Abstract:
The present invention relates to benzimidazole-carboxylic acid amide compounds of the formula I, in which $R^1, R^2, R^3, R^4, R^5, R^6$ and $Z$ are defined as indicated below. The compounds of the formula I are APJ receptor modulators, and are useful for the treatment of diseases associated with increased blood pressure for example. The invention furthermore relates to the use of compounds of the formula I, in particular as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.
Benzoimidazole-carboxylic acid amide derivatives as APJ receptor modulators

The present invention relates to benzoimidazole-carboxylic acid amide compounds of the formula I,

\[
\begin{align*}
\text{R}', \text{R}''', \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6 \text{ and } Z \text{ are defined as indicated below.}
\end{align*}
\]

The compounds of the formula I are APJ receptor modulators, and are useful for the treatment of diseases associated with increased blood pressure for example. The invention furthermore relates to the use of compounds of the formula I, in particular as active ingredients in pharmaceuticals, and pharmaceutical compositions comprising them.

commercially available immunoassay. However, in the light of a recent publication describing a more accurate combined liquid chromatography and tandem mass spectrometry assay for the absolute quantification of different apelin peptides all the immunoassay results may need to be revised. (Mesmin et al. Rapid Commun Mass Spectrom. 2010;24: 2875-2884). Surprisingly these authors could not detect five major forms of circulating apelins in amounts indicated by the immunoassay. The main sources for plasma apelins are currently unclear, although vascular endothelium, atria of the heart and adipocytes are likely to be significant contributors (Foldes et al. Biochem Biophys Res Commun 2003;308:480-485; Bocher et al. Endocrinology 2005; 146:1 764-1 771 . Epub 2005 Jan 27).

Administrations of apelins cause vasodilatation in different pre-clinical models and accordingly, intravenous administration in rodents reduces mean arterial blood pressure, systemic venous tone and cardiac pre- and afterload (for a review see Barnes et al. Heart 2010, 96:1 011-1 016). Vasodilatation to apelin in rodents is dependent on endothelium and mediated through nitric oxide and prostacyclin dependent pathways. Ishida and colleagues demonstrated in 2004, that a functional knockdown of the apelin receptor abolished blood pressure lowering effects of apelins, confirming that vascular effects of apelins are mediated by the apelin receptor specifically (Ishida et al. 2004, J Biol Chem;279:25, 25274-25279).

The vascular effects of apelin in pre-clinical studies translate into similar effects in humans (Japp et al., 2008 J Am Coll Cardiol 2008;52:908-913; Japp et al. Circulation 2010;121:1 818-1 827). Infusions of apelins increased forearm and coronary blood flow and lowered mean arterial pressure and peripheral vascular resistance in heart failure patients and healthy control subjects in heart failure patients without raising heart rates. An increased cardiax index could be noted, which may be explained by either direct effects on the cardiac muscle (see below) and/or reduction of pre- and afterload in the peripheral circulation. In man, vasodilatation by apelins is reduced by two thirds during nitric oxide synthase inhibition but is unaffected by prostacyclin inhibition.
The apelin receptor has been linked to direct cardiac actions. In vitro, exogenous apelin increases contractility at subnanomolar concentrations in atrial strips (Maguire et al. Hypertension 2009;54:598-604) and whole rat hearts (Szekodi et al. Circ. Res. 2002;91, 434-440). In healthy rodents, acute apelin infusion increases myocardial contractility independently of its effects on loading conditions. Uniquely among current inotropic agents, chronic dosing causes a sustained increase in cardiac output without inducing left ventricular hypertrophy (Ashley et al. Cardiovasc Res 2005;65:73-82). While apelin-deficient mice display normal or only slightly impaired basal cardiac function at early life cycles, they demonstrate progressive cardiac dysfunction from 6 months of age and develop severe heart failure when subjected to chronic pressure overload (Kuba et al. Circ Res 2007;101,eS2-42).

Controversial results have been published regarding the involvement of intracellular calcium on the contractility effects of apelin in cardiomyocytes. Two groups described that intracellular calcium is not a signalling mechanism. However, others reported at least a modest increase in the amplitude of the intracellular calcium ion transients in failing rat trabeculae and isolated cardiomyocytes (Dai et al./Eur J Pharmacol 2006;553;222-228; Wang et al. Am J Physiol heart circ Physiol 2008;294;H2540-46).

Additionally, effects of apelins in pre-clinical models have been described. Apelins may have an important counter-regulatory role to vasopressin and hence fluid homeostasis. Apelin and the APJ receptor are both expressed also in the kidney and many areas of the brain. Synthesis in certain brain regions involved in fluid homeostasis are regulated by vasopressin. To the contrary, intracerebral injection of apelin directly inhibits vasopressin release leading to a 40% reduction in plasma vasopressin concentrations (Reaux-Le Goazigo et al. Endocrinology 2004;145:4392-4400).

A link of apelins to metabolic syndrome is suggested by pre-clinical data. Apelins are produced by adipose tissue and may influence glucose and lipid metabolism as adipocytokines (Boucher et al. Endocrinology 2005;146:1 764-1 771). Acute intravenous administration of 1pyr-apelin-13 stimulates glucose utilization in normal
and obese insulin-resistant mice (Dray C et al. Cell Metab 2008;8:437-445). These acute effects were explained by a direct effect of 1\textsuperscript{pyr}-apelin-13 on glucose uptake into skeletal muscle. Mice deficient for the apelins have reduced insulin sensitivity which can be corrected by sub-chronic supplementation with apelin via minipumps.

Furthermore in insulin resistant homozygous leptin receptor mutant mice (db/db mice) a similar sub-chronic administration results in improved glucose utilization (Yue et al. Am J Physiol Endocrinol Metab 2009; 298:E59-67). Results with glucose utilization in apelin receptor knockout mice have not been published. Furthermore it is not reported yet, whether apelins significantly affect glucose handling in man.

The clinical and pre-clinical profile suggests applications of apelin receptor agonists in different patient populations and indications. In heart failure, apelins demonstrate a unique hemodynamic profile in enhancing myocardial contractility without inducing left ventricular hypertrophy. In parallel, ventricular pre- and afterload is reduced by reduced peripheral resistance. In pre-clinical models, apelin increases contractility at least to the same extent in the failing compared to normal myocardium (Dai et al. Eur J Pharmacol 2006;553:222-228). Irrespective of changes in receptor and ligand expression, these studies indicate agonism of the receptor is not diminished in situations of established heart failure. First data from clinical studies with acute apelin infusions are promising. In contrast to acetylcholine, another vaso-active principle, vascular and cardiac hemodynamic effects of apelins are preserved in chronic heart failure patients (Japp et al. Circulation 2010;121:1818-1827). These patients received optimal pharmacological treatment, suggesting that the effects of apelin were additive to established heart failure therapies like ACE-Inhibitors and/or \(\beta\)-blockers.

Regarding therapies targeting the diseased heart, acute beneficial effects of apelins after acute myocardial infarction may be envisaged. Two groups reported that in pre-clinical models of acute myocardial ischemia and reperfusion administration of apelins at reperfusion strongly reduces myocardial injury (Kleinz et al. Regul Pept 2008;146:271-277; Simkin et al. Basic Res Cardiol 2007;1 02:51 8-28). Both groups published opposing results regarding the underlying signaling of this cardioprotective mechanism. Simkin et al favor a mechanism based on activation of phosphatide-3-
kinase, AKT kinase and P70S6 kinase, whereas Kleinz et al could not confirm activation of this pathway. However, signaling pathways independent of PI-3-kinase, AKT-kinase and p70S6 kinase may also explain the beneficial effects of apelin receptor agonists in ischemia-reperfusion injury. Apelin increases both phosphorylation and activity of key components within reperfusion injury salvage kinase pathway (Smith et al. Cardiovasc Drugs Ther 2007;21:409-414). This pro-survival pathway is known to be associated with reduced ischemia-reperfusion-injury by preserving mitochondrial function. Despite the fact, preconditioning agents are difficult to implement in clinical practice, apelin receptor agonists may be administered with the reperfusion solution directly after acute myocardial infarction and thereby display potential benefits in both restoring cardiac survival and function. Another application, especially of oral bioavailable small molecule apelin receptor agonists, could be to start in a patient with an acute myocardial infarction with an intravenous formulation during reperfusion and continue later, e.g. outside the clinic, with an oral bioavailable formulation of the same drug component. Furthermore, intravenous or oral administration of apelin receptor agonists could be envisaged in patients with acute heart failure. Very often acute heart failure develops in the progression of chronic heart failure spontaneously as acute episodes of disease worsening but without signs of myocardial infarction. Patients are then hospitalized and stabilized during hospitalization by agents increasing the contractility of the diseased heart muscle. Apelin receptor agonists display a unique hemodynamic profile suggesting a safe and efficient use in such patients.

Agonists of the apelin receptor may also represent a novel class of anti-hypertensive agents. In preclinical models, administration of apelin peptides lowers blood pressure, greatly enhanced in hypertensive animals compared with normotensive controls. In first clinical studies modest but significant effects on blood pressure lowering could be demonstrated in normotensive middle-aged subjects. Whether intravenously applied apelin peptides lower blood pressure stronger in hypertensive patient populations, similar to the situation in normotensive vs. hypertensive rats, needs to be evaluated. Application of apelin peptides in hypertensive patients is strongly limited by the need of intravenous administration route. However, small
molecule apelin receptor agonists as claimed in this patent application may have a much wider application in these patients due to better oral bioavailability.

Apelin receptor agonists appear to have beneficial effects on additional vascular based diseases. In atherosclerotic mice deficient for the Apolipoprotein-E, apelin infusion inhibits atherosclerosis progress and completely abrogates angiotensin II-accelerated detrimental effects independent of blood pressure (Chun et al. J Clin Invest 2008;1 18:3343-3354). And in double knockout mice, deficient in for the apelin receptor ligand and Apolipoprotein-E, accelerated atherosclerosis could be observed compared versus single Apolipoprotein-E-knockout. It needs to be mentioned, that also pro-atherosclerotic effects of the apelin receptor have been described in a combined mice knockout-model of the apelin receptor and apolipoprotein-E ApoE (Hashimoto et al. Am J Pathol 2007;1 08:1432-1438). Overall these results are difficult to reconcile: Most probably very different fat feeding regimens or different genetic backgrounds and so called off-target genetic effects best explain the observed differences. Independent of effects on atherosclerosis progression, apelin treatment resulted in reduced aneurysm by 50% in a mouse model of abdominal aortic aneurysms (Leeper et al. Am J Physiol Heart Circ Physiol 2009;296:H1 329-1335), an effect explained by the authors by a direct anti-inflammatory effect within the vessel wall.

Furthermore, apelin receptor agonists may play an important role in maturation of newly formed blood vessels. Kidoya et al (Blood 201 0;1 5;31 66-31 74) recently described in a model of vascular remodelling after hindlimb ischemia in mice, that apelins induce the maturation into enlarged and non-leaky blood vessels for functional recovery. Especially pathologically increased vascular permeability induced by VEGF under hypoxic conditions seems to be corrected by apelins.

In humans, apelins cause nitric oxide-mediated vasodilatation in forearm resistance vessels of healthy subjects. Based on promising preclinical data, the role of apelin receptor agonists in preventing human vascular disease merits further investigations. These investigations will be strongly facilitated by small molecule apelin receptor
agonists, as claimed in this patent application, because the oral bioavailability allows for much easier chronic administration routes.

In patients with metabolic syndrome and diabetes, apelin receptor agonists may provide additional benefits. Apelins are produced also by adipose tissue and influence glucose and lipid metabolism as adipocytokines. Mice with no apelin receptor ligands have reduced insulin sensitivity which can be corrected by the administration of exogenous apelin. Acute and sub-chronic positive effects of apelins on glucose utilizations following a glucose load have been described in insulin-resistant animal strains. Although the translation of these effects to man needs to be performed, apelin receptor agonists may offer additional therapeutic options especially in insulin-resistant patients, insufficiently dealing with increased plasma glucose load in metabolic syndrome and diabetes. The simultaneous beneficial effects on blood glucose lowering and vascular and cardiac homeostasis are a unique advantage to therapeutic principles affecting blood glucose alone and open an avenue to macro- and microvascular diabetic late complications, like diabetic cardiomyopathies, diabetic retinophathy, diabetic macular edema, diabetic nephropathy and diabetic neuropathy. Oral bioavailable small molecule apelin receptor agonist would strongly boost these areas of applications because they would be not restricted to intravenous or subcutaneous administration routes.

There continues to be a need for further effective low molecular weight APJ modulators, in particular in view of safety and selectivity. The present invention satisfies this need by providing the Benzoimidazole-carboxylic acid compounds of the formula I.

Benzoimidazole-carboxylic acid derivatives which are useful for pharmaceutical applications, have already been disclosed, for example in WO03053938 (NovoNordisk), WO2004108688 (Astra Zeneca), WO99040072, WO03014377 (Boehringer Ingelheim) and in WO2008153701 (Schering Corp.).
Accordingly, a subject of the present invention is a compound of the formula I.

\[
R', R^*, R'^* \text{ are independently of each other } H, \text{ halogen, } CF_3, OCF_3, O-(Ci-C3)-alkyl;
\]

R' \text{ is }

a) \((C_4-C_7)-alkyl;

b) \((C_5-C_7)-cycloalkyl, \text{ which is unsubstituted or mono-substituted by (C1-C2)-alkyl, or CF}_3;\n
c) \text{ methylene-cyclohexyl;}

d) \text{ phenyl, which is unsubstituted or mono-substituted by methyl or CI;}

R^2 \text{ is }

a) \text{ a 5-membered heteroaryl which contains 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein said 5-membered heteroaryl is unsubstituted or mono-substituted by Cl or (Ci-C}_4)-alkyl;}

b) \text{ phenyl;}

c) \((C_5-C_6)-cycloalkyl; \text{ or}

d) \text{ tetrahydrofuranyl;}

R^3 \text{ is } H, \text{ or (Ci-C}_2)-alkyl;

\text{and}

R^4 \text{ is }

a) \((C3-C_5)-alkyl, \text{ which may be optionally substituted by 1-3 F or S-(Ci-C}_4)-alkyl,}
b) (Co-Ci)-alkylene-(C3-C7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono- or di-substituted by methyl;

c) (Co-C2)-alkylene-phenyl, wherein said phenyl is unsubstituted or mono- or di-substituted by F, Cl, (Ci-C4)-alkyl or CF3; or

d) thienyl;

or

R3 and R4 are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring, which is unsubstituted or mono-substituted by (Ci-C4)-alkyl;

R5 is H, (Ci-C4)-alkyl or OH;

R6 H or (Ci-C4)-alkyl;

n is 0, 1 or 2; and

Z is

CO2-R7, OR8, C(O)NR9R10, S(O)2NR11R12,

\[\text{wherein} \]

v is 0 or 2;
R\(^7\) is H or (Ci-C\(_4\))-alkyl;

R\(^8\) is H or (Ci-C\(_4\))-alkyl;

R\(^9\) is H, (Ci-C\(_4\))-alkyl or ethylene-O-(Ci-C\(_4\))-alkyl;

and

R\(^{10}\) is

a) H;

b) (Ci-C\(_6\))-alkyl, which is unsubstituted or mono-substituted by CF\(_3\);

c) (Ci-C\(_2\))-alkyl, which is substituted by CN or CO\(_2\)R\(^{19}\)

wherein

R\(^{19}\) is H or (Ci-C\(_6\))-alkyl;

d) (C\(_2\)-C\(_4\))-alkyl, which is mono-substituted by a substituent selected from

the group consisting of S-methyl, SO\(_2\)NR\(^{20}\)R\(^{21}\), O-R\(^{22}\) and NR\(^{23}\)R\(^{24}\);

wherein

R\(^{20}\) is H;

R\(^{21}\) is H;

R\(^{22}\) is H, (Ci-C\(_3\))-alkyl, methylene-cyclopropyl, methylene-phenyl, or

methylen-2-tetrahydrofurane;

R\(^{23}\) is H or (Ci-C\(_2\))-alkyl;

R\(^{24}\) is (Ci-C\(_2\))-alkyl or SO\(_2\)-methyl;

e) (C\(_3\)-C\(_5\))-cycloalkyl, which is unsubstituted or mono-substituted by phenyl;

f) (Co-C\(_2\))-alkylene-heterocycloalkyl, wherein said heterocycloalkyi is five

or six membered and contains 1 or 2 O atoms in non-adjacent

positions, and wherein said heterocycloalkyi is unsubstituted or

geminally disubstituted with a spiro cyclopentyl ring or a spiro
cyclohexyl ring;

g) (C\(_2\)-C\(_3\))-alkylene-heterocycloalkyl, wherein said heterocycloalkyi is a

five-, six- or seven-membered ring, which contains at least one N atom,

and which is attached via said N-atom, and which may additionally
contain one heteroatom selected from the group consisting of O, S(O)\textsubscript{x} or NR\textsubscript{25} in a position not adjacent to the N atom, by which the ring is attached to the alkylene, and wherein any carbon atom within said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (CrC\textsubscript{3})alkyl, or methylene-phenyl; wherein

x \quad \text{is} \quad 2;

R\textsubscript{25} \quad \text{is} \quad H, (CrC\textsubscript{2})alkyl, methylene-phenyl or phenyl, which is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of F, Cl and O-(Ci-C\textsubscript{4})-alkyl;

h) (Co-C\textsubscript{2})-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five- or six-membered ring, which contains at least one N atom, and which is not attached via said N-atom, and which may additionally contain one O atom in a position not adjacent to the N atom, and wherein said N-atom is unsubstituted or substituted by a substituent selected from the group consisting of

i) (Ci-C\textsubscript{4})-alkyl, which is unsubstituted or mono-substituted by O(Ci-C\textsubscript{4})-alkyl;

ii) methylene-cyclohexyl;

iii) (Co-C\textsubscript{2})-alkylene-phenyl, wherein phenyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of F and O(Ci-C\textsubscript{4})-alkyl;

iv) (Co-Ci)-alkylene-pyridyl;

v) pyrimidinyl;

25

i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl;

j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;

k) methylene-4-(octahydro-quinolizinyl);

l) (Co-C\textsubscript{2})-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, O(Ci-C\textsubscript{4})-alkyl, N((Ci-C\textsubscript{4})-alkyl)\textsubscript{2}, 4-morpholinyl and methylene-(4-methyl-piperidin)-1 -yl or disubstituted on adjacent positions by the group -O(CH\textsubscript{2})O-;
m) (Ci-C2)-alkylene-heteroaryl, wherein said heteroaryl ring is a five-or six-
membered ring containing 1, 2, 3 or 4 heteroatoms selected from O, S or N; and wherein said heteroaryl ring is unsubstituted or mono-
substituted by oxo (=O);

5 or

R^9 and R^10 together with the N-atom carrying them are

a) a four-, five- or six-membered heterocycloalkyl ring containing only the
N atom, to which R^9 and R^10 are attached, which is unsubstituted or
mono-substituted by a substituent selected from the group consisting of

10 i) (Co-Ci)-alkylene- O R^26, wherein R^26 is H, (Ci-C3)alkyl or
methylenepheryl;

ii) CO_2 R^27, wherein R^27 is is H or (Ci-C6)-alkyl;

ii) NR^28 R^29, wherein R^28 is (Ci-C2)-alkyl and R^29 is (Ci-C2)-alkyl,
methylenepheryl or ethylene-N((Ci-C4)-alkyl)_2;

15 iii) 1-piperidinyl, which is unsubstituted or mono-substituted by
methyl;

iv) 1-piperazinyl, which is unsubstituted or mono-substituted by
methyl;

v) 4-morpholinoyl;

vi) 1-azepanyl;

vii) 2-(2,3-dihydro-1 H-isoindolyl);

b) a six- or seven-membered heterocycloalkyl ring containing the N atom, to
which R^9 and R^10 are attached and one additional heteroatom selected
from O, S or NR^30 in a position non-adjacent to the N atom, to which R^9
and R^10 are attached, wherein the carbon atoms in said heterocycloalkyl
ring are unsubstituted or mono- or disubstituted by methyl and wherein

25 R^30 is

i) H;

ii) (Ci-C4)-alkyl;

iii) (C5-C6)-cycloalkyl;

30 iv) phenyl, which is unsubstituted or mono-substituted by F, CF_3 or
O-(Ci-C4)-alkyl;
v) methylene-phenyl, which is unsubstituted or mono- or disubstituted by F or Cl or disubstituted on adjacent positions by the group -O(CH₂)O-;

vi) pyridyl;

c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is unsubstituted or substituted on the second N atom in 5-position by a substituent selected from the group consisting of (C₁-C₄)-alkyl, methylene-cyclopentyl, phenyl, which is unsubstituted or mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by O-(C₁-C₄)-alkyl or CF₃;

R¹¹ is H;
R¹² is (C₁-C₄)-alkyl;
R¹³ is H;
R¹⁴ is CF₃ or methylene-O-(C₁-C₄)-alkyl;
R¹⁵ is cyclopryopyl or phenyl;
R¹⁶ is H or (C₁-C₄)-alkyl;
R¹⁷ is H or (C₁-C₄)-alkyl;

and

R¹⁸ is (C₁-C₄)-alkyl;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

Structural elements such as groups, substituents, hetero ring members, numbers or other features, for example alkyl groups, groups like R¹, R², R³ etc., which can occur several times in the compounds of the formula I, can all independently of one another have any of the indicated meanings and can in each case be identical to or different from one another. For example, the alkyl groups in a dialkylamino group can be identical or different.
As used here, the terms "including" and "comprising" are used in their open, non-limiting sense. As used herein, the terms "(Ci-Cs)" or "(Cs-Cs)" and so forth, refer to moieties having 1 to 8 or 5 to 8 carbon atoms, respectively. Within terms like "(Co-C₈)-alkyl" or "(C₀-C₆)-alkylen" "C₀-alkyl" or "(Co)-alkylen" refer to a bond, or in case of an unsubstituted "(Co)-alkyl" it refers to a hydrogen.

The term "alkyl", as used herein, refers to saturated, monovalent hydrocarbon radicals. The term "alkenyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term "alkynyl", as used herein, refers to monovalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. The alkyl, alkenyl and alkynyl groups can be linear, i.e. straight-chain, or branched. This also applies when they are part of other groups, for example alkxyo groups (alkoxy groups, O-alkyl groups), alklyoxycarbonyl groups or alkyl-substituted amino groups, or when they are substituted. Depending on the respective definition, the number of carbon atoms in an alkyl group can be 1, 2, 3, 4, 5, 6, 7 or 8, or 1, 2, 3, 4, 5 or 6, or 1, 2, 3 or 4, or 1, 2 or 3. Examples of alkyl are methyl, ethyl, propyl including n-propyl and isopropyl, butyl including n-butyl, sec-butyl, isobutyl and tert-butyl, pentyl including n-pentyl, 1-methylbutyl, isopentyl, neopentyl and tert-pentyl, hexyl including n-hexyl, 3,3-dimethylbutyl and iso-hexyl, heptyl and octyl. Double bonds and triple bonds in alkenyl groups and alkynyl groups can be present in any positions. In one embodiment of the invention, alkenyl groups contain one double bond and alkynyl groups contain one triple bond. In one embodiment of the invention, an alkenyl group or alkynyl group contains at least three carbon atoms and is bonded to the remainder of the molecule via a carbon atom which is not part of a double bond or triple bond. Examples of alkenyl and alkynyl are ethenyl, prop-1- enyl, prop-2-enyl (= allyl), but-2-enyl, 2-methylprop-2-enyl, 3-methylbut-2-enyl, hex-3-enyl, hex-4-enyl, prop-2-ynyl (= propargyl), but-2-ynyl, but-3-ynyl, hex-4-ynyl or hex-5-ynyl. Substituted alkyl groups, alkenyl groups and alkynyl groups can be substituted in any positions, provided that the respective compound is sufficiently stable and is suitable for the desired purpose such as use as a drug substance. The prerequisite that a specific group and a compound of the formula I are sufficiently stable and suitable for
the desired purpose such as use as a drug substance, applies in general with respect to the definitions of all groups in the compounds of the formula \( I \).

Independently of one another and independently of any other substituents, alkyl groups, divalent alkyl groups, alkenyl groups, alkynyl groups, cycloalkyl groups and heterocycloalkyl groups are optionally substituted by one or more fluorine substituents which can be located in any positions, i.e., the said groups can be unsubstituted by fluorine substituents or substituted by fluorine substituents, for example by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, or by 1, 2, 3, 4, 5, 6, 7, 8 or 9, or by 1, 2, 3, 4, 5, 6 or 7, or by 1, 2, 3, 4 or 5, or by 1, 2 or 3, or by 1 or 2, fluorine substituents. Examples of fluorine-substituted said groups are trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, 2,2,3,3,3-pentafluoropropyl, 4,4,4-trifluorobutyl, heptafluoroisopropyl, \(-\text{CH}_2\text{F}_-, \text{CF}_2-, \text{CF}_2\text{CH}_2-,\)
 \(-\text{CH}_2\text{CF}_2-, \text{CF}_2\text{CF}_2-, \text{CF}(\text{CH}_3)-, \text{C}(\text{CF}_3)_2-, \text{C}(\text{CH}_3)_2\text{CF}_2-, \text{CF}_2\text{C}(\text{CH}_3)_2-, 1\text{-fluorocyclopropyl, 2,2-difluorocyclopropyl, 3,3-difluorocyclobutyl, 1-fluorocyclohexyl, 4,4-difluorocyclohexyl, 3,3,4,4,5,5-hexafluorocyclohexyl. Examples of alkyl groups in which the alkyl moiety is fluorine-substituted, are trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and 3,3,3-trifluoropropoxy.\)

The term "alkanediyl" or "alkylene" \(^\text{1}\), as used herein, refers to saturated, divalent hydrocarbon radicals. The term "alkanediyl", as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon double bond, wherein each double bond can have E- or Z-configuration. The term "alkindiyli", as used herein, refers to divalent hydrocarbon radicals, which contain at least one carbon-carbon triple bond. As far as applicable, the preceding explanations regarding alkyl, alkenyl and alkynyl groups apply correspondingly to alkanediyl, alkendiyl and alkindiyl groups, which thus can likewise be linear and branched. Examples of divalent alkyl groups are \(-\text{CH}_2-\) (= methylene), \(-\text{CH}_2\text{CH}_2-, \text{CH}_2\text{CH}_2\text{CH}_2-, \text{CH}_2\text{CH}_2\text{CH}_2-, \text{CH}_2\text{CH}_2-, \text{CH}(\text{CH}_3)-, \text{C}(\text{CH}_3)_2-, \text{CH}(\text{CH}_3)-\text{CH}_2-, \text{CH}_2\text{CH}(\text{CH}_3)-, \text{C}(\text{CH}_3)_2\text{CH}_2-, \text{CH}_2\text{C}(\text{CH}_3)_2-.\)
The term "cycloalkyi", as used herein, unless otherwise indicated, refers to a monovalent radical of a saturated or partially saturated hydrocarbon ring system, which can be monocyclic, bicyclic or tricyclic, i.e. which can contain one, two or three rings. The bicyclic or tricyclic ring system can be a fused ring system, in which two adjacent rings share two adjacent carbon atoms. The bicyclic or tricyclic ring system can be a spiro ring system or a di-spiro-ringsystem, in which two adjacent rings share a single carbon atom. The tricyclic ring system can also be a bicyclic spiro ring system, to which another ring is fused, that means that the latter ring and the ring in the spiro ring system, to which it is attached, share two adjacent carbon atoms; herein the latter ring can be an aromatic, saturated or partially saturated ring. The bicyclic or tricyclic system can also be a non-fused or bridged ring system, in which two adjacent rings share two non-adjacent carbon atoms. The bicyclic or tricyclic ring can be attached by any ring atom except a spiro- or a bridgehead atom.

In a monocyclic cycloalkyi group the number of ring carbon atoms can be 3, 4, 5, 6, 7 or 8. In one embodiment of the invention, the number of ring carbon atoms in a cycloalkyi group, independently of the number of ring carbon atoms in any other cycloalkyi group, is 3, 4, 5 or 6, in another embodiment 3, 4 or 5, in another embodiment 3 or 4, in another embodiment 3, in another embodiment 5, 6 or 7, in another embodiment 5 or 6, in another embodiment 6 or 7, in another embodiment 5, in another embodiment 6. Examples of cycloalkyi groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In a bicyclic cycloalkyi group the number of ring carbon atoms can be 6, 7, 8, 9, 10, 11 or 12. In one embodiment of the invention, the number of ring carbon atoms in a bicyclic cycloalkyi group can be 7, 8, 9, 10 or 11, in another embodiment 8, 9 or 10. In a tricyclic cycloalkyi group the number of ring carbon atoms can be 7, 8, 9, 10, 11, 12, 13, 14 or 15. In one embodiment of the invention, the number of ring carbon atoms in a tricyclic cycloalkyi group can be 10, 11 or 12.

Exemplary bicyclic or tricyclic fused ring cycloalkyls are derived from, but not limited to, the following ring systems: bicyclo[3.1.0]hexane, bicyclo[4.1.0]heptane, bicyclo[5.1.0]octane, bicyclo[3.2.0]heptane, bicyclo[4.2.0]octane, octahydro-pentalene, octa-
hydro-indene, decahydro-azulene, decahydro-naphthalene, decahydro-benzo-
cycloheptene, dodecahydro-heptalene, 1,2,3,3a,4,6a-hexahydro-pentalene, 1,2,3,4-
tetrahydro-pentalene, 2,3,3a,4,5,7a-hexahydro-1H-indene, 2,3,3a,4,7,7a-hexahydro-
1H-indene, 3a,4,5,6,7,7a-hexahydro-1H-indene, 4,5,6,7-tetrahydro-1H-indene, 
indane, 1,2,3,4,4a,5,6,8a-octahydro-naphthalene, 1,2,3,4,4a,5,8,8a-octahydro-
naphthalene, 1,2,3,4,4a,5,8,8a-hexahydro-naphthalene, 1,4,4a,5,8,8a-hexahydro-
naphthalene, 1,2,3,4-tetrahydro-naphthalene, 2,3,4,4a,5,6,9,9a-octahydro-1H-benzo-
cycloheptene, 2,3,4,4a,5,9a-hexahydro-1H-benzocycloheptene, 4,4a,5,6,7,8,9,9a-
octahydro-1H-benzocycloheptene, 6,7,8,9-tetrahydro-5H-benzocycloheptene, 
1,2,3,4,5,5a,6,7,8,1Ododecahydro-heptalene, dodecahydro-as-indacene and 
2,3,3a,4,9,9a-hexahydro-1H-cyclopenta[b]naphthalene.

Exemplary bicyclic or tricyclic spiro ring cycloalkyls are derived from, but not limited 
to, the following ring systems: spiro[2.4]heptane, spiro[2.5]octane, spiro[2.6]nonane, 
spiro[6.6]tridecane, dispiro[2.2.4.2]dodecane, dispiro[2.2.3.2]undecane, dispiro-

Exemplary non-fused or bridged bicyclic or tricyclic ring cycloalkyls are derived from, 
but not limited to, the following ring systems: bicyclo[2.2.1]heptane, bicyclo[2.2.2]oc-
tane, bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane and adamantane.

The term "heterocycloalkyl" or "heterocyclyl", as used herein, unless otherwise 
indicated, refers to a cycloalkyl as defined above, in which 1, 2, 3 or 4 carbon atoms 
are replaced by nitrogen, oxygen or sulfur atoms, provided that a spiro atom is 
always a carbon atom and a bridgehead atom is either a carbon or a nitrogen atom 
and provided that the heterocycloalkyl system is stable and suitable as a subgroup 
for the desired purpose of the compound of the formula I such as use as a drug 
substance. Depending on the definition of the respective heterocyclic group, in one 
embodiment of the invention the number of ring heteroatoms which can be present in 
a heterocyclic group, independently of the number of ring heteroatoms in any other
heterocyclic group, is 1, 2, 3 or 4, in another embodiment 1, 2 or 3, in another embodiment 1 or 2, in another embodiment 2, in another embodiment 1, wherein the ring heteroatoms can be identical or different. The heterocycloalkyl group can be attached by any ring carbon atom or saturated ring nitrogen atom, with the exception of spiro- or bridgehead atoms. A ring sulfur atom in a heterocycloalkyl group can carry zero, one or two oxo groups, it is a non-oxidized sulfur atom S in case it does not carry any oxo group, or it is an S(O) group (= sulfoxide group, S-oxide group) in case it carries one oxo group, or it is an S(O)2 group (= sulfone group, S,S-dioxide group) in case it carries two oxo groups.

Exemplary monocyclic heterocycloalkyls are derived from, but not limited to, the following ring systems: aziridine, oxirane, azetidine, oxetane, pyrrolidine, tetrahydrofurane, tetrahydrothiophene, 4,5-dihydrothiazole, piperidine, piperrazine, morpholine, thiomorpholine, tetrahydropyran, 1,4-dioxane, 1,4-oxathiane, 1,2,3,6-tetrahydropyridine, azepane, 2,3,4,7-tetrahydro-1 H-azepine, 2,7-dihydro-1 H-azepine, 1,4-di-azepane, 1,4-oxazepane, 1,4-thiazepane and 1,4-dioxepane.

In one embodiment monocyclic heterocycloalkyls are derived from azetidine, pyrrolidine, piperrazine, morpholine or 1,4-diazepane.

Exemplary bicyclic fused ring heterocycloalkyls are derived from, but not limited to, the following ring systems: 3-aza-bicyclo[3.1.0]hexane, 2-aza-bicyclo[4.1.0]heptane, 2-oxa-5-aza-bicyclo[5.1.0]octane, 3-aza-bicyclo[3.2.0]heptane, 2-aza-bicyclo[4.2.0]octane, octahydro-pyrrolo[3,4-c]pyrrole, octahydro-pyrrolo[3,4-b]pyrrole, octahydro-pyrrolo[3,4-b]pyridine, octahydro-thieno[3,4-b]pyrazine, octahydro-furo[3,4-b]pyridine, octahydro-cyclopenta[1,4]oxazine, octahydro-pyrrolo[1,2-a]pyrimidine, octahydro-pyrrolo[1,2-a]pyrazine, octahydro-cyclopenta[e][1,4]oxazine, decahydro-quinoxaline, decahydro-[1,6]naphthyridine, octahydro-benzo[1,4]oxazine, octahydro-benzo[1,4]thiazine, octahydro-pyrido[1,2-a]pyrazine, octahydro-pyrano[3,2-b]pyridine, decahydro-1-oxa-9-aza-benzocycloheptene, 1,2,3,3a,6,6a-hexahydro-cyclopenta[b]pyrrole, 5,6-dihydro-4H-cyclopenta[b]thiophene, 2,3,4,4a,7,7a-hexahydro-1 H-[2]pyridine, 2,4a,5,6,7,7a-hexahydro-1 H-[1]pyridine, 2,3,3a,4,7,7a-hexahydro-1 H-indole, 1,2,3,4-tetrahydro-quinoxaline, 4,5,6,7-tetrahydro-benzofuran, benzo[1,3]di-
oxole, 3,4,4a, 7,8,8a-hexahydro-2H-benzo[1,4]oxazine, 1,2,3,4,4a, 5,8,8a-octahydro-
quinoxaline, 4a,5,8,8a-tetrahydro-2H-thiopyrano[3,2-b]pyridine and 1,2,3,4-
tetrahydro-[1,5]naphthyhdine.

Exemplary non-fused or bridged bicyclic or tricyclic ring heterocycloalkyls are derived from, but not limited to, the following ring systems: 2-aza-bicyclo[2.2.1]heptane, 1-aza-bicyclo[2.2.2]octane, 8-aza-bicyclo[3.2.1]octane, 3-aza-bicyclo[3.2.1]octane, 9-aza-bicyclo[3.3.1]nonane, 2,5-diaza-bicyclo[2.2.1]heptane, 2,5-diaza-bicyclo[2.2.2]-

tetrahydro-[1,5]naphthyhdine.

The term "aryl", as used herein, refers to a radical derived from an aromatic hydro-
carbon by removal of one hydrogen, such as phenyl or naphthyl (= naphthalenyl).

The term "heteroaryl" or "hetaryl" as used herein, refers to a radical derived from an

aromatic mono- or bicyclic ring system, in which 1, 2, 3, 4 or 5 carbon atoms are

replaced by heteroatoms. The ring heteroatoms are generally chosen from N, O and

S, wherein N includes ring nitrogen atoms which carry a hydrogen atom or a

substituent as well as ring nitrogen atoms which do not carry a hydrogen atom or a

substituent. Ring heteroatoms can be located in any position, provided that the

heterocyclic system is stable and suitable as a subgroup for the desired purpose of

the compound of the formula I such as use as a drug substance. Heteroaryl radicals

are derived from 5-membered or 6-membered monocyclic rings or 8-membered, 9-

membered or 10-membered bicyclic rings, in another embodiment 5-membered or 6-

membered monocyclic rings or 9-membered or 10-membered bicyclic rings, in

another embodiment 5-membered or 6-membered monocyclic rings.

Exemplary heteroaryl systems are derived from, but not limited to, the following ring

systems: pyrrole, furan, thiophene, imidazole, pyrazole, oxazole (= [1,3]oxazole),

isoxazole (= [1,2]oxazole), thiazole (= [1,3]thiazole), isothiazole (= [1,2]thiazole),

[1,2,3]triazole, [1,2,4]triazole, [1,2,4]oxadiazole, [1,3,4]oxadiazole, [1,2,4]thiadiazole,

[1,3,4]thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, [1,2,3]triazine,

[1,2,4]triazine, [1,3,5]triazine, indole, isoindole, benzofuran, benzothiophene
[1,3]benzoxazole, [1,3]benzothiazole, benzoimidazole, indazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, different naphthyridines, e.g. [1,8]naphthyridine, different thienopyridines, e.g. thieno[2,3-b]pyridine and purine.

Groups like phenyl, naphthyl (= naphthalenyl) and residues of aromatic heterocycles which are optionally substituted by one or more substituents, can be unsubstituted or substituted, for example by 1, 2, 3, 4 or 5, or by 1, 2, 3 or 4, or by 1, 2 or 3, or by 1 or 2, or by 1, identical or different substituents which can be located in any positions.

Aromatic nitrogen heterocycles which in the parent ring system carry a hydrogen atom on a ring nitrogen atom in a 5-membered ring, such as a pyrrole, imidazole, indole or benzoimidazole ring, for example, can be substituted on ring carbon atoms and/or on such ring nitrogen atoms. In one embodiment of the invention, substituents on such ring nitrogen atoms are chosen from (Ci-C₄)-alkyl groups, i.e. such ring nitrogen atoms in aromatic heterocycles carry a hydrogen atom or a (Ci-C₄)-alkyl substituent. When it is stated with respect to ring nitrogen atoms in aromatic heterocycles and any other heterocycles that they can carry a hydrogen atom or a substituent, such ring nitrogen atoms either carry a hydrogen atom or a substituent or they do not carry a hydrogen atom or substituent. Ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in a nitrogen-containing aromatic 5-membered ring as is present in pyrrole, imidazole, indole or benzoimidazole, for example, and in a non-aromatic ring including a saturated ring. Ring nitrogen atoms which do not carry a hydrogen atom or a substituent unless they are present in positively charged form, including any further ring nitrogen atoms in addition to ring nitrogen atoms which carry a hydrogen atom or a substituent, occur in an aromatic ring as is present in thiazole, imidazole, pyridine or benzoimidazole, for example, and in a non-aromatic ring in which they are part of a double bond, and they occur as ring nitrogen atoms via which a ring is bonded. Suitable ring nitrogen atoms in aromatic heterocycles in the compounds of the formula I, such as the ring nitrogen atom in a pyridine ring or a quinoline ring, can in general also be present as N-oxide or as quaternary salt, for example as N-(Ci-C₄)-alkyl salt such as N-methyl salt, wherein in one embodiment of
the invention the counter anion in such quaternary salt is a physiologically acceptable anion which is derived from an acid that forms a physiologically acceptable salt.

In monosubstituted phenyl groups, the substituent can be located in the 2-position, the 3-position or the 4-position. In disubstituted phenyl groups, the substituents can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl groups, the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Naphthyl can be 1-naphthyl (= naphthalen-1-yl) or 2-naphthyl (= naphthalen-2-yl). In monosubstituted 1-naphthyl groups, the substituent can be located in the 2-, 3-, 4-, 5-, 6-, 7- or 8-position. In monosubstituted 2-naphthyl groups, the substituent can be located in the 1-, 3-, 4-, 5-, 6-, 7- or 8-position. In disubstituted naphthyl groups, the substituents can likewise be located in any positions both in the ring via which the naphthyl group is bonded and/or in the other ring.

Ring heteroatoms can be located in any positions, provided that the heterocyclic system is known in the art and is stable and suitable as a subgroup for the desired purpose of the compound of the formula I such as use as a drug substance. In one embodiment of the invention, two ring oxygen atoms cannot be present in adjacent ring positions of any heterocycle, in another embodiment two ring heteroatoms chosen from oxygen and sulfur cannot be present in adjacent ring positions of any heterocycle. Substituents on heterocyclic groups can be located in any positions. For example, in a pyridin-2-yl group substituents can be located in the 3-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-3-yl group substituent can be located in the 2-position and/or 4-position and/or 5-position and/or 6-position, in a pyridin-4-yl group substituents can be located in the 2-position and/or 3-position and/or 5-position and/or 6-position.

Halogen is fluorine, chlorine, bromine or iodine. In one embodiment of the invention, any halogen in a compound of the formula I is independently of any other halogen chosen from fluorine, chlorine and bromine, in another embodiment from fluorine and
chlorine, and in yet another embodiment it is fluorine, and in yet another embodiment it is chlorine.

When an oxo group is bonded to a carbon atom, it replaces two hydrogen atoms on a carbon atom of the parent system. Thus, if a CH₂ group in a chain or a ring is substituted by oxo, i.e. by a doubly bonded oxygen atom, it becomes a CO group. Evidently, an oxo group cannot occur as a substituent on a carbon atom in an aromatic ring such as in a phenyl group, for example. When a ring sulfur atom in a heterocyclic group can carry one or two oxo groups, it is a non-oxidized sulfur atom S in case it does not carry any oxo group, or it is an S(O) group (a sulfoxide group, S-oxide group) in case it carries one oxo group, or it is an S(O)₂ group (a sulfone group, S,S-dioxide group) in case it carries two oxo groups.

The present invention includes all stereoisomeric forms of the compounds of the formula I and their salts and solvates. With respect to each chiral center, independently of any other chiral center, the compounds of the formula I can be present in S configuration or substantially S configuration, or in R configuration or substantially R configuration, or as a mixture of the S isomer and the R isomer in any ratio. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in all ratios including racemates. In the case of a E/Z isomerism, or cis/trans isomerism, for example on double bonds or rings such as cycloalkyl rings, the invention includes both the E form and Z form, or the cis form and the trans form, as well as mixtures of these forms in all ratios. In one embodiment of the invention, a compound which can occur in two or more stereoisomeric forms is a pure, or substantially pure, individual stereoisomer. The preparation of individual stereoisomers can be carried out, for example, by separation of a mixture of isomers by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials in the synthesis, or by stereoselective
synthesis. Optionally, a dehvatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compound of the formula I or at the stage of a starting material or an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of the formula I and their salts and solvates.

In case the compounds of the formula I contain one or more acidic and/or basic groups, i.e. salt-forming groups, the invention also includes their corresponding physiologically or toxicologically acceptable salts, i.e. non-toxic salts, in particular their pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols such as (Ci-C₄)-alkanols, active metabolites of the compounds of the formula I, and also prodrugs and derivatives of the compounds of the formula I which in vitro may not necessarily exhibit pharmacological activity but which in vivo are converted into pharmacologically active compounds, for example esters or amides of carboxylic acid groups.

In another group of embodiments of the compounds of the formula I

R¹, R², R³” are independently of each other H, halogen, CF₃, OCF₃, O-(Ci-Cs)-alkyl;
preferably
R¹, R², R³” are independently of each other H, F, Cl, CF₃, OCF₃, O-CH₃; more preferably
R¹, R², R³” are independently of each other H, F, Cl; most preferably
R¹, R², R³” are H.

In another group of embodiments of the compounds of the formula I

R¹ is

a) (C₄-C₇)-alkyl;
b) (C₅-C₇)-cycloalkyl, which is unsubstituted or mono-substituted by (C1-C2)-alkyl, or CF₃;
c) methylene-cyclohexyl;
d) phenyl, which is unsubstituted or mono-substituted by methyl or Cl; preferably
R¹ is
  a) iso-butyl, sec-butyl, 1-ethyl-propyl, 2-methyl-butyl, 1,3-dimethyl-butyl, 1-isopropyl-2-methyl-propyl;
  b) cyclopentyl, 2-methyl-cyclopentyl, cyclohexyl, 2-methyl-cyclohexyl, 2-(trifluoromethyl)-cyclohexyl, 2-ethyl-cyclohexyl, cycloheptyl;
  c) methylene-cyclohexyl;
  d) phenyl, 2-chloro-phenyl, 4-tolyl; more preferably
R¹ is
  a) 1-ethyl-propyl;
  b) 2-methyl-cyclopentyl, 2-methyl-cyclohexyl; most preferably
R¹ is
  a) 1-ethyl-propyl;
  b) 2-methyl-cyclohexyl.

In another group of embodiments of the compounds of the formula I
R² is
R² is
  a) a 5-membered heteroaryl which contains 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein said 5-membered heteroaryl is unsubstituted or mono-substituted by Cl or Me;
  b) phenyl;
  c) (C₅-C₆)-cycloalkyl; or
d) tetrahydrofuranyl; preferably
R² is
  a) 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazolyl, 1-pyrazolyl; 5-isoxazolyl, 5-methyl-thien-2-yl, 5-chloro-thien-2-yl
  b) phenyl;
  c) (C₅-C₆)-cycloalkyl; or
d) 2-tetrahydrofuranyl; more preferably
$R^2$ is 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazoloyl, even more preferably

$R^2$ is 2-furanyl, 2-thienyl; most preferably

$R^2$ is 2-thienyl.

In another group of embodiments of the compounds of the formula I

$R^3$ is $H$, or (Cl-C$_2$)-alkyl;

and

$R^4$ is

a) (C$_3$-$C_2$)-alkyl, which may be optionally substituted by 1-3 F or S-CH$_3$;

b) (Co-Ci)-alkylene-(C$_3$-C$_2$)-cycloalkyl, wherein said cycloalkyi is unsubstituted or mono- or di-substituted by methyl;

c) (Co-C2)-alkylene-phenyl, wherein said phenyl is unsubstituted or mono- or di-substituted by F, Cl, Me or CF$_3$; or

d) thienyl; preferably

$R^3$ is $H$, or (Ci-C$_2$)-alkyl;

and

$R^4$ is

a) (C$_3$-$C_2$)-alkyl, which may be optionally substituted by 1-3 F or S-CH$_3$;

b) (Co-Ci)-alkylene-(C$_3$-C$_2$)-cycloalkyl, wherein said cycloalkyi is unsubstituted or mono- or di-substituted by methyl;

c) (Co-C2)-alkylene-phenyl, wherein said phenyl is unsubstituted or mono- or di-substituted by F, Cl, Me or CF$_3$; or

d) thienyl; more preferably

$R^3$ is $H$ or CH$_3$;

and

$R^4$ is

a) (C$_3$-$C_2$)-alkyl, which may be optionally substituted by 1-3 F or S-Me,

b) methylene-(C$_4$-$C_6$)-cycloalkyl; most preferably

$R^3$ is $H$;

and
$R^4$ is 

a) $(C_4-C_5)$-alkyl;

b) methylene-$(C_4-C_6)$-cycloalkyl.

5 In another group of embodiments of the compounds of the formula I

$R^3$ and $R^4$

are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring, which is unsubstituted or mono-substituted by CH$_3$;

preferably

10 $R^3$ and $R^4$

are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring.

15 In another group of embodiments of the compounds of the formula I

$R^5$ is H, CH$_3$ or OH;

$R^6$ H or CH$_3$;

n is 0, 1 or 2; preferably

20 $R^5$ is H;

$R^6$ H;

n is 0, 1 or 2.

In another group of embodiments of the compounds of the formula I

$R^5$ is H, CH$_3$ or OH;

25 $R^6$ H or CH$_3$;

n is 1 or 2; preferably

$R^5$ is H;

$R^6$ H;

n is 1 or 2.

30 In another group of embodiments of the compounds of the formula I

$R^5$ is H, CH$_3$ or OH;
R^6 \quad \text{H or CH}_3; \\
\text{n is 0 or 1; preferably} \\
R^5 \quad \text{is H;} \\
R^6 \quad \text{H;} \\
\text{n is 0 or 1.}

In another group of embodiments of the compounds of the formula I \\
R^5 \quad \text{is H, CH}_3 \text{ or OH;} \\
R^6 \quad \text{H or CH}_3; \\
\text{n is 2; preferably} \\
R^5 \quad \text{is H;} \\
R^6 \quad \text{H;} \\
\text{n is 2.}

15 In another group of embodiments of the compounds of the formula I \\
R^5 \quad \text{is H, CH}_3 \text{ or OH;} \\
R^6 \quad \text{H or CH}_3; \\
\text{n is 1; preferably} \\
R^5 \quad \text{is H;} \\
R^6 \quad \text{H;} \\
\text{n is 1.}

In another group of embodiments of the compounds of the formula I \\
\text{n is 0.}

25 In another group of embodiments of the compounds of the formula I \\
R^5 \quad \text{is H or CH}_3; \\
R^6 \quad \text{H;} \\
\text{n is 0, 1 or 2; preferably} \\
R^5 \quad \text{is H or CH}_3; \\
R^6 \quad \text{H or CH}_3; \\
\text{n is 1 or 2.
In another group of embodiments of the compounds of the formula I

\[ R^5 \] is H or OH;

\[ R^6 \] H;

\[ n \] is 0, 1 or 2; preferably

\[ R^5 \] is H or OH;

\[ R^6 \] H or CH₃;

\[ n \] is 1 or 2.

In another group of embodiments of the compounds of the formula I

\[ Z \] is

\[ \text{CO}_2\text{R}^7, \text{OR}^8, \text{C(O)NR}^9\text{R}^{10}, \text{S(O)}_2\text{NR}^{11}\text{R}^{12}, \]

\[ \text{-S(O)}_\nu \text{NNH}_\nu \text{R}^{13}, \text{NNH}_\nu \text{R}^{14}, \]

\[ \text{N-O} \text{R}^{15}, \text{S} \text{R}^{16}, \text{N} \text{R}^{17}, \text{N} \text{R}^{18}, \]

\[ \text{N=}, \text{N=}, \text{N=}, \text{or} \]

\[ \text{N-OH} \]

wherein \( \nu \) is 0 or 2; preferably

\[ Z \] is

\[ \text{CO}_2\text{R}^7, \text{OR}^8, \text{C(O)NR}^9\text{R}^{10}, \text{S(O)}_2\text{NR}^{11}\text{R}^{12}, \]
wherein $v$ is 0 or 2; more preferably $Z$ is $\text{CO}_2\text{-R}_7$, $\text{OR}_8$, $\text{C(O)NR}_9\text{R}_{10}$, $\text{S(O)}_2\text{NR}_1\text{R}_2$ or 5-tetrazolyl, even more preferably $Z$ is $\text{CO}_2\text{-H}$, $\text{OH}$, $\text{C(O)NR}_9\text{R}_{10}$, or 5-tetrazolyl; most preferably $Z$ is $\text{CO}_2\text{-H}$.

Another group of embodiments are compounds of the formula I, wherein $R_7$ is $\text{H}$ or (C$_1$-C$_4$)-alkyl; preferably $R_7$ is $\text{H}$.

Another group of embodiments are compounds of the formula I, wherein $R_8$ is $\text{H}$ or (C$_1$-C$_4$)-alkyl; preferably $R_8$ is $\text{H}$.

Another group of embodiments are compounds of the formula I, wherein $R_9$ is $\text{H}$, CH$_3$ or ethylene-O-methyl;
and

$R^{10}$ is

a) $H$

b) (Ci-C6)-alkyl, which is unsubstituted or mono-substituted by CF$_3$;

c) (Ci-C$_2$)-alkyl, which is substituted by CN or CO$_2$R$^{19}$

wherein

$R^{19}$ is H or (Ci-C$_6$)-alkyl;

d) (C$_2$-C$_4$)-alkyl, which is mono-substituted by a substituent selected from the group consisting of S-methyl, SO$_2$NR$^{20}$R$^{21}$, O-R$^{22}$ and NR$^{23}$R$^{24}$;

wherein

$R^{20}$ is H;

$R^{21}$ is H;

$R^{22}$ is H, (Ci-C3)-alkyl, methylene-cyclopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane;

$R^{23}$ is H or (Ci-C$_2$)-alkyl;

$R^{24}$ is (Ci-C$_2$)-alkyl or SO$_2$-methyl;

e) (C$_3$-C$_5$)-cycloalkyl, which is unsubstituted or mono-substituted by phenyl;

f) (Co-C$_2$)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is five or six membered and contains 1 or 2 O atoms in non-adjacent positions, and wherein said heterocycloalkyl is unsubstituted or geminally disubstituted with a spiro cyclopentyl ring

g) (C$_2$-C$_5$)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five-, six- or seven-membered ring, which contains at least one N atom, and which is attached via said N-atom, and which may additionally contain one heteroatom selected from the group consisting of O, S(O)$_x$ or NR$^{25}$ in a position not adjacent to the N atom, by which the ring is attached to the alkylene, and wherein any carbon atom within said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (Ci-C3)alkyl, or methylene-phenyl;

wherein

$x$ is 2;
R^{25} is H, (Ci-C2)alkyl, methylene-phenyl or phenyl, which is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of F, Cl and OMe;

h) (Co-C3)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five- or six-membered ring, which contains at least one N atom, and which is not attached via said N-atom, and which may additionally contain one O atom in a position not adjacent to the N atom, and wherein said N-atom is unsubstituted or substituted by a substituent selected from the group consisting of

i) (Ci-C_4)-alkyl, which is unsubstituted or mono-substituted by -O-methyl;

ii) methylene-cyclohexyl;

iii) (Co-C2)-alkylene-phenyl, wherein phenyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of F and O-methyl;

iv) (Co-Ci)-alkylene-pyridyl;

v) pyrimidinyl;

i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl;

j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;

k) methylene-4-(octahydro-quinolizinyl);

l) (Co-C2)-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, O-methyl, N(methyl)_2, 4-morpholinyl and methylene-(4-methyl-piperidin)-1 -yl or disubstituted on adjacent positions by the group -O(CH_2)O-;

m) (Ci-C2)-alkylene-heteroaryl, wherein said heteroaryl ring is a five- or six-membered ring containing 1, 2, 3 or 4 heteroatoms selected from O, S or N; and wherein said heteroaryl ring is unsubstituted or monosubstituted by oxo (=O);

or

R^9 and R^{10} together with the N-atom carrying them are
a) a four-, five- or six-membered heterocycloalkyl ring containing only the N atom, to which R⁹ and R¹⁰ are attached, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of

i) \((\text{Co-Ci})\)-alkylene-OR²⁶, wherein R²⁶ is H, (Ci-C₂)-alkyl or methylene-phenyl;

ii) \(\text{CO}_2\text{R}²⁷\), wherein R²⁷ is H or (Ci-C₆)-alkyl;

iii) \(\text{NR}²⁸\text{R}²⁹\), wherein R²⁸ is (C₁-C₂)-alkyl and R²⁹ is (C₁-C₂)-alkyl, methylene-phenyl or ethylene-NMe₂;

iv) 1-piperidinyl, which is unsubstituted or mono-substituted by methyl;

v) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;

vi) 4-morpholinyl;

vii) 1-azepanyl;

vii) 2-(2,3-dihydro-1H-isoindolyl);

b) a six- or seven-membered heterocycloalkyl ring containing the N atom, to which R⁹ and R¹₀ are attached and one additional heteroatom selected from O, S or NR³⁰ in a position non-adjacent to the N atom, to which R⁹ and R¹₀ are attached, wherein the carbon atoms in said heterocycloalkyl ring are unsubstituted or mono- or disubstituted by methyl and wherein R³⁰ is

i) H;

ii) (Ci-C₄)-alkyl;

iii) (C₅-C₆)-cycloalkyl;

iv) phenyl, which is unsubstituted or mono-substituted by F, CF₃ or OMe;

v) methylene-phenyl, which is unsubstituted or mono- or di-substituted by F or Cl or disubstituted on adjacent positions by the group -O(CH₂)O-;

vi) pyridyl;

c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is unsubstituted or substituted on the second N atom in 5-position by a substituent selected
from the group consisting of (Ci-C₄)-alkyl, methylene-cyclopentyl, phenyl, which is unsubstituted or mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by OCH₃ or CF₃:

R¹¹ is H;
R¹² is CH₃;
R¹³ is H;
R¹⁴ is CF₃ or methylene-OCH₃;
R¹⁵ is cyclopryopyl or phenyl;
R¹⁶ is H or CH₃;
R¹⁷ is H or CH₃
and
R¹⁸ is CH₃;

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

Another group of embodiments are compounds of the formula I, wherein

R⁹ is H, CH₃ or ethylene-OCH₃;
and
R¹⁰ is

a) H
b) (Ci-C₆)-alkyl, which is unsubstituted or mono-substituted by CF₃;
c) (Ci-C₂)-alkyl, which is substituted by CN or CO₂R¹⁹
wherein
R¹⁹ is H;
d) (C₂-C₄)-alkyl, which is mono-substituted by a substituent selected from the group consisting of SMe, SO₂NR₂¹, O-R²² and NR²³R²⁴;
wherein

\[ R^{20} \text{ is } H; \]
\[ R^{21} \text{ is } H; \]
\[ R^{22} \text{ is } H, (\text{C}-\text{C})\text{-alkyl, methylene-cyclopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane; } \]
\[ R^{23} \text{ is } H \text{ or } (\text{C})\text{-alkyl; } \]
\[ R^{24} \text{ is } (\text{C})\text{-alkyl or } \text{SO} \text{CH}_{3}; \]
\[ e) \text{ (C-2)}\text{-cycloalkyl, which is unsubstituted or mono-substituted by phenyl; } \]
\[ f) \text{ (Co-2)}\text{-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is five or six membered and contains 1 or 2 O atoms in non-adjacent positions, and wherein said heterocycloalkyl is unsubstituted or geminally disubstituted with a spiro cyclopentyl ring or with a spiro cyclohexyl ring; } \]
\[ g) \text{ (C-2)}\text{-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five-, six- or seven-membered ring, which contains at least one N atom, and which is attached via said N-atom, and which may additionally contain one heteroatom selected from the group consisting of O, S(O)_{x} \text{ or } \text{NR}^{25} \text{ in a position not adjacent to the N atom, by which the ring is attached to the alkylene, and wherein any carbon atom within said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (C-3)alkyl, or methylene-phenyl; } \]
\[ x \text{ is } 2; \]
\[ R^{25} \text{ is } (\text{C})\text{-alkyl, methylene-phenyl or phenyl, which is substituted by 1 or 2 substituents selected from the group consisting of F, Cl and } \text{OCH}_{3}; \]
\[ h) \text{ (Co-3)}\text{-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five- or six-membered ring, which contains at least one N atom, and which is not attached via said N-atom, and which may additionally contain one O atom in a position not adjacent to the N atom, and } \]
wherein said N-atom is unsubstituted or substituted by a substituent selected from the group consisting of

i) \((\text{C}_i-\text{C}_4)-\text{alkyl, which is unsubstituted or mono-substituted by} \ O\text{CH}_3;\)

ii) methylene-cyclohexyl;

iii) \((\text{Co-C}_2)-\text{alkylene-phenyl, wherein phenyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of} \ F \text{ and} \ O\text{CH}_3;\)

iv) \((\text{Co-Ci})-\text{alkylene-pyridyl;}\)

v) pyrimidinyl;

i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl;

j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;

k) methylene-4-(octahydro-quinolizinyl);

l) \((\text{Co-C}_2)-\text{alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of} \ F, \ O\text{CH}_3, \ N(\text{CH}_3)_2, \ 4\text{-morpholinyl and methylene-}(4\text{-methyl-piperidin})-1\text{-yl} \text{ or disubstituted on adjacent positions by the group} \ -\text{O(CH}_2\text{O)-};\)

m) \((\text{Ci-C}_2)-\text{alkylene-heteroaryl, wherein said heteroaryl ring is a five-or six-membered ring containing 1, 2, 3 or 4 heteroatoms selected from} \ O, S \text{ or} \ N; \text{ and wherein said heteroaryl ring is unsubstituted or mono-substituted by oxo} \ (=\text{O});\)

or

\(R^9 \text{ and} \ R^{10} \text{ together with the N-atom carrying them are}\)

a) a four-, five- or six-membered heterocycloalkyl ring containing only the N atom, to which \(R^9 \text{ and} \ R^{10} \text{ are attached, which is unsubstituted or mono-substituted selected from the group consisting of}\)

i) \((\text{Co-Ci})-\text{alkylene-} \text{O}R^{26}, \text{ wherein} \ R^{26} \text{ is} \ H, \text{ (Ci-C}_3\text{-alkyl or methylene-phenyl;}\)

ii) \text{CO}_2R^{27}, \text{ wherein} \ R^{27} \text{ is is} \ H;

\(i) \text{NR}^{28}R^{29}, \text{ wherein} \ R^{28} \text{ is} \ (\text{Ci-C}_2)-\text{alkyl and} \ R^{29} \text{ is} \ (\text{Ci-C}_2)-\text{alkyl, methylene-phenyl or ethylene-N(}\text{CH}_3\text{)_2};\)

\(\text{iii) 1-piperidinyl, which is mono-substituted by methyl;}\)
iv) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;
v) 4-morpholinyl;
vi) 1-azepanyl;
vii) 2-(2,3-dihydro-1H-isoindolyl);

b) a six- or seven-membered heterocycloalkyl ring containing the N atom, to which R⁹ and R¹⁰ are attached and one additional heteroatom selected from O, S or NR₃₀ in a position non-adjacent to the N atom, to which R⁹ and R¹⁰ are attached, wherein the carbon atoms in said heterocycloalkyl ring are unsubstituted or mono- or disubstituted by methyl and wherein R₃₀ is

i) (C₁-C₄)-alkyl;
ii) (C₅-C₆)-cycloalkyl;
iii) phenyl, which is unsubstituted or mono-substituted by F, CF₃ or OCH₃;
iv) methylene-phenyl, which is unsubstituted or mono- or di-substituted by F or Cl or disubstituted on adjacent positions by the group -O(CH₂)O-;
v) pyridyl;

c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is substituted on the second N atom in 5-position by a substituent selected from the group consisting of (C₁-C₄)-alkyl, methylene-cyclopentyl, phenyl, which is mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by OCH₃ or CF₃;

R¹¹ is H;
R¹² is CH₃;
R¹³ is H;
R¹⁴ is CF₃ or methylene-OCH₃;
R¹⁵ is cyclopropyl or phenyl;
R¹⁶ is H or CH₃;
R¹⁷ is H or CH₃;
and

R^{18} \text{ is } \text{CH}_3;\

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

Another group of embodiments are compounds of the formula I, wherein

10

R^9 \text{ is } \text{H}, \text{CH}_3;\

and

R^{10} \text{ is }\

a) \text{H}\

b) (C\text{-C}_6)-\text{alkyl, which is unsubstituted or mono-substituted by CF}_3;\

c) (C\text{-C}_2)-\text{alkyl, which is substituted by CN or CO}_2\text{R}^{19}\

wherein

R^{19} \text{ is } \text{H};\

d) (C\text{2-}-C\text{4})-\text{alkyl, which is mono-substituted by a substituent selected from the group consisting of S}\text{CH}_3, \text{SO}_2\text{NR}^{20}\text{R}^{21}, \text{O-R}^{22} \text{ and NR}^{23}\text{R}^{24};\

wherein

R^{20} \text{ is } \text{H};\

R^{21} \text{ is } \text{H};\

R^{22} \text{ is } \text{H}, (C\text{-C}_3)-\text{alkyl, methylene-cyclopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane};\

R^{23} \text{ is } \text{H or (C\text{-C}_2)-alkyl};\

R^{24} \text{ is } (C\text{-C}_2)-\text{alkyl or SO}_2\text{CH}_3;\

e) cyclobutyl, cyclopentyl or 2-phenyl-cyclopropyl;\

f) (C\text{2-}-C\text{2})-\text{alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 2-tetrahydrofuranyl, 3- tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4- tetrahydropyranyl and 1,4-dioxan-2-yl;
g) \((C_2 - C_5)\)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 1-pyrrolidinyl, 1-piperidinyl, 1-azepanyl, 4-morpholinyl 1,1-dioxo-thiomorpholin-4-yl, and 1-piperazinyl; wherein said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of \((C_2 - C_5)\)alkyl, or methylene-phenyl;

h) \((C_0 - C_3)\)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 3-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 2-morpholinyl and wherein said heterocycloalkyl is substituted by a substituent selected from the group consisting of

i) \((C_1 - C_4)\)-alkyl;

ii) methylene-cyclohexyl;

iii) \((C_0 - C_2)\)-alkylene-phenyl;

iv) \((C_0 - C_1)\)-alkylene-pyridyl;

v) pyrimidinyl;

i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3yl;

j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;

k) methylene-4-(octahydro-quinolizinyl);

l) \((C_0 - C_2)\)-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, OCH₃, N(CH₃)₂;

m) \((C_1 - C_2)\)-alkylene-heteroaryl, wherein said heteroaryl ring is is selected from the group consisting of 2-thienyl, 2-furanyl, 2-thiazolyl, 2-oxazolyl, 5-tetrazolyl and 5-Oxo-4,5-dihydro-1 H-[1,2,4]triazol-3-yl;

or

R⁹ and R¹⁰ together with the N-atom carrying them are

a) azetidinyl substituted by CO₂H ;

b) pyrrolidinyl, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of

i) OH;

ii) methylene-OCH₃;
iii) methylene-O-methylene-phenyl;
iv) CO₂H;
v) NR²⁸R⁹, wherein R²⁸ is (Ci-C₂)-alkyl and R⁹ is (Ci-C₂)-alkyl;
vi) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;
c) piperidinyl, which is mono-substituted by a substituent selected from the group consisting of
i) O-(Ci-C₃)alkyl;
ii) methylene-O CH₃;
iii) NR²⁸R⁹, wherein R²⁸ is (Ci-C₂)-alkyl and R⁹ is methylene-phenyl or ethylene-N(CH₃)₂
iv) 1-piperidinyl, which is mono-substituted by methyl;
v) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;
vi) 4-morpholinyl;
vii) 1-azepanyl;
viii) 2-(2,3-dihydro-1 H-isodindolyl);
d) 4-morpholinyl, which is disubstituted by methyl;
e) 4-thiomorpholinyl;
f) piperazinyl, which is mono-substituted by a substituent selected from the group consisting of
i) (Ci-C₄)-alkyl;
ii) (C₅-C₆)-cycloalkyl;
iii) phenyl, which is unsubstituted or mono-substituted by F, CF₃ or OCH₃;
iv) methylene-phenyl, which is unsubstituted or disubstituted on adjacent positions by the group -O(CH₂)O-;
v) pyridyl;
g) azepanyl, which is substituted by methylene-phenyl, which is unsubstituted or mono- or di-substituted by F or Cl;
c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is substituted on the second N atom in 5-position by a substituent selected from the group consisting
of (C1-C4)-alkyl, methylene-cyclopentyl, phenyl, which is mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by OCH3 or CF3;

5  
\[ R^{11} \text{ is } H; \]
\[ R^{12} \text{ is } CH3; \]
\[ R^{13} \text{ is } H; \]
\[ R^{14} \text{ is } CF3 \text{ or methylene-OCH3; } \]
\[ R^{15} \text{ is cyclopropyl or phenyl; } \]
\[ R^{16} \text{ is } H \text{ or } CH3; \]
\[ R^{17} \text{ is } H \text{ or } CH3; \]
and
\[ R^{18} \text{ is } CH3; \]

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

Another group of embodiments are compounds of the formula I wherein

20  
\[ R^9 \text{ is } H; \]
and
\[ R^{10} \text{ is } \]
\[ a) \text{ H } \]
\[ b) (C1-C4)-alkyl; \]
\[ c) (C1-C2)-alkyl, which is substituted by CN or CO2R^{19} \]
wherein
\[ R^{19} \text{ is } H; \]
\[ d) (C2-C4)-alkyl, which is mono-substituted by a substituent selected from the group consisting of S CH3, SO2NR^{20}R^{21}, O-R^{22} \text{ and } NR^{23}R^{24}; \]

30  
\[ R^{20} \text{ is } H; \]
\[ R^{21} \text{ is } H; \]
R$^{22}$ is H, (C₃₋C₅)-alkyl, methylene-cyclopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane;
R$^{23}$ is H or (C₁-C₂)-alkyl;
R$^{24}$ is (C₁-C₂)-alkyl or SO₂CH₃;

e) cyclobutyl, or cyclopentyl;
f) (C₅-C₂)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl and 1,4-dioxan-2-yl;
g) (C₂-C₅)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 1-pyrrolyl, 1-piperidinyl, 1-azepanyl, 4-morpholinyl, 1,1-dioxo-thiomorpholin-4-yl, and 1-piperazinyl; wherein said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (CrC₂)alkyl, or methylene-phenyl;
h) (C₅-C₃)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 3-pyrrolyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 2-morpholiny1 and wherein said heterocycloalkyl is substituted by a substituent selected from the group consisting of
i) (C₁-C₄)-alkyl;
ii) methylene-cyclohexyl;
iii) (C₅-C₂)-alkylene-phenyl;
iv) (C₅-C₁)-alkylene-pyridyl;
v) pyrimidinyl;
l) (C₅-C₂)-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, OCH₃, N(CH₃)₂;
m) (C₁-C₂)-alkylene-heteroaryl, wherein said heteroaryl ring is is selected from the group consisting of 2-thienyl, 2-furanyl, 2-thiazolyl, 2-oxazolyl, 5-tetrazolyl and 5-Oxo-4,5-dihydro-1 H-[1,2,4]triazol-3-yl; or
R⁹ and R¹⁰ together with the N-atom carrying them are:

a) azetidinyl substituted by CO₂H;

b) pyrrolidinyl, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of:

   i) OH;
   ii) methylene -OCH₃;
   iii) methylene -O-methylene-phenyl;
   iv) CO₂H;
   v) NR²⁸R²⁹, wherein R²⁸ is (C₁-C₂)-alkyl and R²⁹ is (C₁-C₂)-alkyl;
   vi) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;

   c) piperidinyl, which is mono-substituted by a substituent selected from the group consisting of:

      i) 0-(C₁-C₃)alkyl;
      ii) methylene -OCH₃;
      iii) NR²⁸R²⁹, wherein R²⁸ is (C₁-C₂)-alkyl and R²⁹ is methylene-phenyl or ethylene -N(CH₃)₂
      iv) 1-piperidinyl, which is mono-substituted by methyl;
      v) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;
      vi) 4-morpholinyl;
      vii) 1-azepanyl;
      viii) 2-(2,3-dihydro-1 H-isoindolyl);

d) 4-morpholinyl, which is disubstituted by methyl;

e) 4-thiomorpholinyl;

f) piperazinyl, which is mono-substituted by a substituent selected from the group consisting of:

   i) (C₁-C₄)-alkyl;
   ii) (C₅-C₆)-cycloalkyl;
   iii) phenyl, which is unsubstituted or mono-substituted by F, CF₃ or OCH₃;
iv) methylene-phenyl, which is unsubstituted or disubstituted on adjacent positions by the group -O(CH₂)O-;
v) pyridyl;
g) azepanyl, which is substituted by methylene-phenyl, which is unsubstituted or mono- or di-substituted by F or Cl;
c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is substituted on the second N atom in 5-position by a substituent selected from the group consisting of (C₁-C₄)-alkyl, methylene-cyclopentyl, phenyl, which is mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by OCH₃ or CF₃;

\[
R_{11}^{11} \text{ is } H; \\
R_{12}^{12} \text{ is } CH₃; \\
R_{13}^{13} \text{ is } H; \\
R_{14}^{14} \text{ is } CF₃ \text{ or methylene-OCH₃; } \\
R_{15}^{15} \text{ is cyclopryopyl or phenyl; } \\
R_{16}^{16} \text{ is } H \text{ or } CH₃; \\
R_{17}^{17} \text{ is } H \text{ or } CH₃; \\
\text{ and } \\
R_{18}^{18} \text{ is } CH₃; \\
\]

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

Another group of embodiments are compounds of the formula I
Another group of embodiments are compounds of the formula I:

\[
\text{I}
\]

wherein

- \( R', R'', R''' \) are \( H \);
- \( R^1 \) is 1-ethyl-propyl;
- \( R^2 \) is 3-thienyl;
- \( R^3 \) is \( H \);
- \( R^4 \) is 2-methyl-propyl;
- \( n \) is 0;

and

- \( Z \) is \( \text{CO2-R}_7, \text{C(O)NR}_9\text{R}_{10} \).
n is 0, 1, 2;
and
Z is C(O)NR^9R^{10}.

5
Another group of embodiments are compounds of the formula I wherein
R', R'^*, R'' are H;
R^1 is 1-ethyl-propyl or 2-methyl-cyclohexyl;
R^2 is 3-thienyl;
R^3 is H, or (C_i-C_2)-alkyl;
and
R^4 is
a) (C_3-C_5)-alkyl, which may be optionally substituted by 1-3 F or S-(C_i-C_4)-alkyl,
b) (Co-Ci)-alkylene -(C_3-C_7)-cycloalkyl, wherein said cycloalkyl is unsubstituted or
mono- or di-substituted by methyl;
or
R^3 and R^4
are, together with the carbon atom to which they are attached, a 5- to 7-
membered cycloalkyl ring, which is unsubstituted or mono-substituted by (C_i-
C_4)-alkyl;

n is 0; and

Z is CO_2-H;

Another group of embodiments are compounds of the formula I wherein
R', R'^*, R'' are H;
R^1 is 1-ethyl-propyl or 2-methyl-cyclohexyl;
R^2 is 3-thienyl;
R^3 is H, or (C_i-C_2)-alkyl;
and
$R^4$ is

a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(C₄)-alkyl,

b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cycloalkyi is unsubstituted or mono- or di-substituted by methyl;

5

or

$R^3$ and $R^4$

are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyi ring, which is unsubstituted or mono-substituted by (C₄)-alkyl;

10 $R^5$ is H, (C₄)-alkyl or OH;

$R^6$ H or (C₄)-alkyl;

n is 1;

and

$Z$ is CO$_2$-H.

15

Another group of embodiments are compounds of the formula I wherein

$R', R'', R'''$ are H;

$R^1$ is 1-ethyl-propyl or 2-methyl-cyclohexyl;

20 $R^2$ is 3-thienyl;

$R^3$ is H, or (C₂)-alkyl;

and

$R^4$ is

a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(C₄)-alkyl,

b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cycloalkyi is unsubstituted or mono- or di-substituted by methyl;

or

$R^3$ and $R^4$

are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyi ring, which is unsubstituted or mono-substituted by (C₄)-alkyl;

30 $R^5$ is H, (C₄)-alkyl or OH;
Another group of embodiments are compounds of the formula I wherein

R', R", R'" are H;
R^1 is 1-ethyl-propyl;
R^2 is 3-thienyl;
R^3 is H, or (C\textsubscript{i}-C\textsubscript{2})-alkyl;
and
R^4 is

a) (C\textsubscript{3}-C\textsubscript{3})-alkyl, which may be optionally substituted by 1-3 F or S-(C\textsubscript{i}-C\textsubscript{4})-alkyl,

b) (Co-C\textsubscript{i})-alkylene-(C\textsubscript{3}-C\textsubscript{7})-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono- or di-substituted by methyl;

or

R^3 and R^4

are, together with the carbon atom to which they are attached, a 5- to 7-
membered cycloalkyl ring, which is unsubstituted or mono-substituted by (C\textsubscript{i}-
C\textsubscript{4})-alkyl;
R^5 is H, (C\textsubscript{i}-C\textsubscript{4})-alkyl or OH;
R^6 H or (C\textsubscript{i}-C\textsubscript{4})-alkyl;
n is 1 or 2;

and

Z is OR^8, S(O)\textsubscript{2}NR\textsubscript{11}R\textsubscript{12}, CN,

wherein v is 0 or 2;
Another group of embodiments are compounds of the formula I wherein
R', R", R"'
are H;

R¹
is 1-ethyl-propyl;

R²
is 3-thienyl;

R³
is H;

R⁴
is 2-methyl-propyl;

n is 0;

and

Z
is C(O)NR⁹R¹₀.

wherein
R⁹
is H or methyl;

and

R¹₀
is

(c) (C-C₂)-alkyl, which is substituted by CN

d) (C-C₂₄)-alkyl, which is mono-substituted by a substituent selected from NR²³R²⁴;

wherein
R²³
is H;

R²⁴
is (C-C₂)-alkyl or SO₂Methyl;

m) (C-C₂)-alkylene-heteroaryl, wherein said heteroaryl ring is a five-or six-membered ring containing 1, 2, 3 or 4 heteroatoms selected from O, S or N; and wherein said heteroaryl ring is unsubstituted or mono-substituted by oxo (=O);

or

R⁹ and R¹₀ together with the N-atom carrying them are
a) a four-, five- or six-membered heterocycloalkyl ring containing only the N atom, to which \( R^9 \) and \( R^{10} \) are attached, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of
i) \((\text{Co}-\text{Ci})\)-alkylene- \( \text{OR}^{26} \), wherein \( R^{26} \) is \( \text{H} \);
ii) \( \text{CO}_2R^{27} \), wherein \( R^{27} \) is \( \text{H} \).

Another group of embodiments are compounds of the formula I wherein
\( R', R'', R^{1''} \) are \( \text{H} \);

\( R^1 \) is 1-ethyl-propyl;
\( R^2 \) is 3-thienyl;
\( R^3 \) is \( \text{H} \);
\( R^4 \) is 2-methyl-propyl;
\( n \) is 0;
and
\( Z \) is \( \text{C}(\text{O})\text{NR}^9\text{R}^{10} \);
wherein
\( R^9 \) is \( \text{H} \) or methyl;
and
\( R^{10} \) is
a) \((\text{Ci}-\text{C}2)-\text{alkyl}, which is substituted by \( \text{CN};\)
b) \((\text{C}2-\text{C}4)-\text{alkyl}, which is mono-substituted by a substituent selected from \( \text{NR}^{23}\text{R}^{24} \);
wherein
\( R^{23} \) is \( \text{H} \);
\( R^{24} \) is \( \text{(Ci-C}2)\)-alkyl or \( \text{SO}_2\text{Methyl};\)
c) \((\text{Ci-C}2)-\text{alkylene-heteroaryl}, wherein said heteroaryl ring is is selected from 5-Oxo-4,5-dihydro-1 \( \text{H}-[1,2,4]\text{triazol-3-yl};\)
or
\( R^9 \) and \( R^{10} \) together with the N-atom carrying them are
a) a four-, five- or six-membered heterocyclicalkyl ring containing only the N atom, to which $R^9$ and $R^{10}$ are attached, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of

i) $(\text{Co-Ci})$-alkylene-$\text{OR}^{26}$, wherein $R^{26}$ is $H$;

ii) $\text{CO}_2\text{R}^{27}$, wherein $R^{27}$ is $H$.

In another embodiment compounds of the formula I are encompassed selected from the group consisting of

1. $1\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-cycloheptanecarboxylic acid}$

2. $2\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-2-methyl-3-phenyl-propionic acid}$

(S)-3-Cyclohexyl-2-[[2-cyclopentylmethyl-1-(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

4. $2\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-2-methyl-3-phenyl-propionic acid}$

5. $2\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-2,3-dimethyl-butyric acid}$

6. $1\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-cyclopentanecarboxylic acid}$

7. $2\text{-[}[\text{1-}-(\text{1-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]}\text{-amino}}\text{-2-phenyl-butyric acid}$

(S)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

9. (R)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

10. (R)-3-Cyclohexyl-2-[[2-cyclopentylmethyl-1-(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

11. 3-Cyclopentyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
12 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,4-dimethyl-pentanoic acid
13 2-[[1 -(1 -Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,4-dimethyl-pentanoic acid
14 2-[[1 -(1 -Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2-methyl-4-methylsulfanyl-butyric acid
15 (S)-3-Cyclohexyl-2-[[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
16 (S)-2-[[1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
17 (S)-3-Cyclohexyl-2-[[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
18 (S)-2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
19 (S)-2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-(4-fluoro-phenyl)-propionic acid
20 (S)-3-(4-Chloro-phenyl)-2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
21 (S)-3-Octyl-2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
22 (S)-3-Octyl-2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
23 (S)-3-Octyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
24 1-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-cyclohexanecarboxylic acid
25 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2-nitro-pentanoic acid
26 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5,5,5-trifluoro-pentanoic acid
27 5,5,5-Trifluoro-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
28 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-phenyl-butyric acid
29 3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
30 3-(4-Ethyl-phenyl)-2-[[1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
31 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-(4-trifluoromethyl-phenyl)-propionic acid
32 (S)-3-(3,4-Dichloro-phenyl)-2-[[1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
33 3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
34 1-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-n-nethyl-cyclohexanecarboxylic acid
35 4-Methyl-1-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
36 2-[[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-(4-n-nethyl-cyclohexyl)-propionic acid
37 (S)-3-Cyclohexyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
38 1-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
39 3-Cycloheptyl-2-[[1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
40 3-Cycloheptyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
41 3-[[1 -(1 -Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-n-nethyl-pentanoic acid
42 3-[[1 -(1 -Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-phenyl-propionic acid
43 3-[[2-Cyclopentylmethyl-1 -(1 -ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-amino]-3-phenyl-propionic acid
3-Cyclohexyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

46 4-Cyclohexyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid

48 4-Cyclohexyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5,5-dimethyl-hexanoic acid

50 (S)-3-[(1-(1-ethyl-propyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid

52 4-Cyclohexyl-3-[(1-(1S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid

54 (3R,4S)-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-npentyl-hexanoic acid

56 3-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-4-Cyclopentyl-3-\{(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-butyric acid

(S)-4-Cyclopentyl-3-\{(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-butyric acid

3-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2,2,5-trinnethyl-hexanoic acid

3-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2,2-dinnethyl-hexanoic acid

(1 -(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-cyclohexyl]-acetic acid

4-Cyclohexyl-3-\{(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-butyric acid

(1 -(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-cyclohexyl]-acetic acid

(2R,3S)-3-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2-hydroxy-5-nnethyl-hexanoic acid

(2S,3S)-3-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2-hydroxy-5-nnethyl-hexanoic acid

(R)-6-Methyl-4-\{(2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-annino\}-heptanoic acid

(R)-6-Methyl-4-\{(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-heptanoic acid

(4R,5S)-4-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-heptanoic acid

(4R,5S)-5-Methyl-4-\{(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-heptanoic acid

(3R,4S)-5-Cyclohexyl-4-\{(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-3-hydroxy-pentanoic acid

(3R,4S)-5-Cyclohexyl-3-hydroxy-4-\{(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(3S,4S)-4-\{(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-3-hydroxy-6-nnethyl-heptanoic acid
(3R,4S)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-nnethyl-heptanoic acid

(3R,4S)-3-Hydroxy-6-methyl-4-[1-(1R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid

(3S,4S)-3-Hydroxy-6-methyl-4-[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid

(3S,4S)-5-Cyclohexyl-4-[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-3-hydroxy-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid

(S)-2-[(1-(5-Chloro-thiophen-2-ylmethyl)-1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(2S,3S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid

(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid

(S)-4-Methyl-2-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[(2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

(S)-2-[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(S)-4-Methyl-2-[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(2S,3S)-3-Methyl-2-\{[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-2-\{[1 -(2-Ethyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-4-nnethyl-pentanoic acid

(S)-2-\{[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-pentanoic acid

(S)-3-\{[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid

(S)-3-\{[1 -(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid

(S)-3-\{[(1-Cyclohexylmethyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid

(S)-5-Methyl-3-\{[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(S)-5-Methyl-3-\{[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(S)-4-Phenyl-3-\{[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-annino\}-butyric acid

(S)-5-Methyl-3-\{[1 -(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(S)-3-\{[1 -(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid

(S)-3-\{[(1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid

(S)-3-\{[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid
(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nnethyl-pentanoic acid
(S)-2-[(2-Cyclopentylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino)-4-nnethyl-pentanoic acid
(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-Cycloheptyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-Cyclohexyl-2-cyclopentylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nnethyl-pentanoic acid
(S)-4-Methyl-2-[(1-(2-methyl-butyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-4-Methyl-2-[(2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-2-[(2-Benzyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-(1-Ethyl-propyl)-2-(5-methyl-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-2-[(2-Cyclohexylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-butyril acid
(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-butyril acid
(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethylsulfanyl-butyril acid
(S)-2-\((1\text{-ethyl-propyl})-2\text{-thiophen-2-ylmethyl}-1\text{H-benzoimidazole-5-carbonyl}]\text{-amino}\)-3-phenyl-propionic acid

(S)-3-Cyclohexyl-2-\((1\text{-ethyl-propyl})-2\text{-thiophen-2-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl}]\text{-annino}\)-propionic acid

2-\((1\text{-ethyl-propyl})-2\text{-thiophen-2-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl}]\text{-amino}\)-4,4-dinnyl-pentanoic acid

(S)-2-\((1\text{-isobutyl}-2\text{-thiophen-2-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl}]\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-2-\((2\text{-Cyclopentylmethyl}-1\text{-isobutyl}-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-2-\((2\text{-Furan-3-ylmethyl}]\text{-isobutyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-hexanoic acid

(S)-4-Methyl-2-\((1\text{-phenyl}-2\text{-thiophen-2-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-3-Cyclohexyl-2-\((2\text{-cyclohexylmethyl}-1\text{-isobutyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-propionic acid

(S)-2-\((2\text{-Cyclohexylmethyl]-1\text{-isobutyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-4-Methyl-2-\((1\text{-phenyl}-2\text{-thiophen-3-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-4-Methyl-2-\((1\text{-phenyl}-2\text{-thiophen-3-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-nnyl-pentanoic acid

(S)-2-\((1\text{-Cyclohexyl-2-furan-3-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-methyl-pentanoic acid

(S)-4-Methyl-2-\((1\text{-phenyl}-2\text{-thiophen-3-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-4-methyl-pentanoic acid

(S)-4-Methyl-2-\((1\text{-2-methyl-cyclohexyl}-2\text{-thiophen-3-ylmethyl]-1\text{H-benzoimidazole-5-carbonyl]}\text{-amino]}\)-pentanoic acid
(S)-2-[(1-sec-Butyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-3-cyclohexyl-propionic acid
(S)-3-Cyclohexyl-2-[(2-cyclohexylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-annino]-propionic acid
(S)-2-[(1-sec-Butyl-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-n-propyl-pentanoic acid
(S)-2-[(2-Benzyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-n-propyl-pentanoic acid
(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
(S)-2-[(2-Benzyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
(S)-2-[(1-sec-Butyl-2-cyclopentylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
(S)-3-Cyclohexyl-2-[(1-(1-ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-annino]-propionic acid
(S)-2-[(2-Benzyl-1-cyclohexyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
(S)-2-[(1-sec-Butyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
(S)-2-[(2-Benzyl-1-cyclohexyl-1H-benzoimidazole-5-carbonyl)-amino]-3-methyl-pentanoic acid
(S)-3-Cyclohexyl-2-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-3-methyl-pentanoic acid
(S)-2-[(1-Cyclohexyl-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-n-propyl-pentanoic acid
(S)-2-[(2-Benzyl-1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-3-n-propyl-pentanoic acid
(S)-3-[(1-(1-ethyl-propyl)-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-methyl-hexanoic acid
(S)-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-methyl-hexanoic acid
(S)-3-[(1-ethyl-propyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid
(S)-3-[(2-Benzyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid
(S)-3-[(2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[(2-Cyclopentylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(R)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(R)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-6-nnethyl-heptanoic acid
(S)-2-[(1-(1-Isopropyl-2-methyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-(2-Chloro-phenyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-2-[(1-(3-Dimethyl-butyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-3-methyl-[(1H-tetrazol-5-ylmethyl)-carbannoyl]-butyl]-annide
(S)-3-methyl-[(2-H-tetrazol-5-yl)-ethylcarbamoyl]-butyl]-amide
(S)-3-methyl-[(2-sulfamoyl-ethylcarbamoyl)-butyl]-amide
(S)-1-(cyanomethyl-carbannoyl)-3-nnethyl-butyl]-annide
(S)-1-(2-methanesulfonylamino-ethylcarbamoyl)-3-methyl-butyl]-amide
(S)-1-(cyanomethyl-carbannoyl)-3-nnethyl-butyl]-annide
404 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
{(S)-1-(2-cyano-ethylcarbamoyl)-3-nnethyl-butyl]-annide
405 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
{(S)-3-methyl-1-[methyl-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl]-carbamoyl]-butyl]-amide
406 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
{(S)-3-methyl-1-[2-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-ethylcarbamoyl]-butyl]-amide
408 ((S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-nnethyl-pentanoylannino)-acetic acid
409 (S)-1-((S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-nnethyl-pentanoyl]-pyrrolidine-2-carboxylic acid
410 (R)-1-((S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-nnethyl-pentanoyl]-pyrrolidine-2-carboxylic acid
411 1-((S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-nnethyl-pentanoyl]-azetidine-3-carboxylic acid
412 (S)-4-Methyl-2-[(1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid
413 (S)-4-Methyl-2-[(1-((1S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid
414 (S)-4-Methyl-2-[(1-((1R,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid
415 (S)-4-Methyl-2-[(1-((1S,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid
416 (S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
417 (S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
418 (S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
419 (S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid
(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-5-Methyl-3-{[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(S)-5-Methyl-3-{[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(S)-5-Methyl-3-{[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(R)-2-[[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,4-dinnethyl-pentanoic acid

(S)-2-[[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,4-dinnethyl-pentanoic acid

3-Cyclopentyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cyclopentyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(R)-3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(S)-3-Cycloheptyl-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(R)-3-Cycloheptyl-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cycloheptyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cycloheptyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-heptanoic acid

(R)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-heptanoic acid

(S)-4-Cyclohexyl-3-[(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-butyric acid

(R)-4-Cyclohexyl-3-[(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-butyric acid

4-Cyclohexyl-3-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-butyric acid

4-Cyclohexyl-3-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-butyric acid

3-[(1 -((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid

3-[(1 -((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid

3-[(1 -((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-heptanoic acid

3-[(1 -((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-heptanoic acid

3-Cyclohexyl-3-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-propionic acid

3-Cyclohexyl-3-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-propionic acid

(R)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-2,2,5-trinnethyl-hexanoic acid

(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-2,2,5-trinnethyl-hexanoic acid

(R)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-2,2,5-trinnethyl-hexanoic acid

(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-2,2-dinnethyl-hexanoic acid

(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-2,2-dinnethyl-hexanoic acid
468 (S)-3-\{[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2,2-dimethyl-heptanoic acid

469 (R)-3-\{[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-2,2-dimethyl-heptanoic acid

472 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

473 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

474 [(S)-3-methyl-1-(1 H-tetrazol-5-ylmethyl)-butyl]-amide

475 [(S)-1-(N-hydroxycarbamimidoylmethyl)-3-methyl-butyl]-amide

476 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

477 [(S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanyl)-butyl]-amide

478 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

479 [(S)-3-methyl-1-(4H-[1,2,4]triazole-3-sulfonfyl)-butyl]-amide

480 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

481 [(S)-3-methyl-1-methylsulfamoyl-butyl]-amide.

The number denotes the example number of the respective compound.

In another embodiment compounds of the formula I are encompassed selected from the group consisting of

1 1-\{[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-cycloheptane-carboxylic acid

3 (S)-3-Cyclohexyl-2-\{[2-cyclopentylmethyl-1 -(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-propionic acid

6 1-\{[1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-cyclopentane-carboxylic acid

8 (S)-3-Cyclohexyl-2-\{[1 -(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-propionic acid

9 (R)-3-Cyclohexyl-2-\{[1 -(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-propionic acid

10 (R)-3-Cyclohexyl-2-\{[2-cyclopentylmethyl-1 -(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-propionic acid
3-Cyclopentyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dinnethyl-pentanoic acid
2-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dinnethyl-pentanoic acid
2-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-methyl-4-methylsulfanyl-butyric acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-3-Cyclohexyl-2-[[2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-3-Cyclopropyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclobutyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclobutyl-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
1-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexanecarboxylic acid
2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-nnethyl-pentanoic acid
2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5,5,5-trifluoro-pentanoic acid
5,5,5-Trifluoro-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
3-(4,4-Dimethyl-cyclohexyl)-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
33. 3-(4,4-Dimethyl-cyclohexyl)-2-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid

34. 1-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-cyclohexanecarboxylic acid

5. 4-Methyl-1-[[1-(1,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid

35. 2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-(4-nnethyl-cyclohexyl)-propionic acid

36. (S)-3-Cyclohexyl-2-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid

37. 1-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid

38. 3-Cycloheptyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

39. 3-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-phenyl-propionic acid

40. 3-Cyclohexyl-3-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

41. 3-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

42. 3-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-phenyl-propionic acid

43. 3-Cyclohexyl-3-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

44. 3-Cyclohexyl-3-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid

45. 3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

46. 4-Cyclohexyl-3-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid

47. 3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5,5-dinnethyl-hexanoic acid

48. (R)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid

49. (S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
4-Cyclohexyl-3-[(1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-butyric acid

4-Cyclohexyl-3-[(1-(1 S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-butyric acid

(3R,4S)-4-Methyl-3-[(1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(3R,4S)-3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-4-methyl-hexanoic acid

3-[(1-(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

3-[(1-(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-heptanoic acid

3-Cyclohexyl-3-[(1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-[(1-(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,2-dinnethyl-heptanoic acid

3-[(1-(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,2,5-trimethyl-hexanoic acid

(S)-4-Cyclopentyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-butyric acid

(S)-4-Cyclopentyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-butyric acid

3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,2,5-trimethyl-hexanoic acid

3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,2-dinnethyl-hexanoic acid

4-Ethyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-hexanoic acid

(1-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-cyclohexyl)-acetic acid

4-Cyclohexyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-butyric acid

(1-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-cyclohexyl)-acetic acid
(2R,3S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-nnethyl-hexanoic acid

(2S,3S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-nnethyl-hexanoic acid

(R)-6-Methyl-4-[[2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(R)-6-Methyl-4-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(4R,5S)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-heptanoic acid

(4R,5S)-5-Methyl-4-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-heptanoic acid

(3R,4S)-5-Cyclohexyl-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(3R,4S)-5-Cyclohexyl-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-nnethyl-heptanoic acid

(3R,4S)-5-Cyclohexyl-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-6-nnethyl-heptanoic acid

(3S,4S)-3-Hydroxy-6-methyl-4-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(3S,4S)-3-Hydroxy-6-methyl-4-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(3S,4S)-3-Hydroxy-6-methyl-4-[[1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(3S,4S)-5-Cyclohexyl-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(S)-2-[[1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-2-[[1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-2-[[1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(2S,3S)-2-[(1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-pentanoic acid

(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-4-Methyl-2-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

(S)-2-[(2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

(S)-4-Methyl-2-[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-pentanoic acid

(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-3-[(2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(S)-5-Methyl-3-[(1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(S)-5-Methyl-3-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(S)-4-Phenyl-3-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-annino]-butyric acid
(S)-5-Methyl-3-[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-nmethyl-hexanoic acid

(S)-5-Methyl-3-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-nmethyl-hexanoic acid

(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nmethyl-pentanoic acid

(S)-2-[(2-Cyclopentylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nmethyl-pentanoic acid

(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nmethyl-pentanoic acid

(S)-2-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-nmethyl-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-nmethyl-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-4-methyl-sulfanyl-butyric acid

(S)-3-Cyclohexyl-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-propionic acid

2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4,4-dimethyl-pentanoic acid
(S)-2-[[2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid
(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-2-[[2-Furan-3-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-4-Methyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(S)-2-[[2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-hexanoic acid
(S)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-propionic acid
(2S,3R)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-pentanoic acid
(S)-3-[[1-(1-Ethyl-propyl)-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[[2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(R)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(R)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(R)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-6-nnethyl-heptanoic acid
(S)-3-methyl-1-[(1H-tetrazol-5-ylmethyl)-carbannoyl]-butyl}-amide

400 \[(S)-3-methyl-1-[(2-(1H-tetrazol-5-yl)-ethylcarbamoyl]-butyl}\]-amide

401 \[(S)-3-methyl-1-(2-sulfamoyl-ethylcarbamoyl)-butyl\]-amide

402 \[(S)-1-(2-methanesulfonylamomino-ethylcarbamoyl)-3-methyl-butyl\]-amide

403 \[(S)-1-(cyanomethyl-carbannoyl)-3-nnethyl-butyl\]-amide

404 \[(S)-1-(2-cyano-ethylcarbamoyl)-3-nnethyl-butyl\]-amide

405 \[(S)-3-methyl-1-[methyl-(5-oxo-4,5-dihydro-1 H-[1,2,4]triazol-3-ylmethyl)-carbamoyl]-butyl\]-amide

406 \[(S)-3-methyl-1-[2-(5-oxo-4,5-dihydro-1 H-[1,2,4]triazol-3-yl)-ethylcarbamoyl]-butyl\]-amide

408 \[(S)-2-[(S)-2-[(S)-2-[(S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoylannino]-acetic acid


410 \[(R)-1 -((S)-2-[(S)-2-[(S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoyl]-pyrrolidine-2-carboxylic acid

411 \[(S)-2-[(S)-2-[(S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoyl]-azetidine-3-carboxylic acid

412 \[(S)-4-Methyl-2-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

413 \[(S)-4-Methyl-2-[(1-(1S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid

414 \[(S)-4-Methyl-2-[(1-(1R,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-pentanoic acid
(S)-4-Methyl-2-\{[(1 S,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl\]-annino\}-pentanoic acid

(S)-2-\{[(2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-4-methyl-pentanoic acid

(S)-2-\{[(2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-4-nnethyl-pentanoic acid

(S)-2-\{[(2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-4-nnethyl-pentanoic acid

(S)-2-\{[(2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino\}-4-methyl-pentanoic acid

(S)-2-\{[(1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-2-\{[(1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-2-\{[(1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-3-Cyclohexyl-2-\{[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-4-Methyl-2-\{[(1 -(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-4-Methyl-2-\{[(1 -(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-4-Methyl-2-\{[(1 -(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-4-Methyl-2-\{[(1 -(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid
(S)-4-Methyl-2-\{[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino}\}-pentanoic acid
(S)-3-\{[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid
(S)-3-\{[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino\}-5-methyl-hexanoic acid
(S)-3-\{[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid
(S)-3-\{[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino\}-5-nnethyl-hexanoic acid
(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid
(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid
(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid
(R)-2-\{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-2,4-dinnethyl-pentanoic acid
(S)-2-\{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-2,4-dinnethyl-pentanoic acid
3-Cyclopentyl-2-\{[1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid
3-Cyclopentyl-2-\{[1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid
(S)-3-Cycloheptyl-2-\{[1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid
(R)-3-Cycloheptyl-2-\{[1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid
3-Cycloheptyl-2-\{[1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid
451 3-Cycloheptyl-2-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
452 (S)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid
453 (R)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid
454 (S)-4-Cyclohexyl-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid
455 (R)-4-Cyclohexyl-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid
456 4-Cyclohexyl-3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid
457 4-Cyclohexyl-3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid
458 3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid
459 3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid
460 3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid
461 3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid
462 3-Cyclohexyl-3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
463 3-Cyclohexyl-3-[(1 R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
464 (R)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid
465 (S)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid
466 (R)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid
467 (S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid
468 (S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid
469 (R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid
472 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
473 [(S)-3-methyl-1-(1H-tetrazol-5-ylmethyl)-butyl]-amide
474 [(S)-1-(N-hydroxycarbamimidoylmethyl)-3-methyl-butyl]-amide
475 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
476 [(S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanyl)-butyl]-amide
477 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
478 [(S)-3-methyl-1-(4H-[1,2,4]triazole-3-sulfonyl)-butyl]-amide
479 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid
480 [(S)-3-methyl-1-methylsulfamoyl-butyl]-amide.
The number denotes the example number of the respective compound.

In another embodiment compounds of the formula I are encompassed selected from the group consisting of
1 1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cycloheptanecarboxylic acid
3 (S)-3-Cyclohexyl-2-[[2-cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
6 1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclopentancarboxylic acid
8 (S)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
9 (R)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(R)-3-Cyclohexyl-2-{{[2-cyclopentylmethyl-1 -(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cyclopentyl-2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-propionic acid

2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,4-dimethyl-pentanoic acid

2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2-nnethyl-4-nnethylsulfanyl-butync acid

(S)-3-Cyclohexyl-2-{{[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(S)-2-{{[1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-hexanoic acid

(S)-3-Cyclohexyl-2-{{[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(S)-2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-cyclohexanecarboxylic acid

2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2-methyl-pentanoic acid

2-{{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-5,5,5-trifluoro-pentanoic acid

5,5,5-Trifluoro-2-{{[1 -(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-pentanoic acid
29 3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-annino]-propionic acid
33 3-(4,4-Dimethyl-cyclohexyl)-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-
ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
5 34 1-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-4-methyl-cyclohexanecarboxylic acid
35 4-Methyl-1-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
36 2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-3-(4-nnethyl-cyclohexyl)-propionic acid
10 37 (S)-3-Cyclohexyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
38 1-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
15 39 3-Cycloheptyl-2-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
5-carbonyl]-amino]-propionic acid
40 3-Cycloheptyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-annino]-propionic acid
41 3-[[1 -(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-4-methyl-pentanoic acid
20 42 3-[[1 -(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-3-phenyl-propionic acid
44 3-Cyclohexyl-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
5-carbonyl]-amino]-propionic acid
25 45 3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-heptanoic acid
46 4-Cyclohexyl-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
5-carbonyl]-amino]-butyric acid
47 3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino]-5,5-dinmethyl-hexanoic acid
30 48 (R)-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-
carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-3-[(1-(1-Ethyl-propyl)-2-thiazol-5-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

4-Cyclohexyl-3-[(1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

4-Cyclohexyl-3-[(1-(1 S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

(3R,4S)-4-Methyl-3-[(1-(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(3R,4S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-hexanoic acid

3-[(1-(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid

3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-trnnethyl-hexanoic acid

(1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-cyclohexyl)-acetic acid

4-Ethyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid
66 \((1\cdot(1\cdot((1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-cyclohexyl]-acetic\) acid

67 \((2R,3S)-3\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-2\cdot hydroxy-5\cdot n methyl-hexanoic\) acid

5 68 \((2S,3S)-3\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-2\cdot hydroxy-5\cdot n methyl-hexanoic\) acid

69 \((R)-6\cdot Methyl-4\cdot[(2\cdot thiophen-2\cdot ylmethyl-1\cdot -2\cdot trifluoromethyl-cyclohexyl]-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-heptanoic\) acid

70 \((R)-6\cdot Methyl-4\cdot[(1\cdot(1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-heptanoic\) acid

7 1 \((4R,5S)-4\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-5\cdot n methyl-heptanoic\) acid

7 2 \((4R,5S)-5\cdot Methyl-4\cdot[(1\cdot(1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-heptanoic\) acid

15 7 3 \((3R,4S)-5\cdot Cyclohexyl-4\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-3\cdot hydroxy-pentanoic\) acid

7 4 \((3R,4S)-5\cdot Cyclohexyl-3\cdot hydroxy-4\cdot[(1\cdot(1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-pentanoic\) acid

7 5 \((3S,4S)-4\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-3\cdot hydroxy-6\cdot n methyl-heptanoic\) acid

20 7 6 \((3R,4S)-4\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-3\cdot hydroxy-6\cdot n methyl-heptanoic\) acid

7 7 \((3R,4S)-3\cdot Hydroxy-6\cdot methyl-4\cdot[(1\cdot(1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-heptanoic\) acid

25 7 8 \((3S,4S)-3\cdot Hydroxy-6\cdot methyl-4\cdot[(1\cdot(1\cdot R,2R)-2\cdot methyl-cyclohexyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-heptanoic\) acid

7 9 \((3S,4S)-5\cdot Cyclohexyl-4\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot thiophen-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-annino]-3\cdot hydroxy-pentanoic\) acid

8 0 \((S)-2\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot(1\cdot tetrahydro-furan-2\cdot ylmethyl)-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-4\cdot n methyl-pentanoic\) acid

8 1 \((S)-2\cdot[(1\cdot(1\cdot Ethyl-propyl)-2\cdot furan-2\cdot ylmethyl-1\cdot H\cdot benzoimidazole-5\cdot carbonyl]-amino]-4\cdot methyl-pentanoic\) acid
(S)-2-[(1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(2S,3S)-2-[(1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-pentanoic acid

(S)-2-[[2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid

(S)-4-Methyl-2-[[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[[2-Thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-4-Methyl-2-[[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[[1-(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(2S,3S)-3-Methyl-2-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[[1 -(2-Ethyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-3-[[1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-3-[[1 -(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-3-[[2-Furan-2-ylmethyl-1 -(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-3-[[2-Thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

(S)-5-Methyl-3-[[1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-5-Methyl-3-[[2-thiophen-2-ylmethyl-1 -(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-5-Methyl-3-\[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-annino\]-hexanoic acid

(S)-5-Methyl-3-\[(1-(1\ R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-annino\]-hexanoic acid

(S)-3-\[(1-(1-\ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-5-nnethyl-hexanoic acid

(S)-2-\[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-pentanoic acid

(S)-3-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-5-nnethyl-hexanoic acid

(S)-2-\[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-pentanoic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-3-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-pentanoic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-furan-3-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-pentanoic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-3-nnethyl-pentanoic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-sulfanyl-butyric acid

(S)-3-Cyclohexyl-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-annino\]-propionic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-3-nnethyl-pentanoic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-sulfanyl-butyric acid

(S)-3-Cyclohexyl-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-annino\]-propionic acid

(S)-2-\[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-hexanoic acid

(S)-2-\[(2-Furan-3-ylmethyl-1-(2-methyl-cyclohexyl)-1\ H-benzoimidazole-5-carbonyl]-amino\]-4-nnethyl-pentanoic acid

(S)-4-Methyl-2-\[(1-(2-methyl-cyclohexyl)-2-thiophen-3-ylmethyl-1\ H-benzoimidazole-5-carbonyl]-amino\]-pentanoic acid
(S)-4-Methyl-2-[(1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid
(S)-3-Cyclohexyl-2-[(1-(1-ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino]-propionic acid
(2S,3R)-2-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-3-ethyl-pentanoic acid
(S)-3-[(1-(1-ethyl-propyl)-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-ethyl-hexanoic acid
(2S,3R)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-ethyl-pentanoic acid
(S)-4-Methyl-2-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid
(S)-4-Methyl-2-[(1-(1S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid
(S)-4-Methyl-2-[(1-(1R,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid
(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-H-benzoimidazole-5-carbonyl)-amino]-4-ethyl-pentanoic acid
(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-H-benzoimidazole-5-carbonyl)-amino]-4-ethyl-pentanoic acid
(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-H-benzoimidazole-5-carbonyl)-amino]-4-ethyl-pentanoic acid
(S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-n-nethyl-pentanoic acid

(S)-2-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-n-nethyl-pentanoic acid

(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(S)-4-Methyl-2-[[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-4-Methyl-2-[[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-4-Methyl-2-[[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-3-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-n-nethyl-hexanoic acid

(S)-3-[[2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-n-nethyl-hexanoic acid
(S)-3-{[2-Furan-2-ylmethyl]-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino}-5-nnethyl-hexanoic acid

(S)-3-{[2-Furan-2-ylmethyl]-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino}-5-nnethyl-hexanoic acid

(S)-5-Methyl-3-{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(S)-5-Methyl-3-{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(S)-5-Methyl-3-{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(R)-2-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino}-2,4-dinnethyl-pentanoic acid

(S)-2-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino}-2,4-dinnethyl-pentanoic acid

3-Cyclopentyl-2-{[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cyclopentyl-2-{[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-Cycloheptyl-2-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(S)-3-Cycloheptyl-2-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(R)-3-Cycloheptyl-2-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

(R)-3-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino}-heptanoic acid

(S)-3-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino}-heptanoic acid
(S)-4-Cyclohexyl-3-\{1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-butyric acid

(R)-4-Cyclohexyl-3-\{1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-butyric acid

4-Cyclohexyl-3-\{1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-butyric acid

4-Cyclohexyl-3-\{1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-butyric acid

3-\{1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-hexanoic acid

3-\{1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-heptanoic acid

3-\{1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-annino-propionic acid

(R)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2,5-trinnethyl-hexanoic acid

(S)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2,5-trinnethyl-hexanoic acid

(R)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2-dinnethyl-hexanoic acid

(S)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2-dinnethyl-hexanoic acid

(S)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2-dinnethyl-heptanoic acid

(R)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino-2,2-dinnethyl-heptanoic acid.
The number denotes the example number of the respective compound.

In another embodiment compounds of the formula I are encompassed selected from the group consisting of

1. 1-[[1-((1-ethyl-propyl)-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-cycloheptanecarboxylic acid
2. 1-[[1-((1-ethyl-propyl)-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-cyclopentanecarboxylic acid
3. 3-Cyclopentyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
4. 2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dimethyl-pentanoic acid
5. (S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
6. (S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
7. (S)-3-Cyclopropyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
8. (S)-3-Cyclobutyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
9. (S)-3-Cyclobutyl-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
10. 1-[[1-((1-ethyl-propyl)-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexanecarboxylic acid
11. 2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-2-methyl-pentanoic acid
12. 2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-5,5,5-trifluoro-pentanoic acid
27 5,5,5-Trifluoro-2-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-pentanoic acid

29 3-(4,4-Dimethyl-cyclohexyl)-2-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

33 3-(4,4-Dimethyl-cyclohexyl)-2-[(1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

34 1-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-cyclohexanecarboxylic acid

35 4-Methyl-1 -[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-cyclohexanecarboxylic acid

36 2-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-(4-nnethyl-cyclohexyl)-propionic acid

38 1-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-cyclohexanecarboxylic acid

39 3-Cycloheptyl-2-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-propionic acid

40 3-Cycloheptyl-2-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid

44 3-Cyclohexyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-propionic acid

45 3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

46 4-Cyclohexyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-butyric acid

47 3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5,5-dinnethyl-hexanoic acid

48 (R)-3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid

51 4-Cyclohexyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-butyric acid

52 4-Cyclohexyl-3-[(1 -(1 S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-butyric acid
(3R,4S)-4-Methyl-3-{[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino}-hexanoic acid

(3R,4S)-3-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-4-nnethyl-hexanoic acid

3-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino)-hexanoic acid

3-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino)-heptanoic acid

3-Cyclohexyl-3-{[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino}-propionic acid

3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-heptanoic acid

4-Ethyl-3-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-hexanoic acid

(S)-4-Cyclopentyl-3-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino}-butyric acid

(S)-4-Cyclopentyl-3-{[1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino)-butyric acid

3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trimethyl-hexanoic acid

3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-hexanoic acid

(1-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-cyclohexyl)-acetic acid

(1-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino)-cyclohexyl)-acetic acid

(2R,3S)-3-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-2-hydroxy-5-nnethyl-hexanoic acid

(2S,3S)-3-{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-2-hydroxy-5-nnethyl-hexanoic acid

(R)-6-Methyl-4-{[1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino)-heptanoic acid
71 (4R,5S)-4-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-5-nnethyl-heptanoic acid
72 (4R,5S)-5-Methyl-4-([1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-heptanoic acid
73 (3R,4S)-5-Cyclohexyl-4-([1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-3-hydroxy-pentanoic acid
74 (3R,4S)-5-Cyclohexyl-3-hydroxy-4-([1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-pentanoic acid
75 (3S,4S)-4-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-3-hydroxy-6-nnethyl-heptanoic acid
76 (3R,4S)-4-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-3-hydroxy-6-nnethyl-heptanoic acid
77 (3R,4S)-3-Hydroxy-6-methyl-4-([1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-heptanoic acid
78 (3S,4S)-3-Hydroxy-6-methyl-4-([1-(1R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-heptanoic acid
79 (3S,4S)-5-Cyclohexyl-4-([1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-3-hydroxy-pentanoic acid
91 (S)-2-([1-(1R,2R)-2-Methyl-cyclohexyl]-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-pentanoic acid
92 (2S,3S)-3-Methyl-2-([1-(1R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-pentanoic acid
94 (S)-2-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-pentanoic acid
95 (S)-3-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-5-methyl-hexanoic acid
101 (S)-5-Methyl-3-([1-(2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-annino)-hexanoic acid
107 (S)-3-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-5-methyl-hexanoic acid
114 (S)-2-([1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino)-4-methyl-pentanoic acid
(S)-2-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-pentanoic acid
(S)-2-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethylsulfanyl-butyric acid
(S)-3-Cyclohexyl-2-[(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-2-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-4-Methyl-2-[(1 -(2-methyl-cyclohexyl)-2-thiophen-3-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(2S,3R)-2-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-3-nnethyl-pentanoic acid
3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(R)-3-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-nnethyl-pentanoic acid
(R)-4-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(R)-4-[(1 -(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-6-nnethyl-heptanoic acid
(S)-4-Methyl-2-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-4-Methyl-2-[(1 -(1 S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-4-Methyl-2-[(1 -(1 R,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-4-Methyl-2-[(1 -(1 S,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-2-[(1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-2-[[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cyclohexyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-5-Methyl-3-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-5-Methyl-3-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-5-Methyl-3-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(S)-5-Methyl-3-[[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid
(R)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dinmnethyl-pentanoic acid
(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dinmnethyl-pentanoic acid
3-Cyclopentyl-2-[[1-(1,2R)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
3-Cyclopentyl-2-[[1-(1,2R)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
3-Cyclopentyl-2-[[1-(1,2R)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
3-Cyclopentyl-2-[[1-(1,2R)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
3-Cyclopentyl-2-[[1-(1,2R)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-5-Methyl-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,4-dinmnethyl-pentanoic acid
(S)-3-Cycloheptyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(S)-3-Cycloheptyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid
(R)-3-Cycloheptyl-2-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid

3-Cycloheptyl-2-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid

3-Cycloheptyl-2-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid

(S)-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(R)-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(S)-4-Cyclohexyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

(R)-4-Cyclohexyl-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

4-Cyclohexyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

4-Cyclohexyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(R)-3-[(1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid
(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid
(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid
(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid
(S)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid
(R)-3-[(1 -Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid.

The number denotes the example number of the respective compound.

Uses

The present invention provides novel and potent APJ modulators. The efficacy of the compounds of the formula I can be demonstrated in the pharmacological test described below and in other tests which are known to a person skilled in the art.

Selective APJ modulators are useful to substitute or complement apelins in their physiological actions and act in many tissues mediated by the specific interaction with the APJ receptor. Among different uses for such APJ receptor modulation, four major areas of interesting uses include direct cardiac and cardiovascular effects, effects on metabolic dysfunction, diabetes and related complications, effects on the body’s fluid homeostasis, and effects on the vasculature and vascular formation.

First, selective APJ modulators are useful in preventing and treating cardiovascular diseases. These include coronary heart disease, stroke, and heart failure. Heart Failure itself comprises a bundle of clinical syndromes such as systolic heart failure, diastolic heart failure, diabetic heart failure and heart failure with preserved ejection fraction, cardiomyopathy, myocardial infarction, left ventricular dysfunction including left ventricular dysfunction after myocardial infarction, cardiac hypertrophy,
myocardial remodeling including myocardial remodeling after infarction or after cardiac surgery, and valvular heart diseases,

A second major area includes metabolic dysfunction, diabetes and related complications. This area includes diseases with metabolic syndrome, insulin resistance, diabetes melittus and diabetic late complications. Diabetic late complications comprise all end organ damages of micro- or macrovascular origin, such as diabetic macro- and microvasculopathies, diabetic nephropathy, diabetic retinopathy, diabetic neuropathies, and cardiac autonomic neuropathy.

The third major area of uses includes diseases with disturbed body's fluid homeostasis by CNS dependent and -independent effects, such as acute and chronic renal failure or hypertension. Hypertension itself comprises a bundle of syndromes such as pulmonary hypertension, portal hypertension and systolic hypertension.

A fourth major area of use contain diseases with vascular pathology, e.g. with increased vascular permeability and non-functional blood vessels. APJ modulators are useful to treat vascular hypertrophy, vascular remodeling including vascular stiffness, atherosclerosis, peripheral arterial occlusive disease (PAOD), restenosis, thrombosis and vascular permeability disorders, ischemia and/or reperfusion damage including ischemia and/or reperfusion damage of the heart, kidney and retina.

Beside these four major areas of uses, APJ modulators may be useful in pulmonary, liver, renal and retinal diseases, such as chronic obstructive pulmonary disease (COPD), asthma, acute respiratory dystress syndrome (ARDS), liver cirrhosis, and macular degeneration;

The treatment of diseases is to be understood as meaning both the therapy of existing pathological changes or malfunctions of the organism or of existing symptoms with the aim of relief, alleviation or cure, and the prophylaxis or prevention of pathological changes or malfunctions of the organism or of symptoms in humans.
or animals which are susceptible thereto and are in need of such a prophylaxis or prevention, with the aim of a prevention or suppression of their occurrence or of an attenuation in the case of their occurrence. For example, in patients who on account of their disease history are susceptible to myocardial infarction, by means of the prophylactic or preventive medicinal treatment the occurrence or re-occurrence of a myocardial infarction can be prevented or its extent and sequelae decreased, or in patients who are susceptible to attacks of asthma, by means of the prophylactic or preventive medicinal treatment such attacks can be prevented or their severity decreased. The treatment of diseases can occur both in acute cases and in chronic cases.

Combination with other pharmacological actives
The compounds of the formula I and their physiologically acceptable salts and solvates can also be used in combination with other pharmaceutical active compounds, especially those approved for the treatment in the named major area of uses. In such a combination use the compounds of the formula I and/or their physiologically acceptable salts and/or solvates and one or more other pharmaceutical active compounds can be present in one and the same pharmaceutical composition or in two or more pharmaceutical compositions for separate, simultaneous or sequential administration.

They can be combined with an inventive compound of the formula I, especially for a synergistic improvement in action. The active ingredient combination can be administered either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. When the active ingredients are administered by separate administration of the active ingredients, this can be done simultaneously or successively. Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2006 or Rote Liste 2011.

A subject of the present invention also is the said combination use of any one or more of the compounds of the formula I disclosed herein and their physiologically
acceptable salts and solvates, with any one or more, for example one or two, of the mentioned other pharmaceutical active compounds.

Examples of combination of compounds of the formula I with cardiovascular active compounds include all aldosterone antagonists, aquaretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, digoxin, nitric oxide donors, nitrates, hydralazines, ionotropes, vasopressin receptor antagonists, soluble guanylate cyclase activators, statins, anti-arrhythmics, endothelin receptor antagonists, calcium antagonists, phosphodiesterase inhibitors including phosphodiesterase type 5 (PDE5) inhibitors, and renin inhibitors. Examples are further all approved anti-hypertensives and nephro-protectives, e.g. as mentioned in the Rote Liste 2011, and all diuretics as mentioned in the Rote Liste 2011, chapter 36;

Examples of such other pharmaceutical active compounds in the area of metabolic dysfunction and diabetes are all pharmaceutical active compounds approved to treat such diseases. Among them are insulin and insulin derivatives, for example Lantus® (insulin detemir), Humalog®(Insulin Lispro), insulin degludec, insulin aspart, polyethylene glycosidized (PEGylated) Insulin Lispro as described in WO20091 521 28, Humulin®(R), VIAject™, SuliXen®(R), VIAject™ or those as described in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins, for example Exubera®, Nasulin™, or oral insulins, for example IN-1 05 (Nobex) or Oral-lyn™ (Generex Biotechnology), or Technosphere (R) insulin (MannKind) or Cobalamin™ oral insulin or ORMD-0801 or insulins or insulin precursors as described in WO20071 2881 5, WO20071 2881 7, WO2008034881, WO200804971 1, WO20081 45721, WO20090341 17, WO2009060071, WO20091 33099 or insulins which can be administered transdermally; additionally included are also those insulin derivatives which are bonded to albumin by a bifunctional linker, as described, for example, in WO20091 21884;

Furthermore combination of the compounds of the formula I with GLP-1 derivatives and GLP-1 agonists are useful. Examples are exenatide or specific formulations thereof, as described, for example, in WO2008061 355, WO2009080024,
WO2009080032, liraglutide, taspoglutide (R-1 583), albiglutide, lixisenatide or those which have been disclosed in WO 98/08871, WO2005027978, WO200603781 1, WO200603781 0 by Novo Nordisk A/S, in WO 01/041 56 by Zealand or in WO 00/34331 by Beaufour-lpsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), inhalable GLP-1 (MKC-253 from MannKind), AVE-001 0, BIM-51 077 (R-1 583, ITM-077), PC-DAC:exendin-4 (an exendin-4 analog which is bonded covalently to recombinant human albumin), biotinylated exendin (WO20091 07900), a specific formulation of exendin-4 as described in US2009238879, CVX-73, CVX-98 and CVx-96 (GLP-1 analogs which are bonded covalently to a monoclonal antibody which has specific binding sites for the GLP-1 peptide), CNTO-736 (a GLP-1 analog which is bonded to a domain which includes the Fc portion of an antibody), PGC-GLP-1 (GLP-1 bonded to a nanocarrier), agonists or modulators, as described, for example, in D. Chen et al., Proc. Natl. Acad. Sci. USA 104 (2007) 943, those as described in WO20061 24529, WO20071 24461, WO2008062457, WO2008082274, WO20081 0 10 17, WO200808141 8, WO20081 12939, WO20081 12941, WO20081 13601, WO20081 16294, WO20081 16648, WO20081 19238, WO20081 48839, US2008299096, WO20081 52403, WO2009030738, WO2009030771, WO2009030774, WO2009035540, WO2009058734, WO20091 11700, WO20091 25424, WO20091 29696, WO2009149148, peptides, for example obinepitide (TM-30338), orally active GLP-1 analogs (e.g. NN9924 from Novo Nordisk), amylin receptor agonists, as described, for example, in WO20071 04789, WO20090341 19, analogs of the human GLP-1, as described in WO20071 20899, WO200802201 5, WO2008056726, chimeric pegylated peptides containing both GLP-1 and glucagon residues, as described, for example, in WO20081 0 10 17, WO20091 55257, WO20091 55258, glycosylated GLP-1 derivatives as described in WO20091 53960, and orally active hypoglycemic ingredients.

Antidiabetics additionally include poly- or monoclonal antibodies directed, for example, against interleukin 1 beta (IL-1β), for example XOMA-052. Antidiabetics additionally include peptides which can bind to the human pro-islet peptide (HIP) receptor, as described, for example, in WO2009049222. Antidiabetics also include agonists of the glucose-dependent insulinotropic polypeptide (GIP) receptor, as
described, for example, in WO2006121860. Antidiabetics also include the glucose-dependent insulinotropic polypeptide (GIP), and also analogous compounds, as described, for example, in WO2008021560, WO2010016935, WO2010016936, WO2010016938, WO2010016940, WO2010016944. Additionally included are analogs and theivatives of human pancreatic polypeptide, as described, for example, in WO2009007714. Antidiabetics additionally include encapsulated insulin-producing porcine cells, for example DiabeCell(R). Antidiabetics also include analogs and derivatives of fibroblast growth factor 21 (FGF-21), as described, for example, in WO2009149171, WO2010006214.

Combination of the compounds of the formula I with antidiabetics also include orally active hypoglycemic ingredients preferably include sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, PPAR and RXR modulators, inhibitors of dipeptidyl peptidase-IV (DPP-IV), insulin sensitizers, glucosidase inhibitors, inhibitors of glycogen phosphorylase, glucagon receptor antagonists, glucokinase activators, inhibitors of fructose 1,6-bisphosphatase, modulators of glucose transporter 4 (GLUT4), inhibitors of glutamine:fructose-6-phosphate amidotransferase (GFAT), orally active GLP-1 agonists.

Combination of the compounds of the formula I with potassium channel openers are useful, for example pinacidil, cromakalim, diazoxide, diazoxide choline salt, or those as described in R. D. Carr et al., Diabetes 52, 2003, 2513.2518, in J. B. Hansen et al., Current Medicinal Chemistry 11, 2004, 1595-1615, in T. M. Tagmose et al., J. Med. Chem. 47, 2004, 3202-3211 or in M. J. Coghlan et al., J. Med. Chem. 44, 2001, 1627-1653, or those which have been disclosed in WO 97/26265 and WO 99/03861 by Novo Nordisk A/S, and active ingredients which act on the ATP-dependent potassium channel of the beta cells,

In one embodiment of the invention, the compound of the formula I is administered in combination with insulin.
In another embodiment of the invention, the compound of the formula I is administered in combination with an insulin sensitizer, for example PN-2034 or ISIS-1 1371 5.

In one embodiment, the compound of the formula I is administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, for example sulfonylureas, for example tolbutamide, glibenclamide, glipizide, glidazide or glimepiride, or those formulations as described, for example, in EP21 03302.

In one embodiment, the compound of the formula I is administered in combination with a tablet which comprises both glimepiride, which is released rapidly, and metformin, which is released over a longer period (as described, for example, in US2007264331, WO2008050987, WO2008062273).

In one embodiment, the compound of the formula I is administered in combination with a biguanide, for example metformin or one of its salts.

In a further embodiment, the compound of the formula I is administered in combination with a guanidine, for example benzylguanidine or one of its salts, or those guanidines as described in WO2009087395.

In another embodiment, the compound of the formula I is administered in combination with a meglitinide, for example repaglinide, nateglinide or mitiglinide.

In a further embodiment, the compound of the formula I is administered with a combination of mitiglinide with a glitazone, e.g. pioglitazone hydrochloride.

In a further embodiment, the compound of the formula I is administered with a combination of mitiglinide with an alpha-glucosidase inhibitor.
In a further embodiment, the compound of the formula I is administered in combination with antidiabetic compounds, as described in WO2007095462, WO200701060, WO2007105650.

In a further embodiment, the compound of the formula I is administered in combination with antihypoglycemic compounds, as described in WO2007137008, WO2008020607.

In one embodiment, the compound of the formula I is administered in combination with a thiazolidinedione, for example troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41 097 by Dr. Reddy's Research Foundation, especially 5-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]-phenyl)methyl]-2,4-thiazolidinedione.


In one embodiment of the invention, the compound of the formula I is administered in combination with Competact™, a solid combination of pioglitazone hydrochloride with metformin hydrochloride.
In one embodiment of the invention, the compound of the formula I is administered in combination with Tandemact™, a solid combination of pioglitazone with glimepiride.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of pioglitazone hydrochloride with an angiotensin II agonist, for example TAK-536.


In one embodiment of the invention, the compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonist, for example naveglitazar, aleglitazar, LY-5190329, ONO-5129, E-3030, AVE 8042, AVE 8134, AVE 8047, AVE 0897, CKD-501 (lobeglitazone sulfate), MBX-213, KY-201, BMS-759509, or as described in WO00/64888, WO00/64876, WO03/020269, WO2004024726, WO2007099553, US2007276041, WO2007085135, WO2007085136, WO2007141423, WO2008016175, WO2008053331, WO2008190697, WO2008190700, WO2008108735, WO2009026657, WO2009026658, WO2009149819, WO2009149820 or in J.P.Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

In one embodiment of the invention, the compound of the formula I is administered in combination with a pan-SPPARM (selective PPAR modulator alpha, gamma, delta), for example GFT-505, indeglitazar, or those as described in WO2008035359, WO2009072581.

In one embodiment, the compound of the formula I is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

In one embodiment, the compound of the formula I is administered in combination with an a-glucosidase inhibitor, for example miglitol or acarbose, or those as described, for example, in WO2007114532, WO2007140230, US2007287674, US2008103201, WO2008065796, WO2008082017, US2009076129.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of glycogen phosphorylase, for example PSN-357 or FR-258900, or those as described in WO2003084922, WO2004007455, WO2005073229-31, WO2005067932, WO2008062739, WO2008099000, WO2008113760, WO2009016118, WO2009016119, WO2009030715, WO2009045830, WO2009045831, WO2009127723.

In another embodiment, the compound of the formula I is administered in combination with an inhibitor of the interaction of liver glycogen phosphorylase with
the protein PPP1 R3 (GL subunit of glycogen-associated protein phosphatase 1 (PP1)), as described, for example, in WO200903071 5.


In a further embodiment, the compound of the formula I is administered in combination with an antisense compound, e.g. ISIS-325568, which inhibits the production of the glucagon receptor.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of gluconeogenesis, as described, for example, in FR-225654.

WO2008053446.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of fructose 1,6-bisphosphatase (FBPase), for example MB-07729, CS-917 (MB-06322) or MB-07803, or those as described in WO2006023515.


In one embodiment, the compound of the formula I is administered in combination with modulators of glucose transporter 4 (GLUT4), for example KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

In one embodiment, the compound of the formula I is administered in combination with inhibitors of glutamine:fructose-6-phosphate amidotransferase (GFAT), as described, for example, in WO2004101528.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of dipeptidyl peptidase-IV (DPP-IV), for example vildagliptin (LAF-237),
In one embodiment, the compound of the formula I is administered in combination with Janumet™, a solid combination of sitagliptin phosphate with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with Eucreas(R), a solid combination of vildagliptin with metformin hydrochloride.

In a further embodiment, the compound of the formula I is administered in combination with a solid combination of alogliptin benzoate with pioglitazone.

In one embodiment, the compound of the formula I is administered in combination with a solid combination of a salt of sitagliptin with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with a combination of a DPP-IV inhibitor with omega-3 fatty acids or omega-3 fatty acid esters, as described, for example, in WO2007128801.

In one embodiment, the compound of the formula I is administered in combination with a combination of a DPP-IV inhibitor with metformin hydrochloride, as described, for example, in WO2009121945.

In one embodiment, the compound of the formula I is administered in combination with a combination of a DPP-IV inhibitor with a GPR-19 agonist, as described, for example, in WO2009123992.

In one embodiment, the compound of the formula I is administered in combination with a combination of a DPP-IV inhibitor with miglitol, as described, for example, in WO2009139362.

In one embodiment, the compound of the formula I is administered in combination with a solid combination of a salt of sitagliptin with metformin hydrochloride.
In one embodiment, the compound of the formula I is administered in combination with a solid combination of alopliptin benzoate with pioglitazone hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with a substance which enhances insulin secretion, for example KCP-265 (WO2003097064), or those as described in WO2007026761, WO2008045484, US2008194617, WO2009109259, WO2009109341.

In one embodiment, the compound of the formula I is administered in combination with agonists of the glucose-dependent insulinotropic receptor (GDIR), for example APD-668.

In one embodiment of the invention, the compound of the formula I is administered in combination with an ATP citrate lyase inhibitor, for example SB-204990.

In a further embodiment of the invention, the compound of the formula I is
administered in combination with a solid combination of an SGLT inhibitor with a
DPP-IV inhibitor, as described in WO2009091082.

In one embodiment, the compound of the formula I is administered in combination
with a stimulator of glucose transport, as described, for example, in WO2008136392,
WO2008 136393.

In one embodiment, the compound of the formula I is administered in combination
with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11β-HSD1 ), for example
BVT-2733, JNJ-25918646, INCB-13739, INCB-20817, DIO-92 ((-)-ketoconazole) or
those as described, for example, in WO200190090-94, WO200343999,
WO2004112782, WO200344000, WO200344009, WO2004112779,
WO2004113310, WO2004103980, WO2004112784, WO2003065983,
WO2003104207, WO2003104208, WO2004106294, WO2004011410,
WO2004033427, WO2004041264, WO2004037251, WO2004056744,
WO2004058730, WO2004065351, WO2004089367, WO2004089380,
WO2004089470-71, WO2004089896, WO2005016877, WO2005063247,
WO2005097759, WO2006010546, WO2006012227, WO2006012173,
WO2006017542, WO2006034804, WO2006040329, WO2006051662,
WO2006048750, WO2006049952, WO2006048331, WO2006050908,
WO2006024627, WO2006040329, WO2006066109, WO2006074244,
WO2006078006, WO2006106423, WO2006132436, WO2006134481,
WO2006134467, WO2006135795, WO2006136502, WO2006138508,

In a further embodiment, the compound of the formula I is administered in combination with stimulators of tyrosine kinase B (Trk-B), as described, for example, in WO2001 001461 3.


In one embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR1 09A (HM74A receptor agonists; NAR agonists (nicotinic acid receptor agonists)), for example nicotinic acid or extended release niacin in conjunction with MK-0524A (laropiprant) or MK-0524, or those compounds as described in WO2004041 274, WO2006045565, WO2006045564, WO2006069242, WO20060851 08, WO20060851 12, WO20060851 13, WO20061 2490, WO20061 13150, WO2007002557, WO200701 7261, WO200701 7262, WO200701 7265, WO20070 15744, WO2007027532, WO2007092364, WO20071 20575, WO2007 134986, WO20071 50025,
In another embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of niacin with simvastatin.

In another embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or "extended release niacin" in conjunction with MK-0524A (laropiprant).

In a further embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or "extended release niacin" in conjunction with MK-0524A (laropiprant) and with simvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or another nicotinic acid receptor agonist and a prostaglandin DP receptor antagonist, for example those as described in WO2008039882.

In another embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of niacin with meloxicam, as described, for example, in WO2009149056.

In another embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR1 16, as described, for example, in WO2006067531, WO2006067532.

In one embodiment, the compound of the formula I is administered in combination with modulators of GPR40, as described, for example, in WO2007013689, WO2007033002, WO2007106469, US2007265332, WO2007123225, WO2007131619, WO2007131620, WO2007131621, US2007265332,

In a further embodiment, the compound of the formula I is administered in combination with modulators of GPR120, as described, for example, in EP1 688138, WO2008066131, WO2008066131, WO2008103500, WO2008103501, WO2008139879, WO2009038204, WO2009147990, WO2010008831.
In another embodiment, the compound of the formula I is administered in combination with antagonists of GPR105, as described, for example, in WO2009000087, WO2009070873.

In a further embodiment, the compound of the formula I is administered in combination with agonists of GPR43, for example ESN-282.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL) and/or phospholipases, as described, for example, in WO20050573199, WO2006074957, WO2006087309, WO200611321, WO2007042178, WO200719837, WO2008122352, WO2008122357, WO2009009287.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of endothelial lipase, as described, for example, in WO2007045393, WO200710216, WO201157827.

In one embodiment, the compound of the formula I is administered in combination with a phospholipase A2 inhibitor, for example darapladib or A-002, or those as described in WO2008048866, WO2008048867, US2009062369.

In one embodiment, the compound of the formula I is administered in combination with myricitrin, a lipase inhibitor (WO2007119827).

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), for example those as described in WO2004074288.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of phosphoinositide kinase-3 (PI3K), for example those as described in WO2008027584, WO2008070150, WO2008125833, WO2008125835, WO2008125839, WO2009010530, WO2009026345, WO2009071888, WO2009071890, WO2009071895.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of serum/glucocorticoid-regulated kinase (SGK), as described, for example, in WO2006072354, WO2007093264, WO2008009335, WO2008086854, WO2008138448.

In one embodiment, the compound of the formula I is administered in combination with a modulator of the glucocorticoid receptor, as described, for example, in WO2008057855, WO2008057856, WO2008057857, WO2008057859, WO2008057862, WO2008059867, WO2008059866, WO2008059865, WO2008070507, WO2008124665, WO2008124745, WO2008146871, WO2009015067, WO2009040288, WO2009069736, WO2009149139.
In one embodiment, the compound of the formula I is administered in combination with a modulator of the mineralocorticoid receptor (MR), for example drospirenone, or those as described in WO20081 04306, WO20081 19918.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of protein kinase C beta (PKC beta), for example ruboxistaurin, or those as described in WO2008096260, WO20081 25945.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of protein kinase D, for example doxazosin (WO2008088006).


In one embodiment, the compound of the formula I is administered in combination with an inhibitor of ceramide kinase, as described, for example, in WO20071 12914, WO20071 49865.

In a further embodiment, the compound of the formula I is administered in combination with an inhibitor of MAPK-interacting kinase 1 or 2 (MNK1 or 2), as described, for example, in WO20071 04053, WO20071 15822, WO2008008547, WO2008075741.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of "l-kappaB kinase" (IKK inhibitors), as described, for example, in WO2001 00061 0, WO200 1030774, WO2004022057, WO2004022553,
In another embodiment, the compound of the formula I is administered in combination with inhibitors of NF-kappaB (NFKB) activation, for example salsalate.

In a further embodiment, the compound of the formula I is administered in combination with inhibitors of ASK-1 (apoptosis signal-regulating kinase 1), as described, for example, in WO2008016131, WO2009123986.

In one embodiment of the invention, the compound of the formula I is administered in combination with an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin, L-659699, BMS-644950, NCX-6560, or those as described in US2007249583, WO2008083551, WO2009054682.


In another embodiment of the invention, the compound of the formula I is administered in combination with a ligand of the liver X receptor (LXR), as described, for example, in WO2007092965, WO2008041003, WO2008049047, WO2008065754, WO2008073825, US2008242677, WO2009020683, US200903082, WO2009021868, US2009069373, WO2009024550,
In one embodiment of the invention, the compound of the formula I is administered in combination with a fibrate, for example fenofibrate, clofibrate, bezafibrate, or those as described in WO2008093655.

In one embodiment of the invention, the compound of the formula I is administered in combination with fibrates, for example the choline salt of fenofibrate (SLV-348; Trilipix™).

In one embodiment of the invention, the compound of the formula I is administered in combination with fibrates, for example the choline salt of fenofibrate (Trilipix™) and an HMG-CoA reductase inhibitor, for example rosuvastatin.

In a further embodiment of the invention, the compound of the formula I is administered in combination with bezafibrate and diflunisal.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of fenofibrate or a salt thereof with simvastatin, rosuvastatin, fluvastatin, lovastatin, cerivastatin, pravastatin, pitavastatin or atorvastatin.

In a further embodiment of the invention, the compound of the formula I is administered in combination with Synordia (R), a solid combination of fenofibrate with metformin.

In another embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of metformin with an MTP inhibitor, as described in WO2009090210.

In one embodiment of the invention, the compound of the formula I is administered in combination with an NPC1 L1 antagonist, for example those as described in WO200808033464, WO200808033465.

In one embodiment of the invention, the compound of the formula I is administered in combination with Vytorin™, a solid combination of ezetimibe with simvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of ezetimibe with atorvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of ezetimibe with fenofibrate.
In one embodiment of the invention, the further active ingredient is a diphenylazetidinone derivative, as described, for example, in US 6,992,067 or US 7,205,290.

In a further embodiment of the invention, the further active ingredient is a diphenylazetidinone derivative, as described, for example, in US 6,992,067 or US 7,205,290, combined with a statin, for example simvastatin, fluvastatin, pravastatin, lovastatin, cerivastatin, atorvastatin, pitavastatin or rosuvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of lapaquistat, a squalene synthase inhibitor, with atorvastatin.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a conjugate consisting of the HMG-CoA reductase inhibitor atorvastatin with the renin inhibitor aliskiren (WO20090901 58).


In one embodiment of the invention, the compound of the formula I is administered in combination with bile acid reabsorption inhibitors (inhibitors of the intestinal bile acid transporter (IBAT)) (see, for example, US 6,245,744, US 6,221,897 or WOOO/61 568),

In one embodiment, the compound of the formula I is administered in combination with agonists of GPBAR1 (G-protein-coupled bile acid receptor 1; TGR5), for example INT-777 or those as described, for example, in US20060199795, WO200710237, WO2007127505, WO2008009407, WO2008067219, WO2008067222, FR2908310, WO2008091540, WO2008097976, US2009054304, WO2009026241, WO2009146772, WO2010014739, WO2010014836.

In one embodiment, the compound of the formula I is administered in combination with modulators of histone deacetylase, for example ursodeoxycholic acid, as described in WO2009011420.

In one embodiment, the compound of the formula I is administered in combination with inhibitors/modulators of the TRPM5 channel (TRP cation channel M5), as described, for example, in WO2008097504, WO2009038722.

In one embodiment, the compound of the formula I is administered in combination with inhibitors/modulators of the TRPA1 channel (TRP cation channel A1), as described, for example, in US2009176883, WO2009089083, WO2009144548.

In one embodiment, the compound of the formula I is administered in combination with inhibitors/modulators of the TRPV3 channel (TRP cation channel V3), as described, for example, in WO2009084034, WO2009130560.

In one embodiment of the invention, the compound of the formula I is administered in combination with a polymeric bile acid adsorber, for example cholestyramine, colesvelam hydrochloride.
In one embodiment of the invention, the compound of the formula I is administered in combination with colesevelam hydrochloride and metformin or a sulfonylurea or insulin.

In one embodiment of the invention, the compound of the formula I is administered in combination with tocotrienol and insulin or an insulin derivative.

In one embodiment of the invention, the compound of the formula I is administered in combination with a chewing gum comprising phytosterols (Reductol™).

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of the microsomal triglyceride transfer protein (MTP inhibitor), for example implitapide, BMS-201 038, R-1 03757, AS-1 5521 33, SLx-4090, AEGR-733, JTT-130, or those as described in WO2005085226, WO2005121091, WO2006010423, WO2006113910, WO2007143164, WO2008049806, WO2008049808, WO2008090198, WO2008100423, WO2009014674.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a combination of a cholesterol absorption inhibitor, for example ezetimibe, and an inhibitor of the triglyceride transfer protein (MTP inhibitor), for example implitapide, as described in WO2008030382 or in WO2008079398.

In one embodiment of the invention, the compound of the formula I is administered in combination with an active antihypertriglyceridemic ingredient, for example those as described in WO2008032980.

In another embodiment of the invention, the compound of the formula I is administered in combination with an antagonist of the somatostatin 5 receptor (SST5 receptor), for example those as described in WO2006094682.
In one embodiment of the invention, the compound of the formula I is administered in combination with an ACAT inhibitor, for example avasimibe, SMP-797 or KY-382, or those as described in WO2008087029, WO2008087030, WO2008095189, WO2009030746, WO2009030747, WO2009030750, WO2009030752, WO2009070130, WO2009081957, WO2009081957.

In a further embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of liver carnitine palmitoyltransferase-1 (L-CPT1), as described, for example, in WO2007063012, WO2007096251 (ST-3473), WO2008015081, US2008103182, WO2008074692, WO200845596, WO2009019199, WO20091356479, WO2010008473.

In another embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of carnitine O-palmitoyltransferase II (CPT2), as described, for example, in US2009270500, US2009270505, WO2009132978, WO2009132979.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a modulator of serine palmitoyltransferase (SPT), as described, for example, in WO2008031032, WO2008046071, WO2008083280, WO2008084300.

In one embodiment of the invention, the compound of the formula I is administered in combination with a squalene synthetase inhibitor, for example BMS-188494, TAK-475 (lapaquistat acetate), or as described in WO2005077907, JP2007022943, WO2008003424, WO2008132846, WO2008133288, WO2009136396.

In one embodiment of the invention, the compound of the formula I is administered in combination with ISIS-301012 (mipomersen), an antisense oligonucleotide which is capable of regulating the apolipoprotein B gene.
In one embodiment of the invention, the compound of the formula I is administered in combination with apolipoprotein (ApoB) SNALP, a therapeutic product which comprises an siRNA (directed against the ApoB gene).

In one embodiment of the invention, the compound of the formula I is administered in combination with a stimulator of the ApoA-1 gene, as described, for example, in WO2008092231.

In one embodiment of the invention, the compound of the formula I is administered in combination with a modulator of the synthesis of apolipoprotein 0-III, for example ISIS-APOCIIIIRx.

In one embodiment of the invention, the compound of the formula I is administered in combination with an LDL receptor inducer (see US 6,342,512), for example HMR1 171, HMR1 586, or those as described in WO2005097738, WO2008020607.

In another embodiment of the invention, the compound of the formula I is administered in combination with an HDL cholesterol-elevating agent, for example those as described in WO2008040651, WO2008099278, WO2009071099, WO2009086096, US2009247550.

In one embodiment of the invention, the compound of the formula I is administered in combination with an ABCA1 expression enhancer, as described, for example, in WO2006072393, WO2008062830, WO2009100326.

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein lipase modulator, for example ibrolipim (NO-1 886).

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein(a) antagonist, for example gemcabene (CI-1 027).
In one embodiment of the invention, the compound of the formula I is administered in combination with a lipase inhibitor, for example orlistat or cetilistat (ATL-962).

In one embodiment of the invention, the compound of the formula I is administered in combination with an adenosine A1 receptor agonist (adenosine A1 R), for example CVT-3619 or those as described, for example, in EP1 258247, EP1 375508, WO2008028590, WO2008077050, WO2009050199, WO2009080197, WO2009100827, WO200912155.

In one embodiment of the invention, the compound of the formula I is administered in combination with a modulator of adenosine A2A and/or adenosine A3 receptors, as described, for example, in WO2007111954, WO2007121918, WO2007121921, WO2007121923, WO2008070661, WO2009010871.

In another embodiment of the invention, the compound of the formula I is administered in combination with a ligand of the adenosine A1/A2B receptors, as described, for example, in WO2008064788, WO2008064789, WO2009080198, WO2009100827, WO2009143992.

In a further embodiment of the invention, the compound of the formula I is administered in combination with an adenosine A2B receptor antagonist (adenosine A2B R), as described in US2007270433, WO2008027585, WO2008080461, WO2009037463, WO2009037467, WO2009037468, WO200918759.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC1 and/or ACC2), for example those as described in WO199946262, WO200372197, WO2003072197, WO2005044814, WO2005108370, JP2006131559, WO2007011809, WO2007011811,
In another embodiment, the compound of the formula I is administered in combination with modulators of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase 3 (GPAT3, described in WO20071 00789) or with modulators of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase 4 (GPAT4, described in WO20071 00833) or with modulators of mitochondrial glycerol-3-phosphate O-acyltransferase, described in WO201 0005922.

In a further embodiment, the compound of the formula I is administered in combination with modulators of xanthine oxidoreductase (XOR).

In another embodiment, the compound of the formula I is administered in combination with inhibitors of soluble epoxide hydrolase (sEH), as described, for example, in WO2008051 873, WO2008051875, WO2008073623, WO2008094869, WO20081 12022, WO200901 1872, WO20090491 54, WO20090491 57, WO2009049165, WO2009073772, WO2009097476, WO20091 11207, WO20091 29508, WO20091 51800.

In a further embodiment, the compound of the formula I is administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);
NPY antagonists, for example 4-[(4-aminoquinazolin-2-ylamino)methyl]-
cyclohexylmethylene napthalene-1-sulfonamide hydrochloride (CGP 71683A) or
velneperit or those as described in WO20091 10510;

NPY-5 receptor antagonists/receptor modulators, such as L-1 52804 or the compound
"NPY-5-BY" from Banyu, or as described, for example, in WO2006001 318,
WO20071 25952, WO2008026563, WO2008026564,
WO2008052769, WO2008092887, WO2008092888, WO2008092891,
WO20081 29007, WO20081 34228, WO2009054434, WO2009095377,
WO20091 31096;

NPY-4 receptor antagonists, as described, for example, in WO2007038942;

NPY-2 receptor antagonists/modulators, as described, for example, in
WO2007038943, WO200809061 85, US20090991 99, US2009099243,
US2009099244, WO2009079593, WO2009079597;

peptide YY 3-36 (PYY3-36) or analogous compounds, for example CJC-1 682 (PYY3-
36 conjugated with human serum albumin via Cys34) or CJC-1 643 (derivative of
PYY3-36, which is conjugated in vivo to serum albumin), or those as described in
WO2005080424, WO20060951 66, WO2008003947, WO2009080608;

NPY-2 receptor agonists, as described, for example, in WO2009080608;

derivatives of the peptide obestatin, as described by WO2006096847;

CB1 R (cannabinoid receptor 1) antagonists/inverse agonists, for example
rimonabant, surinabant (SR1 47778), SLV-31 9 (ibipinabant), AVE-1 625, taranabant
(MK-0364) or salts thereof, otenabant (CP-945,598), rosonabant, V-24343 or those
compounds as described in, for example, EP 0656354, WO 00/1 5609,
WO2001/64632-64634, WO 02/076949, WO2005080345, WO2005080328,
WO2005080343, WO2005075450, WO2005080357, WO2001 70700,
WO2008074982, WO200807501 2, WO200807501 3, WO200807501 9,
WO20080751 18, WO2008076754, WO2008081 009, WO2008084057, EP1 944295,
US2008090809, US200809081 0, WO200809281 6, WO2008094473,
WO2008094476, WO2008099076, WO20080991 39, WO20081 0195,
US2008207704, WO20081 071 79, WO20081 09027, WO20081 12674,
WO20081 15705, WO20081 18414, WO20081 19999, WO20081 2000,
WO20081 21257, WO20081 27585, WO20081 291 57, WO20081 3061 6,
WO20081 34300, US2008262066, US2008287505, WO2009005645,
WO2009005646, WO2009005671, WO2009023929, WO2009023653,
WO200902481 9, WO20090331 25, EP20421 75, WO2009053548-WO2009053553,
WO2009054923, WO2009054929, WO2009059264, WO20090731 38,
WO2009074782, WO2009075691, WO2009078498, WO2009087285,
WO2009074782, WO2009075690, WO200907995, WO200907996,
WO200907998, WO200907999, WO200908000, WO20091 06708,
US2009239909, WO20091 8473, US2009264436, US2009264476,
WO20091 30234, WO20091 31814, WO20091 3181 5, US2009286758,
WO2009141 532, WO2009141533, WO20091 53569, WO201 003760,
WO201 001 2437, WO201 001 9762;

10 cannabinoid receptor 1/cannabinoid receptor 2 (CB1/CB2) modulating compounds,
for example delta-9-tetrahydrocannabinvarin, or those as described, for example, in
WO2007001 939, WO200704421 5, WO2007047737, WO200709551 3,
WO2007096764, WO20071 12399, WO20071 12402, WO20081 2261 8,
WO2009007697, WO20091 2227, WO2009087564, WO200909301 8,
WO2009095752, WO20091 20660, WO201 001 2964;

20 cannabinoid receptor 2 (CB2) modulating compounds, for example those as
described, for example, in WO2008063625, WO20081 57500, WO20090041 71,
WO2009032754, WO2009055357, WO2009061652, WO2009063495,
WO200906761 3, WO20091 4566;

inhibitors of fatty acid synthase (FAS), as described, for example, in WO2008057585, WO2008059214, WO2008075064, WO2008075070, WO2008075077, WO2009079860;

inhibitors of LCE (long chain fatty acid elongase)/long chain fatty acid CoA ligase, as described, for example, in WO20081 20653, WO2009038021, WO2009044788, WO2009081 789, WO20090909086;


modulators, ligands, antagonists or inverse agonists of the opioid receptors, for example GSK-982 or those as described, for example, in WO2007047397,
WO2008021 849, WO2008021851, WO20080321 56, WO2008059335,
WO20081 25348, WO20081 25349, WO20081 42454, WO2009030962,
WO20091 03552, WO20091 15257;

5 modulators of the "orphan opioid (ORL-1) receptor", as described, for example, in
US20082491 22, WO2008089201;

agonists of the prostaglandin receptor, for example bimatoprost or those compounds
as described in WO20071 11806;

10 MC4 receptor agonists (melanocortin-4 receptor agonists, MC4R agonists, for
example N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl]-1 -(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-
tetrahydronaphthalene-2-carboxamide; (WO 01/91 752)) or LB53280, LB53279,
LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141, MK-0493, or those as
described in WO2005060985, WO2005009950, WO20040871 59, WO200407871 7,
WO200407871 6, WO2004024720, US200501 24652, WO2005051391,
WO20041 12793, WOUS20050222014, US200501 76728, US200501 64914,
US200501 24636, US200501 30988, US200401 67201 , WO2004000324,
WO2004037797, WO2004089307, WO200504251 6, WO20050401 09,
WO2005030797, US20040224901 , WO200501 921 , WO200509184,
WO2005000339, EP1 460069, WO2005047253, WO2005047251, WO20051 18573,
EP1 5381 59, WO2004072076, WO2004072077, WO2006021 655-57,
WO200709894, WO200701 5162, WO2007041061 , WO2007041 052,
JP20071 31570, EP1 842846, WO20070961 86, WO2007096763, WO20071 41343,
WO2008007930, WO200801 7852, WO200803941 8, WO20080871 86,
WO2008087187, WO20080871 89, WO20080871 86-WO20080871 90,
WO2008090357, WO200814231 9, WO200901 5867, WO200906141 1,
US2009076029, US20091 31465, WO2009071 101, US2009305960,
WO20091 44432, WO20091 51383, WO201 001 5972;
MC4 receptor modulators (melanocortin-4 receptor modulators), as described, for example, in WO200901 0299, WO20090741 57;

orexin receptor 1 antagonists (OX1R antagonists), orexin receptor 2 antagonists (OX2R antagonists) or mixed OX1R/OX2R antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A), or those as described, for example, in WO2001 96302, WO2001 85693, WO2004085403, WO2005075458, WO2006067224, WO200708571 8, WO2007088276, WO20071 16374, WO20071 22591, WO20071 26934, WO20071 26935,


histamine H3 receptor antagonists/inverse agonists (e.g. 3-cyclohexyl-1 -(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208), or those as described in WO200064884, WO2005082893, WO20051 2371 6, US20051 7118 1 (e.g. PF-00389027), WO20061 07661, WO2007003804, WO200701 6496, WO200702021 3, WO2007049798, WO200705541 8, WO2007057329, WO2007062999, WO2007065820,


histamine H1/histamine H3 modulators, for example betahistine or its dihydrochloride;

modulators of the histamine H3 transporter or of the histamine H3/serotonin transporter, as described, for example, in WO200800281 6, WO200800281 7, WO200800281 8, WO2008002820;

modulators of vesicular monoamine transporter 2 (VMAT2), as described, for example, in WO20091 26305;

histamine H4 modulators, as described, for example, in WO20071 17399, US20091 5661 3;

CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585) or those CRF1 antagonists as described in WO20071 051 13, WO2007 133756, WO2008036541, WO2008036579, WO2008083070, WO201 001 5628, WO201 001 5655);

CRF BP antagonists (e.g. urocortin);

urocortin agonists;

modulators of the beta-3 adrenoceptor, for example 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-
yloxy)ethylamino]ethanol hydrochloride (WO 01/83451) or solabegron (GW-427353) or N-5984 (KRP-204), or those as described in JP20061 11553, WO2002038543, WO2002038544, WO2007048840-843, WO2008015558, EP1 9471 03, WO20081 32162;

5

MSH (melanocyte-stimulating hormone) agonists;


30

CCK-A (CCK-1) modulators (for example {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-y}l)acetic acid
trifluoroacetic acid salt (WO 99/15525) or SR-1461 31 (WO 0244150) or SSR-1251 80) or those as described in WO20051 16034, WO20071 20655, WO20071 20688, WO20071 2071 8, WO2008091631 ;

serotonin reuptake inhibitors (e.g. dexfenfluramine), or those as described in WO20071 48341, WO20080341 42, WO2008081477, WO20081 20761, WO20081 41081, WO20081 41082, WO20081 451 35, WO20081 50848, WO2009043834, WO2009077858;

mixed serotonin/dopamine reuptake inhibitors (e.g. bupropion), or those as described in WO2008063673, or solid combinations of bupropion with naltrexone or bupropion with zonisamide;

mixed reuptake inhibitors, for example DOV-21 947 or those as described in WO200901 621 4, WO200901 621 5, WO2009077584, WO2009098208, WO2009098209, WO20091 06769, WO20091 0951 7, WO20091 0951 8, WO20091 0951 9, WO20091 09608, WO20091 45357, WO20091 49258;

mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71 549);

5-HT receptor agonists, for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/091 11);

mixed dopamine/norepinephrine/acetylcholine reuptake inhibitors (e.g. tesofensine), or those as described, for example, in WO20060851 18, WO20081 50480;

dopamine antagonists, as described, for example, in WO2008079838, WO2008079839, WO2008079847, WO2008079848;

norepinephrine reuptake inhibitors, as described, for example, in US2008076724, WO200906231 8;
5-HT1A receptor modulators, as described, for example, in WO2009006227, WO20091 37679, WO20091 37732;

5-HT2A receptor antagonists, as described, for example, in WO20071 38343;


agonists of estrogen receptor gamma (ERRy agonists), as described, for example, in WO20071 31005, WO2008052709;

agonists of estrogen receptor alpha (ERRa / ERR1 agonists), as described, for example, in WO20081 09727;

agonists of estrogen receptor beta (ERRβ agonists), as described, for example, in WO2009055734, WO20091 00335, WO20091 27686;
sigma-1 receptor antagonists, as described, for example, in WO2007098953, WO2007098961, WO2008015266, WO2008055932, WO2008055933, WO2009071657;

5 muscarin 3 receptor (M3R) antagonists, as described, for example, in WO200710782, WO2008041184;

bombesin receptor agonists (BRS-3 agonists), as described, for example, in WO2008051404, WO2008051405, WO2008051406, WO2008073311;

galanin receptor antagonists;

growth hormone (e.g. human growth hormone or AOD-9604);

15 growth hormone releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1 H-isoquinoline-2-carboxylate (WO 01/85695));

20 growth hormone secretagogue receptor antagonists (ghrelin antagonists), for example A-7781 93, or those as described in WO2005030734, WO2007127457, WO2008008286, WO2009056707;

growth hormone secretagogue receptor modulators (ghrelin modulators), for example JMV-2959, JMV-3002, JMV-2810, JMV-2951, or those as described in WO2006012577 (e.g. YIL-781 or YIL-870), WO2007079239, WO2008092681, WO2008145749, WO2008148853, WO2008148854, WO2008148856, WO2009047558, WO2009071283, WO2009115503;

30 TRH agonists (see, for example, EP 0 462 884);
decoupling protein 2 or 3 modulators (as described, for example, in WO2009128583);

chemical decouplers (e.g. WO2008059023, WO2008059024, WO2008059025, WO2008059026);

leptin receptor agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881);

leptin receptor modulators, as described, for example, in WO2009019427, WO2009071658, WO2009071668, WO2009071677, WO2009071678, WO2009147211, WO2009147216, WO2009147219, WO2009147221;

DA agonists (bromocriptin, bromocriptin mesylate, doprexin) or those as described in US2009143390;

lipase/amylase inhibitors (e.g. WO 00/40569, WO2008107184, WO2009049428, WO2009125819);

inhibitors of monoacylglycerol acyltransferase (2-acylglycerol O-acyltransferase; MGAT), as described, for example, in WO2008038768;

inhibitors of fatty acid synthase (FAS), for example C75, or those as described in WO2004005277, WO20080061 13;


inhibitors of fatty acid desaturase 1 (delta5 desaturase), as described, for example, in WO200808931 0;
inhibitors of monoglyceride lipase (MGL), as described in WO2008145842;

hypoglycemic/hypertriglyceridemic indoline compounds, as described in WO2008039087, WO2009051119;
inhibitors of "adipocyte fatty acid-binding protein aP2", for example BMS-309403 or those as described in WO2009028248;

activators of adiponectin secretion, as described, for example, in WO2006082978, WO2008105533, WO2008136173;
promoters of adiponectin production, as described, for example, in WO2007125946, WO2008038712;
modified adiponectins, as described, for example, in WO2008121009;
oxynmodulin or analogs thereof (for example, TKS-1225);

oleoyl-estrone

or agonists or partial agonists of the thyroid hormone receptor (thyroid hormone receptor agonists), for example: KB-2115 (eprotirome), QRX-431 (sobetirome) or DITPA, or those as described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421, WO2005092316, WO2007003419, WO2007009913, WO2007039125, WO2007110225, WO2007110226, WO2007128492, WO2007132475, WO2007134864, WO2008001959, WO2008106213, JP2009155261;

or agonists of the thyroid hormone receptor beta (TR-beta), for example MB-07811 or MB-07344, or those as described in WO2008062469.

In one embodiment of the invention, the compound of the formula I is administered in combination with a combination of eprotirome with ezetimibe.
In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of site-1 protease (S1P), for example PF-429242.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a modulator of the "trace amine associated receptor 1" (TAAR1), as described, for example, in US2008146523, WO2008092785.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of growth factor receptor bound protein 2 (GRB2), as described, for example, in WO2008067270.

In a further embodiment of the invention, the compound of the formula I is administered in combination with an RNAi (siRNA) therapeutic agent directed against PCSK9 (proprotein convertase subtilisin/kexin type 9).

In one embodiment, the compound of the formula I is administered in combination with Omacor® or Lovaza™ (omega-3 fatty acid ester; highly concentrated ethyl ester of eicosapentaenoic acid and of docosahexaenoic acid).

In one embodiment, the compound of the formula I is administered in combination with lycopene.

In one embodiment of the invention, the compound of the formula I is administered in combination with an antioxidant, for example OPC-14117, AGI-1067 (succinobucol), probucol, tocopherol, ascorbic acid, β-carotene or selenium, or those as described in WO2009135918.

In one embodiment of the invention, the compound of the formula I is administered in combination with a vitamin, for example vitamin B6 or vitamin B12.
In one embodiment, the compound of the formula I is administered in combination with more than one of the aforementioned compounds, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin (PrandiMet™), insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In a further embodiment, the compound of the formula I is administered in combination with an activator of soluble guanylate cyclase (sGC), as described, for example, in WO2009032249.

In another embodiment, the compound of the formula I is administered in combination with an inhibitor of carboanhydrase type 2 (carbonic anhydrase type 2), for example those as described in WO2007065948, WO2009050252.

In another embodiment, the compound of the formula I is administered in combination with topiramat or a derivative thereof, as described in WO2008027557, US2009304789.

In a further embodiment, the compound of the formula I is administered in combination with a solid combination of topiramat with phentermin (Qnexa™).

In a further embodiment, the compound of the formula I is administered in combination with an antisense compound, e.g. ISIS-377131, which inhibits the production of the glucocorticoid receptor.

In another embodiment, the compound of the formula I is administered in combination with an aldosterone synthase inhibitor and an antagonist of the glucocorticoid receptor, a Cortisol synthesis inhibitor and/or an antagonist of the corticotropin releasing factor, as described, for example, in EP1 886695, WO20081 19744.
In one embodiment, the compound of the formula I is administered in combination with an agonist of the RUP3 receptor, as described, for example, in WO2007035355, WO2008005576.

In another embodiment, the compound of the formula I is administered in combination with an agonist of the RUP3 receptor, as described, for example, in WO2007035355, WO2008005576.

In one embodiment, the compound of the formula I is administered in combination with an activator of the gene which codes for ataxia telangiectasia mutated (ATM) protein kinase, for example chloroquine.

In one embodiment, the compound of the formula I is administered in combination with a tau protein kinase 1 inhibitor (TPK1 inhibitor), as described, for example, in WO2007119463, WO2009035159, WO2009035162.

In one embodiment, the compound of the formula I is administered in combination with a "c-Jun N-terminal kinase" inhibitor (JNK inhibitor), for example B1-78D3 or those as described, for example, in WO2007125405, WO2008028860, WO2008118626.

In one embodiment, the compound of the formula I is administered in combination with an endothelin A receptor antagonist, for example avosentan (SPP-301).

In one embodiment, the compound of the formula I is administered in combination with inhibitors of neutral endopeptidase (NEP inhibitors), as described, for example, in WO2009138122, WO2009135526.

In one embodiment, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor (GR), for example KB-3305 or those compounds as described, for example, in WO2005090336, WO2006071609, WO2006135826, WO2007105766, WO2008120661, WO2009040288, WO2009058944, WO2009108525, WO2009111214.

In one embodiment, the further active ingredient is varenicline tartrate, a partial agonist of the alpha 4-beta 2 nicotinic acetylcholine receptor.
In one embodiment, the further active ingredient is an agonist of the alpha 7-nicotinic acetylcholine receptor, as described, for example, in WO2009018551, WO2009071519, WO2009071576, WO2009071577.

In one embodiment, the further active ingredient is trodusquemine.

In one embodiment, the further active ingredient is a modulator of the enzyme SIRT1 and/or SIRT3 (an NAD+-dependent protein deacetylase); this active ingredient may, for example, be resveratrol in suitable formulations, or those compounds as specified in WO2007019416 (e.g. SRT-1720), WO2008073451, WO2008156866, WO2008156869, WO2009026701, WO2009049018, WO2009058348, WO2009061453, WO2009134973, WO2009146358, WO2010003048.

In one embodiment of the invention, the further active ingredient is DM-71 (N-acetyl-L-cysteine with betahanechol).


In a further embodiment, the compound of the formula I is administered in combination with inhibitors of SREBP (sterol regulatory element-binding protein), for example fatostatin, or those as described, for example, in WO2008097835.

In another embodiment, the compound of the formula I is administered in combination with a cyclic peptide agonist of the VPAC2 receptor, as described, for example, in WO2007101146, WO2007133828.
In a further embodiment, the compound of the formula I is administered in combination with an agonist of the endothelin receptor, as described, for example, in WO20071 12069.

In a further embodiment, the compound of the formula I is administered in combination with AKP-020 (bis(ethylmaltolato)oxovanadium(IV)).

In another embodiment, the compound of the formula I is administered in combination with tissue-selective androgen receptor modulators (SARM), as described, for example, in WO2007099200, WO20071 37874.

In a further embodiment, the compound of the formula I is administered in combination with an AGE (advanced glycation endproduct) inhibitor, as described, for example, in JP2008024673.

In one embodiment of the invention, the further active ingredient is leptin; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001 ), 2(1 0), 1615-1 622.

In another embodiment of the invention, the further active ingredient is metreleptin (recombinant methionyl-leptin) combined with pramlintide.

In a further embodiment of the invention, the further active ingredient is the tetrapeptide ISF-402.

In one embodiment, the further active ingredient is dexamphetamine or amphetamine.

In one embodiment, the further active ingredient is fenfluramine or dexfenfluramine. In another embodiment, the further active ingredient is sibutramine or those derivatives as described in WO2008034142.
In one embodiment, the further active ingredient is mazindol or phentermin.

In a further embodiment, the further active ingredient is geniposidic acid (WO2007100104) or derivatives thereof (JP2008106008).

In another embodiment, the further active ingredient is a neuropeptide FF2 agonist, as described, for example, in WO2009038012.

In one embodiment, the further active ingredient is a nasal calcium channel blocker, for example diltiazem, or those as described in US 7,138,107.

In one embodiment, the further active ingredient is an inhibitor of sodium-calcium ion exchange, for example those as described in WO2008028958, WO2008085711.

In a further embodiment, the further active ingredient is a blocker of calcium channels, for example of CaV3.2 or CaV2.2, as described in WO2008033431, WO2008033447, WO2008033356, WO2008033460, WO2008033464, WO2008033465, WO2008033468, WO2008073461.

In one embodiment, the further active ingredient is a modulator of a calcium channel, for example those as described in WO2008073934, WO2008073936, WO2009107660.

In one embodiment, the further active ingredient is an inhibitor of the calcium metabolism, for example those as described in US2009124680.

In one embodiment, the further active ingredient is a blocker of the "T-type calcium channel", as described, for example, in WO2008033431, WO2008110008, US2008280900, WO2008141446, US2009270338, WO2009146540, US2009325979, WO2009146539.
In one embodiment, the further active ingredient is an inhibitor of KCNQ potassium channel 2 or 3, for example those as described in US2008027049, US2008027090.

In one embodiment, the further active ingredient is a modulator of KCNN potassium channel 1, 2 or 3 (modulators of the SK1, SK2 and/or SK3 channel), for example those as described in US2009036475.

In one embodiment, the further active ingredient is an inhibitor of the potassium Kv1.3 ion channel, for example those as described in WO2008040057, WO2008040058, WO2008046065, WO2009043117.

In one embodiment, the further active ingredient is a potassium channel modulator, for example those as described in WO2008135447, WO2008135448, WO2008135591, WO2009099820.

In a further embodiment, the further active ingredient is a hyperpolarization-activated cyclic nucleotide-gated (HCN) potassium-sodium channel inhibitor, for example those as described in US2009069296.

In another embodiment, the further active ingredient is an inhibitor of the sodium-potassium-2 chloride (NKCCI) cotransporter, for example those as described in WO2009130735.

In another embodiment, the further active ingredient is a voltage-gated sodium channel inhibitor, for example those as described in WO2009049180, WO2009049181.

In another embodiment, the further active ingredient is a modulator of the MCP-1 receptor (monocyte chemoattractant protein-1 (MCP-1)), for example those as described in WO2008014360, WO2008014381.
In one embodiment, the further active ingredient is a modulator of somatostatin receptor 3 (SSTR3), for example those as described in WO200901 1836.

In one embodiment, the further active ingredient is a modulator of somatostatin receptor 5 (SSTR5), for example those as described in WO200801 9967, US2008064697, US20082491 01, WO2008000692, US2008293756, WO20081 4871 0.

In one embodiment, the further active ingredient is a modulator of somatostatin receptor 2 (SSTR2), for example those as described in WO2008051 272.

In one embodiment, the further active ingredient is a compound which is capable of reducing the amount of retinol-binding protein 4 (RBP4), for example those as described in WO2009051 244, WO20091 45286.

In one embodiment, the further active ingredient is an erythropoietin-mimetic peptide which acts as an erythropoietin (EPO) receptor agonist. Such molecules are described, for example, in WO2008042800.

In a further embodiment, the further active ingredient is an anorectic/a hypoglycemic compound, for example those as described in WO2008035305, WO2008035306, WO2008035686.

In one embodiment, the further active ingredient is an inductor of lipoic acid synthetase, for example those as described in WO2008036966, WO2008036967.

In one embodiment, the further active ingredient is a stimulator of endothelial nitric oxide synthase (eNOS), for example those as described in WO2008058641, WO200807441 3.
In one embodiment, the further active ingredient is a modulator of carbohydrate and/or lipid metabolism, for example those as described in WO2008059023, WO2008059024, WO2008059025, WO2008059026.

In a further embodiment, the further active ingredient is an angiotensin II receptor antagonist, for example those as described in WO2008062905, WO2008067378, WO2008062905.

In one embodiment, the further active ingredient is an agonist of the sphingosine 1-phosphate receptor (S1P), for example those as described in WO2008064315, WO2008074820, WO2008074821, WO2008135522, WO2009019167, WO2009043013, WO2009080663, WO2009085847, WO2009151529, WO2009151621, WO2009151626, WO2009154737.

In one embodiment, the further active ingredient is an agent which retards gastric emptying, for example 4-hydroxyisoleucine (WO2008044770).

In one embodiment, the further active ingredient is a tryptophan-5-hydroxylase inhibitor-1 (TPH1 inhibitor), which modulates gastrointestinal motility, as described, for example, in WO2009014972.

In one embodiment, the further active ingredient is a muscle-relaxing substance, as described, for example, in WO2008090200.

In a further embodiment, the further active ingredient is an inhibitor of monoamine oxidase B (MAO-B), for example those as described in WO2008092091, WO2009066152.

In a further embodiment, the further active ingredient is an inhibitor of monoamine oxidase A (MAO-A), for example those as described in WO2009030968.
In another embodiment, the further active ingredient is an inhibitor of the binding of cholesterol and/or triglycerides to the SCP-2 protein (sterol carrier protein-2), for example those as described in US20081 94658.

In a further embodiment, the further active ingredient is a compound which binds to the β-subunit of the trimeric GTP-binding protein, for example those as described in WO20081 26920.

In one embodiment, the further active ingredient is a urate anion exchanger inhibitor 1, as described, for example, in WO2009070740.

In one embodiment, the further active ingredient is a modulator of the ATP transporter, as described, for example, in WO20091 08657.

In another embodiment, the further active ingredient is lisofylline, which prevents autoimmune damage to insulin-producing cells.

In yet another embodiment, the further active ingredient is an extract from Bidens pilosa with the ingredient cytopiloyne as described in EP1 955701.

In one embodiment, the further active ingredient is an inhibitor of glucosylceramide synthase, as described, for example, in WO20081 50486.

In a further embodiment of the invention, the further active ingredient is a glycosidase inhibitor, as described, for example, in WO20091 17829, WO20091 55753.

In another embodiment, the further active ingredient is an ingredient from the plant *Hoodia Gordonii*, as described in US2009042813, EP2044852.

In one embodiment, the further active ingredient is an antidiabetic, for example D-tagatose.
In one embodiment, the further active ingredient is a zinc complex of curcumin, as described in WO2009079902.

In one embodiment, the further active ingredient is an inhibitor of the "cAMP response element binding protein" (CREB), as described in WO2009143391.

In another embodiment, the further active ingredient is an antagonist of the bradykinin B1 receptor, as described in WO2009124746.

In a further embodiment, the further active ingredient is a compound which is capable of modulating diabetic peripheral neuropathy (DPN). Such modulators are, for example, FK-1 706 or SB-509, or those as described in W0 1989005304, WO2009092129, WO2010002956.

In one embodiment, the further active ingredient is a compound which is capable of modulating diabetic nephropathy. Such compounds are described, for example, in WO2009089545, WO2009153261.

In one embodiment, the further active ingredient is an inhibitor (e.g. an anti-CD38 antibody) of CD38, as described in US2009196825.

In one embodiment, the further active ingredient is an inhibitor of human fibroblast growth factor receptor 4 (FGFR4), as described, for example, in WO2009046141.

In a further embodiment of the invention, the further active ingredient is a compound which protects the beta cell, for example 14-alpha-lipolyl-andrographolide (AL-1).

In yet another embodiment of the invention, the further active ingredient is the INGAP (islet neogenesis associated protein) peptide, a peptide which reestablishes insulin production in patients with diabetes mellitus.
In one embodiment of the invention, the further active ingredient is a modulator of the CFTR (cystic fibrosis transmembrane conductance regulator), as described, for example, in US2009246137, US2009264433, US2009264441, US2009264471, US2009264481, US2009264486, WO2010019239.

In one embodiment of the invention, the further active ingredient is a compound which stimulates/modulates insulin release, for example those as described in WO2009109258, WO2009132739, US2009281057, WO2009157418.

In one embodiment of the invention, the further active ingredient is an extract from Hippophae rhamnoides, as described, for example, in WO2009125071.

In one embodiment of the invention, the further active ingredient is an from Huanglian and Ku Ding Cha, as described, for example, in WO2009133458.

In another embodiment, the further active ingredient is a root extract from Cipadessa baccifera, as described in US2009238900.

In one embodiment of the invention, the further active ingredients are borapetoside A and/or borapetoside C, which can be isolated from the plant SDH-V, a species of Tinospora crispa, as described, for example, in US2010016213.

In one embodiment, the compound of the formula I is administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, Carob/Carom ax® (Zunft HJ; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Hochst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be
administered in the form of food products such as, for example, in bakery products or muesli bars.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is considered to be covered within the scope of protection conferred by the present invention.
Solabegron

Lorcanerin Hydrochlorid

L-152804

MB-06322

CS-917

N-5984

MB-07803
AVE 1625 (proposed INN: drinabant)  

TAK-475 (lapaquistat acetate)

CKD-501 (lobeglitazone sulfate)  

MB-0781 1
alogliptin benzoate  

nicotinic acid / laropiprant  

linagliptin  

melagl iptin  

velneperit  

GSK-982  

PSN-119-2  

drospirenone  

lisofylline  

cytopiloin
BI-78D3

FK-1706

CVT-3619

INT-131

remogliflozin

tocotrienol
BMS-759509

Canagliflozin

14-alpha-lipoly-andrographolide (AL-1)

Fatostatin

NCX-6560

Anacetrapib

PF-3246799
Also suitable are the following active ingredients for combination preparations:
all antiepileptics specified in the Rote Liste 2011, chapter 15;
all antihypertensives specified in the Rote Liste 2011, chapter 17;
all hypotonics specified in the Rote Liste 2011, chapter 19;
all anticoagulants specified in the Rote Liste 2011, chapter 20;
all arteriosclerosis drugs specified in the Rote Liste 2011, chapter 25;
all beta receptors, calcium channel blockers and inhibitors of the renin angiotensin system specified in the Rote Liste 2011, chapter 27;
all diuretics and perfusion-promoting drugs specified in the Rote Liste 2011, chapter 36 and 37;
all withdrawal drugs/drugs for the treatment of addictive disorders specified in the Rote Liste 2011, chapter 39;
all coronary drugs and gastrointestinal drugs specified in the Rote Liste 2011, chapter 55 and 60;
all migraine drugs, neuropathy preparations and Parkinson's drugs specified in the Rote Liste 2011, chapter 61, 66 and 70.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is considered to be covered within the scope of protection conferred by the present invention.

Pharmaceutical compositions
APJ modulators can be administered to animals, in particular to mammals including humans, as pharmaceuticals by themselves, in mixtures with one another, or in the form of pharmaceutical compositions. The administration can be carried out orally, for example in the form of tablets, film-coated tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, solutions including aqueous, alcoholic and oily solutions, juices, drops, syrups, emulsions or suspensions, rectally, for example in the form of suppositories, or parenterally, for example in the form of solutions for subcutaneous, intramuscular or intravenous injection or infusion, in particular aqueous solutions.
Suitable pharmaceutical compounds for oral administration may be in the form of separate units, for example capsules, cachets, lozenges or tablets, each of which contains a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surfactant(s)/dispersant(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and has been moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise lozenges which contain a compound of formula I with a flavoring, typically sucrose, and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Coated formulations and coated slow-release formulations, especially acid- and gastric juice-resistant formulations, also belong within the framework of the invention. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.
Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of formula I with one or more conventional solid carriers, for example cocoa butter, and shaping resulting mixture.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain 0.1 to 5% by weight of the active compound.

Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, creams, tinctures, sprays, powders or transdermal therapeutic systems, or inhalative administration, for example in the form of nasal sprays or aerosol mixtures, or forms such as microcapsules, implants or rods.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. The carriers used may be petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of 0.1 to 15% by weight of the composition, for example 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses may be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A
particular option is for the active ingredient to be released by electrotransport or
iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318
(1986).

APJ modulators can additionally be used in systems for local drug delivery, for
example in coated stents for preventing or reducing in-stent restenosis or by applying
them locally by means of a catheter. The appropriate administration form depends,
among others, on the disease to be treated and on its severity.

The dosing of APJ modulators to achieve the desireable therapeutic effect depends
on a number of factors, for example the specific compound chosen, the intended use,
the mode of administration and the clinical condition of the patient. The daily dose is
generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day
and per kilogram of body weight, for example 3-1 0 mg/kg/day. An intravenous dose
may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be
administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable
infusion solutions for these purposes may contain, for example, 0.1 ng to 100 mg,
typically 1 ng to 100 mg, per milliliter. Single doses may contain, for example, 1 mg to
10 g of the active ingredient. Thus, ampoules for injections may contain, for example,
from 1 mg to 100 mg, and orally administrable single-dose formulations, for example
tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10
to 600 mg. For treatment of the abovementioned conditions, the compounds of the
formula 1 themselves may be used as the compound, but they are preferably present
with a compatible carrier in the form of a pharmaceutical composition. The carrier
must, of course, be acceptable in the sense that it is compatible with the other
ingredients of the composition and is not harmful for the patient's health. The carrier
may be a solid or a liquid or both and is preferably formulated with the compound as
a single dose, for example as a tablet, which may contain 0.05% to 95% by weight of
the active ingredient. Other pharmaceutically active substances may likewise be
present, including other compounds of formula 1. The pharmaceutical compositions of
the invention can be produced by one of the known pharmaceutical methods, which
essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Another subject of the present invention are processes for the preparation of the compounds of the formula I and their salts and solvates, by which the compounds are obtainable and which are outlined in the following.

The invention further relates to the following processes for preparing the compounds of the formula I:

Compounds of formula I can be prepared as described in Scheme 1.

Scheme 1
which comprises

a) protection of an acid of formula 1 to form an ester of formula 2,
b) substitution of a leaving group of a compound of formula 2 with an amine of

which comprises

a) protection of an acid of formula 1 to form an ester of formula 2,
b) substitution of a leaving group of a compound of formula 2 with an amine of

which comprises

a) protection of an acid of formula 1 to form an ester of formula 2,
b) substitution of a leaving group of a compound of formula 2 with an amine of

c) reduction of the nitro-group of formula 4 to to a compound of formula 5,
d) reaction of a compound of formula 5 with a compound of formula 6 to form an

amide of formula 7

e) cyclization of a compound of formula 7 to a benzimidazole of formula 8,
f) cleavage of the ester of formula 8 to form an acid of formula 9,
g) coupling of an acid of formula 9 with an amino compound of formula 10 to an

amide of formula 12 and

h) converting a compound of formula 12 to a compound of formula 1,
or alternatively,

coupling of an acid of formula 9 with an amino compound of formula 11 to a

compounds of the formulae 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

R¹, R², R³, R⁴, R⁵, R⁶, n and Z are defined as in formula 1.

R¹ is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu

or tert.-Bu, or -CH₂-phenyl, which may be substituted, e.g. Bn or para-

methoxybenzyl,

R² is CO₂R³, with R³ being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et,
nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or -CH₂-phenyl, which may be substituted, e.g. Bn

or para-Methoxybenzyl,

LG¹ is a leaving group, which can undergo nucleophilic aromatic substitution with an

amin, e.g. F, Cl, Br, CN, OMs, OTf or OTs and

LG² is OH or a leaving group, which can undergo nucleophilic substitution with an

aromatic amine, e.g. (Ci-C₄)-alkoxy, F, Cl, Br or OC(O)-(Ci-C₄)-alkyl, or -
pentafluorophenoxy.

The protection of an acid of formula 1 to form an ester of formula 2 are per se well

known to the skilled person and can be carried out under standard conditions
according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999), preferably the protection is achieved by reacting the acid of formula 1 with the respective alcohol under acidic conditions to obtain a methyl or ethyl ester.

The substitution of a leaving group of a compound of formula 2 with an amine of formula 3 to form a compound of formula 4 is generally carried out under neat conditions or in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, disopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents, it is carried out preferably in the presence of an additional base, for example an amine base such as TEA, DIPEA or N-methylmorpholin or an alkaline metal - or alkaline earth metal-bicarbonate, -carbonate or -hydroxide, such as sodium, potassium or lithium hydrogen carbonate, carbonate or hydroxide or cesium carbonate. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 20°C to 150 °C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The reduction of the nitro-group of formula 4 to a compound of formula 5 is generally carried out in the presence of a suitable catalyst, e. g. a palladium catalyst or a Raney-Nickel catalyst or a homogeneous palladium complex, either under hydrogen atmosphere, usually at ambient pressure or at elevated pressure up to 50 bar, preferably at pressures up to 5 bar or in the presence of a different hydrogen source such as formic acid in a suitable solvent, preferably an alcohol, such as methanol, ethanol or propanol, or an ester, such as ethyl acetate or ethyl butanoate, an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or mixtures of solvents at reaction temperatures from...
0°C to 250°C, preferably from 20°C to 150°, more preferably from 20°C to 60°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range, or alternatively it is carried out in the presence of tin(II) chloride in a suitable solvent such as an ester, e.g. ethyl acetate or ethyl butanoate, at reaction temperatures from 0°C to 250°C, preferably from 20°C to 150°, more preferably from 20°C to 80°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The reaction of a compound of formula 5 with a compound of formula 6, in which LG² is OH, to form an amide of formula 7 is generally carried out in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The acids of formula 6 can be subjected to the reaction in form of their salts, for example their sodium salts. As far as applicable and unless otherwise indicated, it applies to all acidic or basic compounds occurring in the preparation of the compounds of the formula I that they can be present in form of their salts. The reaction of a compound of formula 5 with a compound of formula 6, in which LG² is a leaving group, which can undergo nucleophilic substitution with an aromatic amine, e.g. (Cl-C₄₉)-alkoxy, F, Cl, Br or OC(O)-(CrC₄)-alkyl, or -pentafluorphenoxyl, is generally carried out in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or...
an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents and optionally in the presence of an additional base, such as TEA, DIPEA or N-methylmorpholin. The reaction temperature is generally from 0°C to 250°C, preferably from 0°C to 150°C, more preferably from 20°C to 100°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The cyclization of a compound of formula 7 to a benzimidazole of formula 8 is generally performed under neat conditions or in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, preferably in the presence of an acid, such as hydrochloric acid or trifluoro acetic acid or sulfuric acid, more preferably in the presence of hydrochloric acid in anhydrous dioxane, the reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 80°C to 200°C and the reaction time is generally from 5 min to 6 days, preferably from 5 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The cleavage of the ester of formula 8 to form an acid of formula 9 can be performed by known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999), preferably by reacting the ester of formula 8 with aqueous acids, such as hydrochloric acid or sulfuric acid or with aqueous bases, such as an alkaline metal - or alkaline earth metal-carbonate or -hydroxide, such as sodium, potassium or lithium carbonate or hydroxide or cesium carbonate, optionally in the presence of an additional solvent, such as an ether such as tetrahydrofurane, 1,4-dioxane,
dibutylether, diisopropylether, methyl-tert-butylether, dimethoxylethane or an alcohol, such as methanol, ethanol or propanol, or mixtures of solvents. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 100°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The coupling of an acid of formula 9 with an amino compound of formula 10 to an amide of formula 12 is generally performed in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxylethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyrroline or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The acids of formula 9 can be subjected to the reaction in form of their salts, for example their sodium salts. They can also be transformed into an activated derivative prior to the coupling with the amine, for example into an acid chloride or an acid anhydride by standard transformations. The amines of formula 10 can be subjected to the reaction in form of their salts, for example as hydrochloride or triflate salts, in which case usually an additional equivalent of the base is added to the reaction.

The conversion of a compound of formula 12 to a compound of formula 1, can be performed in one step or in several steps, depending on the meaning of the groups R^b and Z.
If $R^b$ is $CO_2R^c$, with $R^c$ being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or -$CH_2$-phenyl, which may be substituted, e.g. Bn or para-Methoxybenzyl, and $Z$ is $CO_2H$, the conversion of a compound of formula 12 to a compound of formula 1 can be performed by methods known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999), preferably by reacting the ester of formula 8 with acids, such as hydrochloric acid, trifluoro acetic acid or sulfuric acid or with aqueous bases, such as an alkaline metal - or alkaline earth metal-carbonate or -hydroxide, such as sodium, potassium or lithium carbonate or hydroxide or cesium carbonate, optionally in the presence of an additional solvent, such as an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane or an alcohol, such as methanol, ethanol or propanol, or mixtures of solvents. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 100°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

If $R^b$ is $CO_2R^c$, with $R^c$ being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or -$CH_2$-phenyl, which may be substituted, e.g. Bn or para-Methoxybenzyl, and $Z$ is CONR$^7$R$^8$, the conversion of a compound of formula 12 to a compound of formula 1 can be performed in several steps. The first step consists of the cleavage of the ester of formula 12 as described immediately above, followed by a reaction with an amine HNR$^{7a}$R$^{8a}$, wherein $R^{7a}$ and $R^{8a}$ are, independently of each other, either defined as the groups $R^7$ and $R^8$ in the compounds of formula 1 or they are precursors of the groups $R^7$ and $R^8$ in formula 1, they can for example contain functional groups in protected form or functional groups which can be converted to obtain the final groups $R^7$ and $R^8$. This reaction with an amine HNR$^{7a}$R$^{8a}$ is generally performed in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methyl-
morpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The resulting product can already be a compound of formula I, if \( R^7_a \) is \( R^7 \) and \( R^8_a \) is \( R^8 \). If the resulting product is not already a compound of formula I, it can be transformed into a compound of formula I depending on the meaning of the groups \( R^7_a \) and \( R^8_a \). If the groups \( R^7_a \) and/or \( R^8_a \) contain protecting groups that can be cleaved by hydrogenation, e.g. a benzyl group or a 4-methoxybenzyl group, the transformation to a compound of formula I can be a catalytic hydrogenation or a transfer hydrogenation. If the groups \( R^7_a \) and/or \( R^8_a \) contain protecting groups that can be cleaved by treatment with acid, e.g. a tert-butyl group, the transformation to a compound of formula I can be an acidic deprotection. If the groups \( R^7_a \) and/or \( R^8_a \) contain protecting groups that can be cleaved by treatment with base e.g. a methyl or ethyl ester, the transformation to a compound of formula I can be a basic hydrolysis. All deprotection reactions used in the above-described transformations of precursors of compounds of formula I, in which the groups \( R^7_a \) and/or \( R^8_a \) contain protecting groups, to compounds of formula I are per se well known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999).

Alternatively, the coupling of an acid of formula 9 with an amino compound of formula 11 can directly result in a compound of formula I. This transformation is generally performed in the presence of activating agents, such as CDI, DCC, EDC, HOAt,
HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methylpyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

Alternatively compounds of formula I can be prepared as described in Scheme 2
Scheme 2

which comprises

5) protection of an acid of formula 1 to form an ester of formula 2,
6) substitution of a leaving group of a compound of formula 2 with an amine of formula 3 to form a compound of formula 4,
7) cleavage of an ester of formula 4 to an acid of formula 13,
8) reaction of a compound of formula 13 with an amine of formula 10 to form an amide of formula 14,
9) reduction of the nitro-group of a compound of formula 14 to a compound of formula 15,
10) reaction of a compound of formula 15 with a compound of formula 6 to form an amide of formula 16,
11) cyclization of a compound of formula 16 to a benzimidazole of formula 12,
12) converting a compound of formula 12 to a compound of formula 1.
wherein in the compounds of the formulae 1, 2, 3, 4, 6, 10, 12, 13, 14, 15 and 16
$R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, n and Z are defined as in formula 1.
$R^a$ is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu
or tert.-Bu, or -CH$_2$-phenyl, which may be substituted, e.g. Bn or para-

5 Methoxybenzyl,
$R^b$ is CO$_2$R$^c$, with R$^c$ being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et,
nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or -CH$_2$-phenyl, which may be substituted, e.g. Bn
or para-Methoxybenzyl,
LG$^1$ is a leaving group, which can undergo nucleophilic aromatic substitution with an
amine, e.g. F, Cl, Br, CN, OMs, OTf or OTs and
LG$^2$ is OH or a leaving group, which can undergo nucleophilic substitution with an
aromatic amine, e.g. (Ci-C$_4$)-alkoxy, F, Cl, Br or OC(O)-(Ci-C$_4$)-alkyl, or -
pentafluorophenoxy.

The protection of an acid of formula 1 to form an ester of formula 2 can be performed
by methods known to the skilled person and can be carried out under standard
conditions according to, or analogously to, procedures described in the literature, for
example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994
or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley,
New York, 1999), preferably by reacting the acid of formula 1 with the respective
alcohol under acidic conditions.

The substitution of a leaving group of a compound of formula 2 with an amine of
formula 3 to form a compound of formula 4 is generally carried out under neat
conditions or in an appropriate inert solvent, for example a hydrocarbon or a
chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane,
dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane,
dibutylether, disopropylether, methyl-tert-butylether, dimethoxyethane, or an ester
such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide
or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents, it is
carried out preferably in the presence of an additional base, for example an amine
base such as TEA, DIPEA or N-methylmorpholin or an alkaline metal - or alkaline
earth metal-bicarbonate, -carbonate or -hydroxide, such as sodium, potassium or lithium hydrogen carbonate, carbonate or hydroxide or cesium carbonate. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 20°C to 150°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The cleavage of the ester of formula 4 to form an acid of formula 13 can be performed by methods known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999), preferably by reacting the ester of formula 4 with aqueous acids, such as hydrochloric acid or sulfuric acid or with aqueous bases, such as an alkaline metal - or alkaline earth metal-carbonate or -hydroxide, such as sodium, potassium or lithium carbonate or hydroxide or cesium carbonate, optionally in the presence of an additional solvent, such as an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane or an alcohol, such as methanol, ethanol or propanol, or mixtures of solvents. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 100°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The coupling of an acid of formula 13 with an amino compound of formula 10 to an amide of formula 14 is generally performed in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester.
such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The acids of formula 13 can be subjected to the reaction in form of their salts, for example their sodium salts. They can also be transformed into an activated derivative prior to the coupling with the amine, for example into an acid chloride or an acid anhydride by standard transformations. The amines of formula 10 can be subjected to the reaction in form of their salts, for example as hydrochloride or triflate salts, in which case usually an additional equivalent of the base is added to the reaction.

The reduction of the nitro-group of formula 14 to a compound of formula 15 is generally carried out in the presence of a suitable catalyst, e.g. a palladium catalyst or a Raney-Nickel catalyst or a homogeneous palladium complex, either under hydrogen atmosphere, usually at ambient pressure or at elevated pressure up to 50 bar, preferably at pressures up to 5 bar or in the presence of a different hydrogen source such as formic acid in a suitable solvent, preferably an alcohol, such as methanol, ethanol or propanol, or an ester, such as ethyl acetate or ethyl butanoate, an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or mixtures of solvents at reaction temperatures from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 60°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range, or alternatively it is carried out in the presence of tin(II) chloride in a suitable solvent such as an ester, e.g. ethyl acetate or ethyl butanoate, at reaction temperatures from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 80°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.
The reaction of a compound of formula 15 with a compound of formula 6, in which
LG² is OH, to form an amide of formula 16 is generally carried out in the presence of
activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP,
PyBOP or combinations thereof, and optionally an additional base, such as TEA,
DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a
hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene,
dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofurane,
1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane,
or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-
dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of
solvents. The reaction temperature is generally from -30°C to 200°C, preferably from
-20°C to 80°C, more preferably from 0°C to 20 °C. The reaction time is generally from
15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of
the mixture and the chosen temperature range. The acids of formula 6 can be
subjected to the reaction in form of their salts, for example their sodium salts. The
reaction of a compound of formula 15 with a compound of formula 6, in which LG² is
a leaving group, which can undergo nucleophilic substitution with an aromatic amine,
e.g. (C₁-C₉)-alkoxy, F, Cl, Br or OC(O)-(C₉₋₃)-alkyl, or -pentafluorophenoxy, is
generally carried out in an appropriate inert solvent, for example a hydrocarbon or a
chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane,
dichloroethane, chloroform, or an ether such as tetrahydrofurane, 1,4-dioxane,
dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester
such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide
or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents and
optionally in the presence of an additional base, such as TEA, DIPEA or N-
methylmorpholin The reaction temperature is generally from 0°C to 250°C, preferably
from 0°C to 150°C, more preferably from 20°C to 100 °C. The reaction time
is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the
composition of the mixture and the chosen temperature range.

The cyclization of a compound of formula 16 to a benzimidazole of formula 12 is
generally performed under neat conditions or in an appropriate inert solvent, for
example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, preferably in the presence of an acid, such as hydrochloric acid or trifluoro acetic acid or sulfuric acid, more preferably in the presence of hydrochloric acid in anhydrous dioxane, the reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°, more preferably from 80°C to 200 °C and the reaction time is generally from 5 min to 6 days, preferably from 5 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The conversion of a compound of formula 12 to a compound of formula I can be performed as it was described for the reaction sequence in Scheme 1.

Alternatively compounds of formula I can be prepared as described in Scheme 3.
Scheme 3

which comprises

a) reaction of a compound of formula 1 with an amine of formula 10 to form an amide

b) substitution of a leaving group of a compound of formula 17 with an amine of

formula 3 to form a compound of formula 14,

c) reduction of the nitro-group of formula 14 to a compound of formula 15,

d) reaction of a compound of formula 15 with a compound of formula 6 to form an

amide of formula 16,

e) cyclization of a compound of formula 16 to a benzimidazole of formula 12, and

f) converting a compound of formula 12 to a compound of formula 1,
or alternatively, the conversion of a compound of formula 16 to a compound of formula 17 and subsequently the cyclization of a compound of formula 17 to a compound of formula 1.

wherein in the compounds of the formulae 1, 3, 6, 10, 12, 14, 15, 16 and 17

5 \( R^1, R^2, R^3, R^4, R^5, R^6, n \) and \( Z \) are defined as in formula 1.

\( R^a \) is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or \(-\text{CH}_2\)-phenyl, which may be substituted, e.g. Bn or para-Methoxybenzyl,

\( R^b \) is \( \text{CO}_2R^c \), with \( R^c \) being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or \(-\text{CH}_2\)-phenyl, which may be substituted, e.g. Bn or para-Methoxybenzyl, or \( R^c \) is a solid support, like a Wang resin.

\( \text{LG}^1 \) is a leaving group, which can undergo nucleophilic aromatic substitution with an amine, e.g. F, Cl, Br, CN, OMs, OTf or OTs and

\( \text{LG}^2 \) is OH or a leaving group, which can undergo nucleophilic substitution with an aromatic amine, e.g. \((\text{Ci}-\text{C}_4)\)-alkoxy, F, Cl, Br or \( \text{OC}(\text{O})-(\text{Ci}-\text{C}_4)\)-alkyl, or -pentafluorophenoxy.

The coupling of an acid of formula 1 with an amino compound of formula 10 to an amide of formula 17 is generally performed in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBT, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The acids of formula 1 can be subjected to the
reaction in form of their salts, for example their sodium salts. They can also be transformed into an activated derivative prior to the coupling with the amine, for example into an acid chloride or an acid anhydride by standard transformations. The amines of formula 10 can be subjected to the reaction in form of their salts, for example as hydrochloride or triflate salts, in which case usually an additional equivalent of the base is added to the reaction.

The substitution of a leaving group of a compound of formula 17 with an amine of formula 3 to form a compound of formula 14 is generally carried out under neat conditions or in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents, it is carried out preferably in the presence of an additional base, for example an amine base such as TEA, DIPEA or N-methylmorpholin or an alkaline metal - or alkaline earth metal-bicarbonate, -carbonate or -hydroxide, such as sodium, potassium or lithium hydrogen carbonate, carbonate or hydroxide or cesium carbonate. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 20°C to 150 °C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The reduction of the nitro-group of formula 14 to a compound of formula 15 is generally carried out in the presence of a suitable catalyst, e. g. a palladium catalyst or a Raney-Nickel catalyst or a homogeneous palladium complex, either under hydrogen atmosphere, usually at ambient pressure or at elevated pressure up to 50 bar, preferably at pressures up to 5 bar or in the presence of a different hydrogen source such as formic acid in a suitable solvent, preferably an alcohol, such as methanol, ethanol or propanol, or an ester, such as ethyl acetate or ethyl butanoate,
an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or mixtures of solvents at reaction temperatures from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 60°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range, or alternatively it is carried out in the presence of tin(II) chloride in a suitable solvent such as an ester, e.g. ethyl acetate or ethyl butanoate, at reaction temperatures from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 80°C, with reaction times generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The reaction of a compound of formula 15 with a compound of formula 6, in which LG² is OH, to form an amide of formula 16 is generally carried out in the presence of activating agents, such as CDI, DCC, EDC, HOAt, HOBt, HATU, TOTU, TBTU, BEP, PyBOP or combinations thereof, and optionally an additional base, such as TEA, DIPEA or N-methylmorpholin in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents. The reaction temperature is generally from -30°C to 200°C, preferably from -20°C to 80°C, more preferably from 0°C to 20°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. The acids of formula 6 can be subjected to the reaction in form of their salts, for example their sodium salts. The reaction of a compound of formula 15 with a compound of formula 6, in which LG² is a leaving group, which can undergo nucleophilic substitution with an aromatic amine, e.g. (Ci-C₆)-alkoxy, F, Cl, Br or OC(O)-(CrC₂)-alkyl, or -pentafluorphenoxy, is generally carried out in an appropriate inert solvent, for example a hydrocarbon or a
chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, or an ester such as ethyl acetate or ethyl butanoate or an amide such as N,N-dimethylformamide or N,N-dimethylacetamide or N-methyl-pyridone or a in mixture of solvents and optionally in the presence of an additional base, such as TEA, DIPEA or N-methylmorpholine. The reaction temperature is generally from 0°C to 250°C, preferably from 0°C to 150°C, more preferably from 20°C to 100°C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The cyclization of a compound of formula 16 to a benzimidazole of formula 12 is generally performed under neat conditions or in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofuran, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, preferably in the presence of an acid, such as hydrochloric acid or trifluoro acetic acid or sulfuric acid, more preferably in the presence of hydrochloric acid in anhydrous dioxane, the reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 80°C to 200°C and the reaction time is generally from 5 min to 6 days, preferably from 5 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

The conversion of a compound of formula 12 to a compound of formula 1 can be performed as it was described for the reaction sequence in Scheme 1.

Alternatively, the conversion of a compound of formula 16 to a compound of formula 17, wherein R³ is CO₂R⁵, with R⁵ being alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. Me, Et, nPr, iPr, n-Bu, sec-Bu or tert.-Bu, or -CH₂-phenyl, which may be substituted, e.g. Bn or para-Methoxybenzyl, or R⁵ is a solid support, like a Wang
resin, and \( Z \) is \( \text{CO}_2\text{H} \) can be performed by methods known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, Stuttgart, 1994 or T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley, New York, 1999), preferably by reacting the ester of formula 12 with acids, such as hydrochloric acid, trifluoro acetic acid or sulfuric acid or with aqueous bases, such as an alkaline metal - or alkaline earth metal-carbonate or hydroxide, such as sodium, potassium or lithium carbonate or hydroxide or cesium carbonate, optionally in the presence of an additional solvent, such as an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane or an alcohol, such as methanol, ethanol or propanol, or mixtures of solvents. The reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 150°C, more preferably from 20°C to 100 °C. The reaction time is generally from 15 min to 6 days, preferably from 15 min to 16 h, depending on the composition of the mixture and the chosen temperature range. Subsequently, the cyclization of a compound of formula 17 to a compound of formula \( \text{I} \), wherein \( Z \) is \( \text{CO}_2\text{H} \), is generally performed under neat conditions or in an appropriate inert solvent, for example a hydrocarbon or a chlorinated hydrocarbon such as benzene, toluene, chlorobenzene, dichloromethane, dichloroethane, chloroform, or an ether such as tetrahydrofurane, 1,4-dioxane, dibutylether, diisopropylether, methyl-tert-butylether, dimethoxyethane, preferably in the presence of an acid, such as hydrochloric acid or trifluoro acetic acid or sulfuric acid, more preferably in the presence of hydrochloric acid in anhydrous dioxane, the reaction temperature is generally from 0°C to 250°C, preferably from 20°C to 250°C, more preferably from 80°C to 200 °C and the reaction time is generally from 5 min to 6 days, preferably from 5 min to 16 h, depending on the composition of the mixture and the chosen temperature range.

Alternative processes for preparing the compounds are described in the examples and are also part of the invention.
The starting compounds of the formulae 1, 3, 6 and 10 are commercially available or can be prepared by a skilled artisan according to procedures described in the literature.

Another subject of the present invention are the novel intermediates occurring in the synthesis of the compounds of the formula I in any of their stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, and their salts, and solvates of any of them, and their use as intermediates. The invention also includes all tautomeric forms of the said intermediates and starting compounds. All explanations given above and embodiments specified above with respect to the compounds of the formula I apply correspondingly to the said intermediates. Another subject of the invention are in particular the novel specific intermediates disclosed herein. Independently thereof whether they are disclosed as a free compound and/or as a specific salt, they are a subject of the invention both in the form of the free compounds and in the form of their salts, and if a specific salt is disclosed, additionally in the form of this specific salt, and in the form of solvates of any of them.

All reactions used in the above-described syntheses of the compounds of the formula I are per se well known to the skilled person and can be carried out under standard conditions according to, or analogously to, procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. If desired, the obtained compounds of the formula I, as well as any intermediate compounds, can be purified by customary purification procedures, for example by recrystallization or chromatography. As already mentioned, all starting compounds and intermediates employed into the above-described syntheses which contain an acidic or basic group, can also be employed in the form of salts, and all intermediates and final target compounds can also be obtained in the form of salts. As likewise mentioned above, depending on the circumstances of the specific case, in order to avoid an unwanted course of a reaction or side reactions during the synthesis of a compound it can generally be necessary or advantageous to
temporarily block functional groups by introducing protective groups and deprotect them at a later stage of the synthesis, or to introduce functional groups in the form of precursor groups which later are converted into the desired functional groups. As examples of protecting groups amino-protecting groups may be mentioned which can be acyl groups or alkyloxycarbonyl groups, for example a tert-butylloxy carbonyl group (= Boc) which can be removed by treatment with trifluoroacetic acid (= TFA), a benzyloxy carbonyl group which can be removed by catalytic hydrogenation, or a fluoren-9-ylmethoxycarbonyl group which can be removed by treatment with piperidine, and protecting groups of carboxylic acid groups which can be protected as ester groups, such as tert-butyl esters which can be deprotected by treatment with trifluoroacetic acid, or benzyl esters which can be deprotected by catalytic hydrogenation. As an example of a precursor group the nitro group may be mentioned, which can be converted into an amino group by reduction, for example by catalytic hydrogenation, or a furane group, which can be converted to a tetrahydrofurane group for example by catalytic hydrogenation. Such synthesis strategies, and protective groups and precursor groups which are suitable in a specific case, are known to the skilled person.

List of abbreviations:

20 2-bromo-1-ethyl-pyridinium tetrafluoroborate BEP
Bromo-tris-pyrrolidino-phosphoniumhexafluorophosphate PyBoP
Dichloromethane DCM
Diethylamine DEA
4-Dimethylaminopyridine DMAP
N,N-Diisopropylethylamine DIPEA
N,N'-Diisopropylcarbodiimid DIC
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide-Hydrochloride EDC
N,N-Dimethylformamide DMF
Electron spray ionisation Positive mode ESI+ or ESI

30 Ethanol EtOH
Ethyl acetate EtOAc
Heptane Hep
The following examples illustrate the invention.

When example compounds containing a basic group were purified by HPLC on reversed phase (RP) column material, and, as costumary, the eluent was a mixture of water, acetonitrile and trifluoro acetic acid, acetic acid or formic acid, they were in part obtained in the form of the acid addition salt with trifluoro acetic acid, acetic acid or formic acid, depending on the details of the workup such as evaporation or lyophilization conditions. In the names of the example compounds and their formulae any such contained trifluoro acetic acid, acetic acid or formic acid is not specified.

Likewise, when the example compounds containing a basic group were treated with hydrochloric acid during workup, they were in part obtained as their hydrochloric acid salts, depending on further evaporation or lyophilization conditions. In the names of
the example compounds and their formulae any such contained hydrochloric acid is not specified.

Description of the analytical LCMS methods:

1.1.1:
Agilent 1100, Zorbax, 3.5uM, 2’50mm,
A: H2O+0.05%TFA, B: Methanol + 0.05%TFA,
97:3 (Omin) to 80:20(0.2min), and to 0:100 (hold from 3.7min to 4.1 min), and to 97:3 (hold from 4.1 1 to 4.60min)

1.2.1:
Agilent 1100, Zorbax, 3.5uM, 2’50mm,
A: H2O+0.05%TFA, B: Methanol + 0.05%TFA,
97:3 (Omin) to 80:20(0.2min), and to 0:100 (hold from 3.7min to 4.1 min), and to 97:3 (hold from 4.1 1 to 4.60min)
1.0 ml/min / RT

2.1.1:
Javelin C18, 2’20 mm (use two columns), 5u
A: H2O+0.1 %TFA, B: CH3CN + 0.08%TFA,
98:2 (hold from Omin to 0.2min) to 20:80(5.0min), and to 0:100 ( 5.2mins, hold from 5.2min to 5.4min), and to 98:2 (6.2min, hold from 6.2min to 6.4min)
1.0ml/min/RT

3.1.1:
Merck Chromolith FastGrad. RP-1 8e, 50x2mm, 0.05%TFA:AcN+0.05%TFA
98:2(0.2min)to2:98(2.4min)to2:98(3.2min)to98:2(3.3min)to98:2(4min), 2.0ml/min;
2.0ml/min, 50°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1 500

3.2.1:
Merck Chromolith FastGrad. RP-18e, 50x2mm, 0.05%TFA:AcN+0.05%TFA
98:2(0.2min)to2:98(2.4min)to2:98(3.2min)to98:2(3.3min)to98:2(4min), 2.4ml/min.; 2.4ml/min, 50°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

5 Waters UPLC BEH C18 2.1*50 mm; 1.7u, H2O+0.1 %FA:AcN+0.08%FA 95:5 (Omin)to5:95(1.1min)to5:95(1.7min) to 95:5 (1.8min) to 95:5 (2min), 0.9 ml/min 55°C; Waters SQD Single Quadrupol, 0.5s scantime for mass 120-1200

5_1_1:
Waters XBridge C18 4.6*50 mm; 2.5u, H2O+0.1 %FA:AcN+0.08%FA 97:3 (Omin)to 40:60 (3.5 min)to2:98(4min) to2:98(5min) to 97:3 (5.2min) to 97:3 (6.5min); 1.3 ml/min / RT; Waters Ultima Triple Quad MS, 0.75s scantime for mass 100-1200

5_2_1:
Waters XBridge C18 4.6*50 mm; 2.5u, H2O+0.1 %FA:AcN+0.1 %FA 97:3 (Omin)to 40:60 (3.5 min)to2:98(4min) to2:98(5min) to 97:3 (5.2min) to 97:3 (6.5min); 1.3 ml/min 45°C; Waters ZQ Single Quadrupol, 0.5s scantime for mass 100-1200

5_3_1:
Waters XBridge C18 4.6*50,2.5M,H2O+0.05%TFA:AcN+0.05%TFA 95:5(0min)to 95:5(0.2 min)to5:95(2.4min) to5:95(3.2min), to95:5(3.3min) tot95:5(4.0min); 1.7ml/min, 40°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

5_4_1:
Waters XBridge C18 4.6*50,2.5M,H2O+0.05%TFA:AcN+0.05%TFA 95:5(0min)to 95:5(0.2 min)to5:95(2.4min) to5:95(3.5min), to95:5(3.6min) tot95:5(4.5min) , 1.7ml/min, 40°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

5_5_1:
Waters XBridge C18 4.6*50,2.5M,H2O+0.05%TFA:ACN+0.05%TFA 95:5(0min)to 95:5(0.2 min)to5:95(2.4min) to5:95(3.5min), to95:5(3.6min) tot95:5(4.5min) , 1.7ml/min, 50°C; Waters LCT classic TOF -MS, 0.33s scantime for mass 175-1500

5_6_1:
Waters XBridge C18 4.6*50,2.5M,H2O+0.05%TFA:AcN+0.05%TFA
95:5(0min)to5:95(2.6 min)to5:95(3.0min) to95:5(3.1 min) to95:5(4.0min), 1.7ml/min, 40°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

5_7_1:
WatersXBridgeC1 8,4,6*50,2,5M,H2O+0.05%TFA:AcN+0.05%TFA
95:5(0min)to95:5(0.3min)to5:95(3.5 min)to5:95(4min); 1.7ml/min, 40°C; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

6.1.1:

5 YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.05%TFA:AcN+0.05%TFA 95:5
(0min)to5:95(3.7 min); 1ml/min; RT; Waters LCT classic TOF-MS, 8-channel Mux, 0.15s scantime for mass 100-1500

6.2.1:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.1 %FA:AcN+0.08%FA 95:5
(0min)to5:95(2.5 min); 1.3 ml/min RT; Waters Ultima Triple Quad MS, 0.8s scantime for mass 100-1200

6.2.2:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.1 %FA:AcN+0.08%FA 95:5
(0min)to5:95(2.5 min); 1.3 ml/min RT; Waters Ultima Triple Quad MS, 0.5s scantime for mass 100-1200

6.3.1:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.05%TFA:AcN+0.05%TFA 95:5
(0min)to5:95( 2.5 min)to 95:5(3.2min); 1.3 ml/min RT; Waters LCT classic TOF-MS, 0.33s scantime for mass 170-1300

6.4.1:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.05%TFA:AcN+0.05%TFA 95:5
(0min)to5:95(2.5 min); 1.3 ml/min RT; Waters LCT classic TOF-MS, 0.33s scantime for mass 170-1300

6.5.1:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.05%TFA:AcN+0.05%TFA 95:5
(0min)to95:5(0.5min)to5:95(3.5 min)to5:95(4min); 1.3 ml/min RT; Waters LCT classic TOF-MS, 0.33s scantime for mass 175-1500

6.6.1:

YMC-Pack Jsphere H80 33*2.1, 4u, H2O+0.05%TFA:CH3OH+0.05%TFA
98:2(1 min)to5:95(5.0min)to5:95(6.25min); 1.0 ml/min / RT; Waters LCT classic TOF-MS, 8-channel Mux, 0.15s scantime for mass 100-1500

7.1.1:
Column: YMC-Pack Jsphere ODS H80 20 x 2.1 mm, 4um, flow:1.0 ml/min; gradient (eluent A = H2O + 0.05% TFA, eluent B = acetonitrile) from A:B 96:4 to 5:95 in 2.0 min, then 5:95 until 2.4 min, then to 96:4 until 2.45 min; ionization ESI+ (scan for mass 110-1000)

5 8_1_1: Column: Phenomenex 10 x 2 mm, 4 µm; flow: 1.1 ml/min; gradient (eluent A = H2O + 0.05% TFA, eluent B = acetonitrile) from A:B 93:7 to 5:95 in 1.2 min, then 5:95 until 1.4 min, then to 93:7 until 1.45 min; ionization ESI+ (scan for mass 110-1000).

10 Example 1: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cycloheptanecarboxylic acid

![Chemical Structure]

a) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cycloheptanecarboxylic acid methyl ester

15 To a solution of 160 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (The preparation of intermediates is described below) in 3 ml of dry DMF 73 mg of HOAT, 131 mg of EDC and 0.16 ml of DIPEA were added at 0°C. After 15 min 100 mg of methyl 1-amino-cycloheptanecarboxylate-hydrochloride and 0.16 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with saturated
aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by HPLC to yield 200 mg (85%) of 1-
\{(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzimidazole-5-carbonyl]-amino)-cycloheptanecarboxylic acid methyl ester.

C27H35N3O3S (481.66), LCMS (method 3_2_1): R_t = 1.46 min, m/z= 482.26 [M+H]^+

b) 1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-cycloheptanecarboxylic acid

400 mg of 1-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-
carbonyl]-amino)-cycloheptanecarboxylic acid methyl ester were dissolved in 4 ml ethanol and 2 ml THF and 4 ml of 2 M aqueous sodium hydroxide solution were added. After stirring at room temperature over night, the reaction mixture was brought to pH 3 by addition of 2 M aqueous hydrochloric acid and extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulphate and concentrated to yield 100 mg (26%) of 1-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-cycloheptanecarboxylic acid.

C26H33N3O3S (467.63), LCMS (method 3_2_1): R_t = 1.38 min, m/z= 468.21 [M+H]^+

The following examples were prepared in analogy to example 1:
<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]^+</th>
<th>LCMS method</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-methyl-3-phenyl-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>474.1</td>
<td>6_1_1</td>
<td>1.68</td>
</tr>
<tr>
<td>3</td>
<td>(S)-3-Cyclohexyl-2-[[2-cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>468.3</td>
<td>6_1_1</td>
<td>1.87</td>
</tr>
<tr>
<td>4</td>
<td>2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-methyl-3-phenyl-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>490.2</td>
<td>6_4_1</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,3-dimethyl-butyric acid</td>
<td><img src="image" alt="Structure" /></td>
<td>440.7</td>
<td>6_2_2</td>
<td>1.81</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>6</td>
<td>1-[(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-cyclopentanecarboxylic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>438.7</td>
<td>6_2_2</td>
<td>1.75</td>
</tr>
<tr>
<td>7</td>
<td>2-[(1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-2-phenylbutyric acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>490.4</td>
<td>6_4_1</td>
<td>1.55</td>
</tr>
<tr>
<td>8</td>
<td>(S)-3-Cyclohexyl-2-[(1-(1-ethylpropyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>466.3</td>
<td>6_4_1</td>
<td>1.55</td>
</tr>
<tr>
<td>9</td>
<td>(R)-3-Cyclohexyl-2-[(1-(1-ethylpropyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>466.3</td>
<td>6_4_1</td>
<td>1.57</td>
</tr>
<tr>
<td>10</td>
<td>(R)-3-Cyclohexyl-2-[[2-cyclopentylmethyl-1-(1-ethylpropyl)-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>468.3</td>
<td>6_3_1</td>
<td>1.58</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>11</td>
<td>3-Cyclopentyl-2-{{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzimidazole-5-carbonyl] amino}-propionic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>468.3</td>
<td>6_1_1</td>
<td>1.74</td>
</tr>
<tr>
<td>12</td>
<td>2-{{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzimidazole-5-carbonyl] amino}-2,4-dimethyl-pentanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>456.19</td>
<td>6_5_1</td>
<td>2.05</td>
</tr>
<tr>
<td>13</td>
<td>2-{{[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzimidazole-5-carbonyl] amino}-2,4-dimethyl-pentanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>440.21</td>
<td>6_5_1</td>
<td>2.00</td>
</tr>
<tr>
<td>14</td>
<td>2-{{[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzimidazole-5-carbonyl] amino}-2-methyl-4-methylsulfanyl-butyric acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>458.2</td>
<td>6_5_1</td>
<td>1.89</td>
</tr>
<tr>
<td>15</td>
<td>(S)-3-Cyclohexyl-2-{{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzimidazole-5-carbonyl] amino}-propionic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>508.3</td>
<td>5_7_1</td>
<td>3.12</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>16</td>
<td>(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>512.4</td>
<td>5_1_1</td>
<td>4.41</td>
</tr>
<tr>
<td>17</td>
<td>(S)-3-Cyclohexyl-2-[[2-thiophen-2-ylmethyl]-1-(2-trifluoromethyl-cyclohexyl)]-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>562.5</td>
<td>5_2_1</td>
<td>4.75</td>
</tr>
<tr>
<td>18</td>
<td>(S)-2-[(1-1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>442.2</td>
<td>4_1_1</td>
<td>1.19</td>
</tr>
<tr>
<td>19</td>
<td>(S)-2-[(1-1-Ethyl-propyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-3-(4-fluorophenyl)-propionic acid</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>494.3</td>
<td>4_1_1</td>
<td>1.18</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>20</td>
<td>(S)-3-(4-Chlorophenyl)-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>510.2</td>
<td>4_1_1</td>
<td>1.21</td>
</tr>
<tr>
<td>21</td>
<td>(S)-3-Cyclopropyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>440.2</td>
<td>3_1_1</td>
<td>1.42</td>
</tr>
<tr>
<td>22</td>
<td>(S)-3-Cyclobutyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>454.2</td>
<td>3_1_1</td>
<td>1.49</td>
</tr>
<tr>
<td>23</td>
<td>(S)-3-Cyclobutyl-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>480.2</td>
<td>3_1_1</td>
<td>1.56</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>24</td>
<td>1-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexancarboxylic acid</td>
<td>![Structure Image]</td>
<td>454.3</td>
<td>6_6_1</td>
<td>2.87</td>
</tr>
<tr>
<td>25</td>
<td>2-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-methyl-pentanoic acid</td>
<td>![Structure Image]</td>
<td>442.3</td>
<td>6_6_1</td>
<td>2.84</td>
</tr>
<tr>
<td>26</td>
<td>2-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5,5,5-trifluoropentanoic acid</td>
<td>![Structure Image]</td>
<td>482.1</td>
<td>3_1_1</td>
<td>1.46</td>
</tr>
<tr>
<td>27</td>
<td>5,5,5-Trifluoro-2-[[1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td>![Structure Image]</td>
<td>508.1</td>
<td>3_1_1</td>
<td>1.54</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>28</td>
<td>2-{{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl[-amino]-4-phenyl-butyric acid}</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>490.3</td>
<td>6_6_1</td>
<td>3.04</td>
</tr>
<tr>
<td>29</td>
<td>3-{(4,4-Dimethyl-cyclohexyl)-2-{{1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl[-amino]-propionic acid}</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>510.3</td>
<td>3_1_1</td>
<td>1.68</td>
</tr>
<tr>
<td>30</td>
<td>3-{(4-Ethyl-phenyl)-2-{{1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl[-amino]-propionic acid}</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>504.2</td>
<td>3_1_1</td>
<td>1.57</td>
</tr>
<tr>
<td>31</td>
<td>2-{{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl[-amino]-3-(4-trifluoromethyl-phenyl)-propionic acid}</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>544.2</td>
<td>4_1_1</td>
<td>1.24</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>32</td>
<td>(S)-3-[(3,4-Dichloro-phenyl)-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>544.2</td>
<td>4_1_1</td>
<td>1.25</td>
</tr>
<tr>
<td>33</td>
<td>3-[(4,4-Dimethyl-cyclohexyl)-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>536.3</td>
<td>3_1_1</td>
<td>1.73</td>
</tr>
<tr>
<td>34</td>
<td>1-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-cyclohexanecarboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>466.3</td>
<td>5_2_1</td>
<td>4.22</td>
</tr>
<tr>
<td>35</td>
<td>4-Methyl-1-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexanecarboxylic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>494.2</td>
<td>3_1_1</td>
<td>1.55</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>36</td>
<td>2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-(4-methyl-cyclohexyl)-propionic acid</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>496.3</td>
<td>3_1_1</td>
<td>1.62</td>
</tr>
<tr>
<td>37</td>
<td>(S)-3-Cyclohexyl-2-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>509.2</td>
<td>4_1_1</td>
<td>1.26</td>
</tr>
<tr>
<td>38</td>
<td>1-[[1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexanecarboxylic acid</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>478.5</td>
<td>4_1_1</td>
<td>1.27</td>
</tr>
<tr>
<td>39</td>
<td>3-Cycloheptyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>496.4</td>
<td>4_1_1</td>
<td>1.32</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>Rₜ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>40</td>
<td>3-Cycloheptyl-2-{[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>522.6</td>
<td>4_1_1</td>
<td>1.37</td>
</tr>
<tr>
<td>41</td>
<td>3-{[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-4-methyl-pentanoic acid</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>426.2</td>
<td>6_1_1</td>
<td>1.43</td>
</tr>
<tr>
<td>42</td>
<td>3-{[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-3-phenyl-propionic acid</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>460.3</td>
<td>6_1_1</td>
<td>1.50</td>
</tr>
<tr>
<td>43</td>
<td>3-{[2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino}-3-phenyl-propionic acid</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>462.2</td>
<td>6_1_1</td>
<td>1.62</td>
</tr>
<tr>
<td>44</td>
<td>3-Cyclohexyl-3-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-propionic acid</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>482.4</td>
<td>6_1_1</td>
<td>1.70</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>45</td>
<td>3-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>456.1</td>
<td>5_7_1</td>
<td>2.71</td>
</tr>
<tr>
<td>46</td>
<td>4-Cyclohexyl-3-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>496.2</td>
<td>5_7_1</td>
<td>2.93</td>
</tr>
<tr>
<td>47</td>
<td>3-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5,5-dimethyl-hexanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>470.1</td>
<td>5_7_1</td>
<td>2.78</td>
</tr>
<tr>
<td>48</td>
<td>(R)-3-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>456.2</td>
<td>5_7_1</td>
<td>2.75</td>
</tr>
<tr>
<td>49</td>
<td>(S)-3-[[1-(1-Ethylpropyl)-2-pyrazol-1-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>440.2</td>
<td>5_3_1</td>
<td>1.96</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>Rₜ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>50</td>
<td>(S)-3-[[1-(1-Ethylpropyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>457.1</td>
<td>5_3_1</td>
<td>1.88</td>
</tr>
<tr>
<td>51</td>
<td>4-Cyclohexyl-3-[[1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>522.3</td>
<td>5_3_1</td>
<td>2.29</td>
</tr>
<tr>
<td>52</td>
<td>4-Cyclohexyl-3-[[1-((1S,2S)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>522.2</td>
<td>5_5_1</td>
<td>2.25</td>
</tr>
<tr>
<td>53</td>
<td>(3R,4S)-4-Methyl-3-[[1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>482.3</td>
<td>5_5_1</td>
<td>2.12</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>54</td>
<td>(3R,4S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-hexanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>454.1</td>
<td>5_2_1</td>
<td>3.94</td>
</tr>
<tr>
<td>55</td>
<td>3-[[1-((1R,2R)-2-Methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>468.3</td>
<td>5_5_1</td>
<td>2.06</td>
</tr>
<tr>
<td>56</td>
<td>3-[[1-((1R,2R)-2-Methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>480.1</td>
<td>5_2_1</td>
<td>4.33</td>
</tr>
<tr>
<td>57</td>
<td>3-Cyclohexyl-3-[[1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>508.3</td>
<td>3_2_1</td>
<td>1.50</td>
</tr>
<tr>
<td>58</td>
<td>3-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-heptanoic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>484.2</td>
<td>3_1_1</td>
<td>1.52</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>59</td>
<td>4-Ethyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl][-amino]-hexanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>470.4</td>
<td>4_1_1</td>
<td>1.20</td>
</tr>
<tr>
<td>60</td>
<td>(S)-4-Cyclopentyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl][-amino]-butyric acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>482.3</td>
<td>3_1_1</td>
<td>1.55</td>
</tr>
<tr>
<td>61</td>
<td>(S)-4-Cyclopentyl-3-[(1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl][-amino]-butyric acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>508.3</td>
<td>3_1_1</td>
<td>1.60</td>
</tr>
<tr>
<td>62</td>
<td>3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl][-amino]-2,2,5-trimethyl-hexanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>484.3</td>
<td>6_6_1</td>
<td>3.04</td>
</tr>
<tr>
<td>63</td>
<td>3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl][-amino]-2,2-dimethyl-hexanoic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>470.3</td>
<td>6_6_1</td>
<td>2.87</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>64</td>
<td>(1-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexyl)-acetic acid</td>
<td><img src="image64.png" alt="Structure" /></td>
<td>468.3</td>
<td>6_6_1</td>
<td>2.85</td>
</tr>
<tr>
<td>65</td>
<td>4-Cyclohexyl-3-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid</td>
<td><img src="image65.png" alt="Structure" /></td>
<td>523.3</td>
<td>4_1_1</td>
<td>1.24</td>
</tr>
<tr>
<td>66</td>
<td>(1-[[1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-cyclohexyl)-acetic acid</td>
<td><img src="image66.png" alt="Structure" /></td>
<td>494.3</td>
<td>4_1_1</td>
<td>1.26</td>
</tr>
<tr>
<td>67</td>
<td>(2R,3S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-methyl-hexanoic acid</td>
<td><img src="image67.png" alt="Structure" /></td>
<td>472.4</td>
<td>4_1_1</td>
<td>1.19</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>68</td>
<td>(2S,3S)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-methyl-hexanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>472.3</td>
<td>4_1_1</td>
<td>1.20</td>
</tr>
<tr>
<td>69</td>
<td>(R)-6-Methyl-4-[[2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>550.5</td>
<td>5_2_1</td>
<td>4.57</td>
</tr>
<tr>
<td>70</td>
<td>(R)-6-Methyl-4-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>496.3</td>
<td>5_5_1</td>
<td>2.14</td>
</tr>
<tr>
<td>71</td>
<td>(4R,5S)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-heptanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>470.2</td>
<td>6_6_1</td>
<td>2.89</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>Rᵣ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>72</td>
<td>(4R,5S)-5-Methyl-4-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>496.3</td>
<td>3_1_1</td>
<td>1.55</td>
</tr>
<tr>
<td>73</td>
<td>(3R,4S)-5-Cyclohexyl-4-[[1-((1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>526.3</td>
<td>5_2_1</td>
<td>4.30</td>
</tr>
<tr>
<td>74</td>
<td>(3R,4S)-5-Cyclohexyl-3-hydroxy-4-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>552.5</td>
<td>4_1_1</td>
<td>1.27</td>
</tr>
<tr>
<td>75</td>
<td>(3S,4S)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-methyl-heptanoic acid</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>486.4</td>
<td>4_1_1</td>
<td>1.20</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>76</td>
<td>(3R,4S)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-methyl-heptanoic acid</td>
<td><img src="image" alt="Structure 76" /></td>
<td>486.4</td>
<td>4_1_1</td>
<td>1.20</td>
</tr>
<tr>
<td>77</td>
<td>(3R,4S)-3-Hydroxy-6-methyl-4-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image" alt="Structure 77" /></td>
<td>512.4</td>
<td>4_1_1</td>
<td>1.25</td>
</tr>
<tr>
<td>78</td>
<td>(3S,4S)-3-Hydroxy-6-methyl-4-[[1-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td><img src="image" alt="Structure 78" /></td>
<td>512.4</td>
<td>4_1_1</td>
<td>1.25</td>
</tr>
<tr>
<td>79</td>
<td>(3S,4S)-5-Cyclohexyl-4-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid</td>
<td><img src="image" alt="Structure 79" /></td>
<td>526.4</td>
<td>4_1_1</td>
<td>1.27</td>
</tr>
</tbody>
</table>
Example 80: (S)-2-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid

![Chemical Structure]

a) (S)-2-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid tert-butyl ester

To a solution of 55 mg of 1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carboxylic acid in 1 ml of dry DMF 26 mg of HOBT, 37 mg of EDC and 0.05 ml of DIPEA were added at 0°C. After 15 min 100 mg of L-leucine tert-butyl ester-hydrochloride and 0.05 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. 75 mg (88%) of (S)-2-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid tert-butyl ester were obtained.

C28H43N3O3 (485.67), LCMS (method 7_1_1): Rt = 1.30 min, m/z= 486.45 [M+H]^+

b) (S)-2-[(1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid
75 mg of (S)-2-[[1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid tert-butyl ester were dissolved in 0.6 ml dichloromethane and 0.18 µl of trifluoroacetic acid were added. After stirring at room temperature over night the reaction mixture was concentrated. The residue was dissolved in 1 M aqueous sodium hydroxide solution, and precipitated by addition of 2 M aqueous hydrochloric acid. The solid was taken up in ethyl acetate, dried over sodium sulphate and concentrated. The obtained residue was precipitated by addition of pentane. 23 mg (35%) of (S)-2-[[1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid were obtained.

C24H35N3O4 (429.26), LCMS (method 6_3_1): Rt = 1.28 min, m/z= 430.24 [M+H]+

The following examples were prepared in analogy to example 80:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]+</th>
<th>LCMS method</th>
<th>Rt [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td></td>
<td>426.2</td>
<td>6_4_1</td>
<td>1.43</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>Rₜ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>82</td>
<td>(S)-2-[(2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>476.2</td>
<td>6_3_1</td>
<td>1.53</td>
</tr>
<tr>
<td>83</td>
<td>(S)-2-[(1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>468.1</td>
<td>6_3_1</td>
<td>1.51</td>
</tr>
<tr>
<td>84</td>
<td>(S)-2-[(1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>443.2</td>
<td>6_3_1</td>
<td>1.28</td>
</tr>
<tr>
<td>85</td>
<td>(2S,3S)-2-[(1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>443.2</td>
<td>6_3_1</td>
<td>1.21</td>
</tr>
<tr>
<td>86</td>
<td>(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>452.2</td>
<td>6_3_1</td>
<td>1.49</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>87</td>
<td>(S)-4-Methyl-2-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>522.2</td>
<td>6_6_1</td>
<td>3.22</td>
</tr>
<tr>
<td>88</td>
<td>(S)-2-[(2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>508.4</td>
<td>5_2_1</td>
<td>4.37</td>
</tr>
<tr>
<td>89</td>
<td>(S)-3-Phenyl-2-[(2-thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>556.4</td>
<td>5_2_1</td>
<td>4.52</td>
</tr>
<tr>
<td>90</td>
<td>(S)-4-Methyl-2-[(1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>454.2</td>
<td>6_6_1</td>
<td>2.93</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z  [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>91</td>
<td>(S)-2-[[1-((1R,2R)-2-Methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>454.2</td>
<td>6_6_1</td>
<td>2.90</td>
</tr>
<tr>
<td>92</td>
<td>(2S,3S)-3-Methyl-2-[[1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>468.2</td>
<td>5_5_1</td>
<td>2.12</td>
</tr>
<tr>
<td>93</td>
<td>(S)-2-[[1-(2-Ethylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>482.3</td>
<td>5_5_1</td>
<td>2.18</td>
</tr>
<tr>
<td>94</td>
<td>(S)-2-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>426.2</td>
<td>4_1_1</td>
<td>1.16</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>95</td>
<td>(S)-3-[[1-{1-Ethylpropyl}-2-thiophen-2-ylimethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>456.2</td>
<td>6_3_1</td>
<td>1.39</td>
</tr>
<tr>
<td>96</td>
<td>(S)-3-[[1-{1-Ethylpropyl}-2-furan-2-ylimethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>440.3</td>
<td>6_4_1</td>
<td>1.39</td>
</tr>
<tr>
<td>97</td>
<td>(S)-3-[(1-Cyclohexylmethyl)-2-thiophen-2-ylimethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>482.1</td>
<td>6_3_1</td>
<td>1.50</td>
</tr>
<tr>
<td>98</td>
<td>(S)-3-[[1-{1-Ethylpropyl}-2-thiazol-4-ylimethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>457.2</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>99</td>
<td>(S)-3-[[2-Furan-2-ylimethyl-1-(2-methylcyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>466.2</td>
<td>6_3_1</td>
<td>1.47</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>100</td>
<td>(S)-3-[[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-phenylbutyric acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>490.1</td>
<td>5_7_1</td>
<td>2.70</td>
</tr>
<tr>
<td>101</td>
<td>(S)-5-Methyl-3-[[1-(2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>961.6</td>
<td>5_1_1</td>
<td>4.44</td>
</tr>
<tr>
<td>102</td>
<td>(S)-5-Methyl-3-[[2-thiophen-2-ylmethyl-1-(2-trifluoromethylcyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>536.5</td>
<td>5_2_1</td>
<td>4.52</td>
</tr>
<tr>
<td>103</td>
<td>(S)-4-Phenyl-3-[[2-thiophen-2-ylmethyl-1-(2-trifluoromethylcyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-butyric acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>570.5</td>
<td>5_2_1</td>
<td>4.49</td>
</tr>
</tbody>
</table>
Example 107: (S)-3-\{1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl\}-amino\}-5-methyl-hexanoic acid

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]^+</th>
<th>LCMS method</th>
<th>R_t [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>(S)-5-Methyl-3-{[1-(2-methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]}-amino}-5-methyl-hexanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>468.2</td>
<td>5_3_1</td>
<td>2.07</td>
</tr>
<tr>
<td>105</td>
<td>(S)-3-{[1-(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]}-amino}-5-methyl-hexanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>441.4</td>
<td>4_1_1</td>
<td>1.12</td>
</tr>
<tr>
<td>106</td>
<td>(S)-5-Methyl-3-{[1-(1R,2R)-2-methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carbonyl]}-amino}-5-methyl-hexanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>483.3</td>
<td>4_1_1</td>
<td>1.17</td>
</tr>
</tbody>
</table>

Example 107: (S)-3-\{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-5-methyl-hexanoic acid

5 To 300 mg of Wang resin (NovaBioChem 70-90 mesh, loading capacity 1.3 mmol/g), 430 mg of (S)-3-(9H-Fluoren-9-ylmethoxycarbonylamino)-5-methyl-hexanoic acid, 173 mg of DIC, and 14 mg of DMAP were added in DMF in a 20 ml scintillation
bottle. The reaction was kept at rt for 18 h. To deprotect the Fmoc-group 50% Piperidine in DMF was added and the reaction was kept for 30 min at rt. Afterwards the resin was washed thoroughly with DMF. For the amide formation the resin was reacted with 217 mg 4-Fluoro-3-nitrobenzoic acid, 185 mg HOBt, and 173 mg DIC in DMF for 18 h at rt. In the next step nucophilic substitution was achieved by reacting the resin with 680 mg of 1-Ethyl-propylamine in DMF at rt for 24 h. Subsequently, the reduction of the nitro group took place by reaction with 10 ml of 1M SnCl2 in DMF at rt for 23 h. Then, to the resin in dry DMF were added 139 mg 2-thiényl acetic acid, 371 mg of HATU and 250 mg of DIPEA and the reaction was left at rt for 4 h to achieve amide formation. The cleavage from the resin took place by reaction with 3 ml of 95% aqueous TFA for 2 hrs. Then additional 2 ml of aqueous of 95% TFA, 3 ml of acetonitrile and 3 ml water were added and the cleavage solution was heated to 60°C for 24 h. After filtration the solvents were removed and the resulting residue was purified by HPLC to afford 37 mg (8%) of (S)-3-[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid.

C25H33N3O3S (455.62), LCMS (method 6_1_1 ) : Rt = 1.62 min, m/z= 456.40 [M+H]+

The following examples were prepared in analogy to example 107:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]+</th>
<th>LCMS method</th>
<th>Rt [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>(S)-2-[(1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image.png" alt="Structure" /></td>
<td>454.2</td>
<td>2_1_1</td>
<td>3.81</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>109</td>
<td>(S)-2-[[2-Cyclopentylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>428.3</td>
<td>2_1_1</td>
<td>3.11</td>
</tr>
<tr>
<td>110</td>
<td>(S)-2-[[1-Cyclopentyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>440.3</td>
<td>2_1_1</td>
<td>2.78</td>
</tr>
<tr>
<td>111</td>
<td>(S)-2-[[1-Cycloheptyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>468.3</td>
<td>2_1_1</td>
<td>3.08</td>
</tr>
<tr>
<td>112</td>
<td>(S)-2-[[1-Cyclohexyl-2-cyclopentylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>400.3</td>
<td>2_1_1</td>
<td>3.08</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>113</td>
<td>(S)-4-Methyl-2-[[1-(2-methyl-butyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>442.3</td>
<td>2_1_1</td>
<td>2.89</td>
</tr>
<tr>
<td>114</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>442.3</td>
<td>2_1_1</td>
<td>2.79</td>
</tr>
<tr>
<td>115</td>
<td>(S)-4-Methyl-2-[[2-thiophen-2-ylmethyl-1-p-tolyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>462.3</td>
<td>2_1_1</td>
<td>3.02</td>
</tr>
<tr>
<td>116</td>
<td>(S)-2-[[2-Benzyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>436.2</td>
<td>2_1_1</td>
<td>4.11</td>
</tr>
<tr>
<td>117</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>3.30</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>118</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>426.2</td>
<td>2_1_1</td>
<td>3.13</td>
</tr>
<tr>
<td>119</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-(5-methyl-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>456.2</td>
<td>2_1_1</td>
<td>4.27</td>
</tr>
<tr>
<td>120</td>
<td>(S)-2-[[2-Cyclohexylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>3.58</td>
</tr>
<tr>
<td>121</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>3.23</td>
</tr>
<tr>
<td>122</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-butyric acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>428.2</td>
<td>2_1_1</td>
<td>3.02</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>123</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methylsulfanyl-butryic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>460.2</td>
<td>2_1_1</td>
<td>3.08</td>
</tr>
<tr>
<td>124</td>
<td>(S)-2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-phenyl-propionic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>476.3</td>
<td>2_1_1</td>
<td>3.33</td>
</tr>
<tr>
<td>125</td>
<td>(S)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>482.3</td>
<td>2_1_1</td>
<td>3.71</td>
</tr>
<tr>
<td>126</td>
<td>2-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4,4-dimethyl-pentanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>456.2</td>
<td>2_1_1</td>
<td>3.43</td>
</tr>
<tr>
<td>127</td>
<td>(S)-2-[[1-Isobutyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>428.2</td>
<td>2_1_1</td>
<td>3.86</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>$m/z$ [M+H]$^+$</td>
<td>LCMS method</td>
<td>$R_t$ [min]</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>128</td>
<td>(S)-2-[(2-Cyclopentylmethyl-1-isobutyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>414.3</td>
<td>1_1_1</td>
<td>3.29</td>
</tr>
<tr>
<td>129</td>
<td>(S)-2-[(2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>428.2</td>
<td>2_1_1</td>
<td>4.24</td>
</tr>
<tr>
<td>130</td>
<td>(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-5-methyl-hexanoic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>456.2</td>
<td>2_1_1</td>
<td>4.32</td>
</tr>
<tr>
<td>131</td>
<td>(S)-2-[(2-Furan-3-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>452.2</td>
<td>2_1_1</td>
<td>4.18</td>
</tr>
<tr>
<td>132</td>
<td>(S)-4-Methyl-2-[(1-phenyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>448.2</td>
<td>2_1_1</td>
<td>4.12</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>( m/z_{[M+H]^+} )</td>
<td>LCMS method</td>
<td>( R_t ) [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>133</td>
<td>(S)-3-Cyclohexyl-2-[[2-cyclohexylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>482.3</td>
<td>2_1_1</td>
<td>5.10</td>
</tr>
<tr>
<td>134</td>
<td>(S)-3-Cyclohexyl-2-[[2-cyclohexylmethyl-1-isobutyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>468.3</td>
<td>2_1_1</td>
<td>4.87</td>
</tr>
<tr>
<td>135</td>
<td>(S)-2-[[2-Cyclohexylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>4.60</td>
</tr>
<tr>
<td>136</td>
<td>(S)-4-Methyl-2-[[1-phenyl-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>448.2</td>
<td>2_1_1</td>
<td>4.04</td>
</tr>
<tr>
<td>137</td>
<td>(S)-4-Methyl-2-[[1-(2-methyl-butyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>4.14</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>138</td>
<td>(S)-2-[(1-(\text{Cyclohexyl-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl})-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1.png" alt="Structure 138" /></td>
<td>438.3</td>
<td>6_6_1</td>
<td>2.84</td>
</tr>
<tr>
<td>139</td>
<td>(S)-4-Methyl-2-[[1-(2-methyl-cyclohexyl)-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid</td>
<td><img src="image2.png" alt="Structure 139" /></td>
<td>468.2</td>
<td>2_1_1</td>
<td>4.40</td>
</tr>
<tr>
<td>140</td>
<td>(S)-2-[(1-sec-Butyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-3-cyclohexyl-propionic acid</td>
<td><img src="image3.png" alt="Structure 140" /></td>
<td>468.2</td>
<td>2_1_1</td>
<td>4.41</td>
</tr>
<tr>
<td>141</td>
<td>(S)-3-Cyclohexyl-2-[[2-cyclohexylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image4.png" alt="Structure 141" /></td>
<td>482.3</td>
<td>2_1_1</td>
<td>5.00</td>
</tr>
<tr>
<td>142</td>
<td>(S)-2-[(1-sec-Butyl-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image5.png" alt="Structure 142" /></td>
<td>428.2</td>
<td>2_1_1</td>
<td>3.82</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>143</td>
<td>(S)-2-(((2-Benzyl-1-(2-methylcyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino)-4-methyl-pentanoic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>462.2</td>
<td>2_1_1</td>
<td>4.47</td>
</tr>
<tr>
<td>144</td>
<td>(S)-4-Methyl-2-(((1-(2-methylcyclohexyl))-2-(5-methyl-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino)-pentanoic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>482.2</td>
<td>2_1_1</td>
<td>4.65</td>
</tr>
<tr>
<td>145</td>
<td>(S)-3-Cyclohexyl-2-(((1-(2-methylbutyl))-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino)-propionic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>482.2</td>
<td>2_1_1</td>
<td>4.71</td>
</tr>
<tr>
<td>146</td>
<td>(S)-4-Methyl-2-(((1-(2-methylcyclohexyl))-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino)-pentanoic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>468.2</td>
<td>6_3_1</td>
<td>1.50</td>
</tr>
<tr>
<td>147</td>
<td>(S)-2-(((1-sec-Butyl-2-thiophen-2-ylmethyl)-1H-benzoimidazole-5-carbonyl)-amino)-4-methyl-pentanoic acid</td>
<td><img src="image5" alt="Structure" /></td>
<td>428.2</td>
<td>2_1_1</td>
<td>3.81</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>148</td>
<td>(S)-2-[(2-Benzyl-1-cyclohexyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>448.2</td>
<td>2_1_1</td>
<td>4.31</td>
</tr>
<tr>
<td>149</td>
<td>(S)-2-[(1-sec-Butyl-2-cyclopentylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>414.2</td>
<td>2_1_1</td>
<td>4.03</td>
</tr>
<tr>
<td>150</td>
<td>(S)-2-[(2-Cyclopentylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>454.3</td>
<td>2_1_1</td>
<td>4.61</td>
</tr>
<tr>
<td>151</td>
<td>(S)-3-Cyclohexyl-2-[[1-(1-ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>470.2</td>
<td>2_1_1</td>
<td>2.90</td>
</tr>
<tr>
<td>152</td>
<td>(S)-2-[(1-Cyclohexyl-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-4-methyl-pentanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>454.2</td>
<td>2_1_1</td>
<td>4.23</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]&lt;sup&gt;+&lt;/sup&gt;</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>153</td>
<td>(2S,3R)-2-[(1-(1-Ethyl-propyl))-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>3.95</td>
</tr>
<tr>
<td>154</td>
<td>(S)-3-[(1-(1-Ethyl-propyl))-2-furan-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>440.3</td>
<td>6_6_1</td>
<td>2.75</td>
</tr>
<tr>
<td>155</td>
<td>3-[(1-(1-Ethyl-propyl))-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>3.75</td>
</tr>
<tr>
<td>156</td>
<td>(S)-3-[(1-(1-Ethyl-propyl))-2-thiophen-3-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>456.2</td>
<td>2_1_1</td>
<td>4.02</td>
</tr>
<tr>
<td>157</td>
<td>(S)-3-[(2-Benzyl-1-(1-ethyl-propyl))-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>450.4</td>
<td>6_6_1</td>
<td>2.89</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS Method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>158</td>
<td>(S)-3-[[2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>4.23</td>
</tr>
<tr>
<td>159</td>
<td>(S)-3-[[2-Cyclopentylmethyl-1-(2-methyl-butyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>443.3</td>
<td>2_1_1</td>
<td>4.37</td>
</tr>
<tr>
<td>160</td>
<td>(S)-3-[[1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>444.2</td>
<td>2_1_1</td>
<td>3.66</td>
</tr>
<tr>
<td>161</td>
<td>(R)-3-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>442.2</td>
<td>2_1_1</td>
<td>2.53</td>
</tr>
<tr>
<td>162</td>
<td>(R)-4-[[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-methyl-hexanoic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>456.2</td>
<td>2_1_1</td>
<td>3.79</td>
</tr>
</tbody>
</table>
Example 164: (S)-2-[(1-isopropyl-2-methyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid

To a solution of 469 mg of thiophen-2-yl-acetic acid in 7.5 ml of dry DMF 449 mg of HOAT, 633 mg of EDC and 0.75 ml of DIPEA were added at 0°C. After 30 min 1259 mg of (S)-2-[3-Amino-4-(1-isopropyl-2-methyl-propylamino)-benzoylamin]-4-methyl-pentanoic acid tert-butyl ester and 0.75 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by HPLC to yield 250 mg (15%) (S)-
2-[4-(1-lsopropyl-2-methyl-propylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

C30H45N3O4S (543.77), LCMS (method 6_3_1): Rt = 2.35 min, m/z= 544.27 [M+H]^+

b) (S)-2-[(1-(1-lsopropyl-2-methyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid

80 mg of (S)-2-[4-(1-lsopropyl-2-methyl-propylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester and 2 mL of hydrochloric acid (4M in dioxin) were heated in a microwave reactor for 2 min to 100°C and for 15 min to 130°C. The reaction was then concentrated in vacuo and the resulting residue purified by HPLC to obtain 3 mg (4%) of (S)-2-[(1-(1-lsopropyl-2-methyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid.

C26H35N3O3S (469.65), LCMS (method 6_3_1): Rt = 1.50 min, m/z= 470.23 [M+H]^+

The following examples were prepared in analogy to example 164:
<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]^+</th>
<th>LCMS method</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>(S)-2-[[1-(2-Chloro-phenyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>482.1</td>
<td>6_3_1</td>
<td>1.66</td>
</tr>
<tr>
<td>166</td>
<td>(S)-2-[[1-(1,3-Dimethyl-butyl)-2-thiophen-2-ylmethyl]-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>456.2</td>
<td>6_3_1</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Example 167: 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((S)-1-cyclohexylmethyl-2-hydroxy-ethyl)-amide

![Chemical Structure](image3.png)

47 mg of (S)-2-amino-3-cyclohexyl-propan-1-ol and 0.14 mL DIPEA were dissolved in 2 mL dry THF. The mixture was cooled to -10 °C and 67 mg of 2-cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carbonyl chloride in 1 mL of dry THF were added. The mixture was stirred under exclusion of moisture for 15 min at -10°C and then at RT over night. It was then filtered, the filter was washed with 10 mL ethyl acetate. The filtrate was evaporated, the residue was taken up in 20 mL ethyl acetate and extracted with 20 mL 5% NaHCO3. The organic phase was dried and evaporated and the residue was purified by HPLC to yield 24 mg (27%) of 2-cyclopentylmethyl-1-
The following examples were prepared in analogy to example 167:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z</th>
<th>LCMS method</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>168</td>
<td>1-Cyclohexyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-cyclohexylmethyl-2-hydroxy-ethyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>453.2</td>
<td>2_1_1</td>
<td>2.84</td>
</tr>
<tr>
<td>169</td>
<td>2-Cyclopentylmethyl-1-[(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (1-carbamoyl-3-methyl-butyl)]-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>427.3</td>
<td>6_3_1</td>
<td>1.35</td>
</tr>
<tr>
<td>170</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (carbamoyl-phenyl-methyl)]-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>461.2</td>
<td>6_3_1</td>
<td>1.33</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>171</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-carbamoyl-3-methyl-butyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>441.3</td>
<td>6_1_1</td>
<td>1.56</td>
</tr>
<tr>
<td>172</td>
<td>1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-carbamoyl-3-methyl-butyl)-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>442.4</td>
<td>6_1_1</td>
<td>1.24</td>
</tr>
<tr>
<td>173</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-carbamoyl-2-cyclohexyl-ethyl)-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>481.5</td>
<td>6_2_1</td>
<td>1.98</td>
</tr>
<tr>
<td>174</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-carbamoylmethyl-3-methyl-butyl)-amide</td>
<td><img src="image4" alt="Structure" /></td>
<td>455.2</td>
<td>6_3_1</td>
<td>1.34</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>175</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (S)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>414.2</td>
<td>6_3_1</td>
<td>1.42</td>
</tr>
<tr>
<td>176</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (R)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>414.3</td>
<td>6_3_1</td>
<td>1.42</td>
</tr>
<tr>
<td>177</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (S)-1-cyclohexylmethyl-2-hydroxy-ethyl)-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>468.2</td>
<td>6_4_1</td>
<td>1.58</td>
</tr>
<tr>
<td>178</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (S)-1-hydroxymethyl-3-methylsulfanyl-propyl)-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>432.2</td>
<td>6_3_1</td>
<td>1.30</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>179</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (1-hydroxymethyl-cyclopentyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>412.2</td>
<td>6_3_1</td>
<td>1.38</td>
</tr>
<tr>
<td>180</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((1S,2S)-1-hydroxymethyl-2-methyl-butyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>414.3</td>
<td>6_3_1</td>
<td>1.41</td>
</tr>
<tr>
<td>181</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (1-hydroxymethyl-butyl)-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>400.3</td>
<td>6_3_1</td>
<td>1.32</td>
</tr>
<tr>
<td>182</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid (1-hydroxymethyl-pentyl)-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>414.3</td>
<td>6_3_1</td>
<td>1.39</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>183</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((R)-1-hydroxymethyl-pentyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>414.3</td>
<td>6_3_1</td>
<td>1.39</td>
</tr>
<tr>
<td>184</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-pentyl)-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>414.3</td>
<td>6_3_1</td>
<td>1.40</td>
</tr>
<tr>
<td>185</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((R)-1-hydroxymethyl-butyl)-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>400.3</td>
<td>6_3_1</td>
<td>1.32</td>
</tr>
<tr>
<td>186</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-butyl)-amide</td>
<td><img src="image4" alt="Structure" /></td>
<td>400.3</td>
<td>6_3_1</td>
<td>1.33</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>187</td>
<td>2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-2-methyl-propyl)-amide</td>
<td><img src="image1.png" alt="Structure 187" /></td>
<td>400.3</td>
<td>6_1_1</td>
<td>1.51</td>
</tr>
<tr>
<td>188</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-3-methylsulfanyl-propyl)-amide</td>
<td><img src="image2.png" alt="Structure 188" /></td>
<td>446.2</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>189</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-hydroxymethyl-2-methyl-propyl)-amide</td>
<td><img src="image3.png" alt="Structure 189" /></td>
<td>414.2</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>190</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-2-methyl-propyl)-amide</td>
<td><img src="image4.png" alt="Structure 190" /></td>
<td>414.2</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>191</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((R)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>428.2</td>
<td>6_3_1</td>
<td>1.35</td>
</tr>
<tr>
<td>192</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-2,2-dimethyl-propyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>428.2</td>
<td>6_3_1</td>
<td>1.32</td>
</tr>
<tr>
<td>193</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-hydroxymethyl-cyclopentyl)-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>426.2</td>
<td>6_3_1</td>
<td>1.30</td>
</tr>
<tr>
<td>194</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((1S,2S)-1-hydroxymethyl-2-methyl-butyl)-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>428.2</td>
<td>6_3_1</td>
<td>1.34</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>195</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>446.5</td>
<td>6_2_1</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>((R)-1-hydroxymethyl-3-methylsulfanyl-propyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>196</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>414.1</td>
<td>6_3_1</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>(1-hydroxymethyl-butyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>197</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>428.2</td>
<td>6_3_1</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>(1-hydroxymethyl-pentyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>198</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>428.2</td>
<td>6_3_1</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>((R)-1-hydroxymethyl-pentyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>199</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-pentyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>428.3</td>
<td>6_1_1</td>
<td>1.61</td>
</tr>
<tr>
<td>200</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((R)-1-hydroxymethyl-butyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>414.2</td>
<td>6_1_1</td>
<td>1.48</td>
</tr>
<tr>
<td>201</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-butyl)-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>414.2</td>
<td>6_1_1</td>
<td>1.51</td>
</tr>
<tr>
<td>202</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>448.2</td>
<td>6_1_1</td>
<td>1.58</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>203</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>454.3</td>
<td>6_1_1</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>((R)-1-cyclohexyl-2-hydroxy-ethyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>204</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>454.3</td>
<td>6_1_1</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>((S)-1-cyclohexyl-2-hydroxy-ethyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>205</td>
<td>1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>429.4</td>
<td>6_1_1</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td>((S)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>206</td>
<td>1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>443.4</td>
<td>6_1_1</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>((S)-1-methoxymethyl-3-methyl-butyl)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>207</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-methoxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>442.4</td>
<td>6_1_1</td>
<td>1.74</td>
</tr>
<tr>
<td>208</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-ethoxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>456.2</td>
<td>6_4_1</td>
<td>1.60</td>
</tr>
<tr>
<td>209</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>428.2</td>
<td>6_4_1</td>
<td>1.38</td>
</tr>
<tr>
<td>210</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-butoxyymethyl-3-methyl-butyl)-amide</td>
<td><img src="image4" alt="Structure" /></td>
<td>484.2</td>
<td>6_4_1</td>
<td>1.56</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>211</td>
<td>1-((2-Methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-hydroxymethyl-3-methyl-butyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>453.3</td>
<td>5_7_1</td>
<td>2.55</td>
</tr>
<tr>
<td>212</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (3-hydroxy-1-thiophen-3-yl-propyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>468.2</td>
<td>6_1_1</td>
<td>1.61</td>
</tr>
<tr>
<td>213</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-cyclopropyl-3-hydroxy-propyl)-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>426.3</td>
<td>6_1_1</td>
<td>1.48</td>
</tr>
<tr>
<td>214</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [1-(2-hydroxy-ethyl)-butyl]-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>428.2</td>
<td>5_7_1</td>
<td>2.75</td>
</tr>
</tbody>
</table>

Example 215: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-1-cyclobutylcarbamoyl-3-methyl-butyl)-amide
Into a reaction vial were placed 10 mg of cyclobutylamine, 20 mg of HOAt, 53 mg of (S)-2-\{[1 -(1 -ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino\}-4-methyl-pentanoic acid. Then 0.11 ml DIPEA in 1ml DMF were added, followed by 67 mg PyBrOP in 0.5 ml DMF. The reaction was shaken at RT over night, then filtered and purified by HPLC to yield 39 mg (74%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-1-cyclobutylcarbamoyl-3-methyl-butyl)-amide. 

C_{28}H_{28}N_{4}O_{2}S (494.70), LCMS (method 6_3_1): R_t = 1.50 min, m/z= 495.18 [M+H]^+

The following examples were prepared in analogy to example 215:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]^*</th>
<th>LCMS method</th>
<th>R_t [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>216</td>
<td>1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-3-methyl-butyl)-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>495.3</td>
<td>2_1_1</td>
<td>3.50</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>Rt [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>217</td>
<td>1-{(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid}</td>
<td><img src="image1" alt="Structure" /></td>
<td>527.1</td>
<td>6_3_1</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>([S]-3-methyl-1-(thiomorpholine-4-carbonyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>218</td>
<td>1-{(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid}</td>
<td><img src="image2" alt="Structure" /></td>
<td>497.2</td>
<td>6_3_1</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>([S]-1-sec-butylcarbamoyl-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>219</td>
<td>1-{(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid}</td>
<td><img src="image3" alt="Structure" /></td>
<td>552.3</td>
<td>6_3_1</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>([S]-3-methyl-1-[2-(1-methyl-pyrrolidin-2-yl)-ethylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>220</td>
<td>1-{(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid}</td>
<td><img src="image4" alt="Structure" /></td>
<td>531.2</td>
<td>6_3_1</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>([S]-1-benzylcarbamoyl-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>221</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="Image" alt="Structure" /></td>
<td>521.2</td>
<td>6_3_1</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>((S)-1-[[furan-2-ylmethyl]-carbamoyl]-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>222</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="Image" alt="Structure" /></td>
<td>537.1</td>
<td>6_3_1</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-[[thiophen-2-ylmethyl]-carbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>223</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="Image" alt="Structure" /></td>
<td>551.2</td>
<td>6_3_1</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-(2-thiophen-2-yl-ethylcarbamoyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>224</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="Image" alt="Structure" /></td>
<td>526.3</td>
<td>6_3_1</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>((S)-1-(3-dimethylamino-propylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>225</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure1" /></td>
<td>524.3</td>
<td>6_3_1</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(4-methyl-piperazine-1-carbonyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure2" /></td>
<td>511.2</td>
<td>6_3_1</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(1-ethyl-propylcarbamoyl)-3-methyl-buty]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>227</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure3" /></td>
<td>581.3</td>
<td>6_3_1</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-[3-(4-methyl-piperazin-1-yl)-propylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>228</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4.png" alt="Structure4" /></td>
<td>535.2</td>
<td>6_3_1</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(4-fluoropheny]carbamoyl)-3-methyl-buty]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS Method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>229</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [((S)-1-(2,6-dimethylmorpholine-4-carbonyl)-3-methyl-butyl]-amide</td>
<td>![Structure Image]</td>
<td>539.2</td>
<td>6_3_1</td>
<td>1.53</td>
</tr>
<tr>
<td>230</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [((S)-3-methyl-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)-butyl]-amide</td>
<td>![Structure Image]</td>
<td>538.2</td>
<td>6_3_1</td>
<td>1.24</td>
</tr>
<tr>
<td>231</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [((S)-3-methyl-1-(2-morpholin-4-yl-ethylcarbamoyl)-butyl]-amide</td>
<td>![Structure Image]</td>
<td>554.2</td>
<td>6_3_1</td>
<td>1.22</td>
</tr>
<tr>
<td>232</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [((S)-1-(1,3-dimethylbutylcarbamoyl)-3-methyl-butyl]-amide</td>
<td>![Structure Image]</td>
<td>525.2</td>
<td>6_3_1</td>
<td>1.67</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>233</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-(2-piperidin-1-yl-ethylcarbamoyl)-butyl]-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>552.3</td>
<td>6_3_1</td>
<td>1.30</td>
</tr>
<tr>
<td>234</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-(3-morpholin-4-yl-propylcarbamoyl)-butyl]-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>568.3</td>
<td>6_3_1</td>
<td>1.24</td>
</tr>
<tr>
<td>235</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-(4-phenyl-piperazine-1-carbonyl)-butyl]-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>586.2</td>
<td>6_3_1</td>
<td>1.63</td>
</tr>
<tr>
<td>236</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(4-methoxy-benzylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>561.2</td>
<td>6_3_1</td>
<td>1.60</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]*</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>237</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure 237" /></td>
<td>509.2</td>
<td>6_3_1</td>
<td>1.57</td>
</tr>
<tr>
<td>238</td>
<td>[(S)-1-(2-methoxybenzylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image2.png" alt="Structure 238" /></td>
<td>561.2</td>
<td>6_3_1</td>
<td>1.61</td>
</tr>
<tr>
<td>239</td>
<td>[(S)-1-[benzo[1,3]dioxol-5-ylmethyl]-carbamoyl]-3-methyl-butyl]-amide</td>
<td><img src="image3.png" alt="Structure 239" /></td>
<td>575.3</td>
<td>6_1_1</td>
<td>1.87</td>
</tr>
<tr>
<td>240</td>
<td>[(S)-3-methyl-1-[methyl-(2-pyridin-2-yl-ethyl)-carbamoyl]-butyl]-amide</td>
<td><img src="image4.png" alt="Structure 240" /></td>
<td>560.4</td>
<td>6_1_1</td>
<td>1.35</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>241</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(3-pyrrolidin-1-yl-propylcarbamoyl)-butyl]-amide</td>
<td><img src="structure241.png" alt="Structure" /></td>
<td>552.3</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>242</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(4-diethylamino-phenylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="structure242.png" alt="Structure" /></td>
<td>588.4</td>
<td>6_3_1</td>
<td>1.33</td>
</tr>
<tr>
<td>243</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(2-dimethylamino-1-methyl-ethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="structure243.png" alt="Structure" /></td>
<td>526.3</td>
<td>6_3_1</td>
<td>1.25</td>
</tr>
<tr>
<td>244</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(4-fluoro-benzylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="structure244.png" alt="Structure" /></td>
<td>549.2</td>
<td>6_3_1</td>
<td>1.60</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>245</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>540.3</td>
<td>6_3_1</td>
<td>1.21</td>
</tr>
<tr>
<td>246</td>
<td>[(S)-1-(4-dimethylamino-butylicarbamoil)-3-methyl-butyl]-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>563.2</td>
<td>6_3_1</td>
<td>1.65</td>
</tr>
<tr>
<td>247</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>575.3</td>
<td>6_3_1</td>
<td>1.62</td>
</tr>
<tr>
<td>248</td>
<td>[(S)-3-methyl-1-(3-methylsulfanyl-propylcarbamoil)-butyl]-amide</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>529.2</td>
<td>6_3_1</td>
<td>1.51</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>249</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>525.3</td>
<td>6_3_1</td>
<td>1.40</td>
</tr>
<tr>
<td>250</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>538.2</td>
<td>6_3_1</td>
<td>1.40</td>
</tr>
<tr>
<td>251</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>537.2</td>
<td>6_3_1</td>
<td>1.54</td>
</tr>
<tr>
<td>252</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>574.3</td>
<td>6_3_1</td>
<td>1.30</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>$R_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>253</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure1.png" alt="Structure Image" /></td>
<td>566.3</td>
<td>6_3_1</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(4-pyrrolidin-1-yl-butylicarbamoyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>254</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure2.png" alt="Structure Image" /></td>
<td>522.3</td>
<td>6_3_1</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-[[oxazol-2-ylmethyl]-carbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>255</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure3.png" alt="Structure Image" /></td>
<td>547.2</td>
<td>6_3_1</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(2-methoxy-phenylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>256</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure4.png" alt="Structure Image" /></td>
<td>575.2</td>
<td>6_3_1</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-[(2-methoxy-benzyl)-methyl-carbamoyl]-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>Rt [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>257</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-[(1-methylpiperidin-2-ylmethyl)-carbamoyl]-butyl]-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>552.3</td>
<td>6_3_1</td>
<td>1.26</td>
</tr>
<tr>
<td>258</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(2-methylsulfanyl-ethylcarbamoyl)-butyl]-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>515.2</td>
<td>6_3_1</td>
<td>1.47</td>
</tr>
<tr>
<td>259</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-((1S,2R)-2-phenyl-cyclopropylcarbamoyl)-butyl]-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>557.2</td>
<td>6_3_1</td>
<td>1.67</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>260</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>538.3</td>
<td>6_3_1</td>
<td>1.20</td>
</tr>
<tr>
<td>261</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>568.3</td>
<td>6_3_1</td>
<td>1.25</td>
</tr>
<tr>
<td>262</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>563.2</td>
<td>6_3_1</td>
<td>1.65</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>263</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>545.2</td>
<td>6_3_1</td>
<td>1.67</td>
</tr>
<tr>
<td>264</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>559.2</td>
<td>6_3_1</td>
<td>1.71</td>
</tr>
<tr>
<td>265</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>547.2</td>
<td>6_3_1</td>
<td>1.60</td>
</tr>
<tr>
<td>266</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>574.3</td>
<td>6_3_1</td>
<td>1.28</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>267</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(2-dimethylaminoethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>512.3</td>
<td>6_3_1</td>
<td>1.24</td>
</tr>
<tr>
<td>268</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(2-methoxyethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>499.2</td>
<td>6_3_1</td>
<td>1.38</td>
</tr>
<tr>
<td>269</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-[4-(3-trifluoromethylphenyl)piperazine-1-carbonyl]-butyl]-amide</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>654.2</td>
<td>6_1_1</td>
<td>3.67</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>270</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-[4-(4-fluorophenyl)-piperazine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>604.2</td>
<td>6_1_1</td>
<td>3.32</td>
</tr>
<tr>
<td>271</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-[4-benzyl-piperazine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>600.2</td>
<td>6_1_1</td>
<td>2.75</td>
</tr>
<tr>
<td>272</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-[4-isobutyl-piperazine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>566.3</td>
<td>5_7_1</td>
<td>2.54</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>Rₜ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>273</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-((1R,5S)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-ylcarbamoyl]-butyl]-amide</td>
<td><img src="image" alt="Structure 273" /></td>
<td>564.3</td>
<td>5_7_1</td>
<td>2.46</td>
</tr>
<tr>
<td>274</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-[4-(2-chloro-6-fluoro-benzyl)_[1,4]diazepane-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image" alt="Structure 274" /></td>
<td>666.2</td>
<td>5_7_1</td>
<td>2.65</td>
</tr>
<tr>
<td>275</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-[(octahydro-quinolizin-1-ylmethyl)-carbamoyl]-butyl]-amide</td>
<td><img src="image" alt="Structure 275" /></td>
<td>592.3</td>
<td>5_7_1</td>
<td>2.52</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z  [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>276</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>564.3</td>
<td>5_7_1</td>
<td>2.46</td>
</tr>
<tr>
<td>277</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>709.3</td>
<td>5_7_1</td>
<td>2.72</td>
</tr>
<tr>
<td>278</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>595.3</td>
<td>5_7_1</td>
<td>2.35</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>279</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-1-{3-[4-(4-methoxy-phenyl)piperazin-1-yl]-propylcarbamoyl]-3-methyl-butyl}-amide)</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>673.3</td>
<td>5_7_1</td>
<td>2.68</td>
</tr>
<tr>
<td>280</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-{4-(4-methyl-piperazin-1-yl)piperidine-1-carbonyl}-butyl]-amide)</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>607.3</td>
<td>5_7_1</td>
<td>2.35</td>
</tr>
<tr>
<td>281</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-(3-methyl-[1,4]bipiperidinyl-1'-carbonyl)-butyl]-amide)</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>606.3</td>
<td>5_7_1</td>
<td>2.57</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>282</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4-methyl-[1,4']bipiperidinyl-1'-carbonyl)-butyl]-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>606.3</td>
<td>5_7_1</td>
<td>2.57</td>
</tr>
<tr>
<td>283</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-[4-(4-methyl-piperidin-1-ylmethyl)-phenylcarbamoyl]-butyl]-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>628.4</td>
<td>5_7_1</td>
<td>2.70</td>
</tr>
<tr>
<td>284</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(4-dipropylamino-piperidine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>608.3</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>285</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>566.3</td>
<td>5_7_1</td>
<td>2.49</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(1-propyl-piperidin-4-ylicarbamoyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>286</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>628.3</td>
<td>6_1_1</td>
<td>2.82</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-[(1-benzyl-piperidin-3-ylmethyl)-carbamoyl]-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>287</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>608.3</td>
<td>6_1_1</td>
<td>2.84</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(3-azepan-1-yl-2,2-dimethyl-propylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>288</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-1-[1-(2,6-dimethoxy-benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl}-amide</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>674.3</td>
<td>6_1_1</td>
<td>2.82</td>
</tr>
<tr>
<td>289</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-[2-(1-methyl-piperidin-2-yl)-ethylcarbamoyl]-butyl}-amide</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>566.3</td>
<td>6_1_1</td>
<td>2.62</td>
</tr>
<tr>
<td>290</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-1-[(1-benzyl-pyrrolidin-3-ylmethyl)-carbamoyl]-3-methyl-butyl}-amide</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>614.3</td>
<td>6_1_1</td>
<td>2.79</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>291</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-[(1-phenethylpyrrolidin-3-ylmethyl)carbamoyl]-butyl]-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>628.3</td>
<td>6_1_1</td>
<td>2.84</td>
</tr>
<tr>
<td>292</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(9-methyl-9-azabicyclo[3.3.1]non-3-ylcarbamoyl)-butyl]-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>578.3</td>
<td>6_1_1</td>
<td>2.64</td>
</tr>
<tr>
<td>293</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2]bipyridinyl-4-ylcarbamoyl)-butyl]-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>601.2</td>
<td>5_7_1</td>
<td>2.51</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>294</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>596.3</td>
<td>5_7_1</td>
<td>2.25</td>
</tr>
<tr>
<td></td>
<td>([S]-1-{3-(2,6-dimethylmorpholin-4-yl)propylcarbamoyl]-3-methyl-butyl}-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>295</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>615.4</td>
<td>5_7_1</td>
<td>2.09</td>
</tr>
<tr>
<td></td>
<td>([S]-3-methyl-1-{1-pyridin-2-ylmethylpiperidin-4-ylcarbamoyl]-butyl}-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>296</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>640.3</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td></td>
<td>([S]-1-{4-(3,4-dihydro-1H-isoquinolin-2-yl)piperidine-1-carbonyl]-3-methyl-butyl}-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>297</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-[[1-methyl-piperidin-3-ylmethyl]-carbamoyl]-butyl]-amide</td>
<td></td>
<td>552.3</td>
<td>5_7_1</td>
<td>2.43</td>
</tr>
<tr>
<td>298</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-[[1-pyridin-4-ylmethyl-piperidin-4-ylcarbamoyl]-butyl]-amide</td>
<td></td>
<td>615.3</td>
<td>5_7_1</td>
<td>2.38</td>
</tr>
<tr>
<td>299</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-[[3-piperidin-1-yl-pyrrolidine-1-carbonyl]-butyl]-amide</td>
<td></td>
<td>578.3</td>
<td>5_7_1</td>
<td>2.46</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
<td>------------------</td>
</tr>
<tr>
<td>300</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-[3-(4-methyl-piperidin-1-yl)-pyrrolidine-1-carbonyl]-butyl}-amide]</td>
<td><img src="image" alt="Structure" /></td>
<td>592.3</td>
<td>5_7_1</td>
<td>2.52</td>
</tr>
<tr>
<td>301</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-1-[1-(3-fluorobenzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl}-amide]</td>
<td><img src="image" alt="Structure" /></td>
<td>632.3</td>
<td>5_7_1</td>
<td>2.59</td>
</tr>
<tr>
<td>302</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-[1-phenethyl-piperidin-3-ylmethyl]-carbamoyl]-butyl}-amide]</td>
<td><img src="image" alt="Structure" /></td>
<td>642.3</td>
<td>5_7_1</td>
<td>2.99</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>303</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Image" /></td>
<td>566.3</td>
<td>5_7_1</td>
<td>2.48</td>
</tr>
<tr>
<td>304</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Image" /></td>
<td>580.3</td>
<td>5_7_1</td>
<td>2.55</td>
</tr>
<tr>
<td>305</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Image" /></td>
<td>582.3</td>
<td>5_7_1</td>
<td>2.55</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>306</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>582.3</td>
<td>5_7_1</td>
<td>2.48</td>
</tr>
<tr>
<td>307</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>642.3</td>
<td>5_7_1</td>
<td>2.70</td>
</tr>
<tr>
<td>308</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>615.3</td>
<td>5_7_1</td>
<td>2.40</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z  [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>309</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylimethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 309" /></td>
<td>580.3</td>
<td>5_7_1</td>
<td>2.58</td>
</tr>
<tr>
<td>310</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylimethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 310" /></td>
<td>609.3</td>
<td>5_7_1</td>
<td>2.33</td>
</tr>
<tr>
<td>311</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylimethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 311" /></td>
<td>644.2</td>
<td>5_7_1</td>
<td>2.62</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>312</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>587.3</td>
<td>5_7_1</td>
<td>2.50</td>
</tr>
<tr>
<td>313</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>614.3</td>
<td>5_7_1</td>
<td>2.58</td>
</tr>
<tr>
<td>314</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>582.3</td>
<td>5_7_1</td>
<td>2.54</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>315</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>616.3</td>
<td>5_7_1</td>
<td>3.34</td>
</tr>
<tr>
<td>316</td>
<td>[(S)-1-[4-(2-methoxy-phenyl)-piperazine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>560.3</td>
<td>5_7_1</td>
<td>2.60</td>
</tr>
<tr>
<td>317</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>600.3</td>
<td>5_7_1</td>
<td>2.58</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>318</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-(4-cyclohexylpiperazine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>592.3</td>
<td>5_7_1</td>
<td>2.58</td>
</tr>
<tr>
<td>319</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-{1-benzyl-4-pyrrolidin-3-ylcarbamoyl}-3-methyl-butyl]-amide</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>600.2</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td>320</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-{3-(4-methylpiperidin-1-yl)-propylcarbamoyl}-butyl]-amide</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>580.3</td>
<td>5_7_1</td>
<td>2.56</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>321</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>578.3</td>
<td>5_7_1</td>
<td>2.52</td>
</tr>
<tr>
<td>322</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>538.2</td>
<td>5_7_1</td>
<td>2.40</td>
</tr>
<tr>
<td>323</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>614.3</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>324</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>632.3</td>
<td>5_7_1</td>
<td>2.78</td>
</tr>
<tr>
<td>325</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>612.2</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td>326</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>616.2</td>
<td>5_7_1</td>
<td>3.17</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>327</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(1-methyl-piperidin-4-ylcarbamoyl)-butyl]-amide</td>
<td>![Structure Image]</td>
<td>538.2</td>
<td>5_7_1</td>
<td>2.42</td>
</tr>
<tr>
<td>328</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-{(2-(4-methoxy-phenyl)-ethyl}[piperidin-4-ylcarbamoyl]-3-methyl-butyl]-amide</td>
<td>![Structure Image]</td>
<td>658.3</td>
<td>5_7_1</td>
<td>2.64</td>
</tr>
<tr>
<td>329</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-1-{(3-diethylamino-pyrrolidine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td>![Structure Image]</td>
<td>566.3</td>
<td>5_7_1</td>
<td>2.47</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>330</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>630.3</td>
<td>5_7_1</td>
<td>2.60</td>
</tr>
<tr>
<td>331</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>594.3</td>
<td>5_7_1</td>
<td>2.55</td>
</tr>
<tr>
<td>332</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>594.3</td>
<td>5_7_1</td>
<td>2.63</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>333</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>602.2</td>
<td>5_7_1</td>
<td>2.85</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(3-morpholin-4-yl-phenylcarbamoyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>334</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>594.3</td>
<td>5_7_1</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(4-morpholin-4-yl-piperidine-1-carbonyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>335</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>606.3</td>
<td>5_7_1</td>
<td>2.53</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(4-azepan-1-yl-piperidine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>336</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>642.3</td>
<td>5_7_1</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-[4-(benzyl-ethyl-amino)-piperidine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>337</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>580.3</td>
<td>5_7_1</td>
<td>2.51</td>
</tr>
<tr>
<td></td>
<td>[(S)-1-(1-isobutyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>338</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>628.3</td>
<td>5_7_1</td>
<td>2.63</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(1-phenethyl-piperidin-4-ylcarbamoyl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>339</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-[[3-(3-methyl-piperidin-1-yl)-propylcarbamoyl]-butyl]-amide</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>580.3</td>
<td>5_7_1</td>
<td>2.57</td>
</tr>
<tr>
<td>340</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[(1-ethyl-piperidin-4-ylicarbamoyl)-3-methyl-buty]-amide</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>552.3</td>
<td>5_7_1</td>
<td>2.44</td>
</tr>
<tr>
<td>341</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[3-(4-benzyl-piperazin-1-yl)-propylcarbamoyl]-3-methyl-buty]-amide</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>657.3</td>
<td>5_7_1</td>
<td>2.48</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>342</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>616.2</td>
<td>5_7_1</td>
<td>2.47</td>
</tr>
<tr>
<td>343</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>554.2</td>
<td>5_7_1</td>
<td>2.43</td>
</tr>
<tr>
<td>344</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>620.3</td>
<td>5_7_1</td>
<td>2.66</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>345</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[4-(benzylmethyl-amo)) (nilepiderine-1-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>628.3</td>
<td>5_7_1</td>
<td>2.61</td>
</tr>
<tr>
<td>346</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[3-[4-benzylpiperin-1-yl]-propylcarbamoyl]-3-methyl-butyl]-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>656.3</td>
<td>5_7_1</td>
<td>2.78</td>
</tr>
<tr>
<td>347</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-(5-ethyl-2,5-diaza-bicyclo[2.2.1]heptane-2-carbonyl]-3-methyl-butyl]-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>550.2</td>
<td>5_7_1</td>
<td>2.42</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z     [M+H]⁺</td>
<td>LCMS method</td>
<td>Rₜ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>348</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>578.3</td>
<td>5_7_1</td>
<td>2.52</td>
</tr>
<tr>
<td>349</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>604.3</td>
<td>5_7_1</td>
<td>2.62</td>
</tr>
<tr>
<td>350</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>680.2</td>
<td>5_7_1</td>
<td>2.76</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>351</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-1-[5-(4-methoxy-benzyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carbonyl]-3-methyl-butyl]-amide)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>642.3</td>
<td>5_7_1</td>
<td>2.62</td>
</tr>
<tr>
<td>352</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-(1-pyrimidin-2-yl-piperidin-4-ylcarbamoyl)-butyl]-amide)</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>602.2</td>
<td>5_7_1</td>
<td>2.65</td>
</tr>
<tr>
<td>353</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-3-methyl-1-[[1-(1-phenyl-ethyl)-pyrrolidin-3-ylmethyl]-carbamoyl]-butyl]-amide)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>628.3</td>
<td>5_7_1</td>
<td>2.73</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>354</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>608.3</td>
<td>5_7_1</td>
<td>2.73</td>
</tr>
<tr>
<td></td>
<td>{{(S)-3-methyl-1-[3-(4-propyl-piperidin-1-yl)-propylcarbamoyl]-butyl]-amide}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>355</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>596.3</td>
<td>5_7_1</td>
<td>2.54</td>
</tr>
<tr>
<td></td>
<td>{{(S)-1-[(4-isobutylmethyl)-carbamoyl]-3-methyl-butyl]-amide}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>356</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>648.3</td>
<td>5_7_1</td>
<td>2.62</td>
</tr>
<tr>
<td></td>
<td>{{(S)-1-[(4-(4-fluorobenzyl)-morpholin-2-ylmethyl)-carbamoyl]-3-methyl-butyl]-amide}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>357</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-dimethylcarbamoyl-3-methyl-butyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>469.2</td>
<td>5_7_1</td>
<td>3.03</td>
</tr>
<tr>
<td>358</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(3-isopropoxy-propylcarbamoyl)-3-methyl-butyl)-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>541.2</td>
<td>5_7_1</td>
<td>3.05</td>
</tr>
<tr>
<td>359</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(3-ethoxy-propylcarbamoyl)-3-methyl-butyl)-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>527.2</td>
<td>5_7_1</td>
<td>2.96</td>
</tr>
<tr>
<td>360</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-[2-(3-methoxy-phenyl)-ethylcarbamoyl]-3-methyl-butyl)-amide</td>
<td><img src="image4" alt="Structure" /></td>
<td>575.2</td>
<td>5_7_1</td>
<td>3.22</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>$R_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>361</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[2-(4-methoxy-phenyl)-ethylcarbamoyle]-3-methyl-butyl]-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>575.2</td>
<td>5_7_1</td>
<td>3.16</td>
</tr>
<tr>
<td>362</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[2-(2-methoxy-phenyl)-ethylcarbamoyle]-3-methyl-butyl]-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>575.2</td>
<td>5_7_1</td>
<td>3.33</td>
</tr>
<tr>
<td>363</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[bis-(2-methoxy-ethyl)-carbamoyle]-3-methyl-butyl]-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>557.3</td>
<td>6_1_1</td>
<td>3.05</td>
</tr>
<tr>
<td>364</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-[3-methoxy-benzylcarbamoyle]-3-methyl-butyl]-amide</td>
<td><img src="image4" alt="Structure" /></td>
<td>561.2</td>
<td>5_7_1</td>
<td>3.16</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>365</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [[(S)-1-((R)-2-methoxymethyl-pyrroldine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>3.07</td>
</tr>
<tr>
<td>366</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(2-phenoxy-ethylcarbamoyl)-butyl]-amide</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>561.2</td>
<td>5_7_1</td>
<td>3.21</td>
</tr>
<tr>
<td>367</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-{[(R)-1-(tetrahydrofuran-2-yl)methyl]-carbamoyl}-butyl]-amide</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>525.2</td>
<td>5_7_1</td>
<td>2.89</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>368</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-[[[(S)-1-(tetrahydrofuran-2-yl)methyl] carbamoyl]-butyl]-amide</td>
<td>![Structure Image]</td>
<td>525.2</td>
<td>5_7_1</td>
<td>2.90</td>
</tr>
<tr>
<td>369</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-[[tetrahydro-pyran-4-ylmethyl] carbamoyl]-butyl]-amide</td>
<td>![Structure Image]</td>
<td>539.2</td>
<td>5_7_1</td>
<td>2.85</td>
</tr>
<tr>
<td>370</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-((S)-2-methoxy-1-methyl-ethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td>![Structure Image]</td>
<td>513.2</td>
<td>5_7_1</td>
<td>2.90</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>371</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-1-(2-isopropoxyethylcarbamoyl)-3-methyl-butyl]-amide)</td>
<td><img src="image1" alt="Structure" /></td>
<td>527.2</td>
<td>5_7_1</td>
<td>3.07</td>
</tr>
<tr>
<td>372</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-1-[(4-methoxybenzyl)-methyl-carbamoyl]-3-methyl-butyl]-amide)</td>
<td><img src="image2" alt="Structure" /></td>
<td>575.2</td>
<td>5_7_1</td>
<td>3.28</td>
</tr>
<tr>
<td>373</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([(S)-1-{(4-methoxy-piperidine-1-carbonyl)-3-methyl-butyl]-amide)</td>
<td><img src="image3" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>2.97</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>374</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(4-methoxymethylpiperidine-1-carbonyl)-3-methyl-butyl)amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>553.3</td>
<td>5_7_1</td>
<td>3.07</td>
</tr>
<tr>
<td>375</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(4-isopropoxy-piperidine-1-carbonyl)-3-methyl-butyl)amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>567.3</td>
<td>5_7_1</td>
<td>3.23</td>
</tr>
<tr>
<td>376</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(3-methoxy-piperidine-1-carbonyl)-3-methyl-butyl)amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>3.13</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>377</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 377" /></td>
<td>539.3</td>
<td>6_1_1</td>
<td>2.93</td>
</tr>
<tr>
<td>378</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 378" /></td>
<td>553.2</td>
<td>5_7_1</td>
<td>3.14</td>
</tr>
<tr>
<td>379</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure 379" /></td>
<td>495.2</td>
<td>5_7_1</td>
<td>2.98</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>Rt [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>380</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>513.2</td>
<td>5_7_1</td>
<td>2.94</td>
</tr>
<tr>
<td></td>
<td>((S)-1-[(2-methoxy-ethyl)-methylcarbamoyl]-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>381</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>455.2</td>
<td>5_7_1</td>
<td>2.76</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-methylcarbamoyl-buty)-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>382</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>553.2</td>
<td>5_7_1</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-[2-(tetrahydro-pyran-4-yl)-ethylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>383</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>513.2</td>
<td>5_7_1</td>
<td>2.90</td>
</tr>
<tr>
<td></td>
<td>((S)-1-(2-ethoxy-ethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]+</td>
<td>LCMS method</td>
<td>Rt [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>384</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>3.08</td>
</tr>
<tr>
<td></td>
<td>([S]-1-((S)-2-methoxymethyl-pyrroldine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>385</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>527.2</td>
<td>5_7_1</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>([S]-3-methyl-1-(2-propoxy-ethylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>386</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>([S]-3-methyl-1-([tetrahydro-pyran-2-ylmethyl]-carbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>387</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-[methyl-(tetrahydro-furan-2-ylmethyl)-carbamoyl]-butyl}-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>539.2</td>
<td>5_7_1</td>
<td>3.02</td>
</tr>
<tr>
<td>388</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-3-methyl-1-[3-[(tetrahydro-furan-2-ylmethoxy)propylcarbamoyl]-butyl]-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>583.3</td>
<td>5_7_1</td>
<td>2.95</td>
</tr>
<tr>
<td>389</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid {(S)-1-(3-benzyloxy-propylcarbamoyl)-3-methyl-butyl}-amide</td>
<td><img src="image" alt="Structure" /></td>
<td>589.2</td>
<td>5_7_1</td>
<td>3.24</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>390</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-((S)-3-benzzyloxy-pyrrolidine-1-carbonyl)-3-methyl-butyl]-amide</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>601.2</td>
<td>5_7_1</td>
<td>3.38</td>
</tr>
<tr>
<td>391</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-(3-cyclopropylmethoxy-propylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>553.2</td>
<td>5_7_1</td>
<td>3.08</td>
</tr>
<tr>
<td>392</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-(methyl-[3-(tetrahydro-furan-2-yl)-propyl]-carbamoyl]-butyl]-amide</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>567.3</td>
<td>5_7_1</td>
<td>3.11</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>393</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (S)-1-[(1,4)dioxan-2-ylmethyl)-carbamoyl]-3-methyl-butyl]-amide</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>541.2</td>
<td>5_7_1</td>
<td>2.80</td>
</tr>
<tr>
<td>394</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (S)-1-(2-methoxy-2-methyl-propylcarbamoyl)-3-methyl-butyl]-amide</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>527.2</td>
<td>5_7_1</td>
<td>3.05</td>
</tr>
<tr>
<td>395</td>
<td>1-((1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (S)-3-methyl-1-[methyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl]-butyl]-amide</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>553.2</td>
<td>5_7_1</td>
<td>3.23</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]⁺</td>
<td>LCMS method</td>
<td>Rᵣ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>396</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1" alt="Structure" /></td>
<td>567.4</td>
<td>6_1_1</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>((S)-1-[ethyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl]-3-methyl-butyl]amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>397</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2" alt="Structure" /></td>
<td>579.3</td>
<td>5_7_1</td>
<td>3.24</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-(1-oxa-spiro[4.5]dec-3-ylcarbamoyl]-butyl]amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>398</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3" alt="Structure" /></td>
<td>565.2</td>
<td>5_7_1</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-(1-oxa-spiro[4.4]non-3-ylcarbamoyl]-butyl]amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>399</td>
<td>1-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4" alt="Structure" /></td>
<td>523.2</td>
<td>5_3_1</td>
<td>1.96</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-[(1H-tetrazol-5-ylmethyl)-carbamoyl]-butyl]amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]$^+$</td>
<td>LCMS method</td>
<td>R$_t$ [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>400</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>537.2</td>
<td>5_3_1</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-[2-(1H-tetrazol-5-yl)-ethylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>401</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>548.2</td>
<td>3_2_1</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>((S)-3-methyl-1-[2-sulfamoyl-ethylcarbamoyl]-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>402</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>562.2</td>
<td>5_2_1</td>
<td>3.86</td>
</tr>
<tr>
<td></td>
<td>((S)-1-(2-methanesulfonyla mino-ethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>403</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>478.3</td>
<td>4_1_1</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>((S)-1-(cyanomethylcarbamoyl)-3-methyl-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R_t [min]</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>404</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-1-(2-cyanoethylcarbamoyl)-3-methyl-butyl)-amide</td>
<td><img src="image1" alt="Structure" /></td>
<td>538.3</td>
<td>4_1_1</td>
<td>1.18</td>
</tr>
<tr>
<td>405</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-[methyl-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-ylmethyl)-carbamoyl]-butyl)-amide</td>
<td><img src="image2" alt="Structure" /></td>
<td>552.3</td>
<td>3_2_1</td>
<td>1.30</td>
</tr>
<tr>
<td>406</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-[2-(5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-ethylcarbamoyl]-butyl)-amide</td>
<td><img src="image3" alt="Structure" /></td>
<td>552.1</td>
<td>4_1_1</td>
<td>1.11</td>
</tr>
</tbody>
</table>
Example 408: ((S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoylamino)-acetic acid
tert.-butyl ester

To a solution of 100 mg of (S)-2-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoylamino)-acetic acid tert.-butyl ester in 1 ml of dry DMF 12 mg of HOAT, 4.1 mg of EDC and 0.13 ml of DIPEA were added at 0°C. After 15 min 30 mg of glycine tert.-butylester hydrochloride and 0.03 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The
reaction was extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by HPLC to yield 32 mg (32 %) of \((S)-2\text{-}[1\text{-}(1\text{-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl}]\text{-amino}]\text{-4-methyl-pentanoylamino}\text{-acetic acid tert.-butyl ester.}

\[\text{C30H42N4O4S (554.75), LCMS (method 5_3_1): } R_t = 2.30 \text{ min, } m/z= 555.23 \ [M+H]^+\]

b) \((S)-2\text{-}[1\text{-}(1\text{-Ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl}]\text{-amino}]\text{-4-methyl-pentanoylamino}\text{-acetic acid}

32 mg of \((S)-2\text{-}[1\text{-}(1\text{-ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl}]\text{-amino}]\text{-4-methyl-pentanoylamino}\text{-acetic acid tert.-butyl ester} were reacted with 0.8 ml of 4 M hydrochloric acid in dioxane at rt over night. The reaction mixture was then concentrated in vacuo to yield 28 mg (91 %) of \((S)-2\text{-}[1\text{-}(1\text{-Ethyl-propyl})\text{-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl}]\text{-amino}]\text{-4-methyl-pentanoylamino}\text{-acetic acid.}

\[\text{C26H34N4O4S (498.64), LCMS (method 5_5_1): } R_t = 1.91 \text{ min, } m/z= 499.20 \ [M+H]^+\]

The following examples were prepared in analogy to example 408:
The following examples were obtained after separation of the diastereomeric mixtures using chiral stationary phases either by preparative HPLC using a Waters Alliance 2695 system (Flow rate 1 ml/min) or by SFC using a Thar system. The separation conditions are described below. (In the compounds described in the following table, the absolute configuration of the amino acid is as drawn, the
diastereomers separated are the diastereomeric forms of the methyl-cyclohexylamine or methyl cydopentyl amine part).

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Structure and chemical name of diastereomeric mixture</th>
<th>Conditions of chiral sep.</th>
<th>No. of diastereomer</th>
<th>Rt [min] (sep.)</th>
<th>% de</th>
<th>Obs. Mass</th>
<th>LCMS method (non-chiral)</th>
<th>Rt [min] (non-chiral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>412</td>
<td><img src="image.png" alt="Structure" /></td>
<td>Waters HPLC; Chiralpak IA-81; 250 x 4.6 mm; heptane + iPrOH + MeOH 6 + 1 + 1 + 0.1 % NH₄Ac</td>
<td>1</td>
<td>10.06</td>
<td>&gt;99</td>
<td>468.19</td>
<td>6.3.1</td>
<td>1.51</td>
</tr>
<tr>
<td>413</td>
<td>(S)-4-Methyl-2-[(1-(2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino]-pentanoic acid</td>
<td></td>
<td>2</td>
<td>11.18</td>
<td>98.8</td>
<td>468.19</td>
<td>6.3.1</td>
<td>1.51</td>
</tr>
<tr>
<td>414</td>
<td></td>
<td></td>
<td>3</td>
<td>12.83</td>
<td>&gt;99</td>
<td>468.19</td>
<td>6.3.1</td>
<td>1.50</td>
</tr>
<tr>
<td>415</td>
<td></td>
<td></td>
<td>4</td>
<td>14.30</td>
<td>98.3</td>
<td>468.20</td>
<td>6.3.1</td>
<td>1.49</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of diastereomeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of diastereomer</td>
<td>Rt [min] (sep.)</td>
<td>% de</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>416</td>
<td><img src="image" alt="Structure" /></td>
<td>Waters HPLC; Chiralpak IA-81 ; 25 0 x 4.6 mm; heptane + iPrOH + MeOH 5 + 1 + 1 + 0.1 % NH₄Ac</td>
<td>1</td>
<td>7.93</td>
<td>&gt;99</td>
<td>452.4 1</td>
<td>6.2.1</td>
<td>1.92</td>
</tr>
<tr>
<td>417</td>
<td>(S)-2-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carbonyl]-amino]-4-methyl-pentanoic acid</td>
<td></td>
<td>2</td>
<td>8.94</td>
<td>94.6</td>
<td>452.4 1</td>
<td>6.2.1</td>
<td>1.89</td>
</tr>
<tr>
<td>418</td>
<td></td>
<td></td>
<td>3</td>
<td>9.70</td>
<td>79.0</td>
<td>452.4 1</td>
<td>6.2.1</td>
<td>1.87</td>
</tr>
<tr>
<td>419</td>
<td></td>
<td></td>
<td>4</td>
<td>10.42</td>
<td>76.1</td>
<td>452.4 1</td>
<td>6.2.1</td>
<td>1.89</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of diastereomeric mixture</td>
<td>Conditions of diastereomer sep.</td>
<td>No. of diastereomer</td>
<td>Rt [min] (sep.)</td>
<td>% de</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------</td>
<td>---------</td>
<td>------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>420</td>
<td><img src="image" alt="Structure" /></td>
<td>Waters HPLC; Chiralpak IA-103; 25 Ox 4.6 mm; heptane + iPrOH + MeOH + MeCN 7 + 1 + 0.5 + 0.5 + 0.1 % NH4Ac</td>
<td>1</td>
<td>16.84</td>
<td>&gt;99</td>
<td>468.2 7</td>
<td>5_7_1</td>
<td>3.02</td>
</tr>
<tr>
<td>421</td>
<td>(S)-2-[(1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td></td>
<td>2</td>
<td>19.90</td>
<td>98.7</td>
<td>468.1 4</td>
<td>5_7_1</td>
<td>2.99</td>
</tr>
<tr>
<td>422</td>
<td></td>
<td></td>
<td>3</td>
<td>21.52</td>
<td>97.9</td>
<td>468.2 2</td>
<td>5_7_1</td>
<td>2.94</td>
</tr>
<tr>
<td>423</td>
<td></td>
<td></td>
<td>4</td>
<td>26.32</td>
<td>&gt;99</td>
<td>468.2 4</td>
<td>5_7_1</td>
<td>2.94</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of diastereomeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of diastereomer</td>
<td>Rt [min] (sep.)</td>
<td>% de</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>424</td>
<td><img src="image" alt="Structure" /> (S)-3-Cyclohexyl-2-[(1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1-H-benzoimidazole-5-carbonyl]-amino)-propionic acid</td>
<td>Waters HPLC; Chiralpak IA-103; 25 OX 4,6 mm; heptane + iPrOH + MeOH + MeCN 8 + 1 + 0.5 + 0.5 + 0.1 % NH₄Ac</td>
<td>1</td>
<td>18.44</td>
<td>&gt;99</td>
<td>508.2 0</td>
<td>5.7_1</td>
<td>3.1 6</td>
</tr>
<tr>
<td>425</td>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td>2</td>
<td>23.22</td>
<td>86</td>
<td>508.2 0</td>
<td>5.7_1</td>
<td>3.1 7</td>
</tr>
<tr>
<td>426</td>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td>3</td>
<td>24.72</td>
<td>&gt;99</td>
<td>508.2 6</td>
<td>5.7_1</td>
<td>3.1 6</td>
</tr>
<tr>
<td>427</td>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td>4</td>
<td>30.44</td>
<td>95.8</td>
<td>508.2 4</td>
<td>5.7_1</td>
<td>3.1 5</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of diastereomeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of diastereomer</td>
<td>Rt [min] (sep.)</td>
<td>% de</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------</td>
<td>----------</td>
<td>-------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>428</td>
<td><img src="structure.png" alt="Structure" /></td>
<td>Thar SFC; Chiralpak AD-H; 250 x 4.6 mm; MeOH 20%</td>
<td>1</td>
<td>20.78</td>
<td>&gt;99</td>
<td>452.0 9</td>
<td>5_5_1</td>
<td>2.05</td>
</tr>
<tr>
<td>429</td>
<td>(S)-4-Methyl-2-{{1-(2-methylcyclopentyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl}-amino}-pentanoic acid</td>
<td></td>
<td>2</td>
<td>22.93</td>
<td>85.0</td>
<td>452.0 9</td>
<td>5_5_1</td>
<td>2.05</td>
</tr>
<tr>
<td>430</td>
<td></td>
<td></td>
<td>3</td>
<td>25.42</td>
<td>77.7</td>
<td>452.0 9</td>
<td>5_5_1</td>
<td>2.04</td>
</tr>
<tr>
<td>431</td>
<td></td>
<td></td>
<td>4</td>
<td>29.69</td>
<td>79.6</td>
<td>452.0 9</td>
<td>5_5_1</td>
<td>2.06</td>
</tr>
</tbody>
</table>
In first run dia 22 and 23 eluted together at 10.40 min, in a second run this peak was separated into Dia22 and 23 using heptane + iPrOH + MeOH 8 + 1 + 1 + 0.1 % NH4Ac

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Structure and chemical name of diastereomeric mixture</th>
<th>Conditions of chiral sep.</th>
<th>No. of dia- stereomer</th>
<th>Rt [min] (sep.)</th>
<th>% de</th>
<th>Obs. Mass</th>
<th>LCMS method (non-chiral)</th>
<th>Rt [min] (non-chiral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>432</td>
<td></td>
<td>Waters HPLC; Chiralpak IA-81; 25 0 x 4,6 mm; heptane + iPrOH + MeOH 4 + 1 + 1 + 0.3 % NH4Ac</td>
<td>1</td>
<td>7.77</td>
<td>&gt;99</td>
<td>466.25</td>
<td>7_1_1</td>
<td>1.26</td>
</tr>
<tr>
<td>433</td>
<td></td>
<td></td>
<td>2*</td>
<td>7.98</td>
<td>&gt;99</td>
<td>466.20</td>
<td>6_5_1</td>
<td>2.13</td>
</tr>
<tr>
<td>434</td>
<td>(S)-3-[(2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxyl]-5-aminomethyl-hexanoic acid</td>
<td></td>
<td>3*</td>
<td>9.16</td>
<td>96.0</td>
<td>466.20</td>
<td>6_5_1</td>
<td>2.11</td>
</tr>
<tr>
<td>435</td>
<td></td>
<td></td>
<td>4</td>
<td>11.96</td>
<td>95.0</td>
<td>466.19</td>
<td>6_6_1</td>
<td>2.92</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of diastereomeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of diastereomer</td>
<td>Rt [min] (sep.)</td>
<td>% de</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>436</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Waters HPLC; Chiralpak IA-1 03; 25 Ox 4,6 mm; heptane + iPrOH + MeOH 5 + 1 + 1 + 0.1 % NH₄Ac</td>
<td>1</td>
<td>10.51</td>
<td>&gt;99</td>
<td>482.15</td>
<td>5_7_1</td>
<td>2.98</td>
</tr>
<tr>
<td>437</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
<td>2</td>
<td>13.92</td>
<td>&gt;99</td>
<td>482.15</td>
<td>5_7_1</td>
<td>2.98</td>
</tr>
<tr>
<td>438</td>
<td>(S)-5-Methyl-3-[[1-(2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid</td>
<td></td>
<td>3</td>
<td>15.74</td>
<td>91</td>
<td>482.24</td>
<td>5_7_1</td>
<td>2.91</td>
</tr>
<tr>
<td>439</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
<td>4</td>
<td>18.11</td>
<td>85</td>
<td>482.23</td>
<td>5_7_1</td>
<td>2.93</td>
</tr>
</tbody>
</table>
The following enantiomers or diastereomers were obtained after separation of the racemates or diastereomeric mixtures by preparative HPLC using a Waters Alliance 2695 system and chiral columns and solvent mixtures at a flow rate of 1 ml/min as given in the following table. In some cases more than one chiral center is present in the molecule, the starting mixtures consisted of epimers at the amino acid or amino alcohol chiral center.

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Structure and chemical name of epimeric mixture</th>
<th>Conditions of chiral sep.</th>
<th>No. of enantiomer</th>
<th>Rt [min] (sep.)</th>
<th>% ee</th>
<th>Obs. Mass</th>
<th>LCMS method (non-chiral)</th>
<th>Rt [min] (non-chiral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>440</td>
<td><img src="image1.png" alt="Structure" /> 2-{[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,4-dimethylpentanoic acid</td>
<td>LC_8, 1 ml/min, IA 103 4.6 x 250 mm, Hep:EtO H:MeOH 10:1:1 precond. TFA</td>
<td>1</td>
<td>8.73</td>
<td>&gt;99.5</td>
<td>456.2 6</td>
<td>6_1_1</td>
<td>2.90</td>
</tr>
<tr>
<td>441</td>
<td><img src="image2.png" alt="Structure" /> 2-{[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino}-2,4-dimethylpentanoic acid</td>
<td></td>
<td>2</td>
<td>10.77</td>
<td>93</td>
<td>456.2 6</td>
<td>6_1_1</td>
<td>2.90</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiomer</td>
<td>Rt [min] (sep.)</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------</td>
<td>--------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>----------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>442</td>
<td><img src="image" alt="3-Cyclopentyl-2-([1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)propionic acid" /></td>
<td>LC_3, 1 ml/min, Chiralpak AD-H, 67 4.6 x 250 mm, Hep:EtOH:MeOH 1:1:1 precond. TFA</td>
<td>1</td>
<td>4.60</td>
<td>96.6</td>
<td>494.3</td>
<td>6</td>
<td>3.2</td>
</tr>
<tr>
<td>443</td>
<td>3-Cyclopentyl-2-([1-((1R,2R)-2-methylcyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-propionic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>444</td>
<td><img src="image" alt="3-(4,4-Dimethylcyclohexyl)-2-([1-(1-ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-propionic acid" /></td>
<td>LC_01, 1 ml/min, Chiralpak AD-H-55 4.6 x 250 mm, MeCN:MeOH 9:1 precond. TFA</td>
<td>1</td>
<td>4.94</td>
<td>&gt;99.5</td>
<td>510.2</td>
<td>3</td>
<td>1.66</td>
</tr>
<tr>
<td>445</td>
<td>3-(4,4-Dimethylcyclohexyl)-2-([1-(1-ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-propionic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

--
<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Structure and chemical name of epimeric mixture</th>
<th>Conditions of chiral sep.</th>
<th>No. of enantiomer</th>
<th>Rt [min] (sep.)</th>
<th>% ee</th>
<th>Obs. Mass</th>
<th>LCMS method (non-chiral)</th>
<th>Rt [min] (non-chiral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>446</td>
<td><img src="image.png" alt="Image" /> 3-(4,4-Dimethyl-cyclohexyl)-2-((1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino)-propionic acid</td>
<td>LC_01, 1 ml/min, Chiralpak AD-H 119 4.6 x 250 mm, MeCN:EtOH:MeOH H 6:1:1 +0.1 %DEA</td>
<td>1</td>
<td>5.14</td>
<td>&gt;99.5</td>
<td>536.4</td>
<td>4_1_1</td>
<td>1.39</td>
</tr>
<tr>
<td>447</td>
<td><img src="image.png" alt="Image" /> 3-(4,4-Dimethyl-cyclohexyl)-2-((1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl)-amino)-propionic acid</td>
<td>LC_01, 1 ml/min, Chiralpak AD-H 119 4.6 x 250 mm, MeCN:EtOH:MeOH H 6:1:1 +0.1 %DEA</td>
<td>2</td>
<td>11.30</td>
<td>&gt;99.5</td>
<td>536.4</td>
<td>4_1_1</td>
<td>1.40</td>
</tr>
<tr>
<td>448</td>
<td><img src="image.png" alt="Image" /> 3-Cycloheptyl-2-[[1-(1-ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 6:1:1 precond. TFA</td>
<td>1</td>
<td>9.22</td>
<td>99.6</td>
<td>496.2</td>
<td>4_1_1</td>
<td>1.3</td>
</tr>
<tr>
<td>449</td>
<td><img src="image.png" alt="Image" /> 3-Cycloheptyl-2-[[1-(1-ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 6:1:1 precond. TFA</td>
<td>2</td>
<td>14.68</td>
<td>99.7</td>
<td>496.2</td>
<td>4_1_1</td>
<td>1.3</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiomer</td>
<td>Rt [min] (sep.)</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------</td>
<td>--------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------</td>
<td>----------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>450</td>
<td><img src="image1.png" alt="Structure" /> 3-Cycloheptyl-2-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:H:MeOH 6:1:1</td>
<td>1</td>
<td>10.17</td>
<td>&gt;99.5</td>
<td>522.45</td>
<td>4_1_1</td>
<td>1.35</td>
</tr>
<tr>
<td>451</td>
<td><img src="image2.png" alt="Structure" /> 3-Cycloheptyl-2-((1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:H:MeOH 6:1:1</td>
<td>2</td>
<td>17.30</td>
<td>&gt;99.5</td>
<td>522.45</td>
<td>4_1_1</td>
<td>1.36</td>
</tr>
<tr>
<td>452</td>
<td><img src="image3.png" alt="Structure" /> 3-[[1-(1-Ethylpropyl)]-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:H:MeOH 10:1:1</td>
<td>1</td>
<td>9.20</td>
<td>&gt;99.5</td>
<td>456.29</td>
<td>5_1_1</td>
<td>4.1</td>
</tr>
<tr>
<td>453</td>
<td><img src="image4.png" alt="Structure" /> 3-[[1-(1-Ethylpropyl)]-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:H:MeOH 10:1:1</td>
<td>2</td>
<td>13.20</td>
<td>&gt;99.5</td>
<td>456.15</td>
<td>5_7_1</td>
<td>2.74</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiom er</td>
<td>Rt [min] (sep.)</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>-----</td>
<td>---------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>454</td>
<td><img src="image" alt="Structure" /> 4-Cyclohexyl-3- {[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-butyric acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtO H:MeOH 10:1:1</td>
<td>1</td>
<td>9.54</td>
<td>&gt;99.5</td>
<td>496.1</td>
<td>5_7_1</td>
<td>3.00</td>
</tr>
<tr>
<td>455</td>
<td><img src="image" alt="Structure" /> 4-Cyclohexyl-3- {[(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-butyric acid</td>
<td></td>
<td>2</td>
<td>14.14</td>
<td>&gt;99.5</td>
<td>496.1</td>
<td>5_7_1</td>
<td>2.96</td>
</tr>
<tr>
<td>456</td>
<td><img src="image" alt="Structure" /> 4-Cyclohexyl-3- {(1R,2R)-2-methyl-cyclohexyl}-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino}-butyric acid</td>
<td>LC_02, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtO H:1:1, preconc. DEA</td>
<td>1</td>
<td>6.06</td>
<td>&gt;99.5</td>
<td>522.2</td>
<td>5_5_1</td>
<td>1.56</td>
</tr>
<tr>
<td>457</td>
<td><img src="image" alt="Structure" /></td>
<td></td>
<td>2</td>
<td>9.42</td>
<td>99.9</td>
<td>522.2</td>
<td>5_5_1</td>
<td>1.56</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiomer</td>
<td>Rt [min] (sep.)</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------</td>
<td>--------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>458</td>
<td><img src="image1.png" alt="Image" /> 3-[(1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 5:1:1 precond. TFA</td>
<td>1</td>
<td>6.30</td>
<td>&gt;99.5</td>
<td>468.20</td>
<td>3_2_1</td>
<td>1.38</td>
</tr>
<tr>
<td>459</td>
<td><img src="image2.png" alt="Image" /> 3-[(1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 5:1:1 precond. TFA</td>
<td>2</td>
<td>9.28</td>
<td>&gt;99.5</td>
<td>468.20</td>
<td>3_2_1</td>
<td>1.39</td>
</tr>
<tr>
<td>460</td>
<td><img src="image3.png" alt="Image" /> 3-[(1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 5:1:1 precond. TFA</td>
<td>1</td>
<td>5.83</td>
<td>&gt;99.5</td>
<td>468.2</td>
<td>3_2_1</td>
<td>1.39</td>
</tr>
<tr>
<td>461</td>
<td><img src="image4.png" alt="Image" /> 3-[(1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino)-hexanoic acid</td>
<td>LC_04, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:EtOH:MeOH 5:1:1 precond. TFA</td>
<td>2</td>
<td>8.23</td>
<td>&gt;99.5</td>
<td>468.1</td>
<td>3_2_1</td>
<td>1.44</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiomer</td>
<td>Rt ([\text{min}]) (sep.)</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt ([\text{min}]) (non-chiral)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------</td>
<td>--------------------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>------</td>
<td>----------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>462</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>LC_05, 0.75 ml/min, Chiralpak AD-H, 4.6 x 250 mm, EtOH</td>
<td>1</td>
<td>8.82</td>
<td>&gt;99.5</td>
<td>508.27</td>
<td>3_1_1</td>
<td>1.58</td>
</tr>
<tr>
<td>463</td>
<td>3'-Cyclohexyl-3'-(1'-(1 R,2R)-2'-methyl-cyclohexyl)-2'-thiophen-2'-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-propionic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>464</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>LC_11, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, Hep:iPr OH:MeOH 20:1:1</td>
<td>1</td>
<td>6.68</td>
<td>&gt;99.5</td>
<td>484.26</td>
<td>6_6_1</td>
<td>4.04</td>
</tr>
<tr>
<td>465</td>
<td>3'-[1-(1-Ethylpropyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trimethyl-hexanoic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Structure and chemical name of epimeric mixture</td>
<td>Conditions of chiral sep.</td>
<td>No. of enantiomer</td>
<td>% ee</td>
<td>Obs. Mass</td>
<td>LCMS method (non-chiral)</td>
<td>Rt [min] (non-chiral)</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>--------------------------</td>
<td>------------------</td>
<td>------</td>
<td>-----------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>466</td>
<td><img src="image" alt="Structure" /> 3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-hexanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, MeCN:MeOH 9:1, percond. TFA</td>
<td>1</td>
<td>&gt;99.5</td>
<td>470.29</td>
<td>3_1_1</td>
<td>1.44</td>
<td></td>
</tr>
<tr>
<td>467</td>
<td><img src="image" alt="Structure" /> 3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-hexanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, MeCN:MeOH 9:1, percond. TFA</td>
<td>2</td>
<td>99.0</td>
<td>470.27</td>
<td>3_1_1</td>
<td>1.44</td>
<td></td>
</tr>
<tr>
<td>468</td>
<td><img src="image" alt="Structure" /> 3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-hexanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, MeCN:MeOH 9:1, percond. TFA</td>
<td>1</td>
<td>88.6</td>
<td>484.25</td>
<td>3_1_1</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>469</td>
<td><img src="image" alt="Structure" /> 3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dimethyl-hexanoic acid</td>
<td>LC_03, 1 ml/min, Chiralpak AD-H, 4.6 x 250 mm, MeCN:MeOH 9:1, percond. TFA</td>
<td>2</td>
<td>98.9</td>
<td>484.24</td>
<td>3_1_1</td>
<td>1.49</td>
<td></td>
</tr>
</tbody>
</table>
Example 472: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(1H-tetrazol-5-ylmethyl)-butyl]-amide

a) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-cyanomethyl-3-methyl-butyl)-amide
To a solution of 4.93 g of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid in 50 ml of dry DMF 2.04 g of HOAT, 3.45 g of EDC and 4.35 ml of DIPEA were added at 0°C. After 30 min 3.29 g of (S)-3-Amino-5-methyl-hexanenitrile-hydrochloride and 4.35 ml of DIPEA were added and the reaction was stirred at rt for 4 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous sodium hydrogensulphate solution. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. 5.90 g (90%) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-1-cyanomethyl-3-methyl-butyl)-amide were obtained.

C25H32N4OS (436.62), LCMS (method 5_1_1): \( \text{R}_t = 4.58 \text{ min, m/z= 437.21 } [\text{M+H}^+] \)

b) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(1 H-tetrazol-5-ylmethyl)-butyl]-amide

218 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-1-cyanomethyl-3-methyl-butyl)-amide and 124 mg of azidotrimethyltin in 10 ml of dry toluene were heated under Argon for 48 h. The precipitated crude product was isolated by suction and then dissolved in 10% aqueous sodium bicarbonate.
solution and filtered with addition of charcoal. The pH of the filtrated was adjusted to 5, and the precipitated product was isolated by suction, washed with water and dried in vacuo to obtain 100 mg (42%) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(1 H-tetrazol-5-ylmethyl)-butyl]-amide.

C25H32N7OS (479.65), LCMS (method 3_1_1): Rt = 1.48 min, m/z= 480.22 [M+H]⁺

Example 473: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-(N-hydroxycarbamimidoylmethyl)-3-methyl-butyl]-amide

Chiral

To 700 mg 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-cyanomethyl-3-methyl-butyl]-amide in 7 ml of dry THF and 7 ml of dry methanol was added 1.11 g hydroxylamine-hydrochloride, followed by the addition of 2.7 ml of triethylamine. The reaction was heated to reflux overnight, then it was diluted with ethyl acetate and washed with water. The layers were separated and the aqueous phase was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate and concentrated. The residue was purified by HPLC to obtain 175 mg (23%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-(N-hydroxycarbamimidoylmethyl)-3-methyl-butyl]-amide.

C25H35N5O2S (469.65), LCMS (method 5_1_1): Rt = 3.45 min, m/z= 470.32 [M+H]⁺

Example 474: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(5-phenyl-[1,2,4]oxadiazol-3-ylmethyl)-butyl]-amide
A mixture of 88 mg 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-(N-hydroxy carbamimidoylmethyl)-3-methyl-butyl]-amide, 26 mg of benzoyl chloride and 78 mg of potassium carbonate in 0.5 mL of dry THF was reacted in a microwave reactor at 120°C for 15 min. The reaction was taken up in water, the pH was adjusted to 7 by addition of 2 M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate twice. The combined organic layers were concentrated and the resulting residue was purified by HPLC to isolate 19 mg (18%) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(5-phenyl-[1,2,4]oxadiazol-3-ylmethyl)-butyl]-amide.

C32H37N5O2S (555.27), LCMS (method 5_7_1): Rt = 3.59 min, m/z= 556.26 [M+H]^+

Example 475: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-(5-cyclopropyl-[1,2,4]oxadiazol-3-ylmethyl)-3-methyl-butyl]-amide

The title compound was prepared in analogy to example 474 by reaction of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-1-(N-hydroxy carbamimidoylmethyl)-3-methyl-butyl]-amide and cyclopropanecarbonyl chloride.

C29H37N5O2S (519.71 ), LCMS (method 5_7_1): Rt = 3.10 min, m/z= 520.25 [M+H]^+
Example 476: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(5-trifluoromethyl-1H-[1,2,4]triazol-3-ylmethyl)-butyl]-amide

A mixture of 50 mg 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-cyanomethyl-3-methyl-butyl)-amide, 45 mg of trifluoroacetic acid hydrazide and 4 mg of potassium carbonate in 0.6 ml of ethanol was heated to 200°C in a microwave reactor for 24 h. The solvent was removed and the residue was purified by HPLC to obtain 6 mg (10%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(5-trifluoromethyl-1H-[1,2,4]triazol-3-ylmethyl)-butyl]-amide.

C27H33F3N6OS (546.66), LCMS (method 6_6_1): Rt = 3.14 min, m/z= 547.32 [M+H]+

Example 477: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-pyridin-2-yl-butyl)-amide

To a solution of 50 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid in 2 ml of dry DMF 10 mg of HOAT, 35 mg of EDC and 0.1 ml of DIPEA were added at 0°C. After 15 min 25 mg of 1-pyridin-2-ylbutylamine were added and the reaction was stirred at rt for 16 h. The reaction was
then poured into water and the pH was adjusted to 4 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulphate and concentrated. 70 mg (100%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (1-pyridin-2-yl-butyl)-amide were obtained.

C27H32N4OS (460.64), LCMS (method 5_6_1): Rt = 1.79 min, m/z= 461.19 [M+H]+

The following examples were prepared in analogy to example 477:

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Chemical Name</th>
<th>Structure</th>
<th>m/z [M+H]+</th>
<th>LCMS method</th>
<th>Rt [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>478</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (3-methyl-1-pyridin-3-yl-butyl)-amide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>475.2</td>
<td>5_3_1</td>
<td>1.88</td>
</tr>
<tr>
<td>479</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid (3-methyl-1-thiazol-2-yl-butyl)-amide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>481.2</td>
<td>3_2_1</td>
<td>1.46</td>
</tr>
<tr>
<td>480</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [1-(4,5-dimethyl-thiazol-2-yl)-3-methyl-butyl]-amide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>509.3</td>
<td>3_2_1</td>
<td>1.49</td>
</tr>
<tr>
<td>Exp. No.</td>
<td>Chemical Name</td>
<td>Structure</td>
<td>m/z [M+H]^+</td>
<td>LCMS method</td>
<td>R&lt;sub&gt;t&lt;/sub&gt; [min]</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>481</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>480.2</td>
<td>6_6_1</td>
<td>2.97</td>
</tr>
<tr>
<td></td>
<td>[(S)-3-methyl-1-(5-methyl-[1,3,4]oxadiazol-2-yl)-butyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>482</td>
<td>1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid</td>
<td><img src="image" alt="Structure" /></td>
<td>495.3</td>
<td>3_1_1</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>([S]-1-(5-methoxymethyl-2H-[1,2,4]triazol-3-yl)-2-methyl-propyl]-amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example 483: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid ([S]-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-amide

5 a) Toluene-4-sulfonic acid (S)-2-tert-butoxycarbonylamino-4-methyl-pentyl ester
To a solution of 4.50 g of Boc-L-leucinol in 30 ml of THF were added 4.74 g of p-toluenesulfonylchloride, 7.2 ml of TEA and 0.25 g of DMAP. The reaction was stirred at rt overnight. The pH of the reaction was then adjusted to 6 by the addition of 1 M aqueous hydrochloric acid. The phases were separated and the aqueous phase was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate and concentrated to yield 6.94 g of toluene-4-sulfonic acid (S)-2-tert-butoxycarbonylamino-4-methyl-pentyl ester.

\[ C_{18}H_{29}N_{5}O_{5}S \] (371.50) MS (ESI LCMS (method 8_1_1): Rt = 1.14 min, m/z= 271.90 [M+H-Boc] +

b) [(S)-3-Methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-carbamic acid tert-butyl ester

\[
\begin{align*}
\text{O} & \\
\text{N} & \\
\text{S} & \\
\text{N} & \\
\text{N} & \\
\end{align*}
\]

To 250 mg of toluene-4-sulfonic acid (S)-2-tert-butoxycarbonylamino-4-methyl-pentyl ester in 2.5 ml acetone and 0.5 ml water were added 112 mg of potassium carbonate, followed by the addition of 75 mg 4H-1,2,4-triazole-3-thiol. The reaction was heated in a microwave reactor for 5 min to 100 °C. The pH was then adjusted to 7 by the addition of 2 M aqueous hydrochloric acid and the mixture was extracted with ethyl acetate twice. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. 161 mg (80 %) of [(S)-3-Methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-carbamic acid tert-butyl ester were obtained.

\[ C_{13}H_{24}N_{4}O_{2}S \] (300.43), LCMS (method 8_1_1): Rt = 0.84 min, m/z= 301.00 [M+H] +

c) (S)-3-Methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butylamine-hydrochloride
160 mg of [(S)-3-Methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-carbamic acid tert-butyl ester were reacted with 2.6 ml of 4M hydrochloric acid in dioxane at rt for 2 h. The reaction was concentrated in vacuo and the resulting crude product was used without further purification. 125 mg (100%) of (S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butylamine-hydrochloride were obtained. 

C₈H₁₆N₄S (200.31). LCMS (method 8_1_1): Rt = 0.18 min, m/z = 201.00 [M+H]+

d) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-amide

To a solution of 185 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid in 3 ml of dry DMF 84 mg of HOAT, 151 mg of EDC and 0.47 ml of DIPEA were added at 0°C. After 15 min 133 mg of (S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butylamine-hydrochloride were added and the reaction was stirred at rt for 20 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with 2 M aqueous hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. After purification by HPLC 64 mg (22%) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4H-[1,2,4]triazol-3-ylsulfanylmethyl)-butyl]-amide were obtained.
Example 484: 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-amide

To 750 mg of [(S)-3-Methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-carbamic acid tert-butyl ester in 10 ml acetonitrile and 1 ml water was added 6 mg of sodium tungstate and 0.2 ml of hydrogen peroxide (35%). The reaction was stirred overnight, then another 6 mg of sodium tungstate and 0.2 ml of hydrogen peroxide (35%) were added and after 24 h the reaction was diluted with ethyl acetate and water. The phases were separated and the organic phase was concentrated and the resulting residue was purified by HPLC to obtain 126 mg (18%) of [(S)-3-Methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-carbamic acid tert-butyl ester.

C_{13}H_{24}N_{4}O_{4}S (332.42), LCMS (method 8_1_1): Rt = 0.75 min, m/z= 233.1 0 [M+H-Boc]^{+}
200 mg of [(S)-3-Methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-carbamic acid tert-butyl ester were dissolved in 6 ml of dioxane and reacted with 2.2 ml of 4M hydrochloric acid in dioxane at rt for 16 h. The reaction was concentrated in vacuo and the resulting crude product was used without further purification. 120 mg (100%) of S)-3-Methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butylamine-hydrochloride were obtained. 

\[
e_{8}H_{16}N_{4}O_{2}S (232.31), \text{LCMS (method 8_1_1): } R_t = 0.17 \text{ min, } m/z = 233.15 \text{ [M+H]}^{+}
\]

1) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-amide

To a solution of 120 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid in 1 ml of dry DMF 25 mg of HOAT, 85 mg of EDC and 0.36 ml of DIPEA were added at 0°C. After 15 min 108 mg of (S)-3-Methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butylamine-hydrochloride were added and the reaction was stirred at rt for 20 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with 2 M aqueous hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. After purification by HPLC 163 mg (82%) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid [(S)-3-methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl]-amide were obtained.
benzoimidazole-5-carboxylic acid \([(S)-3\text{-methyl-1-(4H-[1,2,4]triazole-3-sulfonylmethyl)-butyl}]\)-annide were obtained. 

C_{26}H_{34}N_{6}S_{3} \text{ (542.73), LCMS (method 3\_1\_1): } R_t = 1.45 \text{ min, } m/z = 543.24 \text{ [M+H]}^{+}

Example 485: \(1\)-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid \([(S)-3\text{-methyl-1-methylsulfamoylmethyl-butyl}]\)-amide

![Chemical structure]

a) Thioacetic acid S-((S)-2-tert-butoxycarbonylamino-4-methyl-pentyl) ester

To 1.00 g of toluene-4-sulfonic acid \((S)-2\text{-tert-butoxycarbonylamino-4-methyl-pentyl ester in 10 ml DMF were added 308 mg of potassium thioacetate. After 24 h at room temperature, the reaction was poured unto water, the pH was then adjusted to 9 and the mixture was extracted with ethyl acetate twice. The combined organic phases were washed with brine until neutral, dried over sodium sulphate and concentrated in vacuo. 0.67 g (90\%) of Thioacetic acid S-((S)-2-tert-butoxycarbonylamino-4-methyl-pentyl) ester were obtained. 

C_{13}H_{25}NO_{3}S \text{ (275.41), LCMS (method 8\_1\_1): } R_t = 1.00 \text{ min, } m/z = 176.15 \text{ [M+H-Boc]}^{+}

b) \((S)-3\text{-Methyl-1-methylsulfamoylmethyl-butyl}-carbamic acid tert-butyl ester
At 10 °C 920 mg Thioacetic acid S-((S)-2-tert-butoxycarbonylamino-4-methyl-pentyl) ester were added in several portions to a solution of 1.78 g N-chlorosuccinimide in 5 ml acetonitrile and 1 ml 2M aqueous hydrochloric acid. The reaction was kept a 0°C for 30 min and at room temperature for 30min. It was then diluted with THF, the layers were separated. The organic layer was washed with brine and concentrated in vacuo at room temperature. The crude sulfonyl chloride was dissolved in 10 ml THF and treated with 30 ml of 2M methylamine solution in THF. After 16 h at rt the reaction was diluted with ethyl acetate and sat. aqueous sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate, concentrated and the resulting residue was purified by HPLC to obtain 53 mg (5%) of ((S)-3-Methyl-1-methylsulfamoylmethyl-butyl)-carbamic acid tert-butyl ester. C_{12}H_{26}N_{2}O_{4}S (294.42), LCMS (method 8_1_1): Rt = 0.87 min, m/z= 195.1 0 [M+H-Boc]^+

c) (S)-2-Amino-4-methyl-pentane-1-sulfonic acid methylamid-hydrochloride

105 mg of ((S)-3-Methyl-1-methylsulfamoylmethyl-butyl)-carbamic acid tert-butyl ester were dissolved in 2 ml of dioxane and reacted with 1.3 ml of 4M hydrochloric acid in dioxane at rt for 16 h. The reaction was concentrated in vacuo and the resulting crude product was used without further purification. 60 mg (100 %) of (S)-2-Amino-4-methyl-pentane-1-sulfonic acid methylamide-hydrochloride were obtained. C_{7}H_{18}N_{2}O_{2}S (194.30), LCMS (method 8_1_1): Rt = 0.18 min, m/z= 195.1 5 [M+H]^+
d) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-methylsulfamoylmethyl-butyl)-amide

To a solution of 80 mg of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid in 0.5 ml of dry DMF 17 mg of HOAT, 56 mg of EDC and 0.24 ml of DIPEA were added at 0°C. After 15 min 60 mg of (S)-2-Amino-4-methyl-pentane-1-sulfonic acid methylamidemethyldioxide were added and the reaction was stirred at rt for 20 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 M aqueous hydrochloric acid. The reaction was extracted with ethyl acetate three times. The combined organic phases were washed with 2 M aqueous hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. After purification by HPLC 55 mg (45 %) of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid ((S)-3-methyl-1-methylsulfamoylmethyl-butyl)-amide were obtained. C25H33N4O3S2 (504.72), LCMS (method 3_1_1): Rt = 1.49 min, m/z= 505.24 [M+H]⁺

Preparation of intermediates:

1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

a) 4-Fluoro-3-nitro-benzoic acid methyl ester
5.55 g of 4-Fluoro-3-nitro-benzoic acid were dissolved in 50 ml of methanol, 6.4 ml of concentrated sulfuric acid were added and the reaction was heated to reflux for 3 h. The reaction was cooled, poured unto ice and the precipitated product was collected by suction and dried in vacuo. 5.40 g (90%) of 4-fluoro-3-nitro-benzoic acid methyl ester were obtained.

C₈H₆FNO₄ (199.14), LCMS (method 7_1_1): Rt = 1.28 min, m/z= 200.05 [M+H]+

b) 4-(1-Ethyl-propylamino)-3-nitro-benzoic acid methyl ester

To a solution of 5.38 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 25 ml of abs. DMF was added 5.60 g of potassium carbonate, followed by 2.67 g of 3-aminopentane. After 3 h at rt, the mixture was poured into water, and extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 7.01 g (97%) of 4-(1-Ethyl-propylamino)-3-nitro-benzoic acid methyl ester as a light brown oil.

C₁₃H₁₈N₂O₄ (266.30), LCMS (method 7_1_1): Rt = 1.80 min, m/z= 267.15 [M+H]+

c) 3-Amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester

7.00 g of 4-(1-Ethyl-propylamino)-3-nitro-benzoic acid methyl ester were dissolved in 70 ml ethanol, 0.35 g of palladium on carbon (10%) were added and the mixture was
hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, the filtrate was concentrated and after crystallization from diethylether 5.00 g (65%) of 3-Amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester were obtained.

C₁₃H₂₀N₂O₂ (236.31), LCMS (method 7_1_1): Rt = 1.09 min, m/z = 237.15 [M+H]+

d) 4-(1-ethyl-propylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester

To a solution of 1.56 g of thiophen-2-yl-acetic acid in 25 ml of dry DMF 1.49 g of HOBT, 2.11 g of EDC and 2.6 ml of DIPEA were added at 0°C. After 30 min 2.36 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester and 2.6 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by crystallization from diethylether to yield 2.78 g (77%) of 4-(1-ethyl-propylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester.

C₁₉H₂₄N₂O₃S (360.48), LCMS (method 7_1_1): Rt = 1.63 min, m/z = 361.15 [M+H]+

e) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester

0.72 g of 4-(1-ethyl-propylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were dissolved in 5 ml of dry dioxane and 10 ml of 4M hydrochloric acid
in dioxane were added. The reaction was heated in a microwave reactor to 120°C for 10 min and concentrated to yield 0.69 g (100%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester as a brown solid which was used in the next step without further purification.

C_{9}H_{22}N_{2}O_{2}S (342.46), LCMS (method 7_1_1): Rt = 1.25 min, m/z = 343.15 [M+H]^+

f) 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To 0.69 g of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester 4 ml of methanol and 4 ml of 1 M aqueous sodium hydroxide solution were added and the reaction was heated in a microwave reactor to 110°C for 5 min. The reaction mixture was adjusted to pH 5 by the addition of 2M aqueous hydrochloric acid and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. After crystallization from diisopropylether 0.46 g (96%) of 1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.

C_{18}H_{20}N_{2}O_{2}S (328.43), LCMS (method 7_1_1): Rt = 1.04 min, m/z = 329.15 [M+H]^+

(S)-2-[3-Amino-4-(1-isopropyl-2-methyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

(S)-2-(4-Fluoro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester

a) (S)-2-(4-Fluoro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester
To a solution of 9.26 g of 4-fluoro-3-nitro-benzoic acid in 100 ml of dry DMF 7.43 g of HOBT, 10.54 g of EDC and 8.9 ml of DIPEA were added at 0°C. After 30 min 12.31 g of L-leucin-tert.-butylester -hydrochloride and 8.9 ml of DIPEA were added and the reaction was stirred at rt for 4 h. The reaction was then concentrated to about a fifth of its volume and poured into water. It was then extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium carbonate solution and brine, dried over magnesium sulphate and concentrated to yield 17.65 g (100%) of (S)-2-(4-Fluoro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester as a brown oil, which was used without further purification in the subsequent step.

C₁₇H₂₃FN₂O₅ (354.38), LCMS (method 7_1_1): Rt = 1.71 min, m/z= 299.15 [M+H⁺-tBu]

b) (S)-2-[4-(1-Isopropyl-2-methyl-propylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

To a solution of 1.06 g of 4(S)-2-(4-Fluoro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester in 10 ml of abs. DMF was added 0.42 g of potassium carbonate, followed by 0.38 g of 3-amino-2,4-dimethylpentane. After 3 h at rt, the mixture was poured into water, and extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulphate and concentrated to yield 1.30 g (96 %) of (S)-2-[4-(1-Isopropyl-2-methyl-propylamino)-3-nitro-benzoylamino]-4-
methyl-pentanoic acid tert-butyl ester as a brown oil, which was used in the next step without further purification.

c) (S)-2-[3-Amino-4-(1-isopropyl-2-methyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{O} \\
\text{H} &\quad \text{O} \\
\text{N} &\quad \text{H} \\
\text{O} &\quad \text{N}
\end{align*}
\]

1.35 g of (S)-2-[4-(1-isopropyl-2-methyl-propylamino)-3-nitro-benzoylemido]-4-methyl-pentanoic acid tert-butyl ester were dissolved in 14 ml ethanol, 0.30 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, and the reaction mixture was concentrated to yield 1.00 g (79%) of (S)-2-[3-Amino-4-(1-isopropyl-2-methyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester as a viscous oil, which was used without further purification.

C_24H_4N_3O_3 (419.61), LCMS (method 7_1_1): Rt = 1.57 min, m/z = 420.36 [M+H]^+

(S)-2-[3-Amino-4-(1-ethyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{O} \\
\text{H} &\quad \text{O} \\
\text{N} &\quad \text{H} \\
\text{O} &\quad \text{N}
\end{align*}
\]

a) 4-(1-Ethyl-propylamino)-3-nitro-benzoic acid ethyl ester
To a solution of 25.0 g of 4-fluoro-3-nitro-benzoic acid ethyl ester in 100 ml of abs.
DMF was added 24.3 g of potassium carbonate, followed by 11.6 g of 3-
aminopentane. After 2 h at rt, the mixture was poured into water, and extracted with
ethyl acetate three times. The combined organic phases were dried over magnesium
sulphate and concentrated to yield 32.8 g (100%) of 4-(1-Ethyl-propylamino)-3-nitro-
benzoic acid ethyl ester as a yellow oil.
C_{14}H_{20}N_{2}O_{4} (280.32), LCMS (method 7_1_1): Rt = 1.90 min, m/z = 281.35 [M+H]^+

b) 4-(1-Ethyl-propylamino)-3-nitro-benzoic acid

30.0 g of 4-(1-ethyl-propylamino)-3-nitro-benzoic acid ethyl ester were dissolved in
100 ml ethanol and 10 ml THF and 107 ml of 2 M aqueous sodium hydroxide solution
were added. After stirring at room temperature over night, the reaction mixture was
brought to pH 1 by addition of 2 M aqueous hydrochloric acid and extracted with ethyl
acetate three times. The combined organic phases were dried over magnesium
sulphate and concentrated to yield 27.0 g (100%) of 4-(1-ethyl-propylamino)-3-nitro-
benzoic acid as a yellow solid.
C_{12}H_{16}N_{2}O_{4} (252.27), LCMS (method 7_1_1): Rt = 1.48 min, m/z = 253.35 [M+H]^+

c) (S)-2-[4-(1-Ethyl-propylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-
butyl ester
To a solution of 6.80 g of 4-(1-ethyl-propylamino)-3-nitro-benzoic acid in 210 ml of dry DMF, 1.82 g of HOBT, 7.23 g of EDC and 6.6 ml of DIPEA were added at 0°C. After 30 min 7.24 g of L-leucin-tert.-butylester-hydrochloride and 4.7 ml of DIPEA were added and the reaction was stirred at rt for 4 h. The reaction was then concentrated to about a fifth of its volume and poured into water. It was then extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium carbonate solution and brine, dried over magnesium sulphate and concentrated to yield 11.50 g (100%) of (S)-2-[4-(1-ethyl-propylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester.

C22H36N3O5 (421.54), LCMS (method 7_1_1): Rt = 2.02 min, m/z = 366.45 [M+H-tBu]+

d) (S)-2-[3-Amino-4-(1-ethyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

11.5 g of (S)-2-[4-(1-ethyl-propylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester were dissolved in 100 ml ethanol, 1.0 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, and the reaction mixture was concentrated and purified by chromatography (silica, heptane/ethyl acetate) to yield 6.5 g (61%) of (S)-
2-[[3-amino-4-(1-ethyl-propylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester as a colourless oil.

C22H37N3O3 (391.55), LCMS (method 7_1_1): Rt = 1.45 min, m/z= 392.65 [M+H]^+

5 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid

a) 3-(2-Cyclopentyl-acetylamino)-4-(1-ethyl-propylamino)-benzoic acid methyl ester

To a solution of 16.41 g of cyclopentyl-acetic acid in 600 ml of dry DMF 17.30 g of HOBT, 24.54 g of EDC and 30 ml of DIPEA were added at 0°C. After 1 h 27.51 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester and 30 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by crystallization from diisopropylether to yield 29.35 g (73%) of 3-(2-cyclopentyl-acetylamino)-4-(1-ethyl-propylamino)-benzoic acid methyl ester as an off-white solid.

C20H30N2O3 (346.47), LCMS (method 6_4_1): Rt = 2.04 min, m/z= 347.32 [M+H]^+

b) 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester
2.93 g of 3-(2-Cyclopentyl-acetylamino)-4-(1-ethyl-propylaminio)-benzoic acid methyl ester were dissolved in 7.5 ml of dry dioxane and 7.5 ml of 4M hydrochloric acid in dioxane were added. The reaction was heated in a microwave reactor to 140°C for 30 min. The reaction mixture was concentrated, the residue was taken up in ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and concentrated to yield 26.9 g (97%) of 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester as a brown solid which was used in the next step without further purification.

No analytical data

c) 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid

To 3.22 g of 2-Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester 5 ml of methanol and 7 ml of 2 M aqueous sodium hydroxide solution were added and the reaction was heated in a microwave reactor to 140°C for 1 h. The methanol was removed by distillation and the mixture was adjusted to pH 5 by the addition of 2M aqueous hydrochloric acid. The precipitated product was collected by filtration, washed with water and dried in vacuo. 2.22 g (65%) of Cyclopentylmethyl-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid were obtained as light-brown solid.

C₁₉H₂₆N₂O₂ (314.43), LCMS (method 6_4_1): Rt = 1.31 min, m/z = 315.18 [M+H]⁺
2-Cyclopentylmethyl-1 -(1-ethyl-propyl)-1 H-benzoimidazole-5-carbonyl chloride

To 8.00 g of 2-cyclopentylmethyl-1 -(1-ethyl-propyl)-1 H-benzoimidazole-5-carboxylic acid in 100 ml of dichloromethane 0.1 ml of DMF and 4 ml of oxalyl chloride were added. The reaction was stirred at rt for 16 h, then concentrated and co-distilled with toluene to obtain 8.45 g (100%) of the crude product as a brown solid, which was used without further purification.

No analytical data

1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl chloride

To 8.00 g of 1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid in 100 ml of dichloromethane 0.1 ml of DMF and 4 ml of oxalyl chloride were added. The reaction was stirred at rt for 16 h, then concentrated and co-distilled with toluene to obtain 8.47 g (100%) of the crude product as a brown solid, which was used without further purification.

No analytical data

1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid
To a solution of 4.48 g of 2-furylacetic acid in 30 ml of dry DMF 1.00 g of HOBT, 3.97 g of EDC and 1.8 ml of DIPEA were added at 0°C. After 30 min 3.50 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester and 1.8 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium carbonate solution and saturated aqueous ammonium chloride solution, dried over magnesium sulphate and concentrated to obtain 4.44 g (87%) of 4-(1-Ethyl-propylamino)-3-(2-furan-2-yl-acetylamino)-benzoic acid methyl ester.

C₁₉H₂₄N₂O₄ (344.41), LCMS (method 7_1_1): Rt = 1.51 min, m/z= 345.15 [M+H]^+

b) 1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester

4.70 g of 4-(1-Ethyl-propylamino)-3-(2-furan-2-yl-acetylamino)-benzoic acid methyl ester were dissolved in 25 ml of dry dioxane and 50 ml of 4M hydrochloric acid in dioxane were added. The reaction was heated to reflux for 10 h and concentrated to
yield 4.70 g (100%) of 1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester which was used in the next step without further purification.

C_{19}H_{22}N_{2}O_{3} (326.40), LCMS (method 7_1_1): Rt = 1.18 min, m/z = 327.35 [M+H]^+

c) 1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To 5.30 g of 1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester 12 ml of methanol and 22 ml THF 22 ml of 1 M aqueous sodium hydroxide solution were added and the reaction was stirred for 16 h. The reaction mixture was adjusted to pH 5 by the addition of 2M aqueous hydrochloric acid and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. 4.83 g (85%) of 1-(1-Ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.

C_{8}H_{20}N_{2}O_{3} (312.37), LCMS (method 6_4_1): Rt = 1.25 min, m/z = 313.07 [M+H]^+

1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1 H-benzoimidazole-5-carboxylic acid

A solution of 348 mg of 1-(1-ethyl-propyl)-2-furan-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid in 5 ml of ethanol was hydrogenated at 5 bar for 24h in the presence of 10 mg platinum oxide. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The resulting residue was purified by HPLC to obtain 55 mg
(17%) of 1-(1-Ethyl-propyl)-2-(tetrahydro-furan-2-ylmethyl)-1H-benzoimidazole-5-carboxylic acid.

C_{18}H_{24}N_{2}O_{3} (316.40), LCMS (method 7_1_1): Rt = 0.97 min, m/z= 317.25 [M+H]^+

2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid

\[
\text{HO C} \quad \text{N} \quad \text{O} \\
\text{Cl} \\
\]

a) 3-[2-(5-Chloro-thiophen-2-yl)-acetylamino]-4-(1-ethyl-propylamino)-benzoic acid methyl ester

\[
\text{HO C} \quad \text{N} \quad \text{O} \\
\text{Cl} \\
\]

To a solution of 1.00 g of 5-Chlorothiophen-2-yl-acetic acid in 15 ml of dry DMF 0.84 g of HOBT, 1.19 g of EDC and 1.5 ml of DIPEA were added at 0°C. After 30 min 1.33 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester and 1.5 ml of DIPEA were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by crystallization from diethylether to yield 2.00 g (89%) of 3-[2-(5-Chloro-thiophen-2-yl)-acetylamino]-4-(1-ethyl-propylamino)-benzoic acid methyl ester.

C_{19}H_{23}CIN_{2}O_{3}S (394.92), LCMS (method 7_1_1): Rt = 1.71 min, m/z= 395.25 [M+H]^+
b) 2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

\[ \text{C}_{19}\text{H}_{21}\text{ClN}_{2}\text{O}_{2}\text{S} (376.91) \], LCMS (method 7_1_1): \( R_t = 1.41 \) min, \( m/z = 377.20 \) [M+H]^+

0.99 g 3-[2-(5-Chloro-thiophen-2-yl)-acetylamino]-4-(1-ethyl-propylamino)-benzoic acid methyl ester were reacted with 10 ml of 4M hydrochloric acid in dioxane in a microwave reactor at 130°C for 15 min. The reaction was concentrated. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulphate and concentrated to yield 0.73 g (77%) of 2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester.

To 0.57 g of 2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid methyl ester in 3 ml of methanol were added 0.08 g of lithium hydroxide and 1 ml of water. The reaction was heated to reflux for 1 h. The reaction mixture was adjusted to pH 5 by the addition of 2M aqueous hydrochloric acid and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. The product precipitated after
treatment with diethylether and 0.30 g (55%) of 2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid were obtained.

C18H19ClN2O2S (362.88), LCMS (method 7_1_1): Rt = 1.19 min, m/z= 363.15 [M+H]+

5

1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carboxylic acid

1-(1-Ethyl-propyl)-2-thiazol-4-ylmethyl-1H-benzoimidazole-5-carboxylic acid was synthesized in analogy to 2-(5-Chloro-thiophen-2-ylmethyl)-1-(1-ethyl-propyl)-1H-benzoimidazole-5-carboxylic acid.

C17H19N3O2S (329.42); LCMS (method 6_4_1): Rt = 1.05 min, m/z= 330.12 [M+H]+

1-(1-Ethyl-propyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid

15 a) 4-(1-Ethyl-propylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester

To a solution of 1.00 g of Thiazol-5-yl-acetic acid acid in 17 ml of dry DMF 0.48 g of HOAT, 1.61 g of EDC and 2.3 ml of DIPEA were added at 0°C. After 30 min 1.65 g of 3-Amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester were added, followed by
the addition of 2 ml of DIPEA and the reaction was stirred at rt for 48 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 2.16 g (85%) of 4-(1-Ethyl-propylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

C₁₈H₂₃N₃O₃S (361.47), LCMS (method 8_1_1): Rt = 0.83 min, m/z= 362.15 [M+H]+

b) 1-(1-Ethyl-propyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid

TO 2.16 g of 4-(1-Ethyl-propylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester were added 15 ml of 4M hydrochloric acid in dioxane. The reaction was divided in three portions and each was heated at 130°C in a microwave reactor for 15 min. 2 ml of water were added to each vial and the reaction mixtures were heated to 140 °C for 15 min. The combined reaction mixtures were concentrated and the residue purified by chromatography (silica, ethyl acetate/heptane) to yield 1.50 g (77%) of 1-(1-Ethyl-propyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid.

C₁₇H₁₉N₃O₂S (329.42), LCMS (method 8_1_1): Rt = 0.62 min, m/z= 330.10 [M+H]+

1-(1-Ethyl-propyl)-2-pyrazol-1-ylmethyl-1H-benzoimidazole-5-carboxylic acid

a) 4-(1-Ethyl-propylamino)-3-(2-pyrazol-1-yl-acetylamino)-benzoic acid methyl ester
To a solution of 1.76 g of Pyrazol-1-yl-acetic acid in 20 ml of dry DMF 2.09 g of HOAT, 3.75 g of EDC and 6.9 ml of DIPEA were added at 0°C. After 30 min 3.3 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by precipitation from heptane to yield 2.28 g (47%) of 4-(1-ethyl-propylamino)-3-(2-pyrazol-1-yl-acetylamino)-benzoic acid methyl ester.

C_{8}H_{24}N_{4}O_{3} (344.42), LCMS (method 8_1_1): Rt = 0.85 min, m/z = 345.15 [M+H]^+

b) 1-(1-Ethyl-propyl)-2-pyrazol-1-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To 2.28 g 4-(1-ethyl-propylamino)-3-(2-pyrazol-1-yl-acetylamino)-benzoic acid methyl ester were added 50 ml of 4M hydrochloric acid in dioxane. Divided into five portions the reaction mixture was heated to 110°C for 15 min in a microwave reactor. After cooling to the reaction mixture 6 ml of 10 M aqueous sodium hydroxide solution were added slowly. After 30 min at rt the reaction mixture was concentrated to a third of its volume and adjusted to pH 4 by the addition of 2M aqueous hydrochloric acid. It was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. 1.86 g (90%) of 1-(1-ethyl-propyl)-2-pyrazol-1-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.
C$_{7}$H$_{20}$N$_{4}$O$_{2}$ (31 2.37), LCMS (method 8_1_1): Rt = 0.65 min, m/z= 313.1 5 [M+H]$^+$

1-(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To a solution of 0.71 g of isoxazol-5-yl-acetic acid in 15 ml of dry DMF 0.38 g of HOAT, 1.29 g of EDC and 3 ml of DIPEA were added at 0°C. After 30 min 1.32 g of 3-amino-4-(1-ethyl-propylamino)-benzoic acid methyl ester were added and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by precipitation from diisopropylether to yield 1.06 g (55 %) of 4-(1-Ethyl-propylamino)-3-(2-isoxazol-5-yl-acetylamino)-benzoic acid methyl ester.

C$_{8}$H$_{23}$N$_{3}$O$_{4}$ (345.40), LCMS (method 8_1_1): Rt = 0.86 min, m/z= 346.1 5 [M+H]$^+$

b) 1-(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1 H-benzoimidazole-5-carboxylic acid
To 1.06 g 4-(1-Ethyl-propylamino)-3-(2-isoxazol-5-yl-acetylannino)-benzoic acid methyl ester were added 7.5 ml of 4M hydrochloric acid in dioxane. The reaction mixture was heated to 130°C for 20 min in a microwave reactor. After cooling to rt 2 ml of water were added and the reaction was again heated to 130°C for 20 min. The reaction was concentrated and the residue purified by chromatography (silica, ethyl acetate/heptane) to yield 0.85 g (90%) of 1-(1-Ethyl-propyl)-2-isoxazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid.

C₁₁H₁₉N₃O₃ (313.36), LCMS (method 8_1_1): Rₜ = 0.62 min, m/z= 314.15 [M+H]⁺

---

1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid

a) 4-(Cyclohexylmethyl-amino)-3-nitro-benzoic acid methyl ester

To a solution of 25.0 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 100 ml of abs. DMF was added 26.0 g of potassium carbonate, followed by 14.2 g of (cyclohexylmethyl)amine. After 16 h at rt, the mixture was poured into water, and extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 36.7 g (100%) of 4-(Cyclohexylmethyl-amino)-3-nitro-benzoic acid methyl ester as an orange solid.

C₁₅H₂₀N₂O₄ (292.33), LCMS (method 6_4_1): Rₜ = 2.32 min, m/z= 293.17 [M+H]⁺

b) 3-Amino-4-(cyclohexylmethyl-amino)-benzoic acid methyl ester
12.00 g 4-(Cyclohexylmethyl-annino)-3-nitro-benzoic acid methyl ester were dissolved in 75 ml ethyl acetate and 75 ml methanol, 0.45 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, the filtrate was concentrated and after precipitation with cyclohexane 12.00 g (93%) of 3-Amino-4-(cyclohexylmethyl-amino)-benzoic acid methyl ester were obtained.

C15H22N2O2 (262.35), LCMS (method 7_1_1): Rt = 1.27 min, m/z= 263.25 [M+H]+

c) 4-(Cyclohexylmethyl-amino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester

To a solution of 8.94 g of thiophen-2-yl-acetic acid in 130 ml of dry DMF 8.56 g of HOAT, 12.06 g of EDC and 30 ml of DIPEA were added at 0°C. After 30 min 15.00 g of 3-Amino-4-(cyclohexylmethyl-amino)-benzoic acid methyl ester were added and the reaction was stirred at 80°C for 48 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated. The crude product was purified by chromatography (silica, ethyl acetate/heptane) to yield 22.00 g (100%) of 4-(Cyclohexylmethyl-amino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester.

C21 H26N2O3S (386.51); LCMS (method 6_4_1): Rt = 2.05 min, m/z= 387.1 6 [M+H]+
d) 1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester

20.0 g 4-(Cyclohexylmethyl-amino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were dissolved in 65 ml dioxane and reacted with 33 ml of 4M hydrochloric acid in dioxane at rt for 4 h. The reaction was concentrated and the residue purified by chromatography (silica, ethyl acetate/heptane) to yield 13.6 g (71%) of 1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester.

C_{21}H_{24}N_{2}O_{2}S (368.50), LCMS (method 6_4_1): Rt = 1.63 min, m/z= 369.06 [M+H]^+

e) 1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To 13.60 g of 1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester in 25 ml of methanol and 100 ml of THF were added 37 ml of 2 M aqueous sodium hydroxide solution. The reaction stirred at rt for 6 h. The reaction mixture was adjusted to pH 4 by the addition of 2M aqueous hydrochloric acid and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. The residue was purified by chromatography (silica, heptane/ethyl acetate) to yield 11.1 g (85%) of 1-Cyclohexylmethyl-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid.
C20H22N2O2S (354.47) LCMS (method 6_4_1): Rt = 1.42 min, m/z = 355.06 [M+H]^+

(S)-2-[3-Amino-4-(2-chloro-phenylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

C23H28CIN3O5 (461.94), LCMS (method 7_1_1): Rt = 1.93 min, m/z = 406.10 [M+H-tBu]^+

To a solution of 300 mg of (S)-2-(4-Fluoro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester in 1.6 ml of abs. DMF was added 1044 mg of cesium carbonate, followed by 90 mg of 2-chloroaniline. The reaction was heated in a microwave reactor to 80°C for 2 min. The mixture was poured into water, and extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulphate and concentrated to yield 149 mg (50%) of (S)-2-[4-(2-Chloro-phenylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl.

b) (S)-2-[3-Amino-4-(2-chloro-phenylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester
140 mg of (S)-2-[4-(2-Chloro-phenylamino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester were dissolved in 5 ml ethyl acetate, 342 mg of tin(II)chloride-dihydrate were added and the mixture was stirred at rt for 4 h. Water was added to the reaction. The mixture was filtrated over celite. The pH of the filtrate was adjusted to 7, the layers were separated and the organic layer was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate and concentrated to yield 103 mg (79 %) of (S)-2-[3-Amino-4-(2-chloro-phenylamino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester.

C23H30ClN3O3 (431.96), LCMS (method 7_1_1): Rt = 1.72 min, m/z= 432.20 [M+H]^+
To a solution of 200 mg of 4(S)-2-(4-chloro-3-nitro-benzoylamino)-4-methyl-pentanoic acid tert-butyl ester in 1.4 ml of abs. DMF was added 878 mg of cesium carbonate, followed by 60 mg of 1,3-dimethylbutylamine. The reaction was heated in a microwave reactor to 100°C for 10 min. Then the mixture was poured into water, and extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulphate and concentrated. The resulting residue was purified by HPLC to yield 56 mg (24%) of (S)-2-[3-Amino-4-(1,3-dimethyl-butyramino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester.

C23H37N3O5 (435.56) LCMS (method 6_4_1): Rt = 2.44 min, m/z= 436.25 [M+H]+

b) (S)-2-[3-Amino-4-(1,3-dimethyl-butyramino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester

50 mg of (S)-2-[4-(1,3-Dimethyl-butyramino)-3-nitro-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester were dissolved in 0.5 ml ethanol, 5 mg of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, and the reaction mixture was concentrated to yield 45 mg (99%) of (S)-2-[3-Amino-4-(1,3-dimethyl-butyramino)-benzoylamino]-4-methyl-pentanoic acid tert-butyl ester, which was used without further purification.
C23H39N3O3 (405.59), LCMS (method 7_1_1): R_t = 1.50 min, m/z = 406.25 [M+H]^+

1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid

5 a) 4-(2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester

To a solution of 20.0 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 100 ml of abs. DMF was added 27.8 g of potassium carbonate, followed by 12.5 g of 2-methylcyclohexylamine. After 16 h at rt, the mixture was poured into water, the pH was adjusted to 4 by the addition of 2 M aqueous hydrochloric acid, and the reaction mixture was extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 29.4 g (100%) of 4-(2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester.

C15H20N2O4 (292.34), LCMS (method 7_1_1): R_t = 1.85 min, m/z = 293.25 [M+H]^+

15 b) 3-Amino-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester

13.50 g 4-(2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester were dissolved in 60 ml methanol, 0.49 g of palladium on carbon (10%) were added and
the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by filtration over celite, the filtrate was concentrated to obtain 12.00 g (99%) of 3-Amino-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester.

C₅H₂₂N₂O₂ (262.35), LCMS (method 7_1_1): Rt = 1.20 min, m/z = 263.50 [M+H]⁺

c) 4-(2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester

![Chemical Structure](image1)

To a solution of 4.34 g of thiophen-2-yl-acetic acid in 40 ml of dry DMF 2.08 g of HOAT, 8.77 g of EDC and 13 ml of DIPEA were added at 0°C. After 30 min 8.00 g of 3-Amino-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester were added, followed by the addition of 6 ml of DIPEA and the reaction was stirred at rt for 48 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 11.75 g (100%) of 4-(2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

C₂₁H₂₆N₂O₃S (386.52), LCMS (method 7_1_1): Rt = 1.69 min, m/z = 387.35 [M+H]⁺

d) 1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid

![Chemical Structure](image2)
0.77 g 4-(2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were reacted with 5 ml of 4M hydrochloric acid in dioxane at 100°C in a microwave reactor for 5 min. 1 ml water was added and the mixture was heated to 135 °C for 15 min. The reaction was concentrated and the residue purified by chromatography (silica, ethyl acetate/heptane) to yield 0.65 g (91 %) of 1-(((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid. C20H22N2O2S (354.47), LCMS (method 7_1_1): Rt = 1.16 min, m/z= 355.25 [M+H]^+

(1R,2R)-2-Methyl-cyclohexylamine-hydrochloride and (1S,2S)-2-Methyl-cyclohexylamine-hydrochloride

\[
\begin{align*}
\text{NH}_2\text{ClH} & \quad \text{and} \quad \text{NH}_2\text{ClH} \\
\end{align*}
\]

To a solution of 200 g cyclohexene and 30.7 g iodine in 800 ml of anhydrous dioxane was added 611.7 g of chloramine T. The mixture was stirred at 80°C for 10 h. After cooling to room temperature the mixture was poured into ice water and extracted with ethyl acetate twice. The combined organic phases were dried over sodium sulphate and concentrated and the residue was purified by chromatography (Silica, hexane/Ethyl acetate) to afford 180 g (29%) of 7-(Toluene-4-sulfonyl)-7-aza-bicyclo[4.1.0]heptane as a white solid.

\[\begin{align*}
\text{N} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\end{align*}\]

\[\begin{align*}
\text{1H-NMR (400 MHz, CDCI3): } \delta = 7.78 (dd, 2H, J = 1.6 Hz, J = 1.6 Hz), 7.30 (dd, 2H, J = 0.4 Hz, J = 10 Hz), 2.94 (d, 2H, J = 1.6 Hz), 2.38 (t, 3H, J = 4.6 Hz), 1.77 (t, 4H, J = 4.6 Hz), 1.38 (m, 2H), 1.32 (m, 2H)
\end{align*}\]

b) 4-Methyl-N-((1 S,2S)-2-methyl-cyclohexyl)-benzenesulphonamide and 4-Methyl-N-((1 R,2R)-2-methyl-cyclohexyl)-benzenesulphonamide
To the solution of 180 g of 7-(Toluene-4-sulfonyl)-7-aza-bicyclo[4.1.0]heptane and 18 g of Copper(II)acetyl acetate in 1500 ml of dry THF was added 86 ml of a 10 M solution of methyllithium dropwise over 30 min. The mixture was stirred under nitrogen atmosphere for 8 h. It was then washed with water and extracted with ethyl acetate twice. The combined organic layers were concentrated. The resulting residue was purified by chromatography (silica, hexan/ethyl acetate) to afford 120 g (62%) of 4-Methyl-N-(trans-2-methyl-cyclohexyl)-benzenesulfonamide.

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.78 (dd, 2H, J = 2 Hz, J = 1.6 Hz), 7.27 (t, 2H, J = 4 Hz), 4.76 (d, 1H, J = 8.4 Hz), 2.69 (q, 1H, J = 4.2 Hz), 2.39 (s, 3H), 1.57 (m, 4 H), 1.20 (m, 4H), 1.08 (m, 1H); 0.79 (t, 3H, J = 3.2 Hz)

The two diastereomers of 4-methyl-N-(trans-2-methyl-cyclohexyl)-benzenesulfonamide were separated using a Berger Multigram SFC instrument from MEttler Toledo on a ChiralPak AD, 20 $\mu$m column (300 x 50 mm) from Daicel Chemical Industries with a mobile phase of supercritical carbon dioxide and IPA 70/30 at 200 ml/min at 38°C. Retention time of the first diastereomer was 7.5 min with > 99 % ee, retention time of the second diastereomer was 9.2 min with 98.2 % ee.

c) ((1S,2S)-2-Methyl-cyclohexyl)-carbamic acid tert-butyl ester and ((1R,2R)-2-Methyl-cyclohexyl)-carbamic acid tert-butyl ester

To a solution of 2.0 g of the first diastereomer of 4-methyl-N-(trans-2-methyl-cyclohexyl)-benzenesulfonamide (rt = 7.5 min) in 20 ml dry THF and 20 of liquid ammonia was added 1 g of sodium at -78°C under nitrogen atmosphere and the solution was stirred for 5 h. Then 20 ml of ethanol and 20 ml of water were added and ammonia was evaporated. The solution was cooled to 0°C and 2.5 g of B0C2O
was added. The resulting solution was stirred overnight, the solvent was removed and the residue was dissolved in ethyl acetate, washed with water and brine and dried over magnesium sulphate. The solvent was evaporated and the resulting residue was purified by chromatography (silica, ethyl acetate/hexane) to obtain 1.2 g (75%) of the first diastereomer of trans-2-Methyl-cyclohexylicarbamic acid tert-butyl ester.

\[ ^1H\text{-NMR (400 MHz, CDCl}_3): \delta = 4.25 \text{ (s, 1H)}, 3.05 \text{ (s, 1H)}, 1.91 \text{ (m, 2H)}, 1.67 \text{ (m, 2H)}, 1.57 \text{ (m, 1H)}, 1.48 \text{ (s, 9H)}, 1.28 \text{ (m, 2H)}, 1.18 \text{ (m, 2H)}, 1.11 \text{ (d, 3H, J = 6 Hz)}. \]

The second diastereomer of trans-2-Methyl-cyclohexylcarbamic acid tert-butyl ester was obtained in analogous manner starting from the second diastereomer of 4-methyl-N-(trans-2-methyl-cyclohexyl)benzenesulfonamide (rt = 9.2 min).

\[ ^1H\text{-NMR (400 MHz, CDCl}_3): \delta = 4.25 \text{ (s, 1H)}, 3.05 \text{ (s, 1H)}, 1.91 \text{ (m, 2H)}, 1.67 \text{ (m, 2H)}, 1.57 \text{ (m, 1H)}, 1.48 \text{ (s, 9H)}, 1.28 \text{ (m, 2H)}, 1.18 \text{ (m, 2H)}, 1.11 \text{ (d, 3H, J = 6 Hz)}. \]

d) (1R,2R)-2-Methyl-cyclohexylamine-hydrochloride and (1S,2S)-2-Methyl-cyclohexylamine-hydrochloride

To 20 g of the first diastereomer of trans-2-Methyl-cyclohexylcarbamic acid tert-butyl ester was added 150 ml of hydrochloric acid (2M in diethyl ether) and the mixture was stirred for 30 min at rt. Then the mixture was filtered and the solid was washed with diethyl ether. 13.6 g (96%) of the first diastereomer of trans-Methyl-cyclohexylamine-hydrochloride were obtained.

\[ ^1H\text{-NMR (400 MHz, CD}_2\text{OD): } \delta = 2.72 \text{ (d, 1H, J = 3.2 Hz)}, 2.03 \text{ (q, 1H, J = 1.6 Hz)}, 1.81 \text{ (m, 2H)}, 1.72 \text{ (m, 1H)}, 1.60 \text{ (m, 1H)}, 1.38 \text{ (m, 4H)}, 1.31 \text{ (m, 1H)}, 1.28 \text{ (d, 2H, J = 3.2 Hz)}. \]

The optical rotation for this first diastereomer of trans-2-Methyl-cyclohexylamine-hydrochloride was determined at rt as \[ \alpha_{D}^0 = -24.66 \pm 0.1 \text{ ° (c=4, MeOH)}. \] Therefore an (1R,2R)-configuration was assigned to this first diastereomer based on the
comparison of the optical rotation described for (1S,2S)-2-Methyl-cyclohexylamine-hydrochloride, which was synthesized by H.C. Brown using a chiral-pool derived borane and for which an optical rotation at 21°C of $[\alpha]_D = +26.63$ ° (c=4, MeOH) was reported (J. Am. Chem. Soc. 1986, 108, 21, 6761).

To 2.1 g of the second diastereomer of trans-2-Methyl-cyclohexyl)-carbamic acid tert-butyl ester was added 150 ml of hydrochloric acid (2M in diethyl ether) and the mixture was stirred for 30 min at rt. Then the mixture was filtered and the solid was washed with diethyl ether. 14.2 g (97%) of the second diastereomer of trans-Methyl-cyclohexylamine-hydrochloride were obtained.

$^1$H-NMR (400 MHz, CD$_3$OD): $\delta = 2.72$ (d, 1H, J= 3.2 Hz), 2.03 (q, 1H, J = 1.6 Hz), 1.81 (m, 2H), 1.72 (m, 1H), 1.60 (m, 1H), 1.38 (m, 4H), 1.31 (m, 1H), 1.28 (d, 2H, J = 3.2 Hz).

The optical rotation for this second diastereomer of trans-2-Methyl-cyclohexylamine-hydrochloride was determined at rt as $[\alpha]_D = +25.15 \pm 0.1 2$ ° (c=4, MeOH). Therefore an (1S,2S)-configuration was assigned to this second diastereomer based on the comparison of the optical rotation described for (1S,2S)-2-Methyl-cyclohexylamine-hydrochloride, which was synthesized by H.C. Brown using a chiral-pool derived borane and for which an optical rotation at 21°C of $[\alpha]_D = +26.63$ ° (c=4, MeOH) was reported (J. Am. Chem. Soc. 1986, 108, 21, 6761).

1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid

\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid

a) 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester
To a solution of 6.47 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 35 ml of abs. DMF was added 13.47 g of potassium carbonate, followed by 4.96 g of (1R,2R)-2-Methyl-cyclohexylamine-hydrochloride. After 1.5 h at 60°C, the mixture was poured into water, the pH was adjusted to 5-6 by the addition of 2 M aqueous hydrochloric acid, and the reaction mixture was extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 9.28 g (98 %) of 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester.

C_{15}H_{20}N_{2}O_{4} (292.34); LCMS (method 8_1_1): Rt = 1.11 min, m/z = 293.15 [M+H]^+

b) 3-Amino-4-((1 R,2R)-2-methyl-cyclohexylamino)-benzoic acid methyl ester

9.27 g 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester were dissolved in 100 ml ethanol, 0.20 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 3 h. The catalyst was removed by filtration over celite, the filtrate was concentrated to obtain 8.20 g (99 %) of 3-Amino-4-((1R,2R)-2-methyl-cyclohexylamino)-benzoic acid methyl ester.

C_{15}H_{22}N_{2}O_{2} (262.35); LCMS (method 8_1_1): Rt = 0.77 min, m/z = 263.15 [M+H]^+

c) 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester
To a solution of 0.49 g of thiazol-5-yl-acetic acid in 10 mL of dry DMF 0.27 g of HOAT, 0.79 g of EDC and 1 mL of DIPEA were added at 0°C. After 30 min 0.9 g of 3-Amino-4-((1 R,2 R)-2-methyl-cyclohexylamino)-benzoic acid methyl ester were added, followed by the addition of 1 mL of DIPEA and the reaction was stirred at rt for 48 h. The reaction was then poured into water, brought to pH3 by the addition of 2 M aqueous hydrochloric acid and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 1.25 g (94 %) of 4-((1 R,2 R)-2-Methyl-cyclohexylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

C20H25N3O3S (387.50), LCMS (method 8_1_1): Rt = 0.92 min, m/z= 388.10 [M+H]+

d) 1-((1 R,2 R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid methyl ester

To 1.26 g 4-((1 R,2 R)-2-Methyl-cyclohexylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester in 10 mL dioxane were added 12 mL of 4M hydrochloric acid in dioxane and the mixture was heated to reflux for 2 h. The reaction was concentrated and the residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and brine. The organic layers were dried over sodium sulphate and concentrated. The resulting residue was purified by
HPLC to yield 0.37 g (31%) of 1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid methyl ester.

C20H23N3O2S (369.45), LCMS (method 7_1_1): Rt = 0.80 min, m/z = 370.1 [M+H]⁺

e) 1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid

0.35 g 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-(2-thiazol-5-yl-acetylamino)-benzoic acid methyl ester was dissolved in 6 ml of THF and 3 ml of methanol and 7 ml of 2 M aqueous sodium hydroxide solution were added at rt for 4 h. The reaction was concentrated and the pH was adjusted to 5 by addition of 2 M aqueous hydrochloric acid, and the mixture was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate and concentrated to afford 0.32 g (95%) of 1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiazol-5-ylmethyl-1H-benzoimidazole-5-carboxylic acid.

C₁₉H₂₁N₃O₂S (355.46), LCMS (method 7_1_1): Rt = 0.65 min, m/z = 356.1 [M+H]⁺

1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid

a) 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester
To a solution of 4.46 g of 2-thienyl-acetic acid in 80 ml of dry DMF 1.94 g of HOAT, 6.56 g of EDC and 9 ml of DIPEA were added at 0°C. After 30 min 7.48 g of 3-Amino-4-((1R,2R)-2-methyl-cyclohexylamino)-benzoic acid methyl ester were added, followed by the addition of 9 ml of DIPEA and the reaction was stirred at rt for 16 h. The reaction was then poured into water, brought to pH3 by the addition of 2 M aqueous hydrochloric acid and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 9.52 g (86%) of 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

b) 1-((1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

To 8.32 g 4-((1R,2R)-2-Methyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were added 40 ml of 4M hydrochloric acid in dioxane and the mixture was heated in four portions in a microwave reactor to 130°C for 20 min. 2 ml of water were added to each vial and the reactions were heated to 130°C for 40 min. The reactions were then combined and concentrated and the pH was adjusted to 6 by addition of saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were dried over
sodium sulphate and concentrated. The product precipitated upon treatment with diisopropylether and 5.65 g (76 %) of 1-((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.

C20H22N2O2S (354.47), LCMS (method 8_1_1): Rt = 0.75 min, m/z= 355.15 [M+H]+

1-((1 S, 2S)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

![Chemical Structure]

1-((1 S,2S)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid was prepared in analogy to the synthesis of 1-((1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid via 3-Amino-4-((1 S,2S)-2-methyl-cyclohexylamino)benzoic acid methyl ester and starting from (1S,2S)-2-Methyl-cyclohexylamine-hydrochloride.

C20H22N2O2S (354.47), LCMS (method 8_1_1): Rt = 0.75 min, m/z= 355.15 [M+H]+

2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1 H-benzoimidazole-5-carboxylic acid

![Chemical Structure]

a) 3-(2-Furan-2-yl-acetylamino)-4-(2-methyl-cyclohexylamino)benzoic acid methyl ester
To a solution of 1.26 g of 2-furyl-acetic acid in 15 ml of dry DMF 1.50 g of HOAT, 2.11 g of EDC and 8 ml of DIPEA were added at 0°C. After 30 min 1.31 g of 3-Amino-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester were added, and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 1.85 g (100 %) of 3-(2-Furan-2-yl-acetylamino)-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester, which was used without further purification.

C21 H26N2O4 (370.45), LCMS (method 7_1_1): Rt = 1.61 min, m/z = 371.15 [M+H]+

b) 2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid methyl ester

1.48 g 3-(2-Furan-2-yl-acetylamino)-4-(2-methyl-cyclohexylamino)-benzoic acid methyl ester with 15 ml of 4M hydrochloric acid in dioxane were heated in a microwave reactor to 130°C for 15 min. Water was added to the reaction mixture and the pH was adjusted to 7 by the addition of saturated sodium bicarbonate solution. The phases were separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried over sodium sulphate, concentrated
and 1.31 g (93%) of 2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid methyl ester were obtained.

C21H24N2O3 (352.43), LCMS (method 7_1_1): Rt = 1.29 min, m/z = 353.15 [M+H]^+

c) 2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid

To 1.30 g of 2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid methyl ester in 15 ml of methanol were added 6 ml of 2 M aqueous sodium hydroxide solution. The reaction stirred at rt for 16 h. The reaction mixture was adjusted to pH 5 by the addition of 2 M aqueous hydrochloric acid and was extracted with ethyl acetate three times. The combined organic phases were dried over sodium sulphate and concentrated in vacuo. The residue was precipitated using heptane to yield 0.68 g (54%) of 2-Furan-2-ylmethyl-1-(2-methyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid.

C20H22N2O3 (338.41), LCMS (method 7_1_1): Rt = 1.13 min, m/z = 339.15 [M+H]^+

2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid

a) 3-Nitro-4-(2-trifluoromethyl-cyclohexylamino)benzoic acid methyl ester
To a solution of 0.92 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 15 ml of abs. DMF was added 0.84 ml of DIPEA, followed by 0.85 g of 2-(trifluoromethyl)cyclohexylamine. After 16 h at rt, the mixture was poured into water, the pH was adjusted to 4 by the addition of 1 M aqueous hydrochloric acid, and the reaction mixture was extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 1.62 g (100%) of 3-Nitro-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester.

C_{15}H_{17}F_{3}N_{2}O_{4} (346.31), LCMS (method 7_1_1): Rt = 1.75 min, m/z = 347.10

b) 3-Amino-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester

1.63 g 3-Nitro-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester were dissolved in 25 ml methanol, 0.03 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 16 h. The catalyst was removed by filtration over celite, the filtrate was concentrated to obtain 1.44 g (97%) of 3-Amino-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester.

C_{15}H_{17}F_{3}N_{2}O_{2} (316.33), LCMS (method 7_1_1): Rt = 1.31 min, m/z = 317.15

c) 3-(2-Thiophen-2-yl-acetylamino)-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester
To a solution of 0.71 g of thiophen-2-yl-acetic acid in 10 ml of dry DMF 0.68 g of HOAT, 1.22 g of EDC and 2.25 ml of DIPEA were added at 0°C. After 30 min 1.44 g of 3-Amino-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester were added, and the reaction was stirred at rt for 16 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 2.00 g (100%) of 3-(2-Thiophen-2-yl-acetylamino)-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester, which was used without further purification.

\[ \text{1H23F3N2O3S (440.49), LCMS (method 7_1_1): Rt = 1.56 min, m/z= 441.15 [M+H]^+} \]

d) 2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1H-benzoimidazole-5-carboxylic acid

0.75 g 3-(2-Thiophen-2-yl-acetylamino)-4-(2-trifluoromethyl-cyclohexylamino)-benzoic acid methyl ester with 10 ml of 4M hydrochloric acid in dioxane were heated in a microwave reactor to 110°C for 5 h. 3 ml water was added to the reaction mixture, which was reacted again to 110°C for 2 h. The mixture was then concentrated in vacuo, the residue taken up in ethyl acetate and water, and the pH of the aqueous phase was brought to 4. The phases were separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were dried
over magnesium sulphate, concentrated and 0.75 g (100 %) of 2-Thiophen-2-ylmethyl-1-(2-trifluoromethyl-cyclohexyl)-1 H-benzoimidazole-5-carboxylic acid were obtained.

C20H19F3N2O2S (408.45), LCMS (method 7_1_1): Rt = 1.26 min, m/z= 409.1 0

5 [M+H]⁺

1-(2-Methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

a) 4-(2-Methyl-cyclopentylamino)-3-nitro-benzoic acid methyl ester

To a solution of 9.32 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 30 ml of abs. DMF was added 16.47 g of potassium carbonate, followed by 5.00 g of 2-methyl-cyclopentylamine. After 16 h at rt, the mixture was poured into water, the pH was adjusted to 5 by the addition of 2 M aqueous hydrochloric acid, and the reaction mixture was extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 12.74 g (100 %) of 4-(2-Methyl-cyclopentylamino)-3-nitro-benzoic acid methyl ester.

C14H18N2O4 (278.31 ), LCMS (method 8_1_1): Rt = 1.10 min, m/z= 279.05 [M+H]⁺

b) 3-Amino-4-(2-methyl-cyclopentylamino)-benzoic acid methyl ester
12.74 g 4-(2-Methyl-cyclopentylamino)-3-nitro-benzoic acid methyl ester were dissolved in 80 ml methanol, 0.39 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 16 h. The catalyst was removed by filtration over celite, the filtrate was concentrated and the residue purified by chromatography (silica, ethyl acetate/hexane) to obtain 8.17 g (72%) of 3-Amino-4-(2-methyl-cyclopentylamino)-benzoic acid methyl ester.

C14H20N2O2 (248.32), LCMS (method 5_1_1): Rt = 4.25 min, m/z= 249.29 [M+H]+

c) 4-(2-Methyl-cyclopentylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester

To a solution of 3.44 g of thiophen-2-yl-acetic acid in 40 ml of dry DMF 3.62 g of HOAT, 6.48 g of EDC and 12 ml of DIPEA were added at 0°C. After 30 min 6.00 g of 3-Amino-4-(2-methyl-cyclopentylamino)-benzoic acid methyl ester were added, and the reaction was stirred at rt for 16 h. The reaction was then poured into water and the pH was adjusted to 3 by the addition of 2 m aqueous hydrochloric acid. Ethyl acetate was added and the layers were separated. The aqueous layer was extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 9.03 g (100%) of 4-(2-Methyl-cyclopentylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

C20H24N2O3S (372.49), LCMS (method 8_1_1): Rt = 0.97 min, m/z= 373.15 [M+H]+
d) 1-(2-Methyl-cyclopentyl)-2-thiophen-2-ylnnethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester

5 0.88 g 4-(2-Methyl-cyclopentylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were reacted with 10 ml of 4M hydrochloric acid in dioxane at 110°C in a microwave reactor for 30 min. The reaction was concentrated and 0.98 g (99 %) of 1-(2-Methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.

C20H22N2O2S (354.47), LCMS (method 8_1_1): Rt = 0.82 min, m/z= 335.1 5 [M+H]+

e) 1-(2-Methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

15 To 9.85 g of 21-(2-Methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid methyl ester in 75 ml of methanol and 40 ml of THF were added 50 ml of 2 M aqueous sodium hydroxide solution. The reaction was stirred at rt for 16 h. The reaction mixture was concentrated in vacuo to a fifth of its volume and the pH was adjusted to 4 by the addition of 2M aqueous hydrochloric acid. The precipitated product was collected by filtration, washed with water and dried in vacuo. 7.28 g (85%) of 1-(2-Methyl-cyclopentyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid were obtained.

C19H20N2O2S (340.45), LCMS (method 8_1_1): Rt = 0.71 min, m/z= 341 .15 [M+H]+
1-(2-Ethyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carboxylic acid

\[
\begin{align*}
&\text{N} \\
\text{H} & \\
\text{O} & \\
\text{N} & \\
\text{O} & \\
\text{O} & \\
\text{N} & \\
\text{HN} & \\
\end{align*}
\]

To a solution of 0.48 g of 4-fluoro-3-nitro-benzoic acid methyl ester in 1.5 ml of abs. DMF was added 1.00 g of potassium carbonate, followed by 0.31 g of 2-ethylcyclohexylamine. After 16 h at rt, the mixture was poured into water, the pH was adjusted to 4 by the addition of 2 M aqueous hydrochloric acid, and the reaction mixture was extracted with ethyl acetate three times. The combined organic phases were washed with water, dried over sodium sulphate and concentrated to yield 0.44 g (60%) of 4-(2-Ethyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester.

C\(\text{C}_{16}\text{H}_{22}\text{N}_{2}\text{O}_{4}\) (306.36), LCMS (method 8_1_1): \(R_t = 1.22\) min, \(m/z = 307.15\ [M+H]^+\)

b) 3-Amino-4-(2-ethyl-cyclohexylamino)-benzoic acid methyl ester

\[
\begin{align*}
&\text{N} \\
\text{H} & \\
\text{O} & \\
\text{N} & \\
\text{O} & \\
\text{O} & \\
\text{N} & \\
\text{HN} & \\
\end{align*}
\]

0.45 g 4-(2-Ethyl-cyclohexylamino)-3-nitro-benzoic acid methyl ester were dissolved in 60 ml methanol, 0.02 g of palladium on carbon (10%) were added and the mixture was hydrogenated at 5 bar for 4 h. The catalyst was removed by
filtration over celite, the filtrate was concentrated to obtain 0.40 g (100%) of 3-Amino-4-(2-ethyl-cyclohexylamino)-benzoic acid methyl ester.

C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2} (276.38), LCMS (method 8_1_1): Rt = 0.84 min, m/z= 277.15 [M+H]+

c) 4-(2-Ethyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester

![Chemical structure]

To a solution of 0.24 g of thiophen-2-yl-acetic acid in 40 ml of dry DMF 0.11 g of HOAT, 0.36 g of EDC and 0.5 ml of DIPEA were added at 0°C. After 30 min 0.41 g of 3-Amino-4-(2-ethyl-cyclohexylamino)-benzoic acid methyl ester were added, followed by the addition of 0.5 ml of DIPEA and the reaction was stirred at rt for 48 h. The reaction was then poured into water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated to obtain 0.60 g (97%) of 4-(2-Ethyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester, which was used without further purification.

C\textsubscript{22}H\textsubscript{28}N\textsubscript{2}O\textsubscript{3}S (400.54), LCMS (method 8_1_1): Rt = 1.09 min, m/z= 401.20 [M+H]+

d) 1-(2-Ethyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid

![Chemical structure]

0.59 g 4-(2-Ethyl-cyclohexylamino)-3-(2-thiophen-2-yl-acetylamino)-benzoic acid methyl ester were reacted with 10 ml of 4M hydrochloric acid in dioxane at 130°C in a microwave reactor for 20 min. 1 ml water was added and the mixture was heated to
130 °C for 30 min. The reaction was concentrated and the residue purified by chromatography (silica, ethyl acetate/heptane) to yield 0.47 g (88 %) of 1-(2-Ethyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carboxylic acid.

C21 H24N2O2S (368.50), LCMS (method 8_1_1 ) : Rt = 0.79 min, m/z= 369.15 [M+H] +

Determination of agonism on the human apelin receptor by a calcium fluorescence assay (FLIPR)

The assay is based on the detection of intracellular calcium changes detected by the selective, calcium-chelating dye Fluo-4 (Molecular Probes). A large fluorescence intensity increase is observed upon calcium association with Fluo-4. The dye is delivered to the cell interior using an acetoxymethylester form of Fluo-4, where the intracellular esterase activity results in the charged species being released and trapped within the cytoplasm of the cell. Hence, influx of calcium to this cytoplasmic pocket, via release from intracellular pools and the phospholipase C cascade can be detected. By co-expressing the human apelin receptor and a promiscuous Giαq protein, agonism of the apelin receptor couples to phospholipase-C resulting in intracellular calcium mobilization.

The HEK293 cells were stably transfected with the human apelin receptor and the Giαq protein. Cells were selected and maintained in a log phase of growth at 37°C and 5% CO2 in the Iscove's minimal essential medium, 10% fetal calf serum, 1X Penicillin-Streptomycin, 400 µg/mL G418. One day prior the assay, cells were passaged by accutase and plated at a density of 50,000 cells/well onto a 96-well plates with black border but clear bottom (Costar, cat# 3904) in a final volume of 200 µl growth medium.

In order to load the cells the next day with the calcium-sensitive dye, growth medium was carefully replaced by dye solution (100µl/well) containing Fluo-4 (4 µM) in basic measurement buffer (135mM NaCl, 5mM KCl, 1mM magnesium sulphate, 5mM glucose, 20mM Hepes, 2.5mM probenecid; adjusted to pH 7.4). Cells were incubated for 1 h at 37°C, and then washed 3x with buffer containing no dye. The washer was programmed to leave a remaining volume of 150 µl after the third wash in the plate.
During the dye-loading of the cells, a serial compound dilution was performed in a separate 96-well plate with overall 4x increased concentrations. Small aliquots of DMSO stock solutions of the compounds (10mM in 100% DMSO) were aliquoted into 150µl buffer in the first rows of the 96-well plates, and then serially diluted by a factor of 1:3 transferring each time 30µl to the next rows already containing 60µl buffer. All compounds were tested in at least 7 concentrations, each condition was performed in triplicates. As comparator, we used freshly prepared apelin-13 solutions, for which also a concentration-response curve was determined at each measurement day. The compound plate was incubated for 10min after the final dilution steps at 37°C before transferring the dye-loaded cell plate and the compound plate into a FLIPR Tetra reader (Molecular Devices). Measurement within this reader started by pipetting the agonist solution (50µl) on the cell plate. Overall perform 60 reads were performed with an interval of 2 sec. The maximum of the fluorescence transient was used to calculate the agonistic response of the cells. In order to normalize this response, which may vary from plate to plate we set the maximum fluorescence achieved by 1µM apelin-13 on this plate as 100%.

EC-50 values for apelin-13 and the apelin receptor compounds described in this patent were determined by standard algorithms using a specific software package. Compounds exhibit agonism in this Apelin receptor calcium fluorescence assay in a range of about 0.01 nM to 100000 nM.

APJ agonism for example compounds:

<table>
<thead>
<tr>
<th>Example No.</th>
<th>EC50 [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.359</td>
</tr>
<tr>
<td>2</td>
<td>20.07</td>
</tr>
<tr>
<td>3</td>
<td>1.199</td>
</tr>
<tr>
<td>4</td>
<td>16.77</td>
</tr>
<tr>
<td>5</td>
<td>9.873</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>3.81</td>
</tr>
<tr>
<td>7</td>
<td>44.331</td>
</tr>
<tr>
<td>8</td>
<td>0.107</td>
</tr>
<tr>
<td>9</td>
<td>0.585</td>
</tr>
<tr>
<td>10</td>
<td>1.699</td>
</tr>
<tr>
<td>11</td>
<td>0.065</td>
</tr>
<tr>
<td>12</td>
<td>0.818</td>
</tr>
<tr>
<td>13</td>
<td>0.535</td>
</tr>
<tr>
<td>14</td>
<td>1.344</td>
</tr>
<tr>
<td>15</td>
<td>0.254</td>
</tr>
<tr>
<td>16</td>
<td>0.117</td>
</tr>
<tr>
<td>17</td>
<td>0.935</td>
</tr>
<tr>
<td>18</td>
<td>0.15</td>
</tr>
<tr>
<td>19</td>
<td>5.03</td>
</tr>
<tr>
<td>20</td>
<td>1.828</td>
</tr>
<tr>
<td>21</td>
<td>0.443</td>
</tr>
<tr>
<td>22</td>
<td>0.08</td>
</tr>
<tr>
<td>23</td>
<td>0.106</td>
</tr>
<tr>
<td>24</td>
<td>0.219</td>
</tr>
<tr>
<td>25</td>
<td>4.753</td>
</tr>
<tr>
<td>26</td>
<td>5.301</td>
</tr>
<tr>
<td>27</td>
<td>1.86</td>
</tr>
<tr>
<td>28</td>
<td>18.52</td>
</tr>
<tr>
<td>29</td>
<td>5.658</td>
</tr>
<tr>
<td>30</td>
<td>2.199</td>
</tr>
<tr>
<td>31</td>
<td>4.11</td>
</tr>
<tr>
<td>32</td>
<td>4.569</td>
</tr>
<tr>
<td>33</td>
<td>3.209</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----</td>
</tr>
<tr>
<td>34</td>
<td>0.489</td>
</tr>
<tr>
<td>35</td>
<td>0.291</td>
</tr>
<tr>
<td>36</td>
<td>1.262</td>
</tr>
<tr>
<td>37</td>
<td>0.886</td>
</tr>
<tr>
<td>38</td>
<td>0.115</td>
</tr>
<tr>
<td>39</td>
<td>1.14</td>
</tr>
<tr>
<td>40</td>
<td>0.915</td>
</tr>
<tr>
<td>41</td>
<td>2.428</td>
</tr>
<tr>
<td>42</td>
<td>1.03</td>
</tr>
<tr>
<td>43</td>
<td>14.49</td>
</tr>
<tr>
<td>44</td>
<td>0.258</td>
</tr>
<tr>
<td>45</td>
<td>0.552</td>
</tr>
<tr>
<td>46</td>
<td>0.112</td>
</tr>
<tr>
<td>47</td>
<td>2.585</td>
</tr>
<tr>
<td>48</td>
<td>4.187</td>
</tr>
<tr>
<td>49</td>
<td>7.066</td>
</tr>
<tr>
<td>50</td>
<td>0.205</td>
</tr>
<tr>
<td>51</td>
<td>0.211</td>
</tr>
<tr>
<td>52</td>
<td>12.33</td>
</tr>
<tr>
<td>53</td>
<td>0.048</td>
</tr>
<tr>
<td>54</td>
<td>0.115</td>
</tr>
<tr>
<td>55</td>
<td>0.196</td>
</tr>
<tr>
<td>56</td>
<td>0.157</td>
</tr>
<tr>
<td>57</td>
<td>0.475</td>
</tr>
<tr>
<td>58</td>
<td>0.172</td>
</tr>
<tr>
<td>59</td>
<td>0.576</td>
</tr>
<tr>
<td>60</td>
<td>0.046</td>
</tr>
<tr>
<td>61</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
</tr>
<tr>
<td>62</td>
<td>0.193</td>
</tr>
<tr>
<td>63</td>
<td>0.343</td>
</tr>
<tr>
<td>64</td>
<td>0.176</td>
</tr>
<tr>
<td>65</td>
<td>0.056</td>
</tr>
<tr>
<td>66</td>
<td>0.087</td>
</tr>
<tr>
<td>67</td>
<td>0.079</td>
</tr>
<tr>
<td>68</td>
<td>0.018</td>
</tr>
<tr>
<td>69</td>
<td>0.339</td>
</tr>
<tr>
<td>70</td>
<td>0.179</td>
</tr>
<tr>
<td>71</td>
<td>0.073</td>
</tr>
<tr>
<td>72</td>
<td>0.047</td>
</tr>
<tr>
<td>73</td>
<td>0.065</td>
</tr>
<tr>
<td>74</td>
<td>0.14</td>
</tr>
<tr>
<td>75</td>
<td>0.066</td>
</tr>
<tr>
<td>76</td>
<td>0.062</td>
</tr>
<tr>
<td>77</td>
<td>0.053</td>
</tr>
<tr>
<td>78</td>
<td>0.101</td>
</tr>
<tr>
<td>79</td>
<td>0.08</td>
</tr>
<tr>
<td>80</td>
<td>1.671</td>
</tr>
<tr>
<td>81</td>
<td>&lt;0.041</td>
</tr>
<tr>
<td>82</td>
<td>23.3</td>
</tr>
<tr>
<td>83</td>
<td>18.24</td>
</tr>
<tr>
<td>84</td>
<td>2.951</td>
</tr>
<tr>
<td>85</td>
<td>7.797</td>
</tr>
<tr>
<td>86</td>
<td>0.088</td>
</tr>
<tr>
<td>87</td>
<td>0.882</td>
</tr>
<tr>
<td>88</td>
<td>0.754</td>
</tr>
<tr>
<td>89</td>
<td>9.331</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
</tr>
<tr>
<td>90</td>
<td>0.472</td>
</tr>
<tr>
<td>91</td>
<td>0.137</td>
</tr>
<tr>
<td>92</td>
<td>&lt;0.041</td>
</tr>
<tr>
<td>93</td>
<td>0.291</td>
</tr>
<tr>
<td>94</td>
<td>0.781</td>
</tr>
<tr>
<td>95</td>
<td>0.095</td>
</tr>
<tr>
<td>96</td>
<td>&lt;0.041</td>
</tr>
<tr>
<td>97</td>
<td>38.959</td>
</tr>
<tr>
<td>98</td>
<td>2.189</td>
</tr>
<tr>
<td>99</td>
<td>0.046</td>
</tr>
<tr>
<td>100</td>
<td>5.842</td>
</tr>
<tr>
<td>101</td>
<td>0.106</td>
</tr>
<tr>
<td>102</td>
<td>0.247</td>
</tr>
<tr>
<td>103</td>
<td>10.99</td>
</tr>
<tr>
<td>104</td>
<td>0.479</td>
</tr>
<tr>
<td>105</td>
<td>5.466</td>
</tr>
<tr>
<td>106</td>
<td>0.048</td>
</tr>
<tr>
<td>107</td>
<td>0.047</td>
</tr>
<tr>
<td>108</td>
<td>1.061</td>
</tr>
<tr>
<td>109</td>
<td>3.863</td>
</tr>
<tr>
<td>110</td>
<td>2.029</td>
</tr>
<tr>
<td>111</td>
<td>0.579</td>
</tr>
<tr>
<td>112</td>
<td>12.77</td>
</tr>
<tr>
<td>113</td>
<td>21.71</td>
</tr>
<tr>
<td>114</td>
<td>0.185</td>
</tr>
<tr>
<td>115</td>
<td>34.593</td>
</tr>
<tr>
<td>116</td>
<td>6.713</td>
</tr>
<tr>
<td>117</td>
<td>0.419</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>118</td>
<td>0.222</td>
</tr>
<tr>
<td>119</td>
<td>33.117</td>
</tr>
<tr>
<td>120</td>
<td>24.09</td>
</tr>
<tr>
<td>121</td>
<td>0.074</td>
</tr>
<tr>
<td>122</td>
<td>4.378</td>
</tr>
<tr>
<td>123</td>
<td>1.879</td>
</tr>
<tr>
<td>124</td>
<td>9.355</td>
</tr>
<tr>
<td>125</td>
<td>0.078</td>
</tr>
<tr>
<td>126</td>
<td>3.933</td>
</tr>
<tr>
<td>127</td>
<td>15.000</td>
</tr>
<tr>
<td>128</td>
<td>10.000</td>
</tr>
<tr>
<td>129</td>
<td>2.675</td>
</tr>
<tr>
<td>130</td>
<td>0.293</td>
</tr>
<tr>
<td>131</td>
<td>0.185</td>
</tr>
<tr>
<td>132</td>
<td>0.700</td>
</tr>
<tr>
<td>133</td>
<td>2.355</td>
</tr>
<tr>
<td>134</td>
<td>7.150</td>
</tr>
<tr>
<td>135</td>
<td>3.800</td>
</tr>
<tr>
<td>136</td>
<td>2.700</td>
</tr>
<tr>
<td>137</td>
<td>9.500</td>
</tr>
<tr>
<td>138</td>
<td>2.935</td>
</tr>
<tr>
<td>139</td>
<td>0.285</td>
</tr>
<tr>
<td>140</td>
<td>3.800</td>
</tr>
<tr>
<td>141</td>
<td>23.000</td>
</tr>
<tr>
<td>142</td>
<td>12.000</td>
</tr>
<tr>
<td>143</td>
<td>2.450</td>
</tr>
<tr>
<td>144</td>
<td>23.000</td>
</tr>
<tr>
<td>145</td>
<td>18.000</td>
</tr>
<tr>
<td></td>
<td>146</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>171</td>
</tr>
<tr>
<td></td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>173</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>174</td>
<td>0.301</td>
</tr>
<tr>
<td>175</td>
<td>0.501</td>
</tr>
<tr>
<td>176</td>
<td>8.906</td>
</tr>
<tr>
<td>177</td>
<td>2.425</td>
</tr>
<tr>
<td>178</td>
<td>17.45</td>
</tr>
<tr>
<td>179</td>
<td>25.1 7</td>
</tr>
<tr>
<td>180</td>
<td>6.1 65</td>
</tr>
<tr>
<td>181</td>
<td>6.949</td>
</tr>
<tr>
<td>182</td>
<td>10.99</td>
</tr>
<tr>
<td>183</td>
<td>26.35</td>
</tr>
<tr>
<td>184</td>
<td>2.902</td>
</tr>
<tr>
<td>185</td>
<td>14.1 2</td>
</tr>
<tr>
<td>186</td>
<td>4.673</td>
</tr>
<tr>
<td>187</td>
<td>29</td>
</tr>
<tr>
<td>188</td>
<td>4.52</td>
</tr>
<tr>
<td>189</td>
<td>12.1 7</td>
</tr>
<tr>
<td>190</td>
<td>6.283</td>
</tr>
<tr>
<td>191</td>
<td>6.295</td>
</tr>
<tr>
<td>192</td>
<td>14.02</td>
</tr>
<tr>
<td>193</td>
<td>6.21 8</td>
</tr>
<tr>
<td>194</td>
<td>0.96</td>
</tr>
<tr>
<td>195</td>
<td>15.1 7</td>
</tr>
<tr>
<td>196</td>
<td>0.922</td>
</tr>
<tr>
<td>197</td>
<td>1.039</td>
</tr>
<tr>
<td>198</td>
<td>8.88</td>
</tr>
<tr>
<td>199</td>
<td>0.71</td>
</tr>
<tr>
<td>200</td>
<td>8.1 84</td>
</tr>
<tr>
<td>201</td>
<td>0.334</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>202</td>
<td>14.42</td>
</tr>
<tr>
<td>203</td>
<td>24.71</td>
</tr>
<tr>
<td>204</td>
<td>1.99</td>
</tr>
<tr>
<td>205</td>
<td>1.751</td>
</tr>
<tr>
<td>206</td>
<td>2.297</td>
</tr>
<tr>
<td>207</td>
<td>0.554</td>
</tr>
<tr>
<td>208</td>
<td>1.16</td>
</tr>
<tr>
<td>209</td>
<td>0.254</td>
</tr>
<tr>
<td>210</td>
<td>10.24</td>
</tr>
<tr>
<td>211</td>
<td>0.705</td>
</tr>
<tr>
<td>212</td>
<td>9.294</td>
</tr>
<tr>
<td>213</td>
<td>29.94</td>
</tr>
<tr>
<td>214</td>
<td>0.926</td>
</tr>
<tr>
<td>215</td>
<td>1.449</td>
</tr>
<tr>
<td>216</td>
<td>1.729</td>
</tr>
<tr>
<td>217</td>
<td>2.21</td>
</tr>
<tr>
<td>218</td>
<td>2.013</td>
</tr>
<tr>
<td>219</td>
<td>0.274</td>
</tr>
<tr>
<td>220</td>
<td>2.863</td>
</tr>
<tr>
<td>221</td>
<td>1.828</td>
</tr>
<tr>
<td>222</td>
<td>3.986</td>
</tr>
<tr>
<td>223</td>
<td>6.959</td>
</tr>
<tr>
<td>224</td>
<td>0.3</td>
</tr>
<tr>
<td>225</td>
<td>0.775</td>
</tr>
<tr>
<td>226</td>
<td>4.874</td>
</tr>
<tr>
<td>227</td>
<td>0.287</td>
</tr>
<tr>
<td>228</td>
<td>8.497</td>
</tr>
<tr>
<td>229</td>
<td>1.942</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>230</td>
<td>0.288</td>
</tr>
<tr>
<td>231</td>
<td>0.525</td>
</tr>
<tr>
<td>232</td>
<td>2.91 8</td>
</tr>
<tr>
<td>233</td>
<td>0.394</td>
</tr>
<tr>
<td>234</td>
<td>0.344</td>
</tr>
<tr>
<td>235</td>
<td>1.302</td>
</tr>
<tr>
<td>236</td>
<td>3.868</td>
</tr>
<tr>
<td>237</td>
<td>2.48</td>
</tr>
<tr>
<td>238</td>
<td>6.554</td>
</tr>
<tr>
<td>239</td>
<td>5.585</td>
</tr>
<tr>
<td>240</td>
<td>0.614</td>
</tr>
<tr>
<td>241</td>
<td>0.257</td>
</tr>
<tr>
<td>242</td>
<td>5.932</td>
</tr>
<tr>
<td>243</td>
<td>0.771</td>
</tr>
<tr>
<td>244</td>
<td>4.283</td>
</tr>
<tr>
<td>245</td>
<td>0.291</td>
</tr>
<tr>
<td>246</td>
<td>6.841</td>
</tr>
<tr>
<td>247</td>
<td>7.21 6</td>
</tr>
<tr>
<td>248</td>
<td>1.798</td>
</tr>
<tr>
<td>249</td>
<td>0.407</td>
</tr>
<tr>
<td>250</td>
<td>0.52</td>
</tr>
<tr>
<td>251</td>
<td>2.559</td>
</tr>
<tr>
<td>252</td>
<td>6.99</td>
</tr>
<tr>
<td>253</td>
<td>0.242</td>
</tr>
<tr>
<td>254</td>
<td>0.233</td>
</tr>
<tr>
<td>255</td>
<td>6.669</td>
</tr>
<tr>
<td>256</td>
<td>5.91 8</td>
</tr>
<tr>
<td>257</td>
<td>0.425</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>258</td>
<td>1.334</td>
</tr>
<tr>
<td>259</td>
<td>6.648</td>
</tr>
<tr>
<td>260</td>
<td>0.17</td>
</tr>
<tr>
<td>261</td>
<td>0.269</td>
</tr>
<tr>
<td>262</td>
<td>4.555</td>
</tr>
<tr>
<td>263</td>
<td>4.301</td>
</tr>
<tr>
<td>264</td>
<td>3.338</td>
</tr>
<tr>
<td>265</td>
<td>8.658</td>
</tr>
<tr>
<td>266</td>
<td>2.717</td>
</tr>
<tr>
<td>267</td>
<td>0.383</td>
</tr>
<tr>
<td>268</td>
<td>0.552</td>
</tr>
<tr>
<td>269</td>
<td>18.51</td>
</tr>
<tr>
<td>270</td>
<td>10.8</td>
</tr>
<tr>
<td>271</td>
<td>3.255</td>
</tr>
<tr>
<td>272</td>
<td>2.768</td>
</tr>
<tr>
<td>273</td>
<td>0.212</td>
</tr>
<tr>
<td>274</td>
<td>12.56</td>
</tr>
<tr>
<td>275</td>
<td>0.242</td>
</tr>
<tr>
<td>276</td>
<td>0.105</td>
</tr>
<tr>
<td>277</td>
<td>2.099</td>
</tr>
<tr>
<td>278</td>
<td>0.405</td>
</tr>
<tr>
<td>279</td>
<td>2.269</td>
</tr>
<tr>
<td>280</td>
<td>0.219</td>
</tr>
<tr>
<td>281</td>
<td>1.215</td>
</tr>
<tr>
<td>282</td>
<td>0.43</td>
</tr>
<tr>
<td>283</td>
<td>4.496</td>
</tr>
<tr>
<td>284</td>
<td>0.252</td>
</tr>
<tr>
<td>285</td>
<td>0.295</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>286</td>
<td>1.097</td>
</tr>
<tr>
<td>287</td>
<td>0.408</td>
</tr>
<tr>
<td>288</td>
<td>0.512</td>
</tr>
<tr>
<td>289</td>
<td>0.341</td>
</tr>
<tr>
<td>290</td>
<td>0.506</td>
</tr>
<tr>
<td>291</td>
<td>0.408</td>
</tr>
<tr>
<td>292</td>
<td>1.216</td>
</tr>
<tr>
<td>293</td>
<td>2.644</td>
</tr>
<tr>
<td>294</td>
<td>0.722</td>
</tr>
<tr>
<td>295</td>
<td>1.828</td>
</tr>
<tr>
<td>296</td>
<td>1.032</td>
</tr>
<tr>
<td>297</td>
<td>0.39</td>
</tr>
<tr>
<td>298</td>
<td>1.26</td>
</tr>
<tr>
<td>299</td>
<td>0.776</td>
</tr>
<tr>
<td>300</td>
<td>0.732</td>
</tr>
<tr>
<td>301</td>
<td>2.461</td>
</tr>
<tr>
<td>302</td>
<td>0.386</td>
</tr>
<tr>
<td>303</td>
<td>0.214</td>
</tr>
<tr>
<td>304</td>
<td>0.461</td>
</tr>
<tr>
<td>305</td>
<td>0.319</td>
</tr>
<tr>
<td>306</td>
<td>1.26</td>
</tr>
<tr>
<td>307</td>
<td>1.826</td>
</tr>
<tr>
<td>308</td>
<td>0.672</td>
</tr>
<tr>
<td>309</td>
<td>0.482</td>
</tr>
<tr>
<td>310</td>
<td>0.162</td>
</tr>
<tr>
<td>311</td>
<td>21.23</td>
</tr>
<tr>
<td>312</td>
<td>2.963</td>
</tr>
<tr>
<td>313</td>
<td>1.888</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>314</td>
<td>0.474</td>
</tr>
<tr>
<td>315</td>
<td>2.453</td>
</tr>
<tr>
<td>316</td>
<td>22</td>
</tr>
<tr>
<td>317</td>
<td>13.97</td>
</tr>
<tr>
<td>318</td>
<td>2.861</td>
</tr>
<tr>
<td>319</td>
<td>1.524</td>
</tr>
<tr>
<td>320</td>
<td>0.386</td>
</tr>
<tr>
<td>321</td>
<td>1.525</td>
</tr>
<tr>
<td>322</td>
<td>0.244</td>
</tr>
<tr>
<td>323</td>
<td>6.745</td>
</tr>
<tr>
<td>324</td>
<td>16.76</td>
</tr>
<tr>
<td>325</td>
<td>4.407</td>
</tr>
<tr>
<td>326</td>
<td>16.35</td>
</tr>
<tr>
<td>327</td>
<td>0.111</td>
</tr>
<tr>
<td>328</td>
<td>1.271</td>
</tr>
<tr>
<td>329</td>
<td>0.362</td>
</tr>
<tr>
<td>330</td>
<td>2.475</td>
</tr>
<tr>
<td>331</td>
<td>0.267</td>
</tr>
<tr>
<td>332</td>
<td>0.692</td>
</tr>
<tr>
<td>333</td>
<td>27.31</td>
</tr>
<tr>
<td>334</td>
<td>0.412</td>
</tr>
<tr>
<td>335</td>
<td>0.384</td>
</tr>
<tr>
<td>336</td>
<td>1.262</td>
</tr>
<tr>
<td>337</td>
<td>0.331</td>
</tr>
<tr>
<td>338</td>
<td>1.593</td>
</tr>
<tr>
<td>339</td>
<td>0.444</td>
</tr>
<tr>
<td>340</td>
<td>0.185</td>
</tr>
<tr>
<td>341</td>
<td>0.918</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>342</td>
<td>0.999</td>
</tr>
<tr>
<td>343</td>
<td>0.419</td>
</tr>
<tr>
<td>344</td>
<td>1.687</td>
</tr>
<tr>
<td>345</td>
<td>1.666</td>
</tr>
<tr>
<td>346</td>
<td>1.315</td>
</tr>
<tr>
<td>347</td>
<td>0.809</td>
</tr>
<tr>
<td>348</td>
<td>2.663</td>
</tr>
<tr>
<td>349</td>
<td>3.037</td>
</tr>
<tr>
<td>350</td>
<td>29.14</td>
</tr>
<tr>
<td>351</td>
<td>9.291</td>
</tr>
<tr>
<td>352</td>
<td>2.981</td>
</tr>
<tr>
<td>353</td>
<td>0.787</td>
</tr>
<tr>
<td>354</td>
<td>0.998</td>
</tr>
<tr>
<td>355</td>
<td>1.521</td>
</tr>
<tr>
<td>356</td>
<td>4.26</td>
</tr>
<tr>
<td>357</td>
<td>0.389</td>
</tr>
<tr>
<td>358</td>
<td>2.57</td>
</tr>
<tr>
<td>359</td>
<td>2.135</td>
</tr>
<tr>
<td>360</td>
<td>21.24</td>
</tr>
<tr>
<td>361</td>
<td>24.97</td>
</tr>
<tr>
<td>362</td>
<td>27.06</td>
</tr>
<tr>
<td>363</td>
<td>1.715</td>
</tr>
<tr>
<td>364</td>
<td>13.55</td>
</tr>
<tr>
<td>365</td>
<td>2.752</td>
</tr>
<tr>
<td>366</td>
<td>16.5</td>
</tr>
<tr>
<td>367</td>
<td>1.662</td>
</tr>
<tr>
<td>368</td>
<td>1.881</td>
</tr>
<tr>
<td>369</td>
<td>2.212</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>370</td>
<td>2.853</td>
</tr>
<tr>
<td>371</td>
<td>3.574</td>
</tr>
<tr>
<td>372</td>
<td>13.23</td>
</tr>
<tr>
<td>373</td>
<td>1.838</td>
</tr>
<tr>
<td>374</td>
<td>2.179</td>
</tr>
<tr>
<td>375</td>
<td>2.88</td>
</tr>
<tr>
<td>376</td>
<td>1.83</td>
</tr>
<tr>
<td>377</td>
<td>1.145</td>
</tr>
<tr>
<td>378</td>
<td>2.445</td>
</tr>
<tr>
<td>379</td>
<td>1.803</td>
</tr>
<tr>
<td>380</td>
<td>0.586</td>
</tr>
<tr>
<td>381</td>
<td>0.97</td>
</tr>
<tr>
<td>382</td>
<td>3.564</td>
</tr>
<tr>
<td>383</td>
<td>2.121</td>
</tr>
<tr>
<td>384</td>
<td>1.626</td>
</tr>
<tr>
<td>385</td>
<td>2.506</td>
</tr>
<tr>
<td>386</td>
<td>2.226</td>
</tr>
<tr>
<td>387</td>
<td>1.141</td>
</tr>
<tr>
<td>388</td>
<td>1.593</td>
</tr>
<tr>
<td>389</td>
<td>17.08</td>
</tr>
<tr>
<td>390</td>
<td>10.91</td>
</tr>
<tr>
<td>391</td>
<td>2.179</td>
</tr>
<tr>
<td>392</td>
<td>1.377</td>
</tr>
<tr>
<td>393</td>
<td>1.358</td>
</tr>
<tr>
<td>394</td>
<td>2.329</td>
</tr>
<tr>
<td>395</td>
<td>1.758</td>
</tr>
<tr>
<td>396</td>
<td>4.039</td>
</tr>
<tr>
<td>397</td>
<td>8.739</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>398</td>
<td>5.458</td>
</tr>
<tr>
<td>399</td>
<td>0.099</td>
</tr>
<tr>
<td>400</td>
<td>0.07</td>
</tr>
<tr>
<td>401</td>
<td>0.6</td>
</tr>
<tr>
<td>402</td>
<td>0.777</td>
</tr>
<tr>
<td>403</td>
<td>1.606</td>
</tr>
<tr>
<td>404</td>
<td>0.788</td>
</tr>
<tr>
<td>405</td>
<td>0.842</td>
</tr>
<tr>
<td>406</td>
<td>1.112</td>
</tr>
<tr>
<td>407</td>
<td>0.708</td>
</tr>
<tr>
<td>408</td>
<td>0.447</td>
</tr>
<tr>
<td>409</td>
<td>0.491</td>
</tr>
<tr>
<td>410</td>
<td>0.578</td>
</tr>
<tr>
<td>411</td>
<td>0.822</td>
</tr>
<tr>
<td>412</td>
<td>0.106</td>
</tr>
<tr>
<td>413</td>
<td>1.016</td>
</tr>
<tr>
<td>414</td>
<td>0.664</td>
</tr>
<tr>
<td>415</td>
<td>0.532</td>
</tr>
<tr>
<td>416</td>
<td>0.025</td>
</tr>
<tr>
<td>417</td>
<td>0.715</td>
</tr>
<tr>
<td>418</td>
<td>0.248</td>
</tr>
<tr>
<td>419</td>
<td>0.313</td>
</tr>
<tr>
<td>420</td>
<td>0.014</td>
</tr>
<tr>
<td>421</td>
<td>20.02</td>
</tr>
<tr>
<td>422</td>
<td>1.859</td>
</tr>
<tr>
<td>423</td>
<td>9.731</td>
</tr>
<tr>
<td>424</td>
<td>0.389</td>
</tr>
<tr>
<td>425</td>
<td>2.685</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>454</td>
<td>0.126</td>
</tr>
<tr>
<td>455</td>
<td>0.16</td>
</tr>
<tr>
<td>456</td>
<td>0.152</td>
</tr>
<tr>
<td>457</td>
<td>1.462</td>
</tr>
<tr>
<td>458</td>
<td>0.124</td>
</tr>
<tr>
<td>459</td>
<td></td>
</tr>
<tr>
<td>460</td>
<td>0.122</td>
</tr>
<tr>
<td>461</td>
<td>3.431</td>
</tr>
<tr>
<td>462</td>
<td>0.137</td>
</tr>
<tr>
<td>463</td>
<td>2.483</td>
</tr>
<tr>
<td>464</td>
<td>0.126</td>
</tr>
<tr>
<td>465</td>
<td>0.948</td>
</tr>
<tr>
<td>466</td>
<td>4.716</td>
</tr>
<tr>
<td>467</td>
<td>0.265</td>
</tr>
<tr>
<td>468</td>
<td>0.719</td>
</tr>
<tr>
<td>469</td>
<td>0.06</td>
</tr>
<tr>
<td>470</td>
<td>0.235</td>
</tr>
<tr>
<td>471</td>
<td>5.023</td>
</tr>
<tr>
<td>472</td>
<td>0.038</td>
</tr>
<tr>
<td>473</td>
<td>0.173</td>
</tr>
<tr>
<td>474</td>
<td>34.546</td>
</tr>
<tr>
<td>475</td>
<td>2.818</td>
</tr>
<tr>
<td>476</td>
<td>3.954</td>
</tr>
<tr>
<td>477</td>
<td>2.717</td>
</tr>
<tr>
<td>478</td>
<td>3.146</td>
</tr>
<tr>
<td>479</td>
<td>16.9</td>
</tr>
<tr>
<td>480</td>
<td>20.04</td>
</tr>
<tr>
<td>481</td>
<td>3.483</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>482</td>
<td>15.72</td>
</tr>
<tr>
<td>483</td>
<td>2.085</td>
</tr>
<tr>
<td>484</td>
<td>0.014</td>
</tr>
<tr>
<td>485</td>
<td>0.813</td>
</tr>
</tbody>
</table>
Claims

1. A compound of the formula I,

wherein

- $R^{'}, R^{''}, R^{'''}$ are independently of each other H, halogen, CF$_3$, OCF$_3$, O-(C$_i$-C$_3$)-alkyl;

- $R^1$ is
  - a) (C$_4$-C$_7$)-alkyl;
  - b) (C$_5$-C$_7$)-cycloalkyl, which is unsubstituted or mono-substituted by (C1-C2)-alkyl, or CF$_3$;
  - c) methylene-cyclohexyl;
  - d) phenyl, which is unsubstituted or mono-substituted by methyl or Cl;

- $R^2$ is
  - a) a 5-membered heteroaryl which contains 1 or 2 identical or different ring heteroatoms chosen from N, O and S, wherein said 5-membered heteroaryl is unsubstituted or mono-substituted by Cl or (C$_i$-C$_4$)-alkyl;
  - b) phenyl;
  - c) (C$_5$-C$_8$)-cycloalkyl; or
  - d) tetrahydrofuranyl;
R³ is H, or (Ci-C₂)-alkyl;
and
R⁴ is
a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(Ci-C₄)-alkyl,
b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono- or di-substituted by methyl;
c) (Co-C₂)-alkylene-phenyl, wherein said phenyl is unsubstituted or mono- or di-substituted by F, Cl, (Ci-C₄)-alkyl or CF₃; or
d) thienyl;

or

R³ and R⁴ are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring, which is unsubstituted or mono-substituted by (Ci-C₄)-alkyl;

R⁵ is H, (Ci-C₄)-alkyl or OH;

R⁶ H or (Ci-C₄)-alkyl;

n is 0,1 or 2; and

Z is

CO₂-R⁷, OR⁸, C(O)NR⁹R¹⁰, S(O)₂NR¹¹R¹²,
wherein

\( v \) is 0 or 2;

\( R^7 \) is H or \((\text{Ci-C}_4)\)-alkyl;

\( R^8 \) is H or \((\text{Ci-C}_4)\)-alkyl;

\( R^9 \) is H, \((\text{Ci-C}_4)\)-alkyl or ethylene-O-(\text{Ci-C}_4)-alkyl;

and

\( R^{10} \) is

a) H;

b) \((\text{Ci-C}_6)\)-alkyl, which is unsubstituted or mono-substituted by \(\text{CF}_3\);

c) \((\text{Ci-C}_2)\)-alkyl, which is substituted by \(\text{CN}\) or \(\text{CO}_2\)\(R^{19}\)

wherein

\( R^{19} \) is H or \((\text{Ci-C}_6)\)-alkyl;

d) \((\text{C}_2\cdot\text{C}_4)\)-alkyl, which is mono-substituted by a substituent selected from the group consisting of S-methyl, \(\text{SO}_2\)\(NR^{20}\)\(R^{21}\), O-\(R^{22}\) and \(NR^{23}\)\(R^{24}\);

wherein

\( R^{20} \) is H;

\( R^{21} \) is H;

\( R^{22} \) is H, \((\text{Ci-C}_3)\)-alkyl, methylene-cydopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane;
e) (C3-C5)-cycloalkyl, which is unsubstituted or mono-substituted by phenyl;

f) (Co-C2)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is five or six membered and contains 1 or 2 O atoms in non-adjacent positions, and wherein said heterocycloalkyl is unsubstituted or geminally disubstituted with a spiro cyclopentyl ring or a spiro cyclohexyl ring;

g) (C2-C3)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five-, six- or seven-membered ring, which contains at least one N atom, and which is attached via said N-atom, and which may additionally contain one heteroatom selected from the group consisting of O, S(O)ₓ or NR²⁵ in a position not adjacent to the N atom, by which the ring is attached to the alkylene, and wherein any carbon atom within said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (Ci-C3)alkyl, or methylene-phenyl; wherein

x is 2;

h) (Co-C3)-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is a five- or six-membered ring, which contains at least one N atom, and which is not attached via said N-atom, and which may additionally contain one O atom in a position not adjacent to the N atom, and wherein said N-atom is unsubstituted or substituted by a substituent selected from the group consisting of

i) (Ci-C₄)-alkyl, which is unsubstituted or mono-substituted by O(Ci-C₄)-alkyl;

ii) methylene-cyclohexyl;
iii) (Co-C2)-alkylene-phenyl, wherein phenyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of F and O(Ci-C₄)-alkyl;
iv) (Co-Ci)-alkylene-pyridyl;
v) pyrimidinyl;
i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3yl;
j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;
k) methylene-4-(octahydro-quinolizinyl);
l) (Co-C2)-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, O(Ci-C₄)-alkyl, N((Ci-C₄)-alkyl)₂, 4-morpholinyl and methylene-(4-methyl-piperidin)-1-yl or disubstituted on adjacent positions by the group -O(CH₂)O-;
m) (Ci-C2)-alkylene-heteroaryl, wherein said heteroaryl ring is a five- or six-membered ring containing 1, 2, 3 or 4 heteroatoms selected from O, S or N; and wherein said heteroaryl ring is unsubstituted or monosubstituted by oxo (=O);
or
R⁹ and R¹⁰ together with the N-atom carrying them are
a) a four-, five- or six-membered heterocycloalkyl ring containing only the N atom, to which R⁹ and R¹⁰ are attached, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of
i) (Co-Ci)-alkylene- O R₂⁶, wherein R₂⁶ is H, (Ci-C₃)alkyl or methylene-phenyl;
ii) CO₂ R²⁷, wherein R²⁷ is H or (Ci-C₆)-alkyl;
ii) NR₂⁸ R²⁹, wherein R₂⁸ is (Ci-C₂)-alkyl and R²⁹ is (Ci-C₂)-alkyl, methylene-phenyl or ethylene-N((Ci-C₄)-alkyl)₂;
iii) 1-piperidinyl, which is unsubstituted or mono-substituted by methyl;
iv) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;
v) 4-morpholinyl;
vi) 1-azepanyl;
vii) 2-(2,3-dihydro-1H-isoindolyl);
b) a six- or seven-membered heterocycloalkyl ring containing the N atom, to which R⁹ and R¹⁰ are attached and one additional heteroatom selected from O, S or NR³⁰ in a position non-adjacent to the N atom, to which R⁹ and R¹⁰ are attached, wherein the carbon atoms in said heterocycloalkyl ring are unsubstituted or mono- or disubstituted by methyl and wherein R³⁰ is
i) H;
ii) (C₁₋C₄)-alkyl;
iii) (C₅₋C₆)-cycloalkyl;
iv) phenyl, which is unsubstituted or mono-substituted by F, CF₃ or O-(C₁₋C₄)-alkyl;
v) methylene-phenyl, which is unsubstituted or mono- or di-substituted by F or Cl or disubstituted on adjacent positions by the group -O(CH₂)O-;
vi) pyridyl;
c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is unsubstituted or substituted on the second N atom in 5-position by a substituent selected from the group consisting of (C₁₋C₄)-alkyl, methylene-cyclopentyl, phenyl, which is unsubstituted or mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by O-(C₁₋C₄)-alkyl or CF₃;

R¹¹ is H;
R¹² is (C₁₋C₄)-alkyl;
R¹³ is H;
R¹⁴ is CF₃ or methylene-O-(C₁₋C₄)-alkyl;
R¹⁵ is cyclopenty1 or phenyl;
R¹⁶ is H or (C₁₋C₄)-alkyl;
R¹⁷ is H or (C₁₋C₄)-alkyl;
and
R^{18} \text{ is (C}_1-\text{C}_4)-\text{alkyl;}

in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

2. A compound of formula I of claim 1 wherein
R^{'}, \text{ } R^{\prime\prime}, \text{ } R^{\prime\prime\prime} \text{ are H;}
R^{1} \text{ is}

10 a) iso-butyll, sec-butyl, 1-ethyl-propyl, 2-methyl-butyl, 1,3-dimethyl-butyl, 1-isopropyl-2-methyl-propyl;
b) cyclopentyl, 2-methyl-cyclopentyl, cyclohexyl, 2-methyl-cyclohexyl, 2-(trifluoromethyl)-cyclohexyl, 2-ethyl-cyclohexyl, cycloheptyl;
c) methylene-cyclohexyl;
d) phenyl, 2-chloro-phenyl, 4-tolyl;
R^{2} \text{ is}
a) 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 4-thiazolyl, 5-thiazoloyl, 1-pyrazolyl; 5-isoxazolyl, 5-methyl-thien-2-yl, 5-chloro-thien-2-yl
b) phenyl;

c) \text{(C}_5-\text{C}_6)-\text{cycloalkyl; or}
d) 2-tetrahydrofuranyl;
R^{3} \text{ is H, or methyl;}
and
R^{4} \text{ is}

25 a) \text{(C}_3-\text{C}_5)-\text{alkyl, which may be optionally substituted by 1-3 F or S-methyl,}
b) methylene-(\text{C}_4-\text{C}_6)-\text{cycloalkyl; or}

R^{3} \text{ and } R^{4}

are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring;

R^{5} \text{ is H, methyl or OH;}
R^6 is H or methyl;

n is 0, 1 or 2; and

Z is

\[ \text{CO}_2\text{-R}^7, \text{OR}^8, \text{C(O)NR}^9\text{R}^{10}, \text{S(O)NR}^1\text{R}^{12}, \]

\[ \text{S(O)}_\nu \text{N-N-R}^{13}, \text{N-N-R}^{14}, \text{N-N-R}^{15}, \text{N-O-R}^{16}, \text{N-S-R}^{17}, \text{N-C-R}^{18}, \]

\[ \text{N-N-R}^{19}, \text{N-N-R}^{20}, \text{S-O-R}^{21}, \text{O-N-R}^{22}, \text{N-N-R}^{23}, \text{N-N-R}^{24}, \]

wherein

v is 0 or 2;

R^7 is H;
R^8 is H or (Ci-C_4)-alkyl;
R^9 is H, CH_3;

and

R^{10} is

a) H
b) (Ci-C_6)-alkyl, which is unsubstituted or mono-substituted by CF_3;
c) (Ci-C_2)-alkyl, which is substituted by CN or CO_2R^{19}

wherein

R^{19} is H;

d) (C_2-C_4)-alkyl, which is mono-substituted by a substituent selected from the group consisting of S CH_3, SO_2NR^{20}R^{21}, O-R^{22} and NR^{23}R^{24};
wherein

R\textsuperscript{20} is H;
R\textsuperscript{21} is H;
R\textsuperscript{22} is H, (Ci-C\textsubscript{3})-alkyl, methylene-cyclopropyl, methylene-phenyl, or methylene-2-tetrahydrofurane;
R\textsuperscript{23} is H or (Ci-C \textsubscript{2})-alkyl;
R\textsuperscript{24} is (Ci-C \textsubscript{2})-alkyl or SO\textsubscript{2}CH\textsubscript{3};
e) cyclobutyl, cyclopentyl or 2-phenyl-cyclopropyl;
f) (Co-C\textsubscript{2})-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl and 1,4-dioxan-2-yl;
g) (C\textsubscript{2}-C\textsubscript{3})-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 1-pyrroli dinyl, 1-piperidinyl, 1-azepanyl, 4-morpholinyl 1,1-dioxo-thiomorpholin-4-yl, and 1-piperazinyl; wherein said heterocycloalkyl is unsubstituted or substituted by 1 or 2 substituents selected from the group consisting of (CrC\textsubscript{2})alkyl, or methylene-phenyl;
h) (Co-C\textsubscript{3})-alkylene-heterocycloalkyl, wherein said heterocycloalkyl is selected from the group consisting of 3-pyrrolidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 2-morpholinyl and wherein said heterocycloalkyl is substituted by a substituent selected from the group consisting of
i) (Ci-C \textsubscript{4})-alkyl;
ii) methylene-cyclohexyl;
iii) (Co-C\textsubscript{2})-alkylene-phenyl;
iv) (Co-C\textsubscript{i})-alkylene-pyridyl;
v) pyrimidinyl;
i) 8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl;
j) 9-methyl-9-aza-bicyclo[3.3.1]non-3-yl;
k) methylene-4-(octahydro-quinoliniziny);
l) \((\text{Co-C}_2)\)-alkylene-phenyl, wherein phenyl is unsubstituted or monosubstituted by substituents chosen from the group consisting of F, OCH\(_3\), N(CH\(_3\))\(_2\):

m) \((\text{Ci-C}_2)\)-alkylene-heteroaryl, wherein said heteroaryl ring is selected from the group consisting of 2-thienyl, 2-furanyl, 2-thiazolyl, 2-oxazolyl, 5-tetrazolyl and 5-Oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl;

or

R\(^9\) and R\(^{10}\) together with the N-atom carrying them are

a) azetidinyl substituted by CO\(_2\)H;

b) pyrrolidinyl, which is unsubstituted or mono-substituted by a substituent selected from the group consisting of

i) OH;

ii) methylene-OCH\(_3\);

iii) methylene-O-methylene-phenyl;

iv) CO\(_2\)H;

v) NR\(^2\)R\(^9\), wherein R\(^2\) is (Ci-C\(_2\))-alkyl and R\(^9\) is (Ci-C\(_2\))-alkyl;

vi) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;

c) piperidinyl, which is mono-substituted by a substituent selected from the group consisting of

i) O-(Ci-C\(_3\))alkyl;

ii) methylene-O CH\(_3\);

iii) NR\(^2\)R\(^9\), wherein R\(^2\) is (Ci-C\(_2\))-alkyl and R\(^9\) is methylene-phenyl or ethylene-N(CH\(_3\))\(_2\);

iv) 1-piperidinyl, which is mono-substituted by methyl;

v) 1-piperazinyl, which is unsubstituted or mono-substituted by methyl;

vi) 4-morpholinyl;

vii) 1-azepanyl;

viii) 2-(2,3-dihydro-1H-isoindolyl);

d) 4-morpholinyl, which is disubstituted by methyl;

e) 4-thiomorpholinyl;
f) piperazinyl, which is mono-substituted by a substituent selected from the group consisting of
i) (C1-C4)-alkyl;
ii) (C5-C6)-cycloalkyl;
iii) phenyl, which is unsubstituted or mono-substituted by F, CF3 or OCH3;
iv) methylene-phenyl, which is unsubstituted or disubstituted on adjacent positions by the group -O(CH2)O-;
v) pyridyl;

g) azepanyl, which is substituted by methylene-phenyl, which is unsubstituted or mono- or disubstituted by F or Cl;
c) a 2,5-diaza-bicyclo[2.2.1]heptyl-ring, which is substituted on the second N atom in 5-position by a substituent selected from the group consisting of (C1-C4)-alkyl, methylene-cyclopentyl, phenyl, which is mono-substituted by F, methylene-phenyl, wherein phenyl is unsubstituted or mono-substituted by OCH3 or CF3;

R11 is H;
R12 is CH3;
R13 is H;
R14 is CF3 or methylene-OCH3;
R15 is cyclopryopyl or phenyl;
R16 is H or CH3;
R17 is H or CH3;

and
R18 is CH3;
in any of its stereoisomeric forms, or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them.

3. A compound of formula I of claim 1 or 2 wherein
R', R", R'" are H;
R¹ is 1-ethyl-propyl;
R² is 3-thienyl;
R³ is H;
R⁴ is 2-methyl-propyl;
n is 0, 1, 2;
and
Z is C(O)NR⁹R¹⁰.

4. A compound of formula I of claim 1 or 2 wherein
R', R", R'" are H;
R¹ is 1-ethyl-propyl or 2-methyl-cyclohexyl;
R² is 3-thienyl;
R³ is H, or (Ci-C₂)-alkyl;
and
R⁴ is
a) (C₃-C₆)-alkyl, which may be optionally substituted by 1-3 F or S-(Ci-C₄)-alkyl,
b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cycloalkyl is unsubstituted or mono- or di-substituted by methyl;
or
R³ and R⁴
are, together with the carbon atom to which they are attached, a 5- to 7-membered cycloalkyl ring, which is unsubstituted or mono-substituted by (Ci-C₄)-alkyl;
n is 0; and
Z is CO₂-H.

5. A compound of formula I of claim 1 or 2 wherein
R', R", R'" are H;
R¹ is 1-ethyl-propyl or 2-methyl-cyclohexyl;
R² is 3-thienyl;
6. A compound of formula I of claim 1 or 2 wherein

R³ is H, or (Ci-C₂)-alkyl;
and
R⁴ is
  a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(Ci-C₄)-alkyl,
  b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cydooalkyi is unsubstituted or
     mono- or di-substituted by methyl;

or
R³ and R⁴
  are, together with the carbon atom to which they are attached, a 5- to 7-
  membered cydooalkyi ring, which is unsubstituted or mono-substituted by (Ci-
  C₄)-alkyl;
R⁵ is H, (Ci-C₄)-alkyl or OH;
R⁶ H or (Ci-C₄)-alkyl;
n is 1;
and
Z is CO₂-H.

20 R', R'', R''' are H;
R¹ is 1-ethyl-propyl or 2-methyl-cyclohexyl;
R² is 3-thienyl;
R³ is H, or (Ci-C₂)-alkyl;
and
R⁴ is
  a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(Ci-C₄)-alkyl,
  b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cydooalkyi is unsubstituted or
     mono- or di-substituted by methyl;

or
R³ and R⁴
are, together with the carbon atom to which they are attached, a 5- to 7-
membered cydoalkyi ring, which is unsubstituted or mono-substituted by (Ci-
C₄)-alkyl;
R⁵ is H, (Ci-C₄)-alkyl or OH;

5  R⁶ H or (Ci-C₄)-alkyl;

n is 2;

and

Z is CO₂-H.

10 7. A compound of formula I of claim 1 or 2 wherein

R', R", R" are H;
R¹ is 1-ethyl-propyl;
R² is 3-thienyl;
R³ is H, or (Ci-C₂)-alkyl;

and

R⁴ is

a) (C₃-C₅)-alkyl, which may be optionally substituted by 1-3 F or S-(Ci-C₄)-alkyl,
b) (Co-Ci)-alkylene-(C₃-C₇)-cycloalkyl, wherein said cydoalkyi is unsubstituted or
mono- or di-substituted by methyl;

20 or

R³ and R⁴

are, together with the carbon atom to which they are attached, a 5- to 7-
membered cydoalkyi ring, which is unsubstituted or mono-substituted by (Ci-
C₄)-alkyl;

25 R⁵ is H, (Ci-C₄)-alkyl or OH;
R⁶ H or (Ci-C₄)-alkyl;

n is 1 or 2;

and

Z is OR⁸, S(O)₂NR¹¹R¹², CN,
8. A compound of formula I of claim 1 or 2 wherein

10 \( R^\prime, R^\prime', R^{\prime\prime} \) are \( H \);
\( R^1 \) is 1-ethyl-propyl;
\( R^2 \) is 3-thienyl;
\( R^3 \) is \( H \);
\( R^4 \) is 2-methyl-propyl;
\( n \) is 0;
and
\( Z \) is \( C(O)NR^9R^{10} \);
wherein
\( R^9 \) is \( H \) or methyl;
and
\( R^{10} \) is

c) \( (Ci-C2) \)-alkyl, which is substituted by \( CN \)
d) \( (C2-C4) \)-alkyl, which is mono-substituted by a substituent selected from
\( NR^{23}R^{24} \);

25 wherein
\( R^{23} \) is \( H \);
\( R^{24} \) is \( (Ci-C_2) \)-alkyl or \( SO_2Methyl \);

m) \( (Ci-C2) \)-alkylene-heteroaryl, wherein said heteroaryl ring is a five-or six-
membered ring containing 1, 2, 3 or 4 heteroatoms selected from \( O, S \)
or N; and wherein said heteroaryl ring is unsubstituted or mono-
substituted by oxo (=O);

or

R\textsuperscript{9} and R\textsuperscript{10} together with the N-atom carrying them are

\textbf{a}) a four-, five- or six-membered heterocylcoalkyl ring containing only the
N atom, to which R\textsuperscript{9} and R\textsuperscript{10} are attached, which is unsubstituted or
mono-substituted by a substituent selected from the group consisting of

\textbf{i}) (Co-Ci)-alkylene- OR\textsuperscript{26}, wherein R\textsuperscript{26} is H;

\textbf{ii}) CO\textsubscript{2}R\textsuperscript{27}, wherein R\textsuperscript{27} is is H.

\textbf{9. A compound of the formula I of claim 1 or 2, selected from the group consisting of}

\textbf{1)} 1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino)-cycloheptanecarboxylic acid

\textbf{6)} 1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino)-cyclopentanecarboxylic acid

\textbf{11)} 3-Cyclopentyl-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
5-carbonyl]-amino)-propionic acid

\textbf{12)} 2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
amino)-2,4-dimethyl-pentanoic acid

\textbf{15)} (S)-3-Cyclohexyl-2-[(1 -(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-amino)-propionic acid

\textbf{16)} (S)-2-[(1 -(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-
carbonyl]-amino)-hexanoic acid

\textbf{18)} (S)-2-[(1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-
carbonyl]-amino)-hexanoic acid

\textbf{21)} (S)-3-Cyclopropyl-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-amino)-propionic acid

\textbf{22)} (S)-3-Cyclobutyl-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-
benzoimidazole-5-carbonyl]-amino)-propionic acid

\textbf{23)} (S)-3-Cyclobutyl-2-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-
1H-benzoimidazole-5-carbonyl]-amino)-propionic acid
1-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-cyclohexanecarboxylic acid
2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-2-nnethyl-pentanoic acid
2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-5,5,5-trifluoro-pentanoic acid
5,5,5-Trifluoro-2-[(1-((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H- benzoimidazole-5-carbonyl]-annino]-pentanoic acid
3-(4,4-Dimethyl-cyclohexyl)-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H- benzoimidazole-5-carbonyl]-annino]-propionic acid
3-(4,4-Dimethyl-cyclohexyl)-2-[(1 -(1,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
3-(4,4-Dimethyl-cyclohexyl)-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
4-Methyl-1-[(1 -(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-3-(4-nnethyl-cyclohexyl)-propionic acid
1-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-4-methyl-cyclohexanecarboxylic acid
4-Methyl-1-[(1 -(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-3-(4-nnethyl-cyclohexyl)-propionic acid
1-[(1 -(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-cyclohexanecarboxylic acid
3-Cycloheptyl-2-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
   5-carbonyl]-amino]-propionic acid
3-Cycloheptyl-2-[(1 -(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-propionic acid
3-Cyclohexyl-3-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
   5-carbonyl]-amino]-propionic acid
3-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-heptanoic acid
4-Cyclohexyl-3-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-
   5-carbonyl]-amino]-butyric acid
3-[(1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-
   amino]-5,5-dinethyl-hexanoic acid
(R)-3-[(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-5-n-nethyl-hexanoic acid

4-Cyclohexyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid

4-Cyclohexyl-3-[(1 -(1 S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid

(3R,4S)-4-Methyl-3-[(1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid

(3R,4S)-3-[(1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4-n-nethyl-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

3-[(1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

3-[(1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-4,2,2-tri-n-nethyl-hexanoic acid

3-[(1 -(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-2,2-din-nethyl-hexanoic acid

(1 -(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino)-cyclohexyl)-acetic acid
(2R,3S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-nnethyl-hexanoic acid

(2S,3S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2-hydroxy-5-nnethyl-hexanoic acid

(R)-6-Methyl-4-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(4R,5S)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-heptanoic acid

(4R,5S)-5-Methyl-4-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(3R,4S)-5-Cyclohexyl-4-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(3R,4S)-5-Cyclohexyl-3-hydroxy-4-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(3S,4S)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-nnethyl-heptanoic acid

(3R,4S)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-6-nnethyl-heptanoic acid

(3R,4S)-3-Hydroxy-6-methyl-4-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(3S,4S)-3-Hydroxy-6-methyl-4-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid

(3S,4S)-5-Cyclohexyl-4-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(3S,4S)-5-Cyclohexyl-4-[(1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-hydroxy-pentanoic acid

(S)-2-[(1-(1R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(2S,3S)-3-Methyl-2-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-nnethyl-hexanoic acid
(S)-5-Methyl-3-[(1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-NNethyl-hexanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-NNethyl-hexanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-NNethyl-pentanoic acid

(S)-3-Cyclohexyl-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid

(S)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-methylsulfanyl-butyric acid

(S)-4-Methyl-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-NNethyl-hexanoic acid

(S)-4-Methyl-2-[(1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(2S,3R)-2-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-3-methyl-pentanoic acid

3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-hexanoic acid

(R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-4-NNethyl-pentanoic acid

(R)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-5-NNethyl-hexanoic acid

(R)-4-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-6-NNethyl-heptanoic acid

(S)-4-Methyl-2-[(1-(1R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid

(S)-4-Methyl-2-[(1-(1S,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-pentanoic acid
(S)-4-Methyl-2-\{[1-(1R,2S)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-4-Methyl-2-\{[1-(1S,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-pentanoic acid

(S)-2-\{[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-2-\{[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-2-\{[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-2-\{[1-(2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-hexanoic acid

(S)-3-Cyclohexyl-2-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-3-Cyclohexyl-2-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-propionic acid

(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(S)-5-Methyl-3-\{[1-(2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-annino\}-hexanoic acid

(R)-2-\{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-2,4-dinnethyl-pentanoic acid

(S)-2-\{[1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino\}-2,4-dinnethyl-pentanoic acid
442 3-Cyclopentyl-2-{[1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
443 3-Cyclopentyl-2-{[1 -((1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
448 (S)-3-Cycloheptyl-2-{[1-(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
449 (R)-3-Cycloheptyl-2-{[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
450 3-Cycloheptyl-2-{[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
451 3-Cycloheptyl-2-{[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino}-propionic acid
452 (S)-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid
453 (R)-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-heptanoic acid
454 (S)-4-Cyclohexyl-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid
455 (R)-4-Cyclohexyl-3-[[1 -(1-ethyl-propyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-amino]-butyric acid
456 4-Cyclohexyl-3-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid
457 4-Cyclohexyl-3-[[1 -(1 R,2R)-2-methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-butyric acid
458 3-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid
459 3-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-hexanoic acid
460 3-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid
461 3-[[1 -(1 R,2R)-2-Methyl-cyclohexyl)-2-thiophen-2-ylmethyl-1 H-benzoimidazole-5-carbonyl]-annino]-heptanoic acid
3-Cyclohexyl-3-[(1R,2R)-2-methyl-cyclohexyl]-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-propionic acid

(R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2,5-trinnethyl-hexanoic acid

(R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-hexanoic acid

(S)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid

(R)-3-[(1-(1-Ethyl-propyl)-2-thiophen-2-ylmethyl-1H-benzoimidazole-5-carbonyl]-amino]-2,2-dinnethyl-heptanoic acid;
a physiologically acceptable salt thereof, or a physiologically acceptable solvate thereof.

10. A pharmaceutical composition comprising at least one compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable solvate of any of them, for use as a pharmaceutical.

11. A compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them, for use as a pharmaceutical.

12. A compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for preventing and treating cardiovascular diseases, include coronary heart disease, stroke, heart failure, systolic heart failure, diastolic heart failure, diabetic heart failure, heart failure with preserved ejection fraction, cardiomyopathy,
myocardial infarction, left ventricular dysfunction, left ventricular dysfunction after myocardial infarction, cardiac hypertrophy, myocardial remodeling, myocardial remodeling after infarction or after cardiac surgery and valvular heart diseases.

13. A compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for preventing and treating metabolic syndrome, insulin resistance, diabetes mellitus, diabetic late complications, diabetic macro- and microvasculopathies, diabetic nephropathy, diabetic retinopathy, diabetic neuropathies and cardiac autonomic neuropathy.

14. A compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for preventing and treating diseases with disturbed body's fluid homeostasis by CNS dependent and -independent effects, acute and chronic renal failure, hypertension, pulmonary hypertension, portal hypertension and systolic hypertension.

15. A compound of the formula I as claimed in any of claims 1 to 9 or a physiologically acceptable salt thereof, or a physiologically acceptable solvate of any of them for preventing and treating increased vascular permeability and non-functional blood vessels, vascular hypertrophy, vascular remodeling, vascular stiffness, atherosclerosis, peripheral arterial occlusive disease (PAOD), restenosis, thrombosis, vascular permeability disorders, ischemia, reperfusion damage, ischemia and/or reperfusion damage of the heart, kidney and retina.
INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/069432

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/08 C07D403/06 C07D405/06 C07D409/14 C07D411/06
C07D413/14 C07D417/06 C07D451/04 C07D487/06 A61K31/4184

According to International Patent Classification (IPC) into both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>wo 03/053938 AI (NOVO NORDISK AS [DK]) 3 July 2003 (2003-07-03) cited in the application on page 5; compound (I) page 18, line 33 - page 19, line 3 example 15</td>
<td>1-15</td>
</tr>
<tr>
<td>A</td>
<td>wo 99/40072 AI (BOEHRINGER INGELHEIM PHARMA [DE]) 12 August 1999 (1999-08-12) cited in the application on page 1; compound (I) page 49, paragraph 2 examples 186, 187 claims 1-10</td>
<td>1-15</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A" document member of the same patent family

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

Date of the actual completion of the international search
4 December 2013

Date of mailing of the international search report
12/12/2013

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016

Authorized officer
Hoepfner, Wolfgang
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>EP 1 903 052 A2 (FAUST PHARMACEUTICALS SA [FR]; INST NAT SANTE RECH MED [FR]) 26 March 2008 (2008-03-26) page 2, paragraph 1 - paragraph 2 page 2; compound (I) page 6, paragraph 19 examples claims</td>
<td>1-15</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2008)
INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. □ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

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

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

□ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/21 0 (continuation of first sheet (2)) (April 2005)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 7, 8 (completely); 1, 2, 4-6, 9-15 (partially)

   Compounds of Formula I where in the substituent R is (C4-C7)alkyl.

   ---

2. claims: 1, 2, 4-6, 9-15 (partially)

   Compounds of Formula I where in the substituent R comprises a cyclic moiety.

   ---
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WO 03053938 A1</td>
<td>03-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2319494 A1</td>
<td>12-08-1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1060166 A1</td>
<td>20-12-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002502844 A</td>
<td>29-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9940072 A1</td>
<td>12-08-1999</td>
</tr>
<tr>
<td>EP 1903052 A2</td>
<td>26-01-2008</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>