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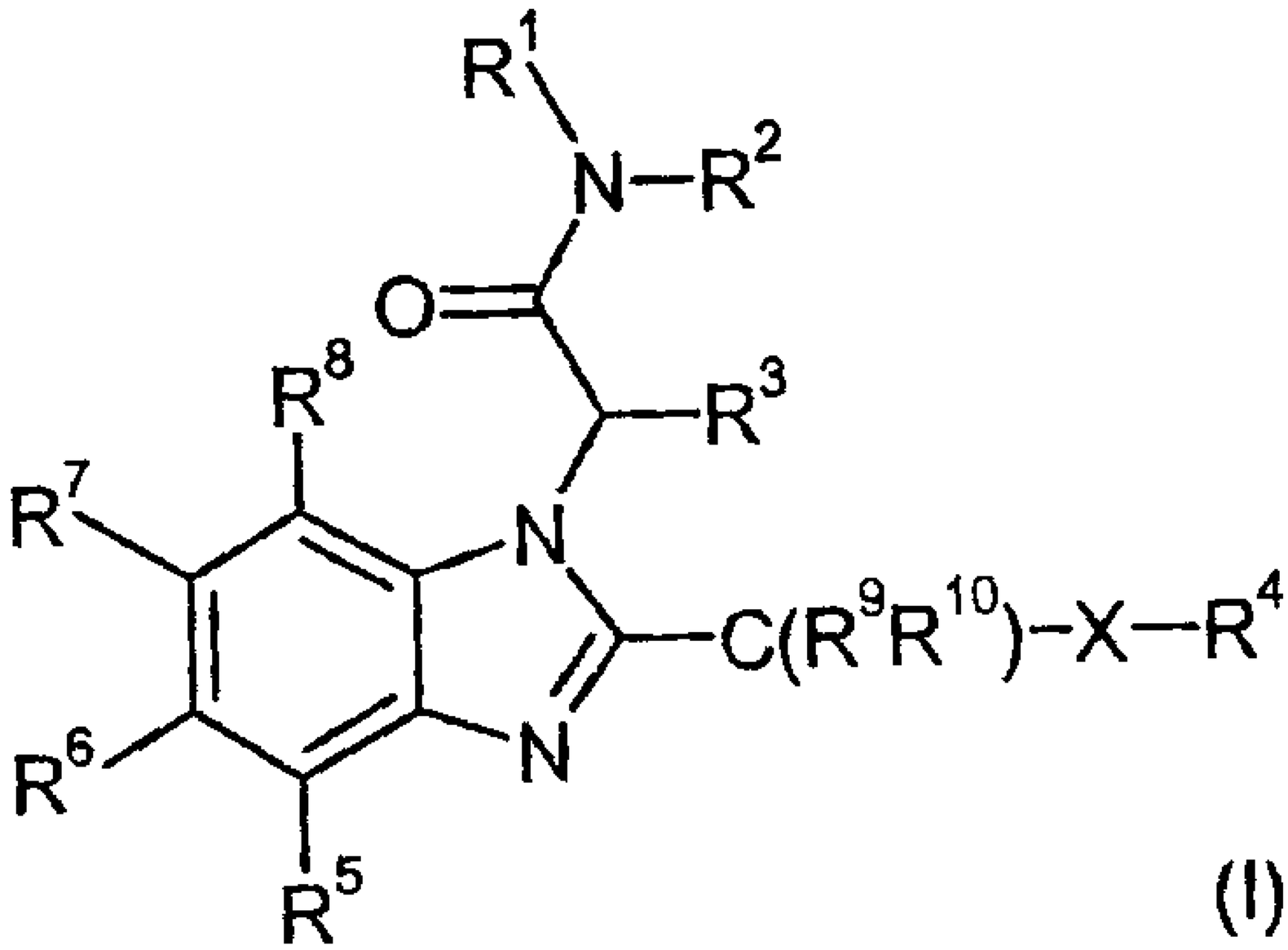
(54) Titre : DERIVES DE BENZIMIDAZOLE UTILISES COMME AGONISTES DU RECEPTEUR FXR
(54) Title: BENZIMIDAZOLE DERIVATIVES USED AS FXR AGONISTS



(I)

(57) Abrégé/Abstract:
The invention is concerned with novel substituted benzimidazole derivatives of formula (I) wherein R^1 to R^{10} and X are as defined in the description and in the claims, as well as physiologically acceptable salts and esters thereof. These compounds bind to FXR and can be used as medicaments.

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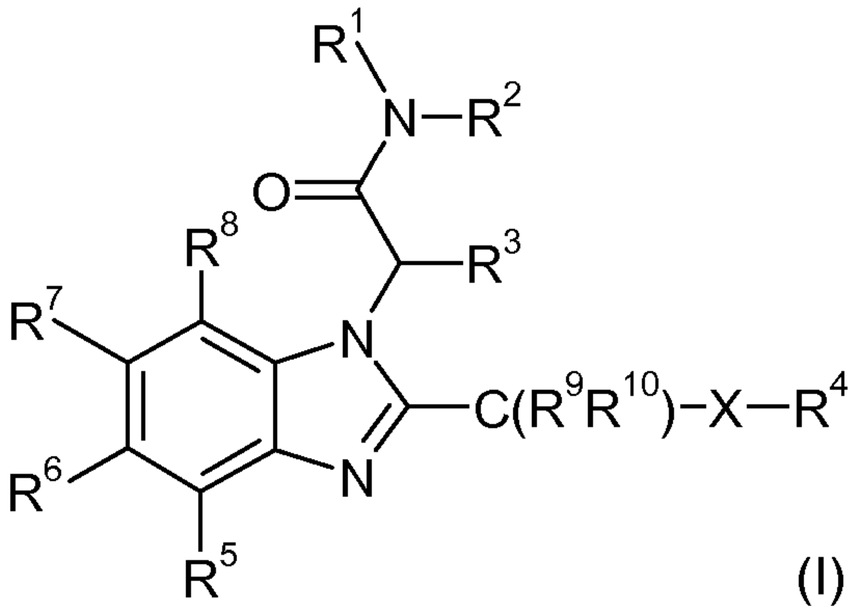

(I)

(57) Abstract: The invention is concerned with novel substituted benzimidazole derivatives of formula (I) wherein R^1 to R^{10} and X are as defined in the description and in the claims, as well as physiologically acceptable salts and esters thereof. These compounds bind to FXR and can be used as medicaments.

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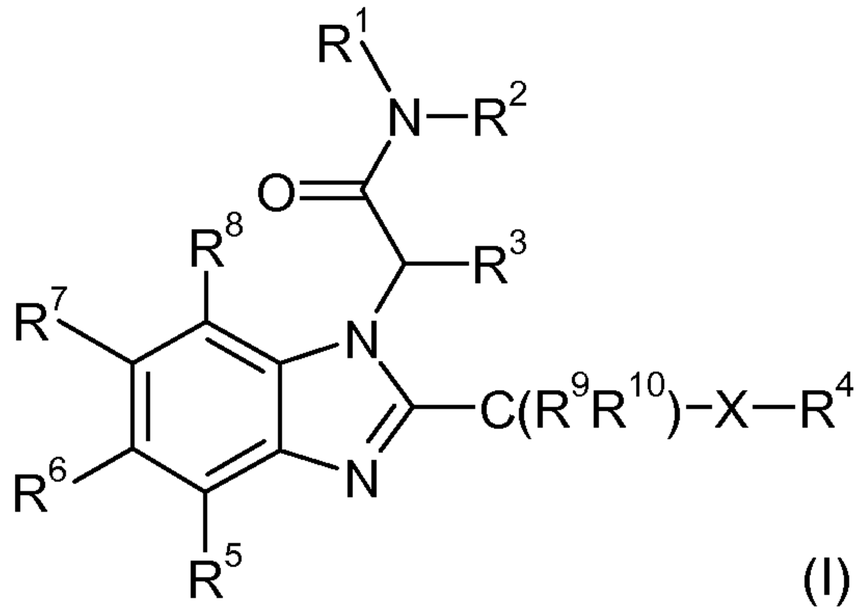
BENZIMIDAZOLE DERIVATIVES USED AS FXR AGONISTS

The invention is concerned with novel substituted benzimidazole derivatives of the formula (I)



(I)

wherein

X is -O-, -S-, -S(O)-, -S(O_2)-, -C($R^{11}R^{12}$)- or -C($R^{11}R^{12}$)-C(O)O-;

R^1 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^2 is hydrogen or lower-alkyl;

R^3 is cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^4 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, hydroxy, lower-alkyl, hydroxy-lower-alkyl, lower-alkyl-O-lower-alkyl-O-lower-

alkyl, fluoro-lower-alkyl, lower-alkyl-carbonyl, lower-alkoxy, fluoro-lower-alkoxy and dioxo-lower-alkylene;

R^5, R^6, R^7 and R^8 independently from each other are hydrogen, halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl, fluoro-lower-alkoxy, cycloalkyl-oxy or heterocyclyl-oxy;

R^9 and R^{10} independently from each other are hydrogen or lower-alkyl, or
R^9 and R^{10} are bound together to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

R^{11} and R^{12} independently from each other are hydrogen or lower-alkyl, or
R^{11} and R^{12} are bound together, to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

and pharmaceutically acceptable salts and esters thereof.

Further, the invention is concerned with a process for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds as well as the use of these compounds for the production of pharmaceutical preparations.

The Farnesoid-X-receptor (FXR) is a member of the nuclear hormone receptor superfamily of transcription factors. FXR was originally identified as a receptor activated by farnesol, and subsequent studies revealed a major role of FXR as a bile acid receptor [Makishima, M., Okamoto, A. Y., Repa, J. J., Tu, H., Learned, R. M., Luk, A., Hull, M. V., Lustig, K. D., Mangelsdorf, D. J. and Shan, B. (1999) Identification of a nuclear receptor for bile acids. Science **284**, 1362-5]. FXR is expressed in liver, intestine, kidney, and the adrenal gland. Four splice isoforms have been cloned in humans.

Among the major bile acids, chenodeoxycholic acid is the most potent FXR agonist. Binding of bile acids or synthetic ligands to FXR induces the transcriptional expression of small heterodimer partner (SHP), an atypical nuclear receptor family member that binds to several other nuclear hormone receptors, including LRH-1 and LXRalpha and blocks their transcriptional functions [Lu, T. T., Makishima, M., Repa, J. J., Schoonjans, K., Kerr, T. A., Auwerx, J. and Mangelsdorf, D. J. (2000) Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. Mol. Cell **6**, 507-15]. CYP7A1 and CYP8B are enzymes involved in hepatic bile acid synthesis. FXR represses their expression via activation of the SHP pathway. FXR directly induces the expression of bile acid-exporting transporters for the ABC family in hepatocytes, including the bile salt export pump (ABCB11) and the multidrug resistance associated protein 2 (ABCC2)

[Kast, H. R., Goodwin, B., Tarr, P. T., Jones, S. A., Anisfeld, A. M., Stoltz, C. M., Tontonoz, P., Kliewer, S., Willson, T. M. and Edwards, P. A. (2002) Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. J. Biol. Chem. 277, 2908-15; Ananthanarayanan, M., Balasubramanian, N., Makishima, M., Mangelsdorf, D. J. and Suchy, F. J. (2001) Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. J. Biol. Chem. **276**, 28857-65]. FXR knockout mice have impaired resistance to bile acid-induced hepatotoxicity and synthetic FXR agonists have been shown to be hepatoprotective in animal models of cholestasis [Liu, Y., Binz, J., Numerick, M. J., Dennis, S., Luo, G., Desai, B., MacKenzie, K. I., Mansfield, T. A., Kliewer, S. A., Goodwin, B. and Jones, S. A. (2003) Hepatoprotection by the farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis. J. Clin. Invest. **112**, 1678-87; Sinal, C. J., Tohkin, M., Miyata, M., Ward, J. M., Lambert, G. and Gonzalez, F. J. (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. Cell **102**, 731-44]. These data show that FXR protects hepatocytes from bile acid toxicity by suppressing both cellular synthesis and import of bile acids and stimulating their biliary excretion.

The process of enterohepatic circulation of bile acids is also a major regulator of serum cholesterol homeostasis. After biosynthesis from cholesterol in the liver, bile acids are secreted with bile into the lumen of the small intestine to aid in the digestion and absorption of fat and fat-soluble vitamins. The ratio of different bile acids determines their ability to solubilize cholesterol. FXR activation decreases the size and changes the composition of the bile acid pool, decreasing the intestinal solubilization of cholesterol, effectively blocking its absorption. Decreased absorption would be expected to result in lower plasma cholesterol levels. Indeed direct inhibitors of cholesterol absorption such as ezetimibe decrease plasma cholesterol, providing some evidence to support this hypothesis. However ezetimibe has limited efficacy which appears due to feedback upregulation of cholesterol synthesis in cells attempting to compensate for depletion of cholesterol. Recent data have shown that FXR opposes this effect in part by directly repressing the expression of HMGCoA reductase via a pathway involving SHP and LRH1 [Datta, S., Wang, L., Moore, D. D. and Osborne, T. F. (2006) Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase promoter by nuclear receptors liver receptor homologue-1 and small heterodimer partner: a mechanism for differential regulation of cholesterol synthesis and uptake. J. Biol. Chem. **281**, 807-12]. FXR also decreases hepatic synthesis of triglycerides by repressing SREBP1-c expression by an alternate pathway involving SHP and LXRalpha. Thus compounds that activate FXR may show superior

therapeutic efficacy on plasma cholesterol and triglyceride lowering than current therapies.

Most patients with coronary artery disease have high plasma levels of atherogenic LDL. The HMGCoA reductase inhibitors (statins) are effective at normalizing LDL-C levels but reduce the risk for cardiovascular events such as stroke and myocardial infarction by only about 30%. Additional therapies targeting further lowering of atherogenic LDL as well as other lipid risk factors such as high plasma triglyceride levels and low HDL-C levels are needed.

A high proportion of type 2 diabetic patients in the United States have abnormal concentrations of plasma lipoproteins. The prevalence of total cholesterol > 240 mg/dl is 37% in diabetic men and 44% in diabetic women and the prevalence for LDL-C > 160 mg/dl are 31% and 44%, respectively in these populations. Diabetes is a disease in which a patient's ability to control glucose levels in blood is decreased because of partial impairment in the response to insulin. Type II diabetes (T2D), also called non-insulin dependent diabetes mellitus (NIDDM), accounts for 80-90% of all diabetes cases in developed countries. In T2D, the pancreatic Islets of Langerhans produce insulin but the primary target tissues (muscle, liver and adipose tissue) develop a profound resistance to its effects. The body compensates by producing more insulin ultimately resulting in failure of pancreatic insulin-producing capacity. Thus T2D is a cardiovascular-metabolic syndrome associated with multiple comorbidities including dyslipidemia and insulin resistance, as well as hypertension, endothelial dysfunction and inflammatory atherosclerosis.

The first line treatment for dyslipidemia and diabetes is a low-fat and low-glucose diet, exercise and weight loss. Compliance can be moderate and treatment of the various metabolic deficiencies that develop becomes necessary with, for example, lipid-modulating agents such as statins and fibrates, hypoglycemic drugs such as sulfonylureas and metformin, or insulin sensitizers of the thiazolidinedione (TZD) class of PPARgamma-agonists. Recent studies provide evidence that modulators of FXR may have enhanced therapeutic potential by providing superior normalization of both LDL-C and triglyceride levels, currently achieved only with combinations of existing drugs and, in addition, may avoid feedback effects on cellular cholesterol homeostasis.

The novel compounds of the present invention exceed the compounds known in the art, inasmuch as they bind to and selectively modulate FXR very efficiently. Consequently, cholesterol absorption is reduced, LDL cholesterol and triglycerides are lowered, and inflammatory atherosclerosis is reduced. Since multiple facets of combined

dyslipidemia and cholesterol homeostasis are addressed by FXR modulators, they are expected to have an enhanced therapeutic potential compared to the compounds already known in the art.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term “lower” is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term “halogen” refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term “alkyl”, alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. Lower-alkyl groups as described below also are preferred alkyl groups.

The term “lower-alkyl”, alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like. Lower-alkyl groups can optionally be substituted, e.g. by hydroxy. Such substituted lower-alkyl-groups are referred to as "hydroxy-lower-alkyl". Unsubstituted lower-alkyl groups are preferred

The term “fluoro-lower-alkyl” refers to lower-alkyl groups which are mono- or multiply substituted with fluorine. Examples of fluoro-lower-alkyl groups are e.g. CFH_2, CF_2H, CF_3, CF_3CH_2, $CF_3(CH_2)_2$, $(CF_3)_2CH$ and CF_2H-CF_2.

The term "amino", alone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substitutents together forming a ring, such as, for example, -NH_2, methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably primary amino, dimethylamino and diethylamino and particularly dimethylamino. The term "formylamino" refers to the group HC(O)-N(H)-.

The term “cycloalkyl” refers to a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. A cycloalkyl group can optionally be substituted as described in the description and claims.

The term “alkoxy” refers to the group R’-O-, wherein R’ is an alkyl. The term “lower-alkoxy” refers to the group R’-O-, wherein R’ is a lower-alkyl.

The term “fluoro-lower-alkoxy” refers to the group R”-O-, wherein R” is fluoro-lower-alkyl. Examples of fluoro-lower-alkoxy groups are e.g. CFH_2-O, CF_2H-O, CF_3-O, CF_3CH_2-O, $CF_3(CH_2)_2$-O, $(CF_3)_2CH$-O, and CF_2H-CF_2-O.

The term "alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 20 carbon atoms, preferably 1 to 16 carbon atoms, more preferably up to 10 carbon atoms. Lower-alkylene groups as described below also are preferred alkylene groups. The term "lower-alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 7, preferably 1 to 6 or 3 to 6 carbon atoms. Straight chain alkylene or lower-alkylene groups are preferred. The term “dioxo-lower-alkylene” refers to a group -O-lower-alkylene-O-.

The term “aryl”, alone or in combination, relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be substituted by 1 to 5 , preferably 1 to 3, substituents independently selected from the group consisting of lower-alkyl, lower-alkoxy, halogen, hydroxy, CN, CF_3, amino, aminocarbonyl, carboxy, NO_2, lower-alkylsufonyl, aminosulfonyl, lower-alkylcarbonyl, lower-alkylcarbonyloxy, lower-alkylcarbonyl-N(H), lower-alkyl-carbonyl-N(lower-alkyl), lower-alkoxycarbonyl, fluoro-lower-alkyl, fluoro-lower-alkoxy, cycloalkyl, phenyloxy, methyl-oxadiazolyl, morpholinyl, formylamino. Preferred substituents are halogen, lower-alkyl, fluoro-lower-alkyl and CN. Furthermore, aryl groups may preferably be substituted as described in the description and claims below.

The term “heteroaryl” refers to an aromatic 5 to 6 membered monocyclic ring or 9 to 10 membered bicyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, such as furyl, pyridinyl, 2-oxo-1,2-dihydro-pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, benzodioxolyl, benzoimidazolyl, indolyl, isoindolyl, 1,3-dioxo-isoindolyl, quinolinyl, indazolyl, benzoisothiazolyl, benzoxazolyl and benzoisoxazolyl. Preferred heteroaryl groups are pyridinyl and isoxazolyl. A heteroaryl group may have a substitution pattern as described

earlier in connection with the term “aryl”. Furthermore, a heteroaryl group may preferably be substituted as described in the description and claims below.

The term "heterocyclyl" refers to 5 to 6 membered monocyclic ring or 8 to 10 membered bi- or tricyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, such as morpholinyl, thiomorpholinyl, tetrahydropyranyl, 1,1-dioxo-thiomorpholinyl, piperidinyl, 2-oxo-piperidinyl, pyrrolidinyl, 2-oxo-pyrrolidinyl, piperazin-2-one, 8-oxa-3-aza-bicyclo[3.2.1]octyl and piperazinyl. A preferred heterocyclyl is tetrahydropyranyl. A heterocyclyl may optionally have a substitution pattern as described earlier in connection with the term "aryl". Furthermore, a heterocyclyl group may preferably be substituted as described in the description and claims below.

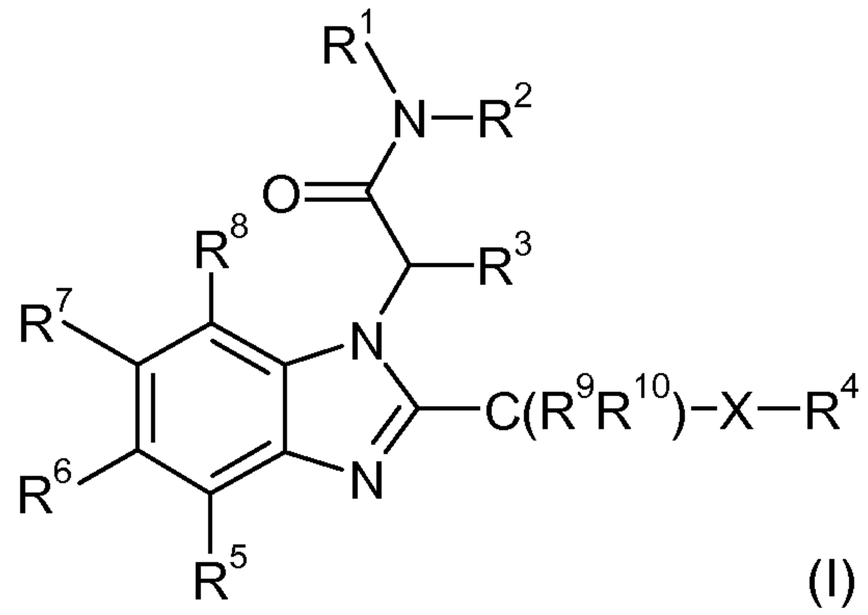
The term "protecting group" refers to groups which are used to protect functional groups, particularly hydroxy groups, temporarily. Examples of protecting groups are benzyl, p-methoxybenzyl, t-butyl-dimethylsilyl, t-butyl-diphenylsilyl and (for protection of amino groups) Boc and benzyloxycarbonyl.

Compounds of formula (I) can form pharmaceutically acceptable acid addition salts. Examples of such pharmaceutically acceptable salts are salts of compounds of formula (I) with physiologically compatible mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, lactic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The term "pharmaceutically acceptable salts" refers to such salts. Compounds of formula (I) in which a COOH group is present can further form salts with bases. Examples of such salts are alkaline, earth-alkaline and ammonium salts such as e.g. Na-, K-, Ca- and trimethylammoniumsalt. The term "pharmaceutically acceptable salts" also refers to such salts. Salts obtained by the addition of an acid are preferred.

The term “pharmaceutically acceptable esters” embraces derivatives of the compounds of formula (I), in which a carboxy group has been converted to an ester. Lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl, amino-lower-alkyl, mono- or di-lower-alkyl-amino-lower-alkyl, morpholino-lower-alkyl, pyrrolidino-lower-alkyl, piperidino-lower-alkyl, piperazino-lower-alkyl, lower-alkyl-piperazino-lower-alkyl and aralkyl esters are examples of suitable esters. The methyl, ethyl, propyl, butyl and benzyl esters are preferred esters. The methyl and ethyl esters are especially preferred. The term “pharmaceutically acceptable esters” furthermore embraces compounds of formula (I) in which hydroxy groups have been converted to the corresponding esters with inorganic or

organic acids such as, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

In detail, the present invention relates to compounds of formula (I)



(I)

wherein

X is -O-, -S-, -S(O)-, -S(O_2)-, -C($R^{11}R^{12}$)- or -C($R^{11}R^{12}$)-C(O)O-;

R^1 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^2 is hydrogen or lower-alkyl;

R^3 is cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^4 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, hydroxy, lower-alkyl, hydroxy-lower-alkyl, lower-alkyl-O-lower-alkyl-O-lower-alkyl, fluoro-lower-alkyl, lower-alkyl-carbonyl, lower-alkoxy, fluoro-lower-alkoxy and dioxo-lower-alkylene;

R^5, R^6, R^7 and R^8 independently from each other are hydrogen, halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl, fluoro-lower-alkoxy, cycloalkyl-oxy or heterocyclyl-oxy;

R^9 and R^{10} independently from each other are hydrogen or lower-alkyl, or

R^9 and R^{10} are bound together to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

R^{11} and R^{12} independently from each other are hydrogen or lower-alkyl, or

R^{11} and R^{12} are bound together, to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

and pharmaceutically acceptable salts and esters thereof.

Compounds of formula (I) are individually preferred and physiologically acceptable salts thereof are individually preferred and pharmaceutically acceptable esters thereof are individually preferred, with the compounds of formula (I) being particularly preferred.

The compounds of formula (I) have one or more asymmetric C atoms and can therefore exist as an enantiomeric mixture, diastereomeric mixture or as optically pure compounds.

Preferred compounds of formula (I) as described above are those,

wherein X is -O-, -S-, -S(O)-, $-C(R^{11}R^{12})-$ or $-C(R^{11}R^{12})$-C(O)O-, wherein R^{11} and R^{12} are as defined above. More preferably, X is -O-, -S- or $-C(R^{11}R^{12})-$, wherein R^{11} and R^{12} are as defined above. Even more preferably, X is $-CH_2$-O-, $-CH(CH_3)$-O-, $-CH_2$-S- or $-CH_2-CH_2$-. Each of the possibilites for X individually constitutes a separate preferred embodiment.

Other preferred compounds are those, wherein R^1 is cycloalkyl, particularly wherein R^1 is cyclohexyl. Furthermore, it is preferred that R^2 is hydrogen.

Another preferred embodiment of the present invention relates to compounds of formula (I) as defined above, wherein R^3 is cycloalkyl or heterocyclyl. If R^3 is heterocyclyl, tetrahydropyranyl is preferred. Preferably, R^3 is cycloalkyl. More preferably, R^3 is cyclohexyl.

Another preferred embodiment of the present invention relates to compounds of formula (I) as described above, wherein R^4 is lower-alkyl, lower-alkyl-O-lower-alkyl-O-lower-alkyl, aryl, aryl-lower-alkyl or a heteroaryl selected from the group consisting of pyridinyl and isoxazolyl, wherein an aryl or heteroaryl can optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxy, lower-alkyl, hydroxy-lower-alkyl, fluoro-lower-alkyl, lower-alkyl-carbonyl, lower-alkoxy, fluoro-lower-alkoxy and dioxo-lower-alkylene. If such substituent on a R^4 group is

dioxo-lower-alkylene, the R^4 is preferably an aryl, particularly phenyl. Examples of aryl which are substituted with dioxo-lower-alkylene are e.g. 2,3-dihydro-benzo[1,4]dioxinyl or benzo[1,3]dioxolyl.

Preferably, R^4 is phenyl or pyridinyl, which phenyl can optionally be substituted with 1 to 2 substituents independently selected from the group consisting of halogen, lower-alkyl and lower-alkoxy. More preferably, R^4 is 4-chloro-2-methyl-phenyl, 2-chloro-phenyl, 4-ethyl-phenyl, 2,4-dichloro-phenyl, phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl or pyridine-2-yl.

Other preferred compounds of formula (I) as described above are those, wherein R^5, R^6, R^7 and R^8 independently from each other are hydrogen or halogen. Preferably, R^5 is hydrogen. Furthermore, it is preferred that R^6 is hydrogen or fluoro. Furthermore, it is preferred that R^7 is hydrogen, fluoro or chloro. Furthermore, it is preferred that R^8 is hydrogen.

Other preferred compounds are those, wherein R^9 and R^{10} independently from each other are hydrogen or lower-alkyl, particularly those, wherein R^9 and R^{10} independently from each other are hydrogen or methyl. Furthermore, it is preferred that R^{11} and R^{12} are hydrogen.

In particular, preferred compounds are the compounds of formula (I) described in the examples as individual compounds as well as pharmaceutically acceptable salts as well as pharmaceutically acceptable esters thereof.

Preferred compounds of formula (I) are those selected from the group consisting of:

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(4-hydroxymethyl-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,

2-[2-(2-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,

2,*N*-Dicyclohexyl-2-(6-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,*N*-Dicyclohexyl-2-(6-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[2-(4-Acetyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2-[2-(2-Chloro-6-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,4-dichloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclohexyl-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclopentyl-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-*N*-cyclopentyl-2-(tetrahydro-pyran-3-yl)-acetamide,
(*S*)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
(*R*)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-(2-Benzyloxymethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide,
2-(2-Butoxymethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{6-fluoro-2-[1-(4-trifluoromethoxy-phenoxy)-ethyl]-benzoimidazol-1-yl}-acetamide,
2-{2-[1-(2-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,
2-{2-[1-(3-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-

acetamide,
2-{2-[1-(4-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2-{2-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
(*S*)-2-{2-[(*S*)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
(*S*)-2-{2-[(*R*)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[6-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-acetamide,
2-{2-[1-(4-Chloro-phenoxy)-1-methyl-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,4-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,6-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[6-fluoro-2-(naphthalen-1-ylsulfanylmethyl)-benzoimidazol-1-yl]-acetamide,
2-(2-Benzenesulfinylmethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide,
2-(2-Benzenesulfinylmethyl-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{2-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-{6-fluoro-2-[2-(4-methoxy-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide,
2-{2-[2-(4-Chloro-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{6-fluoro-2-[2-(4-fluoro-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide,
2-[2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-(5-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(5-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(5-fluoro-2-p-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,*N*-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(3,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,
2-[2-(2-Chloro-6-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclohexyl-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclopentyl-acetamide,
2,*N*-Dicyclohexyl-2-(2-ethoxymethyl-5-fluoro-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide,
2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide,
3-[1-(Cyclohexyl-cyclohexylcarbamoyl-methyl)-5-fluoro-1H-benzoimidazol-2-yl]-propionic acid benzyl ester,
2-[2-(2-Chloro-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-hydroxymethyl-3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-*N*-cyclopentyl-2-(tetrahydro-pyran-2-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(2-ethoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-acetamide,
2-(2-Butoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide,
2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide,
2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide,
2-[6-Chloro-2-(4-chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-{6-Chloro-2-[1-(4-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2-{6-Chloro-2-[1-(3-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2-[6-Chloro-5-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[6-Chloro-2-(3,4-dimethoxy-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,

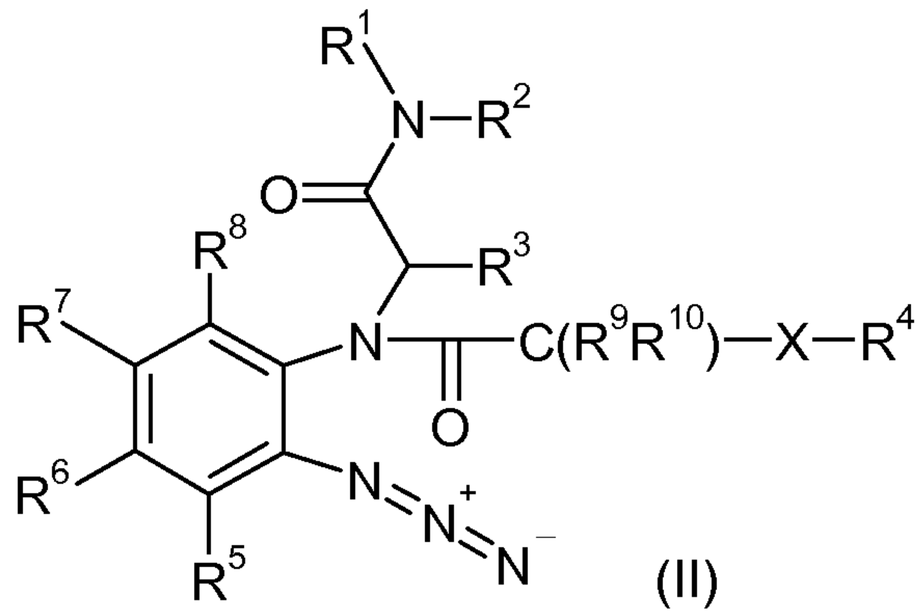
2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[6-Chloro-2-(2,4-dichloro-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[6-Chloro-5-fluoro-2-(4-trifluoromethyl-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-[6-Chloro-2-(8-chloro-naphthalen-1-ylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-(2-Benzenesulfinylmethyl-6-chloro-5-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide, and
2-{6-Chloro-5-fluoro-2-[2-(3-isopropoxy-isoxazol-5-yl)-ethyl]-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
and pharmaceutically acceptable salts and esters thereof.

Particularly preferred compounds of formula (I) are those selected from the group consisting of
(*S*)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2-{2-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide,
2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide,
2,*N*-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,
2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide, and
2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide,
and pharmaceutically acceptable salts and esters thereof.

It will be appreciated that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The invention further relates to a process for the manufacture of compounds of formula (I) as defined above, which process comprises

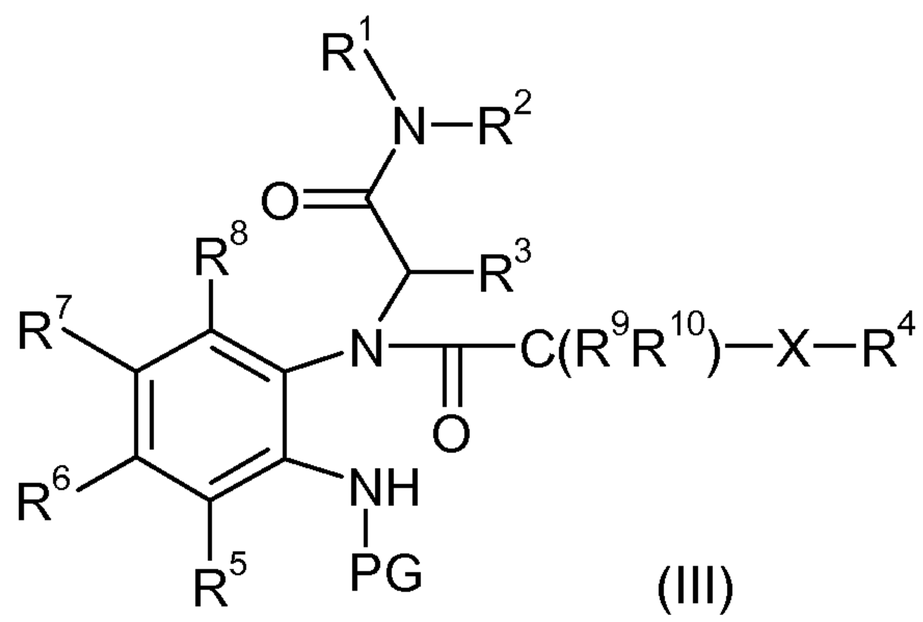
a) cyclisation of a compound of formula (II)



(II)

, or

b) cyclisation of a compound of formula (III)



(III)

,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and X are as defined above and PG is a protecting group.

The cyclisation of a compound of formula (II) or formula (III) can be performed under reaction conditions well known to the person skilled in the art, e.g. by the methods described below and in analogy to the examples described below. Suitable protecting groups in compounds of formula (III) are e.g. t-BOC and benzyloxycarbonyl.

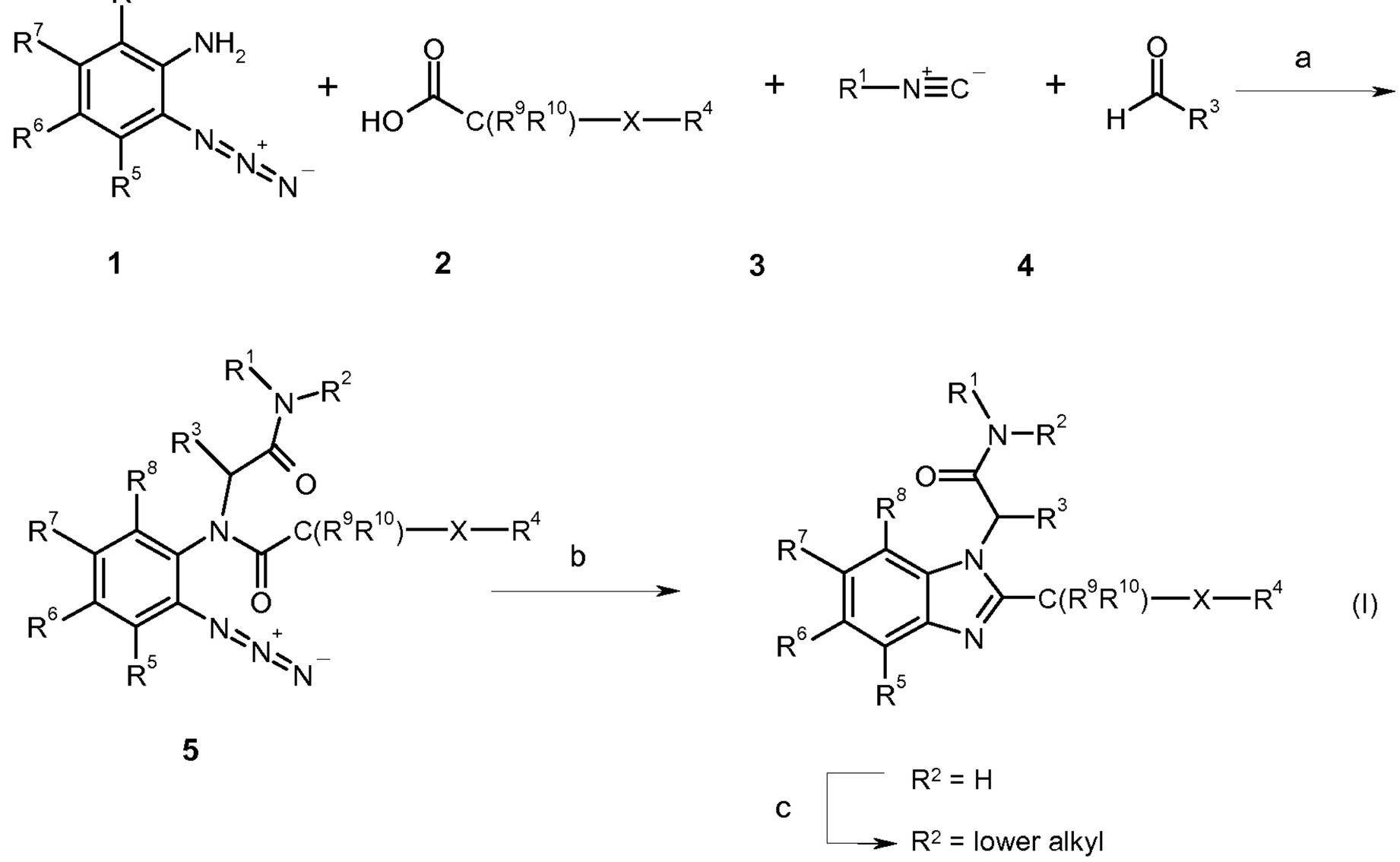
The present invention also relates to compounds of formula (I) as defined above, when prepared by a process as described above.

The compounds of formula (I) as well as the starting materials of formula (II) and (III) can be prepared by methods known in the art or as described below. Unless

otherwise indicated, the substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 , R^9, R^{10} and X are as described above.

Compounds of formula (I) according to the present invention can be prepared *e.g.* by the methods and procedures given below. A typical procedure for the preparation of compounds of formula I is illustrated in scheme 1.

Scheme 1



In a suitable organic solvent such as *e.g.* MeOH a 2-azidoarylamine **1**, a carboxylic acid **2**, an isonitrile **3** and an aldehyde **4** are condensed to **5** in a multi-component reaction (MCR), a so called *Ugi*-type reaction (Scheme 1, step a; typical procedures may *e.g.* be found in "The Peptides" by Gross & Meienhofer Vol. 2, Academic Press, N.Y., 1980, pp 365-381). In a subsequent intramolecular *Staudinger*-type reaction with a suitable reagent such as *e.g.* PPh_3, the azido bisamide **5** is converted to the benzimidazole **I** (Scheme 1, step b), which can be optionally *N*-alkylated by deprotonation with a strong base (*e.g.* NaH or LiHMDA) and subsequent treatment with an alkylating agent R^2-X with X being a typical leaving group such as *e.g.* Cl, Br, I, SO_2alkyl, SO_2fluoroalkyl, SO_2aryl (Scheme 1, step c). Many of the building blocks **2-4**, particularly the carboxylic acids **2**, are commercially available. If not, they may be prepared from commercially available starting materials using procedures described in literature and typically known to those skilled in the art (*e.g.* by alkylation of the corresponding phenols/alcohols with chloro-acetic acid ethyl ester and subsequent ester hydrolysis under aqueous basic conditions using *e.g.* LiOH or NaOH in a mixture of water and THF) . The isonitriles **3**

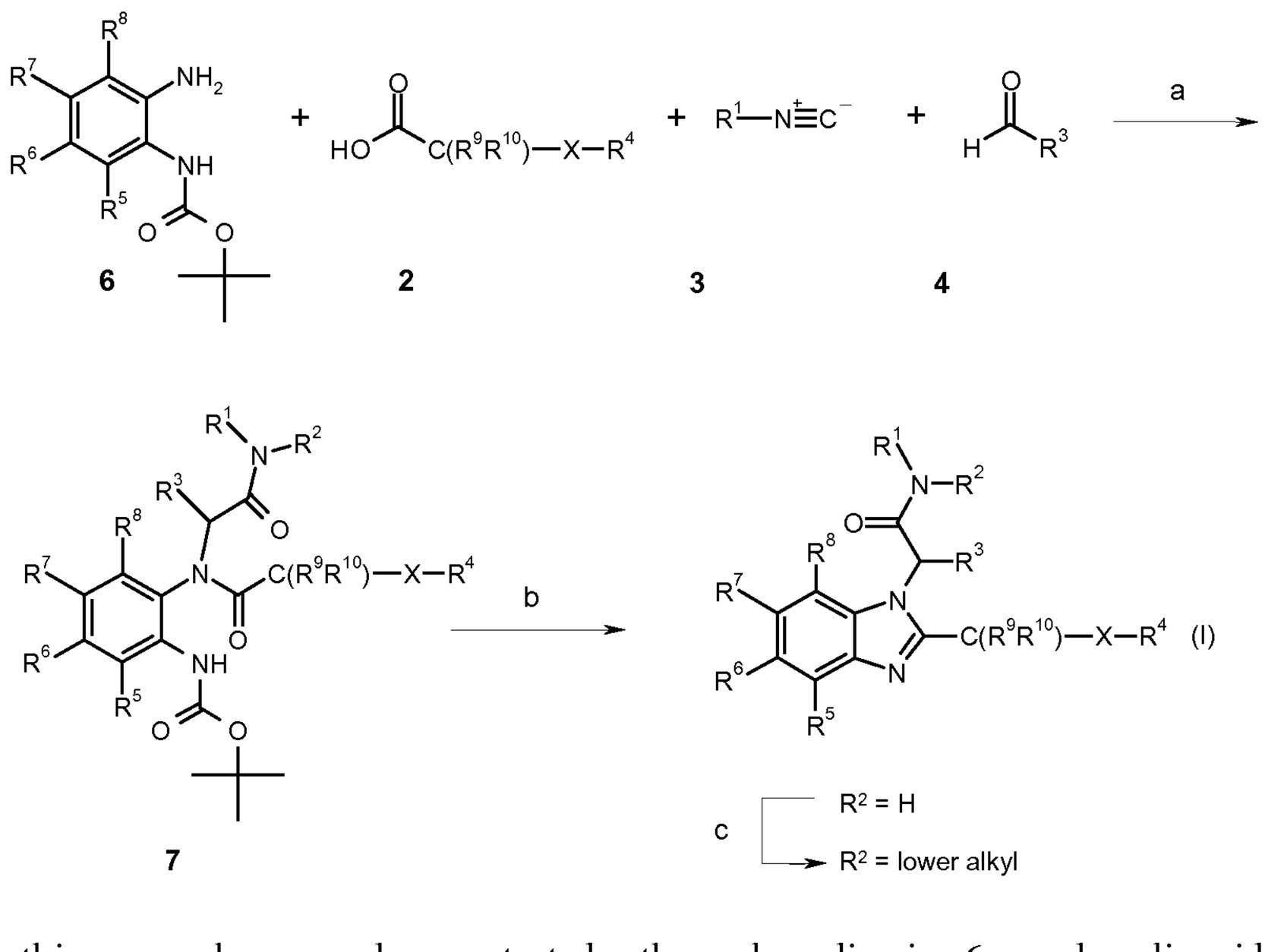
can *e.g.* be obtained by dehydration of the corresponding formamide R^1-NH-CHO with a suitable reagent such as *e.g.* phosgene, $POCl_3$ or $Me_2N=CH^+Cl\ Cl^-$ or by reaction of the corresponding amine R^1-NH_2 with $CHCl_3$ and NaOH in a suitable solvent such as methanol. Aldehydes **4** are either commercially available or can be prepared by numerous methods known to the person skilled in the art. Appropriate synthesis methods include *e.g.* reduction of the corresponding carboxylic acid esters by a suitable reducing agent (*e.g.* diisobutylaluminium hydride at low temperature or with $LiAlH_4$ at elevated or ambient temperature) in a solvent followed by oxidation of the primary alcohol (*e.g.* with tetrapropylammonium perruthenate(VII), activated MnO_2 or Dess-Martin periodinane) to yield aldehydes **4**. The 2-azidoarylamine **1** is usually prepared in three steps from the corresponding 2-aminoarylcarboxylic acid, which is converted into a 2-azidoarylcarboxylic acid by diazotation with $NaNO_2$ in a suitable solvent (*e.g.* methanol) and subsequent treatment with a suitable azide salt such as NaN_3 or $TMSN_3$. The resulting 2-azidoarylcarboxylic acid is then converteted into **1** via *Curtius* rearrangement of the 2-azidoarylcarboxylic azide obtained from the 2-azidoarylcarboxylic acid by its activation with a suitable reagent (*e.g.* chloroethylformiate in the presence of a base such as triethylamine) and subsequent treatment with a suitable source of azide anions (*e.g.* NaN_3). The 2-azidoaryl amine **1** can alternatively be prepared *via* the 2-azidoarylcarboxamide obtained by activation of the 2-azidoarylcarboxylic acid with a suitable reagent (*e.g.* chloroethylformiate in the presence of a base such as triethylamine) and subsequent treatment with ammonia. This amide is converted into **1** in a so called *Hofmann*-rearrangement by treatment with a suitable reagent such as NaOBr.

If one of the starting materials or compounds of formula (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described *e.g.* in "Protective Groups in Organic Chemistry" by T.W. Greene and P.G.M. Wutts, 2nd Ed., 1991, Wiley N.Y.) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature.

If compounds **1**, **2**, **3** or **4** contain stereogenic centers, compounds (I) can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, *e.g.* (chiral) HPLC or crystallization. Racemic compounds can *e.g.* be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbens or a chiral eluent.

An alternative approach to the preparation of compounds of formula (I) is illustrated in scheme 2.

Scheme 2



In this approach a mono boc-protected ortho arylene diamine **6**, a carboxylic acid **2**, an isonitrile **3**, and an aldehyde **4** are condensed in an organic solvent such as *e.g.* methanol to provide the bis-amide 7 again in an *Ugi*-type condensation (Scheme 2, step a). Bisamide 7 is then deprotected with TFA or HCl and spontaneously undergoes cyclization to the desired benzimidazole **I** (Scheme 2, step b), which can be optionally *N*-alkylated by deprotonation with a strong base (*e.g.* NaH or LiHMDA) and subsequent treatment with an alkylating agent R^2-X with X being a typical leaving group such as *e.g.* Cl, Br, I, SO_2alkyl, SO_2fluoroalkyl, SO_2aryl (Scheme 2, step c). Typical procedures applicable to this approach were described *e.g.* by P. Tempest, V. Ma, S. Thomas, Z. Hua, M. G. Kelly, C. Hulme *Tetrahedron Lett.* **2001**, *42*, 4959-4962 and P. Tempest, V. Ma, M. G. Kelly, W. Jones, C. Hulme *Tetrahedron Lett.* **2001**, *42*, 4963-4968, or by W. Zhang, P. Tempest *Tetrahedron Lett.* **2004**, *45*, 6757-6760. Mono boc-protected ortho arylene diamines **6** are commerically available or may be prepared from the corresponding unprotected diamine by treatment with di-*tert*-butyl dicarbonate in an organic solvent such as *e.g.* THF in the presence of a base such as *e.g.* diisopropylethylamine.

If desired or required functional groups present in **I** (such as -CO_2alkyl, amino groups, cyano groups and others) may be derivatized to other functional groups using

typical standard procedures known to those skilled in the art (*e.g.* reduction of -CO_2alkyl to -CH_2OH with $LiAlH_4$, hydrolysis of –CO_2alkyl to CO_2H and subsequent optional conversion to an amide, acylation of amino groups).

If one of the starting materials or compounds of formula (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described *e.g.* in "Protective Groups in Organic Chemistry" by T.W. Greene and P.G.M. Wutts, 2nd Ed., 1991, Wiley N.Y.) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature.

If compounds **2**, **3**, **4** or **6** contain stereogenic centers, compounds (I) can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, *e.g.* (chiral) HPLC or crystallization. Racemic compounds can *e.g.* be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbens or a chiral eluent.

R^1 as present in (I) after steps a and b or steps a, b and c in above shown schemes may be transformed into or replaced by other R^1 using one or a sequence of reaction steps. Two possible examples are given below:

a) $R^1 = CH_2Ph$ may for instance be removed using debenzylation conditions (*e.g.* hydrogenolysis in a solvent such as methanol in presence of a catalyst such as Pd(0) on charcoal powder) and a new R^1 can be introduced *e.g.* by deprotonation of the resulting $CONHR^2$ with a strong base (*e.g.* LiHMDA) and treatment with an alkylating agent R^1-X (X being a typical leaving group such as *e.g.* Cl, Br, I, SO_2alkyl, SO_2fluoroalkyl, SO_2aryl, and R^1 being $C_{1\text{-}10}$-alkyl, lower-alkoxy-lower-alkyl, lower-alkoxy-carbonyl-lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl-lower-alkyl, di-aryl-lower-alkyl, heteroaryl-lower-alkyl or heterocyclyl-lower-alkyl) or alternatively by a Pd(II)-promoted coupling with R^1-X (R^1 being aryl or heteroaryl and X being Cl, Br, I or OSO_2CF_3)

b) Amidolysis of the -$CR^3CONR^1R^2$-moiety of (I) to -CR^3COOH may be carried out using suitable conditions such as heating in isopropanol in presence of NaOH or LiOH. A new amide bond can then be formed using an amine HNR^1R^2 and a typical peptide coupling reagent such as *e.g.* EDCI, DCC or TPTU.

Functional groups present in (I) which are not stable or are reactive under the reaction conditions of one or more of the reaction steps, can be protected with appropriate protecting groups (as described *e.g.* in "Protective Groups in Organic Chemistry" by T.W. Greene and P.G.M. Wutts, 2nd Ed., 1991, Wiley N.Y.) before the critical step applying methods well known in the art. Such protecting groups can be removed at a later stage of the synthesis using standard methods described in the literature.

The conversion of a compound of formula (I) into a pharmaceutically acceptable salt can be carried out by treatment of such a compound with an inorganic acid, for example a hydrohalic acid, such as, for example, hydrochloric acid or hydrobromic acid, or other inorganic acids such as sulfuric acid, nitric acid, phosphoric acid etc., or with an organic acid, such as, for example, acetic acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or *p*-toluenesulfonic acid. The salts with an inorganic or organic acid can be obtained by standard methods known to the person skilled in the art, *e.g.* by dissolving the compound of formula(I) in a suitable solvent such as *e.g.* dioxane or THF and adding an appropriate amount of the corresponding acid. The products can conveniently be isolated by filtration or by chromatography. If a carboxy group is present, the corresponding carboxylate salts can be prepared from the compounds of formula (I) by treatment with physiologically compatible bases. One possible method to form such a salt is *e.g.* by addition of 1/n equivalents of a basic salt such as *e.g.* $M(OH)_n$, wherein M = metal or ammonium cation and n = number of hydroxide anions, to a solution of the compound in a suitable solvent (*e.g.* ethanol, ethanol-water mixture, tetrahydrofuran-water mixture) and to remove the solvent by evaporation or lyophilisation.

The conversion of compounds of formula (I) into pharmaceutically acceptable esters can be carried out *e.g.* by treatment of hydroxy groups present in the molecules with a carboxylic acid such as acetic acid, with a condensating reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), *N*,*N*-dicylohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI) or *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*,*N*-tetra-methyluronium-tetrafluorborate (TPTU) to produce the carboxylic ester. Furthermore, carboxy groups present in the compounds of formula (I) can be reacted with suitable alcohols under analogous conditions as described above.

Insofar as their preparation is not described in the examples, the compounds of formula (I) as well as all intermediate products can be prepared according to analogous

methods or according to the methods set forth above. Starting materials are commercially available, are known in the art, or can be prepared by methods analogous to those described herein.

As described above, the novel compounds of the present invention have been found to bind to and selectively activate FXR. They can therefore be used in the treatment and prophylaxis of diseases which are modulated by FXR agonists. Such diseases include increased lipid and cholesterol levels, particularly high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, particularly non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, particularly gastrointestinal cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are modulated by FXR agonists, particularly as therapeutically active substances for the treatment and/or prophylaxis of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, gastrointestinal cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease.

In another preferred embodiment, the invention relates to a method for the therapeutic and/or prophylactic treatment of diseases which are modulated by FXR agonists, particularly for the therapeutic and/or prophylactic treatment of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, gastrointestinal cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease ,which method comprises administering a compound as defined above to a human being or animal.

The invention also embraces the use of compounds as defined above for the therapeutic and/or prophylactic treatment of diseases which are modulated by FXR agonists, particularly for the therapeutic and/or prophylactic treatment of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol,

dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, gastrointestinal cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are modulated by FXR agonists, particularly for the therapeutic and/or prophylactic treatment of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, gastrointestinal cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease. Such medicaments comprise a compound as described above.

Prevention and/or treatment of high LDL cholesterol levels, high triglycerides, dyslipidemia, cholesterol gallstone disease, cancer, non-insulin dependent diabetes mellitus and metabolic syndrome is preferred, particularly high LDL cholesterol, high triglyceride levels and dyslipidemia.

The following tests were carried out in order to determine the activity of the compounds of formula (I). Background information on the binding assay can be found in: Nichols J S et al. "Development of a scintillation proximity assay for peroxisome proliferator-activated receptor gamma ligand binding domain", (1998) Anal. Biochem. 257: 112-119.

Bacterial and mammalian expression vectors were constructed to produce glutathione-s-transferase (GST) and Gal4 DNA binding domain (GAL) proteins fused to the ligand binding domain (LBD) of human FXR (aa 193-473). To accomplish this, the portions of the sequences encoding the FXR LBD were amplified by polymerase chain reaction (PCR) from a full-length clone by PCR and then subcloned into the plasmid vectors. The final clone was verified by DNA sequence analysis.

The induction, expression, and subsequent purification of GST-LBD fusion protein was performed in *E. coli* strain BL21(pLysS) cells by standard methods (Current Protocols in Molecular Biology, Wiley Press, ed. Ausubel et al.).

Radioligand Binding Assay

Binding of test substances to the FXR ligand binding domain was assessed in a radioligand displacement assay. The assay was performed in a buffer consisting of 50 mM Hepes, pH 7.4, 10 mM NaCl, 5 mM $MgCl_2$, 0.01% CHAPS. For each reaction well in a 96-well plate, 40nM of GST-FXR LBD fusion protein was bound to 10 µg glutathione ytrium silicate SPA beads (PharmaciaAmersham) in a final volume of 50 µl by shaking. A radioligand (e.g. 20nM of 2,N-dicyclohexyl-2-[2-(2,4 dimethoxy-phenyl)-benzoimidazol-1-yl]-acetamide) and test compounds were added, and scintillation proximity counting was performed. All binding assays were performed in 96-well plates and the amount of bound ligand was measured on a Packard TopCount using OptiPlates (Packard). Dose response curves were performed within a range of test compound concentrations from 6 x 10^{-9} M to 2.5 x 10^{-5} M and IC_{50}s were calculated.

Luciferase Transcriptional Reporter Gene Assays

Baby hamster kidney cells (BHK21 ATCC CCL10) were grown in DMEM medium containing 10% FBS at 37 °C in a 95% O2 / 5% CO_2 atmosphere. Cells were seeded in 6-well plates at a density of 10^5 cells/well and then transfected with the pFA-FXR-LBD or expression plasmid plus a reporter plasmid. Transfection was accomplished with the Fugene 6 reagent (Roche Molecular Biochemicals) according to the suggested protocol. Six hours following transfection, the cells were harvested by trypsinization and seeded in 96-well plates at a density of 2 x 10^5 cells/well. After 24 hours to allow attachment of cells, the medium was removed and replaced with 100 µl of phenol red-free medium containing the test substances or control ligands (final DMSO concentration: 0.4%). Following incubation of the cells for 24 hours with substances, 50 µl of the supernatant was discarded and then 50 µl of Luciferase Constant–Light Reagent (Roche Molecular Biochemicals) was added to lyse the cells and initiate the luciferase reaction. Luminescence, as a measure of luciferase activity, was detected in a Packard TopCount. Transcriptional activation in the presence of a test substance was expressed as fold-change in luminescence compared to that of cells incubated in the absence of the substance. EC_{50} values were calculated using the XLfit program (ID Business Solutions Ltd. UK).

The compounds according to formula (I) have an activity in at least one of the above assays (EC_{50} or IC_{50}), preferably of 0.5 nM to 10 µM, more preferably 0.5 nM to 100 nM.

For example, the following compounds showed the following EC_{50} and IC_{50} values in the assays described above:

Example	Transactivation EC_{50} [μM]	SPA binding IC_{50} [μM]
31	0.254	0.118
49	0.095	0.038
56	0.982	0.105

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft

gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 300 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations

Ar = argon, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, $NaHCO_3$ = sodium hydrogen carbonate, Na_2SO_4 = sodium sulfate, h = hour, HCl = hydrogen chloride, HPLC = high performance liquid chromatography, ISP = ion spray positive (mode), ISN = ion spray negative (mode), min = minutes, NMR = nuclear magnetic resonance, MS = mass spectrum, P = protecting group, R = any group, rt = room temperature, SiO_2 = silica gel, THF = tetrahydrofuran, X = halogen.

General remarks

Reactions were carried out under nitrogen or argon atmosphere, when appropriate.

Example 1

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

Step 1:

(2-Amino-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester [CAS RN 579474-47-8] (Intermediate A) was prepared as described in WO 03 / 066 623 A1.

Step 2:

To a solution of (2-amino-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester (22.63 mg, 0.10 mmol, 1.0 equiv; Intermediate A) in MeOH (1.0 mL) was added cyclohexanecarbaldehyde (16.83 mg, 18.05 µl, 0.15 mmol, 1.5 equiv; [2043-61-0]) and the mixture stirred at rt. After 30 min, (4-chloro-2-methyl-phenoxy)-acetic acid (20.06 mg, 0.10 mmol, 1.0 equiv; [CAS RN 94-74-6]) and cyclohexyl isocyanide (10.92 mg, 12.27 µl, 0.10 mmol, 1.0 equiv; [931-53-3]) were added and stirring continued at rt for 2 h. A solution of 4 M HCl in dioxane (0.2 mL) was added and the reaction mixture stirred at rt overnight. Removal of the solvent mixture under reduced pressure and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile / water provided 38.7 mg (50%) of the title compound. MS (ISP): 512.3 $[M+H]^+$.

Example 2

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(4-hydroxymethyl-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (4-hydroxymethyl-phenoxy)-acetic acid ([CAS RN 68858-21-9]). MS (ISP): 494.5 $[M+H]^+$.

Example 3

2-[2-(4-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (4-chloro-phenoxy)-acetic acid ([CAS RN 122-88-3]). MS (ISP): 498.3 $[M+H]^+$.

Example 4

2-[2-(2-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2-chloro-phenoxy)-acetic acid ([CAS RN 614-61-9]). MS (ISN): 497.6 $[M-H]^-$.

Example 5

2,*N*-Dicyclohexyl-2-(6-fluoro-2-*m*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with *m*-tolyloxy-acetic acid ([CAS RN 1643-15-8]). MS (ISP): 478.2 $[M+H]^+$.

Example 6

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2-methoxy-phenoxy)-acetic acid ([CAS RN 1878-85-9]). MS (ISP): 494.3 $[M+H]^+$.

Example 7

2,*N*-Dicyclohexyl-2-(6-fluoro-2-*o*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with *o*-tolyloxy-acetic acid ([CAS RN 1878-49-5]). MS (ISP): 478.2 $[M+H]^+$.

Example 8

2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,4-dimethyl-phenoxy)-acetic acid ([CAS RN 13334-49-1]). MS (ISP): 492.3 $[M+H]^+$.

Example 9

2,*N*-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,5-dimethyl-phenoxy)-acetic acid ([CAS RN 7356-41-4]). MS (ISP): 492.3 $[M+H]^+$.

Example 10

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (4-chloro-2-methyl-phenoxy)-acetic acid ([CAS RN 94-74-6]). MS (ISP): 512.3 $[M+H]^+$.

Example 11

2-[2-(4-Acetyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (4-acetyl-phenoxy)-acetic acid ([CAS RN 1878-81-5]). MS (ISP): 506.3 $[M+H]^+$.

Example 12

2,*N*-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (4-ethyl-phenoxy)-acetic acid ([CAS RN 24431-27-4]). MS (ISP): 492.3 $[M+H]^+$.

Example 13

2,*N*-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,3-dimethyl-phenoxy)-acetic acid ([CAS RN 2935-63-9]). MS (ISP): 492.3 $[M+H]^+$.

Example 14

2-[2-(2-Chloro-6-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2-chloro-6-methyl-phenoxy)-acetic acid ([CAS RN 19094-75-8]). MS (ISP): 512.2 $[M+H]^+$.

Example 15

2,*N*-Dicyclohexyl-2-[2-(2,4-dichloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,4-dichloro-phenoxy)-acetic acid ([CAS RN 94-75-7]). MS (ISP): 532.2 $[M+H]^+$.

Example 16

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing cyclohexanecarbaldehyde with cycloheptanecarbaldehyde ([CAS RN 4277-29-6]). MS (ISP): 526.5 $[M+H]^+$.

Example 17

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclopentyl-acetamide

The title compound was prepared in analogy to Example 1, replacing cyclohexanecarbaldehyde with cycloheptanecarbaldehyde ([CAS RN 4277-29-6]) and cyclohexyl isocyanide with cyclopentyl isocyanide ([CAS RN 68498-54-4]). MS (ISP): 512.5 $[M+H]^+$.

Example 18

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-*N*-cyclopentyl-2-(tetrahydro-pyran-3-yl)-acetamide

The title compound was prepared in analogy to Example 1, replacing cyclohexanecarbaldehyde with tetrahydro-pyran-3-carbaldehyde ([CAS RN 77342-93-9]) and cyclohexyl isocyanide with cyclopentyl isocyanide ([CAS RN 68498-54-4]). MS (ISP): 500.5 $[M+H]^+$.

Example 19

(*S*)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, conducting purification by chiral preparative HPLC (Chiralpak AD) eluting with a gradient of isopropanol / heptane. MS (ISP): 512.5 $[M+H]^+$.

Example 20

(*R*)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, conducting purification by chiral preparative HPLC (Chiralpak AD) eluting with a gradient of isopropanol / heptane. MS (ISP): 512.5 $[M+H]^+$.

Example 21

2-(2-Benzyloxymethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with benzyloxy-acetic acid ([CAS RN 30379-55-6]). MS (ISP): 478.2 $[M+H]^+$.

Example 22

2-(2-Butoxymethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with butoxy-acetic acid ([CAS RN 2516-93-0]). MS (ISP): 444.3 $[M+H]^+$.

Example 23

2,*N*-Dicyclohexyl-2-{6-fluoro-2-[1-(4-trifluoromethoxy-phenoxy)-ethyl]-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(4-trifluoromethoxy-phenoxy)-propionic acid ([CAS RN 175204-35-0]). MS (ISP): 562.3 $[M+H]^+$.

Example 24

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(2-chloro-phenoxy)-propionic acid ([CAS RN 25140-86-7]). MS (ISP): 512.2 $[M+H]^+$.

Example 25

2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(2,4-dichloro-phenoxy)-propionic acid ([CAS RN 120-36-5]). MS (ISP): 546.3 $[M+H]^+$.

Example 26

2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-propionic acid (commercially available from Matrix Scientific, Inc., USA.). MS (ISP): 536.3 $[M+H]^+$.

Example 27

2-{2-[1-(3-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(3-chloro-phenoxy)-propionic acid ([CAS RN 101-10-0]). MS (ISP): 512.3 $[M+H]^+$.

Example 28

2-{2-[1-(4-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(4-chloro-phenoxy)-propionic acid ([CAS RN 3307-39-9]). MS (ISP): 512.5 $[M+H]^+$.

Example 29

2-{2-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(4-chloro-2-methyl-phenoxy)-propionic acid ([CAS RN 93-65-2]). MS (ISP): 526.3 $[M+H]^+$.

Example 30

(*S*)-2-{2-[(*S*)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 29, conducting purification by chiral preparative HPLC (Chiralpak AD) eluting with a gradient of isopropanol / heptane. MS (ISP): 526.5 $[M+H]^+$.

Example 31

(*S*)-2-{2-[(*R*)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 29, conducting purification by chiral preparative HPLC (Chiralpak AD) eluting with a gradient of isopropanol / heptane. MS (ISP): 526.5 $[M+H]^+$.

Example 32

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-phenoxy-butyric acid ([CAS RN 13794-14-4]). MS (ISP): 492.4 $[M+H]^+$.

Example 33

2-{2-[1-(4-Chloro-phenoxy)-1-methyl-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 2-(4-chloro-phenoxy)-2-methyl-propionic acid ([CAS RN 882-09-7]). MS (ISP): 526.3 $[M+H]^+$.

Example 34

2,*N*-Dicyclohexyl-2-[2-(2,4-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,4-dichloro-phenylsulfanyl)-acetic acid ([CAS RN 7720-41-4]). MS (ISP): 548.5 $[M+H]^+$.

Example 35

2,*N*-Dicyclohexyl-2-[2-(2,6-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (2,6-dichloro-phenylsulfanyl)-acetic acid ([CAS RN 21248-45-3]). MS (ISP): 548.5 $[M+H]^+$.

Example 36

2,*N*-Dicyclohexyl-2-[6-fluoro-2-(naphthalen-1-ylsulfanylmethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with (naphthalen-1-ylsulfanyl)-acetic acid ([CAS RN 10404-24-7]). MS (ISP): 530.3 $[M+H]^+$.

Example 37

2-(2-Benzenesulfinylmethyl-6-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with benzenesulfinyl-acetic acid ([CAS RN 3959-08-8]). MS (ISP): 496.6 $[M+H]^+$.

Example 38

2-(2-Benzenesulfinylmethyl-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (2-amino-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester (Intermediate A) with (2-amino-phenyl)-carbamic acid *tert*-butyl ester ([CAS RN 146651-75-4]) and (4-chloro-2-methyl-phenoxy)-acetic acid with benzenesulfinyl-acetic acid ([CAS RN 3959-08-8]). MS (ISP): 478.1 $[M+H]^+$.

Example 39

2,*N*-Dicyclohexyl-2-{2-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 3-(3,4-dimethoxy-phenyl)-propionic acid ([CAS RN 2107-70-2]). MS (ISP): 522.3 $[M+H]^+$.

Example 40

2,*N*-Dicyclohexyl-2-{6-fluoro-2-[2-(4-methoxy-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 3-(4-methoxy-phenyl)-propionic acid ([CAS RN 1929-29-9]). MS (ISP): 492.3 $[M+H]^+$.

Example 41

2-{2-[2-(4-Chloro-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 3-(4-chloro-phenyl)-propionic acid ([CAS RN 2019-34-3]). MS (ISP): 496.3 $[M+H]^+$.

Example 42

2,*N*-Dicyclohexyl-2-{6-fluoro-2-[2-(4-fluoro-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 3-(4-fluoro-phenyl)-propionic acid ([CAS RN 459-31-4]). MS (ISP): 480.3 $[M+H]^+$.

Example 43

2-[2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-6-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 1, replacing (4-chloro-2-methyl-phenoxy)-acetic acid with 3-benzo[1,3]dioxol-5-yl-propionic acid ([CAS RN 2815-95-4]). MS (ISP): 506.3 $[M+H]^+$.

Example 44

2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

Step 1:

(2-Amino-5-fluoro-phenyl)-carbamic acid *tert*-butyl ester [CAS RN 362670-07-3] (Intermediate B) was prepared as described in M. J. Bamford, M. J. Alberti, N. Bailey, S. Davies, D. K. Dean, A. Gaiba, S. Garland, J. D. Harling, D. K. Jung, T. A. Panchal, C. A. Parr, J. G. Steadman, A. K. Takle, J. T. Townsend, D. M. Wilson, J. Witherington *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3402-3406.

Step 2:

To a solution of (2-amino-5-fluoro-phenyl)-carbamic acid *tert*-butyl ester (22.63 mg, 0.10 mmol, 1.0 equiv; Intermediate B) in MeOH (1.0 mL) was added cyclohexanecarbaldehyde (16.83 mg, 18.05 µl, 0.15 mmol, 1.5 equiv; [2043-61-0]) and the mixture stirred at rt. After 30 min, (2-chloro-phenoxy)-acetic acid (18.66 mg, 0.10 mmol, 1.0 equiv; [CAS RN 614-61-9]) and cyclohexyl isocyanide (10.92 mg, 12.27 µl, 0.10 mmol, 1.0 equiv; [931-53-3]) were added and stirring continued at rt for 2 h. A solution of 4 M HCl in dioxane (0.2 mL) was added and the reaction mixture stirred at rt overnight. Removal of the solvent mixture under reduced pressure and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile / water provided 6.3 mg (13%) of the title compound. MS (ISP): 498.1 $[M+H]^+$.

Example 45

2,*N*-Dicyclohexyl-2-(5-fluoro-2-*o*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with *o*-tolyloxy-acetic acid ([CAS RN 1878-49-5]). MS (ISP): 478.3 $[M+H]^+$.

Example 46

2,*N*-Dicyclohexyl-2-(5-fluoro-2-*m*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with *m*-tolyloxy-acetic acid ([CAS RN 1643-15-8]). MS (ISP): 478.3 $[M+H]^+$.

Example 47

2,*N*-Dicyclohexyl-2-(5-fluoro-2-*p*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with *p*-tolyloxy-acetic acid ([CAS RN 940-64-7]). MS (ISP): 478.3 $[M+H]^+$.

Example 48

2,*N*-Dicyclohexyl-2-[5-fluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (4-fluoro-phenoxy)-acetic acid ([CAS RN 405-79-8]). MS (ISP): 482.3 $[M+H]^+$.

Example 49

2,*N*-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (2,3-dimethyl-phenoxy)-acetic acid ([CAS RN 2935-63-9]). MS (ISP): 492.3 $[M+H]^+$.

Example 50

2,*N*-Dicyclohexyl-2-[2-(3,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (3,4-dimethyl-phenoxy)-acetic acid ([CAS RN 13335-73-4]). MS (ISP): 492.3 $[M+H]^+$.

Example 51

2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (2,4-dimethyl-phenoxy)-acetic acid ([CAS RN 13334-49-1]). MS (ISP): 492.3 $[M+H]^+$.

Example 52

2,*N*-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (2,5-dimethyl-phenoxy)-acetic acid ([CAS RN 7356-41-4]). MS (ISP): 492.3 $[M+H]^+$.

Example 53

2-[2-(2-Chloro-6-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (2-chloro-6-methyl-phenoxy)-acetic acid ([CAS RN 19094-75-8]). MS (ISP): 512.3 $[M+H]^+$.

Example 54

2,*N*-Dicyclohexyl-2-[5-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (2-methoxy-phenoxy)-acetic acid ([CAS RN 1878-85-9]). MS (ISP): 494.3 $[M+H]^+$.

Example 55

2,*N*-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (4-methoxy-phenoxy)-acetic acid ([CAS RN 1877-75-4]). MS (ISP): 494.3 $[M+H]^+$.

Example 56

2,*N*-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (pyridin-2-yloxy)-acetic acid ([CAS RN 58530-50-0]). MS (ISP): 465.3 $[M+H]^+$.

Example 57

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclohexyl-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (4-chloro-2-methyl-phenoxy)-acetic acid ([CAS RN 94-74-6]) and cyclohexanecarbaldehyde with cycloheptanecarbaldehyde ([CAS RN 4277-29-6]). MS (ISP): 526.5 $[M+H]^+$.

Example 58

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-*N*-cyclopentyl-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with (4-chloro-2-methyl-phenoxy)-acetic acid ([CAS RN 94-74-6]), cyclohexanecarbaldehyde with cycloheptanecarbaldehyde ([CAS RN 4277-29-6]) and cyclohexyl isocyanide with cyclopentyl isocyanide ([CAS RN 68498-54-4]). MS (ISP): 512.5 $[M+H]^+$.

Example 59

2,*N*-Dicyclohexyl-2-(2-ethoxymethyl-5-fluoro-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with ethoxy-acetic acid ([CAS RN 627-03-2]). MS (ISP): 416.3 $[M+H]^+$.

Example 60

2,*N*-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with butoxy-acetic acid ([CAS RN 2516-93-0]). MS (ISP): 444.3 $[M+H]^+$.

Example 61

2,*N*-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with [2-(2-methoxy-ethoxy)-ethoxy]-acetic acid ([CAS RN 16024-58-1]). MS (ISP): 490.3 $[M+H]^+$.

Example 62

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with 2-(2-chloro-phenoxy)-propionic acid ([CAS RN 25140-86-7]). MS (ISP): 512.3 $[M+H]^+$.

Example 63

2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with 2-(2,4-dichloro-phenoxy)-propionic acid ([CAS RN 120-36-5]). MS (ISP): 546.3 $[M+H]^+$.

Example 64

2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with 2-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-propionic acid (commercially available from Matrix Scientific, Inc., USA.). MS (ISP): 536.4 $[M+H]^+$.

Example 65

2,*N*-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with 3-phenyl-propionic acid ([CAS RN 501-52-0]). MS (ISP): 462.3 $[M+H]^+$.

Example 66

2,*N*-Dicyclohexyl-2-[5-fluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with 4-phenyl-butyric acid ([CAS RN 1821-12-1]). MS (ISP): 476.4 $[M+H]^+$.

Example 67

3-[1-(Cyclohexyl-cyclohexylcarbamoyl-methyl)-5-fluoro-1*H*-benzoimidazol-2-yl]-propionic acid benzyl ester

The title compound was prepared in analogy to Example 44, replacing (2-chloro-phenoxy)-acetic acid with succinic acid monobenzyl ester ([CAS RN 103-40-2]). MS (ISP): 519.6 $[M+H]^+$.

Example 68

2-[2-(2-Chloro-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

Step 1:

(2-Amino-4,5-difluoro-phenyl)-carbamic acid *tert*-butyl ester (Intermediate C)

To a solution of di-*tert*-butyl dicarbonate (14.8 g, 67.8 mmol, 2.0 equiv; [CAS RN 24424-99-5]) and 4-dimethylaminopyridine (0.21 g, 1.7 mmol, 0.05 equiv; DMAP; [CAS RN 1122-58-3]) in THF (100 mL) was added 4,5-difluoro-2-nitro-phenylamine (5.9 g, 33.9 mmol, 1.0 equiv; [CAS RN 78056-39-0]) and the mixture was stirred at rt for 72 h. The solvent was evaporated under reduced pressure and the crude reaction product extracted from a sat. solution of $NaHCO_3$ with ethyl acetate. The organic phases were dried over Na_2SO_4, the residue taken up in dichloromethane and cooled to 0 °C. Trifluoroacetic acid (7.73 g, 67.8 mmol, 2.0 equiv) was added slowly and the reaction mixture stirred at 0° C for 48 h. A solution of 2 N NaOH was added to adjust the pH of the solution to 7. The organic layer was separated and evaporated under reduced pressure. The residue was taken up in ethyl acetate and the product extracted from a sat.

solution of $NaHCO_3$, the organic phase dried over Na_2SO_4 and the intermediate isolated *via* Kieselgel chromatography. The purified product (4.28 g, 15.6 mmol, 1.0 equiv) was dissolved in DMF (50 mL) and a sat. solution of NH_4Cl (13 mL) was added. Zinc powder (5.10 g, 78.0 mmol, 5.0 equiv) was added and the suspension stirred for 30 min at 80 °C and for an additional time period of 2 h at rt. The remaining solid was filtered off and the organic layer evaporated. The product was extracted from a sat. solution of $NaHCO_3$ with ethyl actetate, the organic layer dried over Na_2SO_4 and the crude reaction product purified *via* Kieselgel chromatography. ^{1}H NMR (300 MHz, DMSO): δ 1.46 (s, 9H), 5.03 (br s, 2H), 6.65 (dd, J = 8.2 Hz, J = 12.9 Hz, 1H), 7.30 (dd, J = 8.9 Hz, J = 12.3 Hz, 1H), 8.38 (br s, 1H). MS (ISN): 243.4 $[M-H]^-$.

Step 2:

To a solution of (2-amino-4,5-difluoro-phenyl)-carbamic acid *tert*-butyl ester (24.42 mg, 0.10 mmol, 1.0 equiv; Intermediate C) in MeOH (1.0 mL) was added cyclohexanecarbaldehyde (16.83 mg, 18.05 µl, 0.15 mmol, 1.5 equiv; [2043-61-0]) and the mixture stirred at rt. After 30 min, (2-chloro-phenoxy)-acetic acid (18.66 mg, 0.10 mmol, 1.0 equiv; [CAS RN 614-61-9]) and cyclohexyl isocyanide (10.92 mg, 12.27 µl, 0.10 mmol, 1.0 equiv; [931-53-3]) were added and stirring continued at rt for 2 h. A solution of 4 M HCl in dioxane (0.2 mL) was added and the reaction mixture stirred at rt overnight. Removal of the solvent mixture under reduced pressure and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile / water provided 17.5 mg (34%) of the title compound. MS (ISP): 516.2 $[M+H]^+$.

Example 69

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (4-fluoro-phenoxy)-acetic acid ([CAS RN 405-79-8]). MS (ISP): 500.2 $[M+H]^+$.

Example 70

2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with phenoxy-acetic acid ([CAS RN 122-59-8]). MS (ISP): 482.3 $[M+H]^+$.

Example 71

2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-*m*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with *m*-tolyloxy-acetic acid ([CAS RN 1643-15-8]). MS (ISP): 496.2 $[M+H]^+$.

Example 72

2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-*o*-tolyloxymethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with *o*-tolyloxy-acetic acid ([CAS RN 1878-49-5]). MS (ISP): 496.2 $[M+H]^+$.

Example 73

2,*N*-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (2,4-dimethyl-phenoxy)-acetic acid ([CAS RN 13334-49-1]). MS (ISP): 510.3 $[M+H]^+$.

Example 74

2,*N*-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (4-ethyl-phenoxy)-acetic acid ([CAS RN 24431-27-4]). MS (ISP): 510.3 $[M+H]^+$.

Example 75

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (4-methoxy-phenoxy)-acetic acid ([CAS RN 1877-75-4]). MS (ISP): 512.3 $[M+H]^+$.

Example 76

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (3-methoxy-phenoxy)-acetic acid ([CAS RN 2088-24-6]). MS (ISP): 512.2 $[M+H]^+$.

Example 77

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(4-hydroxymethyl-3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (4-hydroxymethyl-3-methoxy-phenoxy)-acetic acid ([CAS RN 83590-77-6]). MS (ISP): 542.2 $[M+H]^+$.

Example 78

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-*N*-cyclopentyl-2-(tetrahydro-pyran-2-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with (4-chloro-2-methyl-phenoxy)-acetic acid ([CAS RN 94-74-6]), cyclohexanecarbaldehyde with tetrahydro-pyran-2-carbaldehyde ([CAS RN 19611-45-1]) and cyclohexyl isocyanide with cyclopentyl isocyanide ([CAS RN 68498-54-4]). MS (ISP): 518.3 $[M+H]^+$.

Example 79

2,*N*-Dicyclohexyl-2-(2-ethoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with ethoxy-acetic acid ([CAS RN 627-03-2]). MS (ISP): 434.4 $[M+H]^+$.

Example 80

2-(2-Butoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with butoxy-acetic acid ([CAS RN 2516-93-0]). MS (ISP): 462.3 $[M+H]^+$.

Example 81

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with 2-(2-chloro-phenoxy)-propionic acid ([CAS RN 25140-86-7]). MS (ISP): 530.1 $[M+H]^+$.

Example 82

2,*N*-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with 2-(2,4-dichloro-phenoxy)-propionic acid ([CAS RN 120-36-5]). MS (ISP): 564.3 $[M+H]^+$.

Example 83

2,*N*-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with 2-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-propionic acid (commercially available from Matrix Scientific, Inc., USA.). MS (ISP): 554.3 $[M+H]^+$.

Example 84

2,*N*-Dicyclohexyl-2-(5,6-difluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with 3-phenyl-propionic acid ([CAS RN 501-52-0]). MS (ISP): 480.4 $[M+H]^+$.

Example 85

2,*N*-Dicyclohexyl-2-[5,6-difluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide

The title compound was prepared in analogy to Example 68, replacing (2-chloro-phenoxy)-acetic acid with 4-phenyl-butyric acid ([CAS RN 1821-12-1]). MS (ISP): 494.4 $[M+H]^+$.

Example 86

2-[6-Chloro-2-(4-chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

Step 1:

(2-Amino-4-chloro-5-fluoro-phenyl)-carbamic acid *tert*-butyl ester [CAS RN 579474-50-3] (Intermediate D) was prepared as described in WO 03 / 066 623 A1.

Step 2:

To a solution of (2-amino-4-chloro-5-fluoro-phenyl)-carbamic acid *tert*-butyl ester (26.07 mg, 0.10 mmol, 1.0 equiv; Intermediate D) in MeOH (1.0 mL) was added cyclohexanecarbaldehyde (16.83 mg, 18.05 µl, 0.15 mmol, 1.5 equiv; [2043-61-0]) and the mixture stirred at rt. After 30 min, (4-chloro-phenoxy)-acetic acid (18.66 mg, 0.10 mmol, 1.0 equiv; [CAS RN 122-88-3]) and cyclohexyl isocyanide (10.92 mg, 12.27 µl, 0.10 mmol, 1.0 equiv; [931-53-3]) were added and stirring continued at rt for 2 h. A solution of 4 M HCl in dioxane (0.2 mL) was added and the reaction mixture stirred at rt overnight. Removal of the solvent mixture under reduced pressure and purification by preparative HPLC on reversed phase eluting with a gradient of acetonitrile / water provided 19.6 mg (37%) of the title compound. MS (ISP): 532.3 $[M+H]^+$.

Example 87

2-{6-Chloro-2-[1-(4-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with 2-(4-chloro-phenoxy)-propionic acid ([CAS RN 3307-39-9]). MS (ISP): 546.3 $[M+H]^+$.

Example 88

2-{6-Chloro-2-[1-(3-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with 2-(3-chloro-phenoxy)-propionic acid ([CAS RN 101-10-0]). MS (ISP): 546.3 $[M+H]^+$.

Example 89

2-[6-Chloro-5-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with 2-phenoxy-butyric acid ([CAS RN 13794-14-4]). MS (ISP): 526.3 $[M+H]^+$.

Example 90

2-[6-Chloro-2-(3,4-dimethoxy-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with (3,4-dimethoxy-phenylsulfanyl)-acetic acid ([CAS RN 95735-63-0]). MS (ISP): 574.3 $[M+H]^+$.

Example 91

2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with (4-fluoro-phenylsulfanyl)-acetic acid ([CAS RN 332-51-4]). MS (ISP): 532.3 $[M+H]^+$.

Example 92

2-[6-Chloro-2-(2,4-dichloro-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with (2,4-dichloro-phenylsulfanyl)-acetic acid ([CAS RN 7720-41-4]). MS (ISP): 584.3 $[M+H]^+$.

Example 93

2-[6-Chloro-5-fluoro-2-(4-trifluoromethyl-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with (4-trifluoromethyl-phenylsulfanyl)-acetic acid ([CAS RN 102582-93-4]). MS (ISP): 582.3 $[M+H]^+$.

Example 94

2-[6-Chloro-2-(8-chloro-naphthalen-1-ylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with (8-chloro-naphthalen-1-ylsulfanyl)-acetic acid ([CAS RN 129-94-2]). MS (ISP): 598.5 $[M+H]^+$.

Example 95

2-(2-Benzenesulfinylmethyl-6-chloro-5-fluoro-benzoimidazol-1-yl)-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with benzenesulfinyl-acetic acid ([CAS RN 3959-08-8]). MS (ISP): 530.3 $[M+H]^+$.

Example 96

2-{6-Chloro-5-fluoro-2-[2-(3-isopropoxy-isoxazol-5-yl)-ethyl]-benzoimidazol-1-yl}-2,*N*-dicyclohexyl-acetamide

The title compound was prepared in analogy to Example 86, replacing (4-chloro-phenoxy)-acetic acid with 3-(3-isopropoxy-isoxazol-5-yl)-propionic acid ([CAS RN 882624-61-5]). MS (ISP): 545.3 $[M+H]^+$.

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Kernel:	

Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

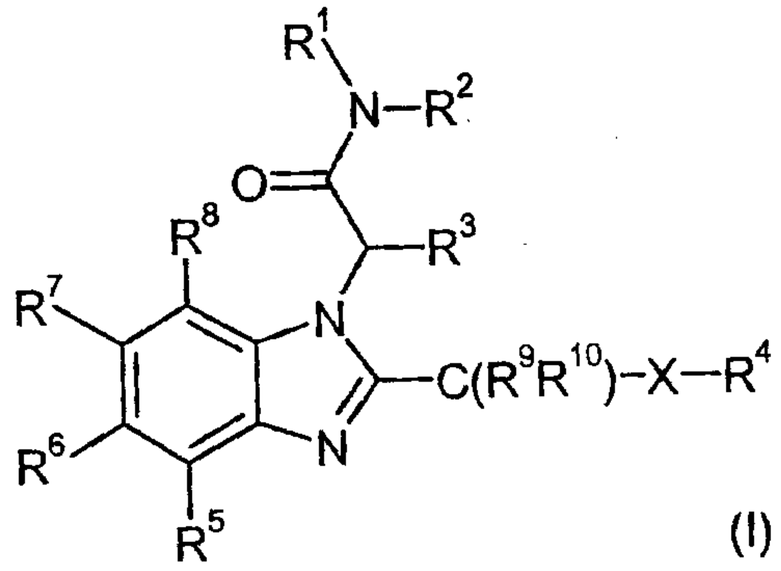
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcristalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcristalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims:

1. A compound of formula (I)



wherein (I)

X is -O-, -S-, -S(O)-, -S(O_2)-, -C($R^{11}R^{12}$)- or -C($R^{11}R^{12}$)-C(O)O-;

R^1 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^2 is hydrogen or lower-alkyl;

R^3 is cycloalkyl, cycloalkyl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a cycloalkyl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl and fluoro-lower-alkoxy;

R^4 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, heterocyclyl or heterocyclyl-lower-alkyl, wherein a lower-alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl can optionally be substituted with 1 to 4 substituents independently selected from the group consisting of halogen, hydroxy, lower-alkyl, hydroxy-lower-alkyl, lower-alkyl-O-lower-alkyl-O-lower-alkyl, fluoro-lower-alkyl, lower-alkyl-carbonyl, lower-alkoxy, fluoro-lower-alkoxy and dioxo-lower-alkylene;

R^5, R^6, R^7 and R^8 independently from each other are hydrogen, halogen, lower-alkyl, lower-alkoxy, fluoro-lower-alkyl, fluoro-lower-alkoxy, cycloalkyl-oxy or heterocyclyl-oxy;

R^9 and R^{10} independently from each other are hydrogen or lower-alkyl, or

R^9 and R^{10} are bound together to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

R^{11} and R^{12} independently from each other are hydrogen or lower-alkyl, or

R^{11} and R^{12} are bound together, to form a cycloalkyl or heterocyclyl together with the carbon atom to which they are attached;

wherein each "heteroaryl" group is an aromatic 5 to 6 membered monocyclic ring or 9 to 10 membered bicyclic ring which can comprise 1, 2 or 3 atoms selected from the group consisting of nitrogen, oxygen and sulphur; and

wherein each "heterocycyl" group is a 5 to 6 membered monocyclic ring or 8 to 10 membered bi- or tricyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and sulphur;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein X is -O-, -S-, -S(O)-, -C($R^{11}R^{12}$)- or -C($R^{11}R^{12}$)-C(O)O-, wherein R^{11} and R^{12} are as defined in claim 1.

3. The compound according to claim 1 or 2, wherein X is -O-, -S- or -C(R11R12)-, wherein R11 and R12 are as defined in claim 1.

4. The compound according to any one of claims 1 - 3, wherein R^1 is cycloalkyl.

5. The compound according to any one of claims 1 - 4, wherein R^1 is cyclohexyl.

6. The compound according to any one of claims 1 - 5, wherein R^2 is hydrogen.

7. The compound according to any one of claims 1 - 6, wherein R^3 is cycloalkyl or heterocyclyl.

8. The compound according to any one of claims 1 - 7, wherein R^3 is cycloalkyl.

9. The compound according to any one of claims 1 - 8, wherein R^3 is cyclohexyl.

10. The compound according to any one of claims 1 - 9, wherein R^4 is lower-alkyl, lower-alkyl-O-lower-alkyl-O-lower-alkyl, aryl, aryl-lower-alkyl or a heteroaryl selected from the group consisting of pyridinyl and isoxazolyl, wherein an aryl or heteroaryl can optionally be substituted with 1 to 3 substituents independently selected from the group consisting of halogen, hydroxy, lower-alkyl, hydroxy-lower-alkyl, fluoro-lower-alkyl, lower-alkyl-carbonyl, lower-alkoxy, fluoro-lower-alkoxy and dioxo-lower-alkylene.

11. The compound according to any one of claims 1 - 10, wherein R^4 is phenyl or pyridinyl, which phenyl can optionally be substituted with 1 to 2 substituents independently selected from the group consisting of halogen, lower-alkyl and lower-alkoxy.

12. The compound according to any one of claims 1 - 11, wherein R^4 is 4-chloro-2-methyl-phenyl, 2-chloro-phenyl, 4-ethyl-phenyl, 2,4-dichloro-phenyl, phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl or pyridine-2-yl.

13. The compound according to any one of claims 1 - 12, wherein R^5, R^6, R^7 and R^8 independently from each other are hydrogen or halogen.

14. The compound according to any one of claims 1 - 13, wherein R^5 is hydrogen.

15. The compound according to any one of claims 1 - 14, wherein R^6 is hydrogen or fluoro.

16. The compound according to any one of claims 1 - 15, wherein R^7 is hydrogen, fluoro or chloro.

17. The compound according to any one of claims 1 - 16, wherein R^8 is hydrogen.

18. The compound according to any one of claims 1 - 17, wherein R^9 and R^{10} independently from each other are hydrogen or lower-alkyl.

19. The compound according to any one of claims 1 - 18, wherein R^9 and R^{10} independently from each other are hydrogen or methyl.

20. The compound according to any one of claims 1 - 19, wherein R^{11} and R^{12} are hydrogen.

21. The compound according to any one of claims 1 - 20, selected from the group consisting of

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[6-fluoro-2-(4-hydroxymethyl-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[2-(2-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-(6-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[6-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-(6-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[2-(4-Acetyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2-[2-(2-Chloro-6-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[2-(2,4-dichloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-

cyclohexyl-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclopentyl-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-N-cyclopentyl-2-(tetrahydro-pyran-3-yl)-acetamide,

(S)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

(R)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-(2-Benzyloxymethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide,

2-(2-Butoxymethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-16-fluoro-2-[1-(4-trifluoromethoxy-phenoxy)-ethyl]-benzoimidazol-1-yl}-acetamide,

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,

2-{2-[1-(3-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2-{2-[1-(4-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2-{2-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

(S)-2-{2-[(S)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

(S)-2-{2-[(R)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[6-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-acetamide,

2-12-[1-(4-Chloro-phenoxy)-1-methyl-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[2-(2,4-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,6-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[6-fluoro-2-(naphthalen-1-ylsulfanylmethyl)-benzoimidazol-1-yl]-acetamide,

2-(2-Benzenesulfinylmethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide,

2-(2-Benzenesulfinylmethyl-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-{2-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-{6-fluoro-2-[2-(4-methoxy-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide,

2-{2-[2-(4-Chloro-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-{6-fluoro-2-[2-(4-fluoro-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide,

2-[2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-(5-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-(5-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-(5-fluoro-2-p-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(3,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide,

2-[2-(2-Chloro-6-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclohexyl-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclopentyl-acetamide,

2,N-Dicyclohexyl-2-(2-ethoxymethyl-5-fluoro-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide,

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide,

3-[1-(Cyclohexyl-cyclohexylcarbamoyl-methyl)-5-fluoro-1H-benzoimidazol-2-yl]-propionic acid benzyl ester,

2-[2-(2-Chloro-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-(5,6-difluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-(5,6-difluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5,6-difluoro-2-(3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-hydroxymethyl-3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-N-cyclopentyl-2-(tetrahydro-pyran-2-yl)-acetamide,

2,N-Dicyclohexyl-2-(2-ethoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-acetamide,

2-(2-Butoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide,

2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,41 dioxin-6-yloxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide,

2,N-Dicyclohexyl-2-(5,6-difluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[5,6-difluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide,

2-[6-Chloro-2-(4-chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-16-Chloro-2-[1-(4-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2-16-Chloro-2-[1-(3-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-5-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-2-(3,4-dimethoxy-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-2-(2,4-dichloro-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-5-fluoro-2-(4-trifluoromethyl-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-[6-Chloro-2-(8-chloro-naphthalen-1-ylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-(2-Benzenesulfinylmethyl-6-chloro-5-fluoro-benzoimidazol-1-yl) -2,N-dicyclohexyl-acetamide, and

2-{6-Chloro-5-fluoro-2-[2-(3-isopropoxy-isoxazol-5-yl)-ethyl]-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

or a pharmaceutically acceptable salt thereof.

22. The compound according to any one of claims 1 - 21, selected from the group consisting of

(S)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2-12-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide,

2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide,

2,N-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide,

2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide, and

2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide,

or a pharmaceutically acceptable salt thereof.

23. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

24. The compound 2,N-Dicyclohexyl-2-[6-fluoro-2-(4-hydroxymethyl-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

25. The compound 2-[2-(4-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt therof.

26. The compound 2-[2-(2-Chloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

27. The compound 2,N-Dicyclohexyl-2-(6-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

28. The compound 2,N-Dicyclohexyl-2-[6-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

29. The compound 2,N-Dicyclohexyl-2-(6-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

30. The compound 2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

31. The compound 2,N-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

32. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

33. The compound 2-[2-(4-Acetyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

34. The compound 2,N-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

35. The compound 2,N-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

36. The compound 2-[2-(2-Chloro-6-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

37. The compound 2,N-Dicyclohexyl-2-[2-(2,4-dichloro-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

38. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

39. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclopentyl-acetamide or a pharmaceutically acceptable salt thereof.

40. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-N-cyclopentyl-2-(tetrahydro-pyran-3-yl)-acetamide or a pharmaceutically acceptable salt thereof.

41. The compound (S)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

42. The compound (R)-2-[2-(4-Chloro-2-methyl-phenoxymethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

43. The compound 2-(2-Benzyloxymethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

44. The compound 2-(2-Butoxymethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

45. The compound 2,N-Dicyclohexyl-2-16-fluoro-2-[1-(4-trifluoromethoxy-phenoxy)-ethyl]-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

46. The compound 2-{2-[1-(2-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

47. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

48. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

49. The compound 2-{2-[1-(3-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

50. The compound 2-{2-[1-(4-Chloro-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

51. The compound 2-{2-[1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

52. The compound (S)-2-{2-[(S)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

53. The compound (S)-2-{2-[(R)-1-(4-Chloro-2-methyl-phenoxy)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

54. The compound 2,N-Dicyclohexyl-2-[6-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

55. The compound 2-12-[1-(4-Chloro-phenoxy)-1-methyl-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

56. The compound 2,N-Dicyclohexyl-2-[2-(2,4-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

57. The compound 2,N-Dicyclohexyl-2-[2-(2,6-dichloro-phenylsulfanylmethyl)-6-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

58. The compound 2,N-Dicyclohexyl-2-[6-fluoro-2-(naphthalen-1-ylsulfanylmethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

59. The compound 2-(2-Benzenesulfinylmethyl-6-fluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

60. The compound 2-(2-Benzenesulfinylmethyl-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

61. The compound 2,N-Dicyclohexyl-2-{2-[2-(3,4-dimethoxy-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

62. The compound 2,N-Dicyclohexyl-2-{6-fluoro-2-[2-(4-methoxy-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

63. The compound 2-{2-[2-(4-Chloro-phenyl)-ethyl]-6-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

64. The compound 2,N-Dicyclohexyl-2-{6-fluoro-2-[2-(4-fluoro-phenyl)-ethyl]-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

65. The compound 2-[2-(2-Benzo[1,3]dioxol-5-yl-ethyl)-6-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

66. The compound 2-[2-(2-Chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

67. The compound 2,N-Dicyclohexyl-2-(5-fluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

68. The compound 2,N-Dicyclohexyl-2-(5-fluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

69. The compound 2,N-Dicyclohexyl-2-(5-fluoro-2-p-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

70. The compound 2,N-Dicyclohexyl-2-[5-fluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

71. The compound 2,N-Dicyclohexyl-2-[2-(2,3-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

72. The compound 2,N-Dicyclohexyl-2-[2-(3,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

73. The compound 2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

74. The compound 2,N-Dicyclohexyl-2-[2-(2,5-dimethyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

75. The compound 2-[2-(2-Chloro-6-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

76. The compound 2,N-Dicyclohexyl-2-[5-fluoro-2-(2-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

77. The compound 2,N-Dicyclohexyl-2-[5-fluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

78. The compound 2,N-Dicyclohexyl-2-[5-fluoro-2-(pyridin-2-yloxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

79. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

80. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2-cycloheptyl-N-cyclopentyl-acetamide or a pharmaceutically acceptable salt thereof.

81. The compound 2,N-Dicyclohexyl-2-(2-ethoxymethyl-5-fluoro-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

82. The compound 2,N-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

83. The compound 2,N-Dicyclohexyl-2-{5-fluoro-2-[2-(2-methoxy-ethoxy)-ethoxymethyl]-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

84. The compound 2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

85. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

86. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

87. The compound 2,N-Dicyclohexyl-2-(5-fluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

88. The compound 2,N-Dicyclohexyl-2-[5-fluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

89. The compound 3-[1-(Cyclohexyl-cyclohexylcarbamoyl-methyl)-5-fluoro-1H-benzoimidazol-2-yl]-propionic acid benzyl ester or a pharmaceutically acceptable salt thereof.

90. The compound 2-[2-(2-Chloro-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

91. The compound 2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-fluoro-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

92. The compound 2,N-Dicyclohexyl-2-(5,6-difluoro-2-phenoxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

93. The compound 2,N-Dicyclohexyl-2-(5,6-difluoro-2-m-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

94. The compound 2,N-Dicyclohexyl-2-(5,6-difluoro-2-o-tolyloxymethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

95. The compound 2,N-Dicyclohexyl-2-[2-(2,4-dimethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

96. The compound 2,N-Dicyclohexyl-2-[2-(4-ethyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

97. The compound 2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

98. The compound 2,N-Dicyclohexyl-2-[5,6-difluoro-2-(3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

99. The compound 2,N-Dicyclohexyl-2-[5,6-difluoro-2-(4-hydroxymethyl-3-methoxy-phenoxymethyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

100. The compound 2-[2-(4-Chloro-2-methyl-phenoxymethyl)-5,6-difluoro-benzoimidazol-1-yl]-N-cyclopentyl-2-(tetrahydro-pyran-2-yl)-acetamide or a pharmaceutically acceptable salt thereof.

101. The compound 2,N-Dicyclohexyl-2-(2-ethoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

102. The compound 2-(2-Butoxymethyl-5,6-difluoro-benzoimidazol-1-yl)-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

103. The compound 2-{2-[1-(2-Chloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

104. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,4-dichloro-phenoxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

105. The compound 2,N-Dicyclohexyl-2-{2-[1-(2,3-dihydro-benzo[1,41 dioxin-6-yloxy)-ethyl]-5,6-difluoro-benzoimidazol-1-yl}-acetamide or a pharmaceutically acceptable salt thereof.

106. The compound 2,N-Dicyclohexyl-2-(5,6-difluoro-2-phenethyl-benzoimidazol-1-yl)-acetamide or a pharmaceutically acceptable salt thereof.

107. The compound 2,N-Dicyclohexyl-2-[5,6-difluoro-2-(3-phenyl-propyl)-benzoimidazol-1-yl]-acetamide or a pharmaceutically acceptable salt thereof.

108. The compound 2-[6-Chloro-2-(4-chloro-phenoxymethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

109. The compound 2-16-Chloro-2-[1-(4-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

110. The compound 2-16-Chloro-2-[1-(3-chloro-phenoxy)-ethyl]-5-fluoro-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

111. The compound 2-[6-Chloro-5-fluoro-2-(1-phenoxy-propyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

112. The compound 2-[6-Chloro-2-(3,4-dimethoxy-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

113. The compound 2-[6-Chloro-5-fluoro-2-(4-fluoro-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

114. The compound 2-[6-Chloro-2-(2,4-dichloro-phenylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

115. The compound 2-[6-Chloro-5-fluoro-2-(4-trifluoromethyl-phenylsulfanylmethyl)-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

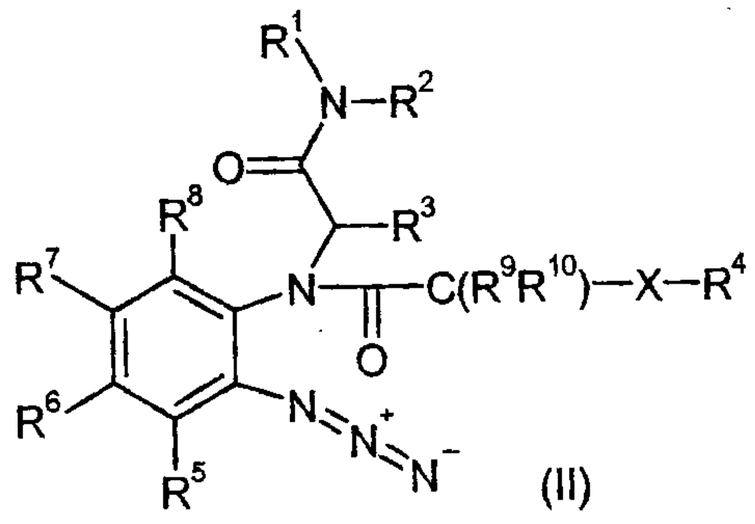
116. The compound 2-[6-Chloro-2-(8-chloro-naphthalen-1-ylsulfanylmethyl)-5-fluoro-benzoimidazol-1-yl]-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

117. The compound 2-(2-Benzenesulfinylmethyl-6-chloro-5-fluoro-benzoimidazol-1-yl) -2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

118. The compound 2-{6-Chloro-5-fluoro-2-[2-(3-isopropoxy-isoxazol-5-yl)-ethyl]-benzoimidazol-1-yl}-2,N-dicyclohexyl-acetamide or a pharmaceutically acceptable salt thereof.

119. A process for the manufacture of the compound of formula (I) as defined in any one of claims 1 - 118, which process comprises

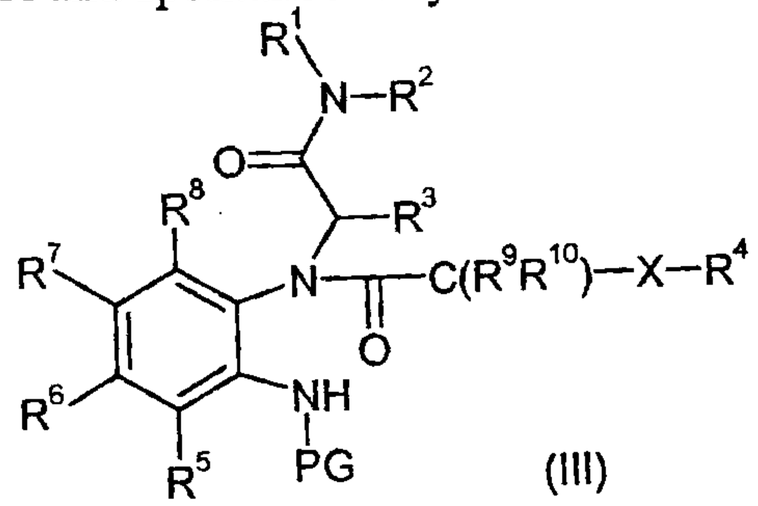
a) cyclisation of a compound of formula (II) in a intramolecular Staudinger-type reaction with a suitable reagent



(II)

, or

b) deprotection with TFA or HCl and spontaneous cyclisation of a compound of formula (III)



(III)

,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and X are as defined in any one of claims 1 - 20 and PG is a protecting group.

120. A pharmaceutical composition comprising the compound defined in any one of claims 1 - 118 and a pharmaceutically acceptable carrier and/or adjuvant.

121. The compound according to any one of claims 1 - 118 for use as a therapeutically active substance for the treatment and/or prophylaxis of a disease modulated by FXR agonists.

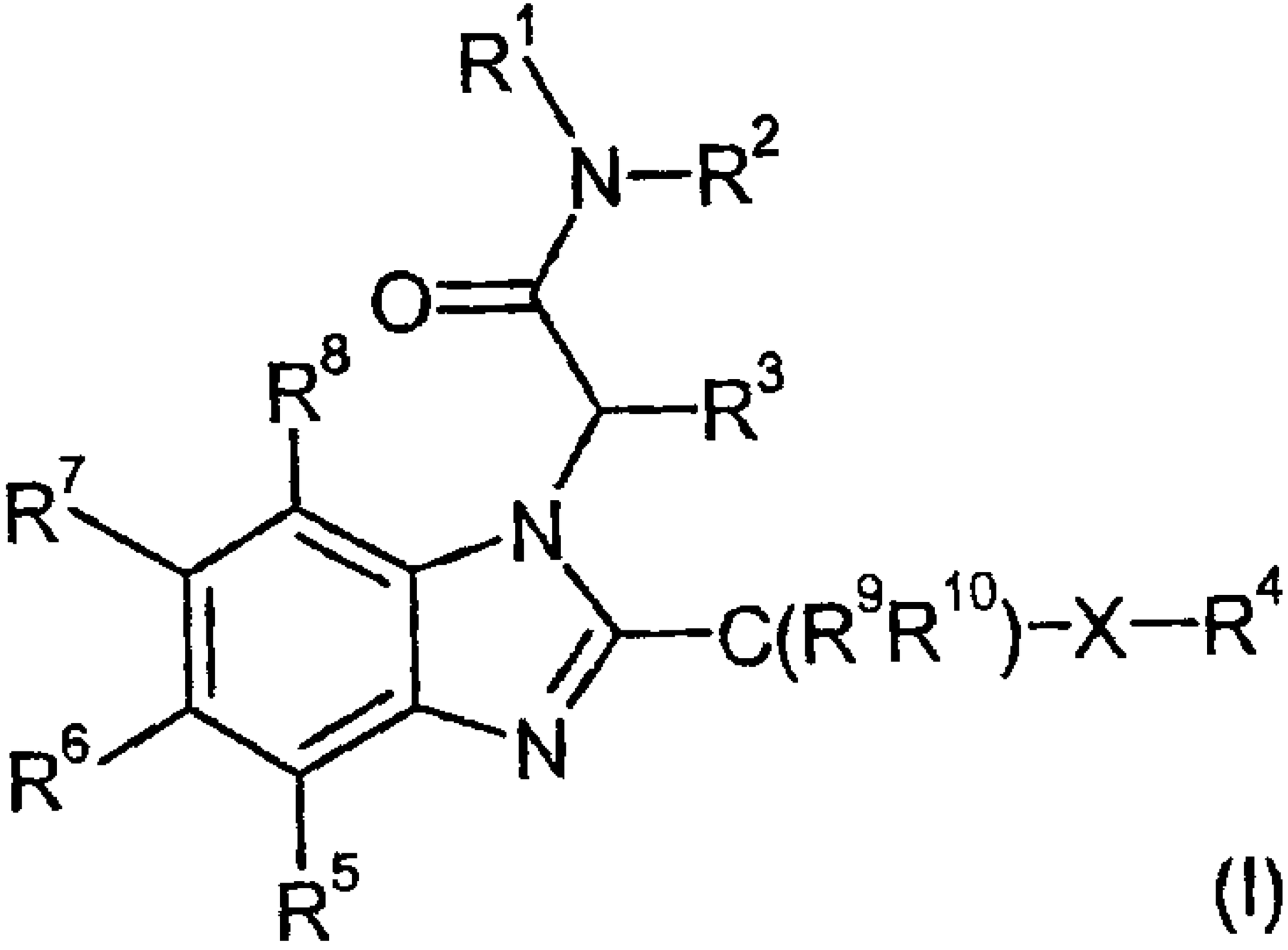
122. A use of the compound defined in any one of claims 1 - 118 for the therapeutic and/or prophylactic treatment of a disease modulated by FXR agonists.

123. A use of the compound defined in any one of claims 1 - 118 for the therapeutic and/or prophylactic treatment of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease.

124. A use of the compound defined in any one of claims 1 - 118 for the preparation of a medicament for the therapeutic and/or prophylactic treatment of disease modulated by FXR agonists.

125. A use of the compound defined in any one of claims 1 - 118 for the preparation of a medicament for the therapeutic and/or prophylactic treatment of increased lipid and cholesterol levels, high LDL-cholesterol, high triglycerides, low HDL-cholesterol, dyslipidemia, atherosclerotic disease, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, cholesterol gallstone disease, cholestasis/fibrosis of the liver, diseases of cholesterol absorption, cancer, osteoporosis, peripheral occlusive disease, ischemic stroke, Parkinson's disease and/or Alzheimer's disease.

126. The use according to claim 123 or 125, wherein the cancer is gastrointestinal cancer.



(I)