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MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG,
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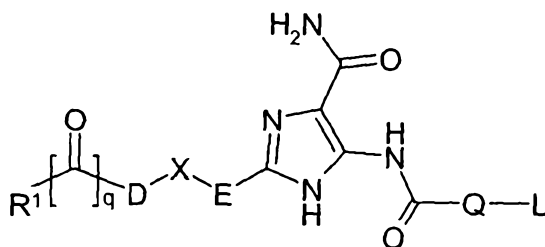
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(54) Title: IMIDAZOLE DERIVATIVES

(54) Bezeichnung: IMIDAZOLDERIVATE



(57) Abstract: The invention relates to
compounds of the formula (I), where R¹,
D, E, L, Q, X, and q have the meanings
given in Claim 1. Said compounds may
be used in the treatment of tumors.

(57) Zusammenfassung: Verbindun-
gen der Formel (I), worin R¹, D, E, L, Q,
X und q die in Anspruch 1 angegebenen
Bedeutungen haben, können und zur
Behandlung von Tumoren eingesetzt
werden.

WO 2009/046804 A1

Imidazole derivatives

BACKGROUND OF THE INVENTION

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The invention was based on the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

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The present invention relates to compounds and to the use of compounds for the treatment of diseases which are accompanied by an increase in the lysophosphatidic acid level, furthermore to pharmaceutical compositions which comprise these compounds.

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In detail, the present invention relates to compounds of the formula I, which preferably inhibit one or more enzymes which regulate and/or modulate the lysophosphatidic acid (or LPA for short) level, to compositions which comprise these compounds, and to processes for the use thereof for the treatment of diseases and complaints, such as angiogenesis, cancer, tumour formation, growth and propagation, arteriosclerosis, ocular diseases, choroidal neovascularisation and diabetic retinopathy, inflammatory diseases, arthritis, neurodegeneration, restenosis, wound healing or transplant rejection. In particular, the compounds according to the invention are suitable for the therapy or prophylaxis of cancer diseases.

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Autotaxin (ATX) is an enzyme which is responsible for the increase in the lysophosphatidic acid level in ascites and plasma (Xu et al. 1995, Clinical Cancer Research Vol. 1, page 1223 and Xu et al. 1995, Biochem. J. Vol. 309, page 933). ATX converts lysophatidylcholine (LPC) into lysophosphatidic acid (Tokumura et al. 2002, J. Biol. Chem., Vol 277, page 39436 and Umezū-Gozo et al. 2002, J. Biol. Chem., Vol. 158, page 227) LPA is an intercellular lipid mediator which influences a multiplicity of biological and

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5 biochemical processes, such as, for example, smooth muscle contraction, thrombocyte aggregation and apoptosis (Tigyi et al. 2003 Prog. Lipid Res. Vol 42 , page. 498 and Mills et al. 2003 Nat. Rev. Cancer Vol. 3, page 582 and Lynch et al. 2001 Prost. Lipid Med. Vol.64, page 33). In addition, LPA can be found in increased concentrations in plasma and ascites fluid from ovarian cancer patients in the early and late phase. LPA plays a role there in tumour cell proliferation and invasion thereof into neighbouring tissue, which can result in metastatisation (Xu et al. 1995, Clinical Cancer Research Vol. 1, page 1223 and Xu et al. 1995, Biochem. J. Vol- 309, page 933). These biological and phatobiological processes are switched on by the activation by LPA of G-protein-coupled receptors (Contos et al. 2000, Mol. Pharm. Vol 58, page. 1188).

15 For this reason, it is desirable to lower the LPA level for the treatment of tumour patients. This can be achieved by the inhibition of enzymes which are involved in LPA biosynthesis, such as, for example, autotaxin (ATX, Sano et al. 2002, J. Biol. Chem. Vol. 277 , page 21197 and Aoki et al. 2003, J. Biol. Chem. Vol. 277 page 48737). Autotaxin belongs to the enzyme family of the nucleotides pyrophosphatases and phosphodiesterases (Goding et al. 1998, Immunol. Rev. Vol. 161, page 11) and represents an important starting point in antitumour therapy (Mills et al. 2003 Nat. Rev. Cancer Vol. 3, page 582 and Goto eta l. 2004 J. Cell. Biochem. Vol. 92, page 1115) since it is expressed to an increased extent in tumours and causes tumour cell proliferation and invasion into neighbouring tissue, which can result in metastases formation (Nam et al. 2000, Oncogene, Vol. 19 page 241). In addition, autotaxin together with other angiogenetic factors causes blood vessel formation in the course of angiogenesis (Nam et al. 2001, Cancer Res. Vol. 61 page. 6938). Angiogenesis is an important process in tumour growth, which ensures supply of the tumour with nutrients. For this reason, inhibition of angiogenesis is an important starting point in cancer and tumour therapy, with which the tumour can be starved to a cer-

tain extent (Folkman, 2007, Nature Reviews Drug Discovery Vol. 6, page 273-286).

5 Surprisingly, it has been found that the compounds according to the invention cause specific inhibition of the enzyme family of the nucleotides pyrophosphatases and phosphodiesterases, in particular autotaxin. The compounds according to the invention preferably exhibit an advantageous biological activity, which can easily be detected in the test described, for
10 example, herein. In tests of this type, the compounds according to the invention preferably exhibit and cause an inhibiting effect, which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferably in the nanomolar range.

15 In general, all solid and non-solid tumours can be treated with the compounds of the formula I, such as, for example, monocytic leukaemia, brain, urogenital, lymphatic system, stomach, laryngeal, ovarian and lung carcinoma, including lung adenocarcinoma and small-cell lung carcinoma. Further examples include prostate, pancreatic and breast carcinoma.
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25 As discussed herein, effects of the compound according to the invention are relevant for various diseases. Accordingly, the compounds according to the invention are useful in the prophylaxis and/or treatment of diseases which are influenced by inhibition of one or more nucleotides pyrophosphatases and/or phosphodiesterases, in particular autotaxin.

30 The present invention therefore relates to compounds according to the invention as medicaments and/or medicament active ingredients in the treatment and/or prophylaxis of the said diseases and to the use of compounds according to the invention for the preparation of a pharmaceutical
35 agent for the treatment and/or prophylaxis of the said diseases, and also to a method for the treatment of the said diseases comprising the administra-

tion of one or more compounds according to the invention to a patient in need of such administration.

5 It can be shown that the compounds according to the invention have an advantageous action in a xenotransplant tumour model.

10 The host or patient can belong to any mammalian species, for example a primate species, in particular humans; rodents, including mice, rats and hamsters; rabbits; horses, cattle, dogs, cats, etc. Animal models are of interest for experimental investigations, where they provide a model for the treatment of a human disease.

15 The sensitivity of a certain cell to treatment with the compounds according to the invention can be determined by testing in vitro. Typically, a culture of the cell is combined with a compound according to the invention at various concentrations for a time which is sufficient to enable the active agents to induce cell death or to inhibit cell migration or to block the cellular secretion
20 of angiogenesis-promoting substances, usually between approximately one hour and one week. For testing in vitro, cultivated cells from a biopsy sample can be used. The viable cells remaining after the treatment are then counted.

25 The dose varies depending on the specific compound used, the specific disease, the patient status, etc. Typically, a therapeutic dose is sufficient to considerably reduce the undesired cell population in the target tissue, while the viability of the patient is maintained. The treatment is generally continued until a considerable reduction has occurred, for example at least about
30 a 50% reduction in the cell burden, and can be continued until essentially no undesired cells can be detected in the body.

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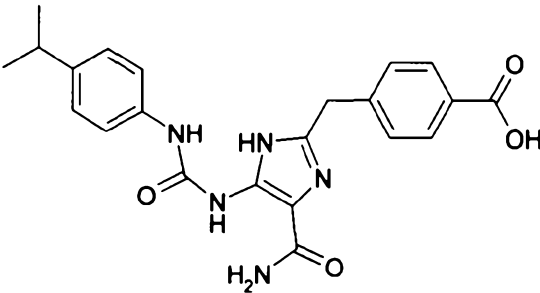
PRIOR ART

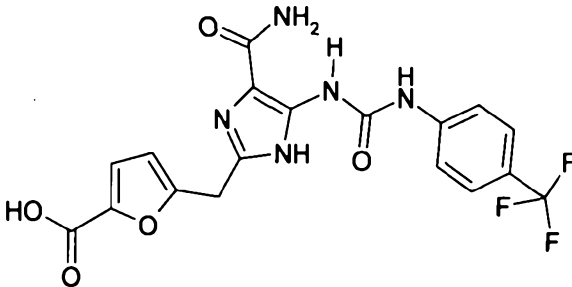
Compounds which are capable of inhibiting autotaxin are described in Peng et al. Bioorganic & Medicinal Chemistry Letters (17, 2007, page 1634-1640). The compounds described therein are lipid analogues, which do not have any structural features in common with the compounds according to the invention.

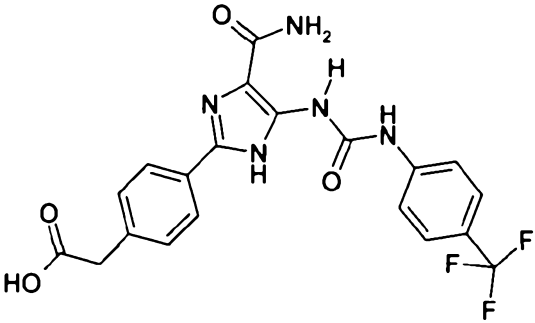
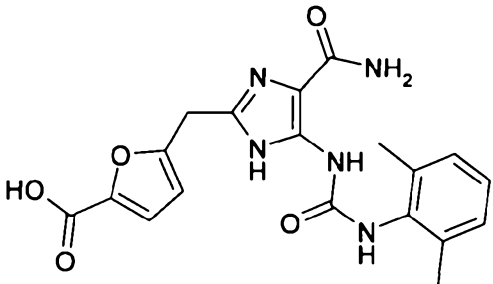
Other imidazolecarboxamides are described in FR 2889190.

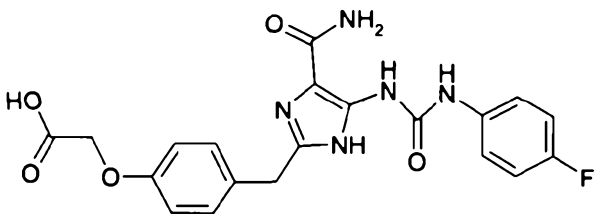
SUMMARY OF THE INVENTION

A first aspect of the invention provides a compound selected from the group consisting of:

No.	Name and/or structure
"A1"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A2"	4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid 
"A3"	4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid
"A4"	4-[4-Carbamoyl-5-(3-hexylureido)-1H-imidazol-2-ylmethyl]-benzoic acid
"A5"	4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]-benzoic acid
"A6"	4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid

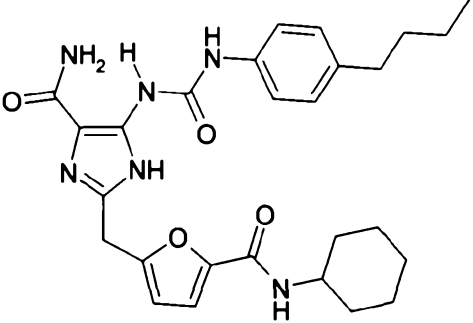
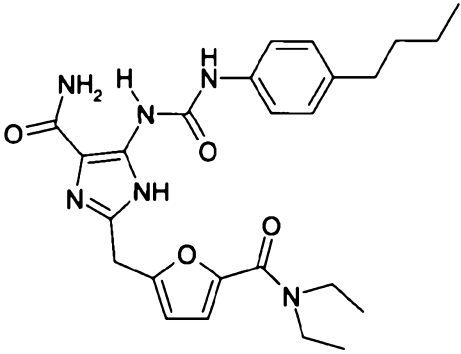
"A7"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A8"	4-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A9"	4-{5-[3-(4-Butoxyphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid
"A10"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid 
"A11"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A12"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A13"	5-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A14"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A15"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A16"	4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A17"	4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A18"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}benzoic acid
"A19"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}benzoic acid

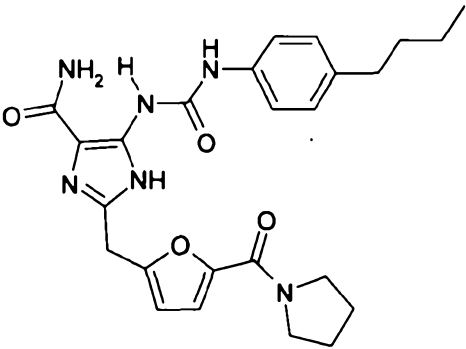
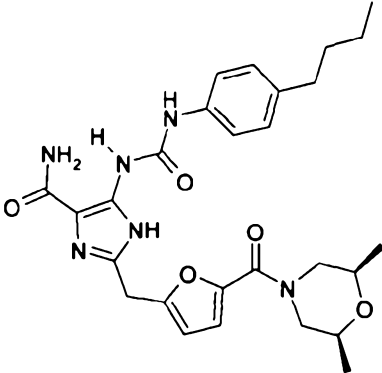
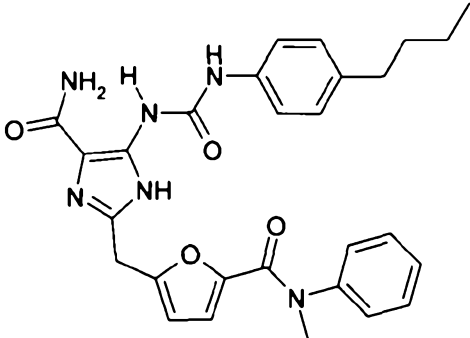
"A20"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid 
"A21"	(4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A22"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A23"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A24"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A25"	(4-{4-Carbamoyl-5-[3-(3,5-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A26"	5-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid 
"A27"	5-[4-Carbamoyl-5-(3-phenethylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid
"A28"	5-{4-Carbamoyl-5-[3-(2,6-diethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A29"	5-{4-Carbamoyl-5-[3-(4-chloro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid

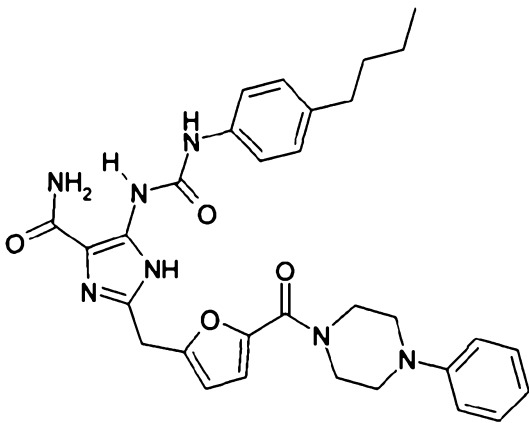
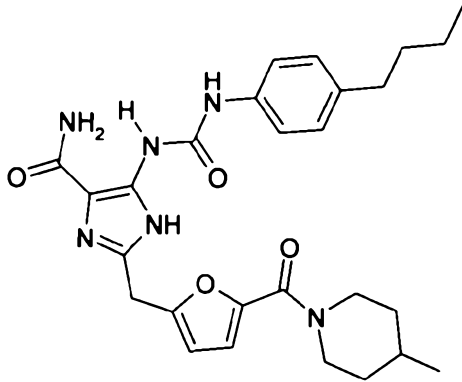
"A30"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A31"	5-{4-Carbamoyl-5-[3-(2,4,6-trimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A32"	5-{4-Carbamoyl-5-[3-(2-ethyl-6-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A33"	5-[4-Carbamoyl-5-(3-naphthalen-2-ylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid
"A34"	5-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A35"	5-{4-Carbamoyl-5-[3-(4-chloro-2-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A36"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid 
"A37"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A38"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A39"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A40"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]-phenoxy}acetic acid
"A41"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A42"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A43"	(4-{4-Carbamoyl-5-[3-(4-pentylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid

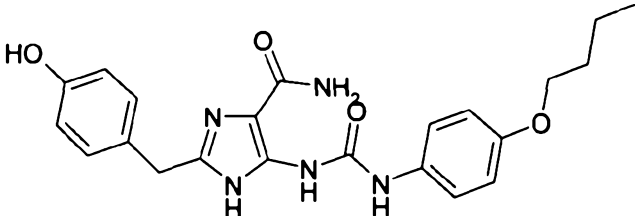
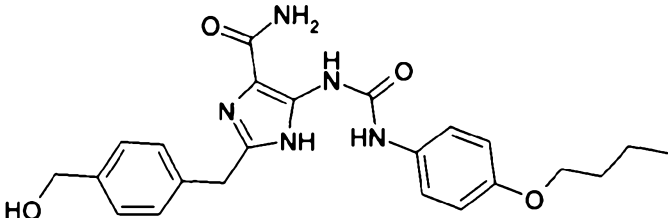
"A44"	(4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A45"	(4-{4-Carbamoyl-5-[3-(4-phenoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A46"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A47"	(4-{4-Carbamoyl-5-[3-(2-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A48"	(4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A49"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A50"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A51"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A52"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-yl}phenoxy)acetic acid
"A53"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-yl]-phenoxy}acetic acid
"A54"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
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"A58"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-yl-methoxy]phenyl}acetic acid
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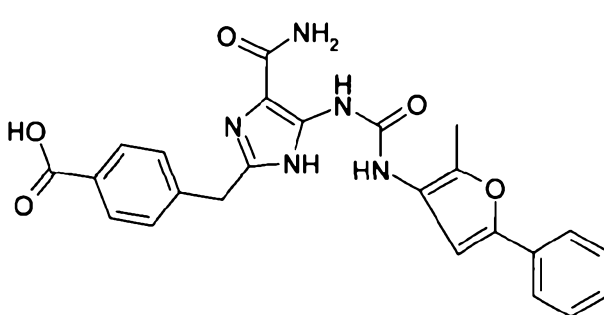
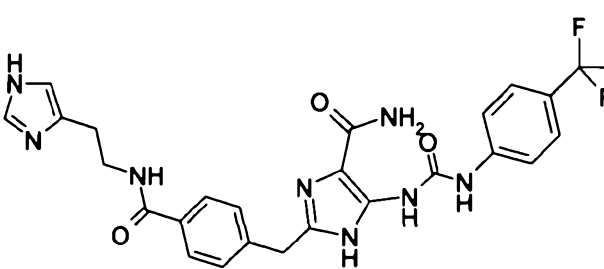
"A60"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
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"A62"	(4-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A63"	(4-{4-Carbamoyl-5-[3-(3,5-dimethoxyphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
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"A65"	5-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A66"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A67"	5-[4-Carbamoyl-5-(3-o-tolylureido)-1H-imidazol-2-ylmethyl]thiophene-2-carboxylic acid
"A68"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A69"	5-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]thiophene-2-carboxylic acid
"A70"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A71"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A72"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A73"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A74"	5-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A75"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid

"A76"	2-[4-(4-Pyridin-2-ylmethylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A77"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclohexylcarbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide 
"A78"	5-[3-(4-Butylphenyl)ureido]-2-(5-diethylcarbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide 
"A79"	2-[5-(Butylmethylcarbamoyl)furan-2-ylmethyl]-5-[3-(4-butylphenyl)ureido]-1H-imidazole-4-carboxamide
"A80"	5-[3-(4-Butylphenyl)ureido]-2-(5-dibutylcarbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide

"A81"	5-[3-(4-Butylphenyl)ureido]-2-[5-(pyrrolidine-1-carbonyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A82"	5-[3-(4-Butylphenyl)ureido]-2-[5-((5R,6S)-2,6-dimethyl-morpholine-4-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A83"	5-[3-(4-Butylphenyl)ureido]-2-[5-(morpholine-4-carbonyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A84"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylphenylcarbamoyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A85"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methylpiperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide

"A86"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-phenylpiperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
	
"A87"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methylpiperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
	
"A88"	5-[3-(4-Butylphenyl)ureido]-2-[5-(piperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A89"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclopropylcarbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide
"A90"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylpropylcarbamoyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A91"	5-[3-(4-Butylphenyl)ureido]-2-[5-[4-(2-hydroxyethyl)-piperidine-1-carbonyl]furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A92"	4-{4-Carbamoyl-5-[3-(2-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A93"	4-{4-Carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid

"A94"	5-[3-(4-Butylphenyl)ureido]-2-[4-(morpholine-4-carbonyl)-benzyl]-1H-imidazole-4-carboxamide
"A95"	5-[3-(4-Butoxyphenyl)ureido]-2-(4-hydroxybenzyl)-1H-imidazole-4-carboxamides 
"A96"	2-(4-Nitrobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A97"	from "A96" by reduction using Fe powder /NH₄Cl: 2-(4-aminobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A98"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate
"A99"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate
"A100"	from methyl 4-{4-carbamoyl-5-[3-(4-butoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate by reduction using DIBALH: 5-[3-(4-butoxyphenyl)ureido]-2-(4-hydroxymethylbenzyl)-1H-imidazole-4-carboxamide 

"A101"	4-[4-Carbamoyl-5-[3-(2-methyl-5-phenylfuran-3-yl)ureido]-1H-imidazol-2-ylmethyl]benzoic acid 
"A102"	4-[4-Carbamoyl-5-(3-thiophen-2-ylureido)-1H-imidazol-2-ylmethyl]benzoic acid
"A103"	2-[4-[2-(1H-imidazol-4-yl)ethylcarbamoyl]benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide 

"B1"	2-(4-Acetylbenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide,
"B2"	2-[4-(3,5-Dimethylpyrazole-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide,
"B3"	5-[3-(4-Butylphenyl)ureido]-2-(4-guanidinocarbonylbenzyl)-1H-imidazole-4-carboxamide,
"B4"	5-[3-(4-Isopropylphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4-carboxamide,
"B5"	2-(4-Methoxybenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic carboxamide,

"B6"	2-(4-Methoxybenzyl)-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B7"	3-{3-[5-Carbamoyl-2-(4-methoxybenzyl)-3H-imidazol-4-yl]-ureido} benzoic acid ester,
"B8"	2-Benzo-1,3-dioxol-5-ylmethyl-5-(3-benzo-1,3-dioxol-5-yl-ureido)-1H-imidazole-4- carboxamide,
"B9"	5-(3-Benzo-1,3-dioxol-5-ylureido)-2-[4-(4-methylpiperazine-1-carbonyl)benzyl]-1H-imidazole-4- carboxamide,
"B10"	5-[3-(4-Isopropylphenyl)ureido]-2-{4-[2-(4-methylpiperazin-1-yl)-2-oxoethoxy]benzyl}-1H-imidazole-4 carboxamide,
"B11"	{4-[5-(3-Benzo-1,3-dioxol-5-ylureido)-4-carbamoyl-1H-imidazol-2-ylmethyl]phenoxy}acetic acid,
"B12"	2-(4-Methanesulfonylbenzyl)-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4- carboxamide,
"B13"	5-[3-(4-Butylphenyl)ureido]-2-(4-methanesulfonylbenzyl)-1H-imidazole-4- carboxamide
"B14"	2-[4-(5-Methylthiazol-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B15"	2-[4-(Pyridin-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,

"B16"	[3-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoylamino)-5-methylpyrazol-1-yl] acetic acid,
"B17"	2-(4-Iodobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B18"	5-[3-(4-Butoxyphenyl)ureido]-2-(4-methylsulfanylbenzyl)-1H-imidazole-4-carboxamide,
"B19"	(4-{4-Carbamoyl-5-[3-(2,7a-dihydrobenzofuran-5-yl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B20"	({4-[5-(3-Benzo[b]thiophen-5-ylureido)-4-carbamoyl-1H-imidazol-2-ylmethyl]phenoxy} acetic acid,
"B21"	5-[3-(2-Fluoro-5-trifluoromethylphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4- carboxamide,
"B22"	5-[3-(3-Chlorophenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4- carboxamide,
"B23"	5-[3-(3-Chloro-4-methoxyphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4-carboxamide,
"B24"	4-{4-Carbamoyl-5-[3-(3-chloro-4-methoxyphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B25"	(4-{4-Carbamoyl-5-[3-(2,3-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,

"B26"	(4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B27"	Benzotriazol-1-yl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoate,
"B28"	2-[4-(4-Pyridin-2-ylmethylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B29"	2-[4-(Morpholine-4-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B30"	2-[4-[(Pyridin-2-ylmethyl)carbamoyl]benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B31"	4-{5-[3-(4-tert-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl} benzoic acid,
"B32"	4-{4-Carbamoyl-5-[3-(2-fluoro-5-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B33"	4-{4-Carbamoyl-5-[3-(3-chloro-4-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B34"	2-[4-(2-Pyridin-3-ylacetyl amino)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B35"	2-[4-(2-1H-Imidazol-4-ylacetyl amino)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,

"B36"	Ethyl (4-{4-carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetate,
"B37"	2-[4-(4-Methylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B38"	2-[4-(1-Pyridin-2-ylmethyl-1H-pyrazol-3-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide,
"B39"	N-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenyl)isonicotinamide,
"B40"	4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B41"	(4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B42"	(4-{4-Carbamoyl-5-[3-(5-isopropyl-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B43"	4-{4-Carbamoyl-5-[3-(5-isopropyl-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B44"	(4-{4-Carbamoyl-5-[3-(4-isopropyl-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B45"	4-{4-Carbamoyl-5-[3-(4-isopropyl-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,

"B46"	(4-{4-Carbamoyl-5-[3-(3-dimethylaminophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B47"	4-{4-Carbamoyl-5-[3-(3-dimethylaminophenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B48"	(4-{4-Carbamoyl-5-[3-(3-methylcarbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B49"	4-{4-Carbamoyl-5-[3-(3-methylcarbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B50"	2-[4-(1H-Imidazol-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B51"	(4-{4-Carbamoyl-5-[3-(3,4-dichlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B52"	(4-{4-Carbamoyl-5-[2-(4-chlorophenyl)acetyl amino]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B53"	2-(4-Hydroxycarbamoylbenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B54"	2-[4-(Hydroxymethylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B55"	(4-{4-Carbamoyl-5-[3-(4-nitrophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid
"B56"	(4-{4-Carbamoyl-5-[3-(4-cyanophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,

"B57"	(4-{4-Carbamoyl-5-[3-(2,4-dichlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B58"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}butyric acid,
"B59"	(4-{4-Carbamoyl-5-[3-(4-carbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B60"	3-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}propionic acid,
"B61"	Methyl {2-[3-(1H-benzotriazol-5-ylcarbamoyl)propyl]-5-carbamoyl-3H-imidazol-4-yl}carbamate,
"B62"	2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B63"	Methyl {2-[2-(1H-benzotriazol-5-ylcarbamoyl)ethyl]-5-carbamoyl-3H-imidazol-4-yl}carbamate,
"B64"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylsulfanylphenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B65"	2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-chlorophenyl)ureido]-1H-imidazole-4- carboxylic acid,
"B66"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-trifluoromethyl-1H-benzimidazol-5-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid,

"B67"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(1H-indazol-5-yl-carbamoyl)propyl]-1H-imidazole-4-carboxylic acid,
"B68"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-oxo-2,3-dihydrobenz-oxazol-6-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid,
"B69"	2-[4-[(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)-methoxy]benzyl]-5-[3-(4-trifluoromethylsulfanylphenyl)-ureido]-1H-imidazole-4-carboxylic acid,
"B70"	2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B71"	2-[3-(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B72"	2-[3-(1H-Indazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B73"	2-[3-(2-Trifluoromethyl-1H-benzimidazol-5-ylcarbamoyl)-propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B74"	2-[2-(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B75"	4-[4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl]-2,2-dimethylbutyric acid,

"B76"	2-(3-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)-2-methylpropionic acid,
"B77"	5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-1H-imidazole-4- carboxamide,
"B78"	5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-1H-imidazole-4- carboxamide,
"B79"	5-[3-(4-Chlorophenyl)ureido]-2-[2-(2-oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)ethyl]-1H-imidazole-4-carboxamide,
"B80"	2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-chlorophenyl)ureido]-1H-imidazole-4-carboxamide,
"B81"	[4-(5-Benzyloxycarbonylamino-4-carbamoyl-1H-imidazol-2-ylmethyl)phenoxy]acetic acid or
"B82"	[4-(4-Carbamoyl-5-{[5-(4-chlorophenyl)-2H-pyrazole-3-carbonyl]amino}-1H-imidazol-2-ylmethyl)phenoxy] acetic acid

and pharmaceutically usable tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

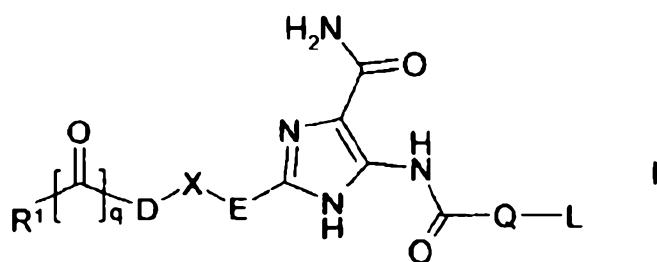
A second aspect of the invention provides a medicament comprising at least one compound as defined in the first aspect and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

A third aspect of the invention provides use of a compound as defined in the first aspect for the preparation of a medicament for the treatment or prophylaxis of cancer.

A fourth aspect of the invention provides use of a compound as defined in the first aspect and/or physiologically acceptable salts thereof, for the preparation of a medicament for the treatment of a tumour, wherein a therapeutically effective amount of the compound as defined in the first aspect is administered in combination with radiotherapy and a compound selected from the group consisting of: 1) an oestrogen receptor modulator, 2) an androgen receptor modulator, 3) a retinoid receptor modulator, 4) a cytotoxic agent, 5) an antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) a HMG-CoA reductase inhibitor, 8) a HIV protease inhibitor, 9) a reverse transcriptase inhibitor and 10) other angiogenesis inhibitors.

A fifth aspect of the invention provides a method for the treatment of a tumour in a subject in need thereof, the method comprising administration to the subject of a therapeutically effective amount of a compound as defined in the first aspect and/or physiologically acceptable salts thereof, or a composition as defined in the second aspect, in combination with radiotherapy and a compound selected from the group consisting of: 1) an oestrogen receptor modulator, 2) an androgen receptor modulator, 3) a retinoid receptor modulator, 4) a cytotoxic agent, 5) an antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) a HMG-CoA reductase inhibitor, 8) a HIV protease inhibitor, 9) a reverse transcriptase inhibitor and 10) other angiogenesis inhibitors.

Disclosed herein are compounds of the formula I



in which

- R¹** denotes OH, OA, N(R²)₂, Ar³ or (CR₂)_nHet,
- D** is absent or denotes Alk, OAlk, O, S or NR²,
- E** is absent or denotes Alk, OAlk, O, S or NR²,
- Q** denotes Alk, OCH₂, NR(CR₂)_n or O,
- Alk** denotes unbranched or branched alkylene having 1, 2, 3 or 4 C atoms, in which 1-5 H atoms may be replaced by F and/or Cl,
- L** denotes A, Ar¹ or Het¹,
- X** denotes Alk, Ar-diyl or Het-diyl,
- R²** denotes H, A, (CR₂)_nAr or (CR₂)_nHet,
- Ar¹** denotes phenyl, indanyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasub-

- stituted by Hal, NO₂, CN, A, (CH₂)_nAr, (CH₂)_nCOOA,
 (CH₂)_nCOOAr, (CH₂)_mCOOHet, (CH₂)_nCON(R²)₂,
 (CH₂)_nCOR², (CH₂)_nN(R²)₂, (CH₂)_nSO_mA, (CH₂)_nSO_mAr,
 (CH₂)_nSO_mHet, (CH₂)_nC(R³)₂(CH₂)_nN(R²)₂,
 (CH₂)_nNR²SO_mR², (CH₂)_nSO_mNRR², (CH₂)_nNR²SO_mNRR²,
 (CH₂)_nOR², O(CH₂)_pHet, NRCOR², NRSO_mR²,
 (CH₂)_nSO_mN(R²)₂, O(CH₂)_pNR₂, O(CH₂)_nCR₂(CH₂)_nN(R²)₂,
 NR(CH₂)_nCR₂(CH₂)_nN(R²)₂, O(CH₂)_pNR²SO_mA,
 O(CH₂)_pNR²SO_mAr, O(CH₂)_pNR²SO_mNRR², O(CH₂)_pSO_mA,
 O(CH₂)_pSO_mAr and/or O(CH₂)_nSO_mNRR²,
- A³ denotes phenyl which is substituted by COA, OCR₂COOH,
 (CH₂)_nCR₂COOH, (CH₂)_nHet³, O(CH₂)_pCONHHet³,
 (CH₂)_nCONHHet³, CONROH, NHCO(CH₂)_nHet³, COOHet³,
 (CH₂)_nCOOH, (CH₂)_nCOOA, CONH(CH₂)_nHet³, S(O)_mA,
 Hal, COHet³, O(CH₂)_pCOHet³, O(CH₂)_pCOOH,
 O(CH₂)_pCOOA, OA or CONHC(=NH)NH₂,
- R³ denotes unbranched or branched alkyl having 1-6 C atoms,
 Het¹ denotes a mono-, bi- or tricyclic saturated, unsaturated or
 aromatic heterocycle having 1 to 4 N, O and/or S atoms,
 which may be unsubstituted or mono-, di- or trisubstituted
 by Hal, NO₂, CN, A, (CH₂)_nAr, (CH₂)_nCOOA, (CH₂)_nCOOAr,
 (CH₂)_mCOOHet, (CH₂)_nCON(R²)₂, (CH₂)_nCOR²,
 (CH₂)_nN(R²)₂, (CH₂)_nSO_mA, (CH₂)_nSO_mAr, (CH₂)_nSO_mHet,
 (CH₂)_nC(R³)₂(CH₂)_nN(R²)₂, (CH₂)_nNR²SO_mR²,
 (CH₂)_nSO_mNRR², (CH₂)_nNR²SO_mNRR², (CH₂)_nOR²,
 O(CH₂)_nHet, NRCOR², NRSO_mR², (CH₂)_nSO_mN(R²)₂,
 O(CH₂)_pNR₂, O(CH₂)_nCR₂(CH₂)_nN(R²)₂,
 NR(CH₂)_nCR₂(CH₂)_nN(R²)₂, O(CH₂)_pNR²SO_mA,
 O(CH₂)_pNR²SO_mAr, O(CH₂)_pNR²SO_mNRR², O(CH₂)_pSO_mA,
 O(CH₂)_pSO_mAr, O(CH₂)_nSO_mNRR², =O (carbonyl oxygen),
 =NR and/or =S,

	R	denotes H or unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 C atoms,
5	Ar	denotes phenyl, indanyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, $(CR_2)_nOR$, $O(CR_2)_nAr^2$, $(CR_2)_nNR_2$, SR, NO_2 , CN, COOR, $CONR_2$, $NRCOA$, $NRSO_2A$, SO_2NR_2 , $S(O)_m A$, CO-Het, $(CR_2)_nHet$, $O(CR_2)_nNR_2$, $O(CR_2)_nHet$, $NHCOOA$, $NHCONR_2$, $NHCOO(CR_2)_nNR_2$, $NHCOO(CR_2)_n$ -
10		Het, $CR=CAR^2$, SO_2Het , $NHCONH(CR_2)_nNR_2$, $NHCONH(CR_2)_nHet$, $CONH(CR_2)_nNR_2$, $CONH(CR_2)_nHet$, $CONR(CR_2)_nNR_2$, $CONR(CR_2)_nHet$ and/or COA,
15	Het	denotes a mono-, bi- or tricyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by Hal, A, Ar^2 , $O(CR_2)_nAr^2$, $(CR_2)_nOR$, $(CR_2)_nNR_2$, SR, NO_2 , CN, COOR, $CONR_2$, $NRCOA$, $NRSO_2A$, SO_2NR_2 , $S(O)_q A$, CO-Het ² , $(CR_2)_nHet^2$, $O(CR_2)_nNR_2$, $O(CR_2)_nHet^2$, $NHCOOA$, $NHCONR_2$, $NHCOO(CR_2)_nNR_2$, $NHCOO(CR_2)_nHet^2$, $NHCONH(CR_2)_nNR_2$, $NHCONH(CR_2)_nHet^2$, $OCONH(CR_2)_nNR_2$, $OCONH(CR_2)_nHet^2$, CO-Het ² , CHO, COA, =S, =NH, =NA and/or =O (carbonyl oxygen),
20		
25	Het ²	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),
30	Het ³	denotes a pyrazolyl which is unsubstituted or mono- di- or trisubstituted by A, CH_2COOH , CH_2Het^4 and/or =O,
	Het ⁴	denotes a monocyclic aromatic heterocycle having 1 to 4 N, O, and/or S atoms,
35	Ar ²	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, CN, A and/or $(CR_2)_nOR$,

- 5 A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by OR, CN, NR₂, F and/or Cl and/or in which one or two non-adjacent CH₂ groups may be replaced by O, NH, S, SO, SO₂ and/or by CH=CH groups,
or
cyclic alkyl having 3-7 C atoms,
- 10 m denotes 0, 1 or 2,
n denotes 0, 1, 2, 3, 4, 5, 6, 7 or 8,
p denotes 1, 2, 3, 4, 5 or 6,
q denotes 0 or 1,
Hal denotes F, Cl, Br or I,
- 15 and pharmaceutically usable, tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

20 The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

25 The compounds of the formula I are also taken to mean the solvates and derivatives.

30 Pharmaceutically usable derivatives are taken to mean, for example, the salts of the compounds according to the invention and also so-called pro-drug compounds.

35 Prodrug derivatives are taken to mean compounds of the formula I which have been modified by means of, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to form the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

5 The expression "effective amount" denotes the amount of a medicament or of a pharmaceutical active ingredient which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

10 In addition, the expression "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence:
improved treatment, healing, prevention or elimination of a disease, syn-
15 drome, condition, complaint, disorder or side effects or also the reduction in the advance of a disease, complaint or disorder.

The expression "therapeutically effective amount" also encompasses the amounts which are effective for increasing normal physiological function.

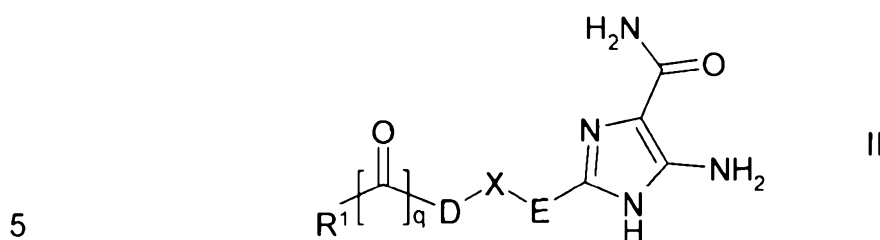
20 The invention also relates to the use of mixtures of the compounds of the formula I, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

25 These are particularly preferably mixtures of stereoisomeric compounds.

The invention relates to the compounds of the formula I and salts thereof and to a process for the preparation of compounds of the formula I according to the patent claims and pharmaceutically usable salts, and stereoisomers thereof, characterised in that

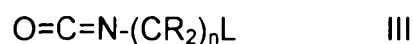
30 a) for the preparation of compounds of the formula I
in which Q denotes $\text{NH}(\text{CR}_2)_n$.

35 a compound of the formula II



in which R^1 , q , D , E and X have the meanings indicated in Claim 1,

10 is reacted with a compound of the formula III



in which

15 R^2 , n and L have the meanings indicated in Claim 1,

or

- 20 b) a radical R^1 is converted into another radical R^1 by
- i) reacting a carboxylic acid derivative with an amine derivative to give an amide,
 - ii) hydrolysing an ester,
- 25 and/or a base or acid of the formula I is converted into one of its salts.

A denotes alkyl and is preferably unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms. Alkyl preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, further preferably, for

35 example, trifluoromethyl.

Alkyl very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl. Alkyl also denotes cycloalkyl.

Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Alk preferably denotes unbranched or branched alkylene having 1, 2, 3 or 4 C atoms, particularly preferably methylene, ethylene, propylene or butylene.

R^1 preferably denotes OH, OA, NH_2 , NHA, NA_2 , NHA_{Ar}, NAA_{Ar} or Het, where

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or $(CR_2)_nOR$,

Het denotes piperidiny, piperaziny, pyrrolidiny, morpholiny, furyl, thienyl, pyrroly, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, Ar^2 , $(CR_2)_nHet^2$ and/or $(CR_2)_nOR$,

A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-7 C atoms,

R denotes H or unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 C atoms,

Ar^2 denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, CN, A and/or $(CR_2)_nOR$,

Het^2 denotes piperidiny, piperaziny, pyrrolidiny, morpholiny, furyl, thienyl, pyrroly, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl, each of which is unsubstituted

or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

n denotes 0, 1, 2, 3 or 4.

R¹ very particularly preferably denotes OH.

R³ preferably denotes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl or hexyl; particularly preferably methyl, ethyl, propyl, isopropyl or butyl.

D preferably denotes Alk, OAlk or is absent; particularly preferably methylene, ethylene, OCH₂, OCH₂CH₂ or is absent.

E preferably denotes Alk, OAlk or is absent; particularly preferably methylene, ethylene, OCH₂, OCH₂CH₂ or is absent.

X preferably denotes Alk, Ar-diyl or Het-diyl,
where

Alk denotes methylene, ethylene, propylene or butylene,

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or (CR₂)_nOR,

Het denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl benzo-1,3-dioxolyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, Ar², (CR₂)_nHet² and/or (CR₂)_nOR,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl,
or

cyclic alkyl having 3-7 C atoms,

R denotes H or unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 C atoms,

Ar² denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, CN, A and/or (CR₂)_nOR,

Het² denotes piperidiny, piperaziny, pyrrolidiny, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thia-
diazolyl, pyridazinyl benzo-1,3- dioxolyl, 2,7a-dihydro-benzofuranyl, benzo[b]thiophenyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

Het³ denotes pyrazolyl, benzo-1,3-dioxolyl, piperaziny, thiazolyl, pyridinyl, benzotriazolyl, morpholinyl, imidazolyl, benzimidazolyl, indazolyl, 2,3-dihydrobenzoxazolyl or 1,3-dihydroisoindolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, CH₂COOH, CH₂Het⁴ and/or =O,

Het⁴ denotes pyrazolyl, benzo-1,3-dioxolyl, piperaziny, thiazolyl, pyridinyl, benzotriazolyl, morpholinyl, imidazolyl, benzimidazolyl, indazolyl, 2,3-dihydrobenzoxazolyl or 1,3-dihydroisoindolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, CH₂COOH, CH₂Het⁴ and/or =O

n denotes 0, 1, 2, 3 or 4.

X very particularly preferably denotes 1,4-phenylene, 2,5-furandiyl or 2,5-thiophenediyl.

Q preferably denotes Alk or NR(CR₂)_n, particularly preferably NH, CH₂, CH₂CH₂, N(CH₃)CH₂, NHCH₂ or NHCH₂CH₂.

L preferably denotes A, Ar¹ or Het¹, where

Ar¹ denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, and/or (CH₂)_nOR²,

Het¹ denotes a mono- or bicyclic, unsaturated aromatic heterocycle having 1 to 4

N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A and/or (CH₂)_nAr,

5

R² denotes H, A or phenyl,

Ar denotes phenyl,

n denotes 0, 1 or 2.

10

L particularly preferably denotes A, Ar¹ or Het¹, where

Ar¹ denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, and/or (CH₂)_nOR²,

15

Het¹ denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, benzo-1,3-dioxolyl, 2,7a-dihydrobenzofuranyl, benzo[b]thiophenyl or tetrazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A and/or (CH₂)_nAr,

20

R² denotes H, A or phenyl,

Ar denotes phenyl,

n denotes 0, 1 or 2.

25

L very particularly preferably denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, OA and/or phenoxy,

or

30

furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl or tetrazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A and/or phenyl.

35

Ar¹ preferably denotes phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or

p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl, 2,5-dimethyl-4-chlorophenyl, naphthyl or biphenyl.

Ar¹ furthermore preferably denotes phenyl, indanyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, NO₂, CN, A, (CH₂)_nAr, (CH₂)_nCOOA, (CH₂)_nCOOAr, (CH₂)_mCOOHet, (CH₂)_nCON(R²)₂, (CH₂)_nCOR², (CH₂)_nN(R²)₂, (CH₂)_nSO_mA, (CH₂)_nSO_mAr, (CH₂)_nSO_mHet, (CH₂)_nC(R³)₂(CH₂)_nN(R²)₂, (CH₂)_nNR²SO_mR², (CH₂)_nSO_mNRR², (CH₂)_nNR²SO_mNRR², (CH₂)_nOR², O(CH₂)_pHet, NRCOR², NRSO_mR², (CH₂)_nSO_mN(R²)₂, O(CH₂)_pNR₂, O(CH₂)_nCR₂(CH₂)_nN(R²)₂, NR(CH₂)_nCR₂(CH₂)_nN(R²)₂, O(CH₂)_pNR²SO_mA, O(CH₂)_pNR²SO_mAr, O(CH₂)_pNR²SO_mNRR², O(CH₂)_pSO_mA, O(CH₂)_pSO_mAr and/or O(CH₂)_nSO_mNRR²,

where

n denotes 0, 1, 2, 3 or 4,

m denotes 0, 1 or 2,

p denotes 1, 2, 3 or 4,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl,
or

cyclic alkyl having 3-7 C atoms,

R denotes H, methyl or ethyl,

R² denotes H, A or phenyl.

Ar¹ very particularly preferably denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A, and/or (CH₂)_nOR², where

n denotes 0, 1, 2, 3 or 4,

A denotes unbranched or branched alkyl having 1-6 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl,
or

cyclic alkyl having 3-7 C atoms,

R denotes H, methyl or ethyl,

R² denotes H, A or phenyl.

Ar preferably denotes phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-,

3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-,
5 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro- or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylamino-phenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl,
10 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl, 2,5-dimethyl-4-chlorophenyl, naphthyl or biphenyl.

15 Ar furthermore preferably denotes phenyl, naphthyl or biphenyl substituted phenyl, indanyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or $(CR_2)_nOR$.

20 Ar² preferably denotes phenyl, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, further preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,5- or 3,4-dimethoxyphenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl,
25 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 2,5-dimethyl-4-chlorophenyl.

35 Irrespective of further substitutions, Het¹ denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-

pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-,
4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore
preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-
5 tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thia-
diazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3-
or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl,
indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl,
2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-,
10 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-
benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7-
or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quin-
azolinyl, 5- or 6-quinoxalyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl,
15 further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzo-
thiadiazol-4- -5-yl, 2,1,3-benzoxadiazol-5-yl or dibenzofuranyl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Irrespective of further substitutions, Het can thus also denote, for example,
20 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetra-
hydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-di-
hydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl,
1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-,
-3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-,
25 -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3-
or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-
dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl,
hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetra-
30 hydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-,
-4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-
benzo-1,4-oxazinyl, further preferably 2,3-methylenedioxyphenyl, 3,4-
methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl,
3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-
35 (2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6-
or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-

oxofuranyl, 3,4-dihydro-2-oxo-1*H*-quinazolinyl, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydrobenzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydro-indole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

5 Het¹ furthermore preferably denotes a monocyclic aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A and/or (CH₂)_nAr.
Het¹ particularly preferably denotes furyl, thienyl, pyrrolyl, imidazolyl, pyra-
10 zolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, benzo-1,3- dioxolyl, 2,7a-dihydrobenzofuranyl, benzo[b]thiophenyl or tetra-
zolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A and/or (CH₂)_nAr.

15 Irrespective of further substitutions, Het denotes, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-,
20 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thia-
diazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3-
25 or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, indazolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7- benzisoxazolyl, 2-, 4-, 5-,
6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-
30 benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quin-
azolinyl, 5- or 6-quinoxalyl, 2-, 3-, 5-, 6-, 7- or 8-2*H*-benzo-1,4-oxazinyl, further preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzo-
thiadiazol-4- -5-yl, 2,1,3-benzoxadiazol-5-yl or dibenzofuranyl.

35 The heterocyclic radicals may also be partially or fully hydrogenated.
Irrespective of further substitutions, Het can thus also denote, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or 5-furyl, tetra-

hydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8- 3,4-dihydro-2H-benzo-1,4-oxazinyl, further preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or 6-yl, 2,3-(2-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxofuranyl, 3,4-dihydro-2-oxo-1H-quinazoliny, 2,3-dihydrobenzoxazolyl, 2-oxo-2,3-dihydrobenzoxazolyl, 2,3-dihydrobenzimidazolyl, 1,3-dihydro-indole, 2-oxo-1,3-dihydroindole or 2-oxo-2,3-dihydrobenzimidazolyl.

Het furthermore preferably denotes a mono- or bicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, Ar², (CR₂)_nHet² and/or (CR₂)_nOR.

Het very particularly preferably denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, Ar², (CR₂)_nHet² and/or (CR₂)_nOR.

Het² preferably denotes, for example piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl,

thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen).

5 Hal preferably denotes F, Cl or Br, but also I, particularly preferably F or Cl.

The indices have the following preferred meanings

m 1, 2, 3 or 4,
10 n 0, 1, 2, 3, 4, 5 or 6,
p 1, 2, 3 or 4.

Throughout the invention, all radicals which occur more than once, such as,
15 for example, R, may be identical or different, i.e. are independent of one another.

The compounds of the formula I may have one or more chiral centres and can therefore occur in various stereoisomeric forms. The formula I encompasses all these forms.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above.

25 Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Ip, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated for the formula I, but in which
30

in Ia D is absent or denotes Alk or OAlk;

35 in Ib E is absent or denotes Alk or OAlk;

in Ic Q denotes O, Alk or $\text{NR}(\text{CR}_2)_n$;

- in Id Alk denotes unbranched or branched alkylene having 1, 2, 3 or 4 C atoms;
- 5 in Ie Ar¹ denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, NO₂, A, (CH₂)_nCOOA and/or (CH₂)_nOR²;
- 10 in If Het¹ denotes a mono- or bicyclic unsaturated aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A and/or (CH₂)_nAr;
- 15 in Ig Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or (CR₂)_nOR;
- 20 in Ih R denotes H, methyl or ethyl;
- in Ii R denotes H;
- 25 in Ij Het denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, Ar², (CR₂)_nHet² and/or (CR₂)_nOR;
- 30 in Ik Het¹ denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl benzo-1,3- dioxolyl, 2,7a-dihydrobenzofuranyl, benzo[b]thiophenyl or tetrazolyl, each of which is unsubstituted or mono-,
- 35 di- or trisubstituted by A and/or (CH₂)_nAr;

in II Het denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, benzo-1,3-dioxolyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, Ar², (CR₂)_nHet² and/or (CR₂)_nOR;

in Im Het³ denote pyrazolyl, benzo-1,3-dioxolyl, piperazinyl, thiazolyl, pyridinyl, benzotriazolyl, morpholinyl, imidazolyl, benzimidazolyl, indazolyl, 2,3-dihydrobenzoxazolyl or 1,3-dihydroisindolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, CH₂COOH, CH₂Het⁴ and/or =O,

in In Het⁴ denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

in Io A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-7 C atoms;

in Ip Ar¹ denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, NO₂, A, (CH₂)_nCOOA, OAr and/or OA;

in Iq R¹ denotes OH, Ar³, OA, NH₂, NHA, NA₂, NHA_r, NAA_r or Het;

R¹ denotes OH, OA, NH₂, NHA, NA₂, NHA_r, NA, Ar, Ar³ or Het,
D is absent or denotes Alk or OAlk,

	E	is absent or denotes Alk or OAlk,
	Q	denotes O, Alk, OCH ₂ or NR(CR ₂) _n ,
	Alk	denotes unbranched or branched alkylene having 1, 2, 3 or
5		4 C atoms,
	L	denotes A, Ar ¹ or Het ¹ ,
	X	denotes Alk, Ar-diyl or Het-diyl,
	R ²	denotes H, A, Ar ³ (CR ₂) _n Ar or (CR ₂) _n Het,
10	Ar ¹	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, NO ₂ , A, (CH ₂) _n COOA, CN, (CH ₂) _n N(R ²) ₂ , (CH ₂) _n SO _m A, (CH ₂) _n CON(R ²) ₂ , and/or (CH ₂) _n OR ² ,
15	Het ¹	denotes a mono- or bicyclic, unsaturated, aromatic hetero- cycle having 1 to 4 N, O and/or S atoms, which may be un- substituted or mono-, di- or trisubstituted by A and/or (CH ₂) _n Ar,
	R	denotes H or unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 C atoms,
20	Ar	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or (CR ₂) _n OR,
25	Ar ²	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, CN, A and/or (CR ₂) _n OR,
	Ar ³	denotes a phenyl which is substituted by COA, OCR ₂ COOH, (CH ₂) _n CR ₂ COOH, (CH ₂) _n Het ³ , O(CH ₂) _p CONHHet ³ , (CH ₂) _n CONHHet ³ , CONROH, NHCO(CH ₂) _n Het ³ , COOHet ³ , (CH ₂) _n COOH, (CH ₂) _n COOA, CONH(CH ₂) _n Het ³ , S(O) _m A, Hal, COHet ³ , O(CH ₂) _p COHet ³ , O(CH ₂) _p COOH, O(CH ₂) _p COOA, OA or CONHC(=NH)NH ₂ ,
30		
35	Het	denotes a mono- or bicyclic saturated, unsaturated or aro- matic heterocycle having 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-, di- or trisubstituted by A, Ar ² , (CR ₂) _n Het ² and/or (CR ₂) _n OR,

	Het ²	denotes a monocyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 N, O and/or S atoms, which may be mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),
5	A	denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl,
		or
10		cyclic alkyl having 3-7 C atoms,
	n	denotes 0, 1, 2, 3, 4, 5 or 6,
	q	denotes 0 or 1,
	Hal	denotes F, Cl, Br or I,
15		where, if q = 0 and R ¹ = NH ₂ , NHA, NA ₂ , NHA _r or NAA _r , then D ≠ OAlk,
20	In Ir R ¹	denotes OH, OA, NH ₂ , NHA, NA ₂ , NHA _r , NAA _r , Ar ³ or Het,
	D	is absent or denotes Alk or OAlk,
	E	is absent or denotes Alk or OAlk,
	Q	denotes O, Alk, OCH ₂ or NH(CR ₂) _n ,
25	Alk	denotes unbranched or branched alkylene having 1, 2, 3 or 4 C atoms,
	L	denotes A, Ar ¹ or Het ¹ ,
	X	denotes Alk, Ar-diyl or Het-diyl,
	R ²	denotes H, A, (CR ₂) _n Ar or (CR ₂) _n Het,
30	Ar ¹	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, NO ₂ , A, (CH ₂) _n COOA, CN, (CH ₂) _n N(R ²) ₂ , (CH ₂) _n SO _m A, (CH ₂) _n CON(R ²) ₂ , and/or (CH ₂) _n OR ² ,
35	Het ¹	denotes furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, benzo-1,3-dioxolyl, 2,7a-dihydro-benzofuranyl,

		benzo[b]thiophenyl or tetrazolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A and/or $(CH_2)_nAr$,
5	R	denotes H or unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 C atoms,
	Ar	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, A and/or $(CR_2)_nOR$,
10	Het	denotes piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl, benzo-1,3-dioxolyl or pyrazinyl, each of which is unsubstituted or
15		mono- or disubstituted by A, Ar^2 , $(CR_2)_nHet^2$ and/or $(CR_2)_nOR$,
	Ar^2	denotes phenyl which is unsubstituted or mono-, di-, tri-, tetra- or pentasubstituted by Hal, CN, A and/or $(CR_2)_nOR$,
20	Het^2	denote piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or pyrazinyl,
25		each of which is unsubstituted or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),
	Het^3	denote pyrazolyl, benzo-1,3-dioxolyl, piperazinyl, thiazolyl, pyridinyl, benzotriazolyl, morpholinyl, imidazolyl, benzimidazolyl, indazolyl, 2,3-dihydrobenzoxazolyl or 1,3-dihydroiso-
30		indolyl, each of which is unsubstituted or mono-, di- or trisubstituted by A, CH_2COOH , CH_2Het^4 and/or =O,
	Het^4	denote piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, tri-
35		azolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridazinyl or

pyrazinyl, each of which is unsubstituted or mono- or disubstituted by A, OA, OH, Hal and/or =O (carbonyl oxygen),

5 A denotes unbranched or branched alkyl having 1-10 C atoms, in which 1-7 H atoms may be replaced by F and/or Cl,

 or

 cyclic alkyl having 3-7 C atoms,

10 n denotes 0, 1, 2, 3, 4, 5 or 6,

 q denotes 0 or 1,

 Hal denotes F, Cl, Br or I,

 where, if $q = 0$ and $R^1 = NH_2, NHA, NA_2, NHA_r$ or $NAAr$, then $D \neq OAlk$,

15 and pharmaceutically usable, tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as

20 described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can

25 also be made here of variants known per se which are not mentioned here in greater detail.

The starting materials can, if desired, also be formed in situ by not isolating

30 them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I.

Compounds of the formula I can preferably be obtained by reacting a compound of the formula II with a compound of the formula III.

35

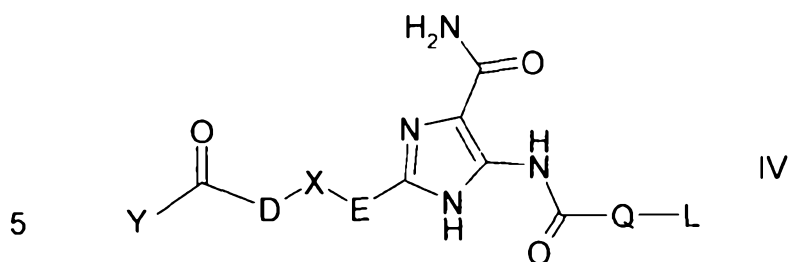
Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between -10° and 90°, in particular between about 0° and about 70°.

5 Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, 10 n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as 15 acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

20 Particular preference is given to pyridine, acetonitrile, dichloromethane and/or DMF.

25 The starting compounds of the formulae II and III are generally known. If they are novel, however, they can be prepared by methods known per se. The starting materials are generally also commercially available.

30 Compounds of the formula I can furthermore preferably be obtained by converting a radical R¹ in a compound of the formula I into another radical by, for example, reacting a carboxylic acid derivative of the formula IV



10 in which D, X, E, Q and L have the meanings indicated in Claim 1 and Y preferably denotes OH, Cl, Br, I or a free or reactively modified OH group, with an amine derivative to give an amide.

Y is preferably OH or an activated ester, an imidazolidine or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy or trifluoromethylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

20 The reaction is preferably carried out in the presence of a dehydrating agent, such as, for example, a carbodiimide, such as N,N'-Dicyclohexylcarbodiimide ("DCCI"), 1,1'-carbonyldiimidazole or N-3-dimethylamino-propyl-N'-ethylcarbodiimide ("DAPECI"), furthermore propanephosphonic anhydride (cf. Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline.

25 The reaction is generally carried out in the presence of an acid-binding agent, preferably an organic base, such as DIPEA, triethylamine, dimethylaniline, pyridine or quinoline.

30 The addition of an alkali or alkaline-earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline-earth metals, preferably of potassium, sodium, calcium or caesium, may also be favourable.

35 Depending on the conditions used, the reaction time is between a few minutes and 14 days, the reaction temperature is between about -30° and 140°, normally between -10° and 90°, in particular between about 0° and about 70°.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

Particular preference is given to acetonitrile, dichloromethane and/or DMF.

The said compounds according to the invention can be used in their final non-salt form. On the other hand, the present invention also encompasses the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceuti-

cally acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like.

Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalene-sulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds according to the invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline-earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally

occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanol-
amine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, etha-
nolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, gluc-
amine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine,
lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperi-
dine, polyamine resins, procaine, purines, theobromine, triethanolamine,
triethylamine, trimethylamine, tripropylamine and tris(hydroxymethyl)-
methamine (tromethamine), but this is not intended to represent a
restriction.

Compounds of the present invention which contain basic nitrogen-contain-
ing groups can be quaternised using agents such as (C₁-C₄)alkyl halides,
for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and
iodide; di(C₁-C₄)alkyl sulfates, for example dimethyl, diethyl and diamyl
sulfate; (C₁₀-C₁₈)alkyl halides, for example decyl, dodecyl, lauryl, myristyl
and stearyl chloride, bromide and iodide; and aryl(C₁-C₄)alkyl halides, for
example benzyl chloride and phenethyl bromide. Both water- and oil-solu-
ble compounds according to the invention can be prepared using such
salts.

The above-mentioned pharmaceutical salts which are preferred include
acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisucci-
nate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate,
meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stea-
rate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and trometh-
amine, but this is not intended to represent a restriction.

The acid-addition salts of basic compounds of the formula I are prepared by
bringing the free base form into contact with a sufficient amount of the
desired acid, causing the formation of the salt in a conventional manner.

5 The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar sol-
vents; for the purposes of the invention, however, the salts otherwise corre-
spond to the respective free base forms thereof.

10 As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline-earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine,
15 ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds according to the invention are prepared by bringing the free acid form into contact with a sufficient amount
20 of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility
25 in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

30 If a compound according to the invention contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the invention also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphos-
phate, disodium and trihydrochloride, but this is not intended to represent a
35 restriction.

With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medication after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acacia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape, which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer

of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

5 Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compound. Syrups can be prepared by dissolving the compound in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compound in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other
10 artificial sweeteners and the like, can likewise be added.
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The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example,
20 by coating or embedding of particulate material in polymers, wax and the like.

25 The compounds of the formula I and salts, solvates and physiologically functional derivatives thereof can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.
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The compounds of the formula I and the salts, solvates and physiologically functional derivatives thereof can also be delivered using monoclonal antibodies as individual carriers to which the compound molecules are coupled.
35 The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone,

pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxy-ethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled
5 release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be
15 delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions,
20 pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient
25 can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended
30 in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.
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Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

5 Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

15 Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

20 Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

25 Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions pre-

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pared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

5 It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

10 A therapeutically effective amount of a compound of the formula I depends on a number of factors, including, for example, the age and weight of the animal, the precise condition that requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately
15 determined by the treating doctor or vet. However, an effective amount of a compound according to the invention for the treatment of neoplastic growth, for example colon or breast carcinoma, is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus,
20 the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as a single dose per day or more usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is
25 the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention *per se*. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.
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The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or pharmaceutically usable and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further
35 medicament active ingredient.

The invention also relates to a set (kit) consisting of separate packs of

- (a) an effective amount of a compound of the formula I and/or pharmaceutically usable and stereoisomers thereof, including mixtures thereof in all ratios,
- and
- (b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules, each containing an effective amount of a compound of the formula I and/or pharmaceutically usable and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

The medicaments from Table 1 are preferably, but not exclusively, combined with the compounds of the formula I. A combination of the formula I and medicaments from Table I can also be combined with compounds of the formula VI.

Table 1.		
Alkylating agents	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa Chlorambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechlorethamine Streptozocin Temozolomide Semustine

5	Platinum agents	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
10	Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine Cytarabine 2-Fluorodesoxycytidine Methotrexate Idatrexate	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen) Clofarabine (Bioenvision) Irofulven (MGI Pharrna) DMDC (Hoffmann-La Roche) Ethynylcytidine (Taiho)
20	Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-Ethyl-10- hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharrna) Rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharrna)	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour- Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
35	Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoantrone Bleomycin sulfate (Blenoxan)

5		Epirubicin Therarubicin Idarubicin Rubidazone Plicamycin Porfiromycin Cyanomorpholinodoxo- rubicin Mitoxantrone (Novantrone)	Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
10	Antimitotic agents	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI) Rhizoxin (Fujisawa) Mivobulin (Warner- Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) !DN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
30	Aromatase inhibitors	Aminoglutethimide Letrozole Anastrozole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)
35	Thymidylate synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)

5	DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafofamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-benzylguanine (Paligent)
10	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Ionafernib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
15	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)
20	Histone acetyl transferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
25	Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
30	TNF-alpha agonists/ antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
35	Endothelin-A receptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
	Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	Alitretinoin (Ligand)
	Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Trogen) Cancer vaccine (Intercell) Norelin (Biostar)

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	PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (Gem- Vax)	BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
Hormonal and antihormonal agents	Oestrogens Conjugated oestrogens Ethinylloestradiol Chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (En- treMed) Arzoxifen (Eli Lilly)
Photodynamic agents	Talaporfin (Light Sciences) Theralux (Theratechnolo- gies) Motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) Lutetium texaphyrin (Pharmacyclics) Hypericin
Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide (Sugen/ Pharmacia) ZD1839 (AstraZeneca) Erlotinib (Oncogene Science) Canertjnib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmith-	Kahalide F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)

		Kline) EKB-509 (Wyeth) EKB-569 (Wyeth)	
5	Various agents	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoGenesys) G17DT immunogen (gastrin inhibitor, Aphton) Efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibitor, Progen) Tesmifen (histamine antagonist, YM BioSciences) Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibitor, Ribapharm) Cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) Exisulind (PDE-V inhibitor, Cell Pathways) CP-461 (PDE-V inhibitor, Cell Pathways) AG-2037 (GART inhibitor, Pfizer) WX-UK1 (plasminogen activator inhibitor, Willex)	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) Seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) Eflornithin (ODC inhibitor, ILEX Oncology) Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai) Aplidin (PPT inhibitor, PharmaMar) Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis promoter, Pharmagenesis) Immunol™ (triclosan mouthwash, Endo) Triacetyluridine (uridine prodrug, Wellstat) SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™
10			(immunotoxin, KS Biomedix) PCK-3145 (apoptosis
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	inhibitor, Millennium) SRL-172 (T-cell stimulant, SR Pharma) TLK-286 (glutathione-S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeutics) Midostaurin (PKC inhibitor, Novartis) Bryostatin-1 (PKC stimulant, GPC Biotech) CDA-II (apoptosis promoter, Everlife) SDX-101 (apoptosis promoter, Salmedix) Ceflatonin (apoptosis promoter, ChemGenex)	promoter, Procyon) Doranidazole (apoptosis promoter, Pola) CHS-828 (cytotoxic agent, Leo) Trans-retinoic acid (differentiator, NIH) MX6 (apoptosis promoter, MAXIA) Apomine (apoptosis promoter, ILEX Oncology) Urocidin (apoptosis promoter, Bioniche) Ro-31-7453 (apoptosis promoter, La Roche) Brostallicin (apoptosis promoter, Pharmacia)
Alkylating agents	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa Chlorambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechlorethamine Streptozocin Temozolomide Semustine
Platinum agents	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen)

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	Cytarabine 2-Fluorodesoxycytidine Methotrexate Idatrexate	Clofarabine (Bioenvision) Irofulven (MGI Pharrna) DMDC (Hoffmann-La Roche) Ethinylcytidine (Taiho)
Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-Ethyl-10-hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharrna) Rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharrna)	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour-Ipsen) TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazole Plicamycinp Porfiromycin Cyanomorpholinodoxo-rubicin Mitoxantrone (Novantrone)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoantrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
Antimitotic agents	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinorelbine Vindesine Dolastatin 10 (NCI)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott)

5		Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
10			
15	Aromatase inhibitors	Aminoglutethimide Letrozole Anastrozole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)
20	Thymidylate synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
25	DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (Isotope Solutions) Thymectacin (NewBiotics) Edotretotid (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-benzylguanine (Paligent)
30	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Ionafernib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
35	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)

	Histone acetyl transferase in- hibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
5	Metalloproteinase inhibitors Ribonucleoside reductase inhibi- tors	Neovastat (Aeterna Labo- ratories) Marimastat (British Bio- tech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
10	TNF-alpha agonists/ antagonists	Virulizin (Lorus Therapeu- tics) CDC-394 (Celgene)	Revimid (Celgene)
	Endothelin-A re- ceptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
15	Retinoic acid re- ceptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (Ligand)	Alitretinoin (Ligand)
20	Immunomodula- tors	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech) Synchrovax vaccines (CTL Immuno) Melanoma vaccine (CTL Immuno) p21-RAS vaccine (Gem- Vax)	Dexosome therapy (Ano- sys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics) !3-Alethin (Dovetail) CLL-Thera (Vasogen)
25			
30	Hormonal and antihormonal agents	Oestrogens Conjugated oestrogens Ethinylloestradiol Chlorotrianisene Idenestrol Hydroxyprogesterone caproate Medroxyprogesterone Testosterone Testosterone propionate	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide
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5		Fluoxymesterone Methyltestosterone Diethylstilbestrol Megestrol Tamoxifen Toremofin Dexamethasone	Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (EntreMed) Arzoxifen (Eli Lilly)
10	Photodynamic agents	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin gadolinium (Pharmacyclics)	Pd-bacteriopheophorbide (Yeda) Lutetium texaphyrin (Pharmacyclics) Hypericin
15	Tyrosine kinase inhibitors	Imatinib (Novartis) Leflunomide (Sugen/Pharmacia) ZD1839 (AstraZeneca) Erlotinib (Oncogene Science) Canertinib (Pfizer) Squalamine (Genaera) SU5416 (Pharmacia) SU6668 (Pharmacia) ZD4190 (AstraZeneca) ZD6474 (AstraZeneca) Vatalanib (Novartis) PKI166 (Novartis) GW2016 (GlaxoSmith-Kline) EKB-509 (Wyeth) EKB-569 (Wyeth)	Kahalide F (PharmaMar) CEP-701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
25			
30	Various agents	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy Medical) P54 (COX-2 inhibitor, Phytopharm) CapCell™ (CYP450 stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist,	BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamine (reducing agent, SRI International) N-Acetylcysteine (reducing agent, Zambon) R-Flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB
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5	GlycoGenesys) G17DT immunogen (gastrin inhibitor, Aphton) Efaproxiral (oxygenator, Allos Therapeutics) PI-88 (heparanase inhibitor, Progen) Tesmifen (histamine antagonist, YM BioSciences) Histamine (histamine H2 receptor agonist, Maxim) Tiazofurin (IMPDH inhibitor, Ribapharm) Cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-1 antagonist, Sanofi-Synthelabo) CCI-779 (mTOR kinase inhibitor, Wyeth) Exisulind (PDE-V inhibitor, Cell Pathways) CP-461 (PDE-V inhibitor, Cell Pathways) AG-2037 (GART inhibitor, Pfizer) WX-UK1 (plasminogen activator inhibitor, Willex) PBI-1402 (PMN stimulant, ProMetic LifeSciences) Bortezomib (proteasome inhibitor, Millennium) SRL-172 (T-cell stimulant, SR Pharma) TLK-286 (glutathione-S transferase inhibitor, Telik) PT-100 (growth factor agonist, Point Therapeutics) Midostaurin (PKC inhibitor, Novartis) Bryostatin-1 (PKC stimulant, GPC Biotech) CDA-II (apoptosis promoter, Everlife) SDX-101 (apoptosis promoter, Salmedix)	inhibitor, Active Biotech) Seocalcitol (vitamin D receptor agonist, Leo) 131-I-TM-601 (DNA antagonist, TransMolecular) Eflornithin (ODC inhibitor, ILEX Oncology) Minodronic acid (osteoclast inhibitor, Yamanouchi) Indisulam (p53 stimulant, Eisai) Aplidin (PPT inhibitor, PharmaMar) Rituximab (CD20 antibody, Genentech) Gemtuzumab (CD33 antibody, Wyeth Ayerst) PG2 (haematopoiesis promoter, Pharmagenesis) Immunol™ (triclosan mouthwash, Endo) Triacetyluridine (uridine prodrug, Wellstat) SN-4071 (sarcoma agent, Signature BioScience) TransMID-107™ (immunotoxin, KS Biomedix) PCK-3145 (apoptosis promoter, Procyon) Doranidazole (apoptosis promoter, Pola) CHS-828 (cytotoxic agent, Leo) Trans-retinoic acid (differentiator, NIH) MX6 (apoptosis promoter, MAXIA) Apomine (apoptosis promoter, ILEX Oncology) Urocidin (apoptosis promoter, Bioniche) Ro-31-7453 (apoptosis promoter, La Roche) Brostallicin (apoptosis
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	Ceflatonin (apoptosis promoter, Pharmacia) promoter, ChemGenex)
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The compounds of the formula I are preferably combined with the with known anti-cancer agents:

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These known anti-cancer agents include the following: oestrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors and other angiogenesis inhibitors. The present compounds are particularly suitable for administration at the same time as radiotherapy. The synergistic effects of inhibition of VEGF in combination with radiotherapy have been described in the art (see WO 00/61186).

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"Oestrogen receptor modulators" refers to compounds which interfere with or inhibit the binding of oestrogen to the receptor, regardless of mechanism. Examples of oestrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY 117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]phenyl 2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone and SH646.

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"Androgen receptor modulators" refers to compounds which interfere with or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole and abiraterone acetate.

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"Retinoid receptor modulators" refers to compounds which interfere with or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine,

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ILX23-7553, trans-N-(4'-hydroxyphenyl)retinamide and N-4-carboxyphenyl-retinamide.

"Cytotoxic agents" refers to compounds which result in cell death primarily through direct action on the cellular function or inhibit or interfere with cell myosis, including alkylating agents, tumour necrosis factors, intercalators, microtubulin inhibitors and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altret-amine, prednimustine, dibromodulcitol, ranimustine, fotemustine, neda-platin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosylate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, loba-platin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methylpyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans,trans,trans)bis-mu-(hexane-1,6-diamine)mu-[diamineplati-num(II)]bis[diamine(chloro)platinum(II)] tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxan-thine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pira-rubicin, pinafide, valrubicin, amrubicin, antineoplastone, 3'-deamino-3'-mor-pholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, eli-nafide, MEN10755 and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulfo-nyldaunorubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzenesulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258 and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exobenzylidenechartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2- (6H)propan-amine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-

benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxyetoposide, GL331, N-[2-(dimethylamino)-ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydro-furo(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one and dimesna.

"Antiproliferative agents" include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231 and INX3001 and anti-metabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine, ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitfur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydrobenzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-mannoheptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b]-1,4-thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-ylacetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabinofuranosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also include monoclonal antibodies to

growth factors other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumour suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see US Patent No. 6,069,134, for example).

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Particular preference is given to the use of the compound according to the invention for the treatment and prophylaxis of tumour diseases.

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The tumour is preferably selected from the group of tumours of the squamous epithelium, of the bladder, of the stomach, of the kidneys, of head and neck, of the oesophagus, of the cervix, of the thyroid, of the intestine, of the liver, of the brain, of the prostate, of the urogenital tract, of the lymphatic system, of the stomach, of the larynx and/or of the lung.

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The tumour is furthermore preferably selected from the group lung adenocarcinoma, small-cell lung carcinomas, pancreatic cancer, ovarian carcinoma, glioblastomas, colon carcinoma and breast carcinoma.

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Preference is furthermore given to the use for the treatment of a tumour of the blood and immune system, preferably for the treatment of a tumour selected from the group of acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia and/or chronic lymphatic leukaemia.

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In another aspect, the invention encompasses a for the treatment of a patient who has a neoplasm, such as a cancer, by administration of a compound of the formula (I) in combination with an antiproliferative agent. Suitable antiproliferative agents encompass those provided in Table 1.

Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means: if necessary, water is added, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation. Rt values are determined by HPLC using eluents mentioned.

Mass spectrometry (MS): EI (electron impact ionisation) M^+

FAB (fast atom bombardment) $(M+H)^+$

ESI (electrospray ionisation) $(M+H)^+$

APCI-MS (atmospheric pressure chemical ionisation – mass spectrometry) $(M+H)^+$

LC/MS method:

Solvent A: water + 0.1% of TFA

Solvent B: acetonitrile + 0.1% of TFA

Flow: 2.4 ml/min

Gradient: 0.0 min 4% of B

2.6 min 100% of B

Column: Chromolith® Speed ROD RP-18e 50-4, 6 mm

HPLC method:

Solvent A: water + 0.1% of TFA

Solvent B: acetonitrile + 0.08% of TFA

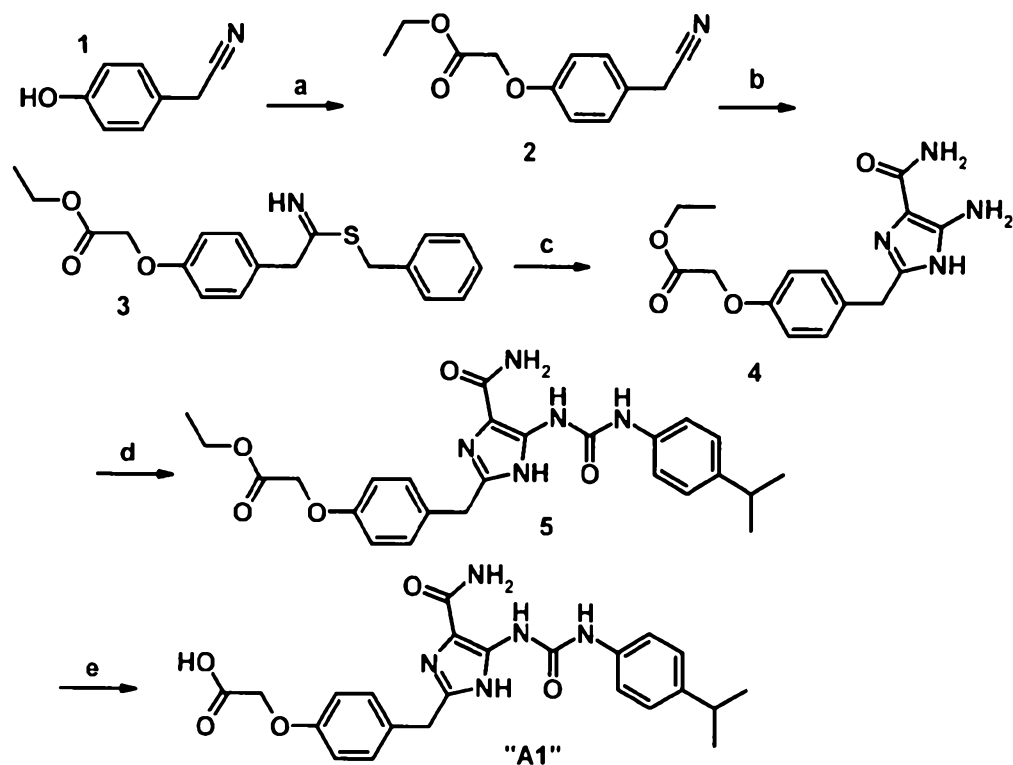
Flow: 1.5 ml/min

Gradient: 0.0 - 0.5 min 100% of A
0.5 - 3.5 min auf 100% of B
3.5 - 4.5 min 100% of B
4.5 - 4.6 min auf 100% of A
4.6 - 5.0 min 1000% of A

Column: Si-ROD[®] UM9423/100, 3 mm

Example 1

The synthesis of (4-{4-carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid ("A1") is carried out analogously to the following scheme



5 **a.** Compound **1** (13 g, 97.6 mmol) is initially introduced in acetonitrile (150 ml), potassium carbonate (16.2 g, 117 mmol), sodium iodide (1.5 g, 9.8 mmol) and ethyl bromoacetate (11.9 ml, 107.4 mmol) are added at RT. The brownish suspension is boiled under reflux for 6 h, and stirring is then continued at RT for 18 h. A yellowish solution with a colourless precipitate forms. Water is added to the reaction mixture, during which the precipitate dissolves, and the aqueous phase is extracted twice with DCM. The combined organic phases are washed twice with water, dried over magnesium sulfate and evaporated. Drying of the resultant precipitate gives 21.2 g (96.7 mmol, 99%) of compound **2**, which is reacted without further purification.

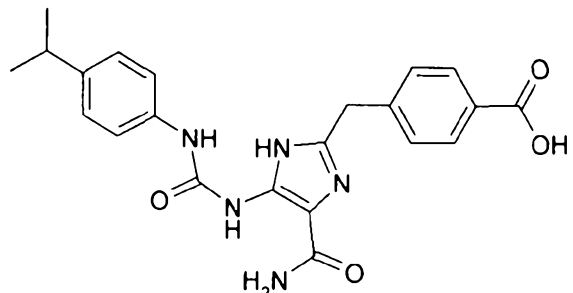
15 **b.** Compound **2** (3.7 g, 17 mmol) and 2 ml of benzyl mercaptan (17 mmol) are initially introduced in 50 ml of absolute ether and cooled to 10°C. Hydrogen chloride gas is carefully passed through the solution for 30 minutes at this temperature. The batch is warmed to RT, and stirring is continued for 16 h. The resultant precipitate is then filtered off and washed with diethyl ether, giving 5.8 g (3.5 mmol, 21%) of the desired product **3** as colourless solid.

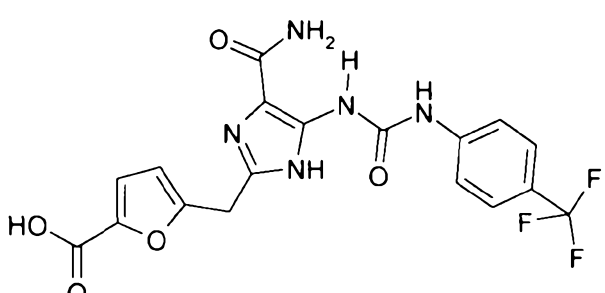
25 **c.** Compound **3** (1 g, 2.6 mmol), 2-cyanoacetamide (261 mg, 2.6 mmol) and sodium hydrogencarbonate (221 mg, 2.6 mmol) are mixed in 20 ml of absolute THF in a microwave vessel, the vessel is sealed and heated at 100°C for 10 min in a microwave. A colourless solid forms, which is allowed to settle. The supernatant solution is carefully removed, the precipitate is suspended in fresh absolute THF, allowed to settle again, and the supernatant solution is removed. This operation is repeated a further time. The precipitate is dried firstly in air and then in vacuo, giving 702 mg (1.8 mmol, 69%) of compound **4** as colourless solid.

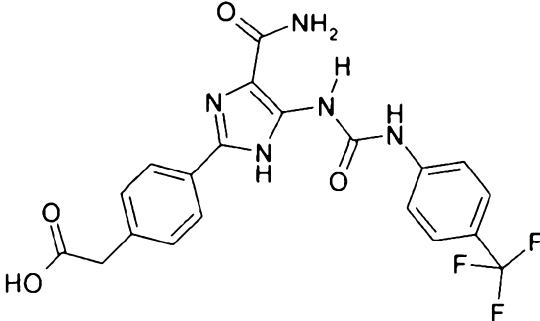
d. Compound **4** (200 mg, 0.6 mmol) is dissolved in pyridine (5 ml). 129 μ l (0.8 mmol) of p-isopropyl isocyanate are then added, and the reaction mixture is stirred at RT for 16 h. The mixture is evaporated in a rotary evaporator, and the purified compound **5** is obtained from the brown residue with the aid of preparative HPLC as brown solid (41 mg, 0.07 mmol, 12%).

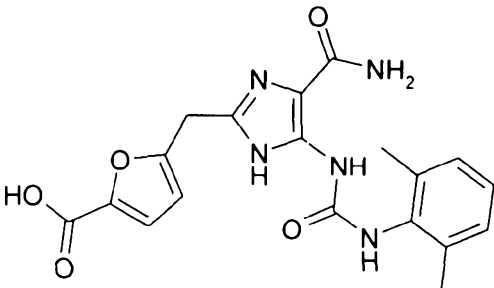
e. Compound **5** (150 mg, 0.3 mmol) is dissolved in 4 ml of dioxane in a microwave vessel, and 0.6 ml of 1 N NaOH is added. The mixture is heated at 100°C for 10 min in the microwave. The mixture is allowed to cool to RT and is acidified using hydrochloric acid, the crude product is partitioned between water and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate, and the combined organic phases are then washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The resultant crude product is purified further on preparative HPLC, giving product "**A1**" (6 mg, 4%) as colourless solid; $[M+H]^+$ 452.19; Rt HPLC 2.61 [min].

The following compounds are obtained analogously

Compound No.	Name and/or structure	ESI $[M+H]^+$	HPLC (RT in min) method
"A2"	4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid 	422.18	2.61
"A3"	4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid	436.19	2.73

¹ H-NMR (MeOD): δ [ppm] = 0.95 (m, 3H), 1.36 (m, 2H), 1.58 (m, 2H), 2.58 (m, 2H), 4.16 (2, 2H), 7.12 (bd, J = 7 Hz, 2H), 7.35 (bd, J = 7 Hz, 2H), 7.41 (bd, J = 7Hz, 2 H), 8.01 (bd, J = 7Hz, 2H)			
5	"A4"	4-[4-Carbamoyl-5-(3-hexylureido)-1H-imidazol-2-ylmethyl]benzoic acid	388.19 2.47
	"A5"	4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]benzoic acid	394.14 2.41
10	"A6"	4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	414.09 2.49
	"A7"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	408.16 2.53
15	"A8"	4-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	428.1 2.65
	"A9"	4-{5-[3-(4-Butoxyphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid	452.19 2.65
20	"A10"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	438.09 2.57
25			
30	"A11"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	398.14 2.51
	"A12"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	412.15 2.6
35	"A13"	5-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	418.08 2.48

5	"A14"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	398.14	2.41
	"A15"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}benzoic acid	448.12	2.61
	¹ H-NMR (DMSO-d ₆): δ [ppm] = 4.10 (bs, 2H), 7.07 (bm, 2H), 7.36 (bs, 2H), 7.64 (bs, 4H), 7.88 (bm, 2H), 9.06 (bs, 1H), 9.69 (bs, 1H), 11.45 (bs, 1H), 12.38 (bs, 1H)			
10	"A16"	4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}benzoic acid	408.16	2.33
	"A17"	4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	466.11	2.62
15	"A18"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-yl}benzoic acid	434.1	2.75
	¹ H-NMR (DMSO-d ₆): δ [ppm] = 7.12 - 7.60 (bm, 2H), 7.61 - 7.89 (bm, 4H), 7.92 - 8.27 (bm, 4H), 9.00 & 9.73 (bs & bs, 1H), 10.44 & 11.03 (bs & bs, 1H), 12.63 (bs, 1H), 13.02 (bs, 1H)			
20	"A19"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}benzoic acid	394.14	2.69
25	"A20"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-yl}phenyl)acetic acid	448.12	2.71
30				
	"A21"	(4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid	414.09	2.62
35	"A22"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid	414.09	2.61

¹ H-NMR (DMSO-d ₆): δ [ppm] = 3.44 (s, 2H), 7.08 (bs, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H), 9.11 (bs, 1H), 9.11 (s, 1 H), 11.42 (s, 1H)				
"A23"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid	422.18	2.72	
"A24"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid	408.16	2.57	
"A25"	(4-{4-Carbamoyl-5-[3-(3,5-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid	408.16	2.65	
"A26"	5-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid		398.14	2.27
"A27"	5-[4-Carbamoyl-5-(3-phenethylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid		398.14	2.31
"A28"	5-{4-Carbamoyl-5-[3-(2,6-diethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	426.17	2.45	
"A29"	5-{4-Carbamoyl-5-[3-(4-chloro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	472.06	2.66	
"A30"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	404.07	2.46	
"A31"	5-{4-Carbamoyl-5-[3-(2,4,6-trimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	412.15	2.27	

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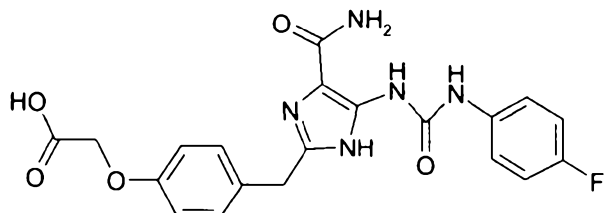
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"A32"	5-{4-Carbamoyl-5-[3-(2-ethyl-6-methylphenyl)-ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	412.15	2.37
"A33"	5-[4-Carbamoyl-5-(3-naphthalen-2-ylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid	420.12	2.52
"A34"	5-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	456.09	2.57
"A35"	5-{4-Carbamoyl-5-[3-(4-chloro-2-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid	472.06	2.61
"A36"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid		
			
"A37"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	478.13	2.56
"A38"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	478.13	2.57
"A39"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	466.2	2.71
"A40"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]phenoxy}acetic acid	424.15	2.39
"A41"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	444.1	2.47

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"A42"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	438.17	2.51
"A43"	(4-{4-Carbamoyl-5-[3-(4-pentylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	480.22	2.8
"A44"	(4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)-acetic acid	496.12	2.59
"A45"	(4-{4-Carbamoyl-5-[3-(4-phenoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	502.16	2.63
"A46"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	414.11	2.47
"A47"	(4-{4-Carbamoyl-5-[3-(2-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	430.08	2.58
"A48"	(4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	424.15	2.41
"A49"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	464.11	2.66
"A50"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	464.11	2.68
"A51"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	438.17	2.7
"A52"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-yl}phenoxy)acetic acid	452.19	2.82
"A53"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-yl]phenoxy}acetic acid	410.14	2.53
"A54"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	424.15	2.65
"A55"	(4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid	482.1	2.6

5	"A56"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	478.13	2.6
	"A57"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	452.19	2.73
	"A58"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethoxy]phenyl}acetic acid	424.15	2.55
10	"A59"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	444.1	2.63
	"A60"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)-ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	438.17	2.57
15	"A61"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	438.17	2.65
	"A62"	(4-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)-ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	458.12	2.66
20	"A63"	(4-{4-Carbamoyl-5-[3-(3,5-dimethoxyphenyl)-ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid	470.16	2.53
	"A64"	(4-{4-Carbamoyl-5-[3-(4-fluoro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)-acetic acid	496.12	2.73
	"A65"	5-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	454.07	2.61
30	"A66"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	454.07	2.61
35	"A67"	5-[4-Carbamoyl-5-(3-o-tolylureido)-1H-imidazol-2-ylmethyl]thiophene-2-carboxylic acid	400.1	2.38

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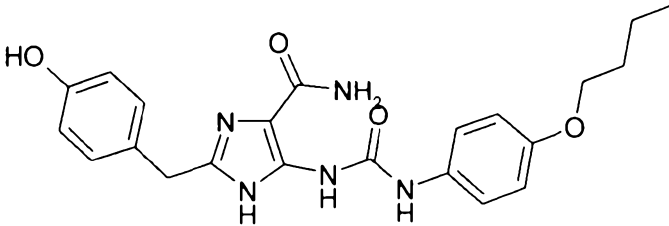
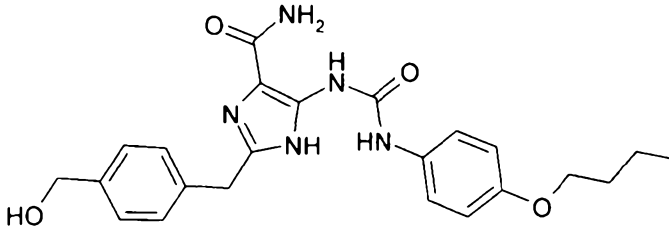
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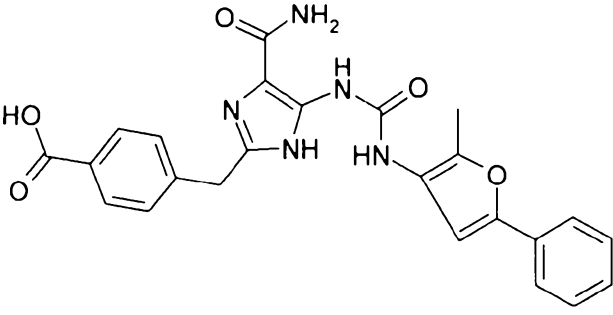
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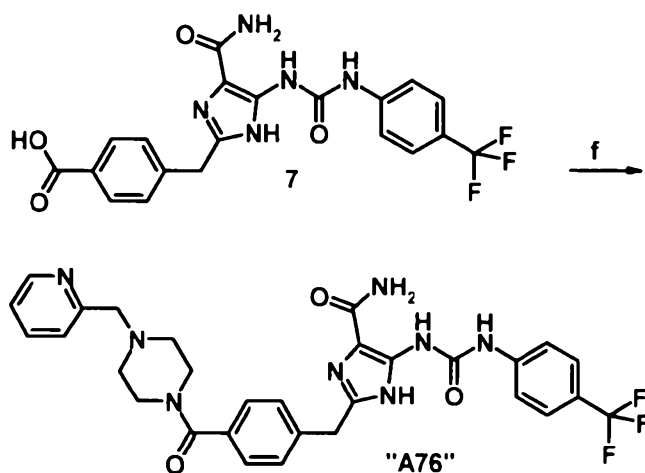
"A68"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	428.13	2.63
"A69"	5-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]thiophene-2-carboxylic acid	400.1	2.43
"A70"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	420.05	2.53
"A71"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	414.12	2.48
"A72"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	414.12	2.54
"A73"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	418.09	2.49
"A74"	5-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	434.06	2.49
"A75"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid	472.06	2.64
"A92"	4-{4-Carbamoyl-5-[3-(2-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	422.18	2.51
"A93"	4-{4-Carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid	464.11	2.61

5	"A95"	5-[3-(4-Butoxyphenyl)ureido]-2-(4-hydroxybenzyl)-1H-imidazole-4-carboxamides		424.19	2.6
10	"A96"	2-(4-Nitrobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		449.11	2.81
	¹ H-NMR (DMSO-d ₆): δ [ppm] = 4.16 (bs, 2H), 7.06 (bs, 1H), 7.15 (bs, 1H), 7.53 (m, 2H), 7.66 (bm, 4H), 8.18 (bm, 2H), 9.72 (bs, 1H), 10.42 (bs, 1H), 12.47 (bs, 1H)				
15	"A97"	from "A96" by reduction using Fe powder/NH ₄ Cl: 2-(4-aminobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		419.14	2.39
	"A98"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate		462.13	2.76
20	"A99"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate		478.13	2.77
25	"A100"	from methyl 4-{4-carbamoyl-5-[3-(4-butoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate by reduction using DIBALH:			
30		5-[3-(4-butoxyphenyl)ureido]-2-(4-hydroxymethylbenzyl)-1H-imidazole-4-carboxamide		438.21	2.61
35					

"A101"	4-{4-Carbamoyl-5-[3-(2-methyl-5-phenylfuran-3-yl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid		
		460.15	2.61
"A102"	4-[4-Carbamoyl-5-(3-thiophen-2-ylureido)-1H-imidazol-2-ylmethyl]benzoic acid	386.08	2.27

Example 2

The synthesis of 2-[4-(4-pyridin-2-ylmethylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide ("A76") is carried out analogously to the following scheme

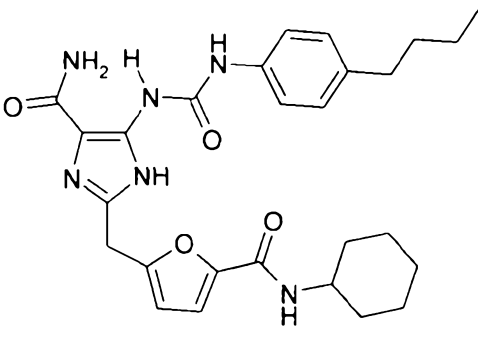
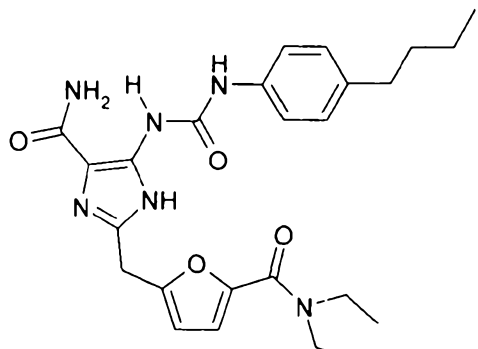


- f. Compound 7 (100 mg, 0.2 mmol) is dissolved in 10 ml of DMF and 0.1 ml of DIPEA. EDCI (64 mg, 0.3 mmol) and HOBT (60.4 mg, 0.4 mmol) are then added, and 1-(2-pyridylmethyl)piperazine (44 mg,

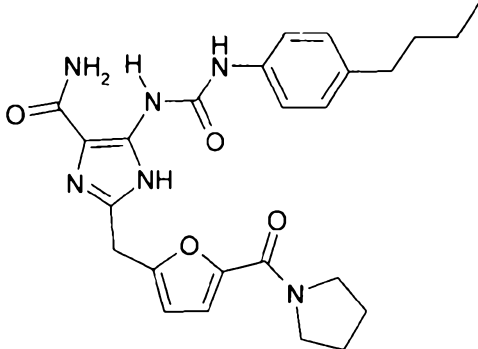
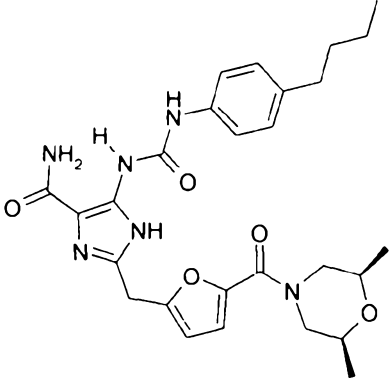
0.2 mmol) is then added. The reaction batch is stirred at RT for 16 h. All volatile constituents are then removed in vacuo, and the desired product "A76" is isolated from the residue as yellow solid by means of preparative HPLC (57 mg, 39%).

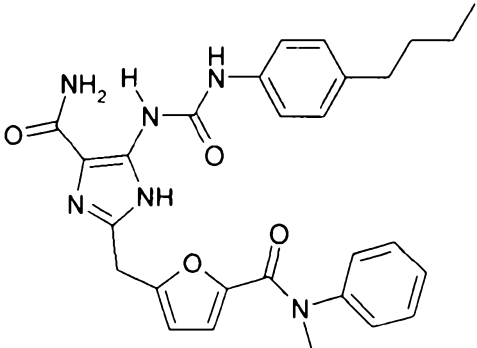
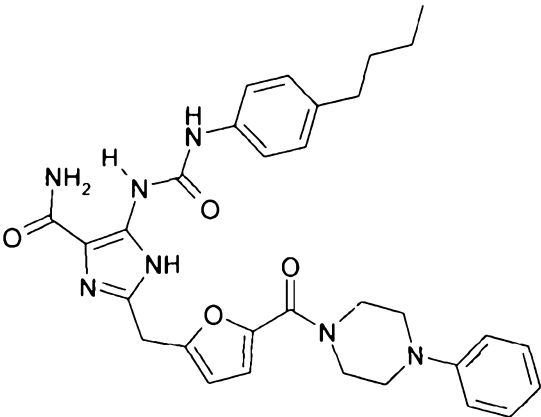
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The following compounds are obtained analogously

Compound No.	Name and/or structure	ESI [M+H] ⁺	HPLC (RT in min) method
"A77"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclohexyl-carbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide 	507.26	3.01
"A78"	5-[3-(4-Butylphenyl)ureido]-2-(5-diethyl-carbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide 	481.25	2.9

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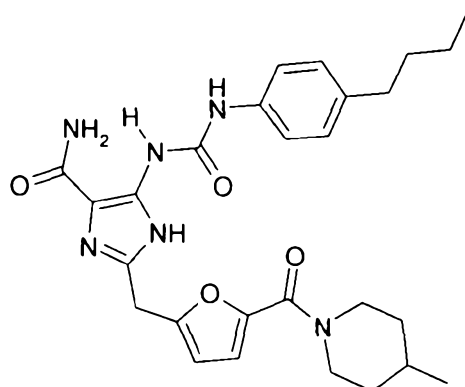
"A79"	2-[5-(Butylmethylcarbamoyl)furan-2-ylmethyl]-5-[3-(4-butylphenyl)ureido]-1H-imidazole-4-carboxamide	495.26	2.99
"A80"	5-[3-(4-Butylphenyl)ureido]-2-(5-dibutylcarbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide	537.31	3.23
"A81"	5-[3-(4-Butylphenyl)ureido]-2-[5-(pyrrolidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide 	479.23	2.85
"A82"	5-[3-(4-Butylphenyl)ureido]-2-[5-((5R,6S)-2,6-dimethylmorpholine-4-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide 	523.26	2.88
"A83"	5-[3-(4-Butylphenyl)ureido]-2-[5-(morpholine-4-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide	495.23	2.78

5	"A84"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylphenyl-carbamoyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide		
10			515.23	2.98
15	"A85"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methyl-piperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide	508.26	2.58
20	"A86"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-phenyl-piperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide		
25			570.28	2.91

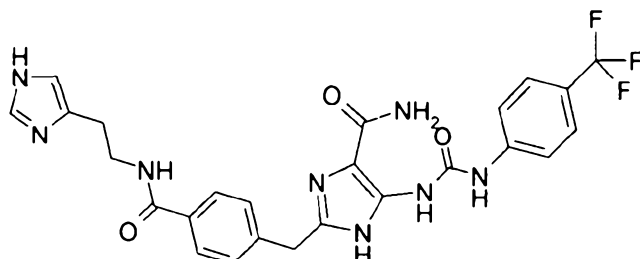
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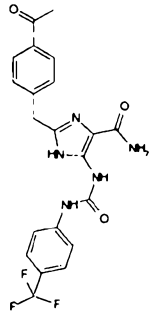
"A87"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methyl-piperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide	507.26	3.02
"A88"	5-[3-(4-Butylphenyl)ureido]-2-[5-(piperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide	493.25	2.94
"A89"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclopropyl-carbamoylfuran-2-ylmethyl)-1H-imidazole-4-carboxamide	465.22	2.79
"A90"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylpropyl-carbamoyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide	481.25	2.91
"A91"	5-[3-(4-Butylphenyl)ureido]-2-[5-[4-(2-hydroxy-ethyl)piperidine-1-carbonyl]furan-2-ylmethyl]-1H-imidazole-4-carboxamide	537.27	2.73
"A94"	5-[3-(4-Butylphenyl)ureido]-2-[4-(morpholine-4-carbonyl)benzyl]-1H-imidazole-4-carboxamide	505.25	2.75



"A103"	2-{4-[2-(1H-Imidazol-4-yl)ethylcarbamoyl]benzyl}- 5-[3-(4-trifluoromethylphenyl)ureido]-1H- imidazole-4-carboxamide	541.18	
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The following compounds can be prepared using methods known to the person skilled in the art. They are preferably prepared by the synthetic methods from Example 1 and 2 of the above-mentioned compounds:

Compound No.	Name and/or structure	ESI [M+H] ⁺	HPLC (RT in min) method
"B1"	 2-(4-Acetylbenzyl)-5-[3-(4-trifluoromethylphenyl)- ureido]-1H-imidazole-4- carboxamide	446	

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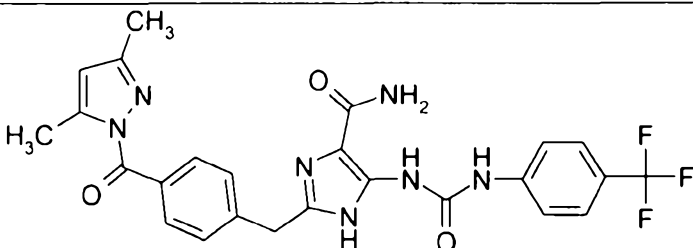
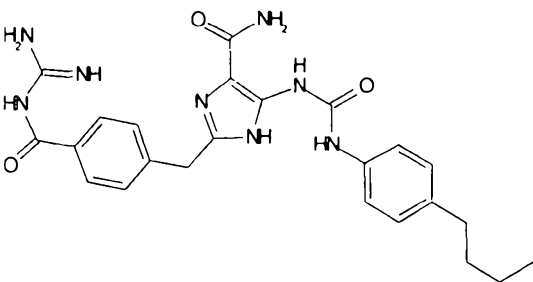
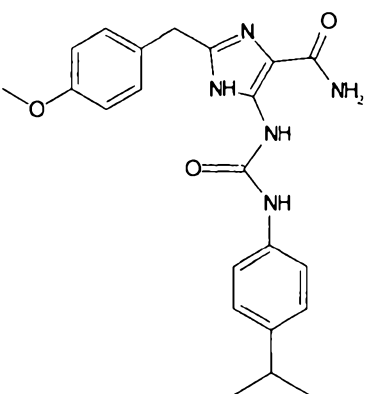
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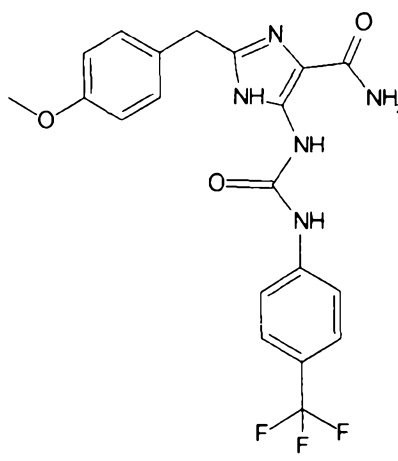
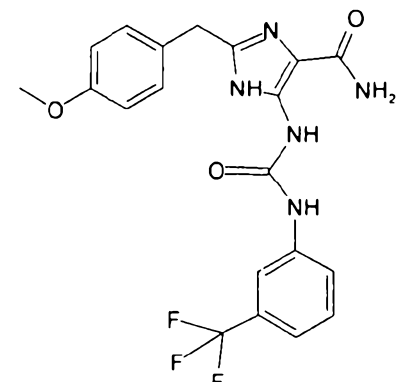
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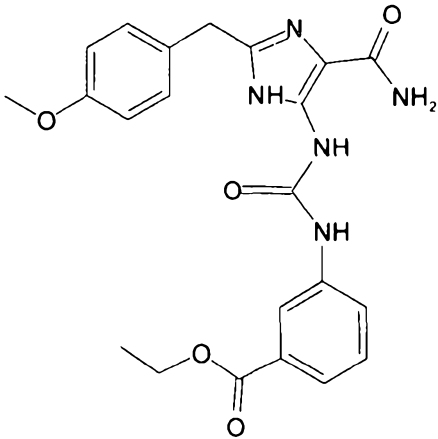
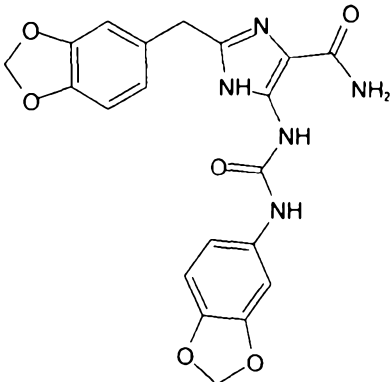
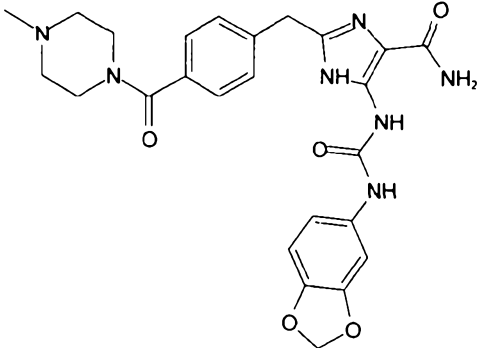
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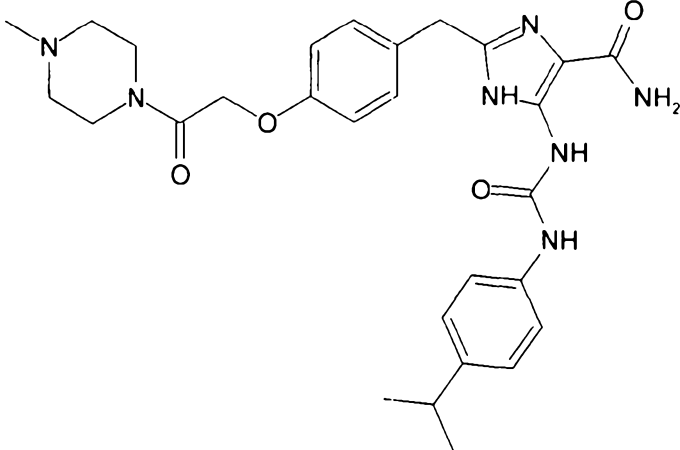
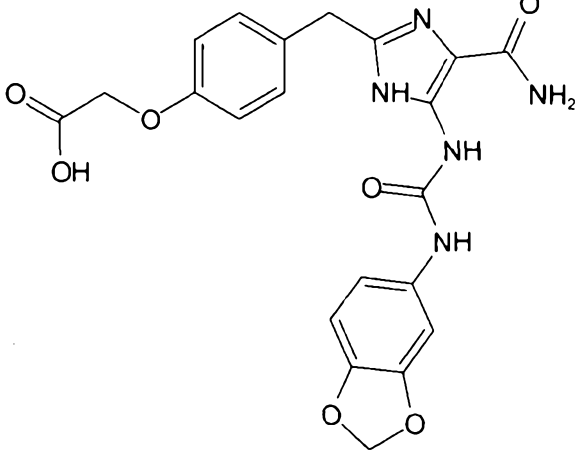
"B2"	 2-[4-(3,5-Dimethylpyrazole-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide	526	
"B3"	 5-[3-(4-Butylphenyl)ureido]-2-(4-guanidinocarbonylbenzyl)-1H-imidazole-4-carboxamide	478	
"B4"	 5-[3-(4-Isopropylphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4-carboxamide	408	2.76

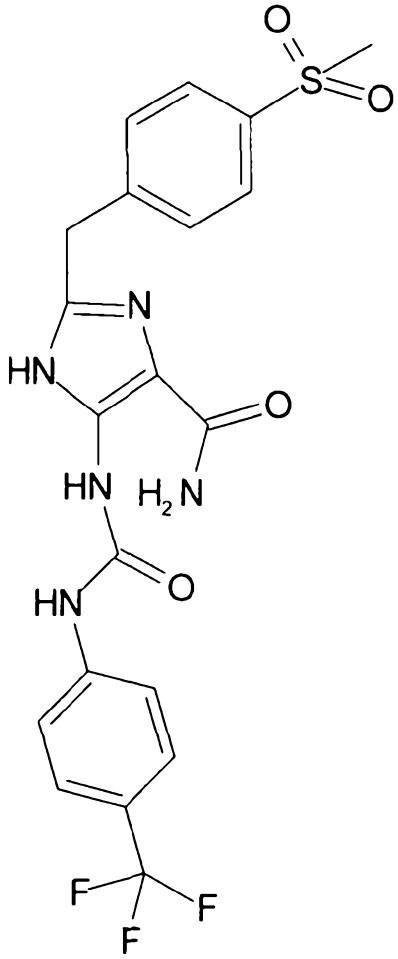
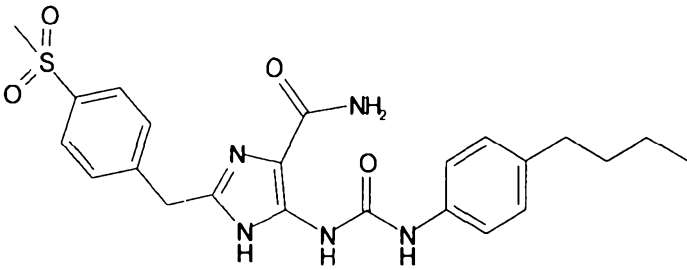
5	"B5"		434	2.73
10		2-(4-Methoxybenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic carboxamide		
15	"B6"		434	2.72
20		2-(4-Methoxybenzyl)-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		
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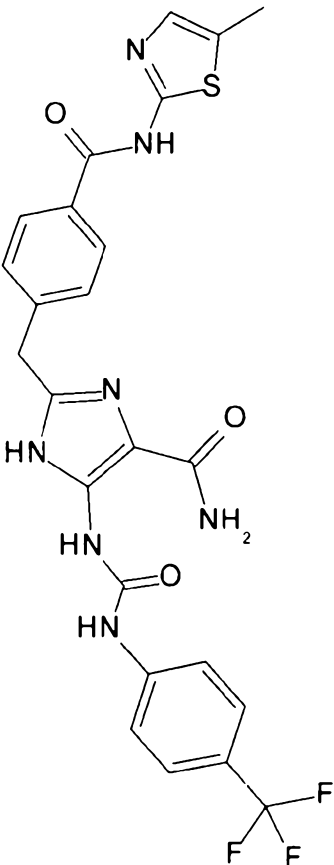
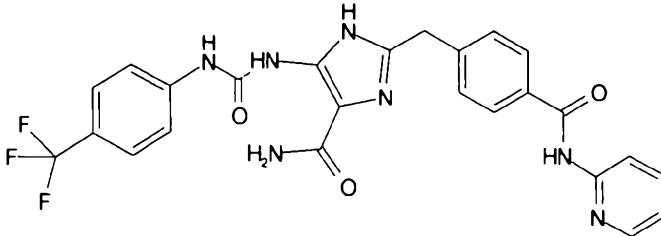
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5	"B7"		438	2.65
15	"B8"		424	2.43
25	"B9"		507	2.10
35		5-(3-Benzo-1,3-dioxol-5-ylureido)-2-[4-(4-methyl-piperazine-1-carbonyl)benzyl]-1H-imidazole-4-carboxamide		

5	"B10"		535	2.44
15	"B11"		454	2.29

5	"B12"		482	
25	"B13"		471	

"B14"	 545	
"B15"	 524	

5

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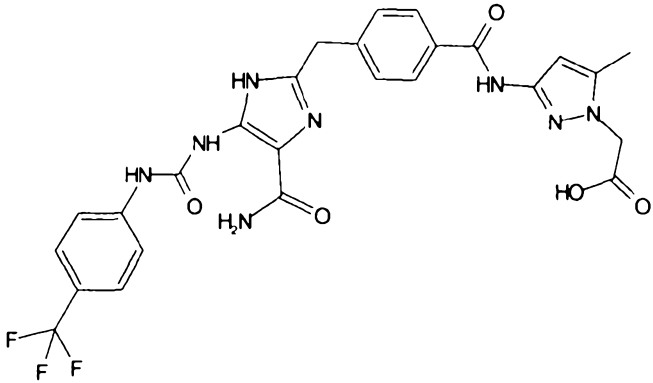
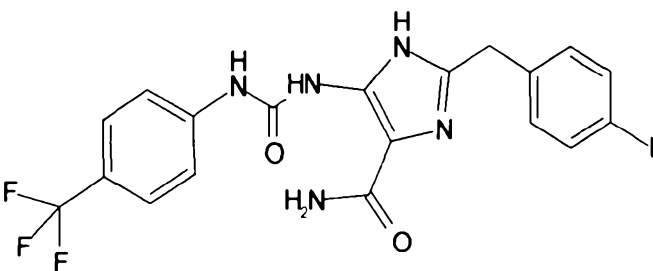
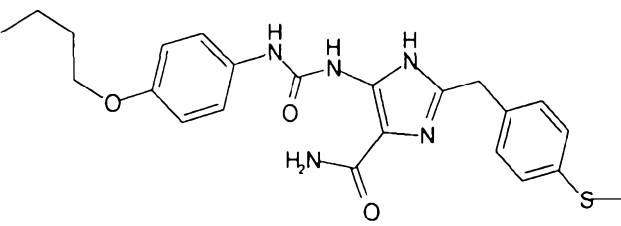
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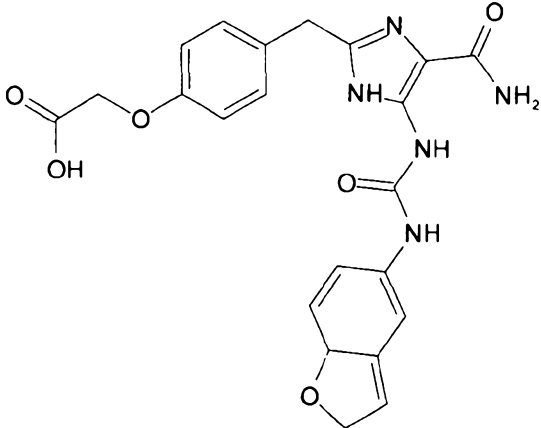
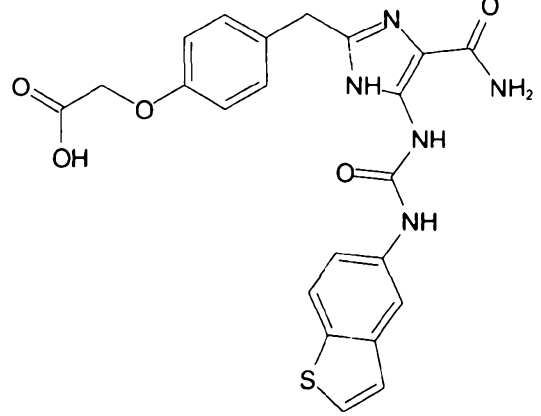
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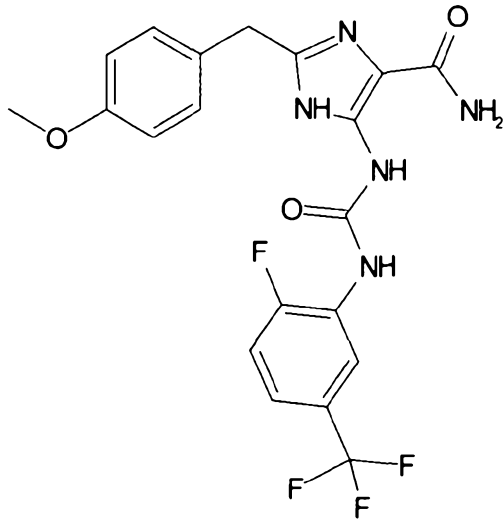
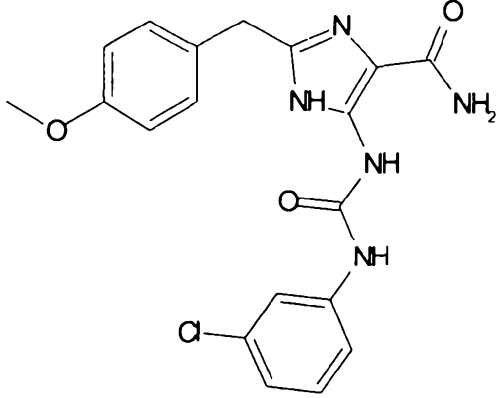
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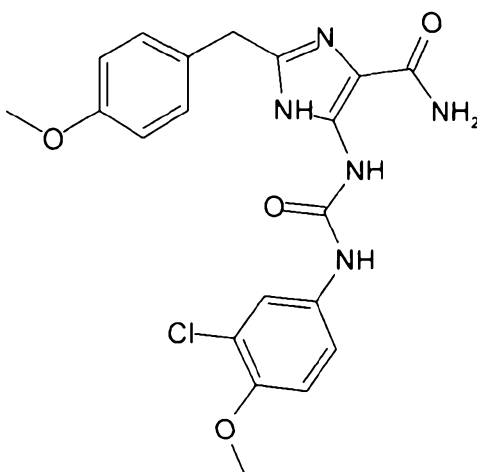
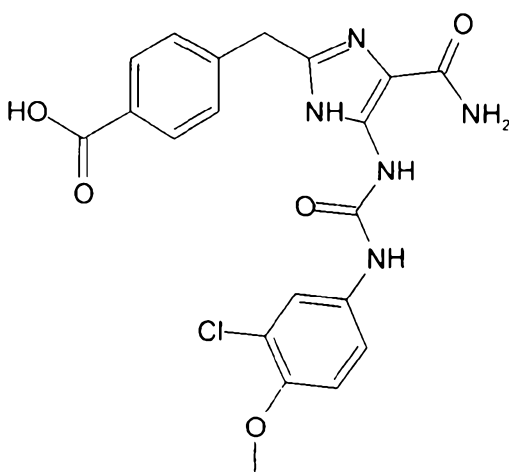
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"B16"	 [3-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoylamino)-5-methylpyrazol-1-yl] acetic acid	586	2.62
"B17"	 2-(4-Iodobenzyl)-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4-carboxamide	530	
"B18"	 5-[3-(4-Butoxyphenyl)ureido]-2-(4-methylsulfanylbenzyl)-1H-imidazole-4-carboxamide	455	

5	"B19"		452	2.24
10		(4-{4-Carbamoyl-5-[3-(2,7a-dihydrobenzofuran-5-yl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid		
15	"B20"		466	2.46
20		{4-[5-(3-Benzo[b]thiophen-5-ylureido)-4-carbamoyl-1H-imidazol-2-ylmethyl]phenoxy}acetic acid		
25				
30				
35				

5	"B21"		452	2.76
15	"B22"		401	2.64

5	"B23"		431	2.56
10		5-[3-(3-Chloro-4-methoxyphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4-carboxamide		
15	"B24"		445	2.43
20		4-{4-Carbamoyl-5-[3-(3-chloro-4-methoxyphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid		
25		acid		

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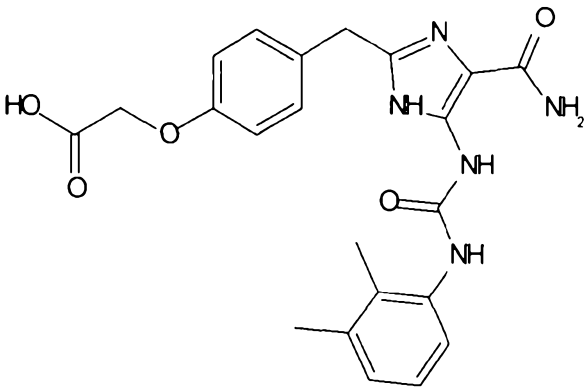
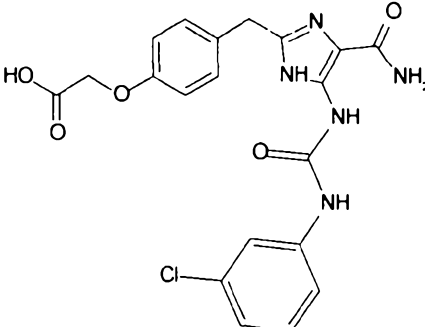
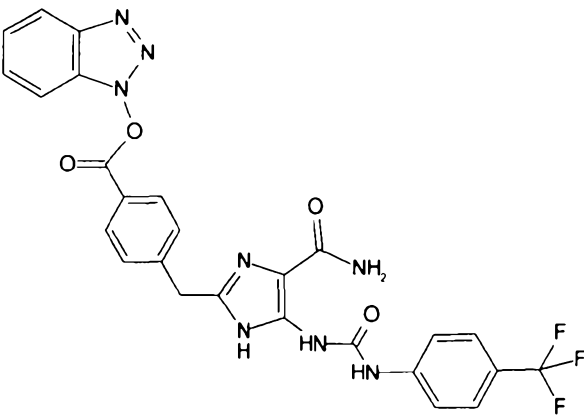
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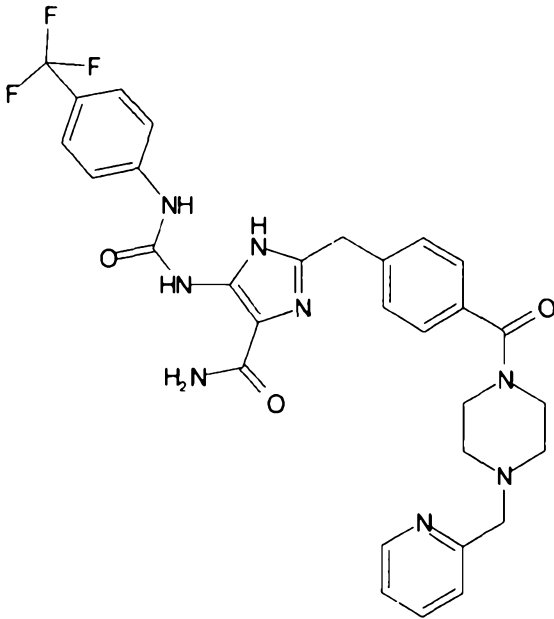
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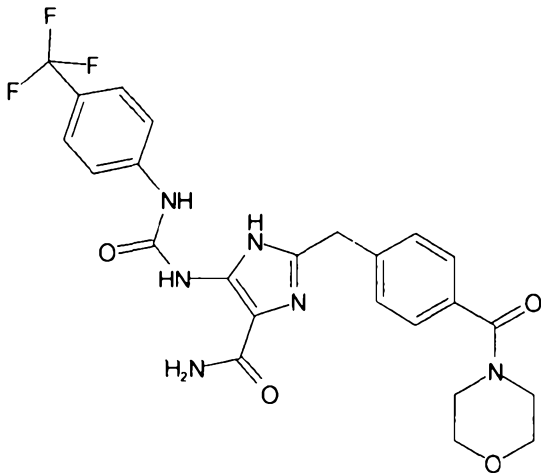
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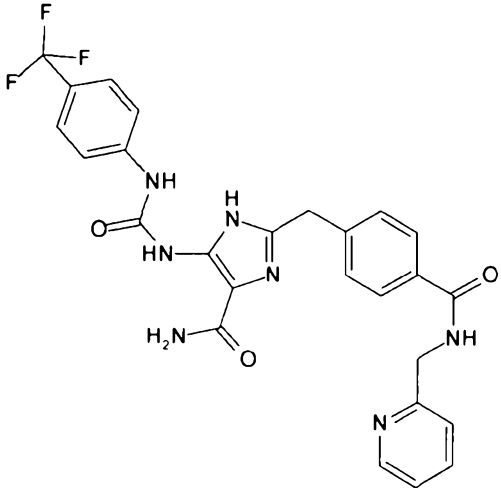
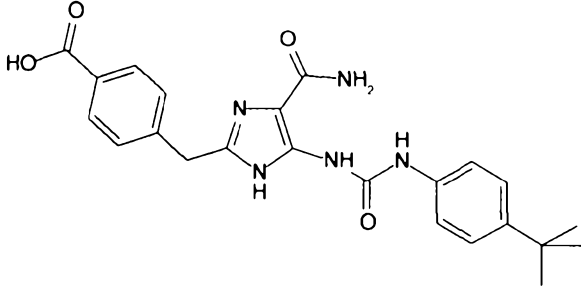
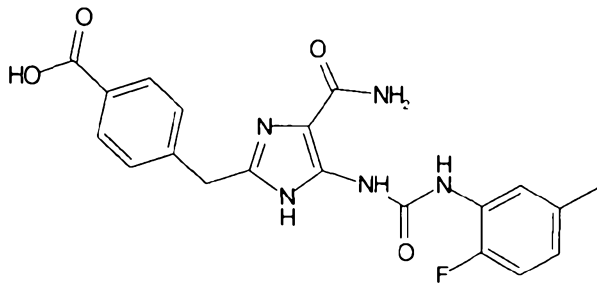
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"B25"	 (4-{4-Carbamoyl-5-[3-(2,3-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid	438	2.39
"B26"	 (4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid	445	2.46
"B27"	 Benzotriazol-1-yl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoate	565	

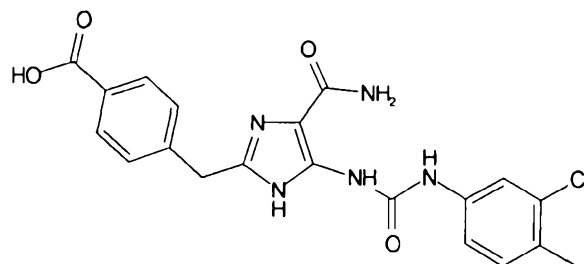
"B28"		608	2.45
2-[4-(4-Pyridin-2-ylmethylpiperazine-1-carbonyl)-benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide			

"B29"		517	2.55
2-[4-(Morpholine-4-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide			

"B30"	 2-{4-[(Pyridin-2-ylmethyl)carbamoyl]benzyl}-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide	538	2.45
"B31"	 4-{5-[3-(4-tert-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl} benzoic acid	436	2.61
"B32"	 4-{4-Carbamoyl-5-[3-(2-fluoro-5-methylphenyl)-ureido]-1H-imidazol-2-ylmethyl} benzoic acid	412	2.47

5

"B33"



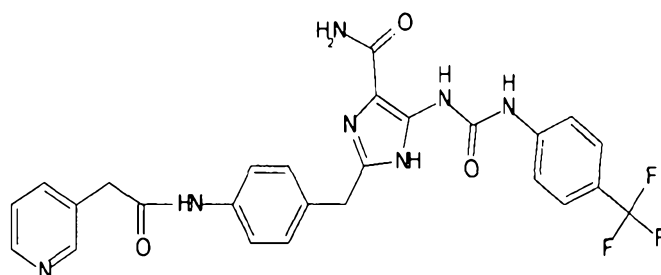
429

2.57

4-{4-Carbamoyl-5-[3-(3-chloro-4-methylphenyl)-ureido]-1H-imidazol-2-ylmethyl} benzoic acid

10

"B34"



538

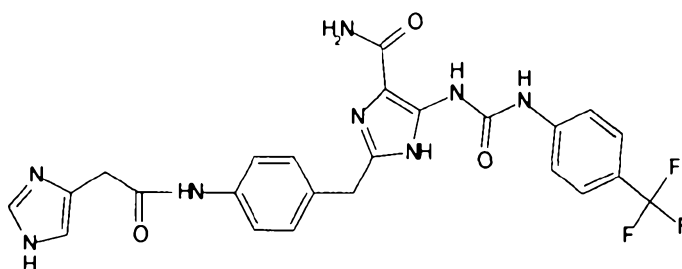
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2-[4-(2-Pyridin-3-ylacetylaminobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide

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"B35"



527

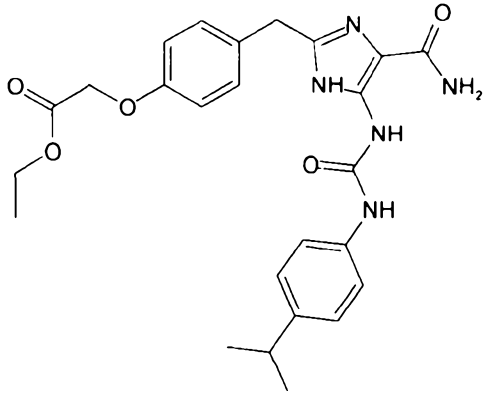
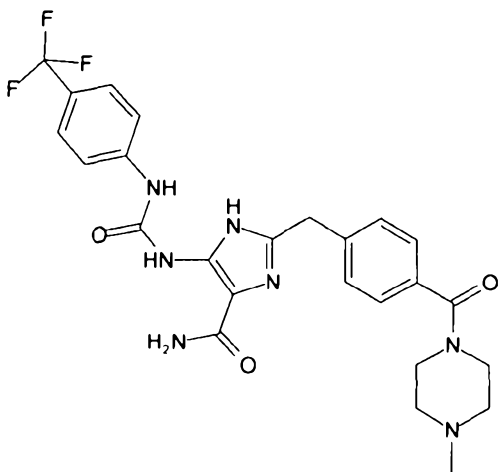
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2-[4-(2-1H-imidazol-4-ylacetylaminobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide

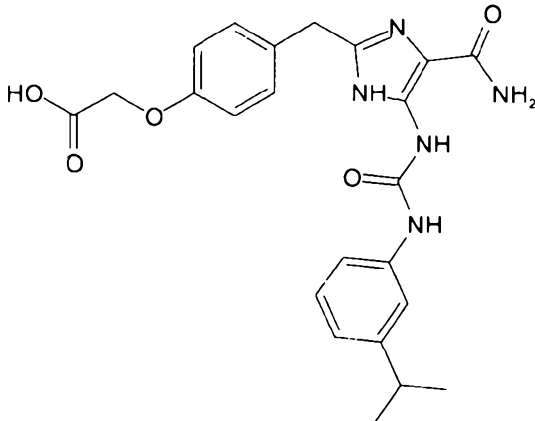
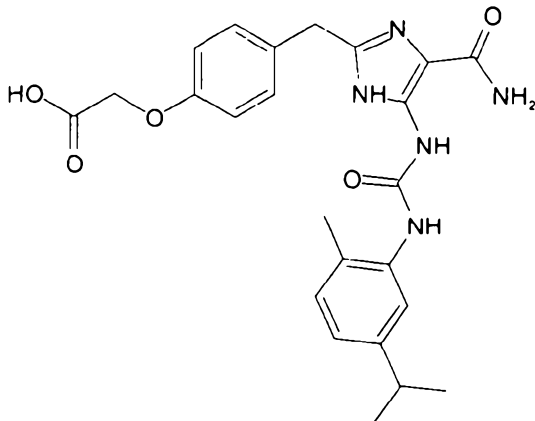
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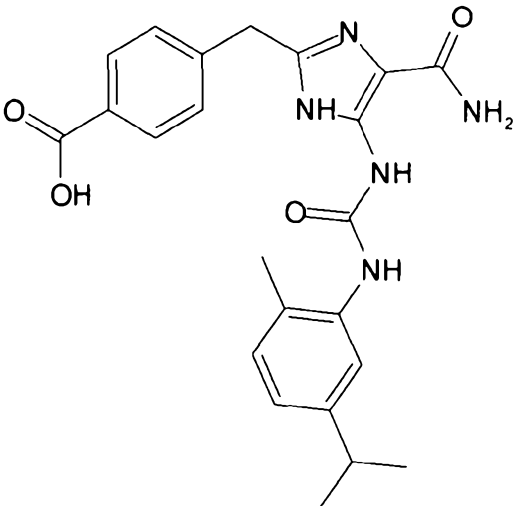
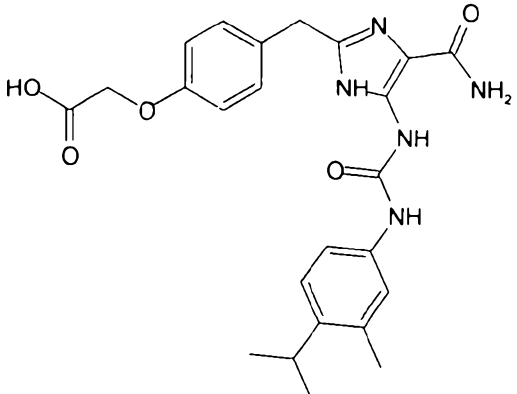
5	"B36"		481	2.81
10		Ethyl (4-{4-carbamoyl-5-[3-(4-isopropylphenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetate		
15	"B37"		531	2.40
20		2-[4-(4-Methylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		
25				
30				
35				

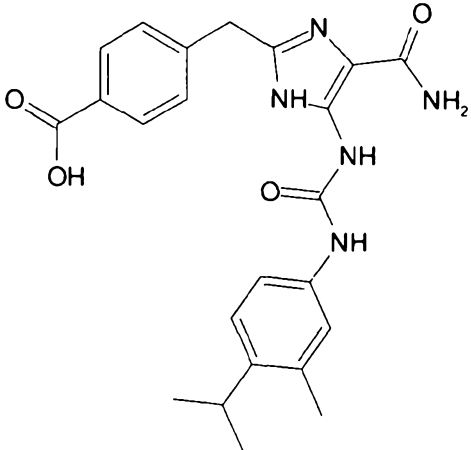
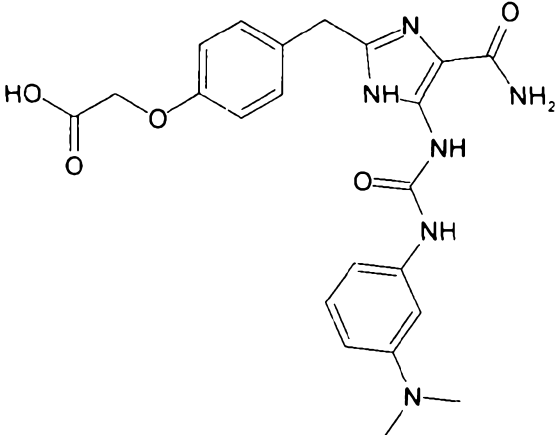
"B38" 5 10	 2-[4-(1-Pyridin-2-ylmethyl-1H-pyrazol-3-yl-carbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4-carboxamide	605	2.51
"B39" 15 20	 N-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenyl)-isonicotinamide	524	2.45
"B40" 25 30 35	 4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid	422	2.59

5		452	2.59
10	(4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
15		467	2.61
20	(4-{4-Carbamoyl-5-[3-(5-isopropyl-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
25			

30

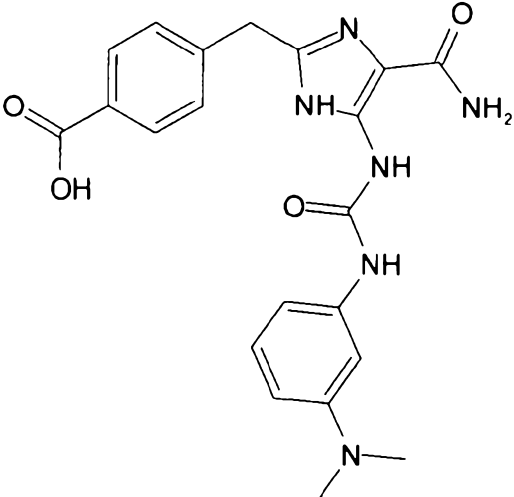
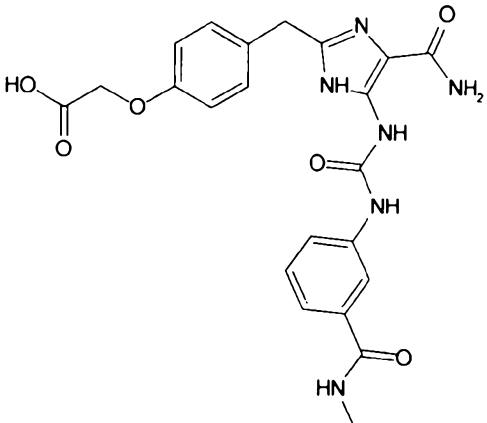
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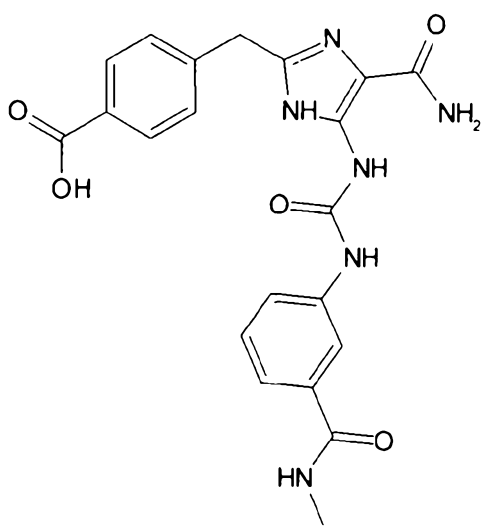
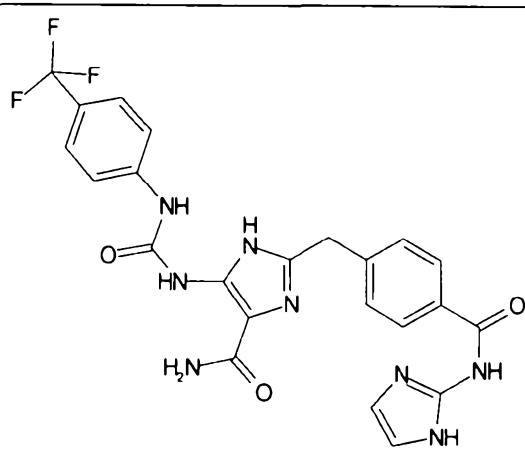
5	"B43"		436	2.61
10				
15				
20	"B44"		467	2.61
25				
30				
35				

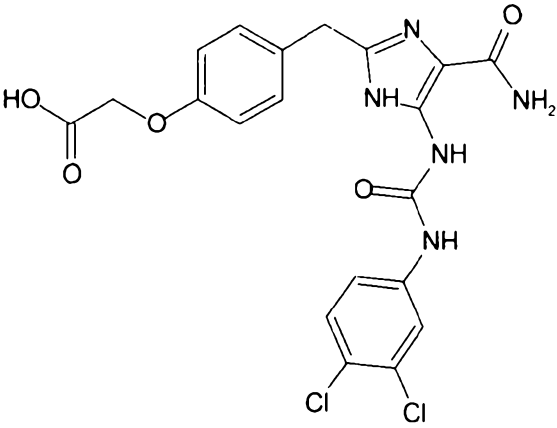
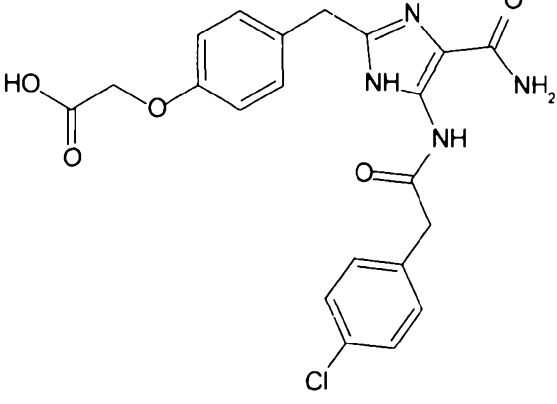
5	"B45"		436	2.65
10		4-{4-Carbamoyl-5-[3-(4-isopropyl-3-methyl-phenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid		
15	"B46"		453	1.98
20		(4-{4-Carbamoyl-5-[3-(3-dimethylaminophenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
25				

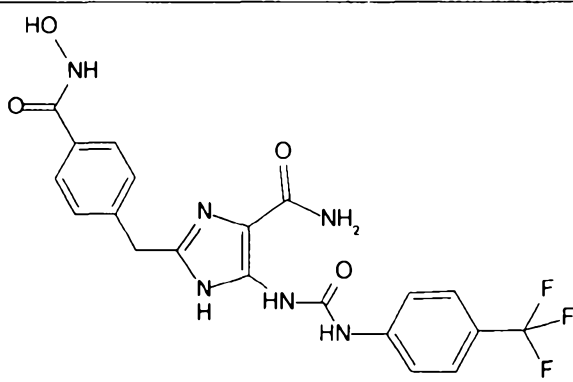
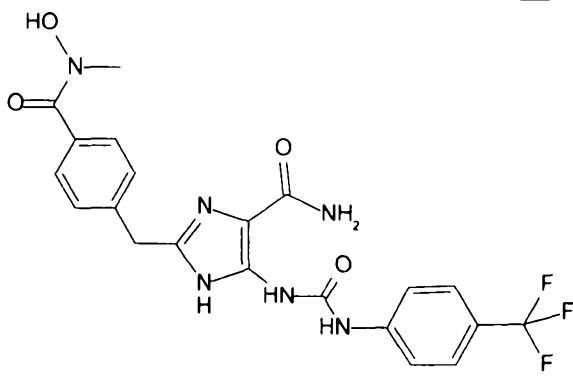
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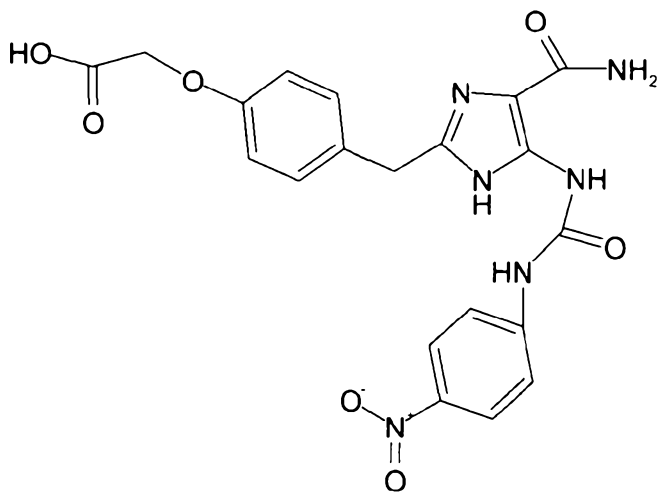
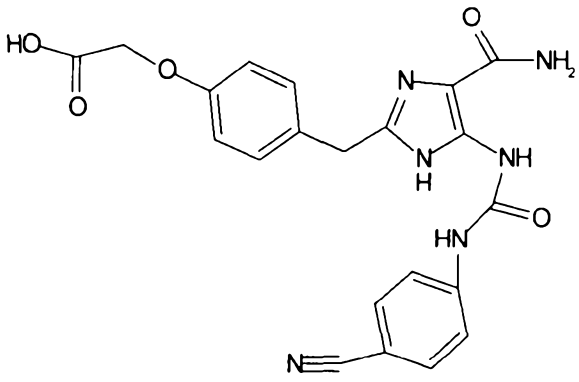
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5	"B47"		423	1.99
15	"B48"		467	2.09

5	"B49"		437	2.09
15	"B50"		513	2.49

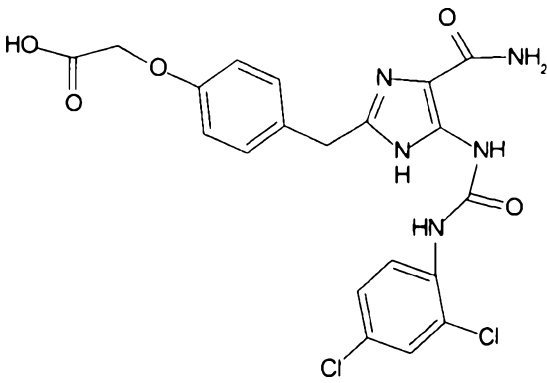
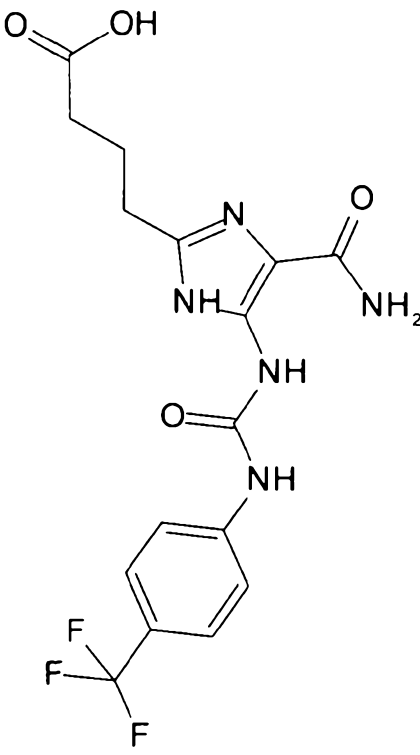
5	"B51"		479	2.59
10		(4-{4-Carbamoyl-5-[3-(3,4-dichlorophenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
15	"B52"		444	2.39
20		(4-{4-Carbamoyl-5-[2-(4-chlorophenyl)acetyl-amino]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
25				
30				
35				

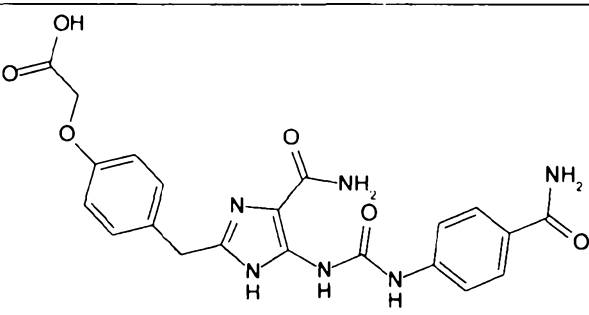
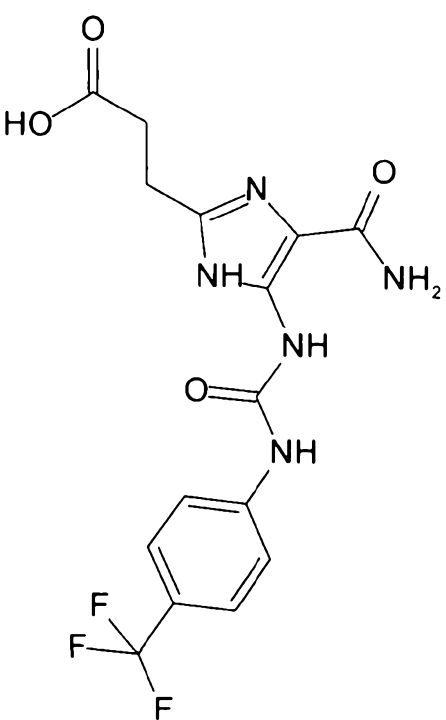
5	"B53"		463	2.42
10		2-(4-Hydroxycarbamoylbenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		
15	"B54"		477	2.48
20		2-[4-(Hydroxymethylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		
25				
30				
35				

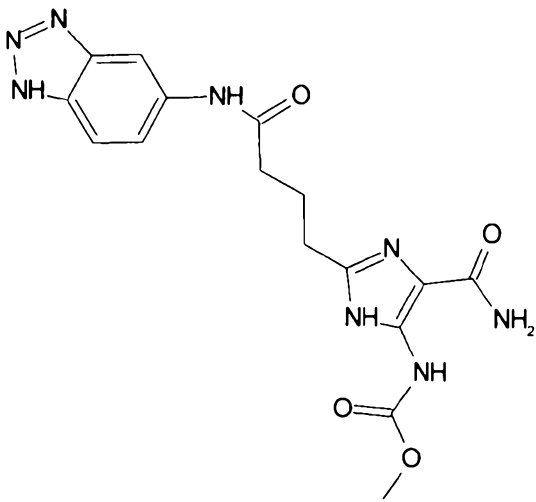
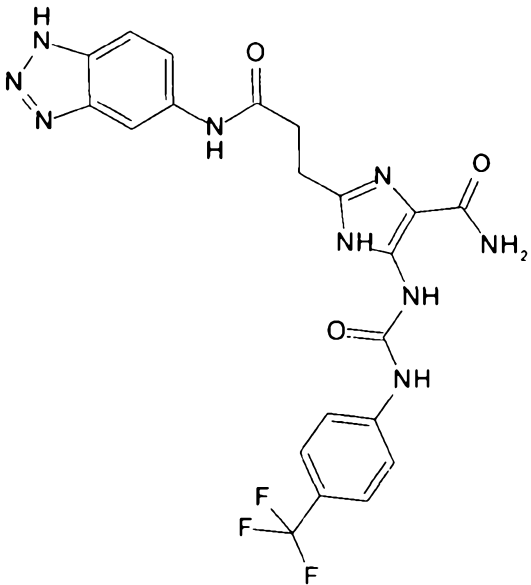
5	"B55"		455	2.65
10		(4-{4-Carbamoyl-5-[3-(4-nitrophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid		
15	"B56"		435	2.04
20		(4-{4-Carbamoyl-5-[3-(4-cyanophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid		
25				

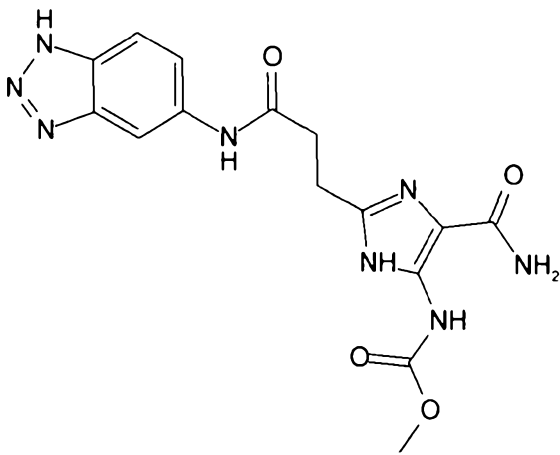
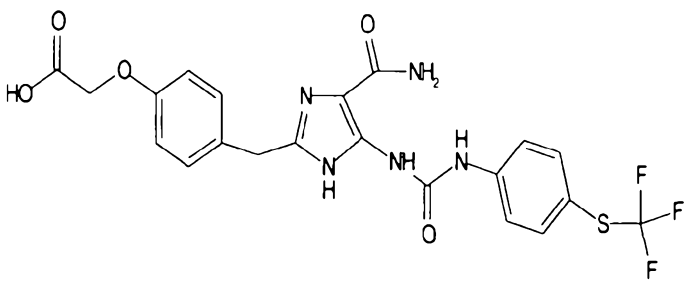
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5	"B57"		479	3.02
10		(4-{4-Carbamoyl-5-[3-(2,4-dichlorophenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid		
15	"B58"		400	2.35
20		4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-yl}butyric acid		
25				
30				

5	"B59"	 (4-{4-Carbamoyl-5-[3-(4-carbamoylphenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid	453	2.17
10				
15	"B60"	 3-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazol-2-yl}propionic acid	386	2.68
20				
25				
30				

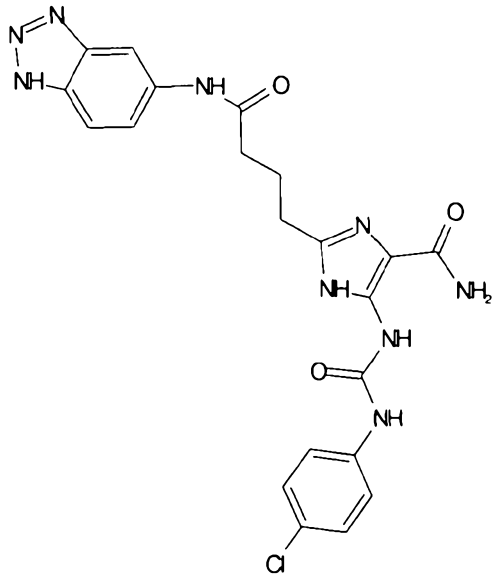
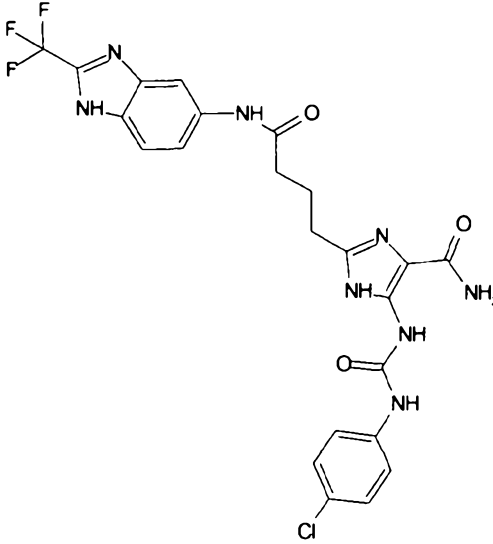
5	"B61"		387	2.16
10		Methyl {2-[3-(1H-benzotriazol-5-ylcarbamoyl)-propyl]-5-carbamoyl-3H-imidazol-4-yl}carbamate		
15	"B62"		502	2.70
20		2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide		
25				
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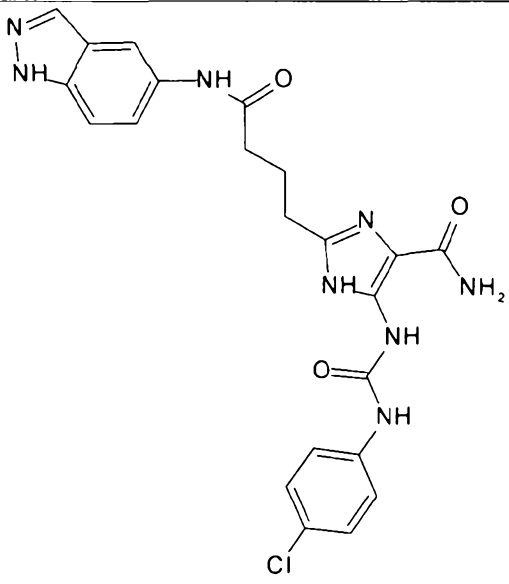
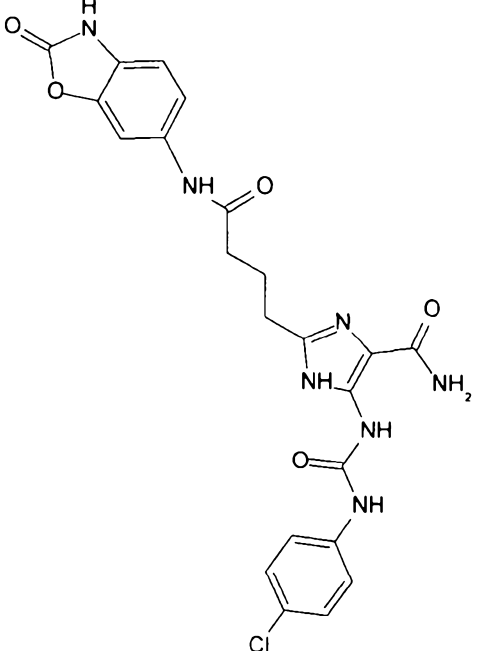
5	"B63"		373	2.19
10		Methyl {2-[2-(1H-benzotriazol-5-yl)carbamoyl]-ethyl}-5-carbamoyl-3H-imidazol-4-yl}carbamate		
15	"B64"		510	3.06
20		(4-{4-Carbamoyl-5-[3-(4-trifluoromethylsulfanyl-phenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid		

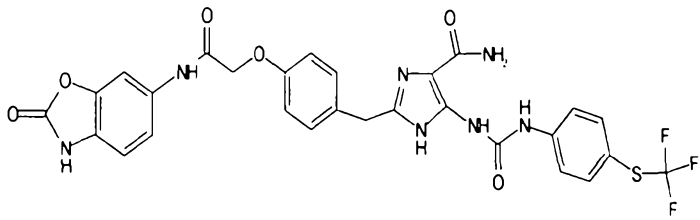
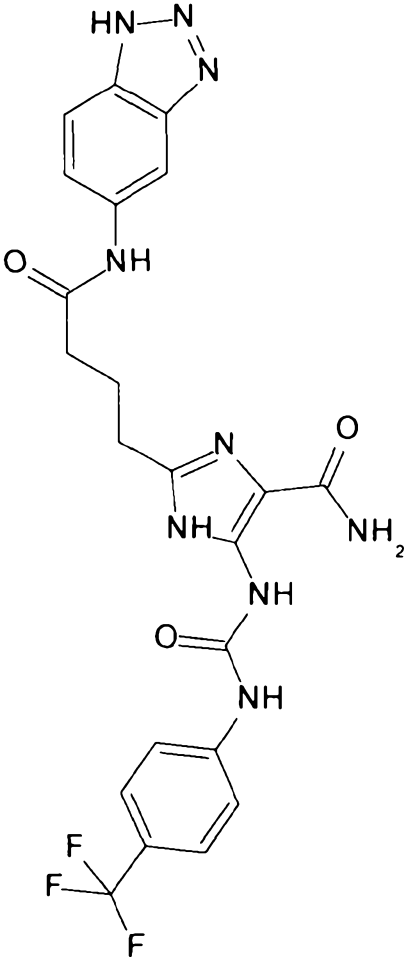
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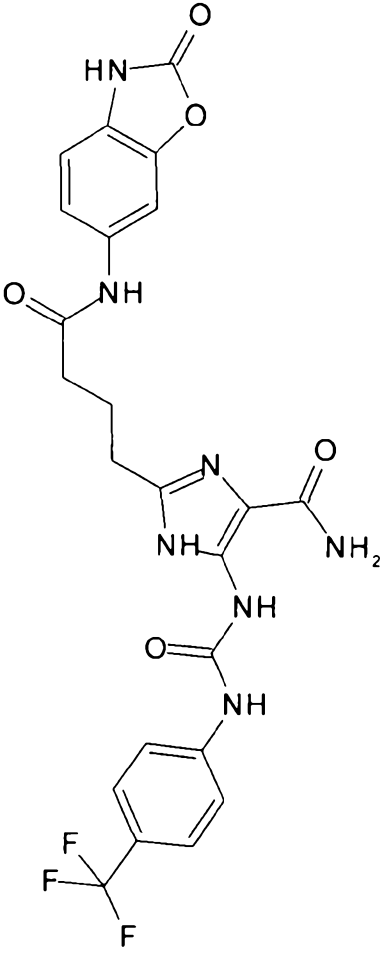
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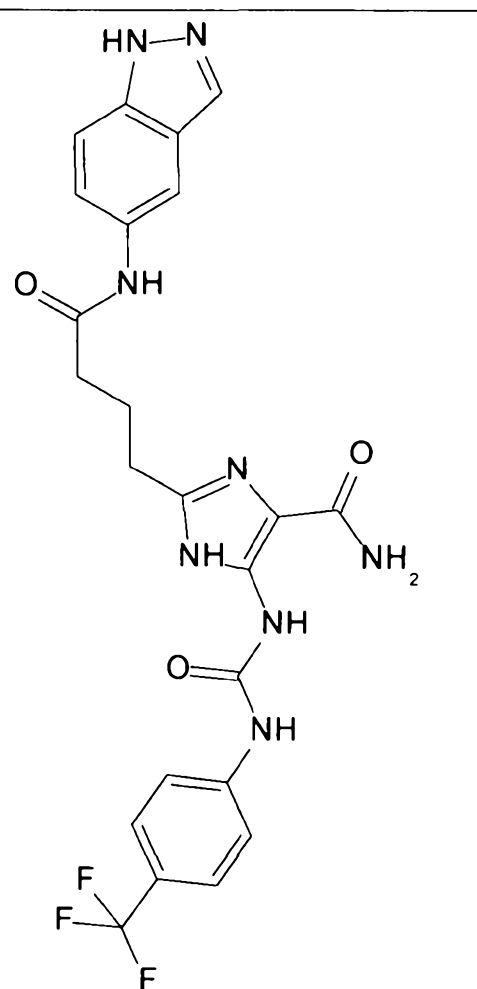
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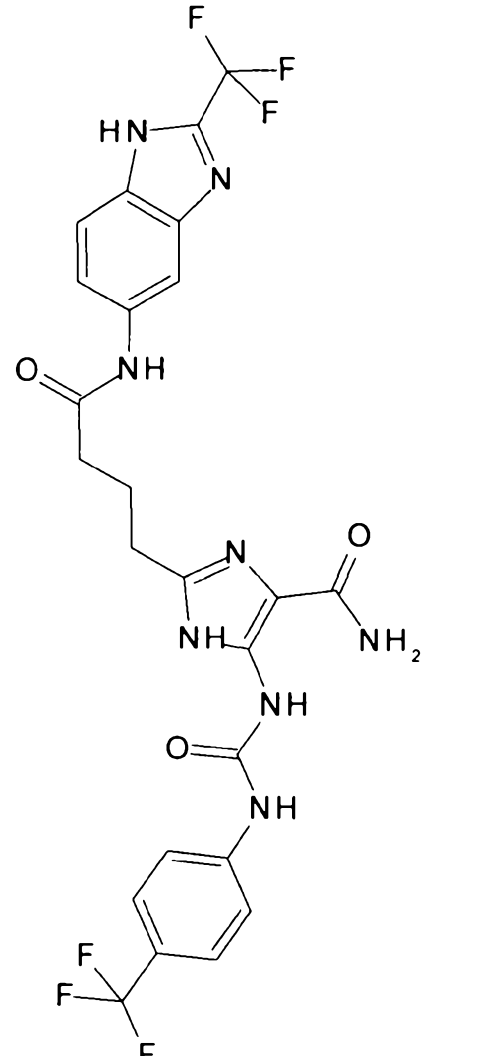
5	"B65"		483	2.53
10		2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-chlorophenyl)ureido]-1H-imidazole-4-carboxylic acid		
15				
20	"B66"		550	2.71
25		5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-trifluoromethyl-1H-benzimidazol-5-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid		
30				
35				

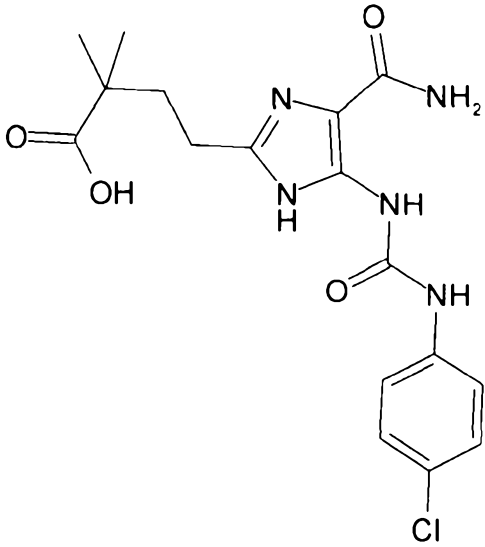
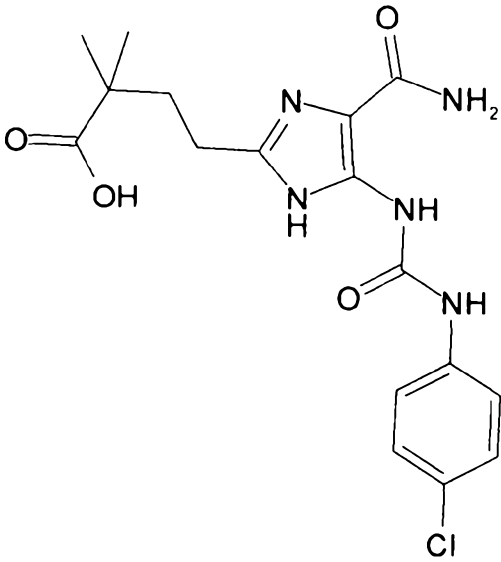
"B67"	 5-[3-(4-Chlorophenyl)ureido]-2-[3-(1H-indazol-5-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid	482	2.55
"B68"	 5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid	499	2.57

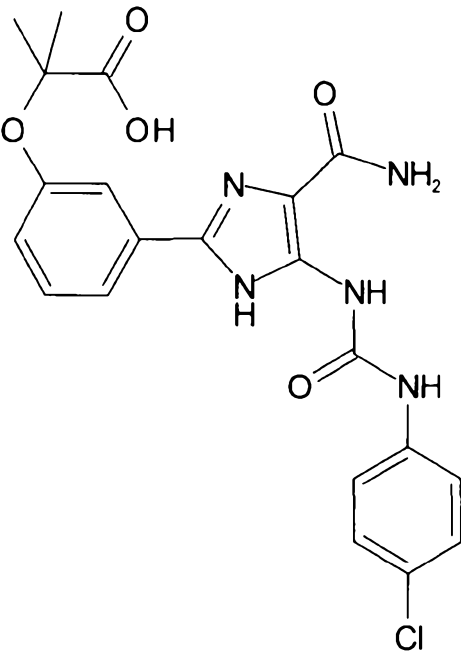
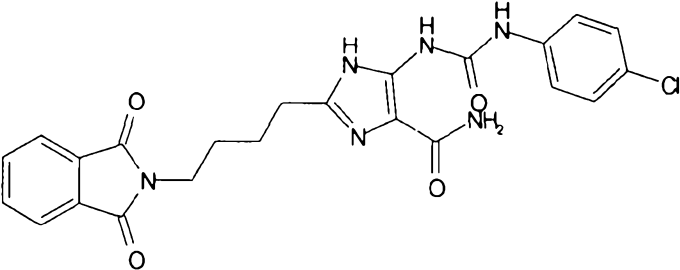
5	"B69"		643	3.08
10		2-{4-[(2-Oxo-2,3-dihydrobenzoxazol-6-yl-carbamoyl)methoxy]benzyl}-5-[3-(4-trifluoromethylsulfanylphenyl)ureido]-1H-imidazole-4-carboxylic acid		
15	"B70"		516	2.70
20		2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid		
25				
30				
35				

"B71"	 2-[3-(2-Oxo-2,3-dihydrobenzoxazol-6-yl-carbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4-carboxylic acid	532	2.72
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"B72"	 <chem>NC(=O)C1=CN=C2C(=C1)C(=CN2)CCCC(=O)Nc1ccc2c(c1)c[nH]2</chem> <chem>NC(=O)Nc1ccc(cc1)NC(=O)Nc2c[nH]c3c2C(=O)O</chem>	515	2.72
	2-[3-(1H-Indazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid		

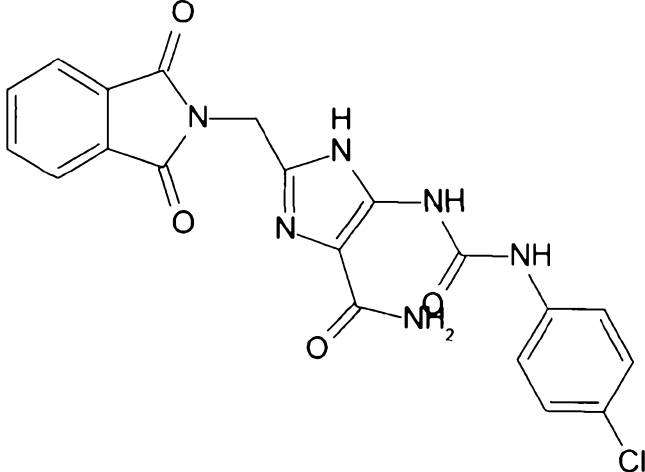
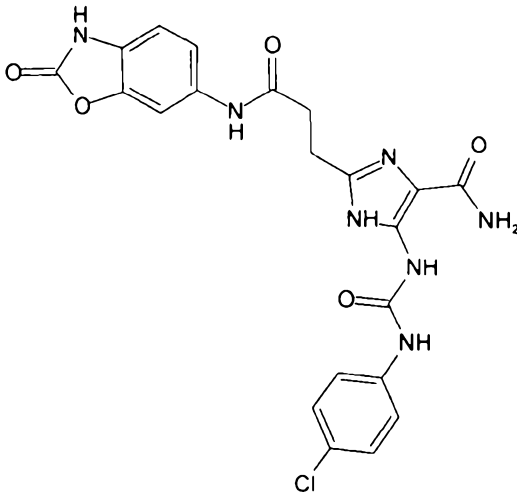
"B73"	 2-[3-(2-Trifluoromethyl-1H-benzimidazol-5-yl-carbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4-carboxylic acid	583	2.87
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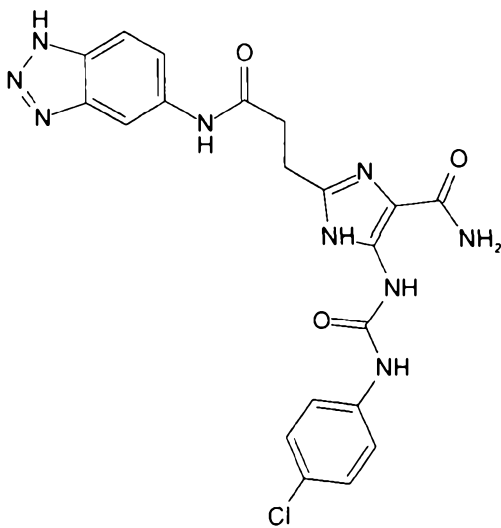
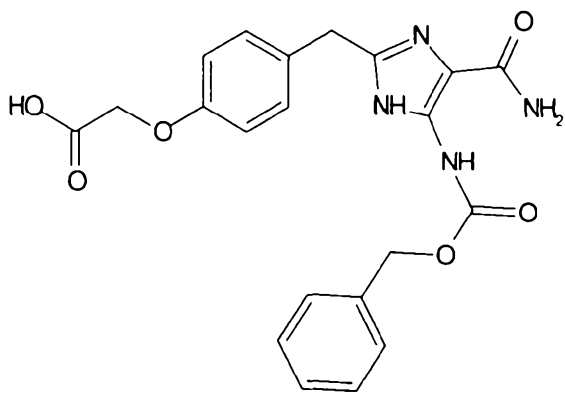
5	"B74"		518	2.74
10		2-[2-(2-Oxo-2,3-dihydrobenzoxazol-6-yl-carbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4-carboxylic acid		
15				
20	"B75"		395	2.75
25		4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}-2,2-dimethylbutyric acid		
30				

5			
10	2-(3-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)-2-methylpropionic acid	459	3.17
15			
20		482	3.04
25	5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroisindol-2-ylmethyl)-1H-imidazole-4-carboxamide		

30

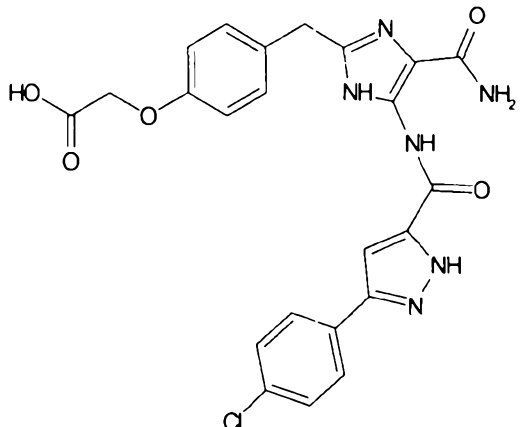
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5	"B78"		440	3.08
10		5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroisindol-2-ylmethyl)-1H-imidazole-4-carboxamide		
15	"B79"		485	2.60
20		5-[3-(4-Chlorophenyl)ureido]-2-[2-(2-oxo-2,3-dihydrobenzoxazol-6-ylcarbonyl)ethyl]-1H-imidazole-4-carboxamide		
25				
30				

5	"B80"		469	2.58
10		2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-chlorophenyl)ureido]-1H-imidazole-4-carboxamide		
15				
20	"B81"		425	2.59
25		[4-(5-Benzyloxycarbonylamino-4-carbamoyl-1H-imidazol-2-ylmethyl)phenoxy]acetic acid		

30

35

"B82"	 <chem>NC(=O)c1nc(NC(=O)c2cc(Cl)cc2)c[nH]1Cc3ccc(OCC(=O)O)cc3</chem>	496	2.85
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[4-(4-Carbamoyl-5-[[5-(4-chlorophenyl)-2H-pyrazole-3-carbonyl]amino]-1H-imidazol-2-yl-methyl)phenoxy] acetic acid

Pharmacological data

Autotaxin inhibition (enzyme test)

Table 1

Compound No.	IC50
"A2"	A
"A6"	A
"A7"	A
"A8"	A
"A9"	A
"A10"	A
"A11"	A
"A12"	A
"A15"	A
"A27"	A
"A30"	A
"A31"	A
"A38"	A
"A1"	A
"A39"	A
"A40"	A
"A41"	A
"A42"	A
"A43"	A
"A49"	A
"A50"	A
"A51"	A
"A54"	A
"A55"	A
"A56"	A
"A57"	A

5	"A60"	A
	"A61"	A
	"A62"	A
	"A66"	A
	"A68"	A
10	"A71"	A
	"A72"	A
	"A74"	A
	"A84"	A
	"A85"	A
15	"A91"	A
	"A93"	A
	"A94"	A
	"A97"	A
	"A102"	A
20	"A3"	B
	"A4"	B
	"A5"	B
	"A13"	B
	"A14"	B
25	"A16"	B
	"A17"	B
	"A18"	B
	"A19"	B
	"A20"	B
30	"A21"	B
	"A22"	B
	"A23"	B
	"A24"	B
	"A25"	B
35	"A26"	B
	"A28"	B
	"A28"	B

	"A29"	B
	"A32"	B
	"A33"	B
5	"A36"	B
	"A37"	B
	"A44"	B
	"A45"	B
	"A46"	B
10	"A47"	B
	"A48"	B
	"A52"	B
	"A53"	B
	"A58"	B
15	"A59"	B
	"A63"	B
	"A64"	B
	"A65"	B
20	"A67"	B
	"A69"	B
	"A73"	B
	"A75"	B
	"A77"	B
25	"A78"	B
	"A79"	B
	"A80"	B
	"A81"	B
	"A82"	B
30	"A83"	B
	"A86"	B
	"A87"	B
	"A88"	B
35	"A89"	B
	"A90"	B

5

10

15

"A92"	B
"A95"	B
"A96"	B
"A98"	B
"A99"	B
"A100"	B
"A101"	B
"A103"	B
"B75"	B
"B77"	B
"B78"	B
"B79"	B
"B80"	B
"B82"	B

IC50: 1 μ M - 10 μ M = A>10 μ M = B

20

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30

35

Example A: Autotaxin test (enzyme test)

Test description

The autotaxin activity is measured indirectly using Amplex Red reagent. Amplex Red is measured here as fluorogenic indicator for the H_2O_2 formed. In detail, autotaxin converts the substrate lysophosphatidylcholine (LPC) into phosphocholine and lysophosphatidyl acid (LPA). After this reaction, the phosphocholine is reacted with alkaline phosphatase to give inorganic phosphate and choline. In the next step, choline is oxidised by choline oxidase to give betaine, with formation of H_2O_2 . H_2O_2 reacts with Amplex Red reagent in the presence of peroxidase (horseradish peroxidase) in a 1:1 stoichiometry and forms the highly fluorescent resorufin. The fluorescence is measured in a reaction-dependent kinetic mode in order that fluorescent signals from possible other fluorescent substances which are not involved in the reaction can be corrected out.

Test procedure

1.5 μl of a standard solution or of the test substances (substances with the name A(n)) in individual concentrations dissolved in 20mM Hepes pH 7.2 with a maximum of 7.7% of DMSO are pre-incubated together with 10 μl (16 ng) of highly purified recombinant autotaxin in a black microtitre plate provided with 384 wells at 22°C for 30 min. The reaction is then initiated by addition of 5 μl of L- α -lysophosphatidylcholine (LPC), where the final concentration of LPC is 75 μM . The mixture is incubated at 37°C for 90 min. After the incubation, Amplex Red reagent, peroxidase (horseradish peroxidase) and choline oxidase is added, and the fluorescence is immediately measured at 612 nm with excitation of 485 nm in a "Tecan Ultra multimode"

reader. The activity of autotaxin is calculated indirectly via detection of the H_2O_2 formed.

Material:

5

Microtitre plate: PS microplate, 384 wells, small volume, black Corning, Cat#3677

10

Protein: recombinant autotaxin (Baculovirale Hi5 Expression)

Substrate: L- α -lysophosphatidylcholine (chicken egg)); Avanti Polar Lipids # 830071P

15

Standard: C14 LPA, Avanti Polar Lipids, Cat# 857120P

Detection reagent: Amplex Red reagent; Invitrogen # A12222; dissolved in 1.923 ml of DMSO peroxidase type VI-A (horseradish) from Sigma # P6782; dissolved in 7.45 ml of test buffer, choline oxidase; Sigma # C5896; dissolved in 2.47 ml of test buffer

20

25

Detection reagent mix: 1:100 dilution of Amplex Red reagent in test buffer

Test buffer: 200 mM Tris HCl, Merck, Cat # 1.08219, pH 7.9, 0.1% of BSA, lipid-free, Roche Cat#775835

30

The following examples relate to medicaments:

35

Example B: Injection vials

5 A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example C: Suppositories

10 A mixture of 20 g of an active ingredient of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and
15 allowed to cool. Each suppository contains 20 mg of active ingredient.

Example D: Solution

20 A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This
25 solution can be used in the form of eye drops.

Example E: Ointment

30 500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example F: Tablets

35 A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed

in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

5

Example G: Dragees

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

10

Example H: Capsules

15

2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

20

Example I: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

25

30

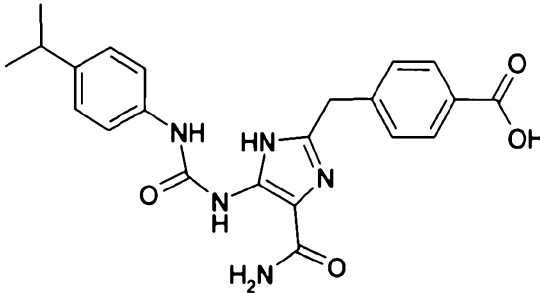
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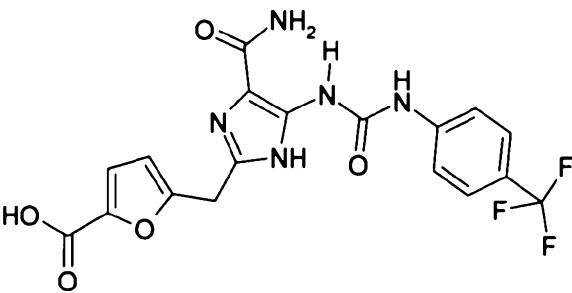
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

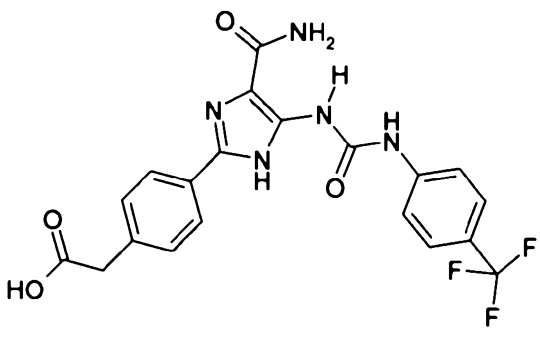
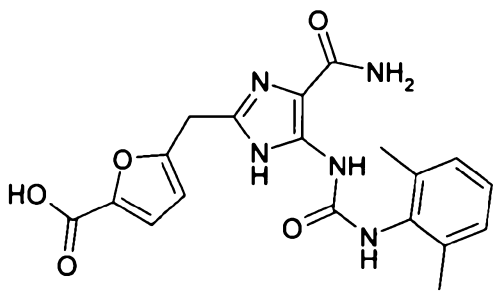
The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

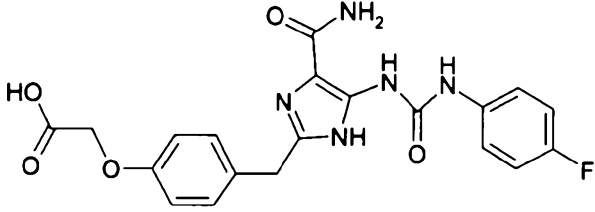
The claims defining the invention are as follows:

1. A compound selected from the group consisting of:

No.	Name and/or structure
"A1"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A2"	4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid 
"A3"	4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid
"A4"	4-{4-Carbamoyl-5-(3-hexylureido)-1H-imidazol-2-ylmethyl}-benzoic acid
"A5"	4-{4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl}-benzoic acid
"A6"	4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A7"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A8"	4-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A9"	4-{5-[3-(4-Butoxyphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}benzoic acid

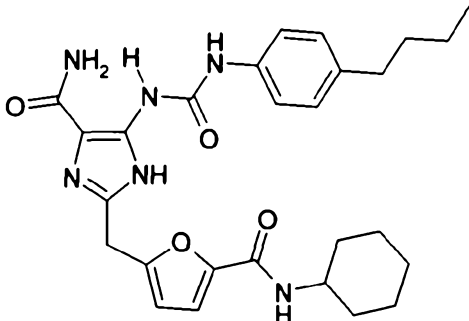
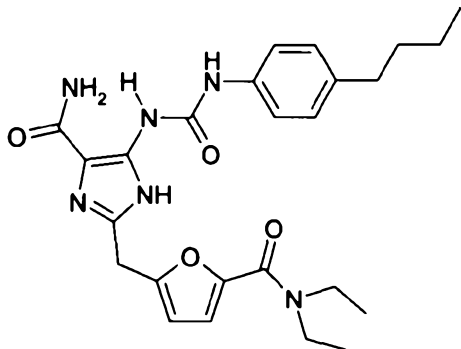
"A10"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid 
"A11"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A12"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A13"	5-{4-Carbamoyl-5-[3-(3-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A14"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A15"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A16"	4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A17"	4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A18"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}benzoic acid
"A19"	4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}benzoic acid

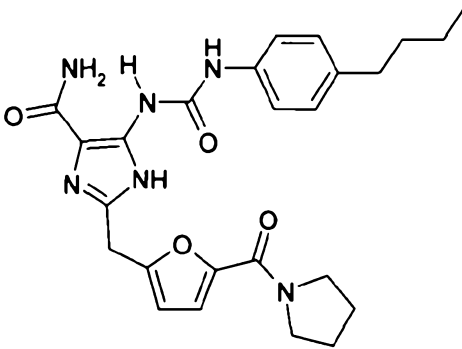
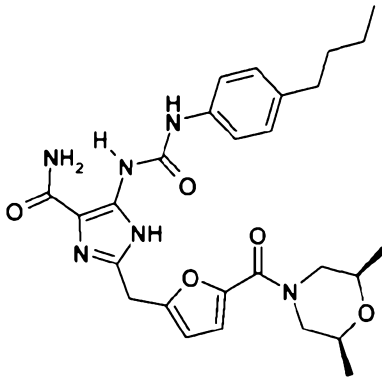
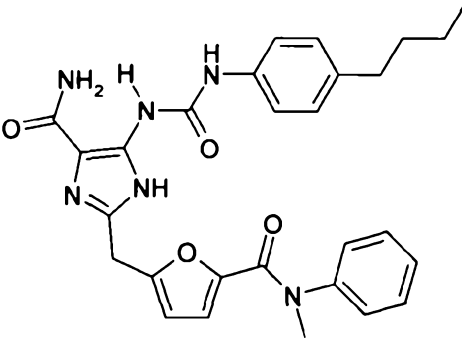
"A20"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
	
"A21"	(4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A22"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A23"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A24"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A25"	(4-{4-Carbamoyl-5-[3-(3,5-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenyl)acetic acid
"A26"	5-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
	
"A27"	5-[4-Carbamoyl-5-(3-phenethylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid
"A28"	5-[4-Carbamoyl-5-[3-(2,6-diethylphenyl)ureido]-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid
"A29"	5-[4-Carbamoyl-5-[3-(4-chloro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid

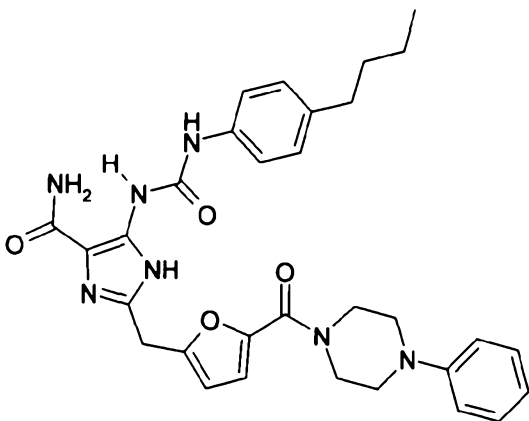
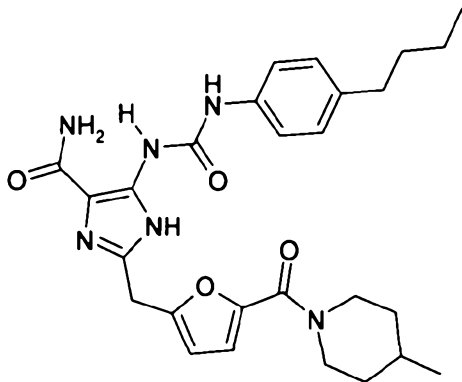
"A30"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A31"	5-{4-Carbamoyl-5-[3-(2,4,6-trimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A32"	5-{4-Carbamoyl-5-[3-(2-ethyl-6-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A33"	5-[4-Carbamoyl-5-(3-naphthalen-2-ylureido)-1H-imidazol-2-ylmethyl]furan-2-carboxylic acid
"A34"	5-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A35"	5-{4-Carbamoyl-5-[3-(4-chloro-2-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}furan-2-carboxylic acid
"A36"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid 
"A37"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A38"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A39"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A40"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]-phenoxy}acetic acid
"A41"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A42"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A43"	(4-{4-Carbamoyl-5-[3-(4-pentylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid

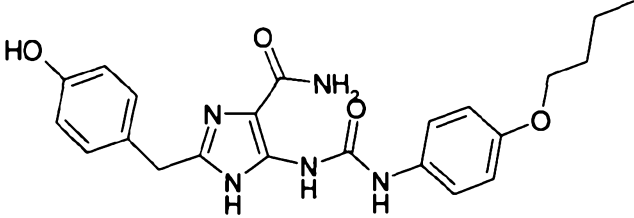
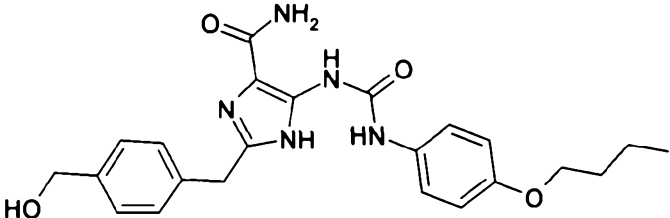
"A44"	(4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)-ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A45"	(4-{4-Carbamoyl-5-[3-(4-phenoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy)acetic acid
"A46"	(4-{4-Carbamoyl-5-[3-(4-fluorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A47"	(4-{4-Carbamoyl-5-[3-(2-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A48"	(4-{4-Carbamoyl-5-[3-(2,6-dimethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A49"	(4-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A50"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A51"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A52"	(4-{5-[3-(4-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-yl}phenoxy)acetic acid
"A53"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-yl]-phenoxy}acetic acid
"A54"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A55"	(4-{4-Carbamoyl-5-[3-(2-fluoro-5-trifluoromethylphenyl)-ureido]-1H-imidazol-2-yl}phenoxy)acetic acid
"A56"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A57"	(4-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A58"	{4-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-yl-methoxy]phenyl}acetic acid
"A59"	(4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid

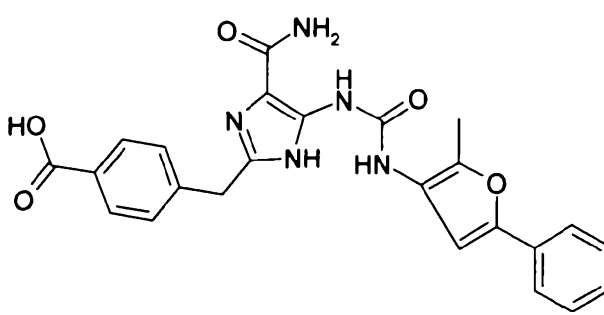
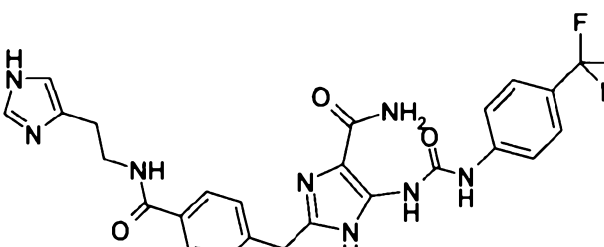
"A60"	(4-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A61"	(4-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A62"	(4-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A63"	(4-{4-Carbamoyl-5-[3-(3,5-dimethoxyphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A64"	(4-{4-Carbamoyl-5-[3-(4-fluoro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethoxy}phenyl)acetic acid
"A65"	5-{4-Carbamoyl-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A66"	5-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A67"	5-[4-Carbamoyl-5-(3-o-tolylureido)-1H-imidazol-2-ylmethyl]-thiophene-2-carboxylic acid
"A68"	5-{4-Carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A69"	5-[4-Carbamoyl-5-(3-p-tolylureido)-1H-imidazol-2-ylmethyl]-thiophene-2-carboxylic acid
"A70"	5-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A71"	5-{4-Carbamoyl-5-[3-(2,4-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A72"	5-{4-Carbamoyl-5-[3-(4-ethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A73"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A74"	5-{4-Carbamoyl-5-[3-(4-chloro-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid
"A75"	5-{4-Carbamoyl-5-[3-(4-fluoro-3-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}thiophene-2-carboxylic acid

"A76"	2-[4-(4-Pyridin-2-ylmethylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A77"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclohexylcarbamoylefuran-2-ylmethyl)-1H-imidazole-4-carboxamide 
"A78"	5-[3-(4-Butylphenyl)ureido]-2-(5-diethylcarbamoylefuran-2-ylmethyl)-1H-imidazole-4-carboxamide 
"A79"	2-[5-(Butylmethylcarbamoylefuran-2-ylmethyl)-5-[3-(4-butylphenyl)ureido]-1H-imidazole-4-carboxamide
"A80"	5-[3-(4-Butylphenyl)ureido]-2-(5-dibutylcarbamoylefuran-2-ylmethyl)-1H-imidazole-4-carboxamide

"A81"	5-[3-(4-Butylphenyl)ureido]-2-[5-(pyrrolidine-1-carbonyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A82"	5-[3-(4-Butylphenyl)ureido]-2-[5-((5R,6S)-2,6-dimethyl-morpholine-4-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A83"	5-[3-(4-Butylphenyl)ureido]-2-[5-(morpholine-4-carbonyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A84"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylphenylcarbamoyl)-furan-2-ylmethyl]-1H-imidazole-4-carboxamide 
"A85"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methylpiperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide

"A86"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-phenylpiperazine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
	
"A87"	5-[3-(4-Butylphenyl)ureido]-2-[5-(4-methylpiperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
	
"A88"	5-[3-(4-Butylphenyl)ureido]-2-[5-(piperidine-1-carbonyl)furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A89"	5-[3-(4-Butylphenyl)ureido]-2-(5-cyclopropylcarbamoylefuran-2-ylmethyl)-1H-imidazole-4-carboxamide
"A90"	5-[3-(4-Butylphenyl)ureido]-2-[5-(methylpropylcarbamoylefuran-2-ylmethyl)-1H-imidazole-4-carboxamide
"A91"	5-[3-(4-Butylphenyl)ureido]-2-[5-[4-(2-hydroxyethyl)-piperidine-1-carbonyl]furan-2-ylmethyl]-1H-imidazole-4-carboxamide
"A92"	4-{4-Carbamoyl-5-[3-(2-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid
"A93"	4-{4-Carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid

"A94"	5-[3-(4-Butylphenyl)ureido]-2-[4-(morpholine-4-carbonyl)-benzyl]-1H-imidazole-4-carboxamide
"A95"	5-[3-(4-Butoxyphenyl)ureido]-2-(4-hydroxybenzyl)-1H-imidazole-4-carboxamides 
"A96"	2-(4-Nitrobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A97"	from "A96" by reduction using Fe powder /NH₄Cl: 2-(4-aminobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide
"A98"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate
"A99"	Methyl 4-{4-carbamoyl-5-[3-(4-trifluoromethoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate
"A100"	from methyl 4-{4-carbamoyl-5-[3-(4-butoxyphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoate by reduction using DIBALH: 5-[3-(4-butoxyphenyl)ureido]-2-(4-hydroxymethylbenzyl)-1H-imidazole-4-carboxamide 

"A101"	4-{4-Carbamoyl-5-[3-(2-methyl-5-phenylfuran-3-yl)ureido]-1H-imidazol-2-ylmethyl}benzoic acid 
"A102"	4-[4-Carbamoyl-5-(3-thiophen-2-ylureido)-1H-imidazol-2-ylmethyl]benzoic acid
"A103"	2-[4-[2-(1H-Imidazol-4-yl)ethylcarbamoyl]benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide 

"B1"	2-(4-Acetylbenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B2"	2-[4-(3,5-Dimethylpyrazole-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B3"	5-[3-(4-Butylphenyl)ureido]-2-(4-guanidinocarbonylbenzyl)-1H-imidazole-4- carboxamide,
"B4"	5-[3-(4-Isopropylphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4- carboxamide,
"B5"	2-(4-Methoxybenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic carboxamide,

"B6"	2-(4-Methoxybenzyl)-5-[3-(3-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B7"	3-{3-[5-Carbamoyl-2-(4-methoxybenzyl)-3H-imidazol-4-yl]-ureido} benzoic acid ester,
"B8"	2-Benzo-1,3-dioxol-5-ylmethyl-5-(3-benzo-1,3-dioxol-5-yl-ureido)-1H-imidazole-4- carboxamide,
"B9"	5-(3-Benzo-1,3-dioxol-5-ylureido)-2-[4-(4-methylpiperazine-1-carbonyl)benzyl]-1H-imidazole-4- carboxamide,
"B10"	5-[3-(4-Isopropylphenyl)ureido]-2-{4-[2-(4-methylpiperazin-1-yl)-2-oxoethoxy]benzyl}-1H-imidazole-4 carboxamide,
"B11"	{4-[5-(3-Benzo-1,3-dioxol-5-ylureido)-4-carbamoyl-1H-imidazol-2-ylmethyl]phenoxy}acetic acid,
"B12"	2-(4-Methanesulfonylbenzyl)-5-[3-(4-trifluoromethylphenyl)-ureido]-1H-imidazole-4- carboxamide,
"B13"	5-[3-(4-Butylphenyl)ureido]-2-(4-methanesulfonylbenzyl)-1H-imidazole-4- carboxamide
"B14"	2-[4-(5-Methylthiazol-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B15"	2-[4-(Pyridin-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,

"B16"	[3-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}benzoylamino)-5-methylpyrazol-1-yl] acetic acid,
"B17"	2-(4-Iodobenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B18"	5-[3-(4-Butoxyphenyl)ureido]-2-(4-methylsulfanylbenzyl)-1H-imidazole-4-carboxamide,
"B19"	(4-{4-Carbamoyl-5-[3-(2,7a-dihydrobenzofuran-5-yl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B20"	({4-[5-(3-Benzo[b]thiophen-5-ylureido)-4-carbamoyl-1H-imidazol-2-ylmethyl]phenoxy} acetic acid,
"B21"	5-[3-(2-Fluoro-5-trifluoromethylphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4- carboxamide,
"B22"	5-[3-(3-Chlorophenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4- carboxamide,
"B23"	5-[3-(3-Chloro-4-methoxyphenyl)ureido]-2-(4-methoxybenzyl)-1H-imidazole-4-carboxamide,
"B24"	4-{4-Carbamoyl-5-[3-(3-chloro-4-methoxyphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B25"	(4-{4-Carbamoyl-5-[3-(2,3-dimethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,

"B26"	(4-{4-Carbamoyl-5-[3-(3-chlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B27"	Benzotriazol-1-yl 4-{4-carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoate,
"B28"	2-[4-(4-Pyridin-2-ylmethylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B29"	2-[4-(Morpholine-4-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B30"	2-[4-[(Pyridin-2-ylmethyl)carbamoyl]benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B31"	4-{5-[3-(4-tert-Butylphenyl)ureido]-4-carbamoyl-1H-imidazol-2-ylmethyl} benzoic acid,
"B32"	4-{4-Carbamoyl-5-[3-(2-fluoro-5-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B33"	4-{4-Carbamoyl-5-[3-(3-chloro-4-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B34"	2-[4-(2-Pyridin-3-ylacetyl amino)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B35"	2-[4-(2-1H-Imidazol-4-ylacetyl amino)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,

"B36"	Ethyl (4-{4-carbamoyl-5-[3-(4-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetate,
"B37"	2-[4-(4-Methylpiperazine-1-carbonyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B38"	2-[4-(1-Pyridin-2-ylmethyl-1H-pyrazol-3-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxamide,
"B39"	N-(4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenyl)isonicotinamide,
"B40"	4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B41"	(4-{4-Carbamoyl-5-[3-(3-isopropylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B42"	(4-{4-Carbamoyl-5-[3-(5-isopropyl-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B43"	4-{4-Carbamoyl-5-[3-(5-isopropyl-2-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B44"	(4-{4-Carbamoyl-5-[3-(4-isopropyl-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B45"	4-{4-Carbamoyl-5-[3-(4-isopropyl-3-methylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,

"B46"	(4-{4-Carbamoyl-5-[3-(3-dimethylaminophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B47"	4-{4-Carbamoyl-5-[3-(3-dimethylaminophenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B48"	(4-{4-Carbamoyl-5-[3-(3-methylcarbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B49"	4-{4-Carbamoyl-5-[3-(3-methylcarbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl} benzoic acid,
"B50"	2-[4-(1H-Imidazol-2-ylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B51"	(4-{4-Carbamoyl-5-[3-(3,4-dichlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B52"	(4-{4-Carbamoyl-5-[2-(4-chlorophenyl)acetyl amino]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B53"	2-(4-Hydroxycarbamoylbenzyl)-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B54"	2-[4-(Hydroxymethylcarbamoyl)benzyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B55"	(4-{4-Carbamoyl-5-[3-(4-nitrophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid
"B56"	(4-{4-Carbamoyl-5-[3-(4-cyanophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,

"B57"	(4-{4-Carbamoyl-5-[3-(2,4-dichlorophenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B58"	4-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}butyric acid,
"B59"	(4-{4-Carbamoyl-5-[3-(4-carbamoylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B60"	3-{4-Carbamoyl-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazol-2-yl}propionic acid,
"B61"	Methyl {2-[3-(1H-benzotriazol-5-ylcarbamoyl)propyl]-5-carbamoyl-3H-imidazol-4-yl}carbamate,
"B62"	2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4- carboxamide,
"B63"	Methyl {2-[2-(1H-benzotriazol-5-ylcarbamoyl)ethyl]-5-carbamoyl-3H-imidazol-4-yl}carbamate,
"B64"	(4-{4-Carbamoyl-5-[3-(4-trifluoromethylsulfanylphenyl)ureido]-1H-imidazol-2-ylmethyl}phenoxy) acetic acid,
"B65"	2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-chlorophenyl)ureido]-1H-imidazole-4- carboxylic acid,
"B66"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-trifluoromethyl-1H-benzimidazol-5-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid,

"B67"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(1H-indazol-5-yl-carbamoyl)propyl]-1H-imidazole-4-carboxylic acid,
"B68"	5-[3-(4-Chlorophenyl)ureido]-2-[3-(2-oxo-2,3-dihydrobenz-oxazol-6-ylcarbamoyl)propyl]-1H-imidazole-4-carboxylic acid,
"B69"	2-[4-[(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)-methoxy]benzyl]-5-[3-(4-trifluoromethylsulfanylphenyl)-ureido]-1H-imidazole-4-carboxylic acid,
"B70"	2-[3-(1H-Benzotriazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B71"	2-[3-(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B72"	2-[3-(1H-Indazol-5-ylcarbamoyl)propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B73"	2-[3-(2-Trifluoromethyl-1H-benzimidazol-5-ylcarbamoyl)-propyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B74"	2-[2-(2-Oxo-2,3-dihydrobenzoxazol-6-ylcarbamoyl)ethyl]-5-[3-(4-trifluoromethylphenyl)ureido]-1H-imidazole-4-carboxylic acid,
"B75"	4-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}-2,2-dimethylbutyric acid,

"B76"	2-(3-{4-Carbamoyl-5-[3-(4-chlorophenyl)ureido]-1H-imidazol-2-yl}phenoxy)-2-methylpropionic acid,
"B77"	5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroiso-indol-2-ylmethyl)-1H-imidazole-4- carboxamide,
"B78"	5-[3-(4-Chlorophenyl)ureido]-2-(1,3-dioxo-1,3-dihydroiso-indol-2-ylmethyl)-1H-imidazole-4- carboxamide,
"B79"	5-[3-(4-Chlorophenyl)ureido]-2-[2-(2-oxo-2,3-dihydrobenz-oxazol-6-ylcarbamoyl)ethyl]-1H-imidazole-4-carboxamide,
"B80"	2-[2-(1H-Benzotriazol-5-ylcarbamoyl)ethyl]-5-[3-(4-chloro-phenyl)ureido]-1H-imidazole-4-carboxamide,
"B81"	[4-(5-Benzyloxycarbonylamino-4-carbamoyl-1H-imidazol-2-ylmethyl)phenoxy]acetic acid or
"B82"	[4-(4-Carbamoyl-5-{[5-(4-chlorophenyl)-2H-pyrazole-3-carbonyl]amino}-1H-imidazol-2-ylmethyl)phenoxy] acetic acid

and pharmaceutically usable tautomers, salts and stereoisomers thereof, including mixtures thereof in all ratios.

2. A medicament comprising at least one compound according to Claim 1 and/or pharmaceutically usable derivatives, salts, solvates, tautomers and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.
3. Use of a compound according to Claim 1 for the preparation of a medicament for the treatment or prophylaxis of cancer.

4. The use according to Claim 3, wherein the cancer is a tumour of the squamous epithelium, of the bladder, of the stomach, of the kidneys, of the head and/or neck, of the oesophagus, of the cervix, of the thyroid, of the intestine, of the liver, of the brain, of the prostate, of the urogenital tract, of the lymphatic system, of the larynx or of the lung.
5. The use according to Claim 4, wherein the tumour originates from monocytic leukaemia, lung adenocarcinoma, a small-cell lung carcinoma, pancreatic cancer, ovarian carcinoma, a glioblastoma, breast carcinoma or colon carcinoma.
6. The use according to Claim 3, wherein the cancer is a tumour of the blood and/or immune system.
7. The use according to Claim 6, wherein the tumour originates from acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphatic leukaemia or chronic lymphatic leukaemia.
8. Use of a compound according to Claim 1 and/or physiologically acceptable salts thereof, for the preparation of a medicament for the treatment of a tumour, wherein a therapeutically effective amount of the compound of Claim 1 is administered in combination with radiotherapy and a compound selected from the group consisting of: 1) an oestrogen receptor modulator, 2) an androgen receptor modulator, 3) a retinoid receptor modulator, 4) a cytotoxic agent, 5) an antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) a HMG-CoA reductase inhibitor, 8) a HIV protease inhibitor, 9) a reverse transcriptase inhibitor and 10) other angiogenesis inhibitors.
9. A method for the treatment of a tumour in a subject in need thereof, the method comprising administration to the subject of a therapeutically effective amount of a compound according to Claim 1 and/or

physiologically acceptable salts thereof, or a composition according to claim 2, in combination with radiotherapy and a compound selected from the group consisting of: 1) an oestrogen receptor modulator, 2) an androgen receptor modulator, 3) a retinoid receptor modulator, 4) a cytotoxic agent, 5) an antiproliferative agent, 6) a prenyl-protein transferase inhibitor, 7) a HMG-CoA reductase inhibitor, 8) a HIV protease inhibitor, 9) a reverse transcriptase inhibitor and 10) other angiogenesis inhibitors.