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Microglia Inhibitors for Interrupting Immune Reactions Mediated by Interleukin 12 and IFN_γ

The invention pertains to the use of microglia inhibitors for the manufacturing of a medication, which inhibits the immune reactions mediated by interleukin 12 (IL 12) and interferon-γ, and its use for the treatment of immune diseases mediated by T cells and inflammatory reactions that are not mediated by T cells.

The immune system includes a multitude of cells and tissue complexes, which communicate among themselves mainly through soluble agents. It is known that many immune diseases are triggered by imbalance of the soluble immune agents, as, for instance, the cytokines (Mosmann and Coffmann., Ann. Rev. Immunol. Z: 145 -173 (1989 Street and Mosmann, FASEB J. 5: 171-177 (1991); Lucey et al., Clin. Microbiol. Rev. 4: 532 -562 (1 996); Powrie and Coffman, Trends Pharmacol. Sci 14:164 -168 (1 993); Singh et al., Immunolog. Res.. 20: 164 - 168 (1999)). So there are, for instance, many indications that pointing to a certain role of interferon gamma and interleukin 12 in the pathogenesis of the autoimmune diseases. Particularly, we can mention diseases, which can be characterized by means of T cells mediated inflammatory reactions, as multiple sclerosis, diabetes, chronic inflammatory bowel diseases. The cytokine interleukin 12 (IL 12) is produced by phagocyte cells like monophages/monocytes, dendrites, B-cells, and other antigen-presenting cells (APC) and influences both the function of the natural killer cells (NC cells) and the function of the of the T lymphocytes. The IL 12 can trigger the production of interferon gamma (IFN_γ) in both types of cells. The T lymphocytes can be divided roughly in two categories, which can be characterized by the expression of certain surface antigens (CD4 and CD8): CD4-positive T cells (helper T cells) and CD8-positive T cells (cytotoxic T cells). The CD4 cells can be divided again in T helper cells 1 (Th1) and T helper cells 2 (Th2). Particularly, the immune responses mediated by the Th1 cells are associated with the pathogenesis of many immune diseases, especially with the autoimmune diseases, as, for

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instance: Type 1 insulin-dependent diabetes mellitus (IDDM), multiple sclerosis, allergic contact eczema, psoriasis, rheumatoid arthritis, chronic inflammatory bowel diseases (morbus Crohn, ulcerous colitis), lupus diseases,, and other collagenoses as well as acute rejection reactions in the allotransplantations ("host-versus-graft" – allotransplantation rejection, "graft-versus-host disease). It is known about the interleukin 12 that it plays a critical role in the regulation of the Th1 response. Interleukin 12 induces in these cells mainly the production of IL-2, IFN_γ, TNF_α, and TNF_β (Mosmann and Sad, Immunol. Today 17: 138 -146 (1996) ;Gately et al., Annu. Rev. Immunol. B:495 -521-(1 998)). Particularly, the IFN_γ is a potential mediator of the IL-12 action. For instance, the overproduction of interferon gamma can be responsible for the autoimmune diseases that are associated with the MHC II (Major Histocompatibility Complex). (Additionally, there is also sufficient evidence regarding the pathological role of interferon gamma in allergic diseases as well as in the sarcoidosis and the psoriasis (Billiau A., Adv. Immunol., 62: 61-130 (1996); Basham et al. J. Immunol. 130:1492 -1494 (1983); Hu et al., Immunology, 98: 379-385 (1999); Seery JP., Arthritis Res., 2: 437-440 (2000)). In addition to that, the IL-12 and IL-12/IL-18 induced IFN_γ from NK cells essentially participates in the pathological mechanism of not T cell mediated inflammatory reactions (for example, "toxic shock syndrome", endotoxinemia, sepsis and sepsic shock, ARDS, "first dose response" in antibody therapy, for instance, OKT3 in allotransplantations) – (Kum et al., Infect Immun. 69: 25 7544-7549 (2001); Arad et al., J Leukoc. Biol. B: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 play also certain role in inflammations with pathogenic mechanisms (for instance, eclampsia) that are not clear for now (Hayakawa et al., J. Reprod. Immunol. 47: 121-1 38 (2000); Daniel et al., Am. J. , Reprod. Immunol. 39:376-380 (1998)).

Besides interleukin 12 and IFN_γ, other cyclokines are also ascribed certain role in the pathogenesis of the immune diseases and the systemic inflammatory

reactions, as, for instance, the TNF_α. The TNF_α 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, 3: 279 -292 (1990); Waage A., Lancet, 351: 603 (1998); Cohen et al., Lancet, 351: 1731 (1998), but also in many other immune-mediated diseases.

For the treatment of the diseases mediated by IL 12 and for reducing the acute symptoms of these diseases, corticosteroids are often used whose side effects, particularly in the case of long treatment, often lead to interruption of the treatment.

The activation of the microglia represents a central step in the inflammation occurrence in almost all degenerative diseases of the central nervous system. The microglia can remain in an activated state for a long time, during which they produce and secrete various inflammatory agents, for instance, reactive oxygen/hydrogen intermediate, proteases, cytokines, complement agents, and neurotoxins. On the other hand, these cause neuronal dysfunction and degeneration. The activation of the microglia can take place through various stimuli, as, for instance, Aβ-peptide (β-amyloid, Araujo, D.M. and Cotman, C.M., Brain 25 Res. 569: 141-145 (1992)), prion protein, cytokine, or through cell fragments (Combs, C. K. et al., J. Neurosci. 19:928 -939 (1999); Wood, P. L., Neuroinflammation: Mechanisms and Management, Humana Press (1998).

Compounds that inhibit the activation of the microglia after stimulation with the Aβ-peptide are described in WO 01151473, DE - reference number101 34 775.8 and DE – reference number 101 35 050.3. It is also known from there that benzimidazoles, which inhibit the activation of the microglia, are used in the treatment of neuro-inflammatory diseases like AIDS dementia, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, Down's syndrome, diffuse Lewy body disease, Huntington's disease, leukoencephalopathy, multiple scleroses,

Parkinson's disease, Pick's disease, Alzheimer disease, apoplectic stroke, temporary lobe-epilepsy, as well as of tumors.

The invention is based on solving the following problem: To provide a medication that is suitable for the treatment of immune diseases, since the immune diseases are caused by the increased production of cytokines, as, for instance, IL 12, IFN_{γ}, and TNF_{α}, and does not affect other factors of the immune system, whereby the side effect can be reduced or prevented.

Now it has been found out that, surprisingly, the microglia inhibitors inhibit the production of IL 12 and IFN_{γ}, and induce the production of interleukin 10 (IL 10), and because of that they are used in the manufacturing of a medication for the treatment of immune diseases mediated by monocyte cells, macrophage cells, or T cells, and particularly by Th1 cells, as well as of not T cell mediated patho-physiological inflammatory reactions.

As it has been mentioned above, the T lymphocytes can be divided in CD4 positive T cells (helper T cells) and CD8-positive T cells (cytotoxic T cells) depending on the expression of their surface antigen, and the CD4 helper T cells can be divided again in T helper cells 1 (Th1) and T helper cells 2 (Th2), which, among other things, differentiate themselves in their ability to prevent tolerance. The cyclokines IL 12 and IFN_{γ} play an important role in the induction and the maintenance of the Th1 cells differentiation. The differentiated Th1 cells secrete IFN_{γ}, interleukin 2, and $TNF_{\alpha/\beta}$. These cytokines activate again the macrophages and the cytotoxic CD8 positive T cells.

The invention regards particularly the use of the microglia inhibitors for the manufacturing of a medication that will cause interruption of the production of the IL 12 and, respectively, the IFN_{γ} in the cells of monocytic origin – T cells and NK cells, respectively. On the basis of their ability to interrupt the production of IL 12 and IFN_{γ} in monophages/monocytes/dendrites as well as the production of IFN_{γ}

in the T cells and the NK cells and to enhance the induction of the production of IL 10, the microglia inhibitors are suitable for the treatment of many diseases, which are caused by the increased production of cytokines, as, for instance, $TNF_{\alpha/\beta}$, IFN_{γ}, Il 2, and IL 12, like some inflammatory diseases, which are not based on neuro-inflammation, autoimmune diseases, allergic and infectious diseases, toxin-induced inflammations, pharmacologically induced inflammatory reactions as well as patho-physiologically relevant inflammatory reactions with unclear genesis for the time being.

Examples of inflammatory and autoimmune diseases are: chronic inflammatory bowel diseases (inflammatory bowel diseases, Crohn's disease, ulcerative colitis), arthritis, allergic contact eczemas, psoriasis, pemphigus, asthma, multiple scleroses, diabetes, type 4 Insulin-dependent diabetes mellitus, rheumatoid arthritis, Lupus-diseases and other collagenoses, Graves' disease, Hashirnoto's disease, "graft-versus-host disease" and transplant rejection.

Examples of allergic, infectious, and toxin-induced diseases as well as ischemic - induced diseases are: sarcoidosis, asthma, hypersensitive pneumonitis, sepsis, septic shock, endotoxin shock, toxic shock syndrome, toxic liver failure, ARDS (acute shortness of breath syndrome), eclampsia, cachexia, acute virus infections (for example, mononucleosis, fulminant hepatitis), organ damages following reperfusion.

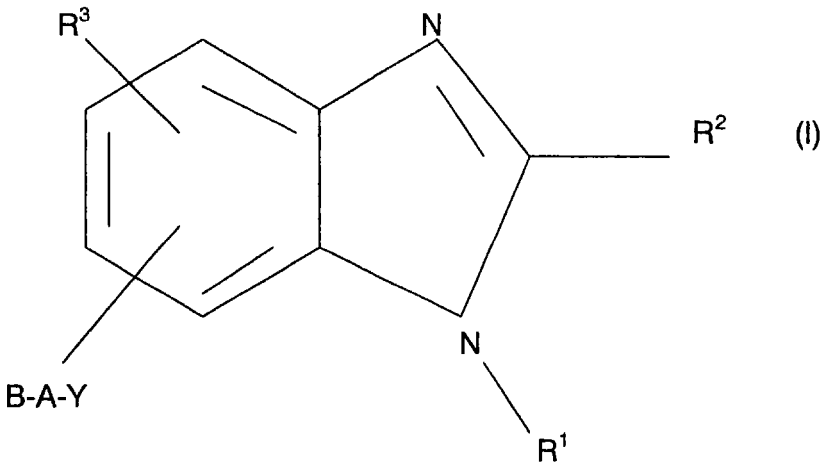
An example of a pharmacologically induced inflammation with patho-physiological relevance is the "first dose response" after the administration of anti-T-cell antibodies like OKT3.

An example of systemic inflammatory reactions, which for now are with unclear genesis, is the eclampsia.

According to the invention, compounds, which after stimulation with the Aβ peptide achieve an inhibition of the microglia activity of at least 20 per cent and an inhibition of the cytokine activity of at least 30 per cent, are suitable to be used as microglia inhibitors. The biological properties of the microglia inhibitors can be shown by means of the methods that are known to the specialists, for example with the help of the research methods described below as well as those described in WO 01151473.

Particularly suitable microglia inhibitors with the properties described above are the benzimidazoles in formula I and their tautomeric and isomeric forms and salts.

Formula (I)



Among them there are:

R^1 An aryl group or a five or six-member hetero-aryl group with one or two hetero-atoms, selected from the group and containing N, S, and O, whereby the aryl or the hetero-aryl group can be substituted with up to three rests that are independent of each other and selected from the group containing:

F, Cl, Br,
$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$,
$C(NR^4)N\ R^4R^{4'}$,
X-OH, $X\text{-}OR^4$, $X\text{-}OCOR^4$, $X\text{-}OCONHR^4$,
$X\text{-}COR^4$, $X\text{-}C(NOH)R^4$,
X-CN, X-COOH, $X\text{-}COOR^4$, $X\text{-}CONH_2$, $X\text{-}CONR^4R^4$, $X\text{-}CONHR^4$,
X-CONHOH,

$X\text{-}SR^4$, $X\text{-}SO_2$, $X\text{-}SO_2R^4$,

SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,

NO_2, $X\text{-}NH_2$, $X\text{-}NHR^4$, $X\text{-}NR^4R^{4'}$, $X\text{-}NHSO_2R^4$, $X\text{-}NR^4SO_2R^4$,

$X\text{-}NHCOR^4$, $X\text{-}NHCOOR^4$, $X\text{-}NHCONHR^4$ and

R^4,

Whereby X is a compound CH_2, $(CH_2)_2$, or $CH(CH_3)_2$, whereby further under the given conditions the rests R^4 and $R^{4'}$, are selected independently from each other and whereby two substitutions of R^1 – when they are orthogonally standing – can be connected to each other, so that they form together a methan-diyl-bisoxy-, ethan-1,2-diyl-bisoxy propan-1,3-diyl- or butan-1,4-diyl group, or

a rest selected from the group containing $C_{1\text{-}6}$Alkyl, ($C_{0\text{-}3}$-Alkandiyl-$C_{3\text{-}7}$-Cycloalkyl), and $C_{3\text{-}6}$Alkenyl, where one H-atom can be exchanged in such a way with one heterocyclic rest selected from the group containing piperazin, morpholine, piperidin, and pyrrolidin, so that a bond to one first N-atom of the heterocyclic rest can be built, whereby the above mentioned alkyl, cycloalkyl, and alkenyl rests and the heterocyclic rest can be substituted with up to two rests selected from the group containing $C_{0\text{-}2}$-Alkandiyl-OH, $C_{0\text{-}2}$-Alkandiyl-OR^7,
$C_{0\text{-}2}$-Alkandiyl-NH_2, $C_{0\text{-}2}$-Alkandiyl-NHR^7, $C_{0\text{-}2}$-Alkandiyl-$NR^7R^{7'}$,
$C_{0\text{-}2}$-Alkandiyl-$NHCOR^7$, $C_{0\text{-}2}$-Alkandiyl-$NR^7\ COR^{7'}$, $C_{0\text{-}2}$-Alkandiyl-$NHSO_3R^7$, $C_{0\text{-}2}$-Alkandiyl-$NR^7SO_2R^{7'}$, $C_{0\text{-}2}$-Alkandiyl-CO_2H,
$C_{0\text{-}2}$-Alkandiyl-CO_2R^7,
$C_{0\text{-}2}$-Alkandiyl-$CONH_2$, $C_{0\text{-}2}$-Alkandiyl-$CONHR^7$, $C_{0\text{-}2}$-Alkandiyl-$CONR^7\ R^{7'}$,
phenyl, and one five or six-member heteroaryl rest, whereby the

heteroaryl rest contains one or two hetero-atoms selected from the group containing N, S, and O, whereby further the phenyl and the heteroaryl rests can be substituted with up to two rests selected from the group that contains 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 CO_2NH_2, and/or also can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl- bisoxy group, whereby the piperazin rest can be substituted at a second oxygen atom also with R^7, COR^7, or SO_2R^7, whereby R^7 and $R^{7'}$ can be selected independently of each other in accordance with the meanings given further below,

R^2 -Z-R^2 – an aryl group or a five or six-member heteroaryl group with one or two hetero-atoms selected from the group containing N, S, and O, a benzothienyl group or an indolyl group, whereby the above mentioned aryl or heteroaryl group can be substituted with up to three rests independently of each other selected from the group containing
F, Cl, Br,
$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$,
$C(NR^4)N\ R^4R^{4'}$,
X-OH, X-OR^4, X-$OCOR^4$, X-$OCONHR^4$,
X-COR^4, X-$C(NOH)R^4$,
X-CN, X-COOH, X-$COOR^4$, X-$CONH_2$, X-$CONR^4R^4$, X-$CONHR^4$,
X-CONHOH,
X-SR^4, X-SO_2, X-SO_2R^4,
SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,
NO_2, X-NH_2, X-NHR^4, X-$NR^4R^{4'}$, X-$NHSO_2R^4$, X-$NR^4SO_2R^4$,
X-$NHCOR^4$, X-$NHCOOR^4$, X-$NHCONHR^4$ and
R^4,
Whereby X is a compound CH_2, $(CH_2)_2$, or $CH(CH_3)_2$, whereby further under the given conditions the rests R^4 and $R^{4'}$, are selected independently from each other and whereby two rests of R^1 – when they are orthogonally standing – can be connected to each other, so that they

form together a methan-diyl-bisoxy-, ethan-1,2-diyl-bisoxy propan-1,3-diyl- or butan-1,4-diyl group,

Z NH, $NR^{2"}$, O, S, SO or SO_2, whereby R" has the meaning that is given below,

$R^{2'}$ and $R^{2"}$ each one is a rest independent of the other and selected from the group that contains:
C_{1-4}-Perfluoralkyl, C_{1-6}-Alkyl, (C_{0-3}-Alkandiyl-C_{3-7}- Cycloalkyl), (C_{0-3}Alkandiyl-Aryl), and (C_{0-3}Alkandiyl-Heteroaryl), where the heteroaryl group is a five or six-member one and contains one or two hetero-atoms selected from the group containing N, S, and O, and whereby the aryl and the heteroaryl groups can be each one substituted with up to two rests selected from the group containing 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_5, and/or also can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, and further a ring link can be in a five-member cycloakryl ring N or ring O and one or two ring links in a six- or seven-member cycloakryl ring N and/or ring O atoms, whereby the ring N atoms can eventually be substituted with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, or $R^{4'}$ and $R^{2"}$ together with Z can build one six- or seven-member hetero-cyclic, where Z is an atom, whereby Z has the meaning that has been mentioned above, whereby further the hetero-cyclic ring contains another N, O, or S atom and can optionally be substituted with a rest selected from the group containing C_{1-4}-Alkyl, (C_{0-3}-Alkandiyl-C_{1-3}- Alcoxy), C_{1-4}-Alkanoyl, C_{1-4}-Alkoxycarbonoyl, Aminocarbonyl, and Aryl,

R^3 one or two rests that are independent of each other and are selected from the group that contains:
Hydrogen,
F, Cl, Br,

OH, OR^4, $OCOR^4$, $OCONHR^4$,
COR^4,
CN, COOH, $COOR^4$, $CONH_2$, $CONHR^4$, CONHOH,
$CONHOR^4$,
SR^4, SOR^4, SO_2R^4, SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,
NO_2, NH_2, NHR^4, $NR^4R^{4'}$,
$NHSO_2R^4$, $NR^4SO_2R^{4'}$, $NHSO_2R^6$, $NR^4SO_2R^6$,
$NHCOR^4$, $NHCOOR^4$, $NHCONHR^4$, and R^4,
whereby the rests R^4, $R^{4'}$, and R^6, can be selected independently of each other and according to the meanings that are given further below,

A a group selected from the group containing C_{1-10}-Alkandiyl, C_{2-10}-Alkendiyl, C_{2-10}-Alkindiyl, and (C_{0-3}-Alkandiyl-C_{3-7}-Cycloalkandiyl- C_{0-3}-Alkandiyl), whereby in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, whereby in the above mentioned aliphatic chains one C atom can be exchanged with O, OH, N-C_{1-3}-Alkyl, or C_{1-3}-Alkanoyl and whereby the alkyl or the cycloalkyl groups can be substituted optionally with a rest selected from the group containing = O, OH, O-C_{1-3}-Alkyl, NH_2, NH-C_{1-3}-Alkyl, NH-C_{1-3}-Alkanoyl, N(C_{1-3}-Alkyl)$_2$, and N(C_{1-3}-Alkyl)(C_{1-3}-Alkanoyl),

B a rest selected from the group containing COOH, $COOR^5$, $CONH_2$, $CONHNH_2$, $CONHR^5$, $CONR^5R^{5'}$, CONHOH, $CONHOR^5$, and tetrazolyl, With each one linked to a C atom of the group A, whereby the rests R^5 and $R^{5'}$ can be selected independently of each other under the meanings specified below,

Y a group selected from the group containing O, NH, NR^4, $NCOR^4$, NSO_2R^4, and NSO_2R^6, whereby the rests R^4 and R^6 have the meanings given

further below and where among the aforementioned rests the rests R^4, $R^{4'}$, R^5, $R^{5'}$, and R^6 have the following meanings; Among them there are:

R^4 and $R^{4'}$ each of them is a rest independent of the other and selected from the group containing CF_3, C_2F_5, C_{1-4}-Alkyl, C_{2-4}-Alkenyl, C_{2-3}-Alkinyl, and (C_{0-3}-Alkandiyl-C_{3-7}- Cycloalkyl), whereby in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl,

R^5 and $R^{5'}$ each of them is a rest independent of the other and selected from the group containing C_{1-6}-Alkyl, C_{2-6}-Alkenyl, and C_{2-6}-Alkinyl, whereby one C atom can be exchanged with O, S, SO, SO_2, NH, N-C_{1-3}-Alkyl, or N-C_{1-3}-Alkanoyl, and further in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl and further with (C_{0-3}-Alkandiyl-Aryl) and (C_{0-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is five or six member one and contains one or two hetero-atoms selected from the group containing N, S, and O, whereby all aforementioned alkyl and cycloalkyl rests can be substituted with up to two rests selected from the group containing SF_3, S_2F_5, OH, O-C_{1-6}-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 aforementioned aryl and heteroaryl groups can be substituted with up to two rests selected from the group containing 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, and/or can also carry one anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, or R^5 and $R^{5'}$ together with the amid N atom of B can build a five to seven-member saturated or unsaturated heterocyclic ring, which

can contain another N or O atom and which can be replaced with C_{1-4}-Alkyl, (C_{1-4}-Alkandiyl-C_{1-4}-Alkoxy), C_{1-4}-Alkoxycarbonyl, aminocarbonyl, or aryl,

R^6 a rest selected from the group containing (C_{0-3}-Alkandiyl-Aryl) and (C_{0-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is a five-member or a six-member one and contain one or two hetero-atoms selected from the group containing N, S, and O, and whereby the aryl and heteroaryl groups can be substituted with up to two rests selected from the group containing 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, and/or can carry also one anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group,

R^7 and $R^{7'}$ independent of each other R^4 or R^6.

Such benzimidazole derivatives are preferred, in which the substituent B-A-Y is linked to the 6th position of the benzimidazole.

The present invention includes also physiologically digestible salts as well as esters of the aforementioned compounds, particularly acid salts of nitrogen base of the benzimidazole derivatives in accordance with the present invention, further the salts of the carbon acids of the derivatives in accordance with the present invention with bases, and the esters of the carbon acids of the derivatives as well as the carbon acids, which are derived from carbon acid derivatives, eventually from carbon acid amides.

The benzimidazole derivatives can show one chorale center or many chorale centers, so that the compounds can appear in many isomeric forms. The compounds of Formula I can also appear as tautomers, stereo-isomers, or geometrical isomers. The invention comprises also all possible isomers as E- and Z-isomers, S- and R-enantiomers, diastereomers, razemates, and mixtures

of those, including the tautomer compounds. All these isomer compounds are – also when this has not been explicitly stated – a constituent part of the present invention. The isomer mixtures can be undone into enantiomers or E/Z isomers using the traditional methods, as, for instance, crystallization, chromatography, or salt formation.

The heteroaryl groups that are contained in the benzimidazole derivatives are built of five or six structural atoms and can contain one or two hetero-atoms. The hetero-atoms are oxygen (O), nitrogen (N), and sulfur (S). Some examples of heteroaryl groups are pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, and pyridazinyl. When the heteroaryl groups are part of R^1 or R^2, the group is linked through a C atom to the particular N atom of the benzimidazole structure or to the substituent Z, respectively.

As aryl rests can be considered above all the phenyl rests, but also the naphtyl rests. The aryl rests and the hetero-rests can be connected in an arbitrary way to the benzimidazole base structure or to another group, fro example as 1- or 2-naphthyl or as 2-, 3-, or 4-pyridinyl.

The alkyl groups can be in strait chains or in branched chains. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, tert-pentyl, neo-pentyl, n-hexyl, sec-hexyl, heptyl, octyl, nonyl, decyl. Also the higher-level homologues include both the linear as well as the branched alkyl groups, as, for example, 2-ethylhexyl for octyl and 3-propyl-hexyl for nonyl.

Perfluorated alkyls are preferably CF_3 and C_2F_5.

The alkenyl groups can be in strait chains or in branched chains. Examples for that in the sense of the present invention are: vinyl, 2-Propenyl, I-Propenyl, 2-

butenyl, I-Butenyl, I-Methyl-I -propenyl, 2- Methyl-2-propenyl, and 3-Methyl-2-propenyl Akenyl rests.

The alkinyl groups can be in strait chains or in branched chains. Examples for that are: ethinyl, 1-Propinyl, 2- Propinyl, 1-Butinyl, and 2-Butinyl.

Preferentially, the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl (corresponds to C_{3-7}-cycloalkyl), respectively, are to be understood under the cycloalkyl groups.

The following compounds can be mentioned as an example of a saturated heterocyclic ring with one or many hetero-atoms: Piperidin, Pyrrolidin, Tetrahydrofuran, Morpholin, Piperazin, Hexahydroazepin as well as 2,6-Dimethyl- morpholin, N-Phenyl-piperazin, and Methoxymethyl-pyrrolidin, whereby the linking with one of the C atoms close to the ring can take place through the eventually available N atoms of the ring.

The Alkandiyl-, Alkendiyl, Alkindiyl, and Cyloalkandiyl rests, which are mentioned in the invention description, have the same meaning as the Alkylen, Alkenylen, Alkinylen, and Cycloalkylen. As far as the number of the contained C atoms in the general formulas of the alkandiyl rests is given and when this number is assigned the value of 0 as the bottom range limit, this alkandiyl rest is in any case not contained.

As an example, the following compounds are named as alkane, alkene, and alkine for A: alkandiyl in a straight chain or in branched chain with one and up to eight atoms, for example, Methandiyl, Ethandiyl, Propandiyl, Butandiyl, Pentandiyl, Hexandiyl, and further 1-Methylethandiyl, 1-Ethylethandiyl, 1-Methylpropandiyl, 2-Methylpropandiyl, 1-Methylbutandiyl, 2-Methylbutandiyl, 1-Ethylbutandiyl, 2-Ethylbutandiyl, 1-Methylpentandiyl, 2-Methylpentandiyl, 3-Methylpentandiyl as well as analogous compounds.

The alkendiyl and alkindiyl in a straight chain or in branched chain with two up to eight C atoms are alkendiyl, respectively, alkindiyl groups with double and triple links in all possible positions as well as with all possible methyl or ethyl substitutions. In these rests, one or two C atoms can be exchanged with O, NH, N-C_{1-3}-alkyl, or N-C_{1-3}-alkanoyl, whereby the exchanged group is separated from Y by at least two C atoms.

When two rests stand orthogonally, they can build a common ring with the neighboring aromatics. The connections, in which the V, O, or S atoms are linked to olefinic or acetylenic manifold formations or in which several N, O, S, or halogen atoms are linked to the same aliphatic C atom or in which the N, O, or S atoms are immediately connected to each other, are excluded so long as these connections are not explicitly defined in the particularly mentioned functional groups or in the hetero-aromatics.

The physiologically compatible acid salts on nitrogen bases of the benzimidazole derivatives corresponding to the present invention can be built with inorganic and organic acids, for example with oxal acid, lactic acid, citric acid, fumaric acid, acetic acid, maleic acid, tartaric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, sulphuric acid, p-toluol-sulfonic acid, and methane-sulfonic acid.

For the generation of salts of acid groups, and particularly of carbon acid groups, also the inorganic or organic bases are suitable, which are known for the generation of physiologically compatible salts, as, for example, alkali hydroxide, and particularly sodium and potassium hydroxide, alkaline-earth hydroxide, as well as calcium hydroxide, and further ammonia, as well as amines, as ethanol amine, di-ethanol amine, tri-ethanol amine, N-methyl-glucamine, and tris-(hydroxymethy1)- 4 –methyl amine.

All univalent, bivalent, and trivalent alcohols are suitable for the formation of esters, and particularly the methanol, ethanol, iso-propanol and tert-butanol as well as the ethylene-glycol and glycerin.

Particularly preferred are the benzimidazoles with the general formula I, in which the following given below rests and groups have independently of each other the following meaning:

R^1 a phenyl group, which can be substituted with up to two rests that are independent of each other and are selected from the group containing:
F, Cl, Br,
$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$, $C(NR^4)NR^4R^{4'}$,
OH, OR^4, $OCOR^4$, $OCONHR^4$,
COR^4, $C(NOH)R^4$,
CN, COOH, $COOR^4$, $CONH_2$, $CONR^4R^{4'}$, $CONHR^4$, CONHOH,
SR^4, SOR^4, SO_2R^4,
SO_2NH_2, SO_2NHR^4, $SO_2NR^4\ R^{4'}$,
NO_2, NH_2, NHR^4, $NR^4R^{4'}$, $NHCONHR^4$, and
R^4,
whereby the rests R^4 and $R^{4'}$, according to the below meaning, can be selected independently of each other and whereby two substituents of R^1 can be linked with each other in such a way that they form together one methandiylbisoxy, ethan-1,2- diylbisoxy, propan-1,3-diyl, or butan-1,4-diyl group when they are standing orthogonally to one another.

R^2 means a mono- or bi-cyclic C_{6-10}-argyl group or a mono- or bi-cyclic 5 – 10-member heteroaryl group with 1 – 2 hetero-atoms selected from the group consisting of N, S, or O, whereby the aforementioned aryl or heteroaryl group can be substituted independently of one another with up to three of the following substituents:

F, Cl, Br,
XOH, XOR^4, $XOCOR^4$, $XOCONHR^4$, $XOCOOR^4$,
$XCOR^4$, $XC(NOH)R^4$, $XC(N0R^4)R^4$, $XC(NO(COR^4))R^4$,
XCOOH, $XCOOR^4$, $XCONH_2$, $XCONHR^4$, $XCONR^4R^4$, XCONHOH,
$XCONHOR^4$, $XCOSR^4$,
XSR^4, $XSOR^4$, XSO_2R^4, SO_2NH_2, SO_2NHR^4,,$SO_2NR^4R^4$,
NO_2, $XNHR^4$, XNR^4R^4, $XNHSO_2R^4$, $XN(SO_2R^4)$ SO_2R^4, $XNR^4SO_2R^4$,
R^4,
whereby two substituents of R^2, when they are orthogonally standing to one another, can be linked one to the other in such a way that they build together methandiylbisoxy, ethan-1 ,2-diylbisoxy, propan-1,3-diyl, butan-1,4- diyl,

R^3 a rest selected from the group containing hydrogen, F, Cl, Br, CH_3, C_2H_5, CF_3, C_2F_5, OH, OR^4, $NHSO_2R^6$, and $NHCOR^4$, whereby R^4 and R^6 have the meaning given below,

A C_{1-10}-Alkandiyl, C_{2-10}-Alkendiyl, C_{2-10}-Alkindiyl, (CO_{0-5}-Alkandiyl-C_{3-7}-Cycloalkandiyl-C_{0-5}-Alkandiyl), whereby in one five-member cycloacryl ring there can be one ring link, one N, or one O, and in one six- or seven-member cycloacryl ring there can be one or two ring links N, and/or one O, whereby the ring hydrogen can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, whereby in the above mentioned aliphatic chains one carbon atom or two carbon atoms can be exchanged with O, NH, NC_{1-3}-Alkyl, NC_{1-3}-Alkanoyl,

B a rest selected from the group containing COOH, $COOR^5$, $CONH_2$, $CONHR^5$, and $CONR^5R^{5'}$ where every one is linked to a C atom in the A group, whereby the rests R^5 and $R^{5'}$ can be selected independently of one another in accordance with the meanings given below,

Y O

whereby in the above rests the rests R^4, $R^{4'}$, R^5, $R^{5'}$, and R^6 have the following meanings; there they mean:

R^4 and $R^{4'}$ the same as it was given further above,

R^5 and $R^{5'}$ both are rests independent of each other and selected from the group containing C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, whereby one C atom can be exchanged with O, S, SO, SO_2, NH, N-C_{1-3}-Alkyl, or N-C_{1-3}-Alkanoyl, and further (C_{0-3}-Alkandiyl-C_{3-7}-Cycloalkyl), whereby in one five-member cycloalkyl ring there can be one ring link ring N or ring O, and in one six- or seven-member cycloacryl ring there can be one or two ring links each one ring N and/or ring O atoms, whereby the ring N atoms can be substituted where applicable with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, and further with (C_{1-3}-Alkandiyl-Phenyl) and (C_{1-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is a five- or six-member group and contains one or two hetero atoms selected from the group containing N, S, and O, whereby all above mentioned alkyl and cycloalkyl rests can be replaced with one rest selected from the group containing 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 can be replaced with up to two rests selected from the group containing 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 and/or can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, or R^5 and $R^{5'}$ can build together with the amid N atom of B one five- to seven-member saturated or unsaturated heterocyclic ring, which can contain a further N or O or S atom and which can be substituted with C_{1-4}-Alkyl, (C_{0-2}-Alkandiyl-C_{1-4}-Alkoxy), C_{1-4}-Alkoxy-carbonyl, amino-carbonyl, or phenyl,

R^6 a phenyl or heteroaryl group, whereby the heteroaryl group is a five- or six-member one and contains one or two hetero atoms selected from the group containing N, S, and U, and whereby the phenyl and heteroaryl groups can be replaced with up to two rests selected from the group containing 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 they can also carry an anellated ethandiyl-bisoxy or ethan-1,2-diyl-bisoxy group.

R^3 is preferably hydrogen. The grouping Y – A is reproduced in a preferable implementation form by means of a C_{1-6}-Alkylenoxy group, which is linked to the benzimidazole structure by means of an O atom.

The invention pertains further to the pharmaceutical means, which contain one or more compounds of the general formula I as well as one or more carrier substances. The pharmaceutical means, and respectively the compositions of the invention, are manufactured in the known ways with the customary solid or liquid carrier substances or diluting means as well with the customary pharmaceutical and technological auxiliary materials according to the desired method of administration as well as with a suitable dosage. The preferred preparations consist in an administrable form, which is suitable for oral, enteral or parenteral, for example i. p. (intraperitoneal), i. v. (intravenous), i. m. (intramuscular), or percutaneous application. Such administrable forms are for example tablets, film tablets, dragees, pills, capsules, powders, creams, ointments, lotions, liquids like syrups, gels, injectable liquids, for instance i. p., i. v., i. m., or percutaneous shots, etc. Further, there are also suitable depot forms like implantable formulations as well as suppositories. Moreover, the separate formulations of the derivatives according to the present invention in accordance with their way of administration deliver the whole amount to the body gradually or in a short time.

For oral administration, capsules, pills, tablets, dragees, and liquids or other forms of administration like pharmaceutical preparations can be used. In these cases, the medications can be formulated in such a way that they could release the active substances and deliver them to the body either in a short period of time or to effect a depot action so that a longer lasting and slower delivery of the active substance could be achieved. The dosage units can contain along with at least one benzimidazole derivative one or more pharmaceutically compatible carriers, for instance substances for regulation of the rheology of the medication, surface-active substances, solving agents, micro capsules, micro particles, granulates, diluters, binding substances like starch, sugar, sorbit, and gelatin, and further filling substances like silicic acid and talc, lubricants, pigments, scents, and other substances.

The corresponding tablets can be offered for instance by means of mixing the active substance with known auxiliary substances, for example inert diluting agents like dextrose, sugar, sorbit, mannit, polyvinylpyrrolidon, exploders like corn starch or alginic acid, binding substances as, for instance, starches or gelatin, lubricants like carboxypolymethylen, carboxymethylcellulose, celluloseacetatphthalat, or polyvinylacetat. The tablets can consist also of many layers.

Correspondingly, the dragees can be manufactured with coatings using materials similar to those normally used in the manufacturing of the tablets with kernels, for example polyvinylpyrrolidon or schellack, Arabic gum, talc, titan oxide, or sugar. Thereby the shell of the dragee can also consist of several layers, whereby the tablet auxiliary materials mentioned above can be used.

Capsules containing the active substances can be manufactured for instance in a way where the active substance is mixed with an inert carrier like milk sugar or sorbit and encapsulated in gelatin capsules.

The active substances can also be prepared in the form of a solution, which is intended for oral administration and which contains as composition components along with the active benzimidazole derivatives also pharmaceutically compatible oil and/or pharmaceutically compatible lipophile, a surface active substance and/or a pharmaceutically compatible hydrophile, a surface active substance and/or a pharmaceutically compatible solvent that can be mixed with water.

In order to achieve better biological availability of the active substances, the compounds can be formulated also as cyclodextrin chlathrates. Here the compounds are transformed with α-, β-, or γ-cyclodextrin or their derivatives.

In the case when crèmes, ointments, lotions, or other externally applicable liquids have to be used, they have to be conditioned in such a way that the compounds could be supplied to the body in sufficient amount. In these forms of preparation, auxiliary substances are contained, for example substances for regulating the rheology of the medication, surface-active agents, preservation substances, solution facilitators, dilutors, substances for increasing the permeation capability for the active substances through the skin, pigments, scents, and skin protection agents such as conditioners and humidity regulators. Along with the compounds, the medication can contain also other active substances (Ullmanns Enzyklopädie der technischen Chemie, Band 4 (1953), Seiten 1-39; J. Pharm. Sci., 52, 918 ff. (1963); H. v.Czetsch-Lindenwald, Hilfsstoffe für Pharmazie und angrenzende Gebiete; Pharm. Ind., 2,72 ff (I 961); Dr. H. P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Cantor AG, Aulendorf/Württ., 1971).

The substances can be applied also in suitable solutions as, for instance, physiological table salt solution, infusion solution, or injection solution. For parenteral application, the active substances can be solved or put in a suspension in physiologically compatible dilution agent. The oily solutions such as for instance solutions in sesame seed oil, castor oil, and cotton seed oil are

particularly suitable as dilution agents. Solving facilitators such as for instance benzyl benzoate or benzyl alcohol can be added for increasing the solvability.

For the formulation of an injectable preparation, an arbitrary liquid carrier can be used, into which the compounds prepared in accordance with the present invention can be solved or emulsified. These liquids often contain also substances for the regulation of the viscosity, surface-active agents, preservation agents, solving agent, diluters, and other additional substances, through which the solution can be isotonically regulated. Along with the benzimidazole derivatives, other active substances can also be administered.

It is also possible the substances to be incorporated into a transdermal system and in this way to be applied transdermally. For this purpose, the benzimidazole derivatives can be applied in the form of a depot shot or as an implantation preparation, for example in a subcutane manner. Such preparations can be formulated in such a way that a delayed release of the active substance to become possible. For this purpose, some known techniques can be used, for example self-terminating depots or depots functioning with a membrane. The implantates can contain as inert materials biologically degradable polymers or synthetic silicones, for instance silicone rubber. The benzimidazole derivatives can further be incorporated for percutane administration, for instance into a plaster.

The dosage of the substances is determined by the attending physician and depends among other things on the administered substance, the way of administration, the ailment to be treated, and the gravity of the ailment. The daily dose amounts to no more than 1000 mg, preferably no more than 100 mg, whereby the dose can be administered as a single dose that is to be administered once or it can be divided into two or more daily doses.

Research Regarding the Biological Properties

Example 1:

Activation of the Macrophages

For testing the substances on the macrophages/monocytes, LPS-activated THP-1 cells have been used. For this purpose, 2.5 x 106 cells/ml were sown in RPMI medium (RPMI 1640 + 10 % FCS). The compounds prepared in accordance with the present invention were added in concentration of 5 μM and were pre-incubated for 30 minutes. The stimulation of the cells took place during the night at 37° C with 0.1 μg/ml LPS. Afterwards, the medium was reaped and the TNFα amount was quantitatively determined. The treatment of the cells with the substances prepared in accordance with the present invention led to a reduction of the TNFα amount of at least 30 per cent.

Example 2:

Inhibition of the TNFα and IL 12 Production in THP-1 Cells

The inhibition of the cytokin production can be represented for instance by means of measurement of the TNFα and the interleukin 12 in the lipopolysaccharid (LPS) stimulated THP-1 cells.

For this purpose, 2.5 x 10^6 THP-1 cells (American Type Culture Company, Rockville, Md) / ml RPMI 1640 Medium (Life Technologies) /10 % FCS (Life Technologies, Cat.-No. 10270-1 06) were sown (100 μl/hole) on 96-holes flat-bottom cell-culture plate (TPP, Product-No. 9296). The compounds prepared in accordance with the present invention were adder in different concentrations and were pre-incubated for 30 minutes. The preliminary dilution of the test substances was performed in the incubation medium. The addition of the test substances was performed as twice concentrated substance solution (100 μl/hole). The stimulation of the cells was performed during the night at 37° C with 0.1 μg/ml LPS (Sigma L2630 of E. Coli serotype 0111.B4). Afterwards, the medium was reaped and the TNFα amount and, respectively, the interleukin 12

amount were quantitatively determined. For the measurement of the TNFα, a commercially available TNFα kit of the company CIS bio international (product No. 62TNFPEB) was used. The interleukin 12 amount was determined by using the ORIGEN technology (IGEN International, Inc., Gaithersburg, Maryland). The obtained IC50 value corresponds to the concentration of the test substance that is necessary in order to achieve a 50 % inhibition of the maximum TNFα and, respectively, interleukin 12 production.

In this experiment, the substances show an IC50 below 10 μM. By means of similar methods, the inhibition of IL 12 and TNFα with the substances can be represented also in the case of using peripheral blood leucocytes and other comparable stimuli.

Example 3

Inhibition of the Production of IFNγ by Peripherial Mononuclear Blood Cells

In order to represent the effect of the substances on the T-cell activation, for instance the measurement of the IFNγ secretion can be used.

Human full blood was used for isolation of the peripherial mononuclear cells (blood taking via Na-Zitrat S-Monovettes, "coagulation 9 NC/10 ml"/Sarstedt). The enrichment of the blood cells was performed by means of thickness gradient centrifugation: for this purpose, 15 ml Histopaque 1077 (Sigma, Cat. No. H8880) in LEUCOSEP tubule (Greiner, Cat. No. 227290) were used and were centrifuged for 30 seconds at 1000 g. Thereafter, 15 ml of full blood were added and were centrifuged for 10 minutes at 1000 g. Subsequently, the upper plasma layer was removed with a pipette and the cell layer lying below (peripherial mononuclear blood cells) was transferred in 15 ml test tube (Falcon) and was subsequently washed many times with 10 ml HBSS (HANKS balanced 25 Solution (without Mg2+ and Ca2+), Cat. No. 14175-53). Finally, the cell pellet was re-suspended (1 X 10^6 cells/ml) in culture medium RPMI 1640 + 25 mM Hepes (Life Technologies Cat. No. 52400-041 10 % FCS (Life Technologies, Cat. No. 10270-1 O6), 0,4 % Penicillin-Streptomycin-solution (Life Technologies,

Cat. No. 151 40-1 06). Every 100 µl cell suspension solution were spread on 96-holes flat- bottom cell-culture plate (TPP, Product-No. 9296) and were stimulated by means of 5 µg/ml phytohaemaglutinin. The substance prepared in accordance with the present invention were added in different concentrations and were pre-incubated for 30 minutes. The stimulation of the cells took place during a period of 48 hours. Afterwards, the medium was reaped and the IFNγ amount was quantitatively determined. The IFNγ amount was determined by using the ORIGEN technology (IGEN International, Inc., Gaithersburg, Maryland). The calculated IC50 value corresponds to the concentration of the test substance, which is necessary in order to achieve a 50m per cent inhibition of the maximum IFNγ production.

The treatment of the cells with the test substances has led to a reduction of the IFNγ amount of at least 30 per cent at concentration of 10 µM. By using similar methods, the inhibition of IFNγ with the substances can be represented also in the case of using specific T-cell activators as, for instance, monoclonal anti-CD3 antibodies.

Table 1

Substance	Inhibition of the IL 12 Secretion (IC50)	Inhibition of the TNFα Secretion (IC50)	Inhibition of the IFNγ Secretion (IC50)	Inhibition of the Microglia Activation (IC50)
1	2.2 µM	3 µM	1.3 µM	0.75 µM
2	< 0.3 µM	0.15 µM	0.11 µM	0.16 µM

Substance 1:

6-[[1-(4-Methylpheny1)-2-phenyl-1H-benzimidazol-6-yl]oxy]hexan-acid-isopropylester

Substance 2:

6-[[1-(4-Methylphenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]hexan-acid.

Example 4:

Induction of the IL 10 Production by Peripherial Mononuclear Blood Cells

The induction of the IL 12 production is represented for example through measurement of IL 10 in phytohaemaglutinin (PHA) or lipoplysaccharid (LPS) simulated peripherial mononuclear blood cells.

For isolation of the peripherial mononuclear blood cells, human full blood has been used (blood taking via Na-Zitrat S-Monovettes, "coagulation 9 NC/10 ml"/Sarstedt). The enrichment of the lymphocytes and the monocytes has been performed by means of thickness gradient centrifugation. For this purpose, 15 ml Histopaque 1077 (Sigma, Cat. No. H8880) in 50 ml LEUCOSEP tubule (Greiner, Cat. No. 227290) were used and were pressed down through the frit in the tubules by means of centrifugation for 30 seconds at 250 g. Subsequently, 20 ml full blood were added and centrifuged for 15 minutes at 800 g and at room temperature. After the centrifugation, the residue (plasma and thrombocytes) was removed with a pipette and thrown out while the cell layer lying below (lymphocytes and monocytes) was transferred to a 50 ml centrifuge tubule (Falcon) and was subsequently washed (centrifugation every time for 10 minutes at 250 g and at room temperature) three times in culture medium VLE RPMI 1640 (Seromed, No. FG1415). Finally, the cell pellet was re-suspended in culture medium VLE RPMI 1640 (Seromed, No. FG1415), 10 % FCS (Life Technologies, Cat. No. 16000-044, low endotoxin, heat activated 1 hour, 56° C), 50 µg/ml penicillin/streptomycin solution (Life Technologies, Cat. No. 15140-106) and after cell counting by means of trypan blue coloring was set to 3 x 10^6 cells. Every 100 µl of cell suspension solution were spread on 96-holes flat- bottom cell-culture plate (Costar, Product No. 3599). Added to every one of them were 100 µl triply concentrated stimulation solution (3 µg/ml LPS of E. coli Serotype 0127:B8; Sigma, Cat. No. L-4516, respectively 300 µg/ml PHA-L, Biochrom KG, Cat No. M5030). The substances prepared in accordance with the present invention were added in different concentrations as a triply concentrated substance solution (100

µl/well). The stimulation of the cells took place at 37° C and 5 % CO_2 during a period of 24 hours. Afterwards, the cell culture residue was reaped and the IL 10 was quantitatively determined. The IL 10 concentration was determined by means of a commercially available ELISA kit of the company BioSource International (Human IL-10, Cat.No. KHCOIOIC). The calculated value of EC_{50} corresponds to the concentration of the test substance that is necessary in order to increase the IL 10 secretion with 50 % of the maximum increase.
The substances prepared in accordance with the present invention increase the IL 10 production of peripherial mononuclear blood cells.

Example 5:

Inhibition of the TNFα and IL 12 HD Production of Peripherial Mononuclear Blood Cells

The inhibition of the TNFα and IL 12 HD p70 production is represented for instance through the measurement of the TNFα and IL 12 HD p70 in the peripherial mononuclear blood cells stimulated with lipopolysaccharid (LPS) and interferon gamma (IFNγ).
For isolation of the peripherial mononuclear blood cells, human full blood has been used (blood taking via Na-Zitrat S-Monovettes, "coagulation 9 NC/10 ml"/Sarstedt). The enrichment of the lymphocytes and the monocytes has been performed by means of thickness gradient centrifugation. For this purpose, 15 ml Histopaque 1077 (Sigma, Cat. No. H8880) in 50 ml LEUCOSEP tubule (Greiner, Cat. No. 227290) were used and were pressed down through the frit in the tubules by means of centrifugation for 30 seconds at 250 g. Subsequently, 20 ml full blood were added and centrifuged for 15 minutes at 800 g and at room temperature. After the centrifugation, the residue (plasma and thrombocytes) was removed with a pipette and thrown out and the cell layer lying below (lymphocytes and monocytes) was transferred to a 50 ml centrifuge tubule (Falcon) and was subsequently washed (centrifugation every time for 10 minutes at 250 g and at room temperature) three times in culture medium VLE RPMI

1640 (Seromed, No. FG1415). Finally, the cell pellet was re-suspended in culture medium VLE RPMI 1640 (Seromed, No. FG1415), 10 % FCS (Life Technologies, Cat. No. 16000-044, low endotoxin, heat activated 1 hour, 56° C), 50 µg/ml penicillin/streptomycin solution (Life Technologies, Cat. No. 15140-106) and after cell counting by means of trypan blue coloring was set to 3 x 10^6 cells. Every 100 µl of cell suspension solution were spread on 96-holes flat- bottom cell-culture plate (Costar, Product No. 3599). Added to every one of them were 100 µl triply concentrated stimulation solution (3 µg/ml LPS of E. coli Serotype 0127:B8; Sigma, Cat.No. L-4516 and 30 ng/ml INF_γ 1b, imukin, Boehringer, Ingelheim). The substances prepared in accordance with the present invention were added in different concentrations as a triply concentrated substance solution (100 µl/well). The stimulation of the cells took place at 37° C and 5 % CO_2 during a period of 24 hours. Afterwards, the cell culture residue was reaped and the concentrations of the TNFα and the IL 12 were determined by means of the commercially available ELISA kit of the companies BioSource International (TNF-α EASIA, Cat. No. KAC1752) and R&D Systems (Quantikine™ HS IL 12, Cat. No. HS 120).

The calculated value of IC_{50} corresponds to the concentration of the test substance that is necessary in order to achieve a 50 % inhibition of the maximum TNFα production and, respectively, of the interleukin 12 HD p70 production.

The substances prepared in accordance with the present invention inhibit the TNFα and the IL 12 HD p70 production of peripherial mononuclear blood cells.

Table 2

Substance	Inhibition of the IL 12 HD Secretion after LPS&IFNg Stimulation		Inhibition of the TNF-alpha Secretion after LPS&IFNg Stimulation		Induction of the IL 10 Secretion after PHA Stimulation	
	IC50 (mol/l)	Efficiency (%)	IC50 (mol/l)	Efficiency (%)	IC50 (mol/l)	Efficiency (%)
1	9.2E-08	81	6.5E-07	65	> 1.0E-6	245
2	3.0E-08	93	1.2E-07	83	1.8E-07	283

Substance 1:

6-[[l-(4-Methylphenyl)-2-phenyl-1H-benzimidazol-6-yl]oxy]hexan acid-isopropylester.

Substance 2:

6-[[1-(4-Methylphenyl)-2-phenyl-1 H-benzimidazol-6-yl]oxy]hexan acid.

Patent Claims

1. Application of Microglia inhibitors for the manufacturing of medication for the treatment of monocyte mediated, macrophage mediated, or T cell mediated immune reactions.

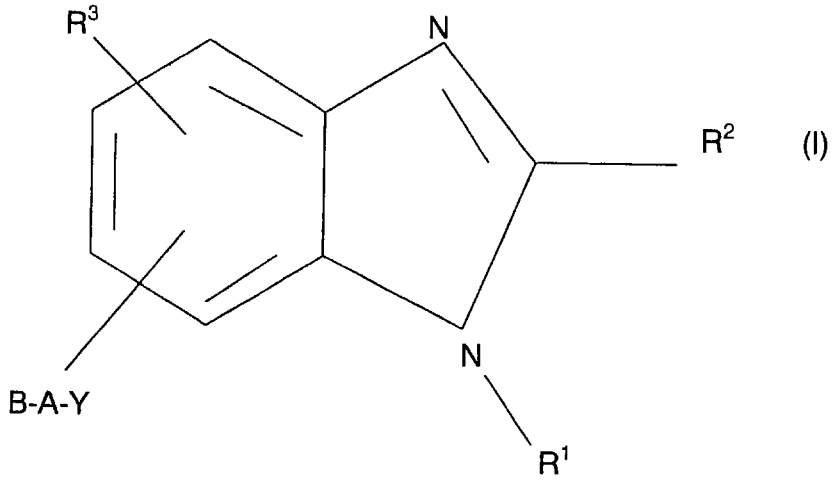
2. Application in accordance with Claim 1 for treatment of interleukin 12 (IL 12) and interferon γ (IFNγ) mediated immune reactions.

3. Application in accordance with Claim 1 for treatment of not T cell mediated inflammatory reactions.

4. Application in accordance with Claim 1 for treatment of autoimmune diseases, inflammatory diseases, which are not based on neuro-inflammation, allergic, and infectious diseases.

5. Application in accordance with Claim 4 for treatment of chronic inflammatory intestinal diseases, for example the inflammatory bowel disease, Crohn's disease, or ulcerous colitis, arthritis, allergic contact eczema, psoriasis, pemphigus, asthma, 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, sarcoidose, asthma, hypersensitive pneumonitis, sepsis, septic shock, endotoxin shock, toxic shock syndrome, toxic lever failure, ARDS (acute shortness of breath syndrome), eclampsia, cachexia, acute virus infections, organ damage after re-perfusion, "first dose response" after administration of anti-T-cell antibodies.

6. Application of the benzimidazole of Formula I, its tautomer or isomer form or salt.



Among them there are:

R^1 An aryl group or a five or six-member hetero-aryl group with one or two hetero-atoms, selected from the group and containing N, S, and O, whereby the aryl or the hetero-aryl group can be substituted with up to three rests that are independent of each other and selected from the group containing:

F, Cl, Br,
$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$, $C(NR^4)N\ R^4R^{4'}$,
X-OH, $X\text{-}OR^4$, $X\text{-}OCOR^4$, $X\text{-}OCONHR^4$,
$X\text{-}COR^4$, $X\text{-}C(NOH)R^4$,
X-CN, X-COOH, $X\text{-}COOR^4$, $X\text{-}CONH_2$, $X\text{-}CONR^4R^4$, $X\text{-}CONHR^4$,
X-CONHOH,

$X\text{-}SR^4$, $X\text{-}SO_2$, $X\text{-}SO_2R^4$,

SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,

NO_2, $X\text{-}NH_2$, $X\text{-}NHR^4$, $X\text{-}NR^4R^{4'}$, $X\text{-}NHSO_2R^4$, $X\text{-}NR^4SO_2R^4$,

$X\text{-}NHCOR^4$, $X\text{-}NHCOOR^4$, $X\text{-}NHCONHR^4$ and

R^4,

Whereby X is a compound CH_2, $(CH_2)_2$, or $CH(CH_3)_2$, whereby further under the given conditions the rests R^4 and $R^{4'}$, are selected

independently from each other and whereby two substitutions of R^1 – when they are orthogonally standing – can be connected to each other, so that they form together a methan-diyl-bisoxy-, ethan-1,2-diyl-bisoxy propan-1,3-diyl- or butan-1,4-diyl group, or

a rest selected from the group containing C_{1-6}Alkyl, (C_{0-3}-Alkandiyl-C_{3-7}-Cycloalkyl), and C_{3-6}Alkenyl, where one H-atom can be exchanged in such a way with one heterocyclic rest selected from the group containing piperazin, morpholine, piperidin, and pyrrolidin, so that a bond to one first N-atom of the heterocyclic rest can be built, whereby the above mentioned alkyl, cycloalkyl, and alkenyl rests and the heterocyclic rest can be substituted with up to two rests selected from the group containing C_{0-2}-Alkandiyl-OH, C_{0-2}-Alkandiyl-OR^7,
C_{0-2}-Alkandiyl-NH_2, C_{0-2}-Alkandiyl-NHR^7, C_{0-2}-Alkandiyl-$NR^7R^{7'}$,
C_{0-2}-Alkandiyl-$NHCOR^7$, C_{0-2}-Alkandiyl-NR^7 $COR^{7'}$, C_{0-2}-Alkandiyl-$NHSO_3R^7$, C_{0-2}-Alkandiyl-$NR^7SO_2R^{7'}$, C_{0-2}-Alkandiyl-CO_2H,
C_{0-2}-Alkandiyl-CO_2R^7,
C_{0-2}-Alkandiyl-$CONH_2$, C_{0-2}-Alkandiyl-$CONHR^7$, C_{0-2}-Alkandiyl-$CONR^7$ $R^{7'}$, phenyl, and one five or six-member heteroaryl rest, whereby the heteroaryl rest contains one or two hetero-atoms selected from the group containing N, S, and O, whereby further the phenyl and the heteroaryl rests can be substituted with up to two rests selected from the group that contains 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 CO_2NH_2, and/or also can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl- bisoxy group, whereby the piperazin rest can be substituted at a second oxygen atom also with R^7, COR^7, or SO_2R^7, whereby R^7 and $R^{7'}$ can be selected independently of each other in accordance with the meanings given further below,

R^2 $-Z-R^2$ – an aryl group or a five or six-member heteroaryl group with one or two hetero-atoms selected from the group containing N, S, and O, a

benzothienyl group or an indolyl group, whereby the above mentioned aryl or heteroaryl group can be substituted with up to three rests independently of each other selected from the group containing

F, Cl, Br,

$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$, $C(NR^4)N\ R^4R^{4'}$,

X-OH, $X\text{-}OR^4$, $X\text{-}OCOR^4$, $X\text{-}OCONHR^4$,

$X\text{-}COR^4$, $X\text{-}C(NOH)R^4$,

X-CN, X-COOH, $X\text{-}COOR^4$, $X\text{-}CONH_2$, $X\text{-}CONR^4R^4$, $X\text{-}CONHR^4$, X-CONHOH,

$X\text{-}SR^4$, $X\text{-}SO_2$, $X\text{-}SO_2R^4$,

SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,

NO_2, $X\text{-}NH_2$, $X\text{-}NHR^4$, $X\text{-}NR^4R^{4'}$, $X\text{-}NHSO_2R^4$, $X\text{-}NR^4SO_2R^4$, $X\text{-}NHCOR^4$, $X\text{-}NHCOOR^4$, $X\text{-}NHCONHR^4$ and

R^4,

Whereby X is a compound CH_2, $(CH_2)_2$, or $CH(CH_3)_2$, whereby further under the given conditions the rests R^4 and $R^{4'}$, are selected independently from each other and whereby two rests of R^1 – when they are orthogonally standing – can be connected to each other, so that they form together a methan-diyl-bisoxy-, ethan-1,2-diyl-bisoxy propan-1,3-diyl- or butan-1,4-diyl group,

Z NH, $NR^{2''}$, O, S, SO or SO_2, whereby R" has the meaning that is given below,

$R^{2'}$ and $R^{2''}$ each one is a rest independent of the other and selected from the group that contains:

$C_{1\text{-}4}$-Perfluoralkyl, $C_{1\text{-}6}$-Alkyl, ($C_{0\text{-}3}$-Alkandiyl-$C_{3\text{-}7}$- Cycloalkyl), ($C_{0\text{-}3}$Alkandiyl-Aryl), and ($C_{0\text{-}3}$Alkandiyl-Heteroaryl), where the heteroaryl group is a five or six-member one and contains one or two hetero-atoms selected from the group containing N, S, and O, and whereby the aryl and

the heteroaryl groups can be each one substituted with up to two rests selected from the group containing 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_5, and/or also can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, and further a ring link can be in a five-member cycloakryl ring N or ring O and one or two ring links in a six- or seven-member cycloakryl ring N and/or ring O atoms, whereby the ring N atoms can eventually be substituted with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, or $R^{4'}$ and $R^{2''}$ together with Z can build one six- or seven-member hetero-cyclic, where Z is an atom, whereby Z has the meaning that has been mentioned above, whereby further the hetero-cyclic ring contains another N, O, or S atom and can optionally be substituted with a rest selected from the group containing C_{1-4}-Alkyl, (C_{0-3}-Alkandiyl-C_{1-3}- Alcoxy), C_{1-4}-Alkanoyl, C_{1-4}-Alkoxycarbonoyl, Aminocarbonyl, and Aryl,

R^3 one or two rests that are independent of each other and are selected from the group that contains:
Hydrogen,
F, Cl, Br,
OH, OR^4, $OCOR^4$, $OCONHR^4$,
COR^4,
CN, COOH, $COOR^4$, $CONH_2$, $CONHR^4$, CONHOH,
$CONHOR^4$,
SR^4, SOR^4, SO_2R^4, SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,
NO_2, NH_2, NHR^4, $NR^4R^{4'}$,
$NHSO_2R^4$, $NR^4SO_2R^{4'}$, $NHSO_2R^6$, $NR^4SO_2R^6$,
$NHCOR^4$, $NHCOOR^4$, $NHCONHR^4$, and R^4,
whereby the rests R^4, $R^{4'}$, and R^6, can be selected independently of each other and according to the meanings that are given further below,

A a group selected from the group containing C_{1-10}-Alkandiyl, C_{2-10}-Alkendiyl, C_{2-10}-Alkindiyl, and (C_{0-3}-Alkandiyl-C_{3-7}-Cycloalkandiyl- C_{0-3}-Alkandiyl), whereby in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, whereby in the above mentioned aliphatic chains one C atom can be exchanged with O, OH, N-C_{1-3}-Alkyl, or C_{1-3}-Alkanoyl and whereby the alkyl or the cycloalkyl groups can be substituted optionally with a rest selected from the group containing = O, OH, O-C_{1-3}-Alkyl, NH_2, NH-C_{1-3}-Alkyl, NH-C_{1-3}-Alkanoyl, N(C_{1-3}-Alkyl)$_2$, and N(C_{1-3}-Alkyl)(C_{1-3}-Alkanoyl),

B a rest selected from the group containing COOH, $COOR^5$, $CONH_2$, $CONHNH_2$, $CONHR^5$, $CONR^5R^{5'}$, CONHOH, $CONHOR^5$, and tetrazolyl, With each one linked to a C atom of the group A, whereby the rests R^5 and $R^{5'}$ can be selected independently of each other under the meanings specified below,

Y a group selected from the group containing O, NH, NR^4, $NCOR^4$, NSO_2R^4, and NSO_2R^6, whereby the rests R^4 and R^6 have the meanings given further below and where among the aforementioned rests the rests R^4, $R^{4'}$, R^5, $R^{5'}$, and R^6 have the following meanings; Among them there are:

R^4 and $R^{4'}$ each of them is a rest independent of the other and selected from the group containing CF_3, C_2F_5, C_{1-4}-Alkyl, C_{2-4}-Alkenyl, C_{2-3}-Alkinyl, and (C_{0-3}-Alkandiyl-C_{3-7}- Cycloalkyl), whereby in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl,

R^5 and $R^{5'}$ each of them is a rest independent of the other and selected from the group containing C_{1-6}-Alkyl, C_{2-6}-Alkenyl, and C_{2-6}-Alkinyl, whereby one C atom can be exchanged with O, S, SO, SO_2, NH, N-C_{1-3}-Alkyl, or N-C_{1-3}-Alkanoyl, and further in one five-member cycloacryl ring there can be one ring-link ring N or ring O and in one six- or seven-member cycloacryl ring there can be one or two ring links - ring N and/or ring O atoms, respectively, whereby the ring N atoms can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl and further with (C_{0-3}-Alkandiyl-Aryl) and (C_{0-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is five or six member one and contains one or two hetero-atoms selected from the group containing N, S, and O, whereby all aforementioned alkyl and cycloalkyl rests can be substituted with up to two rests selected from the group containing SF_3, S_2F_5, OH, O-C_{1-6}-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 aforementioned aryl and heteroaryl groups can be substituted with up to two rests selected from the group containing 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, and/or can also carry one anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, or R^5 and $R^{5'}$ together with the amid N atom of B can build a five to seven-member saturated or unsaturated heterocyclic ring, which can contain another N or O atom and which can be replaced with C_{1-4}-Alkyl, (C_{1-4}-Alkandiyl-C_{1-4}-Alkoxy), C_{1-4}-Alkoxycarbonyl, aminocarbonyl, or aryl,

R^6 a rest selected from the group containing (C_{0-3}-Alkandiyl-Aryl) and (C_{0-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is a five-member or a six-member one and contain one or two hetero-atoms selected from the group containing N, S, and O, and whereby the aryl and heteroaryl groups can be substituted with up to two rests selected from the group containing 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, and/or can carry also one anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group,

R^7 and $R^{7'}$ independent of each other R^4 or R^6.

Means for manufacturing a medication for the treatment of a disease in accordance with claims 1 - 5.

7. Application of benzimidazole in accordance with Claim 6 and characterized with the following meaning:

R^1 a phenyl group, which can be substituted with up to two rests that are independent of each other and are selected from the group containing:
F, Cl, Br,
$C(NH)NH_2$, $C(NH)NHR^4$, $C(NH)NR^4R^{4'}$, $C(NR^4)NH_2$, $C(NR^4)NHR^{4'}$, $C(NR^4)NR^4R^{4'}$,
OH, OR^4, $OCOR^4$, $OCONHR^4$,
COR^4, $C(NOH)R^4$,
CN, COOH, $COOR^4$, $CONH_2$, $CONR^4R^{4'}$, $CONHR^4$, CONHOH,
SR^4, SOR^4, SO_2R^4,
SO_2NH_2, SO_2NHR^4, $SO_2NR^4R^{4'}$,
NO_2, NH_2, NHR^4, $NR^4R^{4'}$, $NHCONHR^4$, and
R^4,
whereby the rests R^4 and $R^{4'}$, according to the below meaning, can be selected independently of each other and whereby two substituents of R^1 can be linked with each other in such a way that they form together one methandiylbisoxy, ethan-1,2- diylbisoxy, propan-1,3-diyl, or butan-1,4-diyl group when they are standing orthogonally to one another.

R^2 means a mono- or bi-cyclic C_{6-10}-argyl group or a mono- or bi-cyclic 5 – 10-member heteroaryl group with 1 – 2 hetero-atoms selected from the group consisting of N, S, or O, whereby the aforementioned aryl or

heteroaryl group can be substituted independently of one another with up to three of the following substituents:
F, Cl, Br,
XOH, XOR^4, $XOCOR^4$, $XOCONHR^4$, $XOCOOR^4$,
$XCOR^4$, $XC(NOH)R^4$, $XC(N0R^4)R^4$, $XC(NO(COR^4))R^4$,
XCOOH, $XCOOR^4$, $XCONH_2$, $XCONHR^4$, $XCONR^4R^4$, XCONHOH,
$XCONHOR^4$, $XCOSR^4$,
XSR^4, $XSOR^4$, XSO_2R^4, SO_2NH_2, SO_2NHR^4,,$SO_2NR^4R^4$,
NO_2, $XNHR^4$, XNR^4R^4, $XNHSO_2R^4$, $XN(SO_2R^4)$ SO_2R^4, $XNR^4SO_2R^4$,
R^4,
whereby two substituents of R^2, when they are orthogonally standing to one another, can be linked one to the other in such a way that they build together methandiylbisoxy, ethan-1 ,2-diylbisoxy, propan-1,3-diyl, butan-1,4- diyl,

R^3 a rest selected from the group containing hydrogen, F, Cl, Br, CH_3, C_2H_5, CF_3, C_2F_5, OH, OR^4, $NHSO_2R^6$, and $NHCOR^4$, whereby R^4 and R^6 have the meaning given below,

A C_{1-10}-Alkandiyl, C_{2-10}-Alkendiyl, C_{2-10}-Alkindiyl, (CO_{0-5}-Alkandiyl-C_{3-7}-Cycloalkandiyl-C_{0-5}-Alkandiyl), whereby in one five-member cycloacryl ring there can be one ring link, one N, or one O, and in one six- or seven-member cycloacryl ring there can be one or two ring links N, and/or one O, whereby the ring hydrogen can be eventually replaced with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, whereby in the above mentioned aliphatic chains one carbon atom or two carbon atoms can be exchanged with O, NH, NC_{1-3}-Alkyl, NC_{1-3}-Alkanoyl,

B a rest selected from the group containing COOH, $COOR^5$, $CONH_2$, $CONHR^5$, and $CONR^5R^{5'}$ where every one is linked to a C atom in the A group, whereby the rests R^5 and $R^{5'}$ can be selected independently of one

another in accordance with the meanings given below,

Y O

whereby in the above rests the rests R^4, $R^{4'}$, R^5, $R^{5'}$, and R^6 have the following meanings; there they mean:

R^4 and $R^{4'}$ the same as it was given further above,

R^5 and $R^{5'}$ both are rests independent of each other and selected from the group containing C_{1-6}-Alkyl, C_{2-6}-Alkenyl, C_{2-6}-Alkinyl, whereby one C atom can be exchanged with O, S, SO, SO_2, NH, N-C_{1-3}-Alkyl, or N-C_{1-3}-Alkanoyl, and further (C_{0-3}-Alkandiyl-C_{3-7}-Cycloalkyl), whereby in one five-member cycloalkyl ring there can be one ring link ring N or ring O, and in one six- or seven-member cycloacryl ring there can be one or two ring links each one ring N and/or ring O atoms, whereby the ring N atoms can be substituted where applicable with C_{1-3}-Alkyl or C_{1-3}-Alkanoyl, and further with (C_{1-3}-Alkandiyl-Phenyl) and (C_{1-3}-Alkandiyl-Heteroaryl), whereby the heteroaryl group is a five- or six-member group and contains one or two hetero atoms selected from the group containing N, S, and O, whereby all above mentioned alkyl and cycloalkyl rests can be replaced with one rest selected from the group containing 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 can be replaced with up to two rests selected from the group containing 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 and/or can carry an anellated methandiyl-bisoxy or ethan-1,2-diyl-bisoxy group, or R^5 and $R^{5'}$ can build together with the amid N atom of B one five- to seven-member saturated or unsaturated heterocyclic ring, which can contain a further N or O or S atom and which can be substituted with C_{1-4}-Alkyl, (C_{0-2}-Alkandiyl-C_{1-4}-Alkoxy), C_{1-4}-Alkoxy-

carbonyl, amino-carbonyl, or phenyl,

R^6 a phenyl or heteroaryl group, whereby the heteroaryl group is a five- or six-member one and contains one or two hetero atoms selected from the group containing N, S, and U, and whereby the phenyl and heteroaryl groups can be replaced with up to two rests selected from the group containing 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 they can also carry an anellated ethandiyl-bisoxy or ethan-1,2-diyl-bisoxy group.

8. Application of benzimidazole in accordance with Claim 6 or Claim 7 characterized by the fact that R^3 is hydrogen and Y – A is C_{1-6}-Alkylenoxy.