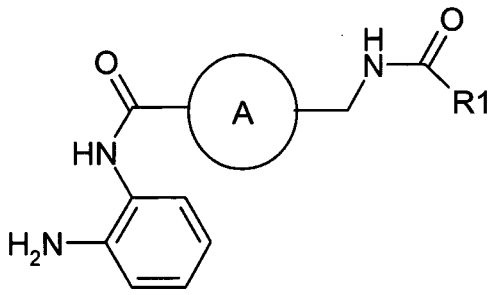
ARYLENE-CARBOXYLIC ACID (2-AMINO-PHENYL)-AMIDE DERIVATIVES AS PHARMACEUTICAL AGENTS

The present invention relates to novel arylene-carboxylic acid (2-amino-phenyl)-amide derivatives, to a process for their manufacture, medicaments containing them and their manufacture as well as the use of these compounds as pharmaceutically active agents.

EP-A 0 847 992 describes monoacylated o-phenylendiamine derivatives as cell differentiation inducers. The same type of compounds is also the subject of EP-A 0 242 851. The compounds described in these applications are almost exclusively o-phenylene derivatives monoacylated with derivatives of benzoic acid. However, there is still a need to provide compounds with improved properties such as increased tolerability, less toxicity and less side effects.

Monoacylated o-phenylendiamines are known in the art as precursors for the preparation of the corresponding benzimidazoles, such preparation methods are e.g. described in DE-A 2 062 265; FR 2 167 954; Rastogi, R., and Sharma, S., Indian J. Chem., Sect. B, 21B (5) (1982) 485-487; Moll, R., et al., Z. Chem. 17 (1977) 133-134; and Hassan, H., et al., Indian J. Chem. 39B (2000) 764-768.

The present derivatives are new compounds of the general formula



I

wherein

A represents thiophene-diyl, phenylene or pyridine-diyl;

R^1 represents alkyl, alkenyl, alkynyl which are all optionally substituted; or

$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;

$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl; or

a group $-NR^3R^4$, wherein R^3 and R^4 independently represent
hydrogen;
alkyl, alkenyl or alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-(O)-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

The compounds according to this invention are inhibitors of Histone Deacetylase (HDAC) and therefore show antiproliferative and differentiation-inducing activity, which results in inhibition of tumor cell proliferation, induction of apoptosis and inhibition of invasion.

Transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. Transcriptional activation of a set of genes determines cell destination and for this reason transcription is tightly regulated by a variety of factors. One of its regulatory mechanisms involved in the process is an alteration in the tertiary structure of DNA, which affects transcription by modulating the accessibility of transcription factors to their target DNA segments. Nucleosomal integrity is regulated by the acetylation status of the core histones. In a hypoacetylated state, nucleosomes are tightly compacted and thus are nonpermissive for transcription.

On the other hand, nucleosomes are relaxed by acetylation of the core histones, with the result being permissiveness to transcription. The acetylation status of the histones is governed by the balance of the activities of histone acetyl transferase (HAT) and histone deacetylase (HDAC). Recently, HDAC inhibitors have been found to arrest growth and apoptosis in several types of cancer cells, including colon cancer, T-cell lymphoma, and erythroleukemic cells. Given that apoptosis is a crucial factor for cancer progression, HDAC inhibitors are promising reagents for cancer therapy as effective inducers of apoptosis (Koyama, Y., et al., Blood 96 (2000) 1490-1495).

A further shortcoming of many anti-cancer drugs is a lack of selectivity. They do not sufficiently differentiate between tumor cells and normal cell, and therefore adverse reactions expressed in normal cells have limited their use in therapy. Up to now, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity, better tolerability and a high therapeutic effect is very much desired. The compounds of the present invention surprisingly show low toxicity, together with a potent anti-proliferative and cell differentiation activity.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts and their enantiomeric forms, 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 or in the manufacture of corresponding medicaments.

As used herein, the term "alkyl" means a straight-chain or branched-chain hydrocarbon group containing from 1 to 14, preferably from 1 to 8, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, 1-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, n-heptyl as well as their isomers. The alkyl group is optionally substituted once or several times with halogen, hydroxy, cyano, nitro, amino, –NH-alkyl or -N(alkyl)$_2$. Preferably the alkyl group is mono or multiply substituted by fluor or mono substituted by –NH-alkyl or -N(alkyl)$_2$. Examples for fluorinated alkyl groups are perfluormethyl, 2,2,2-trifluorethyl, perfluorethyl. The alkyl group in -N(alkyl)$_2$ substituents is the same or different alkyl group and has the meaning as defined above. Examples for –NH-alkyl or -N(alkyl)$_2$ substituents are methylamino, ethylamino, propylamino, isopropylamino, 1-butylamino, 2-butylamino, t-butylamino, di-methylamino, di-ethylamino, di-propylamino, di-

isopropylamino, di-1-butylamino, di-2-butylamino, di-t-butylamino, ethyl-methylamino, ethyl-propylamino.

The term "alkenyl" means an unsaturated alkyl chain as defined above, containing one or two isolated double bonds, preferably one double bond. Examples are 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl or 1-hexenyl.

The term "alkynyl" means an unsaturated alkyl chain as defined above, containing a triple bond. Examples are 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl or 1-hexynyl.

The term "optionally substituted" as used herein in combination with alkenyl or alkynyl refers to the substitution of one or several hydrogen atoms at any of the aforementioned groups with halogen, hydroxy, cyano, nitro, amino, oxo, -NHalkyl or $-N(alkyl)_2$.

The term "halogen" means fluorine, chlorine, bromine or iodine.

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

A represents thiophene-diyl, phenylene or pyridine-diyl;
R^1 is a group $-NR^3R^4$, wherein R^3 is hydrogen and R^4 is as defined above;

and pharmaceutically acceptable salts thereof.

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

A represents thiophene-diyl, phenylene or pyridine-diyl;
R^1 represents alkyl, alkenyl, alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents thiophen-2,5-diyl;
R^1 represents alkenyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl; or
$-(CH_2)_n$-C(O)alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

5-[(2-ethoxy-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(pent-4-enoylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-acetylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-({2-[2-(2-methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(4-oxo-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents thiophen-2,5-diyl;
R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen;
R^4 is alkenyl;
alkynyl;

$-(CH_2)_n-(O)$-alkyl;
$-(CH_2)_n-NH-C(O)$-alkyl; or
$-(CH_2)_n-C(O)-O$-alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

5-[3-(3-ethoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-prop-2-ynyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-acetylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-methoxy-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-allyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-butoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
4-{3-[5-(2-amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-ureido}-butyric acid ethyl ester.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents 1,4-phenylene;
R^1 represents alkenyl;
$-CH_2-(O-CH_2-CH_2-)_mO-CH_3$;
$-(CH_2)_n-O$-alkyl; or
$-(CH_2)_n-NH-C(O)$-alkyl;
n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

N-(2-amino-phenyl)-4-[(2-ethoxy-acetylamino)-methyl]-benzamide,

N-(2-amino-phenyl)-4-(pent-4-enoylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-({2-[2-(2-methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-benzamide,
4-[(2-acetylamino-acetylamino)-methyl]-N-(2-amino-phenyl)-benzamide.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents 1,4-phenylene;
R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen;
R^4 is alkenyl;
alkynyl;
$-(CH_2)_n-(O)$-alkyl;
$-(CH_2)_n-NH-C(O)$-alkyl; or
$-(CH_2)_n-C(O)-O$-alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

4-[3-(2-acetylamino-ethyl)-ureidomethyl]-N-(2-amino-phenyl)-benzamide,
N-(2-amino-phenyl)-4-[3-(2-methoxy-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-butoxy-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-ethoxy-propyl)-ureidomethyl]-benzamide,
4-[(3-allyl-ureido)-methyl]-N-(2-amino-phenyl)-benzamide,
N-(2-amino-phenyl)-4-[3-(3-isopropoxy-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[(3-prop-2-ynyl-ureido)-methyl]-benzamide,
4-{3-[4-(2-amino-phenylcarbamoyl)-benzyl]-ureido}-butyric acid methyl ester.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents pyridin-2,5-diyl;
R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen, and
R^4 is -(CH2)n-(O)-alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

Such a compound is for example:

N-(2-amino-phenyl)-6-[3-(3-butoxy-propyl)-ureidomethyl]-nicotinamide.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents pyridin-2,5-diyl;
R^1 represents alkenyl; or
$-(CH_2)_n$-O-alkyl;
n is 1-6;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

N-(2-amino-phenyl)-6-[(2-methoxy-acetylamino)-methyl]-nicotinamide,
N-(2-amino-phenyl)-6-(pent-4-enoylamino-methyl)-nicotinamide.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents thiophen-2,5-diyl;
pyridin-2,5-diyl; or
1,4-phenylene;

R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen;
R^4 is alkyl which is unsubstituted or substituted once or several times by
halogen;
-NH-alkyl; or
$-N(alkyl)_2$;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

5-[3-(2-dimethylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-diisopropylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-diethylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(1-methyl-hexyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(3-sec-butyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-methyl-butyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(3-isobutyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-dibutylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-[(3-pentyl-ureido)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-diethylamino-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(1-methyl-hexyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-dibutylamino-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-dimethylamino-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-diisopropylamino-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-methyl-butyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-(3-isobutyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-4-(3-sec-butyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-6-[(3-pentyl-ureido)-methyl]-nicotinamide,
N-(2-amino-phenyl)-6-[3-(1-methyl-hexyl)-ureidomethyl]-nicotinamide.

Yet another embodiment of the invention are compounds of formula I, wherein

A represents thiophen-2,5-diyl;

pyridin-2,5-diyl; or
1,4-phenylene;

R^1 represents alkyl; wherein
the alkyl group is unsubstituted or substituted once or several times by
halogen;
-NH-alkyl; or
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

Such compounds are for example:

5-[(4-methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(propionylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(butyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(isobutyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2,2,3,3,3-pentafluoro-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-ethyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2,2,2-trifluoro-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(4-dimethylamino-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-methyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl amide,
5-[(2-dipropylamino-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-dimethylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-(propionylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-(isobutyrylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-[(4-methyl-pentanoylamino)-methyl]-benzamide,

N-(2-amino-phenyl)-4-[(2-ethyl-butyrylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-(butyrylamino-methyl)-benzamide,.
N-(2-Amino-phenyl)-6-[(4-methyl-pentanoylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(3-methyl-pentanoylamino)-methyl]-nicotinamide.

Yet another embodiment of the invention are compounds of formula I, wherein

A	represents	thiophene-diyl, phenylene or pyridine-diyl;
R^1	represents	a group $-NR^3R^4$, wherein R^3 and R^4 independently represent alkyl, alkenyl or alkynyl which are all optionally substituted; or $-CH_2-(O-CH_2-CH_2-)_mO$-alkyl; $-(CH_2)_n-(O)$-alkyl; $-(CH_2)_n-C(O)-NH$-alkyl; $-(CH_2)_n-NH-C(O)$-alkyl; $-(CH_2)_n-C(O)$alkyl; $-(CH_2)_n-C(O)-O$-alkyl; or $-(CH_2)_n-O-C(O)$-alkyl;
n	is 1-6;	
m	is 1-4;	

and pharmaceutically acceptable salts thereof.

Yet another embodiment of the invention are compounds of formula I, wherein

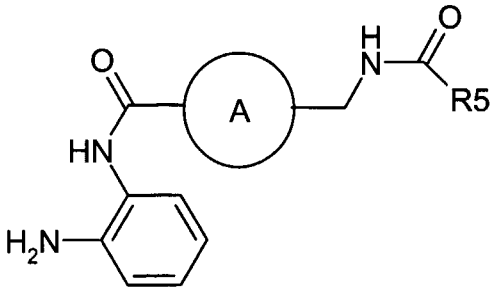
A	represents	1,4-phenylene;
R^1	is a group	$-NR^3R^4$, wherein R^3 and R^4 independently represent alkyl;

and pharmaceutically acceptable salts thereof.

Such a compound is for example:

N-(2-amino-phenyl)-4-(3-butyl-3-methyl-ureidomethyl)-benzamide

Yet another embodiment of the invention are compounds of formula I-A



I-A,

wherein

A	represents	thiophen-2,5-diyl;
		pyridin-2,5-diyl; or
		1,4-phenylene;
R^5	represents	$-(CH_2)_k$-cyclopropyl;
		$-(CH_2)_k$-cyclopentyl;
		$-(CH_2)_k$-cyclohexyl;
		$-(CH_2)_k$-cyclopent-2-enyl;
		$-(CH_2)_k$-(5-oxo-pyrrolidin-2-yl);
		$-(CH_2)_k$-(2-oxo-pyrrolidin-1-yl);
		$-NH-(CH_2)_k$-cyclopropyl;
		$-NH-(CH_2)_k$-cyclopentyl;
		$-NH-(CH_2)_k$-cyclohexyl;
		$-NH-(CH_2)_k$-cyclopent-2-enyl;
		$-NH-(CH_2)_k$-(5-oxo-pyrrolidin-2-yl); or
		$-NH-(CH_2)_k$-(2-oxo-pyrrolidin-1-yl);

k is 0-6;

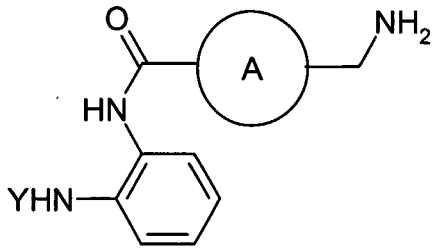
and pharmaceutically acceptable salts thereof.

Such compounds are for example:

5-[(cyclopentanecarbonyl-amino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-cyclopent-2-enyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-oxo-pyrrolidine-2-carboxylic acid [5-(2-amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-amide,
5-[(3-cyclopentyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-cyclohexyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-cyclopentyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-cyclopropyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-[(cyclopentanecarbonyl-amino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[(2-cyclopent-2-enyl-acetylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[(3-cyclopentyl-propionylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-benzamide,
N-(2-amino-phenyl)-4-(3-cyclopropylmethyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-6-[(3-cyclopentyl-propionylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-nicotinamide,
N-(2-Amino-phenyl)-6-[(2-cyclopent-2-enyl-acetylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(2-cyclopentyl-acetylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(3-cyclohexyl-propionylamino)-methyl]-nicotinamide.

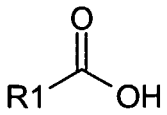
A further embodiment of the invention is the process for the manufacture of the present (acylamino-methyl)-arylene-carboxylic acid (2-amino-phenyl)-amide derivatives of the formula I, or a pharmaceutically-acceptable salt thereof by

(a) reacting a compound of formula II



II,

wherein A has the meaning defined above and Y represents a suitable protecting group, with a compound of the general formula III



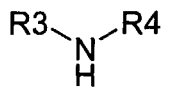
III,

wherein

R^1 is alkyl, alkenyl, alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

or

reacting said compound of formula II with a compound of formula X



X,

wherein R^3 and R^4 independently represent

hydrogen;
alkyl, alkenyl, alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

(b) subsequent cleavage of the protection group; and
(c) if desired, turning the product into a pharmaceutically acceptable salt by addition of a suitable acid or base.

Necessary starting materials for the above-mentioned process 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.

Protection groups for the amino group in process step (a) and methods for their cleavage (process step (b)) are known from peptide chemistry. Example are benzyloxycarbonyl (cleavage by hydrogenation or hydrobromic acid in acetic acid), t-butoxycarbonyl (cleavage by strong acids such as trifluoroacetic acid, neat or in dichloromethane, or hydrochloric acid (HCl) in dioxane), 9-fluorenmethoxy-carbonyl (cleavage by secondary amines, such as, piperidine).

The manufacture of compounds of the general formula I will now be described in detail and according to the nature of the group A, as well as the cases wherein R^1 is or is not a group $-NR^3R^4$ as defined above.

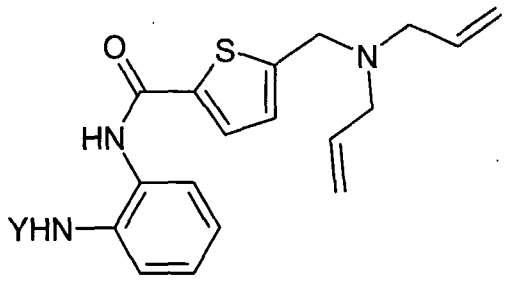
The reaction of compounds of formula II with compounds of formula III wherein R^1 is not a group $-NR^3R^4$ typically involves a three-step one-pot procedure. In the first step, the carboxylate of the formula III becomes activated. This reaction is carried out in an inert solvent or diluent, for example in dichloromethane, dioxane or tetrahydrofuran (THF) and in the presence of an activating agent. A suitable reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride or oxalic acid dichloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an active ester formed by the reaction of the acid and N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N-3-dimethylaminopropyl-N-ethylcarbodiimid or dicyclohexylcarbodiimide, or the product of the reaction of the acid with N,N'-carbonyldiimidazole; or the product of the reaction of the acid and uroniumsalts such as O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium tetrafluoroborate; or the product of the reaction of the acid and phosphorus based reagents, e.g. bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride.

In the second step a compound of formula II is added to the solution. These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide chemistry as described in e.g. Houben-Weyl, "Methoden der organischen Chemie", Vol. XV/1 and XV/2 are also applicable.

If Y is t-butoxycarbonyl it can be finally cleaved in the third step by addition of trifluoroacetic acid to the reaction mixture to yield compounds of formula I. Alternatively the amide product is isolated after the second step and the cleavage of the protecting group Y is carrried out in a separate step under reaction conditions as described above.

The preparation of compound II wherein A is phenyl and Y is t-butoxycarbonyl ([2-(4-Aminomethyl-benzoylamino)-phenyl]-carbamic acid t-butyl ester) is described in the literature, e.g. EP 0 847 992.

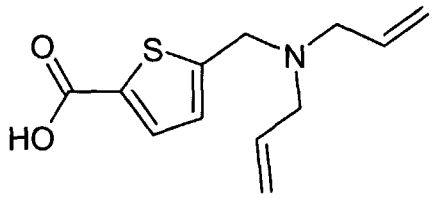
A preferred method for the preparation of compounds of the formula II wherein A is 2,5-thiophene involves the removal of the allylgroups of compounds IV



IV

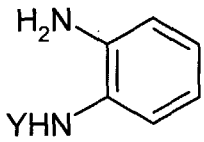
The cleavage of the allyl groups can be accomplished for example by palladium-catalyzed reaction in the presence of sulfinic acids, carboxylic acids, morpholine, dimedone or N,N'-dimethylbarbituric acid as allyl scavengers.

The compounds of formula IV can be obtained by the reaction of compound V



V

with a compound of the formula VI



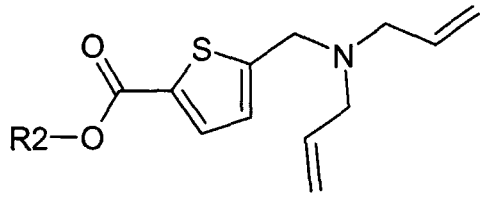
VI

wherein Y represents suitable protecting group as defined above.

This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of compound V becomes activated. This reaction is carried out in an inert solvent or diluent, for example in dichloromethane, dioxane or THF and in the presence of an activating agent. A suitable reactive derivative of an acid is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride or oxalic acid dichloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol; an active ester formed by the reaction of the acid and N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N-3-dimethylaminopropyl-N-ethylcarbodiimid or dicyclohexylcarbodiimide, or the product of the reaction of the acid with N,N'-carbonyldiimidazole; or the product of the reaction of the acid and uroniumsalts such as O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium tetrafluoroborate; or the product of the reaction of the acid and phosphorus based reagents, e.g. bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride.

In the second step, compound VI is added to the solution to yield compound IV. These methods are well known to those skilled in the art. In principle, all methods for the synthesis of amides as used in peptide chemistry as described in e.g. Houben-Weyl, "Methoden der organischen Chemie", Vol. XV/1 and XV/2 are also applicable.

The compounds of formula V are prepared by hydrolysis from compounds of the formula VII.

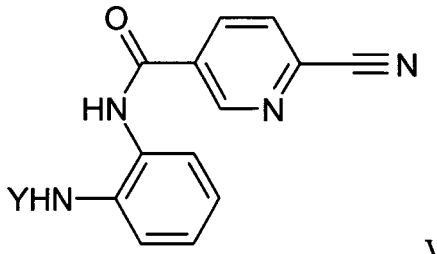


VII

wherein R^2 is alkyl or optionally substituted benzyl. Alkyl as used herein has the significance given before. Examples for R^2 are methyl, ethyl, t-butyl, benzyl or p-methoxybenzyl. The conditions under which the hydrolysis is carried out depend on the nature of the group R^2. When R^2 is a methyl or ethyl group, the reaction is carried out in the presence of a base, for example, lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent or diluent, for example in methanol, ethanol, dioxane, THF, water. When R^2 is the t-butyl group, the reaction is carried out in the presence of an acid, for example, a solution of hydrochloric acid in an inert solvent such as diethyl ether or dioxane, or trifluoroacetic acid in dichloromethane. When R^2 is the benzyl group, the reaction is carried out by hydrogenolysis in the presence of a noble metal catalyst such as palladium or platinum on a suitable carrier, such as carbon.

5-Diallylaminomethyl-thiophene-2-carboxylic esters are described in the literature, in e.g. Millot, N., et al., Synthesis 7 (2000) 941-948.

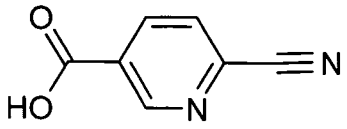
One preferred method for the production of compounds of the formula II wherein A is 2,5-pyridine involves the reduction of the cyano group of compound VIII.



VIII

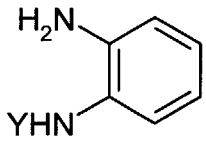
The reduction of the nitrile can be accomplished for example by hydrogen in the presence of a catalyst e.g. palladium on carbon or Raney-nickel in a suitable solvent e.g. THF, methanol, ethanol or dimethyl formamide (DMF) optionally in the presence of e.g. HCl, triethylamine, ammonia or hydroxylamine.

One preferred method for the production of compounds of the formula VIII involves the reaction of compound IX



IX

with a compound of the formula VI

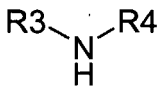


VI

wherein Y represents suitable protecting group as defined above. The reaction can be carried out under conditions as described for the preparation of compound IV. 6-Cyano-nicotinic acid is described in the literature, in e.g. Vorbrueggen, H., and Krolikiewicz, K., Synthesis 4 (1983) 316-319.

The ureidomethyl derivatives of the general formula I in which R^1 is a group -NR^3R^4 as defined herein before may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes are illustrated by the following representative examples. 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.

One preferred method for the production of said ureidomethyl derivatives of formula I involves the reaction of compounds of the formula II wherein Y is preferably t-butoxycarbonyl with an amine of the formula X



X

wherein R^3 and R^4 have the meaning defined above.

This reaction typically involves a three-step one-pot procedure. In the first step compound X is reacted with carbonyldiimidazol in an appropriate solvent e.g. THF. In the second step compound II is added to the reactive intermediate to form the

corresponding ureido derivative. Finally Y is cleaved by addition of trifluoroacetic acid to the reaction mixture to yield the ureidomethyl derivatives of formula I.

Alternatively the ureido product is isolated after the second step and the cleavage of the protecting group Y is carrried out in a separate step under reaction conditions as described above.

If Y is t-butoxycarbonyl it can be finally cleaved in the third step by addition of trifluoroacetic acid to the reaction mixture to yield said derivatives of formula I.

The compounds of the general 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 High Performance Liquid Chromatography (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 or base-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 or organic or inorganic bases. Acid-addition salts include for example 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, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Ansel, H., et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., 1995, pp. 196 and 1456-1457.

The compounds according to this invention and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations 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 preparations can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, 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 preparations 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.

Medicaments containing one or more compounds according to this invention as active ingredients together with pharmaceuticaly acceptable adjuvants are also an object of the present invention.

A further object of this invention is the use of such medicaments for the treatment of cancer, characterized by the inhibition of tumor cell proliferation due to induction of histone acetylation in said tumor cell.

Yet another object of this invention is a method for inhibiting tumor cell proliferation, characterized by induction of histone acetylation in a tumor cell, due to administring to said tumor cell an effective amount of one or more compounds according to the present invention.

The activity of the compounds according to this invention as HDAC Inhibitors is demonstrated using a cellular acetylation assay. Therein acetylation of histones is monitored in PC3 cells. High acetylation means inhibition of histone deacetylase by compounds. Cell viability is monitored in parallel to estimate the cytotoxicity of compounds.

PC3 cells, human prostate carcinoma cells, are seeded as 1800 cells per well of 384-well microtiterplate in RPMI 1640 (including 5% FCS, 2mM glutamine and pen / strep).

After 48 h at 37 °C pre-diluted compounds are added at a final concentration of 1 uM. Compounds are pre-diluted 1:10 in dimethyl sulfoxide (DMSO) or medium resulting in final concentration of DMSO of 0.5 %.

After 24 h incubation the cell viability is determined by adding cell proliferation reagent WST1. Another 60 min. later the optical density (OD) is measured (450 nm versus 690 nm).

After WST1 assay the cell layer is prepared for the ELISA reaction. Medium is aspirated and cells are fixed in Ethanol at –20 °C for 60 min. After washing with PBS / Tween the blocking solution (PBS/ 5% FCS / Tween) is added and the cell layer is washed again. Antibodies against histone H3 or H4 (Anti-Acetylated Histone (rabbit polyklonal IgG), Upstate Biotechnologie) are added at a dilution of 1:200 for 60 min at 37 °C. As second antibody Goat anti rabbit IgG(H+L)humanIgG adsorbed-HRP Conjugate (Dako) is used (1:2000 diluted). Cells are washed 3 times and the peroxidase substrate ABTS is allowed to react for 30-60 min at 37 °C. Oxalic acid stopps the reaction and the OD is measured at 405 nm.

The percentage of acetylation is calculated after substraction of blank O.D.s :

$$\frac{\text{mean O.D. acetylation}}{\text{mean O.D. DMSO control}} * 100\ \%$$

$$\frac{\text{mean O.D. WSTI}}{\text{mean O.D. DMSO control}}$$

Example No.	Compound Name	cell acetylation (PC3, 1 μM) [% of control]
	Reference Compound CI 994	152
4-1	5-[(4-Methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	170
4-3	5-[(2-Ethoxy-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	194
4-6	5-(Butyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	238
6-8	5-[3-(2-Methyl-butyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	198
6-12	5-[(3-Allyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	170
6-13	5-(3-Isobutyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	178
4-31	N-(2-Amino-phenyl)-4-[(2-cyclopent-2-enyl-acetylamino)-methyl]-benzamide	176
6-19	N-(2-Amino-phenyl)-4-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-benzamide	205
6-25	N-(2-Amino-phenyl)-4-[3-(1-methyl-hexyl)-ureidomethyl]-benzamide	192
6-26	N-(2-Amino-phenyl)-4-[3-(3-ethoxy-propyl)-ureidomethyl]-benzamide	179
6-27	4-[(3-Allyl-ureido)-methyl]-N-(2-amino-phenyl)-benzamide	175
6-28	N-(2-Amino-phenyl)-4-[3-(3-isopropoxy-propyl)-ureidomethyl]-benzamide	177
6-29	N-(2-Amino-phenyl)-4-(3-cyclopropylmethyl-ureidomethyl)-benzamide	187
6-38	N-(2-Amino-phenyl)-6-[(3-pentyl-ureido)-methyl]-nicotinamide	178

The effect of the compounds according to the invention may further be assessed by the following test:

Method

Male NMRI nu/nu-mice(n = 15 per group), aged 8-10 weeks, were subcutaneously injected with 5*106 PC-3 prostate carcinoma cells. On day 10, animals with tumor volumes of about 150 mm3 were randomly assigned to treatment groups. The test compound was administered as a microsuspension in 7,5% Gelatine - 0,22% NaCl-Suspension with an application volume of 10 ml/kg based on actual body weights. Once daily oral treatment was performed from approximately day 10 to day 27 on a, 5-7 times per week treatment schedule.

The volume of the tumor is determined from the following equation:

Volume of a tumor = 1/2ab2, where "a" and "b" are the long and the short diameters of the tumor, respectively,

The invention will now be illustrated in the following non-limiting examples in which, unless otherwise stated:

i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD using electrospray);

(vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography;

(viii) the following abbreviations have been used:

DMF	N,N-dimethyl formamide;
DMSO	dimethyl sulfoxide;
THF	tetrahydrofuran;
MeOH	methanol;
HCl	hydrochloric acid;
NaH	sodium hydride
CH_2Cl_2	dichloromethane;
H_2SO_4	sulfuric acid
sat.	saturated
sol.	solution
rt	room temperature
eq	equivalent
MW found	molecular weight (as determined by mass spectrometry)
MW calc'd	molecular weight (as calculated from the chemical formula)

Example 1

Step 1: {2-[(6-Cyano-pyridine-3-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester

To a solution of 444mg (3.0mmol) 6-cyano-nicotinic acid and 354mg (3.5mmol) N-methylmorpholine in 7ml DMF at –20°C was added 450mg (3.3mmol) isobutyl chloroformate. The reaction mixture was warmed to 5°C and 625mg (3.0mmol) mono-boc-ortho-phenylenediamine were added. The reaction mixture was warmed to rt overnight and then poured into 50ml 5% aqueous citric acid. The aqueous phase was extracted with ethyl acetate, the combined organic phases were washed with bicarbonate and brine and dried over Na2SO4. The solvent was evaporated and the residue was subjected to silica gel chromatography (petrol ether/ethyl acetate 2:1) to yield 795mg (2.35mmol) {2-[(6-Cyano-pyridine-3-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester; mp.183-184°C.

Step 2: {2-[(6-Aminomethyl-pyridine-3-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester

In a flask 2920mg (8.72mmol) {2-[(6-Cyano-pyridine-3-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester and 1000mg Pd (10% on Carbon) were placed under nitrogen and 10ml THF and 120ml methanol were added. The starting material was hydrogenated under atmospheric pressure and at rt for 3.5h. The catalyst was filtered off. The solvent was evaporated and the residue was subjected to silica gel chromatography (toluene/isopropanol/NH3(conc.) 16:20:1) to yield 2600mg (7.6mmol) {2-[(6-Aminomethyl-pyridine-3-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester; exact MW [M+H] calc'd: 343.18; MW found [M+H]: 343.2.

Example 2

Step 1: 5-Diallylaminomethyl-thiophene-2-carboxylic acid

To a solution of 4.5g (17.9mmol) 5-diallylaminomethyl-thiophene-2-carboxylic acid methyl ester in 45ml methanol were added 17.9ml of a 1N aqueous solution of KOH (17.9mmol). The reaction mixture was stirred at 50°C for 16h and 1h at reflux. The solvent was evaporated, 20ml water were added to the residue and 9ml of a 2N aqueous solution of HCl. The aqueous phase was extracted with ethyl acetate, the combined organic phases were dried over Na2SO4. The solvent was evaporated and the residue was subjected to silica gel chromatography (ethyl acetate) to yield 4.05g (17.06mmol) 5-diallylaminomethyl-thiophene-2-carboxylic acid; exact MW [M+H] calc'd: 238.09; MW found [M+H]: 238.3.

Step 2: {2-[(5-Diallylaminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester

To a solution of 2.70g (11.38mmol) 5-diallylaminomethyl-thiophene-2-carboxylic acid in 50ml THF was added 2.03g (12.51mmol) carbonyldiimidazol. After 45min at rt 2.48g (11.95mmol) mono-boc-ortho-phenylenediamine were added to the reaction mixture and it was stirred for 3h at rt. The solvent was evaporated and the residue dissolved in ethyl acetate. The organic phase was washed twice with sat. NaHCO3, once with water and dried over Na2SO4. The solvent was evaporated and the residue was subjected to silica gel chromatography (ethyl acetate/heptane 2:8) to

yield 4.10g (9.59mmol) {2-[(5-Diallylaminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester; exact MW [M+H] calc'd: 428.20; MW found [M+H]: 428.3.

Step 3: {2-[(5-Aminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester

To a solution of 22.35g (143.13mmol) N,N'-dimethylbarbituric acid and 0.55g (0.477mmol) tetrakis(triphenylphosphine)palladium (0) in 200ml CH2Cl2 were added 10.20g (23.86mmol) Diallylaminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester. After 1h at 35°C the solvent was evaporated and 0.1N aqueous HCL was added to the residue. The aqueous phase was extracted three times with diethylether and the combined organic phases were extracted with sat. NaHCO3. The acidic aqueous phase was neutralized with sat. NaHCO3 and the combined aqueous phases were extracted three times with CH2Cl2. The organic phase was dried over Na2SO4. The solvent was evaporated and the residue was subjected to silica gel chromatography (dichloromethane/methanol 9:1) to yield 4.63g (13.32mmol) {2-[(5-Aminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester; exact MW [M+H] calc'd: 348.14; MW found [M+H]: 348.1.

<u>Example 3</u>

5-[(3-Methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide

To a solution of 33.43mg (0.288mmol) 3-methylpentanoic acid in 1ml THF were added 46.67mg (0.288mmol) 1,1'-carbonyldiimidazol. After 1h at rt 100mg (0.288mmol) {2-[(5-Aminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester were added and the reaction mixture was stirred for 3h at rt. 1.7ml trifluoroacetic acid were added and after 2h at rt sat. aqueous NaHCO3 was added carefully and the aqueous phase was extracted three times with ethyl acetate . The combined organic phases were dried over Na2SO4. The solvent was evaporated and the residue was subjected to silica gel chromatography (ethyl acetate/heptane 6:4) to yield 59.3mg (0.171mmol) 5-[(3-Methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; exact MW [M+H] calc'd: 346.16; MW found [M+H]: 346.4.

Example 4

In an analogous manner to that described in the example 3, and using known methods as described in the literature (e.g. in standard works such as Houben-Weyl, "Methoden der Organischen Chemie, Georg Thieme Verlag", Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York) the following compounds are prepared :

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-1 5-[(Cyclopentanecarbonyl-amino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	344.14	344.2
4-2 5-[(4-Methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 9.63 (s, 1H), 8.52 (t, J = 6.1 Hz, 1H), 7.79-7.78 (m, 1H), 7.12-7.09 (m, 1H), 7.00-6.99 (m, 1H), 6.97-6.95 (m, 1H), 6.78-6.76 (m, 1H), 6.61-6.57 (m, 1H), 4.42 (d, J = 6.1 Hz, 2H), 2.13 (t, J = 7.6 Hz, 2H), 1.56-1.39 (m, 3H), 0.86 (d, J = 6.1 Hz, 6H)	346.16	346.2
4-3 5-[(2-Ethoxy-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 9.63 (s, 1H), 8.48 (t, J = 6.1 Hz, 1H), 7.79-7.78 (m, 1H), 7.11-7.09 (m, 1H), 7.01-7.00 (m, 1H), 6.99-6.95 (m, 1H), 6.78-6.76 (m, 1H), 6.61-6.56 (m, 1H), 4.89 (s, 2H), 4.47 (d, J = 6.1 Hz, 2H), 3.89 (s, 2H), 3.50 (q, J = 6.9 Hz, 2H), 1.16 (t, J = 6.8 Hz, 3H)	334.12	334.1
4-4 5-(Propionylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	304.11	304.2

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-5 5-(Pent-4-enoylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	330.13	330.3
4-6 5-(Butyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	318.13	317.9
4-7 5-(Isobutyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	340.11 [M+Na]	340.0 [M+Na]
4-8 5-[(2,2,3,3,3-Pentafluoro-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	394.06	394.1
4-9 5-[(2-Acetylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	347.12	347.2
4-10 5-[(2-Ethyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	346.16	346.2
4-11 5-[(2-Cyclopent-2-enyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 9.62 (s, 1H), 8.53 (t, J = 5.8 Hz, 1H), 7.79-7.78 (m, 1H), 7.12-7.10 (m, 1H), 7.01-7.00 (m, 1H), 6.99-6.95 (m, 1H), 6.78-6.76 (m, 1H), 6.61-6.57 (m, 1H), 5.75-5.72 (m, 1H), 5.68-5.65 (m, 1H), 4.88 (s, 2H), 4.44 (d, J = 5.6 Hz, 2H), 3.04-2.95 (m, 1H), 2.36-1.94 (m, 5H), 1.45-1.37 (m, 1H)	356.14	356.2

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-12 5-({2-[2-(2-Methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	408.16	408.2
4-13 5-[(4-Oxo-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	346.12	346.2
4-14 5-Oxo-pyrrolidine-2-carboxylic acid [5-(2-amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-amide	359.12	359.2
4-15 5-[(2,2,2-Trifluoro-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	344.07	344.1
4-16 5-[(4-Dimethylamino-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	361.17	361.2
4-17 5-[(3-Cyclopentyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 9.63 (s, 1H), 8.52 (t, J = 6.1 Hz, 1H), 7.79-7.78 (m, 1H), 7.11-7.09 (m, 1H), 7.00-6.99 (m, 1H), 6.97-6.95 (m, 1H), 6.78-6.76 (m, 1H), 6.61-6.57 (m, 1H), 4.89 (s, 2H), 4.42 (d, J = 5.6 Hz, 2H), 2.13 (t, J = 7.6 Hz, 2H), 1.76-1.67 (m, 3H), 1.60-1.44 (m, 6H), 1.10-1.00 (m, 2H)	372.17	372.2

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-18 5-[(3-Cyclohexyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	386.19	386.3
4-19 5-[(3-Methyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	332.14	332.3
4-20 5-[(2-Dipropylamino-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	403.22	403.4
4-21 5-[(2-Dimethylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	333.14	333.3
4-22 5-[(2-Cyclopentyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	358.16	358.3
4-23 5-[(2-Cyclopropyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	330.13	330.3
4-24 N-(2-Amino-phenyl)-4-[(cyclopentanecarbonyl-amino)-methyl]-benzamide	338.19	338.3
4-25 N-(2-Amino-phenyl)-4-(propionylamino-methyl)-benzamide	298.16	298.3

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-26 N-(2-Amino-phenyl)-4-(isobutyrylamino-methyl)-benzamide	312.17	312.4
4-27 N-(2-Amino-phenyl)-4-[(2-ethoxy-acetylamino)-methyl]-benzamide	328.17	328.3
4-28 N-(2-Amino-phenyl)-4-(pent-4-enoylamino-methyl)-benzamide	324.17	324.3
4-29 N-(2-Amino-phenyl)-4-[(4-methyl-pentanoylamino)-methyl]-benzamide	340.2	340.3
4-30 N-(2-Amino-phenyl)-4-[(2-ethyl-butyrylamino)-methyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.62 (s, 1H), 8.44 (t, J = 5.8 Hz, 1H), 7.94-7.92 (m, 2H), 7.39-7.36 (m, 2H), 7.17-7.15 (m, 1H), 6.99-6.95 (m, 1H), 6.79-6.77 (m, 1H), 6.61-6.58 (m, 1H), 4.89 (s, 2H), 4.36 (d, J = 5.6 Hz, 2H), 2.11-2.01 (m, 1H), 1.55-1.33 (m, 4H), 0.81 (t, J = 7.3 Hz, 6H)	340.2	340.4

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-31 N-(2-Amino-phenyl)-4-[(2-cyclopent-2-enyl-acetylamino)-methyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.62 (s, 1H), 8.43 (t, J = 5.8 Hz, 1H), 7.95-7.92 (m, 2H), 7.37-7.35 (m, 2H), 7.17-7.15 (m, 1H), 6.99-6.95 (m, 1H), 6.79-6.77 (m, 1H), 6.62-6.58 (m, 1H), 5.76-5.66 (m, 2H), 4.89 (s, 2H), 4.34 (d, J = 5.1 Hz, 2H), 3.04-2.96 (m, 1H), 2.37-2.09 (m, 4H), 2.04-1.95 (m, 1H), 1.47-1.39 (m, 1H)	350.19	350.3
4-32 N-(2-Amino-phenyl)-4-(butyrylamino-methyl)-benzamide	310.16 [M-H]	310.3 [M-H] (AP-)
4-33 N-(2-Amino-phenyl)-4-({2-[2-(2-methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-benzamide	400.19 [M-H]	400.3 [M-H] (AP-)
4-34 4-[(2-Acetylamino-acetylamino)-methyl]-N-(2-amino-phenyl)-benzamide	341.16	341.3
4-35 N-(2-Amino-phenyl)-4-[(3-cyclopentyl-propionylamino)-methyl]-benzamide	366.22	366.3
4-36 N-(2-Amino-phenyl)-6-[(2-methoxy-acetylamino)-methyl]-nicotinamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.79 (s, 1H), 9.10 (s, 1H), 8.51 (t, J = 6.1 Hz, 1H), 8.31-8.28 (m, 1H), 7.42-7.40 (m, 1H), 7.19-7.17 (m, 1H), 7.02-6.98 (m, 1H), 6.80-6.78 (m, 1H), 6.63-6.59 (m, 1H), 4.99 (br s, 2H), 4.50 (d, J = 5.6 Hz, 2H), 3.94 (s, 2H), 3.39 (s, 3H)	315.15	315.2

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
4-37 N-(2-Amino-phenyl)-6-(pent-4-enoylamino-methyl)-nicotinamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.78 (s, 1H), 9.05 (s, 1H), 8.55 (t, J = 5.8 Hz, 1H), 8.29-8.26 (m, 1H), 7.39-7.37 (m, 1H), 7.17-7.15 (m, 1H), 7.00-6.96 (m, 1H), 6.79-6.76 (m, 1H), 6.61-6.57 (m, 1H), 5.89-5.79 (m, 1H), 5.08-4.97 (m, 2H), 4.97 (s, 2H), 4.42 (d, J = 6.1 Hz, 2H), 2.30-2.29 (m, 4H)	325.17	325.2
4-38 N-(2-Amino-phenyl)-6-[(3-cyclopentyl-propionylamino)-methyl]-nicotinamide	367.21	367.2
4-39 N-(2-Amino-phenyl)-6-[(2-cyclopent-2-enyl-acetylamino)-methyl]-nicotinamide	351.18	351.2
4-40 N-(2-Amino-phenyl)-6-[(4-methyl-pentanoylamino)-methyl]-nicotinamide	341.20	341.2
4-41 N-(2-Amino-phenyl)-6-[(3-methyl-pentanoylamino)-methyl]-nicotinamide	341.20	341.2
4-42 N-(2-Amino-phenyl)-6-[(2-cyclopentyl-acetylamino)-methyl]-nicotinamide	353.20	353.2
4-43 N-(2-Amino-phenyl)-6-[(3-cyclohexyl-propionylamino)-methyl]-nicotinamide	381.23	381.2

Example 5

5-[(3-Prop-2-ynyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide

To a solution of 15.8mg (0.288mmol) in 1ml THF were added 46.7mg (0.288mmol) 1,1'-carbonyldiimidazol. After 1h at rt 100mg (0.288mmol) {2-[(5-Aminomethyl-thiophene-2-carbonyl)-amino]-phenyl}-carbamic acid t-butyl ester were added and the reaction mixture was stirred for 1h at rt. 1.7ml trifluoroacetic acid were added and after 16h at rt sat. aqueous NaHCO3 was added carefully and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by HPLC/MS to yield 75mg (0.228mmol5-[(3-Prop-2-ynyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide; exact MW [M+H] calc'd: 329.11; MW found [M+H]: 329.3.

Example 6

In an analogous manner to that described in the example 5, and using known methods as described in the literature (e.g. in standard works such as Houben-Weyl, "Methoden der Organischen Chemie, Georg Thieme Verlag", Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York) the following compounds are prepared :

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-1 5-[3-(2-Dimethylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	362.16	362.2
6-2 5-[3-(2-Diisopropylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	418.23	418.3

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-3 5-[3-(3-Diethylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	404.21	404.3
6-4 5-[3-(3-Dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 7.80-7.79 (m, 1H), 7.31-7.25 (m, 2H), 7.18-7.07 (m, 3H), 4.56 (s, 2H), 3.18 (s, 2H), 2.99 (s, 2H), 2.94 (s, 6H), 1.10 (s, 6H)	404.21	404.3
6-5 5-[3-(3-Ethoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 7.83-7.82 (m, 1H), 7.45-7.41 (m, 4H), 7.07-7.06 (m, 1H), 4.54 (s, 2H), 3.54-3.48 (m, 4H), 3.26-3.22 (m, 2H), 1.79-1.73 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H)	377.16	377.3
6-6 5-[3-(1-Methyl-hexyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	389.2	389.3
6-7 5-(3-sec-Butyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	347.15	347.2
6-8 5-[3-(2-Methyl-butyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	361.17	361.3

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-9 5-[3-(2-Acetylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	376.14	376.3
6-10 5-{3-[3-(2-Oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	416.18	416.3
6-11 5-[3-(2-Methoxy-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	349.13	349.3
6-12 5-[(3-Allyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	331.12	331.4
6-13 5-(3-Isobutyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide ^{1}H-NMR (400 MHz, CD_3OD): δ = 7.80-7.79 (m, 1H), 7.36-7.21 (m, 4H), 7.06-7.05 (m, 1H), 4.54 (s, 2H), 2.98 (d, J = 6.6 Hz, 2H), 1.80-1.70 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H)	347.15	347.4
6-14 5-[3-(3-Butoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	405.2	405.3
6-15 5-[3-(3-Dibutylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide	460.27	460.4

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-16 4-{3-[5-(2-Amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-ureido}-butyric acid ethyl ester	405.16	405.2
6-17 N-(2-Amino-phenyl)-4-[(3-pentyl-ureido)-methyl]-benzamide	355.21	355.2
6-18 N-(2-Amino-phenyl)-4-[3-(3-diethylamino-propyl)-ureidomethyl]-benzamide	398.26	398.3
6-19 N-(2-Amino-phenyl)-4-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.63 (s, 1H), 7.95-7.93 (m, 2H), 7.38-7.36 (m, 2H), 7.18-7.16 (m, 1H), 7.00-6.96 (m, 1H), 6.80-6.78 (m, 1H), 6.62-6.59 (m, 1H), 6.47 (t, J = 5.8 Hz, 1H), 5.98 (t, J = 5.8 Hz, 1H), 4.89 (s, 2H), 4.30 (d, J = 6.1 Hz, 2H), 2.94 (d, J = 6.1, 2H), 2.23 (s, 6H), 2.07 (s, 2H), 0.81 (s, 6H)	398.26	398.3
6-20 N-(2-Amino-phenyl)-4-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-benzamide	410.22	410.2
6-21 4-[3-(2-Acetylamino-ethyl)-ureidomethyl]-N-(2-amino-phenyl)-benzamide	370.19	370.2
6-22 N-(2-Amino-phenyl)-4-(3-butyl-3-methyl-ureidomethyl)-benzamide	355.21	355.3

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-23 N-(2-Amino-phenyl)-4-[3-(2-methoxy-ethyl)-ureidomethyl]-benzamide	343.18	343.2
6-24 N-(2-Amino-phenyl)-4-[3-(3-butoxy-propyl)-ureidomethyl]-benzamide	399.24	399.3
6-25 N-(2-Amino-phenyl)-4-[3-(1-methyl-hexyl)-ureidomethyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.62 (s, 1H), 7.94-7.92 (m, 2H), 7.37-7.35 (m, 2H), 7.18-7.16 (m, 1H), 7.00-6.96 (m, 1H), 6.80-6.78 (m, 1H), 6.62-6.59 (m, 1H), 6.26 (t, J = 6.1 Hz, 1H), 5.79 (d, J = 8.1 Hz, 1H), 4.89 (s, 2H), 4.28 (d, J = 6.1 Hz, 2H), 3.65-3.55 (m, 1H), 1.35-1.26 (m, 8H), 1.02 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H)	383.24	383.3
6-26 N-(2-Amino-phenyl)-4-[3-(3-ethoxy-propyl)-ureidomethyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.62 (s, 1H), 7.94-7.92 (m, 2H), 7.37-7.35 (m, 2H), 7.18-7.16 (m, 1H), 7.00-6.96 (m, 1H), 6.80-6.78 (m, 1H), 6.62-6.59 (m, 1H), 6.42 (t, J = 5.8 Hz, 1H), 6.00 (t, J = 5.6 Hz, 1H), 4.89 (s, 2H), 4.28 (d, J = 6.1 Hz, 2H), 3.42-3.35 (m, 4H), 3.10-3.05 (m, 2H), 1.65-1.58 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H)	371.21	371.3

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-27 4-[(3-Allyl-ureido)-methyl]-N-(2-amino-phenyl)-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ= 9.63 (s, 1H), 7.95-7.93 (m, 2H), 7.38-7.36 (m, 2H), 7.19-7.17 (m, 1H), 7.00-6.96 (m, 1H), 6.80-6.78 (m, 1H), 6.63-6.59 (m, 1H), 6.49 (t, J = 6.1 Hz, 1H), 6.15 (t, J = 5.8 Hz, 1H), 5.89-5.79 (m, 1H), 5.16-5.03 (m, 2H), 4.90 (s, 2H), 4.30 (d, J = 6.1 Hz, 2H), 3.69-3.67 (m, 2H)	325.17	325.2
6-28 N-(2-Amino-phenyl)-4-[3-(3-isopropoxy-propyl)-ureidomethyl]-benzamide	385.22	385.2
6-29 N-(2-Amino-phenyl)-4-(3-cyclopropylmethyl-ureidomethyl)-benzamide	339.18	339.2
6-30 N-(2-Amino-phenyl)-4-[(3-prop-2-ynyl-ureido)-methyl]-benzamide	323.15	323.2
6-31 4-{3-[4-(2-Amino-phenylcarbamoyl)-benzyl]-ureido}-butyric acid methyl ester	385.19	385.2
6-32 N-(2-Amino-phenyl)-4-[3-(3-dibutylamino-propyl)-ureidomethyl]-benzamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.63 (s, 1H), 7.94-7.92 (m, 2H), 7.37-7.35 (m, 2H), 7.18-7.16 (m, 1H), 7.00-6.96 (m, 1H), 6.80-6.78 (m, 1H), 6.63-6.59 (m, 1H), 6.41 (t, J = 5.8 Hz, 1H), 5.98 (t, J = 5.6 Hz, 1H), 4.88 (s, 2H), 4.28 (d, J = 5.6 Hz, 2H), 3.05-3.01 (m, 2H), 2.37-2.31 (m, 6H), 1.53-1.46 (m, 2H), 1.39-1.23 (m, 8H), 0.88 (t, J = 7.1, 6H)	454.32	454.4

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-33 N-(2-Amino-phenyl)-4-[3-(2-dimethylamino-ethyl)-ureidomethyl]-benzamide	356.21	356.3
6-34 N-(2-Amino-phenyl)-4-[3-(2-diisopropylamino-ethyl)-ureidomethyl]-benzamide	412.27	412.3
6-35 N-(2-Amino-phenyl)-4-[3-(2-methyl-butyl)-ureidomethyl]-benzamide	355.21	355.3
6-36 N-(2-Amino-phenyl)-4-(3-isobutyl-ureidomethyl)-benzamide	341.2	341.2
6-37 N-(2-Amino-phenyl)-4-(3-sec-butyl-ureidomethyl)-benzamide	341.2	341.2
6-38 N-(2-Amino-phenyl)-6-[(3-pentyl-ureido)-methyl]-nicotinamide	356.21	356.2
6-39 N-(2-Amino-phenyl)-6-[3-(1-methyl-hexyl)-ureidomethyl]-nicotinamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 10.08 (s, 1H), 9.09 (s, 1H), 8.35-8.33 (m, 1H), 7.46-7.44 (m, 1H), 7.29-7.28 (m, 1H), 7.16-7.12 (m, 1H), 7.01-6.99 (m, 1H), 6.90-6.87 (m, 1H), 6.43 (br s, 1H), 6.02 (br d, J = 7.6 Hz, 1H), 4.40 (s, 2H), 3.61-3.59 (m, 1H), 1.36-1.27 (m, 8H), 1.04 (d, J = 6.57 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H)	384.24	384.2

Compound Name	exact MW [M+H] calc'd [g / mol]	MW found [M+H] [g / mol]
6-40 N-(2-Amino-phenyl)-6-[3-(3-butoxy-propyl)-ureidomethyl]-nicotinamide ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): δ = 9.86 (s, 1H), 9.07 (s, 1H), 8.32-8.29 (m, 1H), 7.43-7.41 (m, 1H), 7.21-7.19 (m, 1H), 7.06-7.01 (m, 1H), 6.86-6.84 (m, 1H), 6.70-6.66 (m, 1H), 6,56-6.53 (m, 1H), 6.18 (t, J = 5.3 Hz, 1H), 4.39 (d, J = 4.6 Hz, 2H), 3.38 (t, J = 6.3 Hz, 2H), 3.36 (t, J = 6.3 Hz, 2H), 3.11-3.06 (m, 2H), 1.66-1.59 (m, 2H), 1.53-1.45 (m, 2H), 1.38-1.29 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H)	400.23	400.2
6-41 N-(2-Amino-phenyl)-6-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-nicotinamide	411.21	411.2

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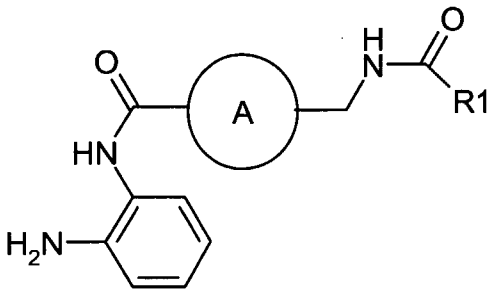
Vorbrueggen, H., and Krolikiewicz, K., Synthesis 4 (1983) 316-319

Patent Claims

1. A compound of the general formula I



I

wherein

A	represents	thiophene-diyl, phenylene or pyridine-diyl;
R^1	represents	alkyl, alkenyl, alkynyl which are all optionally substituted; or $-CH_2-(O-CH_2-CH_2-)_mO$-alkyl; $-(CH_2)_n$-O-alkyl; $-(CH_2)_n$-C(O)-NH-alkyl; $-(CH_2)_n$-NH-C(O)-alkyl; $-(CH_2)_n$-C(O)alkyl; $-(CH_2)_n$-C(O)-O-alkyl; or $-(CH_2)_n$-O-C(O)-alkyl; or

a group $-NR^3R^4$, wherein R^3 and R^4 independently represent

hydrogen;
alkyl, alkenyl or alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-(O)-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

A represents thiophene-diyl, phenylene or pyridine-diyl;
R1 is a group $-NR^3R^4$, wherein R^3 is hydrogen and R^4 is as defined in claim 1;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1, wherein

A represents thiophene-diyl, phenylene or pyridine-diyl;
R1 represents alkyl, alkenyl, alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

4. A compound according to claim 1 or 3, wherein

A represents thiophen-2,5-diyl;
R^1 represents alkenyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl; or

$-(CH_2)_n-C(O)alkyl$;

n is 1-6;

and pharmaceutically acceptable salts thereof.

5. A compound according to claim 4, wherein the compound is

5-[(2-ethoxy-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(pent-4-enoylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-acetylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-({2-[2-(2-methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(4-oxo-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide.

6. A compound according to claim 1 or 2, wherein

A represents thiophen-2,5-diyl;

R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen;
R^4 is alkenyl;
alkynyl;
$-(CH_2)_n-(O)-alkyl$;
$-(CH_2)_n-NH-C(O)-alkyl$; or
$-(CH_2)_n-C(O)-O-alkyl$;

n is 1-6;

and pharmaceutically acceptable salts thereof.

7. A compound according to claim 6 whereby the compound is

5-[3-(3-ethoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-prop-2-ynyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-acetylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-methoxy-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-allyl-ureido)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-butoxy-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
4-{3-[5-(2-amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-ureido}-butyric acid ethyl ester.

8. A compound according to claim 1 or 3, wherein

A	represents	1,4-phenylene;
R^1	represents	alkenyl;
		$-CH_2-(O-CH_2-CH_2-)_mO-CH_3$;
		$-(CH_2)_n$-O-alkyl; or
		$-(CH_2)_n$-NH-C(O)-alkyl;

n is 1-6;
m is 1-4;

and pharmaceutically acceptable salts thereof.

9. The compounds according to claim 8,

N-(2-amino-phenyl)-4-[(2-ethoxy-acetylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-(pent-4-enoylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-({2-[2-(2-methoxy-ethoxy)-ethoxy]-acetylamino}-methyl)-benzamide,
4-[(2-acetylamino-acetylamino)-methyl]-N-(2-amino-phenyl)-benzamide.

10. A compound according to claim 1 or 2, wherein

A represents 1,4-phenylene;
R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen;
R^4 is alkenyl;
alkynyl;
$-(CH_2)_n-(O)-$alkyl;
$-(CH_2)_n-NH-C(O)-$alkyl; or
$-(CH_2)_n-C(O)-O-$alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

11. The compounds according to claim 10,

4-[3-(2-acetylamino-ethyl)-ureidomethyl]-N-(2-amino-phenyl)-benzamide,
N-(2-amino-phenyl)-4-[3-(2-methoxy-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-butoxy-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-ethoxy-propyl)-ureidomethyl]-benzamide,
4-[(3-allyl-ureido)-methyl]-N-(2-amino-phenyl)-benzamide,
N-(2-amino-phenyl)-4-[3-(3-isopropoxy-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[(3-prop-2-ynyl-ureido)-methyl]-benzamide,
4-{3-[4-(2-amino-phenylcarbamoyl)-benzyl]-ureido}-butyric acid methyl ester.

12. A compound according to claim 1 or 2, wherein

A represents pyridin-2,5-diyl;

R^1 is a group $-NR^3R^4$, wherein
R^3 is hydrogen, and
R^4 is -(CH2)n-(O)-alkyl;

n is 1-6;

and pharmaceutically acceptable salts thereof.

13. The compound according to claim 12,

N-(2-amino-phenyl)-6-[3-(3-butoxy-propyl)-ureidomethyl]-nicotinamide.

14. A compound according to claim 1 or 3, wherein

A	represents	pyridin-2,5-diyl;
R^1	represents	alkenyl; or
		$-(CH_2)_n$-O-alkyl;
n	is 1-6;	

and pharmaceutically acceptable salts thereof.

15. The compounds according to claim 14,

N-(2-amino-phenyl)-6-[(2-methoxy-acetylamino)-methyl]-nicotinamide,
N-(2-amino-phenyl)-6-(pent-4-enoylamino-methyl)-nicotinamide.

16. A compound according to claim 1 or 2, wherein

A	represents	thiophen-2,5-diyl;
		pyridin-2,5-diyl; or
		1,4-phenylene;
R^1	is a group	$-NR^3R^4$, wherein
		R3 is hydrogen;
		R4 is alkyl which is unsubstituted or substituted once or several times by
		halogen;
		-NH-alkyl; or
		$-N(alkyl)_2$;

and pharmaceutically acceptable salts thereof.

17. The compounds according to claim 16,

5-[3-(2-dimethylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-diisopropylamino-ethyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-diethylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(1-methyl-hexyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(3-sec-butyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(2-methyl-butyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(3-isobutyl-ureidomethyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[3-(3-dibutylamino-propyl)-ureidomethyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-[(3-pentyl-ureido)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-diethylamino-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-dimethylamino-2,2-dimethyl-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(1-methyl-hexyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(3-dibutylamino-propyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-dimethylamino-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-diisopropylamino-ethyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-[3-(2-methyl-butyl)-ureidomethyl]-benzamide,
N-(2-amino-phenyl)-4-(3-isobutyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-4-(3-sec-butyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-6-[(3-pentyl-ureido)-methyl]-nicotinamide,
N-(2-amino-phenyl)-6-[3-(1-methyl-hexyl)-ureidomethyl]-nicotinamide.

18. A compound according to claim 1 or 3, wherein

A represents thiophen-2,5-diyl;
pyridin-2,5-diyl; or
1,4-phenylene;

R^1 represents alkyl; wherein
the alkyl group is unsubstituted or substituted once or several
times by
halogen;
-NH-alkyl; or
-N(alkyl)$_2$;

and pharmaceutically acceptable salts thereof.

19. The compounds according to claim 18,

5-[(4-methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(propionylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(butyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-(isobutyrylamino-methyl)-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2,2,3,3,3-pentafluoro-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-ethyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2,2,2-trifluoro-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(4-dimethylamino-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-methyl-butyrylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-dipropylamino-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-dimethylamino-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-methyl-pentanoylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-(propionylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-(isobutyrylamino-methyl)-benzamide,
N-(2-amino-phenyl)-4-[(4-methyl-pentanoylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[(2-ethyl-butyrylamino)-methyl]-benzamide,

N-(2-amino-phenyl)-4-(butyrylamino-methyl)-benzamide,
N-(2-Amino-phenyl)-6-[(4-methyl-pentanoylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(3-methyl-pentanoylamino)-methyl]-nicotinamide.

20. A compound according to claim 1, wherein

A	represents	thiophene-diyl, phenylene or pyridine-diyl;
R^1	represents	a group $-NR^3R^4$, wherein R^3 and R^4 independently represent
		alkyl, alkenyl or alkynyl which are all optionally substituted; or $-CH_2-(O-CH_2-CH_2-)_mO$-alkyl; $-(CH_2)_n-(O)$-alkyl; $-(CH_2)_n-C(O)-NH$-alkyl; $-(CH_2)_n-NH-C(O)$-alkyl; $-(CH_2)_n-C(O)$alkyl; $-(CH_2)_n-C(O)-O$-alkyl; or $-(CH_2)_n-O-C(O)$-alkyl;
n	is 1-6;	
m	is 1-4;	

and pharmaceutically acceptable salts thereof.

21. A compound according to claim 1 or 20, wherein

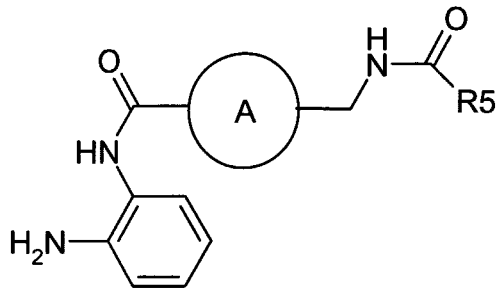
A	represents	1,4-phenylene;
R^1	is a group	$-NR^3R^4$, wherein R^3 and R^4 independently represent alkyl;

and pharmaceutically acceptable salts thereof.

22. A compound according to claim 21 whereby the compound is

N-(2-amino-phenyl)-4-(3-butyl-3-methyl-ureidomethyl)-benzamide

23. A compound of formula I-A



I-A

wherein

A	represents	thiophen-2,5-diyl;
		pyridin-2,5-diyl; or
		1,4-phenylene;
R^5	represents	$-(CH_2)_k$-cyclopropyl;
		$-(CH_2)_k$-cyclopentyl;
		$-(CH_2)_k$-cyclohexyl;
		$-(CH_2)_k$-cyclopent-2-enyl;
		$-(CH_2)_k$-(5-oxo-pyrrolidin-2-yl);
		$-(CH_2)_k$-(2-oxo-pyrrolidin-1-yl);
		$-NH-(CH_2)_k$-cyclopropyl;
		$-NH-(CH_2)_k$-cyclopentyl;
		$-NH-(CH_2)_k$-cyclohexyl;
		$-NH-(CH_2)_k$-cyclopent-2-enyl;
		$-NH-(CH_2)_k$-(5-oxo-pyrrolidin-2-yl); or
		$-NH-(CH_2)_k$-(2-oxo-pyrrolidin-1-yl);
k	is 0-6;	

and pharmaceutically acceptable salts thereof.

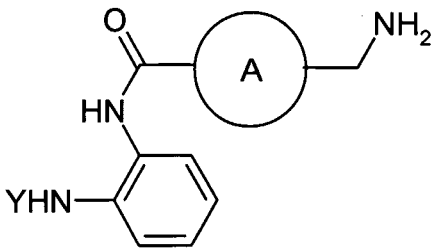
24. The compounds according to claim 23,

5-[(cyclopentanecarbonyl-amino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,

5-[(2-cyclopent-2-enyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-oxo-pyrrolidine-2-carboxylic acid [5-(2-amino-phenylcarbamoyl)-thiophen-2-ylmethyl]-amide,
5-[(3-cyclopentyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(3-cyclohexyl-propionylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-cyclopentyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-[(2-cyclopropyl-acetylamino)-methyl]-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
5-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-thiophene-2-carboxylic acid (2-amino-phenyl)-amide,
N-(2-amino-phenyl)-4-[(cyclopentanecarbonyl-amino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[(2-cyclopent-2-enyl-acetylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-[(3-cyclopentyl-propionylamino)-methyl]-benzamide,
N-(2-amino-phenyl)-4-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-benzamide,
N-(2-amino-phenyl)-4-(3-cyclopropylmethyl-ureidomethyl)-benzamide,
N-(2-amino-phenyl)-6-[(3-cyclopentyl-propionylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-{3-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-ureidomethyl}-nicotinamide,
N-(2-Amino-phenyl)-6-[(2-cyclopent-2-enyl-acetylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(2-cyclopentyl-acetylamino)-methyl]-nicotinamide,
N-(2-Amino-phenyl)-6-[(3-cyclohexyl-propionylamino)-methyl]-nicotinamide.

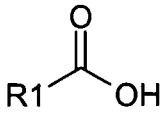
25. A process for the manufacture of a compound according to claim 1, characterized by

(a) reacting a compound of formula II



II,

wherein A has the meaning defined in claim 1 and Y represents a suitable protecting group, with a compound of the general formula III



III,

wherein

R^1 is alkyl, alkenyl, alkynyl which are all optionally substituted;

or

$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;

$-(CH_2)_n$-O-alkyl;

$-(CH_2)_n$-C(O)-NH-alkyl;

$-(CH_2)_n$-NH-C(O)-alkyl;

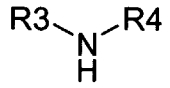
$-(CH_2)_n$-C(O)alkyl;

$-(CH_2)_n$-C(O)-O-alkyl; or

$-(CH_2)_n$-O-C(O)-alkyl;

or

reacting said compound of formula II with a compound of formula X



X,

wherein R^3 and R^4 independently represent

hydrogen;
alkyl, alkenyl, alkynyl which are all optionally substituted; or
$-CH_2-(O-CH_2-CH_2-)_mO$-alkyl;
$-(CH_2)_n$-O-alkyl;
$-(CH_2)_n$-C(O)-NH-alkyl;
$-(CH_2)_n$-NH-C(O)-alkyl;
$-(CH_2)_n$-C(O)alkyl;
$-(CH_2)_n$-C(O)-O-alkyl; or
$-(CH_2)_n$-O-C(O)-alkyl;

n is 1-6;
m is 1-4;

(b) subsequent cleavage of the protection group; and
(c) if desired, turning the product into a pharmaceutically acceptable salt by addition of a suitable acid or base.

26. A medicament containing one or more compounds according to any of the claims 1 to 24 as active ingredients together with pharmaceutically acceptable adjuvants.

27. A medicament according to claim 26 for the inhibition of tumor cell proliferation by induction of histone acetylation in said tumor cell.

28. A medicament according to claim 26 for the treatment of cancer.

29. The use of one or more compounds according to any of the claims 1 to 24 for the manufacture of medicaments for the inhibition of tumor cell proliferation by induction of histone acetylation in said tumor cell.

30. The use of one or more compounds according to any of the claims 1 to 24 for the treatment of cancer.

31. A method for inhibiting tumor cell proliferation by induction of histone acetylation in a tumor cell, due to administring to said tumor cell an effective amount of one or more compounds according to one of the claims 1 to 24.

32. A compound according to any of the claims 1 to 22, whenever prepared by a process as claimed in claim 25 or by an equivalent method.

33. The invention as hereinbefore described.