1-PHENYL-2-HETEROARYL-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES, THEIR USE TO PREPARE DRUGS FOR TREATMENT OF IMMUNOLOGICAL DISEASES

The invention concerns new benzimidazole derivatives, their production and use for preparation of drugs for treatment and prevention of diseases that are associated with microglia activation and T-cell mediated immunological diseases, as well as pharmaceutical preparations that contain the new benzimidazole derivatives.

The immune system includes a number of cells and tissue complexes that mostly communicate with each other via soluble factors. It is known that many immunological diseases are triggered by an imbalance of soluble immune factors, for example, the cytokines (Mosmann and Coffmann, Ann. Rev. Immunol. 7: 145-173 (1989 Street and Mosmann, FASEB J. 5: 171-177 (1991); Lucey et al., Clin. Microbiol. Rev. 4: 532-562 (1996); Powrie and Coffman, Trends Pharmacol. Sci 14: 164-168 (1993); Singh et al., Immunolog. Res., 20: 164-168 (1999)). For example, there are a number of indicates of a role of interferon gamma and interleukin 12 in the pathogenesis of autoimmune diseases. Diseases that are characterized by T-cell-mediated inflammatory reaction, like multiple sclerosis, diabetes, chronic inflammatory intestinal diseases (inflammatory bowel diseases), can be mentioned, in particular. The cytokine interleukin 12 (IL 12) is produced by phagocyte cells, like macrophages/monocytes, dendrites, B-cells and other antigen-presenting cells (APC), and influences both the function of natural killer cells (NK cells) and that of T-lymphocytes. IL 12 can induce production of interferon gamma (IFNγ) in both cell types. T-lymphocytes can be roughly divided into two categories that are characterized by expression of specific surface antigens (CD4 and CD8): CD4 positive T-cells (helper T-cells) and CD8 positive T-cells (cytotoxic T-cells). The CD4 cells can again be divided to T-helper cells 1 (Th1) and T-helper cells (Th2). Th1-mediated immune responses, in particular, are associated with numerous immune diseases, especially autoimmune diseases, like: type I insulin-dependent diabetes mellitus (IDDM), multiple sclerosis, allergic contact eczema, psoriasis, rheumatoid arthritis, chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis),

lupus diseases and other collagenoses, as well as acute rejection reactions in allotransplantation (host-versus-graft - allotransplant rejection, graft-versus-host disease).

It is known in interleukin 12 that it plays a critical role in regulation of the Th1 response. Interleukin 12 in the cells induces production of mainly IL-2, IFNγ, TNFα and TNFβ (mOssman and Sad, Immunol. Today 17: 138-146 (1996); Gately et al., Annu. Rev. Immunol. 16: 495-521 (1998)). IFNγ, in particular, is a potent mediation of IL-12 action. Overproduction of interferon gamma, for example, can be responsible for MHC II (major histocompatibilitiy complex)-associated autoimmune diseases. There is also sufficient evidence concerning a pathological role of interferon gamma in allergic diseases, as well as sarcoidosis and psoriasis (Billiau A., Advantageous. Immunol., 62: 61-130 (1996); Basham et al. J. Immunol. 130: 1492-1494 (1993); Hu et al., Immunology, 98: 379-385 (1999); Seery JP., Arthritis Res., 2: 437-440 (2000)). In addition, IL-12 and IL-12/IL-18-induced IFNγ from NK-cells participate significantly in the pathomechanism of non-T-cell mediated inflammatory reactions (for example, toxic shock syndrome, endotoxinemia, sepsis and septic shock, ARDS, first dose response in antibody therapy, for example, OKT3 administration in allotransplantation) (Kum et al., Infect Immun. 69: 7544-7549 (2001); Arad et al., J Leukoc. Biol. 69: 921-927 (2001); Hultgren et al., Arthritis Res. 3: 41-47 (2001), Arndt et al., Am. J. Respir. Cell. Mol. Biol. 22: 708-713 (2000); Grohmann et al., J. Immunol. 164: 4197-4203 (2000); Muraille et al., Int. Immunol. 11: 1403-1410 (1999)). IL-12 also plays a role in inflammation with now unclear pathomechanisms (for example, eclampsia) (Hayakawa et al., J. Reprod. Immunol. 47: 121-138 (2000); Daniel et al., Am. J. Reprod. Immunol. 39: 376-380 (1998)).

In addition to interleukin 12 and INFγ, other cytokines are also attributed a role in the pathogenesis of immune diseases and systemic inflammatory reactions, like TNFα. TNFα plays a significant pathological role in infectious diseases (like sepsis, toxic shock syndrome (Tracey et al., Nature 330: 662-664 (1987); Basger et al., Circ. Shock, 27: 51-61 (1989); Hinshaw et al., Circ. Shock, 30: 279-292 (1990); Waage A., Lancet, 351: 603 (1998); Cohen et al., Lancet, 351: 1731 (1998)), but also numerous other immune-mediated diseases.

Corticosteroids, whose side effects, in particular, during long-term treatment often lead to interruption of treatment, are often used to treat IL 12-mediated diseases and to reduce the acute symptom of these diseases.

Activation of microglia represents a central step in the inflammatory event of almost all degenerative diseases of the central nervous system. The microglia can remain in the activated state over a longer period, in which they produce and secrete different inflammation factors, for example, reactive oxygen/nitrogen intermediates, proteases, cytokines, complement factors and neurotoxins. These again cause neuronal dysfunction and degeneration. Activation of microglia can also occur from different stimuli, like αβ-peptide (β-amyloid, Araujo, D. M. and Cotman, C. M., Brain Res. 569: 141-145 (1992)), prion protein, cytokines or cell fragments (Combs, C. K. et al., J. Neurosci. 19: 928-939 (1999); Wood, P. L., Neuroinflammation: Mechanisms and Management, Humana Press (1998).

Benzimidazoles, which, after stimulation with the αβ-peptide, inhibit activation with of microglia, are described in WO 01/51473. It is also known from this that benzimidazoles that inhibit activation of microglia are used to treat neuroinflammatory diseases, like AIDS dementia, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Down's Syndrome, diffuse Lewy Body diseases, Huntington's disease, leukencephalopathy, multiple sclerosis, Parkinson's disease, Pick's disease, Alzheimer's disease, stroke, temporary lobe epilepsy and tumors.

EP 0 104 727 A1 describes benzimidazole derivatives that are not substituted in the 1-position and have an alkyl group in the 2-position. Substituents on the benzene ring of the derivatives include pyridyloxy-, pyridylalkyl-, pryidylalkyloxy- and pryidyloxyalkanediyl-residues.

Benzimidazole derivatives that can be substituted in the 1-position with an alkanediylamido group, in the 2-position with a substituted phenyl or heteroaryl group and on the anellated benzene ring with at least a substituted alkoxy, alkylamino, alkylsulfonyl and alkyl sulfoxide group are also described in WO 01/21634 A1. It is stated that these substances can be used for a variety of possible indications as an active ingredient in drug preparations.

Substituted benzimidazoles having a phenyl or naphthyl group in the 1-position and a phenyl or heterocyclic group in the 2-position are mentioned in US-A-5,552,426. The anellated benzene ring of the benzimidazoles is preferably substituted with an alkoxy or aminoalkoxy group. Such compounds are attributed efficacy against diseases based on neurotoxicity associated with a β-amyloid peptide.

Different inflammation-inhibiting and arteriosclerosis-reducing agents are described in WO 97/12613 A1. For example, benzimidazoles that are substituted in position 1 with a phenyl or substituted phenyl group and in position 2 with an alkoxy group are mentioned as active ingredients. Substituents on the benzene ring of the active compounds can be alkyl, nitro, halo, alkoxy, amino, ester, amide, alkanediylalkoxy and alkanediylamino groups.

Benzimidazole derivatives having substituted aryl groups in position 1 and mono-, di-substituted or unsubstituted amino groups in position 2 are mentioned in EP 0 520 200 A2. The benzene ring in the benzimidazole framework can be substituted with halogen, trifluoromethyl and/or cyano. These compounds are used for treatment of diseases connected with increased activation of Ca channels.

Benzimidazole rings that are used for treatment of cystitis are also mentioned in WO 97/33873 A1. These compounds can have phenyl, naphthyl and unsaturated heterocyclic groups in position 1. The derivatives can be substituted in position 2 with alkoxy, phenylalkoxy, naphthylalkoxy, heterocyclo-alkoxy and unsaturated heterocyclo-alkoxy groups. The benzene ring of the basic framework of the derivatives can be substituted with nitro, alkanoyl, amino, alkyl, alkoxy, cycloalkyl, heterocyclo, unsaturated heterocyclo, halo, alkylthio, hydroxyalkylidenyl, hydroxyalkylidenylamino, aminoalkylidenyl, aminoalkoxy, hydroxyalkyl, heterocyclo-alkoxy, aminoalkylidenyl or trifluoromethyl groups.

Condensed 5-membered heterocycles, for example, substituted benzimidazole derivatives, are mentioned in EP 0 531 883 A1, in which these compounds, according to the general description of the compounds, are substituted in position 1, preferably with a substituted alkyl group, and in position 2 with an O-alkanediyl, S-alkanediyl, NH-alkanediyl, N(alkyl)-alkanediyl, SO-

alkanediyl or SO_2-alkanediyl group. The described compounds are supposed to exhibit anti-thrombic activity.

For possible therapy of neuroinflammation, non-steroidal inflammation inhibitors (Coxx II inhibitors) have thus far been described (McGeer, P. L., Roger, Neurology, 42, 447-449 (1992), Rogers J., Kirby, L. C., Hempleman, S. R., Berry, D. L., McGeer, P. L., Kaszniak, A. W., Zalinski, J., Cofield, M., Mansukhani, L., Wilson, P., Kogan, F., *Neurology*, 43, 1609-1611 (1993), Andersen, K., Launer, L. J., Ott, A., Hoes, A. W., Breteler, M. M. B., Hofman, A., *Neurology*, 45, 1441-1445 (1995), Breitner, J. C. S., Gau, B. A., Welsh, K. A., Plassman, B. L., McDonald, W. M., Helms, M. J., Anthony, J. C., *Neurology*, 44, 227-232 (1994), The Canadian Study of Health and Aging, *Neurology*, 44, 2073-2079 (1994)), cytokine-modulated (McGeer, P. L., McGeer, E. G., *Brain Res. Rev.*, 21,: 1995-218 (1995), McGeer, E. G., McGeer, P. L., *CNS Drugs*, 7, 214-228 (1997), Barone, F. C. and Feuerstein, G. Z., *J. Cerebral Blood Flow and Metabolism*, 19, 819-834 (1999)) and complement-cascade inhibitors (Chen, S., Frederickson, R. C. A., and Brunden, K. R., *Neurobiol. Aging* (1996), McGeer, E. G., McGeer, P. L., *Drugs*, 55: 739-746 (1998)).

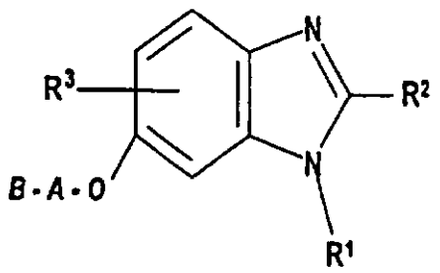
The compounds known for treatment of immunological diseases, like steroids, often act on several factors in the immune system and, in so doing, trigger numerous side effects. The task is therefore to furnish substances that inhibit cytokine activity based on their microglia activity, without triggering serious toxic side effects.

The problem is solved by new benzimidazole derivatives according to Claim 1, and also by the use of a measurement benzimidazole derivative according to the invention to prepare a drug for interruption of IL 12 and INFγ production in cells of monocytes origin or T-cells and NK-cells.

Because of their capability of interrupting production of IL 12 and TNFα in monocytes/macrophages/dendrites and IFNγ production in T-cells and NK-cells, microglia inhibitors are suitable for treatment of numerous diseases that are triggered by increased production of cytokines, like TNFα,β, IFNγ, IL-2 and IL12, like inflammatory diseases not based on neuroinflammation, autoimmune diseases, allergic and infectious diseases, toxin-

induced inflammations, pharmacologically triggered inflammation reactions, as well as pathophysiologically relevant inflammation reactions of now unclear origin.

The benzimidazole derivatives have the following general structure formula I:



(I)

in which:

R^1 denotes a phenyl group, optionally substituted with up to three of the following substituents, independently of each other:

F, CI, Br, J

OH, OR^4, $OCOR^4$,

SR^4, SOR^4, SO_2R^4,

R^4

NH_2, NHR^4, NR^4R^4

or two adjacent substituents on R^1 together form a -O-CH_2-O-, -O-CH_2- CH_2-O- or -CH_2- group,

R^2 denotes a monocyclic or bicyclic 5 - 10-membered heteroaryl group with 1 - 2 hetero atoms, chosen from N, S, and O, optionally substituted with up to two of the following substituents, independently of each other:

F, CI, Br, J

OH, OR^4, $OCOR^4$

COR^4,

SR^4, SOR^4, SO2R^4,

R^4

or two adjacent substituents on R^2 together form a -O-CH_2-O-, -O-CH_2- CH_2-O- or -CH_2-CH_2-CH_2- group,

R^3 denotes H, OH or O-C_{1-6}-alkyl,

R^4 and $R^{4'}$, independently of each other, denote C_{1-4}-perfluoroalkyl or C_{1-6}-alkyl,

A denotes a C_{2-6}-alkylene group, optionally substituted with = O, OH, O-C_{1-3}-alkyl, NH_2, NH-C_{1-3}-alkyl, N(C_{1-3}-alkyl)$_2$, and N(C_{1-3}-alkyl)(C_{1-3}-alkanoyl),

B denotes COOH, $CONH_2$, $CONHNH_2$, $CONHR^5$, $CONR^5R^{5'}$, each bonded to a carbon atom of group A,

R^5 and $R^{5'}$, independently of each other, each denote a group chosen from the group comprising C_{1-6}-alky, C_{2-6}-alkenyl, C_{2-6}-alkynyl, in which a C-atom can be replaced with O, S, SO, SO_2, NH, N-C_{1-3}-alkyl or N-C_{1-3}-alkanoyl, also (C_{0-3}-alkanediyl-C_{3-7}-cycloalkyl), in which one ring member in a five-membered cycloalkyl ring can be a ring N or ring O and, in a six- or seven-membered cycloalkyl ring, one or two ring elements can be ring N and/or ring O atoms, in which the ring N atoms can optionally be substituted with C_{1-3}-alkyl or C_{1-3}-alkanoyl, and also (C_{0-3}-alkanediyl-phenyl) and (C_{0-3}-alkanediyl-heteroaryl), in which the heteroaryl group is five- or six-membered and contains one or two heteroatoms, chosen from the group comprising N, S and O, in which all the aforementioned alkyl and cycloalkyl groups can optionally be substituted with two groups, chosen from the group comprising CF_3, C_2F_5, OH, O-C_{1-3}-alkyl, NH_2, NH-C_{1-3}-alkyl, NH-C_{1-3}-alkanoyl, N(C_{1-3}-alkyl)$_2$, N(C_{1-3}-alkyl)(C_{1-3}-alkanoyl), COOH, $CONH_2$ and COO-C_{1-3}-alkyl, and all the aforementioned phenyl and heteroaryl groups can optionally be substituted with up to two groups, chosen from the group comprising F, Cl, Br, CH_3, C_2H_5, OH, OCH_3, OC_2H_5, NO_2 N(CH_3)$_2$, CF_3, C_2F_5 and SO_2NH_2, or R^5 and $R^{5'}$, together with the N-atom, can form a five- to seven-membered heterocyclic ring that can contain another N- or O- or S-atom and can be substituted with C_{1-4}-alkyl (C_{0-2}-alkanediyl-C_{1-4}-alkoxy), C_{1-4}-alkoxycarbonyl, aminocarbonyl or phenyl

as well as their optic or geometric isomers or tautomeric forms or pharmaceutically applicable salts,
in which the following compounds are ruled out:

6-[[1-phenyl-2-(pyridine-4-yl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid,

6-[[1-phenyl-2-(benzothien-2-yl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid.

Compounds are preferred, in which

R^1 is a phenyl group, optionally substituted with up to two of the following substituents, independently of each other:
F, CI,
OH, OR^4, $OCOR^4$
SR^4,
R^4 or
two adjacent substituents on R^1 together form a -O-CH_2-O- or CH_2- CH_2-CH_2- group,

Benzimidazole derivatives, in which

R^2 is a monocyclic 5 - 6-membered heteroaryl group with 1 - 2 hetero atoms, chosen from the group comprising N, S, and O, optionally substituted with up to two of the following substituents, independently of each other:
F, CI
OR^4, $OCOR^4$
SR^4, SOR^4, SO_2R^4,
R^4 or
two adjacent substituents on R^2 form a -O-CH_2-O- or CH_2- CH_2-CH_2- group are preferred.

Benzimidazole derivatives, in which

R^3 is H, are also preferred.

Benzimidazole derivatives, in which

R^4 and $R^{4'}$, independently of each other, are C_{1-2}-perfluoroalkyl, C_{1-4}-alkyl, are also preferred.

Benzimidazole derivatives, in which

R^5 and $R^{5'}$, independently of each other, are C_{1-6}-alky, in which a carbon atom can be replaced with O, S, SO, SO_2, C_{3-5}-cycloalkyl-C_{0-3}-alkylene, in which one ring member in a 5-membered ring can be an N or an O, the ring nitrogen optionally being substituted with C_{1-3}-alkyl or C_{1-3}-alkanoyl,

C_{0-2}-alkylene (5-6-membered heteroaryl with 1-2 heteroatoms from N, S and O)

in which all the aforementioned alkyl and cycloalkyl groups scan be substituted with CF_3, OH, NH_2, NH-C_{1-3}-alkyl, NH-C_{1-3}-alkanoyl, N(C_{1-3}-alkyl)$_2$, N(C_{1-3}-alkyl)(C_{1-3}-alkanoyl), COOH, $CONH_2$, and all the aforementioned heteroaryl groups can be substituted with one or two substituents from the group consisting of F, Cl, CH_3, C_2H_5, OCH_3, OC_2H_5, CF_3, C_2F_5,

or R^5 and $R^{5'}$, together with the nitrogen atom, can form a 5-7-membered heterocycle that can contain an additional oxygen, nitrogen
or sulfur atom and can be substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy-C_{0-2}-alkyl, are also preferred.

Benzimidazole derivatives, in which

A is a straight-chain C_{3-6}-alkylene, are preferred.

Benzimidazole derivatives, in which

B is COOH or $CONH_2$,
each bonded to a carbon atom of group A, are preferred.

The following benzimidazoles are particularly preferred:
6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
4-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
5-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
4-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
5-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
4-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
6-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
6-[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
5-[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
6-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
5-[[1-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
4-[[1-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
6-[[1-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
N-(3-methoxypropyl)-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide
6-[[1-4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]-1-morpholin-1-ylhexan-1-one
N-methyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide
N,N-dimethyl-6- [[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide
6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide
N-cyclopropyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide

N-methyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide
6-[[1-(4-methylphenyl)-2-1*H*-benzimidazol-6-yl]oxy]-1-[thiazolidin-3-yl)hexan-1-one
N-(2-methoxyethyl)-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide
N,N-dimethyl-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide
5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide
6-[[1-(4-methylphenyl)-2-(2-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid.

The present invention includes the physiologically compatible salts of the aforementioned compounds, especially the acid salts of nitrogen bases of the benzimidazole derivatives according to the invention, and also the salts of carboxylic acids of the derivatives according to the invention with bases.

The benzimidazole derivatives according to the invention can have one or more asymmetric centers, so that the compounds can occur in several isomeric forms. The compounds of formula I can also occur as tautomers, stereo isomers or geometric isomers. The invention also includes all possible isomers, like E- and Z-isomers, S- and R-enantiomers, diastereomers, racemates and mixtures of these, including the tautomeric compounds. All these isomeric compounds, even if not expressly mentioned, are a component of the present invention.

The isomer mixtures can be separated according to the usual methods, like crystallization, chromatography or salt formation, into the enantiomers or E/Z-isomers.

The heteroaryl groups contained in the benzimidazole compounds according to the invention are constructed from five or ten framework atoms and can contain one or two hetero atoms. Hetero atoms are oxygen (O), nitrogen (N) and sulfur (S).

Examples of monocyclic heteroaryl groups are pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl.

Examples of a bicycle heteroaryl group are indolyl, isoindolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, cinnolinyl, quinoxalinyl, naphthyridinyl. If the heteroaryl group is part of R^1, bonding to N of the benzimidazole occurs via a carbon atom.

Heteroaryl groups can be bonded arbitrarily to the benzimidazole basic framework or another group, for example, as 2-, 3- or 4-pyridinyl, as 2- or 3-thienyl or as 1-imidazolyl.

Alkyl groups can be straight-chain or branched. Examples of alkyl groups are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, *tert*-pentyl, *neo*-pentyl, *n*-hexyl, *sec*-hexyl.

Perfluorinated alkyls are preferably CF_3 and C_2F_5.

Cycloalkyl groups are understood to mean preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The following can be mentioned of examples of saturated heterocyclic rings or as cycloalkyl with one or more hetero atoms: piperidine, pyrrolidine, tertrahydrofuran, morpholine, piperazine, hexahydroazepine, as well as 2,6-dimethylmorpholine, N-phenylpiperazine, 2-methoxymethyl-pyrrolidine, piperidine-4-carbonamide, thiomorpholine, thiazolidine, in which coupling can occur via optionally present ring N-atoms.

The following can be mentioned as straight-chain or branched alkylene for A with up to six C-atoms: ethylene, propylene, butylene, pentylene, hexylene, and also 1-methylethylene, 1-ethylene, 1-methylpropylene, 2-methylpropylene, 1-methylbutylene, 2-methylbutylene, 1-ethylbutylene, 2-ethylbutylene, 1-methylpentylene, 2-methylpentylene, 3-methylpentylene, as well as similar compounds.

A can be disubstituted, preferably monosubstituted, with OH, NH_2, NH-C_{1-3}-alkyl or NH-C_{1-3}-alkanoyl.

The physiologically compatible acid salts of nitrogen basis of the benzimidazole derivatives according to the invention can be formed with inorganic and organic acids, for example, with oxalic acid, lactic acid, citric acid, fumaric acid, acetic acid, maleic acid, tartaric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, p-toluenesulfonic acid and methanesulfonic acid.

The inorganic or organic bases that are known for formation of physiologically compatible salts are also suitable for salt formation of acid groups, especially carboxylic acid groups, like alkali hydroxides, especially sodium and potassium hydroxide, alkaline earth hydroxides, like calcium hydroxide, also ammonia, as well as amines, like ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and tris-(hydroxymethyl)-methylamine.

The compounds of formula I inhibit activation of microglia and production of interleukin 12 (IL 12) and interferon γ (IFNγ). The invention therefore also concerns the use of a compound of formula I, as well as its optical or geometric isomers or their tautomers or physiologically compatible salts, for preparation of a drug for treatment or prevention of a disease associated with microglia activation, especially a disease triggered by overproduction of IL 12 and IFNγ and for induction of interleukin 10 (IL-10).

In a preferred variant, the compounds according to the invention find application for treatment of T-cell-mediated, especially Th1-cell-mediated immunological disease, and non-T-cell-mediated inflammatory reactions. In particular, the compounds according to the invention are used to prepare a drug for interruption of IL 12 and INFγ production in cells of monocytes origin or T-cells and NK-cells. Based on their capability of interrupting production of IL 12 and TNFα in monocytes/macrophages and INFγ production in T-cells, the compounds according to the invention are suitable for treatment of numerous diseases that are triggered by increased production of cytokines, for example, TNFα,β, IFNγ, IL 2 and IL 12, like inflammatory diseases that are not based on neuroinflammation, autoimmune diseases, allergic and infectious diseases, toxin-induced inflammations, pharmacologically triggered inflammatory reactions, as well as pathophysiologically relevant inflammatory reactions of now unclear origin.

Examples of inflammatory and autoimmune diseases are: chronic inflammatory intestinal diseases (intestinal bowel disease, Crohn's disease, ulcerative colitis), arthritis, allergic contact eczema, psoriasis, pemphigus, asthma, multiple sclerosis, diabetes, type-I insulin-dependent diabetes mellitus, rheumatoid arthritis, lupus diseases and other collagenoses, Graves' disease, Hashimoto's disease, graft-versus-host disease and transplant rejection.

Examples of allergic, infectious and toxin-triggered and ischemia-triggered diseases are: sarcoidosis, asthma, hypersensitive pneumonitis, sepsis, septic shock, endotoxin shock, toxic shock syndrome, toxic liver failure, ARDS (acute respiratory distress syndrome), eclampsia, cachexia, acute virus infections (for example, mononucleosis, fulminating hepatitis), organ damage following reperfusion.

An example of a pharmacologically triggered inflammation with pathophysiological relevance is the first dose response after administration of anti-T-cell antibodies, like OKT3.

An example of systematic inflammatory reactions of now unclear origin is eclampsia.

Examples of neuroinflammatory diseases associated with microglia activation are AIDS dementia, amyotrophic lateral sclerosis, Creuzfeldt-Jakob disease, Down's Syndrome, diffuse Lewy Body disease, Huntington's disease, leukencephalopathy, multiple sclerosis, Parkinson's disease, Pick's disease, Alzheimer's disease, stroke, temporary lobe epilepsy and tumors. The invention therefore also concerns the use of the mentioned benzimidazole derivatives for treatment of these diseases and for prevention of these diseases.

Appropriate microglia inhibitors according to the invention are compounds that achieve inhibition of microglia activity of at least 20% and inhibition of cytokine activity of at least 20%, when stimulated with the Aβ-peptide. The biological properties of the microglia inhibitors can be demonstrated according to methods known to one skilled in the art, for example, with the investigation methods described below and in WO 01/51473.

It is described in example 29 how inhibition of microglia activation can be measured. The microglia can then be activated by different stimuli, for example, with Aβ-peptide (β-amyloid, Araujo, D. M., and Cotman, C. M., *Brain Res.*, 569, 141-145 (1992), with prion protein, cytokines or cell fragments [Combs, C. K., et al., *J. Neurosci.*, 19, 928-939 (1999), Wood, P. L., Neuroinflammation: Mechanisms and Management, *Human Press* (1998)].

Stimulation with the Aβ-peptide corresponds to the pathophysiological situation in Alzheimer's disease. In this test, the substances according to the invention, during stimulation with the Aβ-peptide, exhibited inhibition of microglia activation. Inhibition of microglia activation with the substances according to the invention leads to a strong reduction of cytokine production and secretion, for example, of IL1β and TNFα (measured by ELISA and mRNA expression analysis), and to reduce secretion of reactive oxygen/nitrogen intermediates. Several inflammatory factors are also equally inhibited.

The *in vivo* efficacy of the substances according to the invention was demonstrated in an MCAO model in rats. This model simulates the state of a stroke. The substances according to the invention reduce microglia activation that occurs in acute brain lesions in the brains of the animals.

Inhibition of cytokine production is represented, for example, by measuring TNFα and interleukin 12 in lipopolysaccharide (LPS)-stimulated THP-1 cells.

The compounds according to the invention inhibit TNFα and interleukin 12 production in lipopolysaccharide (LPS)-stimulated THP-1 cells.

To demonstrate the effect of the substances on T-cell activation, for example, measurement of INFγ secretion is used. The compounds according to the invention inhibition INFγ production of peripheral mononuclear blood cells.

The invention also concerns pharmaceutical agents that contain one or more compounds according to the invention of general formula I, as well as one or more carriers. The

pharmaceutical agents or compositions of the invention are prepared with ordinary solid or liquid vehicles or diluents and ordinary pharmaceutical and technical inactive ingredients according to the desired type of application with an appropriate dose in known fashion. Preferred preparations consist of a form of administration for oral, enteral or parenteral, for example, *i.p.* (intraperitoneal), *i.v.* (intravenous), *i.m.* (intramuscular) or percutaneous administration. Such forms of administration include tablets, film tablets, coated tablets, pills, capsules, powders, creams, salves, lotions, liquids, like syrups, gels, injectable liquids, for example, or *i.p., i.v., i.m.* or percutaneous injection, etc. Depot forms, like implantable preparations, as well as suppositories, are also suitable. The individual preparations release to the body the derivatives according to the invention according to their type gradually or the entire amount in a short time.

Capsules, pills, tablets, coated tablets and liquids or other known oral forms of administration can be used as pharmaceutical preparations for oral administration. In this case, the drugs are formulated so that they liberate the active ingredients either in a short time and release them to the body, or have a depot effect, so that a longer persisting, slow supply of active ingredient to the body is achieved. In addition to the at least one benzimidazole derivative, the dose units can contain one or more pharmaceutically compatible carriers, for example, substances for adjustment of the rheology of the drug, surfactants, solubilizers, microcapsules, microparticles, granulates, diluents, binders, like starch, sugar, sorbitol, and gelatins, as well as fillers, like silica and talc, lubricants, dyes, fragrances and other substances.

Corresponding tablets can be obtained by mixing the active ingredient with known inactive ingredients, for example, inert diluents, like dextrose, sugar, sorbitol, manitol, polyvinylpyrrolidone, disintegrants, like corn starch or alginic acid, binders, like starch or gelatin, lubricants, like carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can consist of several layers.

Coated tablets can be produced by coating of cores produced similarly to tablets with agents ordinarily used in coatings, for example, polyvinylpyrrolidone or shellac, gum Arabic talc, titanium oxide or sugar. The coating shell can also consist of several layers, in which the inactive ingredients mentioned above under tablets can be used.

Capsules containing active ingredients can be prepared, for example, by mixing the active ingredient with an inert carrier, like lactose or sorbitol, and encapsulating it in gelatin capsules.

The benzimidazole derivatives according to the invention can also be formulated in the form of a solution that is intended for oral administration and contains, in addition to the active benzimidazole derivative, a pharmaceutically compatible oil and/or a pharmaceutically compatible lipophilic, surfactant substance and/or a pharmaceutically compatible hydrophilic, surfactant substance and/or a pharmaceutically compatible water-miscible solvent as ingredients.

In order to achieve better bioavailability of the active ingredients according to the invention, the compounds can also be formulated as cyclodextrin clathrate. For this purpose, the compounds are converted with α-, β- or γ-cyclodextrin or their derivatives.

If creams, salves, lotions and externally applicable liquids are to be used, they must be devised so that the compounds according to the invention are supplied to the body in sufficient amount. These forms of administration contain inactive ingredients, for example, substances for adjustment of the rheology of the drug, surfactants, preservatives, solubilizers, diluents, substances to increase permeation capability for the benzimidazole derivatives according to the invention through the skin, dyes, fragrances and skin protective agents, like conditioners and moisture regulators. Other active ingredients can also be contained, together with the compounds according to the invention, in the drug [*Ullmann's Encyclopedia of Industrial Chemistry*, Volume 4 (1953), pages 1 - 39; *J. Pharm. Sci.*, 52, 918 ff. (1963); H. V. Czetsch-Lindenwald, *Excipients for Pharmacy and Allied Fields; Pharm Ind.*, 2, 72 ff. (1961); Dr. H. P. Fielder, *Lexicon of Excipients for Pharmacy, Cosmetics and Allied Fields*, Cantor AG, Aulendorf/Württ, 1971].

The substances according to the invention can also be used in appropriate solutions, like physiological saline, as infusion or injection solutions. For parenteral administration, the active ingredients can be dissolved or suspended in a physiologically compatible diluent. Oil solutions,

like solutions in sesame oil, castor oil and cottonseed oil, are particularly suitable as diluents. To increase the solubility, solubilizers, like benzyl benzoate or benzyl alcohol, can be added.

For formulation of an injectable preparation, any liquid vehicle can be used, in which the compounds according to the invention are dissolved or emulsified. These liquids often contain substances for regulation of viscosity, surfactants, preservatives, solubilizers, diluents and other additives, with which the solution is made isotonic. Other active ingredients can also be administered with the benzimidazole derivatives.

It is also possible to incorporate the substances according to the invention in a transdermal system and to administer them transdermally with it. For this purpose, the benzimidazole derivatives are used in the form of a depot injection or an implant preparation, for example, subcutaneously. Such preparations can be formulated, so that delayed active ingredient release is made possible. Known techniques can be used for this purpose, for example, dissolving depots or those operating with a membrane. Implants can contain as inert materials biodegradable polymers or synthetic silicones, for example, silicone rubber. The benzimidazole derivatives can also be incorporated in a plaster for percutaneous administration.

The dosage of the substances of general formula I according to the invention is determined by the treating physician and depends, among other things, on the administered substance, the route of administration, the disease being treated and the severity of the disease. The daily dose is no more than 1000, preferably no more than 100 mg, in which the dose can be administered as a single dose to be administered once, or divided into two or more daily doses.

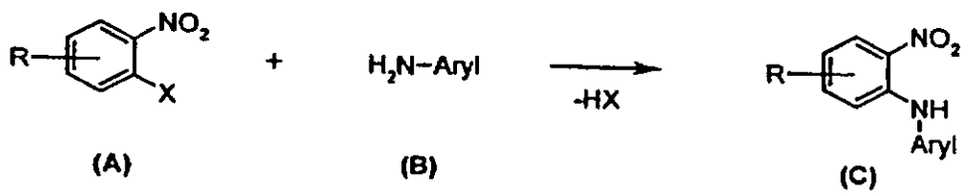
The benzimidazoles of formula I are accessible in different ways according to methods known from the literature.

The following can be mentioned, among others, as possible methods:

1. By reaction of an ortho-leaving group-substituted (preferably halogen-substituted) nitrobenzene derivatives (*A*) with arylamines (*B*), *N*-aryl-2-nitrobenzenes (*C*) can be

produced under various reaction conditions, like heating of the reactants without or with an appropriate inert solvent, like alkylbenzenes. The amine used as reactant can also be used in excess as solvent. The conversions are run both without and with bases (for example, potassium carbonate, sodium hydride). Additional auxiliaries can also find application, for example, copper salts. Examples of the procedure mentioned here can be found in numerous papers, like D. Jerchel, H. Fischer, M. Graft, *Ann. Chem.*, 575, 162 (1952), *CAS*, 53 (2138); R. A. Abramovitch, *Can. J. Chem.*, 38, 2273, 1960).

SCHEME 1

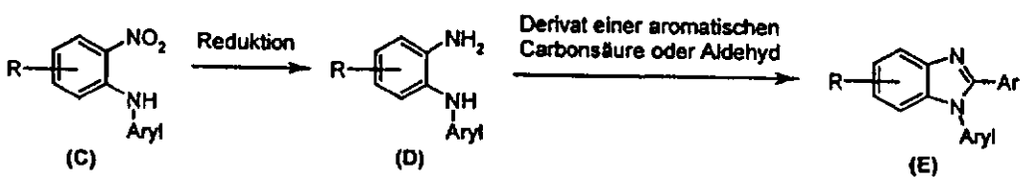


X = leaving group

R = Substituent(s) or H

The so-obtained *N*-arylnitroaniline derivatives (*C*) can be converted in different ways to 1,2-disubstituted benzimidazoles (*E*):

SCHEME 1



Key left to right: Reduction, Derivative of an aromatic carboxylic acid or aldehyde

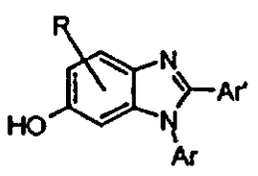
Reduction of the nitro group (*C*) is preferably conducted by hydrogenation in polar solvents, like acetic acid, lower alcohols or acetates, with addition of catalysts, like Raney nickel or palladium on carbon, or by chemical reduction, for example, with tin in

hydrochloric acid, $SnCl_2$ (F. D. Bellamy, *Tet. Lett.* (1984)) or Fe/acetic acid [D. C. Owsily, J. J. Bloomfield, *Synthesis*, 118, 150 (1977)].

The benzimidazoles (*E*) can be obtained from diamines (*D*) by conversion with acid derivatives, like orthoesters, iminoesters, acid anhydrides, aldehydes, or also free carboxylic acids with or without acid catalysis and/or water-removing agents. As an example, preparation of 1,2-diphenylbenzimidazole can be mentioned from benzoic acid and *N*-phenyl-*o*-phenylenediamine, using triphenylphosphine oxide and trifluoromethane sulfonic acid anhydride [J. B. Hendrickson, M. S. Hussoin, *J. Organ. Chem.*, 52, 4137 (1987)].

When aromatic aldehydes are used, nitrobenzene is used as solvent, in order to be able to run the oxidation of the initially formed benzimidazoline in situ. Cyclization to benzimidazoles is also possible by converting aromatic aldehydes as bisulfite adducts with diamines (*D*).

2. Another access to benzimidazoles (*E*) is described by T. Benincori and F. Sannicolo in J. Heterocyclic Chem. 25, 1029 (1988), which permits a broad variation of substitution pattern, both in the two aryl substituents and on the benzene ring of the benzimidazole. It is self-evident to one skilled in the art that these substituents must be compatible with the reagents and reaction conditions employed during the synthesis sequence. The substituents can occasionally be modified later. A hydroxy function is always contained here in the 6-position of benzimidazole (cf. structure *F*).



(F)

3. Finally, it can be mentioned that, in some cases, there is a possibility of direct *N*-arylation of an already prepared benzimidazole, for example, according to M. J. Sansone, M. S. Dwiatek, US Patent 4 933 397, or D. M. T. Chan, K. L. Manoco, R. P. Want, M. P.

Winters, Tet. Lett. 39 (1988) 2933 or A. P. Combs, S. Saubern, M. Rafalski, P.Y.S. Lam, Tet. Lett. 40 (1999) 1623.

It is self-evident to one skilled in the art that the substituents ***R*** must be compatible with the reagents and reaction conditions employed during the synthesis sequence. The substituents can optionally be modified later.

Of the structure element ***B-A-O*** (formula I) is established in protected or unprotected form, because of incompatibility with the reaction conditions during the corresponding benzimidazole synthesis, or only after benzimidazole synthesis is completed for other synthetic reasons, then, depending on the substituents R^3 present on the benzene ring on benzimidazole, different procedures are possible for establishing the ***B-A-O*** structure element (formula I), during which, which is self-evident to one skilled in the art, compatibility of the employed methods with the aryl substituents and the other R^3 groups must be kept in mind.

Some possibilities for establishing the ***B-A-O*** structure element are given below:

Oxygen can be introduced in free-form (for example, ***R*** = OH in formula (***A***)), or also in protected form, for example, as alkyl ether (cf., for example, B. D. Jerchel, H. Fischer, M. Graft, *Ann. Chem.*, 575 162 (1952)) from the outset as a substituent in a benzimidazole synthesis. By alkyl ether cleavage with concentrated hydrobromic acid with the possible aid of solubilizers, like halogenated hydrocarbons, or also boron tribromide in inert solvents, like dichloromethane, the hydroxyl group can be liberated. The hydroxyl function can be converted according to known methods with a terminal group ***B*** (formula I) or a precursor of it containing alkyl halides to ethers, in which the conversion is preferably run with the alkylating agents in polar solvents, like dimethyl formamide, dimethyl sulfoxide, ethers, like tetrahydrofuran, or also lower ketones, like acetone or methyl ethyl ketone, with addition of bases, like alkali and alkaline earth hydroxides, but preferably sodium hydride, or addition of alkali carbonates, like potassium or cesium carbonate, in a temperature range from 0°C to 120°C. In addition, conversion can occur in a two-phase system under phase transfer catalysis, in which the reactants are dissolved in an appropriate inert organic solvent, like haloalkanes, but preferably in dichloromethane. The other

phase is a solid alkali hydroxide, preferably sodium or potassium hydroxide, or also a concentrated aqueous solution of the corresponding hydroxide. Quaternary ammonium salts are used, for example, as phase transfer catalysts. Reactions under phase transfer catalysis are preferably run at room temperature.

For example, a compound of formula *A* (with R = OH) is dissolved in dimethyl formamide and converted with 6-bromohexanoic acid methyl ester with addition of cesium carbonate at temperatures from 0°C to 50°C. Cleavage of the ester by acid or alkaline hydrolysis can be conducted according to methods known to one skilled in the art, for example, with basic catalysts, like alkali or alkaline earth carbonates or hydroxides in water, or an aqueous solution of an alcohol. Aliphatic alcohols, like methanol, ethanol, butanol, etc., are considered as aliphatic alcohols, but preferably methanol. Aqueous solutions of ethers, like tetrahydrofuran, are also used. Lithium, sodium and potassium salts can be mentioned as alkali carbonates and hydroxides. Lithium and sodium salts are preferred. Calcium carbonate, calcium hydroxide and barium carbonate are suitable as alkaline earth carbonates and hydroxides. The conversion generally occurs at -10°C to 70°C, but preferably at 25°C. Ester cleavage, however, can also occur under acid conditions, for example, in aqueous hydrochloric acid, optionally with the aid of a solubilizers, like a lower alcohol, preferably methanol.

A carboxylic acid function can be generated by hydrolysis from a nitrile present in the alkylating reagent or generated subsequently. The alkylation reagent can also contain functional groups, like hydroxyl functions in free or protected form, which, after conversion to leaving groups, like tosylate, mesylate, bromide or iodide, can be exchanged with amino or alkyl groups. The alkylating reagents can also contain functional groups, like halogens or optionally protected amino groups, which can then be further modified.

Depending on the sought substitution, the substituents R^3 are contained from the outset in the synthesis components or are established as required at the appropriate location of the corresponding synthesis sequence or generated from suitable precursors.

The free acid derivatives of formula I or ester precursors can be converted to amide derivatives of formula I according to various methods known in the literature.

The free acid derivatives of formula I can be converted with appropriate amounts of corresponding organic bases under neutralization and salts. For example, when the corresponding acids are dissolved in water, containing stoichiometric amounts of base, after evaporation of the water or addition of a solvent miscible with water, for example, alcohol or acetone, the solid salt is obtained.

The amine salts can be prepared in the usual manner. For this purpose, the corresponding acid is dissolved in an appropriate solvent, like ethanol, acetone, diethyl ether or benzene, and one to five equivalents of the corresponding amine are added to this solution. The salt usually precipitates in solid form or is isolated in the usual way after evaporation of the solvent.

The clathrates with α-, β- or γ-cyclodextrin are obtained similar to the procedure in WO-A-87/05297. β-cyclodextrin is preferably used. Liposomes are prepared according to the method described in *Pharmazie in unserer Zeit*, 11, 98 (1982).

Preparation of some precursors, intermediates and products are described as examples below. If preparation of the starting compounds is not described, the starting compounds are known and commercially available, or the compounds are synthesized in similar fashion to the described methods.

The following procedure is used in preparation of the substances according to the invention:

General work procedure 1:

Reduction of nitro groups

The compound being reduced is dissolved in ethyl acetate, tetrahydrofuran, methanol or ethanol or mixtures of solvents, and hydrogenated at normal pressure on 2-5% (referred to the nitro compound) palladium on carbon (10%). After the end of hydrogen absorption, it is filtered by suction, the residue washed with ethyl acetate or methanol or ethanol and the filtrate

concentrated in vacuum. The crude product is generally converted without additional purification.

General work procedure 2:

Ether cleavage with hydrobromic acid

5 g arylmethyl ether is mixed with 160 mL 48% aqueous HBr and heated for 1-5 hours under reflux. After cooling, it is filtered. The residue is taken up in ethyl acetate and extracted three times with concentrated saturated sodium hydrogen carbonate solution. After drying over sodium sulfate, it is concentrated in vacuum. The residue is purified, if necessary, by crystallization or column chromatography on silica gel.

General work procedure 3:

Alkylation of hydroxybenzimidazole derivatives and phenol derivatives with alkyl halides

A solution of 1.85 mmol of hydroxybenzimidazole derivative in 12 mL *N,N*-dimethylformamide is mixed with 1.85 mmol cesium carbonate and 2.25 mmol alkyl bromide or alkyl iodide. When alkyl bromides are used, 1.85 mmol sodium iodide is optionally added. This is agitated for 12-96 hours, then poured onto water, taken up with ethyl acetate, the organic phase washed four times with water, dried over sodium sulfate and concentrated in vacuum.

As an alternative to this aqueous workup, the reaction mixture can be mixed with dichloromethane, separated from the precipitating salts by filtration and the filtrate concentrated in vacuum.

Regardless of the workup method, the residue is purified by crystallization or column chromatography on silica gel.

General work procedure 4:

Saponification of carboxylic acid alkyl esters

0.77 mmol of carboxylic acid alkyl ester is dissolved in 5 mL methanol and 5 mL tetrahydrofuran and mixed with 5 mL of a 0.5 N aqueous lithium or sodium hydroxide solution. After 2-12 hours of agitation, it is thoroughly concentrated in vacuum, neutralized by addition of aqueous hydrochloric acid and extracted with ethyl acetate. It is dried over sodium sulfate and

concentrated in vacuum. The residue, if necessary, is purified by column chromatography on silica gel.

General work procedure 5:

Cyclization to benzimidazoles with aldehydes

1 mmol of a 1,2-diaminobenzene derivative is dissolved in 3 mL nitrobenzene. 1 mmol of an aryl or heteroaryl aldehyde is added to this. This is heated for 2-6 hours at 150°C and allowed to cool. The residue is directly purified by column chromatography on silica gel without further workup.

General work procedure 6:

Conversion of carboxylic acids to carboxylic acid amides

0.36 mmol of an amine is dissolved in 3 mL toluene and mixed dropwise during cooling in an ice bath with 0.18 mL of a 2M solution of trimethylaluminum in toluene. This is mixed with a solution of 0.33 mmol carboxylic acid methyl ester in 3 mL toluene and agitated for 2-8 hours at 95°C. For workup, water is added after cooling, extraction carried out three times with ethyl acetate, washing of the combined organic phases with saturated sodium chloride solution, drying over sodium sulfate and concentration in vacuum. The residue is purified by column chromatography on silica gel.

Example 1

6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 3-(4-methylphenyl)amino-4-nitrophenol

5.4 g 3-fluoro-4-nitrophenol and 4.8 mL 4-methylaniline were mixed and agitated for 6 hours at 120°C. After cooling, it was taken up in ethyl acetate and water and extracted three times with 1N hydrochloric acid. The combined aqueous phases were extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate, concentrated in vacuum and the residue crystallized.

MS (EI): 244 (molecular ion peak)

b) 6-[3-(4-methylphenyl)amino-4-nitrophenyl]oxyhexanoic acid methyl ester

was obtained by conversion of 3-(4-methylphenyl)amino-4-nitrophenol with 6-bromohexanoic acid methyl ester according to the general work procedure 3.

MS (EI): 372 (molecular ion peak)

c) 6-[[4-amino-3-(4-methylphenyl)amino)phenyl]oxy]hexanoic acid methyl ester

was obtained by conversion of 6-[3-(4-methylphenyl)amino-4-nitrophenyl]oxyhexanoic acid methyl ester according to the general work procedure 1.

MS (EI): 342 (molecular ion peak)

d) 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

was obtained by conversion of 6-[[4-amino-3-(4-methylphenyl)amino)phenyl]oxy]hexanoic acid methyl ester with 3-pyridylcarbaldehyde according to general work procedure 5.

MS (EI): 429 (molecular ion peak)

e) 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was obtained by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work proceure 4.

MS (EI): 415 (molecular ion peak)

Example 2

5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 5-[3-(4-methylphenyl)amino-4-nitrophenyl]oxypentanoic acid methyl ester

was obtained by conversion of 3-(4-methylphenyl)amino-4-nitrophenol with 5-bromopentanoic acid methyl ester according to general work procedure 3.

MS (EI): 358 (molecular ion peak)

b) 5-[[4-amino-3-(4-methylphenyl)amino)phenyl]oxy]pentanoic acid methyl ester

was obtained by conversion of 5-[3-(4-methylphenyl)amino-4-nitrophenyl]oxypentanoic acid methyl ester according to general work procedure 1.

MS (EI): 328 (molecular ion peak)

c) 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

was obtained by conversion of 5-[[4-amino-3-(4-methylphenyl)amino)phenyl]oxy]pentanoic acid methyl ester with 3-pyridylcarbaldehyde according to general work procedure 5.

MS (EI): 415 (molecular ion peak)

d) 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

was obtained by conversion of 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid according to general work procedure 4.

MS (EI): 401 (molecular ion peak)

Example 3

4-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid

a) 4-[3-(4-methylphenyl)amino-4-nitrophenyl]oxybutyric acid methyl ester

was obtained by conversion of 3-(4-methylphenyl)amino-4-nitrophenyl with 4-bromobutyric acid methyl ester according to general work procedure 3.

MS (EI): 344 (molecular ion peak)

b) 4[[4-amino-3-((4-methylphenyl)amino)phenyl]oxy]butyric acid methyl ester

was obtained by conversion of 4-[3-(4-methylphenyl)amino-4-nitrophenyl]oxybutyric acid methyl ester according to general work procedure 1.

MS (EI): 314 (molecular ion peak)

c) 4[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester

was obtained by conversion of 4[[4-amino-3-((4-methylphenyl)amino)phenyl]oxy]butyric acid methyl ester with 3-pyridylcarbaldehyde according to general work procedure 5.

MS (EI): 401 (molecular ion peak)

d) 4[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid

was obtained by conversion of 4[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester according to general work procedure 4.

MS (EI): 387 (molecular ion peak)

Example 4

6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

was obtained by conversion of 6-[[4-amino-3-((4-methylphenyl)amino)-phenyl]oxy]hexanoic methyl ester with 4-pyridylcarbaldehyde according to general work procedure 45.

MS (EI): 429 (molecular ion peak)

b) 6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.

MS (EI): 415 (molecular ion peak)

Example 5

6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

was prepared by conversion of 6-[[4-amino-3-((4-methylphenyl)amino)-phenyl]oxy]hexanoic methyl ester with 3-thienylcarbaldehyde according to general work procedure 5.
MS (EI): 434 (molecular ion peak)

b) 6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.
MS (EI): 420 (molecular ion peak)

Example 6

5-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 5-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester

was prepared by conversion of 5-[[4-amino-3-((4-methylphenyl)phenyl]oxy]pentanoic acid methyl ester with 3-thienylcarbaldehyde according to general work procedure 5.
MS (EI): 420 (molecular ion peak)

b) 5-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

was prepared by conversion of 5-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester according to general work procedure 4.
MS (EI): 406 (molecular ion peak)

Example 7

4-[[1-(4-methylphenyl)-2-(3-thieny)-1*H*-benzimidazol-6-yl]oxy]butyric acid

a) 4-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester

was prepared by conversion 4-[[4-amino-3-((4-methylphenyl)amino)phenyl]oxy]butyric acid methyl ester with 3-thiophenecarbaldehyde according to general work procedure 5.
MS (EI): 406 (molecular ion peak)

b) 4-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
was prepared by conversion 4-[[1-(4-methylphenyl)-2-(3-thienyl)1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester according to general work procedure 4.
MS (EI): 392 (molecular ion peak)

Example 8

5-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 4-methoxy-N^2-phenyl-*o*-phenylenediamine
was obtained by conversion of (5-methoxy-2-nitrophenyl)phenylamine (Kottenhahn et al.; J. Org. Chem.: 28; 1963; 3114, 3118; Banthorpe, Cooper; J. Chem. Soc. B.; 1968; 605) according to general work procedure 1.
^{1}H-NMR ($CDCl_3$): δ = 3.42 ppm (s) (br) (2H); 3.72 s (3H); 533 s (br) (1H); 6.56 dd (J = 10.2 Hz, 1H); 6.76 d (J = 10 Hz, 1H); 6.79 d (J = 2 Hz, 1H); 6.82-6.90 m (3H); 7.25 dd (J = 8.8 Hz, 2H).

b) 6-Methoxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole
was obtained by conversion of 4-methoxy-N^2-phenyl-*o*-phenylenediamine with thiophene-3-carbaldehyde according to general work procedure 5.
MS(EI): 306 (molecular ion peak)

c) 6-Hydroxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole
was obtained by conversion of 6-methoxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole according to general work procedure 2.
MS(EI): 292 (molecular ion peak)

d) 5[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester

was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole with 5-bromopentanoic acid methyl ester according to general work procedure 3.
MS(EI): 406 (molecular ion peak)

e) 5[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid
was obtained by conversion of 5[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester according to general work procedure 4.
MS(EI): 392 (molecular ion peak)

Example 9

4-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxybutyric acid

a) 4-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester
was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole with 4-bromobutyric acid methyl ester according to general work procedure 3.
MS(EI): 392 (molecular ion peak)

b) 4-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid
was obtained by conversion of 4-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester according to general work procedure 4.
MS(EI): 378 (molecular ion peak)

Example 10

6-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxyhexanoic acid

a) 6-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester
was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-thienyl)-1*H*-benzimidazole with 6-bromohexanoic acid methyl ester according to general work procedure 3.
MS(EI): 420 (molecular ion peak)

b) 6-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was obtained by conversion of 6-[[1-phenyl-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.
MS(EI): 406 (molecular ion peak)

Example 11

6-[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxyhexanoic acid

a) (5-chloro-2-nitrophenyl)-(4-fluorophenyl)amine

50 g 1 chloro-3,4-dinitrobenzene in 250 mL ethanol was mixed with 50 mL 4-fluoroaniline and agitated for 35 hours at 60°C. After concentration to half-volume, it was divided between water and dichloromethane. After washing of the organic phase with 1N aqueous HCl, it was dried over sodium sulfate, filtered and concentrated. After chromatography in silica gel, 62.33 g (5-chloro-2-nitrophenyl)-(4-fluorophenyl)amine was obtained.
^{1}H-NMR ($CDCl_3$): δ = 6.71 dd (J = 9.2 Hz, 1H); 6.97 d (J = 2 Hz, 1H); 7.13 dd (J = 9.9 Hz, 2H); 7.22 dd (J = 9.6 Hz, 2H); 8.15 d (J = 10 Hz, 1H); 9.45 s (br) (1H).

b) (5-methoxy-2-nitrophenyl)-(4-fluorophenyl)amine

36.44 g (5-chloro-2-nitrophenyl)-(4-fluorophenyl)amine was added to a solution of 6.6 g sodium in 450 mL methanol and heated for 16 hours under reflux. After another 30 hours of agitation at 60°C, it was cooled and the crystalline product filtered by suction. 34 g (5-methoxy-2-nitrophenyl)-(4-fluorophenyl)amine was obtained.
^{1}H-NMR ($CDCl_3$): δ = 3.72 s (3H); 6.44 dd (J = 9.2 Hz, 1H); 6.48 d (J = 2 Hz, 1H); 7.13 dd (J = 9.9 Hz, 2H); 7.27 dd (9.6 Hz, 2H); 8.20 d (J = 9 Hz, 1H); 9.65 s (br) (1H).

c) N^2-(4-fluorophenyl)-4-methoxybenzene-1,2-diamine

33.5 g (0.128 mL) (5-methoxy-2-nitrophenyl)-(4-fluorophenyl)amine was converted according to general work procedure 1. The crude product was further processed without purification.
^{1}H-NMR ($CDCl_3$): δ = 3.70 ppm s (3H); 6.49 d (br) (J = 9 Hz, 1H); 6.68 d (J = 2 Hz, 1H); 6.78-6.97 m (5H).

d) 6-Methoxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole

7.48 g thiophene-3-aldehyde was agitated in 65 mL 40% $NaHSO_3$ solution for 2 hours. After addition of 15 g N^2-(4-fluorophenyl)-4-methoxybenzene-1,2-diamine in 50 mL ethanol, it was boiled for 4 hours and further agitated overnight. The charge was distributed between water and ethyl acetate and the organic phase washed with water. After drying over sodium sulfate and concentration of the filtrate, 18.1 g crude 6-methoxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole was obtained.

Mp. 154-158°C

e) 6-Hydroxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole

18 g (55.5 mmol) 6-methoxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole was converted in similar fashion to the general work procedure 2. 12.65 g (40 mmol) of crude 6-hydroxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole was obtained.

Mp. 212-218°C

f) 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

6-Hydroxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole was converted with 6-bromohexanoic acid methyl ester according to general work procedure 3.

Mp. 131-134°C

g) 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was obtained by conversion of 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.

Mp. 170-175°C

Example 12

5[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 5[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester

6-Hydroxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole was converted according to general work procedure 3 with 5-bromopentanoic acid methyl ester.

Mp. 90.5-92.5°C

b) 5[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

5[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester was converted according to general work procedure 4.

Mp. 184-189°C

Example 13

6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 6-Methoxy-1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazole

N^2-(4-fluorophenyl)-4-methoxybenzene-1,2-diamine was converted similar to example 11 d with pyridine-3-carbaldehyde.

Mp. 132.5-134°C

b) 6-hydroxy-1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazole

6-Methoxy-1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazole was converted according to general work procedure 2.

Mp. 238-241°C

c) 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

6-Hydroxy-1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazole was converted with 6-bromohexanoic acid methyl ester according to general work procedure 3.

Mp. 105.5-111.5°C

d) 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was obtained by conversion of 6[[1-(4-fluorophenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.

Mp. 127-129°C

Example 14

5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester

6-Hydroxy-1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazole was converted with 5-bromopentanoic acid methyl ester according to general work procedure 3.

Mp. 52-55°C

b) 5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid was obtained by conversion of 5[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester according to general work procedure 4.

Mp. 181.5-183°C.

Example 15

5-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

a) 6-Methoxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole

was obtained conversion of 4-methoxy-N^2-phenyl-*o*-phenylenediamine with pyridine-3-carbaldehyde according to general work procedure 5.

MS (EI): 301 (molecular ion peak)

b) 6-Hydroxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole

was obtained by conversion of 6-methoxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole according to general work procedure 2.

^{1}H-NMR (D_6-DMSO): δ = 6.52 ppm d (J = 2 Hz, 1H); 6.81 dd (J = 8.2 Hz, 1H); 7.34-7.48 m (3H); 7.53-7.68 m (4H); 7.80 (ddd, J - 8.2, 1 Hz, 1H); 8.53 dd (J = 2.1 Hz, 1H); 8.67 d (J = 1 Hz, 1H); 9.42 (s, 1H).

c) 5-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole with 5-bromopentanoic acid methyl ester according to general work procedure 3

MS (EI): 401 (molecular ion peak)

d) 5-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid

was obtained by conversion of 5[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester according to general work procedure 4.

^{1}H-NMR (CD_3OD): δ =1.72-1.88 m (4H); 2.30 t (J = 8 Hz, 2H); 3.98 t (J - 8 Hz, 2H); 6.72 ppm d (J = 2 Hz, 1H); 7.03 dd (J = 8.2 Hz, 1H); 7.40-7.48 m (3H); 7.55-7.65 m (3H); 7.70 (d, J = 8 Hz, 1H); 7.92 ddd (J = 8.2, 1 Hz, 1H); 8.53 dd (J = 8.2 Hz, 1H); 8.70 dd (J = 2.1 Hz, 1H).

Example 16

4-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid

a) 4-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester

was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole with 4-bromobutyric acid methyl ester according to general work procedure 3.

MS (EI): 387 (molecular ion peak)

b) 4-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid

was obtained by conversion of 4-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]butyric acid methyl ester according to general work procedure 4.

MS (EI): 373 (molecular ion peak)

Example 17

6-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 6-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

was obtained by conversion of 6-hydroxy-1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazole with 6-bromohexanoic acid methyl ester according to general work procedure 3.

MS (EI): 415 (molecular ion peak)

b) 6-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

was obtained by conversion of 6-[[1-phenyl-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general formula 4.
MS (EI): 410 (molecular ion peak)

Example 18

***N*-(3-methoxypropyl)-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide**

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with 3-methoxypropylamine according to general work procedure 6.
MS (EI): 486 (molecular ion peak)

Example 19

6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]-1-morpholine-1-ylhexan-1-one

was obtained by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with morpholine according to general work procedure 6.
MS (EI): 442 (molecular ion peak)

Example 20

***N*-methyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide**

was obtained by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with *N*-methylamine hydrochloride according to general work procedure 6.
MS (EI): 428 (molecular ion peak)

Example 21

***N,N*-dimethyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide**

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide methyl ester with dimethylamine hydrochloride according to general work procedure 6.

MS (EI): 442 (molecular ion peak)

Example 22

6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with ammonium chloride according to general work procedure 6.

MS (EI): 414 (molecular ion peak)

Example 23

***N*-cyclopropyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide**

was obtained by conversion of 6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with cyclopropylamine according to general work procedure 6.

MS (EI): 459 (molecular ion peak)

Example 24

***N*-methyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanamide**

was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(3-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester with N-methylamine hydrochloride according to general work procedure 6.

MS (EI): 433 (molecular ion peak)

Example 25

***N*-(2-methoxyethyl)-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide**

was prepared by conversion of 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester with 2-methoxyethylamine according to general work procedure 6.

MS (EI): 458 (molecular ion peak)

Example 26

***N,N*-dimethyl-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide**

was prepared by conversion of 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester (example 56c) with dimethylamine according to general work procedure 6.

MS (EI): 428 (molecular ion peak)

Example 27

5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanamide

was obtained by conversion of 5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1*H*-benzimidazol-6-yl]oxy]pentanoic acid methyl ester with ammonium chloride according to general work procedure 6.

MS (EI): 400 (molecular ion peak)

Example 28

6-[[1-(4-methylphenyl)-2-(2-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid

a) 6-[[1-(4-methylphenyl)-2-(2-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester

was obtained by conversion of 6-[[4-amino-3-((4-methylphenyl)amino)phenyl]oxy]hexanoic acid methyl ester with 2-thienylcarbaldehyde according to general work procedure 5.
MS (EI): 434 (molecular ion peak)

b) 6-[[1-(4-methylphenyl)-2-(2-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid
was prepared by conversion of 6-[[1-(4-methylphenyl)-2-(2-thienyl)-1*H*-benzimidazol-6-yl]oxy]hexanoic acid methyl ester according to general work procedure 4.
MS (EI): 420 (molecular ion peak)

Example 29

Inhibition of microglia activation

For *in vitro* preparation of Aβ-activated microglia, primary rat microglia with synthetic Aβ-peptide were incubated.

For stimulation of Aβ-deposits synthetic Aβ-peptide was dried on 96-well tissue culture plates. For this purpose a peptide stock solution of 2 mg/mL H_2O 1:50 in was diluted in H_2O. For coating of the 96-well plates, 30 µL of this diluted peptide solution/well was used and dried overnight at room temperature.

Primary rat microglia are harvested from mixed glia cultures obtained from P3 rat brains. To prepare mixed glia cultures, the brains are removed from 3-day-old rats and freed of brain meninges. Cell separation is achieved by trypsinization (0.25% trypsin solution, 15 minutes, 37°C). After separation of undigested tissue fragments by means of 40 µm nylon gauze, the isolated cells are centrifuged (800 rpm/10 min.). The cell pellet is resuspended in culture medium and transferred to 100 mL tissue culture bottles. (1 brain/tissue culture bottle). Cultivation of cells occurs over a period of 5-7 days in Delbecco's modified eagle medium (DMEM, with glutamine), supplemented with penicillin (50 U/mL), streptomycin (40 µg/mL) and 10% (v/v) fetal calf serum (FCS) at 37°C and 5% CO_2. During this incubation, an adhesive cell lawn is formed, consisting mostly of astrocytes. Microglia proliferate as non- or weakly adhesive cells on it and are harvested by rocking incubation (420 rpm/1 hour).

For activation of microglia with Aβ-peptide, 2.5 times 10^4 microglia/well are inoculated onto Aβ-coated tissue culture plates and incubated over a period of 7 days in DMEM (with glutamine), supplemented with penicillin (50 U/mL), streptomycin (40 µg/mL) and 10% (v/v) fetal calf serum (FCS) at 37°C and 5% CO_2. On day 5, addition of a compound according to the invention occurs in different concentrations (0.1, 0.3, 1.3 and 10 µm).
For quantification of microglia reactivity, the metabolic activity is measured on culture day 7 via reduction of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(sulfophenyl)-2H-tetrazolium), Owen's reagent, Baltrop, J. A. et al., Bioorg. & Med. Chem., Lett 1, 6111 (1991)). The percentage of inhibition refers to a control treated only with DMSO. The compounds according to the invention inhibit microglia activation.

Example 30

Cerebral infarction in the rat (MCAO model)

The compounds according to the invention were tested for *in vivo* activity in an animal model for cerebral ischemia (stroke), the MCAO (permanent middle cerebral artery occlusion) model. By one-sided occlusion of the middle cerebral artery (MCA), a cerebral infarction is triggered, which is due to undersupply of the corresponding region of the brain with oxygen and nutrients. The result of this undersupply is pronounced cell depression, as well as a strong microglia activation subsequently. This microglia activation, however, only reaches its maximum after several days and can persist over several weeks. To test the substances, the compounds according to the invention were administered intraperitoneially 1-6 days after occlusion. The animals were perfused and killed on day 7. The degree of microglia activation was measured by a modified immune histochemical method. For this purpose, vibratome sections of fixed brains were incubated with antibodies that recognized the CR3 complement receptor or the MHCII complex on activated microglia. Quantification of the primary antibody bonding occurred with an enzyme-coupled detection system. Treatment with the compounds according to the invention led to a reduction of microglia activation in the brain hemisphere affected by cerebral infarction.

Example 31

Inhibition of TNFα and IL 12 production in THP-1 cells

Inhibition of cytokine production is presented by measuring TNFα and interleukin 12 in lipopolysaccharide (LPS)-stimulated THP-1 cells.

For this purpose, 2.5×10^6 THP-1 cells (American Type Culture Company, Rockville, MD)/ mL RPMI 1640 medium (Life Technologies)/ 10% FCS (Life Technologies, Catalog No. 10270-106) are inoculated onto 96-well flat-bottomed cell culture plates (TPP, product no. 9296) (100 µL/well). The compounds according to the invention are added in different concentrations and preincubated for 30 minutes. Predilution of the test substances was conducted in the incubation medium. Addition of the test substances occurs as 2-fold concentrated substance solution (100 µL/well). Stimulation of the cells occurred overnight at 30°C with 0.1 µg/mL LPS (Sigma L2630, from E. Coli Serotype 0111.B4). The medium was then harvested and the TNFα or interleukin 12 amount determined quantitatively. A commercially available TNFα kit from *CIS bio international* was used for measurement of TNFα (product no. 62TNFPEB). The amount of interleukin 12 was determined with the ORIGEN technology (IGEN International, Inc., Gaithersburg, Maryland). The calculated IC_{50} value corresponds to the concentration of test substance required to achieve 50% inhibition of maximum TNFα or interleukin 12 production. The compounds according to the invention inhibit TNFα and interleukin 12 production in lipopolysaccharide (LPS)-stimulated THP-1 cells.

Example 32

Inhibitin of INFγ production of peripheral mononuclear blood cells

To represent the effect of the substances on T-cell activation, measurement of INFγ secretion is used.

For isolation of peripheral mononuclear cells, human whole blood was used (blood sampling via Na-citrate S-monovettes "Coagulation 9 NC/10 mL" / Sarstedt). Enrichment of the blood cells was carried out with density gradient centrifuging: for this purpose, 15 mL of Histopaque 1077 Sigma, catalog no. H8880 was introduced to LEUCOSEP tubes (Greiner, catalog no. 227290) and centrifuged for 30 seconds at 1000 g. 15 mL of whole blood was then added and centrifuged

for 10 minutes at 1000 g. The upper plasma layer is then pipetted and the underlying cell layer (peripheral mononuclear blood cells) transferred to 10 mL sample tubes (Falcon) and then washed several times with 10 mL HBSS HANKS Balanced Solution (without Mg^{2+} and Ca^{2+}), catalog no. 14175-53. The cell pellet is finally resuspended in culture medium RPMI 1650 ± 25 mM Hepes (Life Technology, catalog no. 52400-04110% FCS (Life Technologies, catalog no. 10270-106), 0.4% penicillin-streptomycin solution (Life Technologies, catalog no. 15140-106) (1×10^6 cells/mL). 100 µL cell suspension solution is distributed to 96-well flat bottom cell culture plates (TPP, production no. 9296) and stimulated with 2.5 µg/mL anti-CD3 antibodies. The substances according to the invention were added in different concentrations and preincubated for 30 minutes. Stimulation of the cells occurred over a period of 24 hours. The medium was then harvested and the INFγ determined quantitatively. The amount of INFγ was determined with the ORIGEN technology (IGEN International, Gaithersburg, Maryland). The calculated IC_{50} value corresponds to the concentration of test substance required to achieve 50% inhibition of maximum INFγ production.

The compounds according to the invention inhibit INFγ production of peripheral mononuclear blood cells.

Example 33

Inhibition of TNFα and IL-12 HD production of peripheral mononuclear blood cells

Inhibition of TNFα and IL-12 HD p70 production is presented, for example, by measuring TNFα and IL-12 HD p70 in peripheral mononuclear blood cells stimulated with lipopolysaccharide (LPS) and interferon gamma (IFNγ).

For isolation of peripheral mononuclear blood cells, human whole blood was used (blood sampling via Na-citrate S-monovettes "Coagulation 9NC/10 mL" / Sardstedt). Enrichment of lymphocytes and monocytes was conducted with density gradient centrifuging: for this purpose, 15 mL Histopaque-1077 (Sigma, catalog No. H8880) was introduced to 50 mL LEUCOSEP tubes (Greiner, catalog no. 227290) and forced downward by centrifuging for 30 seconds at 250 g through the frit situated in the tubes. 20 mL whole blood was then added and centrifuged for 15 minutes at 800 g and room temperature. After centrifuging, the supernatant (plasma and

thrombocytes) is pipetted and discarded and the underlying cell layer (lymphocytes and monocytes) transferred to 50 mL centrifuge tubes (Falcon) and then washed 3 × in culture medium VLE RPMI 1640 (Seromed, No. FG1415) (centrifuging 10 minutes at 250 g, room temperature). The cell pellet is finally resuspended in culture medium VLE RPMI 1640 (Seromed No. FG1415), 10% FCS (Life Technologies, catalog no. 16000-0044, low endotoxin, heat-inactivated 1 hour, 56°C), 50 µg/mL penicillin-streptomycin solution (Life Technologies, catalog no. 15140-106) and set at 3×10^6 cells/mL after cell counting by means of trypan blue staining. 100 µL cell suspension solution was distributed to 96-well flat bottom cell culture plates (Costar, product no. 3599). For this purpose, 100 µL of 3-fold concentrated stimulation solution (3 µg/mL of *E. coli* Serotype 0127:B8; Sigma, catalog no. L-4516 and 30 ng/mL IFNγ 1b, Imukin, Boehringer Ingelheim) were added. The substances according to the invention were added in different concentrations as 3-fold concentrated substance solutions (100 µL/well). Stimulation of the cells occurred at 37°C and 5% CO_2 over a period of 24 hours. The cell culture supernatant was then harvested and the concentrations of TNFα and IL-12 HD p-70 determined by means of commercially available ELISA kits from *BioSource International* (TNFα EASIA, catalog no. KAC 1752) and *R&D Systems* (Quantikine™ HS IL-12, catalog no. HS 120).
The calculated IC_{50} value corresponds to the concentration of test substance required to achieve 50% inhibition of maximum TNFα and interleukin 12 HD p70 production.
The compounds according to the invention inhibit TNFα and IL-12 HD p70 production of peripheral mononuclear blood cells.

Example 34

Induction of IL-10 production of peripheral mononuclear blood cells

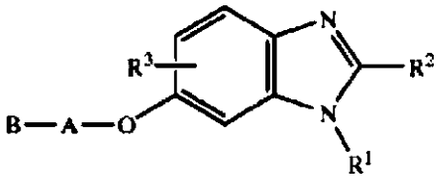
Induction of IL-10 production is presented, for example, by measuring IL-10 in phytohemagglutinin (PHA) or lipopolysaccharide (LPS)-stimulated perpipheral mononuclear blood cells.

For isolation of peripheral mononuclear blood cells, human whole blood was used (blood sampling via NA-Citrate S-Monovettes "Coagulation 9 NC/10 mL" / Sarstedt). Enrichment of lymphocytes and monocytes was conducted by means of density gradient centrifuging: for this

purpose, 15 mL Histopaque 1077 (Sigma, catalog no. H8880) is introduced to 50 mL LEUCOSEP tubes (Greiner, catalog no. 227290) and forced downward by centrifuging for 30 seconds at 250 g through the frit situated in the tubes. 20 mL whole blood is then added and centrifuged for 15 minutes at 800 g and room temperature. After centrifuging, the supernatant (plasma and thrombocytes) are pipetted and discarded and the underlying cell layer (lymphocytes and monocytes) transferred to 50 mL centrifuge tubes (Falcon) and then washed 3 × in culture medium VLE RPMI 1640 (Seromed, No. FG1415) (centrifuging 10 minutes at 250 g, room temperature). Finally, the cell pellet is resuspended in culture medium VLE RPMI 1640 (Seromed, No. FG1415), 10% FCS (Life Technologies, catalog no. 16000-0044, low endotoxin, heat-inactivated 1 hour, 56°C), 50 µg/mL penicillin-streptomycin solution (Life Technologies, catalog no. 15140-106) and set at 3×10^6 cells/mL after cell counting by trypan blue staining. 100 µL cell suspension solution was distributed to 96-well flat bottom cell culture plates (Costar, product no. 3599). For this purpose, 100 µL of 3-fold concentrated stimulation solution (3 µg/mL LPS of *E. coli* Serotype 0127:B8; Sigma, catalog no. L-4516 and 300 µg/mL PHA-L, Biochem KG, catalog no. M5030) were added. The substances according to the invention were added in different concentrations as 3-fold concentrated substance solutions (100 µL/well). Stimulation of the cells occurred at 37°C and 5% CO_2 over a period of 24 hours. The cell culture supernatant was then harvested and IL-10 determined quantitatively. The IL-10 concentration was determined by a commercially available ELISA kit from *BioSource International* (human IL-10, catalog no. KHC0101C). The calculated EC_{50} value corresponds to the concentration of test substance required to increase the IL-10 secretion by 50% and a maximum increase.
The compounds according to the invention increase IL-10 production of peripheral mononuclear blood cells.

What is claimed is:

1. A benzimidazole compound of the formula I



(I)

in which R^1 is a phenyl group that is optionally substituted with up to three of the following substituents, independently of one another: F, Cl, Br, I, OH, OR^4, $OCOR^4$, SR^4, SOR^4, SO_2 R^4, R^4, NH_2, NHR^4, or NR^4 R^4 ', or two substituents at adjacent positions on the phenyl ring together form an $-O-CH_2-O-$, $-O-CH_2-$, CH_2-O- or $-CH_2-CH_2-CH_2-$ group, R^2 is a monocyclic or bicyclic 5- to 10-membered heteroaryl group with 1-2 heteroatoms, selected from N, S and O, which optionally is substituted with up to two of the following substituents, independently of one another: F, Cl, Br, I, OH, OR^4, $OCOR^4$, COR^4, SR^4, SOR^4, SO2R^4, R^4, or two substituents at adjacent positions on the R^2ring(s) together form an $-O-CH_2$ $-O-$, $-O-CH_2-$, CH_2-O-or $-CH_2-CH_2-CH_2-$ group, R^3 is H, OH or $O-C_{1-6}$-alkyl, R^4 and R^4 ', independently of one another, are C_{1-4}-perfluoroalkyl or C_{1-6}-alkyl, A is a C_{2-6}-alkylene group, which optionally is substituted with =O, OH, $O-C_{1-3}$-alkyl, NH_2, $NH-C_{1-3}$-alkyl, $NH-C_{1-3}$-alkanoyl, $N(C_{1-3}\text{-alkyl})_2$, or $N(C_{1-3}\text{-alkyl})(C_{1-3}\text{-alkanoyl})$. B is COOH, $CONH_2$, $CONHNH_2$, $CONHR^5$, or $CONR^5R^5$', in each case bonded to a carbon atom of group A, R^5 and R^5', independently of one another, are in each case a radical, selected from the group consisting of: C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkinyl, wherein a C atom is optionally exchanged for O, S, SO, SO_2, NH, $N-C_{1-3}$-alkyl or $N-C_{1-3}$-alkanoyl; C_{0-3}-alkanediyl-C_{3-7}-cycloalkyl, whereby in a five-membered cycloalkyl ring, a ring member is optionally a ring N or ring O, and in a six- or seven-membered cycloalkyl ring, one or two ring members in each case are

optionally ring-N atoms and/or ring-O atoms, whereby the ring-N atoms optionally can be substituted with C_{1-3}-alkyl or C_{1-3}-alkanoyl; C_{0-3}-alkanediyl-phenyl or C_{0-3}-alkanediyl-heteroaryl, whereby the heteroaryl group is five- or six-membered and contains one or two heteroatoms that are selected from the group consisting of N, S and O, whereby all above-mentioned alkyl and cycloalkyl radicals optionally can be substituted with up to two radicals that are selected from the group consisting of CF_3, C_2F_5, OH, O-C_{1-3}-alkyl, NH_2, NH-C_{1-3}-alkyl, NH-C_{1-3}-alkanoyl, N(C_{1-3}-alkyl)$_2$, N(C_{1-3}-alkyl)(C_{1-3}-alkanoyl), COOH, $CONH_2$ and COO-C_{1-3}-alkyl, and all above-mentioned phenyl and heteroaryl groups optionally can be substituted with up to two radicals that are selected from the group consisting of F, Cl, Br, CH_3, C_2H_5, OH, OCH_3, OC_2H_5, NO_2, N(CH_3)$_2$, CF_3, C_2F_5 and SO_2NH_2, or R^5 and $R^{5'}$ together with the N atom form a five- to seven-membered heterocyclic ring that optionally contains another N or O or S atom and is optionally substituted with C_{1-4}-alkyl, C_{0-2}-alkanediyl-C_{1-4}-alkoxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl or phenyl, or an optical or geometric isomer or tautomer form thereof or pharmaceutically acceptable salt thereof,

whereby the following compounds are excluded: 6-[[1-Phenyl-2-(pyridin-4-yl)-1H-benzimidazol-6-yl]oxy]hexanoic acid, 6-[[1-phenyl-2-(benzothien-2-yl)-1H-benzimidazol-6-yl]oxy]hexanoic acid.

2. A compound according to claim 1, wherein: R^1 is a phenyl group that optionally is substituted with up to two of the following substituents, independently of one another: F, Cl, OH, OR^4, $OCOR^4$, SR^4, or R^4 or two substituents at adjacent positions on the phenyl ring together form an -O-CH_2-O- or -CH_2-CH_2-CH_2- group.

3. A compound according to claim 1, wherein $R^2$is a monocyclic 5- to 6-membered heteroaryl group with 1-2 heteroatoms, selected from the group consisting of N, S and O, which optionally is independently substituted with up to two of the following substituents: F, Cl, OR^4, $OCOR^4$, SR^4, SOR^4, SO_2 R^4, R^4 or two substituents at adjacent positions on the R^2ring(s) together form an $-O-CH_2-O-$ or $-CH_2-CH_2-CH_2-$ group.

4. A compound according to claim 1, wherein R^3 is H.

5. A compound according to claim 1, wherein R^4 and $R^{4'}$, independently of one another, are C_{1-2} perfluoroalkyl, or C_{1-4} alkyl.

6. A compound according to claim 1, wherein R^5 and $R^{5'}$, independently of one another, are C_{1-6} alkyl, whereby a carbon atom is optionally exchanged for O, S, SO, or SO_2, C_3-5 cycloalkyl-C_{0-3} alkylene, whereby in a 5-membered cycloalkyl ring, a ring member is optionally a ring N or ring O, whereby the ring nitrogen optionally is substituted with C_{1-3} alkyl or C_{1-3} alkanoyl, C_{0-2} alkylene-(5- to 6-membered heteroaryl with 1-2 heteroatoms from N, S and O), whereby all above-mentioned alkyl and cycloalkyl radicals are optionally substituted with CF_3, OH, NH_2, NH C_{1-3} alkyl, NH C_{1-3} alkanoyl, N(C_{1-3} alkyl)$_2$, N(C_{1-3} alkyl)(C_{1-3} alkanoyl), COOH, or $CONH_2$ and all above-mentioned heteroaryl groups are optionally substituted with one or two substituents selected from the group consisting of F, Cl, CH_3, C_2 H_5, OCH_3, OC_2 H_5, CF_3, and C_2 F_5, or R^5 and $R^{5'}$ together with the nitrogen atom form a 5- to 7-membered heterocyclic compound, which optionally contains another oxygen, nitrogen or sulfur atom and is optionally substituted with C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{0-2}-alkyl.

7. A compound according to claim 1, wherein A is straight-chain C_3-6 -alkylene.

8. A compound according to claim 1, wherein B is COOH or $CONH_2$

in each case bonded to a carbon atom of group A.

9. A compound according to claim 1, which is:
6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
5-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
6-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
5-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
5-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
6-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
6-[[1-(4-fluorophenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
5-[[1-(4-fluorophenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
6-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;

5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
5-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
6-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
N-(3-methoxypropyl)-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol- 6-yl]oxy]hexanamide;
6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]-1-morpholi n-1-ylhexan-1-one;
N-methyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanamide;
N,N-dimethyl-6-[[1-(4-methyphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanamide;
6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanamide;
N-cyclopropyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanamide;
N-methyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanamide;
N-(2-methoxyethyl)-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6 -yl]oxy]pentanamide;
N,N-dimethyl-5-[[1-(4-methyphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanamide;
5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanamide ; or
6-[[1-(4-methylphenyl)-2-(2-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid.

10. A pharmaceutical composition which comprises one or more compounds according to claim 1 and one or more vehicles and/or adjuvants.

11. A pharmaceutical composition according to claim 10, wherein: R^1 is a phenyl group that optionally is substituted with up to two of the following substituents, independently of one another: F, CI, OH, OR^4, $OCOR^4$, SR^4, or R^4 or two substituents at adjacent positions on the phenyl ring together form an $-O-CH_2-O-$ or $-CH_2-CH_2-CH_2-$ group.

12. A pharmaceutical composition according to claim 10, wherein R^2 is a monocyclic 5- to 6-membered heteroaryl group with 1-2 heteroatoms, selected from the group consisting of N, S and O, which optionally is independently substituted with up to two of the following substituents: F, CI, OR^4, $OCOR^4$, SR^4, SOR^4, SO_2 R^4, R^4 or two substituents at adjacent position on the R^2ring(s) together form an $-O,CH_2-O-$ or $-CH_2-CH_2-CH_2-$ group.

13. A pharmaceutical composition according to claim 10, wherein $R^3$is H.

14. A pharmaceutical composition according to claim 10, wherein R^4 and R^4, independently of one another, are C_{1-2} perfluoroalkyl, Or C_{14} alkyl.

15. A pharmaceutical composition according to claim 10, wherein R^5 and R^5, independently of one another, are C_{1-5} alkyl, whereby a carbon atom is optionally exchanged for O, S, SO, or SO_2 C_3-5 cycloalkyl-C_{0-3} alkylene, whereby in a 5- membered cycloalkyl ring, a ring member is optionally a ring N or ring O, whereby the ring nitrogen optionally is substituted with C_{1-3} alkyl or C_{1-3} alkanoyl, C_{0-2} alkylene-(5- to 6-membered heteroaryl with 1-2 heteroatoms from N, S and O), whereby all above-mentioned alkyl and cycloalkyl radicals are optionally substituted with CF_3, OH, NH_2, NH C_{1-3} alkyl, NH C_{1-3} alkyl, NH C_{1-3} alkanoyl, N(C_{1-3} alkyl)$_2$, N(C_{1-3} alkyl)(C_{1-3} alkanoyl), COOH, or $CONH_2$ and all

above-mentioned heteroaryl groups are optionally substituted with one or two substituents selected from the group consisting of F, CI, CH_3, C_2H_5, OCH_3, OC_2H_5, CF_3, and C_2F_5, or R^5 and R^5 together with the nitrogen atom form a 5- to 7-membered heterocyclic compound, which optionally contains another oxygen, nitrogen or sulfur atom and is optionally substituted with C_{1-4}-alkyl or C_{1-4}-alkoxy-C_{0-2}-alkyl.

16. A pharmaceutical composition according to claim 10, wherein A is straight-chain C_3-5-alkylene.

17. A pharmaceutical composition according to claim 10, wherein B is COOH or $CONH_2$ in each case bonded to a carbon atom of group A.

18. A pharmaceutical composition according to claim 10, wherein the compound is: 6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
6-[[1-(4-methylphenyl)-2-(4-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
6-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;
5-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]butyric acid;
5-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;
4-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]butyric acid;

6-[[1-phenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;

6-[[1-(4-fluorophenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;

5-[[1-(4-fluorophenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;

6-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;

5-[[1-(4-fluorophenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;

5-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanoic acid;

4-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]butyric acid;

6-[[1-phenyl-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid;

N-(3-methoxypropyl)-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol- 6-yl]oxy]hexanamide;

6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]-1-morpholi n-1-ylhexan-1-one;

N-methyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]he xanamide;

N,N-dimethyl-6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6yl]oxy]hexanamide;

6-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]hexanamide;

N-cyclopropyl-6-[[1-(4-methylphenyl)-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexanamide;

N-methyl-6-[[1-(4-methylphenyl-2-(3-thienyl)-1H-benzimidazol-6-yl]oxy]hexan amide;

N-(2-methoxyethyl-5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6- yl]oxy]pentanamide;

N,N-dimethyl-5-[[1-(4-methyphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanamide;

5-[[1-(4-methylphenyl)-2-(3-pyridinyl)-1H-benzimidazol-6-yl]oxy]pentanamide ; or

6-[[1-(4-methylphenyl)-2-(2-thienyl)-1H-benzimidazol-6-yl]oxy]hexanoic acid.