polyhaloC_{1-6}alkoxy, and C_{3-7}cycloalkyl;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, *oxo*, aryl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, morpholinyl; or Het^2 is substituted with a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 0 or 1 and X is -C_{1-6}alkanediyl-, C_{1-6}alkenediyl-, $-NR^{21}$-, -NR^{21}-C_{1-6}alkanediyl-, -NR^{21}-CO-C_{1-6}alkanediyl-, -CO-NR^{21}-C_{1-6}alkanediyl-, -O-, -O-C_{1-6}alkanediyl-, -O-CO-, -O-CO-C_{1-6}alkanediyl-, -S-, or -S-C_{1-6}alkanediyl-
in which R^{21} is hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted independently with one, two or three substituents selected from halo, C_{1-6}alkoxyaryl and Het; or with a cyano, polyhaloC_{1-6}alkoxy or C_{3-7}cycloalkyl.

2. A compound of the formula (I)



(I)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, Het, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

aryl^2; or

Het^2;

R^6 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, Het-C_{1-6}alkylaminocarbonyl;

–C(=O)-C_{1-7}alkyl, the C_{1-7}alkyl being optionally substituted independently with one, two or three substituents selected from halo, aryl, and cyano;

–C(=O)-C_{2-6}alkenyl;

–C(=O)-aryl;

–C(=O)-Het;

–C(=O)-$NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, aryl, or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from aryl and Het;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; $-NR^{14a}R^{14b}$; or -C(=O)-$NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from mono- or diC_{1-6}alkylamino, and Het;

R^5 is hydrogen; or C_{1-6}alkyl optionally substituted with aryl;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, mono- or diC_{1-6}alkylamino; or

(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of C_{1-6}alkyl, and aminocarbonyl;

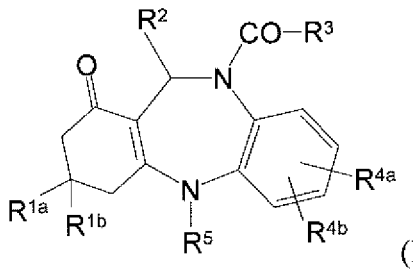
$aryl^2$ as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

(e) halo, C_{1-6}alkyl, hydroxy, trifluoromethyl, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, carboxyl, nitro, mono- or diC_{1-6}alkylamino; or

(f) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 1 and X is -O-, -CO-NH-, -NH-CO-, -NH-SO_2-, -SO_2-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, aryl, and nitro.

3. A compound of the formula (Ia)



(Ia)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, Het, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

aryl^2; or

Het^2;

R^3 is C_{1-7}alkyl optionally substituted independently with one, two or three substituents selected from halo, aryl, and cyano;

C_{2-6}alkenyl;

aryl;

Het;

$-NR^{12a}R^{12b}$,

in which each R^{12a} and R^{12b} is, independently, hydrogen, aryl, or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from aryl and Het;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, Het, $-OR^{14a}$, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with amino, hydroxy, C_{1-6}alkoxy, hydroxycarbonyl, aryl, or Het; aryloxy; Het-oxy; carboxyl; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; $-NR^{14a}R^{14b}$; or $-C(=O)-NR^{14a}R^{14b}$;

in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl optionally substituted independently with one or two substituents selected from mono- or diC_{1-6}alkylamino, and Het;

R^5 is hydrogen; or C_{1-6}alkyl optionally substituted with aryl;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with

(a) one, two or three substituents selected from halo, C_{1-6}alkyl, trifluoromethyl, C_{1-6}alkoxy, carboxyl, C_{1-6}alkylcarbonyl, cyano, cyanoC_{1-6}alkyl, nitro, mono- or diC_{1-6}alkylamino; or

(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed

with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of C_{1-6}alkyl, and aminocarbonyl;

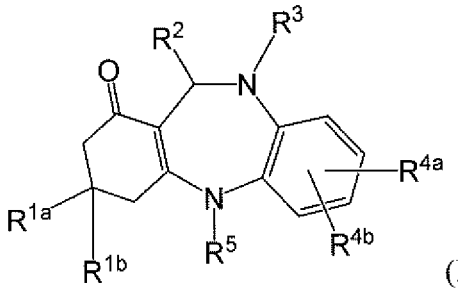
$aryl^2$ as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from

(g) halo, C_{1-6}alkyl, hydroxy, trifluoromethyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyloxy, polyhaloC_{1-6}alkoxy, nitro, mono- or diC_{1-6}alkylamino; or

(h) a radical of formula $-(X)_n$-aryl or $-(X)_n$-Het in which n is 1 and X is -O-, -CO-NH-, -NH-CO-, -NH-SO_2-, -SO_2-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, aryl, and nitro.

4. A compound of the formula (Ib)



(Ib)

and the salts, stereoisomeric forms, and racemic mixtures thereof in which

R^{1a} and R^{1b} are independently, hydrogen, aryl, or C_{1-6}alkyl;

R^2 is C_{2-6}alkenyl optionally substituted independently with one or two substituents selected from halo, and aryl;

$aryl^2$; or

Het^2;

R^3 is hydrogen;

C_{1-6}alkyl optionally substituted with carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, Het-C_{1-6}alkylaminocarbonyl;

R^{4a} and R^{4b} are independently hydrogen; halo; cyano; C_{1-6}alkyl optionally substituted with halo, hydroxy, or $-NR^{14a}R^{14b}$; C_{1-6}alkoxy optionally substituted with C_{1-6}alkoxy; carboxyl; or $-NR^{14a}R^{14b}$;
in which each R^{14a} and R^{14b} is, independently, hydrogen; or C_{1-6}alkyl;

R^5 is hydrogen;

aryl as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with
(a) one, two or three substituents selected from halo, and C_{1-6}alkoxy; or
(b) phenyl-alkoxy optionally substituted with one, two or three substituents defined for (a) above;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings;

$aryl^2$ as a group or part of a group is phenyl or naphthyl, each of which may be optionally independently substituted with one, two or three substituents selected from
c) halo, hydroxy, polyhalo-C_{1-6}alkoxy, carboxyl, nitro; or
d) a radical of formula $-(X)_n$-aryl in which n is 1 and
X is -O-, -CO-NH-, $-SO_2$-NH-, -O-C_{1-6}alkanediyl-, -O-CO-, -CO-;

Het^2 as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, being optionally condensed with one or two benzene rings, and wherein the group Het as a whole may be optionally substituted with one, two or three halo.

5. The use as claimed in claim 1 or the compounds according to any one of claims 2-4 wherein

at least one of R^{1a} and R^{1b} is hydrogen, halo, C_{1-6}alkyl, aryl or Het.

R^2 is hydrogen; C_{2-6}alkenyl optionally substituted with aryl or halo; C_{4-8}cycloalkenyl-C_{1-6}alkyl; $aryl^2$; or Het^2.

at least one of R^{4a} and R^{4b} is hydrogen or arylcarbonyl.

R^5 is hydrogen.

6. The use as claimed in claim 1 or the compounds according to any one of claims 2-3 wherein wherein R^3 or R^6 is C_{1-6}alkyl or polyhaloC_{1-6}alkyl.

7. The use as claimed in claim 1 or the compounds according to any one of claims 2 and 4 wherein wherein R^3 or R^6 is hydrogen or C_{1-6}alkyl.

8. A method of treating an HCV infection, comprising administering to a mammal in need thereof an effective amount of a compound of formula (I) as defined in claim 1 or a salt, stereoisomeric form, or racemic mixture thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of a novel compound of formula (I) according to any one of claims 2-4, and a pharmaceutically acceptable carrier.

10. A process of preparing a pharmaceutical composition as claimed in claim 9, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of formula (I) according to any one of claims 2-4.