Amide derivatives, their manufacture and use as pharmaceutical agents

The present invention relates to novel amide derivatives, to a process for their manufacture, pharmaceutical compositions containing them and their manufacture as well as the use of these compounds as pharmaceutically active agents.

Protein tyrosine kinases (PTKs) catalyse the phosphorylation of tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (Wilks, A.F., Progress in Growth Factor Research 2 (1990) 97-111; Chan, A.C., and Shaw, A.S., Curr. Opin. Immunol. 8 (1996) 394-401). Such PTKs can be divided into receptor tyrosine kinases (e.g. EGFR/HER-1, c-erB2/HER-2, c-met, PDGFr, FGFr) and non-receptor tyrosine kinases (e.g. src, lck). It is known that many oncogenes encode proteins which are aberrant tyrosine kinases capable of causing cell transformation (Yarden, Y., and Ullrich, A., Annu. Rev. Biochem. 57 (1988) 443-478; Larsen et al., Ann. Reports in Med. Chem., 1989, Chpt. 13). Also over-expression of a normal proto-oncogenic tyrosine kinase may result in proliferative disorders.

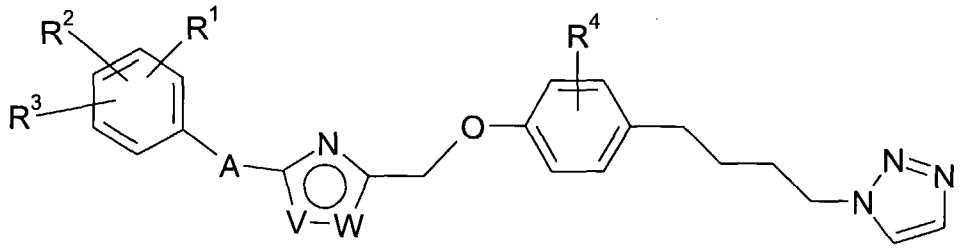
It is known that receptor tyrosine kinases of the HER-family like HER-2 and EGFR (HER-1) are frequently aberrantly expressed in common cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukaemia and ovarian, bronchial and pancreatic cancer. High levels of these receptors correlate with poor prognosis and response to treatment (Wright, C., et al., Br. J. Cancer 65 (1992) 118-121).

Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. Therefore several small molecule compounds as well as monoclonal antibodies are in clinical trials for the treatment of various types of cancer (Baselga, J., and Hammond, L.A., Oncology 63 (Suppl. 1) (2002) 6-16; Ranson, M., and Sliwkowski, M.X., Oncology 63 (suppl. 1) (2002) 17-24).

Some substituted oxazoles are known in the art. WO 98/03505, EP 1 270 571, WO 01/77107, WO 03/031442 and WO 03/059907 disclose related heterocyclic compounds as -tyrosine kinase inhibitors.

However there remains a need for new compounds with improved therapeutic properties, such as enhanced activity, decreased toxicity, better solubility and improved pharmacokinetic profile, to name only a few.

The present invention relates to compounds of the general formula I,



formula I,

wherein

R^1 is hydrogen,
halogen,
nitro,
$-SF_5$,
-O-alkyl,
$-S(O)_n$-alkyl,
$-S(O)_2NH_2$,
$-S(O)_2NH$-acyl,
$-S(O)_2NH$-heteroaryl,
-NH-alkyl, or
alkyl, all alkyl groups being optionally substituted once or several times with halogen;

n is 0, 1 or 2

R^2 is hydrogen; or alternatively

R^1 and R^2 are
adjacent and together with the carbon atoms of the phenyl ring to which they are attached form a 5 or 6 membered heterocyclic ring;

R^3 is hydrogen, halogen or nitro;

R^4 is hydrogen or alkyl;

A is -NHC(O)-; -C(O)NH-; -N(alkyl)C(O)- or -C(O)N(alkyl)-;

V is -CH-; and
W is -S- or –O-; or alternatively
V is -S-; and
W is -CH-; and

pharmaceutically acceptable salts thereof.

The compounds of the present invention show activity as inhibitors of the HER-signaling pathway and therefore possess anti-proliferative activity. Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts, enantiomeric forms, diastereoisomers and racemates, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders as mentioned above like common human cancers (e.g. breast cancer, gastrointestinal cancer (colon, rectal or stomach cancer), leukaemia and ovarian, bronchial and pancreatic cancer) or in the manufacture of corresponding medicaments.

As used herein, the term "alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 4, preferably from 1 to 2, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl.

If said alkyl group is optionally substituted with one or several halogen atoms, it is one to five, preferably one to three, times substituted preferably with fluorine or chlorine, most preferred it is substituted with fluorine. Examples are difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluorethyl and the like, preferably trifluoromethyl.

The term “halogen” as used herein means fluorine, chlorine or bromine preferably fluorine and chlorine.

The term "acyl" as used herein means a C_2-C_4-, preferably a C_2-C_3-, acyl group such as acetyl, propionyl, butyryl and isobutyryl.

The term "heteroaryl" as used herein means a unsaturated cyclic hydrocarbon with 5 or 6 ring atoms, preferably 5 ring atoms, of which 1, 2 or 3 atoms are replaced by heteroatoms selected from O, N or S. Such ring can be substituted, where appropriate, one or two times, preferably one time, by C_1-C_4-alkyl, preferably by C_1-C_2-alkyl,. Examples for such rings are thiazole, oxazole, isoxazole, thiadiazole, triazole and the like, preferably thiazole, isoxazole, thiadiazole.

As used herein the heterocyclic ring formed by R^1 and R^2 means a saturated or unsaturated cyclic hydrocarbon with 5 or 6 ring atoms of which 1 or 2 atoms are replaced by heteroatoms selected from S, N or O, preferably from N or O, and the remaining carbon-atoms, where possible, being optionally once or several times substituted with halogen, preferably fluorine. Preferably said "5 or 6 membered heterocyclic ring" is formed by R^1 and R^3 being located on two adjacent carbon-atoms of the phenyl ring to which they are attached. Examples of a "5 or 6 membered heterocyclic ring", including the phenyl ring to which it is attached, are benzo[1,3]dioxole, 2,2-difluoro-benzo[1,3]dioxole, 1H-benzimidazole, 2,3-dihydro-benzo[1,4]dioxine, 3,4-dihydro-2H-benzo[1,4]oxazine and the like preferably benzo[1,3]dioxole and 2,2-difluoro-benzo[1,3]dioxole.

Preferred substituents in the definition of R^1 are trifluoromethyl, pentafluorosulfanyl, trifluoromethylsulfanyl, methoxy, difluoromethoxy, trifluoromethoxy, chloro and fluoro, especially trifluoromethoxy, trifluoromethyl and chlorine. A preferred position of the substituent R^1 on the phenyl ring to it is attached, is para to the group A.

When "R^1 and R^2 together with the carbon atoms to which they are attached form a 5 or 6 membered heterocyclic ring", the resulting bicyclic ring system, including the phenyl ring to which R^1 and R^2 are attached is preferably a 2,2-difluoro-benzo[1,3]dioxolyl or benzo[1,3]dioxolyl moiety.

The preferred substituent in the definition of R^2 is hydrogen.

Preferred substituents in the definition of R^3 are hydrogen, fluoro and chloro, especially hydrogen and fluoro. A preferred position of the substituents R^3 on the phenyl ring to which they are attached, is ortho to the group A.

If R^4 is alkyl, the preferred position of R^4 on the phenyl ring to which it is attached is meta to the oxygen of the phenolic ether.

As used herein, when referring to the receptor tyrosine kinases of the HER-family like HER-2 and EGFR (HER-1), the acronym "HER" refers to human epidermal receptor and the acronym "EGFR" refers to epidermal growth factor receptor.

As used herein, in relation to mass spectrometry (MS) the term "ESI+" refers to positive electrospray ionization mode and the term "API+" refers to positive atmospheric pressure ionization mode.

As used herein, a "pharmaceutically acceptable carrier" is intended to include any and all material compatible with pharmaceutical administration including solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and other materials and compounds compatible with pharmaceutical administration. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions of the invention are contemplated. Supplementary active compounds can also be incorporated into the compositions.

An embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or

alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen; and

R^3 is hydrogen or fluorine.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen; and

R^3 is hydrogen or fluorine; and

R^4 is hydrogen.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -NHC(O)- or-N(alkyl)C(O)-.

An embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen; and

A is -NHC(O)- or-N(alkyl)C(O)-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen;
R^3 is hydrogen or fluorine; and
A is -NHC(O)- or-N(alkyl)C(O)-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine;
R^4 is hydrogen; and
A is -NHC(O)- or-N(alkyl)C(O)-.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine.
R^4 is hydrogen;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
$-O-CF_3$,
$-O-CF_2$,
$-S-CF_3$,
$-S-CF_2$,
$-CF_3$, or
$-SF_5$;
R^2 is hydrogen;
R^3 is hydrogen, fluorine, chlorine or nitro;
R^4 is hydrogen;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Such compounds are for example:

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-methyl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-nitro-4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-4-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-(4-trifluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-nitro-2-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,6-dichloro-phenyl)-amide; and

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-dichloro-phenyl)-amide.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is hydrogen,
fluorine,
bromine,
-O-alkyl,
-S-alkyl,
alkyl,
$-S(O)_2NH_2$,
$-S(O)_2NH$-acyl, or
$-S(O)_2NH$-heteroaryl;

R^2 is hydrogen; or alternatively

R^1 and R^2 are
adjacent and together with the carbon atoms of the phenyl ring to which they are attached form a 2,2-difluoro-benzo[1,3]dioxolyl moiety or a benzo[1,3]dioxolyl moiety, and

R^3 is hydrogen, fluorine or nitro;

R^4 is hydrogen;

A is -NHC(O)- or-N(alkyl)C(O)-;

V is -CH-; and

W is -S-, or –O-.

Such compounds are for example:

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid benzo[1,3]dioxol-5-yl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,5-difluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-difluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-(thiazol-2-ylsulfamoyl)-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-phenyl]-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-isoxazol-3-ylsulfamoyl)-phenyl]-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-bromo-2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-2-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-2-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid p-tolylamide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-phenyl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methoxy-phenyl)-amide; and

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,4-difluoro-phenyl)-amide.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -NHC(O)- or-N(alkyl)C(O)-;
V is -S-; and
W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -S-; and
W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine.
R^4 is hydrogen;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -S-; and
W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-SF_5, or

alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen;

R^3 is hydrogen or fluorine;

R^4 is hydrogen;

A is -NHC(O)- or-N(alkyl)C(O)-;

V is -S-; and

W is -CH-.

Such compounds are for example:

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-chloro-phenyl)-amide;

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-trifluoromethoxy-phenyl)-amide; and

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-pentafluorosulfanyl-phenyl)-amide.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -C(O)NH- or- C(O)N(alkyl)-.

An embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen; and

A is -C(O)NH- or- C(O)N(alkyl)-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,

-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen;

R^3 is hydrogen or fluorine; and

A is -C(O)NH- or- C(O)N(alkyl)-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen;

R^3 is hydrogen or fluorine;

R^4 is hydrogen; and

A is -C(O)NH- or- C(O)N(alkyl)-.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -C(O)NH- or- C(O)N(alkyl)-;

V is -S-; and

W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen;

A is -C(O)NH- or- C(O)N(alkyl)-;

V is -S-; and

W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine.
R^4 is hydrogen;
A is -C(O)NH- or- C(O)N(alkyl)-;
V is -S-; and
W is -CH-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen, chlorine or fluorine;
R^4 is hydrogen;
A is -C(O)NH- or- C(O)N(alkyl)-;
V is -S-; and
W is -CH-.

Such compounds are for example:

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-3-trifluoromethyl-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethoxy-benzamide;

4-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Chloro-3-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3,4-Dichloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide;

3-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Chloro-2-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Methyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-6-trifluoromethyl-benzamide;

3-Chloro-4-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide;

4-tert-Butyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide; and

4-Difluoromethoxy-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is nitro,
cyano,
-S-alkyl,
fluorine; or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine;
R^4 is hydrogen;
A is -C(O)NH- or- C(O)N(alkyl)-;
V is -S-; and
W is -CH-.

Such compounds are for example:

4-Nitro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,4-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethylsulfanyl-benzamide;

4-Cyano-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid {4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-amide;

2,5-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,3-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3,5-Difluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide; and

4-Fluoro-3-methyl-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide.

Another embodiment of the invention are the compounds according to formula I, wherein

A is -C(O)NH- or- C(O)N(alkyl)-;
V is -CH-; and
W is -S-, or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^4 is hydrogen;
A is -C(O)NH- or- C(O)N(alkyl)-;
V is -CH-; and
W is -S-, or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine.
R^4 is hydrogen;
A is -C(O)NH- or- C(O)N(alkyl)-;
V is -CH-; and
W is -S- or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^4 is methyl.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-alkyl,
-S-alkyl, or
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;
R^2 is hydrogen;
R^3 is hydrogen or fluorine.
R^4 is methyl;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Another embodiment of the invention are the compounds according to formula I, wherein

R^1 is chlorine,
-O-CF_3, or
-CF_3,;
R^2 is hydrogen;
R^3 is hydrogen.
R^4 is methyl;
A is -NHC(O)- or-N(alkyl)C(O)-;
V is -CH-; and
W is -S- or –O-.

Such compounds are for example:

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-phenyl)-amide;

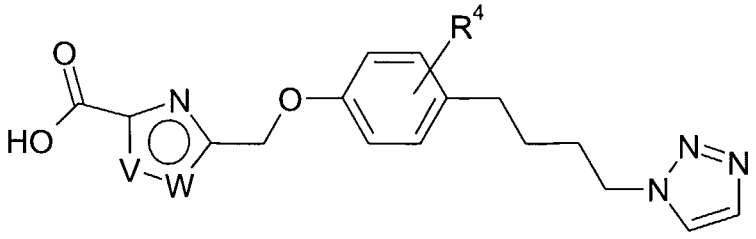
2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide; and

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (3-chloro-phenyl)-amide.

Still another embodiment of the invention is a process for the manufacture of the compounds of formula Ia , wherein

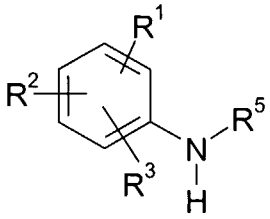
a) the compound of formula V



V,

wherein R^4 , V and W have the significance given above for formula I,

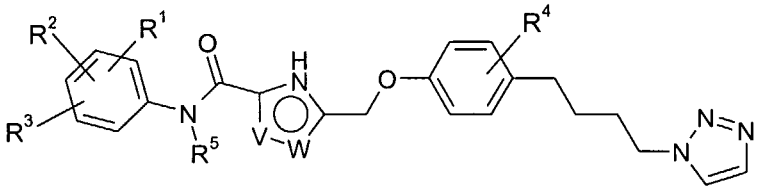
is reacted with a compound of formula VI



VI,

wherein R^1, R^2 and R^3 have the significance given above for formula I and R^5 is hydrogen;

to give the respective compound of formula Ia;



Ia

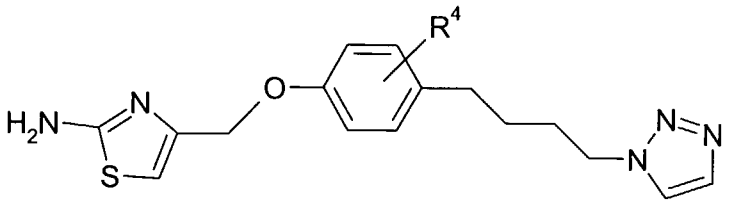
wherein R^1, R^2, R^3 and R^4 have the significance given above for formula I and R^5 is hydrogen or alkyl;

b) said compound of formula Ia is isolated from the reaction mixture, and

c) if desired, converted into a pharmaceutically acceptable salt.

Still another embodiment of the invention is a process for the manufacture of the compounds of formula Ib , wherein

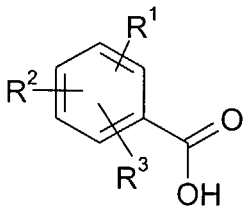
a) the compound of formula IX,



IX,

wherein R^4 has the significance given above for formula I;

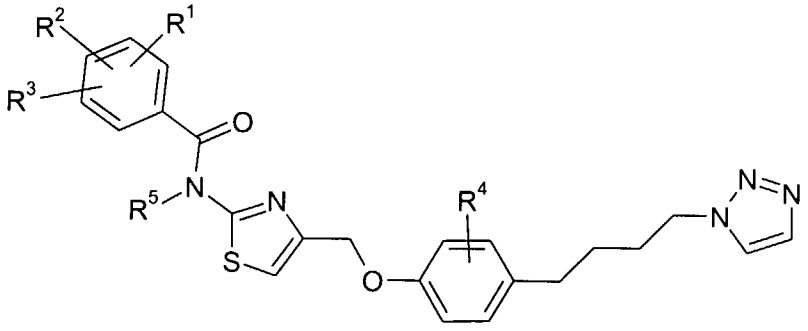
is reacted with a compound of formula X



X,

wherein R^1, R^2, R^3 have the significance given above for formula I,

to give the respective compound of formula Ib;



Ib

wherein R^1, R^2, R^3 and R^4 have the significance given above for formula I and R^5 is hydrogen;

b) if desired, the compound of formula Ib obtained in a) is further reacted with a suitable alkyl halide to give the respective compound of formula Ib; wherein R^5 is alkyl.

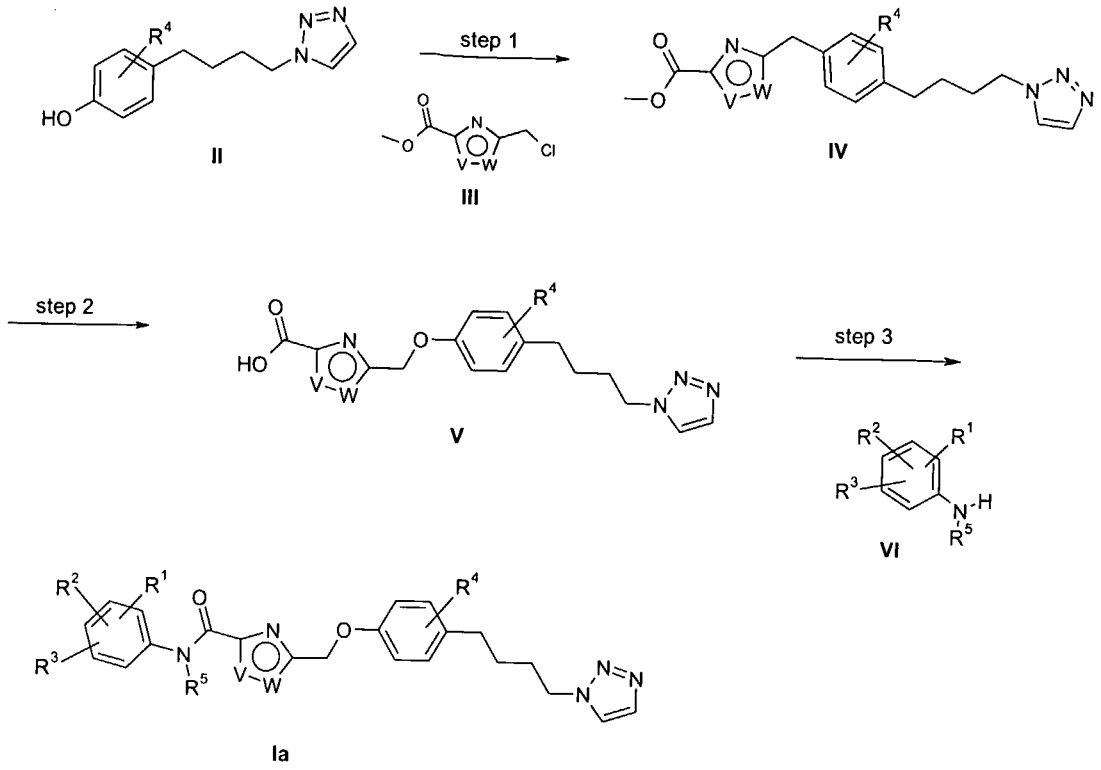
c) said compound of formula Ib is isolated from the reaction mixture, and

d) if desired, converted into a pharmaceutically acceptable salt.

The amide derivatives of the general formula I, or a pharmaceutically acceptable salt thereof, may be prepared by any process known to be applicable for the preparation of chemically-related compounds by the one skilled in the art. Such processes, when used to prepare the amide derivatives of formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples of scheme 1, in which, unless otherwise stated, V, W, A, R^1, R^2, R^3 and R^4 have the significance given herein before. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Scheme 1:

The manufacture of the compounds of formula I varies according to the nature of "A" in formula I. The compounds of the present invention wherein "A" is -$NR^5C(O)$- and R^5 is hydrogen or alkyl can be prepared according to scheme 1, and are named Ia.



Scheme 1

In scheme 1, V, W, R^1, R^2, R^3 and R^4 have the significance given herein before for formula I and R^5 is hydrogen or alkyl.

Step 1

In step 1, scheme 1 the compounds of formula II can be obtained by reactions well known to someone skilled in the art, e.g. by alkylation of 4-(4-[1,2,3]Triazol-1-yl-butyl)-phenol with compounds of formula III. Typical bases for this reaction are sodium methylate, sodium hydride, lithium diisopropyl amide and cesium carbonate. The alkylation can be carried out in the presence of potassium iodide or sodium iodide in solvents like methanol, ethanol, isopropanol and *N,N*-dimethylformamide (DMF). The reaction temperatures may vary from 50°C to 150°C.

Oxazoles or thiazoles of formula III can be synthesized by a commonly known method or a modification thereof. (2-Chlormethyl-oxa/thiazole-4-carboxylic acid

methyl ester: Hermitage, S.A., et al., Organic Process Research & Development 5 (2001) 37-44; 4-Chlormethyl-thiazole-2-carboxylic acid ethyl ester: Lee, C.B., et al., J. Am. Chem. Soc. 123 (2001) 5249-5259.)

Step 2

In step 2 the hydrolysis of the esters of formula IV is achieved by standard methods for someone skilled in the art. Typically used bases are e.g. sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH) in solvents like water, tetrahydrofuran (THF), methanol, ethanol or mixtures thereof at temperature between 0°C and 150°C, yielding the carboxylic acids of formula V.

Step 3

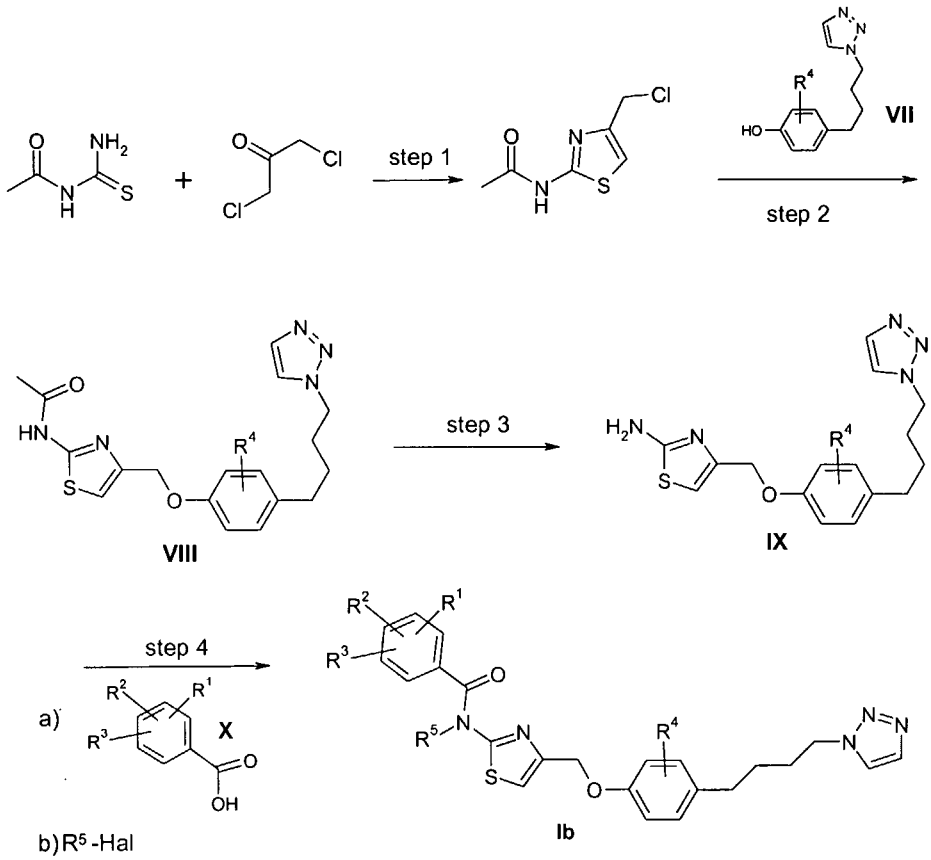
In step 3 the obtained carboxylic acids of formula V are reacted with anilines of formula VI using standard methods (e.g. Han, S.-Y., and Kim, Y.-A., Tetrahedron 60 (2004) 2447-2467) for someone skilled in the art, e.g. by activating the carboxylic acid group in the compounds of formula V with 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI), *N,N'*-carbonyl diimidazole (CDI), hydroxybenzotriazole (HOBt) or thionylchloride in solvents like THF, dichloromethane, DMF or mixtures thereof and at temperatures varying from -30 °C to 50 °C, yielding derivatives of formula Ia.

Alternatively the compounds of formula Ia wherein R^5 is alkyl can be obtained by introducing the R^5-alkyl group after the last reaction step by alkylation of the corresponding amides of formula Ia (R^5 is hydrogen). This reaction is typically achieved with alkyl halides such as for example the alkyl halides of the formula R^5-Hal, wherein "Hal" is a halogen-atom, preferably iodine or bromine and R^5 is alkyl. The reaction is carried out in the presence of a base like NaOH, KOH, triethyl amine or sodium hydride and in solvents like acetone, ethyl acetate, methanol, ethanol, DMF or mixtures thereof at temperatures varying from 0 °C to 150 °C.

Furthermore the sequence of the reaction steps can vary.

Scheme 2:

The manufacture of the compounds of formula I varies according to the nature of "A" in formula I. The compounds of the present invention wherein "A" is -O-, and V is -S- and W is -CH- can be prepared according to scheme 1, and are named Ib.



Scheme 2

In scheme 2, R^1, R^2, R^3 and R^4 have the significance given herein before for formula I and R^5 is hydrogen or alkyl.

Step 1

N-acetylated thiourea and 1,3-dichloroacetone are subjected to a condensation/dehydration sequence yielding the *N*-acetylated 2-amino-4-chloromethylthiazole. Typical solvents for reactions of this kind are toluene,

benzene, acetone and chloroform. If desired the reaction can be carried out under solvent free conditions. The reaction temperatures may vary from 50°C to 150°C.

Step 2

The thiazole derivatives of formula VIII can be obtained by reactions well known to someone skilled in the art, e.g. by alkylation of 4-(4-[1,2,3]triazol-1-yl)phenol of formula VII with *N*-acetylated 2-amino-4-chloromethylthiazole. Typically the alkylation is carried our in the presence of potassium iodide or sodium iodide in solvents like methanol, ethanol, isopropanol, acetone, 2-butanone and DMF. Typical bases for this reaction are sodium methylate, sodium hydride, lithium diisopropylamide and cesium carbonate. The reaction temperatures may vary from 50°C to 150°C. Yields can be improved by use of an excess of the phenol and reisolation of the unreacted reactant.

Step 3

The thiazoles derivatives of formula IX are further obtained by deacetylation either under basic or acidic conditions. Methods of deacetylation are described in the literature and well known to those skilled in the art. Typical bases are NaOH, KOH or LiOH and typical acids are HCl or H_2SO_4. The reactions were carried out in solvents like water, methanol, ethanol or 2-propanol. The reaction temperatures may vary from room temperature to 100°C.

Step 4

The obtained anilines of formula IX are reacted with carboxylic acids of formula X using standard methods for someone skilled in the art, e.g. by activating the carboxylic group in the compounds of formula X with EDCI, CDI, HOBt or thionylchloride in solvents like THF, dichloromethane, DMF or mixtures thereof and at temperatures varying from -30 °C to 50 °C, yielding derivatives of formula Ib wherein R^5 is hydrogen (part reaction a)).

When the synthesis is further proceeded by reaction b) in step 4 the compounds of formula Ib wherein R^5 is alkyl are obtained. The alkylation of amides is typically achieved with alkyl halides such as for example the alkyl halides of the formula

R^5-Hal, wherein "Hal" is a halogen-atom, preferably iodine or bromine and R^5 is alkyl. The reaction is carried out in the presence of a base like NaOH, KOH, triethyl amine or sodium hydride and in solvents like acetone, ethyl acetate, methanol, ethanol, DMF or mixtures thereof at temperatures varying from 0 °C to 150 °C.

The compounds of formula I can contain one or several chiral centers and can then be present in a racemic or in an optically active form. The racemates can be separated according to known methods into the enantiomers. For instance, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid. Alternatively separation of the enantiomers can also be achieved by using chromatography on chiral HPLC-phases which are commercially available.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, methanesulfonic acid, ethanesulfonic acid, salicylic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. The chemical modification of a pharmaceutical compound (i.e. a drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., Stahl, P. H., and Wermuth, G., (editors), Handbook of Pharmaceutical Salts, Verlag Helvetica Chimica Acta (VHCA), Zürich, (2002) or Bastin, R.J., et al., Organic Proc. Res. Dev. 4 (2000) 427-435.

Preferred are the pharmaceutically acceptable salts, which are formed with p-toluenesulfonic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, methanesulfonic acid and hydrochloric acid.

Pharmacological activity

The compounds of formula I and their pharmaceutically acceptable salts possess valuable pharmacological properties. It has been found that said compounds inhibit the HER-signaling pathway and show anti-proliferative activity. Consequently the compounds of the present invention are useful in the therapy and/or prevention of illnesses with known over-expression of receptor tyrosine kinases of the HER-family like HER-2 and EGFR (HER-1), especially in the therapy and / or prevention of illnesses mentioned above. The activity of the present compounds as HER-signaling pathway inhibitors is demonstrated by the following biological assay:

Inhibition of HER-2 phosphorylation in Calu-3 tumor cell line

$2x10^5$ Calu-3 (ATTC HTB-55) cells per well were plated in a 12-well plate. After 4 days cells were starved for 16h in Dulbecco's Modified Eagle Medium (DMEM)/0.5% Fetal Calf Serum (FCS) /1% Glutamine. During this 16h period cells were incubated with a solution of the test compound in dimethylsulfoxide(DMSO), so that the final concentration of the compound is 1 µM and the final volume of DMSO is 0.5%.Afterwards cells were lysed in lyses buffer containing 1% Triton®X-100, 10% Glycerol, 1mM Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA), 1.5mM $MgCl_2$, 150mM NaCl, 50mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer pH 7.5, 1mM Phenylmethylsulfonyl fluoride (PMSF), 10µg/mL Aprotinin and 0.4 mm Orthovanadate. Cell lysates were analyzed on a Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS PAGE) and after transfer to a nitrocellulose membrane detected with an antibody specifically recognizing the pY 1248 in HER-2. Inhibition of HER-2 phosphorylation is calculated as percentage of the control, which is treated with DMSO only.

With all compounds a significant inhibition of HER-2-phosphorylation was detected, which is exemplified by the compounds shown in Table 1. The reference compound as used herein is 1-[4-(4-{2-[2-(4-Trifluoromethyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-phenyl)-butyl]-1H-[1,2,3]triazole (Example 4, p. 88, WO 01/77107).

Table 1:

	Control (DMSO)	Percent inhibition of HER2-phosphorylation (compound concentration 1 µM)
reference compound	0	52
example 11	0	69
example 14	0	72
example 10		75
example 39		87
example 2, 9, 22, 31	0	55-70
example 36, 37, 40, 52-5	0	70-80
example 13, 41, 43, 52-21	0	>80

Antiproliferative activity

The activity of the present compounds as antiproliferative agents is demonstrated by the following biological assay:

CellTiter-Glo™ assay in HEK293 cells

The CellTiter-Glo™ Luminescent Cell Viability Assay (Promega) is a homogeneous method of determining the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells.

HEK293 cells (human embryonic kidney cell line transformed by Adenovirus 5 fragments, ATCC-No. CRL 1573) were cultivated in Dulbecco's Modified Eagle Medium (DMEM) with Glutamax™ (Invitrogen, 31966-021), 5% Fetal Calf Serum (FCS, Sigma Cat-No. F4135 (FBS)), 100Units/ml penicillin / 100µg/ml streptomycin (= Pen/Strep from Invitrogen Cat. No. 15140). , For the assay the cells were seeded in 384 well plates, 5000 cells per well, in the same medium. The next day the test compounds were added in various concentrations ranging from 3 µM to 0.00015 µM (10 concentrations, 1:3 diluted). After 7 days the CellTiter-Glo™ assay was done according to the instructions of the manufacturer (CellTiter-Glo™

Luminescent Cell Viability Assay, from Promega). In brief: the cell-plate was equilibrated to room temperature for approximately 30 minutes and than the CellTiter-Glo™ reagent was added. The contents were carefully mixed for 15 minutes to induce cell lysis. After 45 minutes the luminescent signal was measured in Victor 2, (scanning multiwell spectrophotometer, Wallac).

Details:

1st day:

- Medium: Dulbecco's Modified Eagle Medium (DMEM) with Glutamax™ (Invitrogen, 31966-021), 5 % Fetal Calf Serum (FCS, Sigma Cat-No. F4135 (FBS)), Pen/Strep (Invitrogen Cat. No. 15140).
- HEK293 (ATCC-No. CRL 1573) : 5000 cells in 60 µl per well of 384 well plate (Greiner 781098, white plates)
- Incubate 24 h at 37°C, 5% CO_2

2nd day: Induction (Substance testing):

In general the dilution steeps are 1:3

a) Add 8 µl of 10 mM stock solution of compound to 72 µl DMSO
b) dilute 9x 1:3 (always 30 µl to 60 µl DMSO) in this DMSO dilution row (results in 10 wells with concentrations from 1000 µM to 0.06 µM)
c) dilute each concentration 1: 4.8 (10 µl compound dilution to 38 µl medium)
d) dilute each concentration 1: 10 (10 µl compound dilution to 90 µl medium)
e) add 10 µl of every concentration to 60 µl medium in the cell plate
   - -resulting in final concentration of DMSO : 0.3 % in every well
   - and resulting in final concentration of compounds from 3 µM to 0.00015 µM
   - Incubate 168 h (7 days) at 37°C, 5% CO_2

Analysis:

- Add 30 µl CellTiter-Glo™ Reagent/well,
- shake 15 minutes at room temperature

- incubate further 45 minutes at room temperature without shaking.

Measurement:

- Victor 2 scanning multiwell spectrophotometer (Wallac), Luminescence mode
- Determine IC50 with XL-fit (XLfit software (ID Business Solution Ltd., Guilford, Surrey, UK)).

A significant inhibition of HEK293 cell viability was detected, which is exemplified by the compounds shown in Table 1.

Results: Table 1

Examples	IC50 HEK293 [nM]
4	127
9	116
24	1063
5, 8, 10, 11, 12, 13, 21, 25, 27, 30, 33, 36, 39, 40, 41, 42, 44, 46, 48, 51, 52-1, 52-4, 52-5, 52-6, 52-7, 52-9, 52-11, 52-12, 52-14, 52-15, 52-19,52-21, 52-22, 52-23, 52-25, 52-26	5-500
6, 14, 16, 20, 28, 29, 31, 43, 52-2, 52-16	500-3000

The compounds according to this invention and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical composition. The pharmaceutical compositions can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The above-mentioned pharmaceutical compositions can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. For example, lactose, corn starch or derivatives thereof, talc, stearic acids or it's salts and the like can be used as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine

capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical compositions can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Preferred pharmaceutical compositions comprise the following:

a) Tablet Formulation (Wet Granulation):

Item	Ingredients	mg/tablet			
1.	Compound of formula (I)	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure:

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

b) Capsule Formulation:

Item	Ingredients	mg/capsule			
1.	Compound of formula (I)	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure:

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

c) Micro suspension

1. Weigh 4.0 g glass beads in custom made tube GL 25, 4 cm (the beads fill half of the tube).
2. Add 50 mg compound, disperse with spatulum and vortex.
3. Add 2 ml gelatin solution (weight beads: gelatin solution = 2:1) and vortex.
4. Cap and wrap in aluminium foil for light protection.
5. Prepare a counter balance for the mill.
6. Mill for 4 hours, 20/s in a Retsch mill (for some substances up to 24 hours at 30/s).
7. Extract suspension from beads with two layers of filter (100 µm) on a filter holder, coupled to a recipient vial by centrifugation at 400 g for 2 min.
8. Move extract to measuring cylinder.
9. Repeat washing with small volumes(here 1 ml steps) until final volume is reached or extract is clear.
10. Fill up to final volume with gelatin and homogenise.

The above described preparation yields micro-suspensions of the compounds of formula I-A with particle sizes between 1 and 10 µm. The suspensions are suitable for oral applications and can be used in the in vivo assays.

Medicaments containing a compound of the present invention or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of the present invention and/or pharmaceutically acceptable salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention the compounds of the present invention as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses. Based on their HER-signaling pathway inhibition and their antiproliferative activity, said compounds are useful for the treatment of diseases such as cancer in humans or animals and for the production of corresponding medicaments. The dosage depends on various factors such as manner of administration, species, age and/or individual state of health.

Another embodiment of the invention is pharmaceutical composition, containing one or more compounds of formula I together with pharmaceutically acceptable excipients.

Still another embodiment of the invention is said pharmaceutical composition for the inhibition of tumor growth.

Still another embodiment of the invention is the use of a compound of formula I for the treatment of cancer.

Still another embodiment of the invention is the use of a compound of formula I for the manufacture of corresponding medicaments for the inhibition of tumor growth.

The following examples and references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

Example 1

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid benzo[1,3]dioxol-5-yl-amide

100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid are dissolved in 2 ml dichloromethane/ tetrahydrofuran (1:1) and heated to 45°C. After the addition of 52.1 mg (0.321 mmol) 1,1' Carbonyldiimidazole the mixture is stirred for 45 min. Then 44.1 mg (0.321 mmol) Benzo[1,3]dioxol-5-ylamine are added and the reaction mixture is stirred for 16 h at room temperature. The reaction mixture is extracted twice with 6 ml saturated sodium hydrogen carbonate solution. The organic layer is evaporated and the residue is purified by preparative HPLC-MS to give the title compound.

Yield: 57 mg (38%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.13(s, 1H, NH), 8.79(s, 1H, 5-H oxazole), 8.10(s, 1H, triazole), 7.70(s, 1H, triazole), 7.44(d, 1H, 6-H-benzo[1,3]dioxole), 7.27 (dd, 1H, 4-H-benzo[1,3]dioxole), 7.12 (d, 2H, Ar-H, phenoxy), 6.96 (d, 2H, Ar-H, phenoxy), 6.88 (d, 1H, 3-benzo[1,3]dioxole, 5.998 (s, 2H, CH_2-oxol), 5.26 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 462.3(API+)

Example 2

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-methyl-amide

99.1 mg (0.290 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid are stirred in 10 ml dichloromethane to give a suspension. After the addition of 83.3 mg (0.434 mmol) (3-Dimethylamino-propyl)-ethyl-carbodiimide hydrochloride, 66.5 mg (0.434 mmol) 1-Hydroxy-benzotriazole hydrate and 60.5 µl (0.434 mmol) triethylamine the mixture is stirred for 30 min at room temperature. Then 35.1 µl (0.290 mmol) (4-Chloro-phenyl)-methyl-amine are given to the reaction mixture and stirred for 16 h at room temperature. After addition of 10 ml 1N HCl the organic phase is separated and extracted twice with

water. The organic layer is evaporated and the residue is purified by preparative HPLC-MS to give the title compound.

Yield: 55 mg (41%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 8.10 (s, 1H, triazole), 8.07 (s, 1H, 5-H oxazole), 7.70(s, 1H, triazole), 7.42-7.38 (m, 2H, Ar-H, 4-Cl-phenyl), 7.30-7.27 (m, 2H, Ar-H, 4-Cl-phenyl), 7.07 (d, 2H, Ar-H, phenoxy), 6.81 (d, 2H, Ar-H, phenoxy), 5.06 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 3.34 (s, 3H, N-CH_3), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 466.1(API+)

Example 3

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-chloro-phenyl)-amide

100 mg (0.292 mmol) 4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid are activated with 42 µl (0.584 mmol) thionyl chloride. The mixture is heated to 45°C and stirred for 1 hour. After evaporation to dryness the residue is dissolved in 6 ml dichloromethane/ tetrahydrofuran (1:1). 37 mg (0.292 mmol) 4-Chloro-phenyl amine are added and the resulting reaction mixture is stirred for 16 h at room temperature. The precipitate is collected and washed twice with ethyl ether to give the title compound.

Yield 90 mg (66%).

^{1}H-NMR (400 MHz, MeOD): δ= 8.42(s, 1H, thiazole), 8.29(s, 1H, triazole), 7.89(s, 1H, triazole), 7.80-7.78 (m, 2H, Ar-H, 4-Cl-phenyl), 7.41-7. 38 (m, 2H, Ar-H, 4-Cl-phenyl), 7.14 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.26 (s, 2H, CH_2-O-Ph), 4.61 (t, 2H, 1H-butyl), 2.65 (t, 2H, 4H-butyl), 2.01 (m, 2H, 2H-butyl), 1.65 (m, 2H, 3H-butyl).

MS: M = 468.0 (API+)

Example 4

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-nitro-4-trifluoromethyl-phenyl)-amide

The title compound is prepared from 30 mg (0.146 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 52.3 mg (0.153 mmol) 2-Nitro-4-trifluoromethyl-phenylamine as described in Example 1. Yield 24 mg (31%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 11.45 (s, 1H), 9.025(d, 1H), 8.64-8.59(m, 1H), 8.45(s, 1H,), 8.19(m, 1H), 8.10(s, 1H), 7.70(s, 1H), 7.13 (d, 2H,), 6.99 (d, 2H), 5.32 (s, 2H), 4.39 (t, 2H), 2.54 (t, 2H), 1.81 (m, 2H,), 1.48 (m, 2H).

MS: M = 531.3 (API+)

Example 5

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,5-difluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 29 mg (0.225 mmol) 3,5-Difluoro-phenylamine as described in Example 1. Yield 17 mg (18%).

^{1}H-NMR (400 MHz, MeOD): δ= 8.58(s, 1H, oxazole), 7.96(s, 1H, triazole), 7.72(s, 1H, triazole), 7.47 (m, 2H, 2,6-H-3,5-F-Ph), 7.13 (d, 2H, Ar-H, phenoxy), 6.96 (d, 2H, Ar-H, phenoxy), 6.73 (m, 1H, 4-H-3,5-F-Ph), 5.24 (s, 2H, CH_2-O-Ph), 4.46 (t, 2H, 1H-butyl), 2.62 (t, 2H, 4H-butyl), 1.93 (m, 2H, 2H-butyl), 1.59 (m, 2H, 3H-butyl).

MS: M = 454.3 (API+)

Example 6

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 41 mg (0.321 mmol) 4-Chloro-phenylamine as described in Example 1. Yield 57 mg (39%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.39 (s, 1H, NH), 8.84 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.86 (d, 2H, Ar-H, 4-Cl-phenyl), 7.70 (s, 1H, triazole), 7.40 (d, 2H, Ar-H, 4-Cl-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 452.3 (API+)

Example 7

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-difluoro-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 41 mg (0.321 mmol) 2,4-Difluoro-phenylamine as described in Example 1. Yield 34 mg (23%).

MS: M = 454.2 (API+)

Example 8

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethylsulfanyl-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 56 mg (0.321 mmol) 4-Difluoromethylsulfanyl-phenylamine as described in Example 1. Yield 45 mg (28%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.47 (s, 1H, NH), 8.86 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.92 (m, 2H, Ar-H, 4-F_2HC-thiophenyl), 7.70 (s, 1H, triazole), 7.56 (m, 2H, Ar-H, 4-F_2HC-thiophenyl), 7.55-7.28 (m, 1H, F_2HC), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 500.3 (API+)

Example 9

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 55 mg (0.321 mmol) 5-Amino-2,2-difluoro-1,3-benzodioxole as described in Example 1. Yield 64 mg (40%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.49 (s, 1H, NH), 8.85 (s, 1H, oxazole), 8.11 (s, 1H, triazole), 7.92-7.92 (m, 1H, Ar-H, benzo[1,3]dioxole), 7.71 (s, 1H, triazole), 7.40-7.37 (m, 1H, Ar-H, benzo[1,3]dioxole), 7.33-7.30 (m, 1H, Ar-H, benzo[1,3]dioxole), 7.55-7.28 (m, 1H, F_2HC), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 498.3 (API+)

Example 10

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methoxy-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 57 mg (0.321 mmol) 4-Trifluoromethoxy-phenylamine as described in Example 1. Yield 60 mg (37%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.46 (s, 1H, NH), 8.85 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.93 (d, 2H, Ar-H, 4-F_3C-O-phenyl), 7.70 (s, 1H, triazole), 7.36

(dm, 2H, Ar-H, 4-F_3C-O-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 502.3 (API+)

Example 11

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methylsulfanyl-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 62 mg (0.321 mmol) 4-Trifluoromethylsulfanyl-phenylamine as described in Example 1. Yield 8 mg (5%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.57 (s, 1H, NH), 8.88 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.99 (m, 2H, Ar-H, 4-F_3C-S-phenyl), 7.71-7.69 (m, 2H, Ar-H, 4-F_3C-S-phenyl), 7.70 (s, 1H, triazole), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 518.2 (API+)

Example 12

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-4-fluoro-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 62 mg (0.321 mmol) 3-Chloro-4-fluoro-phenylamine as described in Example 1. Yield 15 mg (10%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.50 (s, 1H, NH), 8.85 (s, 1H, oxazole), 8.12 (m, 1H, 2-H-3-Cl-4-F-phenyl), 8.11 (s, 1H, triazole), 7.80 (m, 1H, 6-H-3-Cl-4-F-phenyl), 7.70 (s, 1H, triazole), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 470.2 (API+)

Example 13

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 52 mg (0.321 mmol) 4-trifluoromethyl-phenylamine as described in Example 1. Yield 102 mg (65%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.61 (s, 1H, NH), 8.88 (s, 1H, oxazole), 8.11 (s, 1H, triazole), 8.05 (m, 2H, Ar-H, 4-CF_3-phenyl), 7.71 (m, 2H, Ar-H, 4-CF_3-phenyl), 7.70 (s, 1H, triazole), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 486.0 (API+)

Example 14

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 47 mg (0.321 mmol) 3-Chloro-4-fluoro-phenylamine as described in Example 1. Yield 15 mg (10%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 9.95 (s, 1H, NH), 8.87 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.76-7.72 (m, 1H, 6-H-4-Cl-2-F-phenyl), 7.70 (s, 1H, triazole), 7.56-7.53 (m, 1H, 3-H-4-Cl-2-F-phenyl), 7.33-7.31 (m, 1H, 5-H-4-Cl-2-F-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 470.3 (API+)

Example 15

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-(thiazol-2-ylsulfamoyl)-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 52 mg (0.204 mmol) 4-Amino-N-thiazol-2-yl-benzenesulfonamide as described in Example 1. Yield 7 mg (6%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.54 (s, 1H, NH), 8.87 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.97-7.94 (m, 2H, Ar-H, SO_2-phenyl), 7.77-7.75 (m, 2H, Ar-H, SO_2-phenyl), 7.70 (s, 1H, triazole), 7.24 (d, 1H, thiazole), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 6.81 (d, 1H, thiazole), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 580.4 (API+)

Example 16

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-phenyl]-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 55 mg (0.204 mmol) 4-Amino-N-(5-methyl-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide as described in Example 1. Yield 10 mg (8%).

MS: M = 595.3 (API+)

Example 17

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-isoxazol-3-ylsulfamoyl)-phenyl]-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 52 mg (0.204 mmol) 4-

Amino-N-(5-methyl-isoxazol-3-yl)-benzenesulfonamide as described in Example 1. Yield 11 mg (9%).

MS: M = 578.4 (API+)

Example 18

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 44 mg (0.204 mmol) N-Acetyl-4-amino-benzenesulfonamide as described in Example 1. Yield 9 mg (8%).

MS: M = 539.2 (API+)

Example 19

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-bromo-2-fluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 39 mg (0.204 mmol) 4-Bromo-2-fluoro-phenylamine as described in Example 1. Yield 65 mg (62%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 9.93 (s, 1H, NH), 8.87 (s, 1H, oxazole), 8.11 (s, 1H, triazole), 7.71-7.69 (m, 1H, 6-H-2-F-4-Br-phenyl), 7.70 (s, 1H, triazole), 7.67-7.64 (m, 1H, 3-H-2-F-4-Br-phenyl), 7.24 (d, 1H, thiazole), 7.457-7.43 (m, 1H, 5-H-2-F-4-Br-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 516.2 (API+)

Example 20

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-2-methyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 26 mg (0.204 mmol) 3-fluoro-2-methyl-phenylamine as described in Example 1. Yield 35 mg (38%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 9.92 (s, 1H, NH), 8.82 (s, 1H, oxazole), 8.11 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.30 (d, 1H, 6-H-3-F-2-Br-methyl), 7.24 (dd, 1H, 5-H-3-F-2-Br-methyl), 7.12 (d, 2H, Ar-H, phenoxy), 7.09-7.05 (m, 1H, 4-H-3-F-2-Br-methyl), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 450.3 (API+)

Example 21

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 32 mg (0.204 mmol) 4-fluoro-3-nitro-phenylamine as described in Example 1. Yield 24 mg (24%).

MS: M = 481.3 (API+)

Example 22

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethoxy-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 32 mg (0.204 mmol) 4-difluoromethoxy-phenylamine as described in Example 1. Yield 41 mg (41%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.34 (s, 1H, NH), 8.83 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.85-7.83 (m, 2H, Ar-H, 4-F_2HCO-phenyl), 7.70 (s, 1H, triazole),

7.17-7.15 (m, 2H, Ar-H, 4-F_2HCO-phenyl), 7.17 (t, 1H, H-CF_2), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 450.3 (API+)

Example 23

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-trifluoromethyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 33 mg (0.204 mmol) 3-trifluoromethyl-phenylamine as described in Example 1. Yield 21 mg (21%).

MS: M = 486.2 (API+)

Example 24

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methylsulfanyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 28 mg (0.204 mmol) 4-methylsulfanyl-phenylamine as described in Example 1. Yield 22 mg (23%).

MS: M = 464.2 (API+)

Example 25

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-2-methyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 26 mg (0.204 mmol) 4-fluoro-2-methyl-phenylamine as described in Example 1. Yield 10 mg (11%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 9.77 (s, 1H, NH), 8.80 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.42-7.38 (m, 1H, 6H-4-F-2-methyl-phenyl),

7.15-7.11 (m, 1H, 3H-4-F-2-methyl-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 7.06-7.01 (m, 1H, 5H-4-F-2-methyl-phenyl), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 450.3 (API+)

Example 26

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 31 mg (0.204 mmol) 4-tert-butyl-phenylamine as described in Example 1. Yield 16 mg (17%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.12 (s, 1H, NH), 8.80 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.71-7.68 (m, 2H, Ar-H, tBu-phenyl), 7.70 (s, 1H, triazole), 7.36-7.34 (m, 2H, Ar-H, tBu-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl), 1.27 (s, 9H, tBu).

MS: M = 474.4 (API+)

Example 27

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-amide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 40 mg (0.204 mmol) 4-chloro-3-trifluoromethyl-phenylamine as described in Example 1. Yield 16 mg (15%).

MS: M = 520.2 (API+)

Example 28

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid p-tolylamide

The title compound is prepared from 70 mg (0.204 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 22 mg (0.204 mmol) p-Tolylamine as described in Example 1. Yield 13 mg (15%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.10 (s, 1H, NH), 8.80 (s, 1H, oxazole), 8.10 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.67 (d, 2H, Ar-H, 4-methyl-phenyl), 7.14 (d, 2H, Ar-H, 4-methyl-phenyl), 7.12 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 2.27 (s, 3H, methyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 432.3 (API+)

Example 29

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-phenyl-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 31.6 µl (0.292 mmol) Methyl-phenyl-amine as described in Example 2. Yield 87 mg (69%).

MS: M = 432.3 (API+)

Example 30

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-(4-trifluoromethoxy-phenyl)-amide

The title compound is prepared from 100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 56 mg (0.292 mmol) Methyl-(4-trifluoromethoxy-phenyl)-amine as described in Example 2. Yield 42 mg (28%).

MS: M = 516.3 (API+)

Example 31

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 23 mg (0.205 mmol) 4-Fluoro-phenylamine as described in Example 1. Yield 25 mg (28%).

MS: M = 436.2 (API+)

Example 32

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-methyl-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 26 mg (0.205 mmol) 4-Fluoro-3-methyl-phenylamine as described in Example 1. Yield 2.3 mg (2.5%).

MS: M = 450.2 (API+)

Example 33

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-fluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 23 mg (0.205 mmol) 2-Fluoro-phenylamine as described in Example 1. Yield 5 mg (6%).

MS: M = 458.4 (API+ Na)

Example 34

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-nitro-2-trifluoromethyl-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 42 mg (0.205 mmol) 4-

Nitro-2-trifluoromethyl-phenylamine as described in Example 1. Yield 2 mg (1.8%).

MS: M = 531.1 (API+)

Example 35

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 23 mg (0.205 mmol) 3-fluoro-phenylamine as described in Example 1. Yield 11 mg (12%).

^{1}H-NMR (400 MHz, MeOD): δ= 8.44(s, 1H, oxazole), 7.84(s, 1H, triazole), 7.60(s, 1H, triazole), 7.59-7.55 (m, 1H, 2-H-3-F-Ph), 7.28-7.22 (m, 1H, 5-H-3-F-Ph), 7.20-7.14 (m, 1H, 6-H-3-F-Ph), 7.17 (d, 2H, Ar-H, phenoxy), 6.85 (d, 2H, Ar-H, phenoxy), 6.81-6.76 (m, 1H, 4-H-3-F-Ph), 5.13 (s, 2H, CH_2-O-Ph), 4.34 (t, 2H, 1H-butyl), 2.50 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 436.2 (API+)

Example 36

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 26 mg (0.205 mmol) 3-fluoro-4-methyl-phenylamine as described in Example 1. Yield 1.3 mg (1.4%).

MS: M = 450.3 (API+)

Example 37

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methoxy-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 25 mg (0.205 mmol) 3-fluoro-4-methyl-phenylamine as described in Example 1. Yield 37 mg (40%).

^{1}H-NMR (400 MHz, MeOD): δ= 8.39(s, 1H, oxazole), 7.83(s, 1H, triazole), 7.60(s, 1H, triazole), 7.50-7.46 (m, 2H, Ar-H, 4-MeO-Ph), 7.01 (d, 2H, Ar-H, phenoxy), 6.856 (d, 2H, Ar-H, phenoxy), 6.84-6.81 (m, 2H, Ar-H, 4-MeO-Ph), 5.12 (s, 2H, CH_2-O-Ph), 4.34 (t, 2H, 1H-butyl), 2.50 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 448.3 (API+)

Example 38

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,4-difluoro-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 26 mg (0.205 mmol) 3,4-Difluoro-phenylamine as described in Example 1. Yield 15 mg (16%).

^{1}H-NMR (400 MHz, MeOD): δ= 8.55(s, 1H, oxazole), 7.96(s, 1H, triazole), 7.88-7.82 (m, 1H, 2-H-3,4-F-phenyl), 7.72(s, 1H, triazole), 7.47-7.44 (m, 1H, 6-H-3,4-F-phenyl), 7.30-7.23 (m, 1H, 5-H-3,4-F-phenyl), 7.13 (d, 2H, Ar-H, phenoxy), 6.97 (d, 2H, Ar-H, phenoxy), 5.24 (s, 2H, CH_2-O-Ph), 4.46 (t, 2H, 1H-butyl), 2.61 (t, 2H, 4H-butyl), 1.93 (m, 2H, 2H-butyl), 1.60 (m, 2H, 3H-butyl).

MS: M = 454.0 (API+)

Example 39

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-trifluoromethoxy-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid and 36 mg (0.205 mmol) 4-Trifluoromethoxy-phenylamine as described in Example 1. Yield 12 mg (11%).

^{1}H-NMR (400 MHz, MeOD): δ= 7.84(s, 1H, thiazole), 7.78(s, 1H, triazole), 7.79-7.76 (m, 2H, 2,6-H-4-CF_3O-phenyl), 7.60(s, 1H, triazole), 7.21-7.18 (m, 2H, 2,6-H-4-CF_3O-phenyl), 7.01 (d, 2H, Ar-H, phenoxy), 6.85 (d, 2H, Ar-H, phenoxy), 5.15 (s, 2H, CH_2-O-Ph), 4.34 (t, 2H, 1H-butyl), 2.50 (t, 2H, 4H-butyl), 1.82 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 518.1 (API+)

Example 40

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-pentafluorosulfanyl-phenyl)-amide

The title compound is prepared from 70 mg (0.205 mmol) 4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid and 45 mg (0.205 mmol) 4-pentafluorosulfanyl-phenylamine as described in Example 1. Yield 2 mg (2%).

MS: M = 560.2 (API+)

Example 41

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide

The title compound is prepared from 100 mg (0.279 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid and 45 mg (0.279 mmol) 4-Trifluoromethyl-phenylamine as described in Example 3. After stirring 16 h at room temperature, 10 ml 1N HCl are added to the reaction mixture. The organic layer is extracted twice with dichloromethane. The extract is evaporated to give 76 mg (54%) of product.

^{1}H-NMR (400 MHz, MeOD): δ= 8.40(s, 1H, thiazole), 7.99(d, 2H, Ar-H, F_3C-phenyl), 7.76(s, 1H, triazole), 7.72(s, 1H, triazole), 7.69 (d, 2H, Ar-H, F_3C-phenyl), 7.15 (d, 2H, Ar-H, phenoxy), 6.99 (d, 2H, Ar-H, phenoxy), 5.46 (s, 2H, CH_2-O-Ph), 4.46 (t, 2H, 1H-butyl), 2.63 (t, 2H, 4H-butyl), 1.93 (m, 2H, 2H-butyl), 1.61 (m, 2H, 3H-butyl).

MS: M = 502.1 (API+)

Example 42

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide

The title compound is prepared from 100 mg (0.279 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid and 36 mg (0.279 mmol) 4-Chloro-phenylamine as described in Example 3. After stirring 16 h at room temperature, 10 ml 1N HCl are added to the reaction mixture. The organic layer is extracted twice with dichloromethane. The extract is evaporated to give 85 mg (65%) of product.

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.47 (s, 1H, NH), 8.49(s, 1H, thiazole), 8.11(s, 1H, triazole), 7.89(m, 2H, Ar-H, 4-Cl-phenyl), 7.71(s, 1H, triazole), 7.41 (m, 2H, Ar-H, 4-Cl-phenyl), 7.14 (d, 2H, Ar-H, phenoxy), 7.00 (d, 2H, Ar-H, phenoxy), 5.48 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.55 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.49 (m, 2H, 3H-butyl).

MS: M = 468.1 (API+)

Example 43

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethoxy-phenyl)-amide

The title compound is prepared from 100 mg (0.279 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid and 49 mg (0.279 mmol) 4-Trifluoro-methoxy-phenylamine as described in Example 3. After stirring 16 h at room temperature, 10 ml 1N HCl are added to the reaction mixture. The organic

layer is extracted twice with dichloromethane. The extract is evaporated to give 98 mg (68%) of product.

^{1}H-NMR (400 MHz, MeOD): δ= 8.40(s, 1H, thiazole), 7.99(d, 2H, Ar-H, F_3CO-phenyl), 7.96(s, 1H, triazole), 7.72(s, 1H, triazole), 7.69 (d, 2H, Ar-H, F_3CO-phenyl), 7.15 (d, 2H, Ar-H, phenoxy), 6.99 (d, 2H, Ar-H, phenoxy), 5.46 (s, 2H, CH_2-O-Ph), 4.46 (t, 2H, 1H-butyl), 2.63 (t, 2H, 4H-butyl), 1.93 (m, 2H, 2H-butyl), 1.61 (m, 2H, 3H-butyl).

MS: M = 518.1 (API+)

Example 44

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,6-dichloro-phenyl)-amide

100 mg (0.292 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 106 µl (1.460 mmol) thionyl chloride are stirred at 45°C until development of gas stops. The reaction mixture is evaporated to dryness. The residue is dissolved in 6 ml dichloromethane. After the addition of 47 mg (0.292 mmol) 2,6-Dichloro-phenylamine the reaction mixture is stirred for 16 h at room temperature. 10 ml 1N HCl are added and the organic layer is extracted three times with dichloromethane. The collected extracts are evaporated to give 142 mg (99.9%) of product

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.26 (s, 1H, NH), 8.83(s, 1H, oxazole), 8.11(s, 1H, triazole), 7.70(s, 1H, triazole), 7.57 (d, 2H, 3,5-H-2,6-Cl-phenyl), 7.39 (m, 1H, 4-H-2,6-Cl-phenyl) 7.13 (d, 2H, Ar-H, phenoxy), 6.98 (d, 2H, Ar-H, phenoxy), 5.28 (s, 2H, CH_2-O-Ph), 4.39 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 1.81 (m, 2H, 2H-butyl), 1.48 (m, 2H, 3H-butyl).

MS: M = 485.9 (API+)

Example 45

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-dichloro-phenyl)-amide

The title compound is prepared from 100 mg (0.29 mmol) 2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 52 mg (0.32 mmol) 2,4-dichloro-phenylamine as described in example 1. Purification of the product is achieved by preparative HPLC. Yield: 3 mg (2%).

MS: M = 486.3 (API+)

Example 46

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide

170 mg (0.48 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid are dissolved in 0.2 ml dichloromethane and activated with 0.4 ml (5.51 mmol) thionyl chloride. The mixture is heated to 45°C and stirred for 1 hour. After evaporation to dryness the residue is dissolved in 2 ml dichloromethane. 77.0 mg (0.48 mmol) 4-trifluoromethyl-phenyl)-amine and 0.33ml (2.39 mmol) triethylamine are added. The resulting mixture is stirred for 2 h at room temperature. After the addition of 1N hydrochloric acid the mixture is extracted twice with dichloromethane. The organic layer is evaporated and the residue is purified by silica column flash chromatography with ethyl acetate/heptane (1:1) to give the title compound. Yield: 69 mg (29%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.59 (s, 1H, NH), 8.88 (s, 1H, 5-H oxazole), 8.11 (s, 1H, triazole), 8.05 (m, 2H, Ar-H, Ph-CF_3), 7.72 (m, 2H, Ar-H, Ph-CF_3), 7.70(s, 1H, triazole), 7.03 (m, 1H, Ar-H, phenoxy-methyl), 6.85 (m, 1H, Ar-H, phenoxy-methyl), 6.80 (m, 1H, Ar-H, phenoxy3-methyl), 5.26 (s, 2H, CH_2-O-Ph), 4.40 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 2.21 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.42 (m, 2H, 3H-butyl).

MS: M = 500.4 (API+)

Example 47

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide

The title compound is prepared from 168 mg (0.47 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 60.0 mg (0.47 mmol) 4-chloro-phenylamine as described in example 46. Purification of the product is achieved by preparative HPLC. Yield: 80 mg (37%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.37 (s, 1H, NH), 8.83 (s, 1H, 5-H oxazole), 8.11 (s, 1H, triazole), 7.85 (m, 2H, Ar-H, Ph-Cl), 7.72 (s, 1H, triazole), 7.40 (m, 2H, Ar-H, Ph-Cl), 7.03 (m, 1H, Ar-H, phenoxy-methyl), 6.84 (m, 1H, Ar-H, phenoxy-methyl), 6.80 (m, 1H, Ar-H, phenoxy-methyl), 5.25 (s, 2H, CH_2-O-Ph), 4.40 (t, 2H, 1H-butyl), 2.53 (t, 2H, 4H-butyl), 2.21 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.42 (m, 2H, 3H-butyl).

MS: M = 466.3(API+)

Example 48

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-phenyl)-amide

The title compound is prepared from 196 mg (0.55 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 70.0 mg (0.55 mmol) 3-chloro-phenylamine as described in example 46. Yield: 137 mg (54%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.42 (s, 1H, NH), 8.84 (s, 1H, 5-H oxazole), 8.11 (s, 1H, triazole), 7.99 (m, 1H, Ar-H, 3-Cl-Ph), 7.76 (m, 1H, Ar-H, 3-Cl-Ph), 7.70 (s, 1H, triazole), 7.37 (m, 1H, Ar-H, 3-Cl-Ph), 7.17 (m, 1H, Ar-H, 3-Cl-Ph), 7.03 (m, 1H, Ar-H, phenoxy-methyl), 6.85 (m, 1H, Ar-H, phenoxy-methyl), 6.80 (m, 1H, Ar-H, phenoxy-methyl), 5.25 (s, 2H, CH_2-O-Ph), 4.40 (t, 2H, 1H-butyl), 2.53 (t, 2H, 4H-butyl), 2.21 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.42 (m, 2H, 3H-butyl).

MS: M = 466.3 (API+)

Example 49

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide

The title compound is prepared from 178 mg (0.48 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid and 60.0 mg (0.55 mmol) 4-trifluoromethyl-phenylamine as described in example 46. Purification of the product is achieved by preparative HPLC. Yield: 145 mg (59%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.67 (s, 1H, NH), 8.53 (s, 1H, 5-H thiazole), 8.11 (s, 1H, triazole), 8.09 (m, 2H, Ar-H, Ph-CF_3), 7.73 (m, 2H, Ar-H, Ph-CF_3), 7.71 (s, 1H, triazole), 7.05 (m, 1H, Ar-H, phenoxy-methyl), 6.89 (m, 1H, Ar-H, phenoxy-methyl), 6.83 (m, 1H, Ar-H, phenoxy-methyl), 5.47 (s, 2H, CH_2-O-Ph), 4.41 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 2.22 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.43 (m, 2H, 3H-butyl).

MS: M = 516.3 (API+)

Example 50

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide

The title compound is prepared from 204 mg (0.55 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid and 70.0 mg (0.55 mmol) 4-chloro-phenylamine as described in example 46. Purification of the product is achieved by preparative HPLC. Yield: 55 mg (21%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ = 10.44 (s, 1H, NH), 8.47 (s, 1H, 5-H thiazole), 8.11 (s, 1H, triazole), 7.88 (m, 2H, Ar-H, Ph-Cl), 7.70 (s, 1H, triazole), 7.41 (m, 2H, Ar-H, Ph-Cl), 7.04 (m, 1H, Ar-H, phenoxy-methyl), 6.88 (m, 1H, Ar-H, phenoxy-methyl), 6.83 (m, 1H, Ar-H, phenoxy-methyl), 5.46 (s, 2H, CH_2-O-Ph), 4.41 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 2.22 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.43 (m, 2H, 3H-butyl).

MS: M = 482.1 (API+)

Example 51

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (3-chloro-phenyl)-amide

The title compound is prepared from 204 mg (0.55 mmol) 2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid and 70.0 mg (0.55 mmol) 3-chloro-phenylamine as described in example 46. Purification of the product is achieved by preparative HPLC. Yield: 77 mg (29%).

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 10.49 (s, 1H, NH), 8.49 (s, 1H, 5-H thiazole), 8.11 (s, 1H, triazole), 8.04 (m, 1H, Ar-H, Ph-Cl), 7.79 (m, 1H, Ar-H, Ph-Cl), 7.70 (s, 1H, triazole), 7.38 (m, 1H, Ar-H, Ph-Cl), 7.17 (m, 1H, Ar-H, Ph-Cl), 7.04 (m, 1H, Ar-H, phenoxy-methyl), 6.88 (m, 1H, Ar-H, phenoxy-methyl), 6.83 (m, 1H, Ar-H, phenoxy-methyl), 5.46 (s, 2H, CH_2-O-Ph), 4.41 (t, 2H, 1H-butyl), 2.54 (t, 2H, 4H-butyl), 2.21 (s, 3H, Ph-CH_3), 1.86 (m, 2H, 2H-butyl), 1.43 (m, 2H, 3H-butyl).

MS: M = 482.2 (API+)

Example 52-1

4-Nitro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide

Preparation of N-(4-Chloromethyl-thiazol-2-yl)-acetamide

A solution of 50 g (0.42 mol) acetyl thiourea and 108.5 g 1,3-dichloro-propan-2-one (0.84 mol) in 500 ml acetone is heated to reflux for 5 hours. All volatiles were removed in vacuo and the residue was taken up in 200 ml acetone. After addition of 600 ml of water the precipitate was collected, washed with 250 ml n-heptane and dried in vacuo at 40°C. Yield: 56.9 g (71%) white solid.

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 2.13 (s, 3H); 4.71 (s, 2H); 7.22 (s, 1H); 12.21 (s, 1H)

Preparation of N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-acetamide

To a solution of 8.55 g (39 mmol) 4-(4-[1,2,3]Triazol-1-yl-butyl)-phenol in 150 ml 2-butanone 12.81 g (39 mmol) cesium carbonate were added and the mixture was stirred at 80°C for 30 minutes. Then 3.75 g (20 mmol) N-(4-Chloromethyl-thiazol-2-yl)-acetamide and 5.90 g (39 mmol) sodium iodide were added and the mixture was stirred at 60°C overnight. After concentration in vacuo 50 ml of a saturated aqueous solution of sodium chloride was added and the mixture was extracted with a mixture of CH_2Cl_2 and methanol (5:1, 60 ml each time). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. Purification by preparative scale HPLC (RP 18, methanol-water-gradient) returned 2.08 g (47 %) of the title compound and 5.97 g unreacted 4-(4-[1,2,3]-triazol-1-yl-butyl)-phenol.

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 1.47 (quintet, 2H); 1.81 (quintet 2H); 2.13 (s, 3H); 2.52 (t, 2H); 4.39 (t, 2H); 5.00 (s, 2H); 6.91 (d, 2H); 7.07 (d, 2H); 7.16 (s, 1H); 7.70 (s, 1H); 8.10 (s, 1H); 12.15 (s, 1H)

Preparation of 4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-ylamine

To a solution of 2.05 g (5.5 mmol) N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-acetamide in 60 ml methanol a solution of 396 mg (16.6 mmol) lithium hydroxide in 60 ml water was added and the mixture was stirred at 60°C overnight. After evaporation to dryness 20 ml of a saturated aqueous solution of sodium chloride was added and the pH was adjusted to 3 with 1 N HCl. The mixture was washed twice with ethyl acetate (discarded) and then the pH was adjusted to 9 with aqueous NaOH (30%). Subsequent extraction with a mixture of CH_2Cl_2 and methanol (5:1, three times 50), drying of the combined organic layers over Na_2SO_4 and evaporation to dryness yielded 1.55 g (85%) of the title compound.

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 1.47 (quintet, 2H); 1.80 (quintet 2H); 2.52 (t, 2H); 4.39 (t, 2H); 4.79 (s, 2H); 6.53 (s, 1H); 6.88 (d, 2H); 6.97 (s, 2H); 7.06 (d, 2H); 7.70 (s, 1H); 8.13 (s, 1H)

Preparation of 4-Nitro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide

4-Nitrobenzoyl chloride (84mg, 0.45mmol) was added to a solution of 4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-ylamine (50mg, 0.15mmol) in DCM (2ml). Polymer supported methylpiperidine (150mg, 0.45mmol) was then added to the reaction mixture and the reaction mixture was shaken for 48 hours at room temperature. AMPS (aminomethylpolystyrene) (200mg, 0.45mmol) was then added and the reaction mixture was shaken for a further 16 hours. The reaction mixture was filtered and the resin was washed with methanol (5ml). The organics were combined and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC under neutral conditions to give 4-Nitro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide, 31.1mg (46% yield).

MS(ESI+)

^{1}H-NMR (400 MHz, D_6-DMSO): δ= 1.48 (quintet, 2H); 1.81 (quintet 2H); 2.53 (t, 2H); 4.39 (t, 2H); 5.07 (s, 2H); 6.93 (s, 1H); 7.09 (d, 2H); 7.35 (s, 1H); 7.70 (s, 1H); 8.11 (s, 1H); 8.31 (d, 2H); 8.37 (d, 2H); 13.10 (s, 1H)

The following examples are prepared in an analogous manner to Example 52-1 starting from the appropriate materials:

Example No.	Systematic name	MS (Method)
52-2	N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-3-trifluoromethyl-benzamide	502,3 (ESI+)
52-3	2,4-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	470.2 (ESI+)
52-4	N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethoxy-benzamide	518.3 (ESI+)
52-5	4-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	468.2 (ESI+)

Example No.	Systematic name	MS (Method)
52-6	4-Chloro-3-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	486.1 (ESI+)
52-7	N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethylsulfanyl-benzamide	534.3 (ESI+)
52-8	4-Cyano-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	459.0 (ESI+)
52-9	3,4-Dichloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	502.2 (ESI+)
52-10	2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide	520.2 (ESI+)
52-11	2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid {4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-amide	514.0 (ESI+)
52-12	3-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	468.2 (ESI+)
52-13	4-Chloro-2-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	486.0 (ESI+)
52-14	4-Methyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	448.4 (ESI+)
52-15	2,5-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	470.3 (ESI+)
52-16	2-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	468.3 (ESI+)
52-17	2,3-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	470.3 (ESI+)
52-18	2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-6-trifluoromethyl-benzamide	520.3 (ESI+)
52-19	3-Chloro-4-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	486.3 (ESI+)

Example No.	Systematic name	MS (Method)
52-20	N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide	502.2 (ESI+)
52-21	4-tert-Butyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	490.2 (ESI+)
52-22	4-Difluoromethoxy-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	500.2 (ESI+)
52-23	3,5-Difluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	470.2 (ESI+)
52-24	2-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	452.1 (ESI+)
52-25	3-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	452.1 (ESI+)
52-26	4-Fluoro-3-methyl-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide	466.2 (ESI+)

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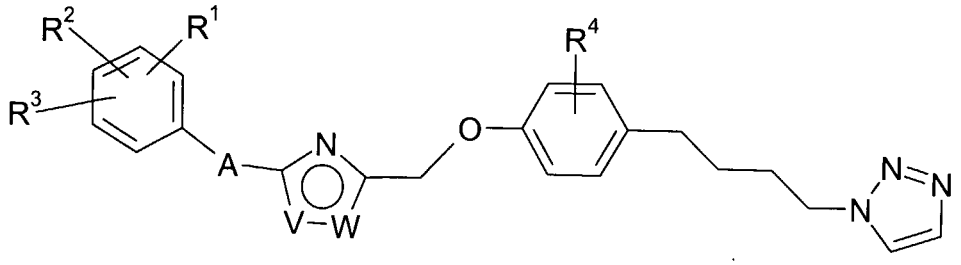
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Patent Claims

1. A compound according to formula I,



formula I,

wherein

R^1 is hydrogen,
halogen,
nitro,
$-SF_5$,
-O-alkyl,
$-S(O)_n$-alkyl,
$-S(O)_2NH_2$,
$-S(O)_2NH$-acyl,
$-S(O)_2NH$-heteroaryl,
-NH-alkyl, or
alkyl, all alkyl groups being optionally substituted once or several times with halogen;

n is 0, 1 or 2

R^2 is hydrogen; or alternatively

R^1 and R^2 are
adjacent and together with the carbon atoms of the phenyl ring to which they are attached form a 5 or 6 membered heterocyclic ring;

R^3 is hydrogen, halogen or nitro;

R^4 is hydrogen or alkyl;

A is -NHC(O)-; -C(O)NH-; -N(alkyl)C(O)- or -C(O)N(alkyl)-;

V is -CH-; and
W is -S- or –O-; or alternatively
V is -S-; and
W is -CH-; and

all pharmaceutically acceptable salts thereof.

2. The compounds according to claim 1, wherein
R^4 is hydrogen.

3. The compounds according to any one of claim 1 or 2, wherein

R^1 is chlorine;
-O-alkyl;
-S-alkyl
alkyl, all alkyl groups being optionally once or several times substituted with fluorine;

R^2 is hydrogen; and

R^3 is hydrogen or fluorine;

4. The compounds according to any one of claim 1 to 3, wherein
A is -NHC(O)- or-N(alkyl)C(O)-.

5. The compounds according to claim 4:

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-methyl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-nitro-4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoro-methylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-4-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-difluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-(4-trifluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-nitro-2-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,6-dichloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-dichloro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid benzo[1,3]dioxol-5-yl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,5-difluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,4-difluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2,2-difluoro-benzo[1,3]dioxol-5-yl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-(thiazol-2-ylsulfamoyl)-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfamoyl)-phenyl]-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid [4-(5-methyl-isoxazol-3-ylsulfamoyl)-phenyl]-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-acetylsulfamoyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-bromo-2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-2-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-nitro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methylsulfanyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-2-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-tert-butyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid p-tolylamide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid methyl-phenyl-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-fluoro-3-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (2-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-fluoro-4-methyl-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-methoxy-phenyl)-amide;

2-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3,4-difluoro-phenyl)-amide;

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-chloro-phenyl)-amide;

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-trifluoromethoxy-phenyl)-amide; and

4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazole-2-carboxylic acid (4-pentafluorosulfanyl-phenyl)-amide.

6. The compounds according to any one of claims 1 to 3, wherein
A is -C(O)NH- or- C(O)N(alkyl)-.

7. The compounds according to claim 6

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-3-trifluoromethyl-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethoxy-benzamide;

4-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Chloro-3-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3,4-Dichloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide;

3-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Chloro-2-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Methyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Chloro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-6-trifluoromethyl-benzamide;

3-Chloro-4-fluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethyl-benzamide;

4-tert-Butyl-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Difluoromethoxy-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

4-Nitro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,4-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

N-{4-[4-(4-[1,2,3]Triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-4-trifluoromethylsulfanyl-benzamide;

4-Cyano-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,2-Difluoro-benzo[1,3]dioxole-5-carboxylic acid {4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-amide;

2,5-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2,3-Difluoro-N-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3,5-Difluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

2-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide;

3-Fluoro-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide; and

4-Fluoro-3-methyl-*N*-{4-[4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazol-2-yl}-benzamide.

8. The compounds according to claim 1, wherein
R^4 is methyl.

9. The compounds according to claim 8:

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (4-chloro-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-oxazole-4-carboxylic acid (3-chloro-phenyl)-amide;

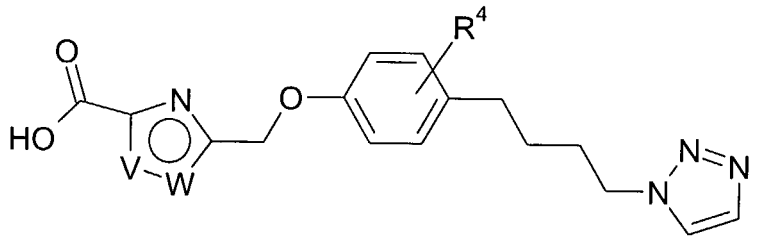
2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-trifluoromethyl-phenyl)-amide;

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (4-chloro-phenyl)-amide; and

2-[3-Methyl-4-(4-[1,2,3]triazol-1-yl-butyl)-phenoxymethyl]-thiazole-4-carboxylic acid (3-chloro-phenyl)-amide.

10. A process for the manufacture of the compounds of formula I , wherein

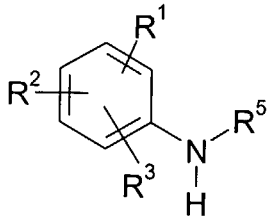
a) the compound of formula V



formula V,

wherein R^4 , V and W have the significance given above for claim,

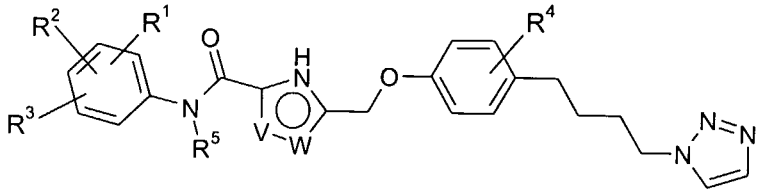
is reacted with a compound of formula VI



formula VI,

wherein R^1, R^2, R^3 and R^5 have the significance given above for formula I,

to give the respective compound of formula Ia;



formula Ia

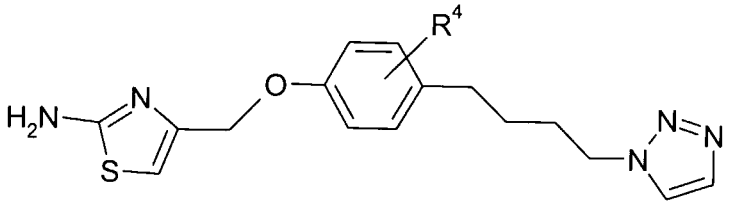
wherein R^1, R^2, R^3, R^4 and R^5 have the significance given above for formula I;

b) said compound of formula Ia is isolated from the reaction mixture, and

c) if desired, converted into a pharmaceutically acceptable salt.

11. A process for the manufacture of the compounds of formula I , wherein

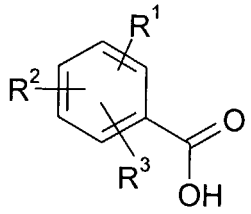
a) the compound of formula IX,



formula IX,

wherein R^4 has the significance given above for formula I;

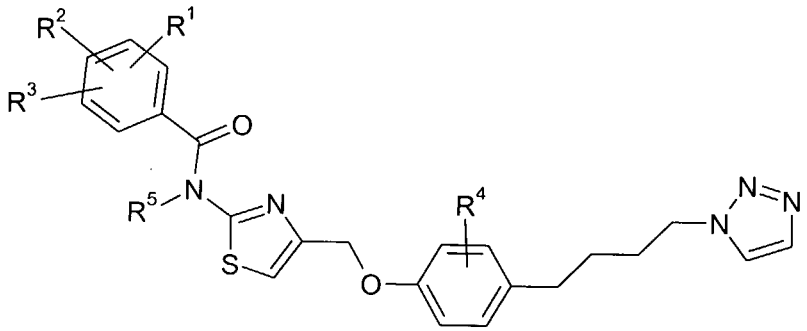
is reacted with a compound of formula X



formula X,

wherein R^1, R^2, R^3 have the significance given above for formula I,

to give the respective compound of formula Ib;



formula Ib

wherein R^1, R^2, R^3 and R^4 have the significance given above for formula I and R^5 is hydrogen;

b) if desired, compound of formula Ib obtained in a) is further reacted with a suitable alkyl halide to give the respective compound of formula Ib; wherein R^5 is alkyl.

c) said compound of formula Ib is isolated from the reaction mixture, and

d) if desired, converted into a pharmaceutically acceptable salt.

12. A pharmaceutical composition, containing one or more compounds as claimed in any one of the claims 1 to 9 together with pharmaceutically acceptable excipients.

13. A pharmaceutical composition according to claim 12 for the inhibition of tumor growth.

14. The use of a compound in any one of claims 1 to 9 for the treatment of cancer.

15. The use of a compound in any one of claims 1 to 9 for the manufacture of corresponding medicaments for the inhibition of tumor growth.