ETHER DERIVATIVES, THEIR MANUFACTURE AND USE AS PHARMACEUTICAL AGENTS

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

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

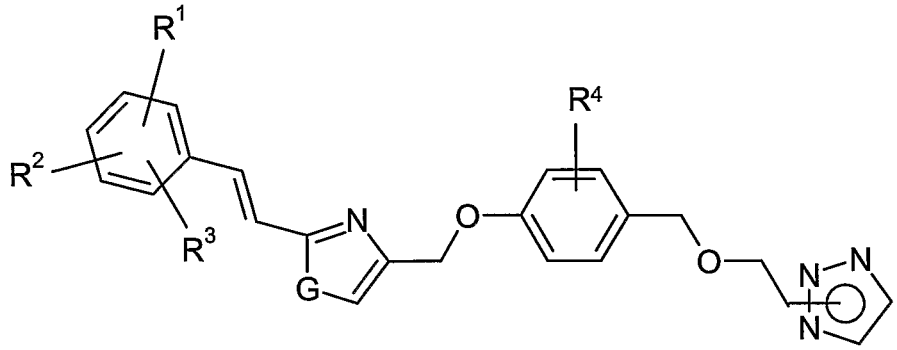
It is known that receptor tyrosine kinases of the HER-family like HER-2 and EGFR (HER-1) are frequently aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, leukaemia and ovarian, bronchial and pancreatic cancer. High levels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

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

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

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

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



formula I,

wherein

R^1 is -O-alkyl;
-S-alkyl;
-NH-alkyl;
all alkyl groups being optionally substituted with one or several halogen atoms;

R^2 is hydrogen; or
halogen; and

R^3 is hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form a 5 or 6 membered heterocyclic ring, being optionally once or several times substituted with halogen; and

R^3 is hydrogen; or
halogen;

G is oxygen; or
sulfur and

R^4 is hydrogen;
C_1-C_3 alkyl;
C_1-C_3 alkoxy; or

halogen; and

pharmaceutically acceptable salts thereof.

The compounds of the present invention show activity as inhibitors of the HER-signalling pathway and therefore possess anti-proliferative activity. Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts, enantiomeric forms, diastereoisomers and racemates, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders as mentioned above or in the manufacture of corresponding medicaments.

As used herein, the term "alkyl" means a saturated, straight-chain or branched-chain hydrocarbon containing from 1 to 4, preferably from 1 or 2, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, t-butyl. Said alkyl group is optionally substituted with one or several halogen atoms, preferably fluorine. Examples are difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluorethyl and the like.

The term "halogen" as used herein denotes fluorine, chlorine, bromine and iodine, preferably fluorine.

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

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

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

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

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

Preferred substituents in R^1 are methoxy, difluoromethoxy, trifluoromethoxy and trifluoromethylsulfanyl.

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

A preferred embodiment are the compounds of formula I, wherein G is oxygen and the remaining substituents have the significance given above.

Another preferred embodiment are the compounds of formula I, wherein G is sulfur and the remaining substituents have the significance given above.

Still a preferred embodiment of the invention are the compounds of formula I, wherein

R^1	is	$-O-CF_3$; $-O-CHF_2$ or $-S-CF_3$;
R^2, R^3 and R^4	are all	hydrogen; and
G	is	oxygen; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

1-[2-(4-{2-[2-(E)-(4-Trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)- ethyl]-1H-[1,2,3]triazole;

2-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-2H-[1,2,3]triazole; or

4-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole.

Such pharmaceutically acceptable salts are for example:

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium methanesulfonate;

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium *p*-toluenesulfonate; or

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium chloride.

A preferred embodiment of the present invention is the compound:

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

Another preferred embodiment of the present invention is the compound:

1-[2-(4-{2-[2-(E)-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

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

R^1	is	$-O-CF_3$; $-O-CHF_2$ or $-S-CF_3$;
R^2	is	halogen; and
R^3 and R^4		are hydrogen; and

pharmaceutically acceptable salts thereof.

Such compounds are for example:

1-[2-(4-{2-[2-(E)-(2-Fluoro-4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole; or

1-[2-(4-{2-[2-(E)-(2-Fluoro-4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)- ethyl]-1H-[1,2,3]triazole.

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

R^1 and R^2	together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl;
R^3 and R^4	are hydrogen; and

pharmaceutically acceptable salts thereof.

Such a compound is for example:

1-[2-(4-{2-[2-(E)-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

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

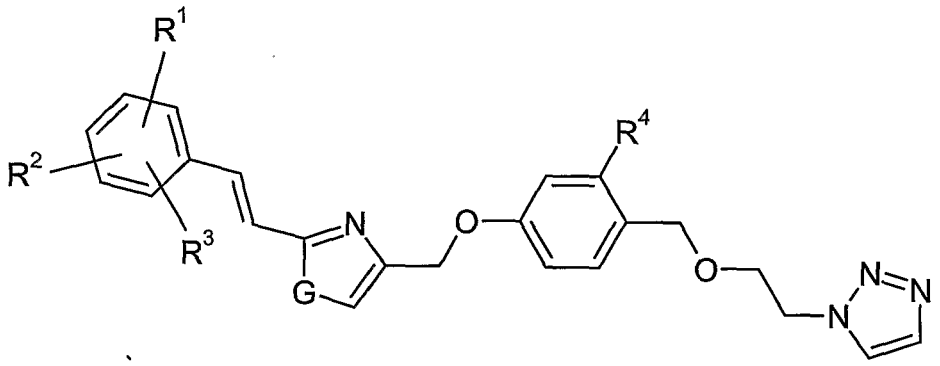
R^1 and R^2		together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl;
R^3	is	halogen;
R^4	is	hydrogen; and

pharmaceutically acceptable salts thereof.

Such a compound is for example:

1-[2-(4-{2-[2-(E)-(2,2,6-Trifluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

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



formula I-A,

wherein

R^1	is	-O-alkyl; -S-alkyl; -NH-alkyl; all alkyl groups being optionally substituted with one or several halogen atoms;
R^2	is	hydrogen; or halogen; and
R^3	is	hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form a 5 or 6 membered heterocyclic ring, being optionally once or several times substituted with halogen; and

	R^3	is	hydrogen; or halogen;
G	is		oxygen; or sulfur and
R^4	is		fluorine; methyl; or methoxy; and

their pharmaceutically acceptable salts.

Such compounds are for example:

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;
1-[2-(2-Methyl-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole; or

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole.

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

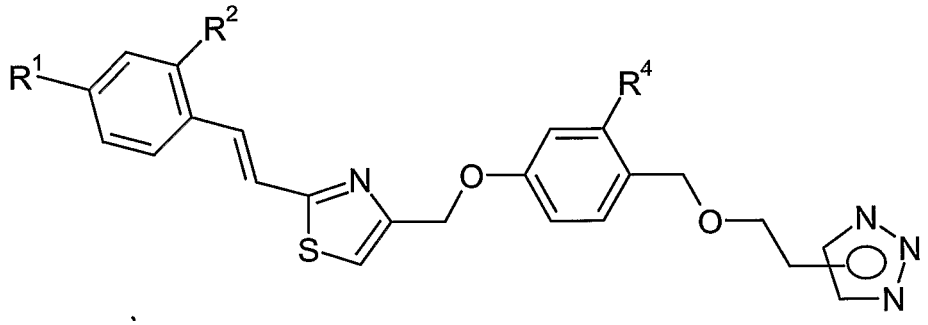
R^1 is -O-alkyl;
-S-alkyl;
all alkyl groups being optionally substituted with one or several fluorine atoms;
R^2 is hydrogen; and
R^3 is hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl; and
R^3 is hydrogen; or

G is oxygen;
R^4 is hydrogen;
C_1-C_3 alkyl; or
fluorine; and

pharmaceutically acceptable salts thereof.

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



formula I-B,

wherein

R^1 is -O-CF_3 or -O-CHF_2;
R^2 is hydrogen; or
halogen; and
R^4 is hydrogen; methyl; methoxy; or fluorine; and

their pharmaceutically acceptable salts.

Such compounds are for example:

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole;

1-[2-(4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole; or

4-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole.

Still another embodiment are the pharmaceutically acceptable salts of the compounds of formula I-B:

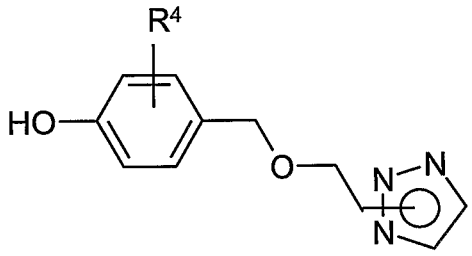
1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium methanesulfonate;

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium *p*-toluenesulfonate; or

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium chloride.

Still another embodiment of the invention is a process for the manufacture of the compounds of formula (I) , wherein

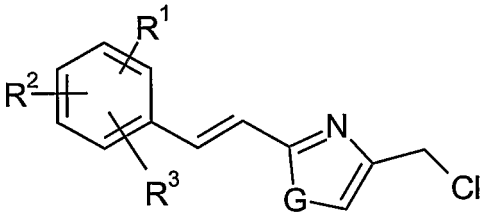
(a) the compound of formula (V)



formula (V),

wherein R^4 has the significance given,

is reacted with a compound of formula (IV)



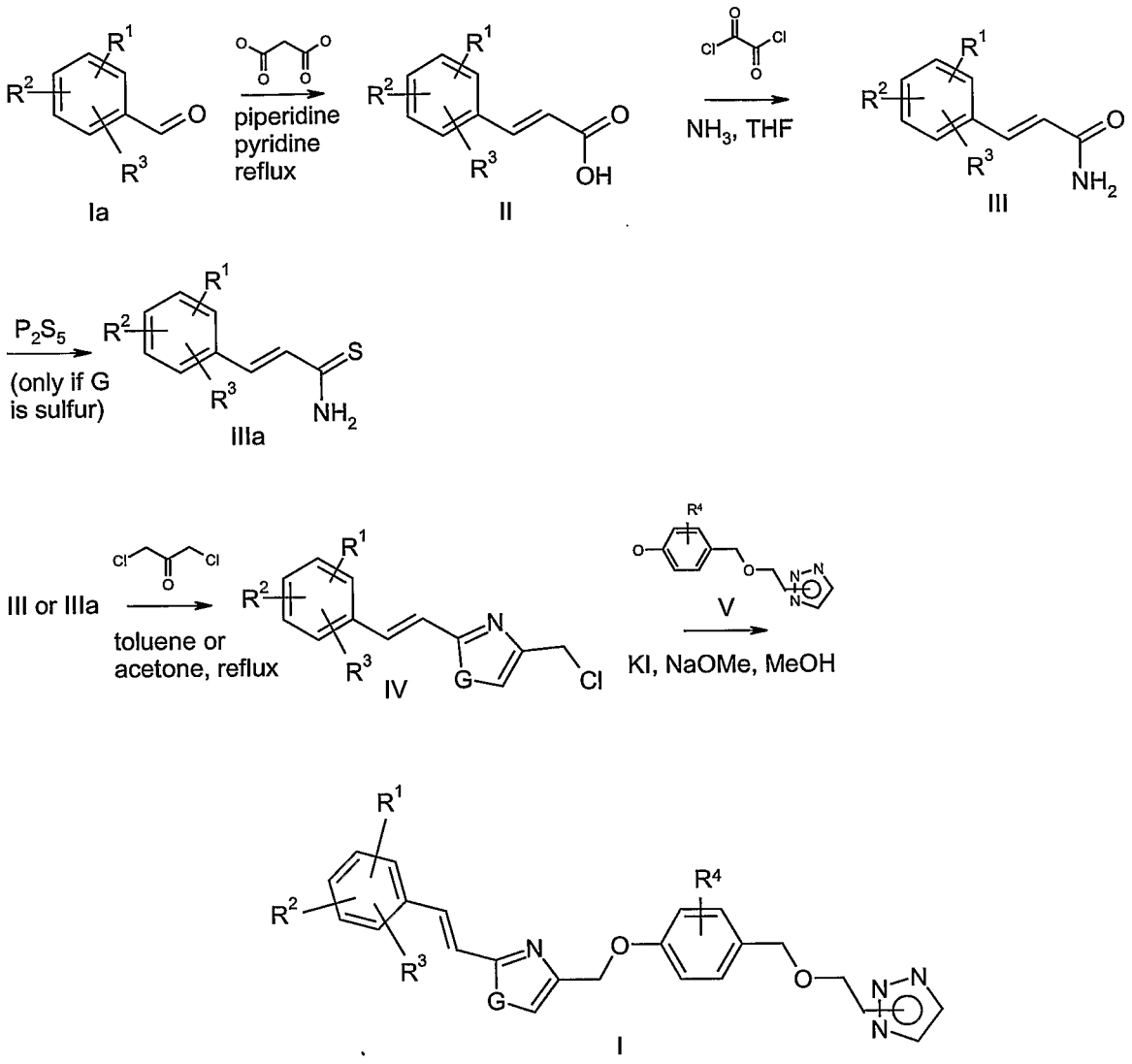
formula (IV),

wherein R^1, R^2, R^3 and G have the significance given, to give the respective compound of formula (I);

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

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

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



Scheme 1

A preferred method for the synthesis of the compounds of the present invention is described in scheme 1, and starts from the corresponding benzaldehydes (Ia). The first step of the reaction sequence is a Knoevenagel condensation with malonic acid and concomitant decarboxylation, yielding acrylic acids of formula (II). The reaction is typically carried out in solvents like pyridine, *N*-methylpyrrolidinone (NMP), acetonitrile, *N,N*-dimethylformamide (DMF) and mixtures thereof at temperatures up to 140°C. Typically used bases are piperidine, triethylamine and diisopropylamine.

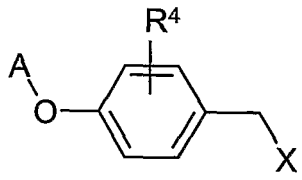
The obtained acrylic acids of formula (II) are converted into their corresponding amides of formula (III) by standard methods for someone skilled in the art, e.g. by activating the carboxylic group in (II) with oxalyl chloride in solvents like tetrahydrofuran (THF), dichloromethane, DMF and mixtures thereof at temperatures varying from -30 °C to 40 °C. The addition of ammonia yields said amides of formula (III).

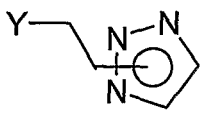
In order to obtain the compounds of formula (I) wherein "G" is sulfur, the carboxamides of formula (III) need to be converted into the corresponding thioamides of formula (IIIa), e.g. by reaction with phosphorous pentasulfide in a solvent like THF or dioxane, preferably at reflux temperature. On the other hand, in order to obtain the compounds of formula (I) wherein "G" is oxygen, this reaction step is avoided and the compounds of formula (III) are immediately reacted with 1,3-dichloro-propan-2-one to give the corresponding chlorides of formula (IV).

Chlorides of formula (IV) can be synthesized by a commonly known method or a modification thereof. Amides of formula (III) or (IIIa) and 1,3-dichloroacetone are subjected to a condensation/dehydration sequence yielding the compounds of formula (IV). Typical solvents for reactions of this kind are toluene, xylene, benzene, acetone and chloroform. If desired, the reaction can be carried out under solvent free conditions. The reaction temperatures may vary from 50°C to 150°C, the thioamides of formula (IIIa) being more reactive than the amides of formula (III).

The ether derivatives of formula (I) can be obtained by reactions well known to someone skilled in the art, e.g. by alkylation of compounds of formula (V) with compounds of formula (IV) according to scheme 1. Typically the alkylation is carried out in the presence of potassium iodide or sodium iodide in solvents like methanol, ethanol and isopropanol. Typical bases for this reaction are sodium methylate, sodium hydride or lithium diisopropyl amide. The reaction temperatures may vary from 50°C to 150°C.

The phenolic compounds of formula (V) may be prepared by reaction of a compound of formula (VI) with a compound of formula (VII)





formula (VI) formula (VII),

wherein "A" denotes a suitable protecting group as defined below, R^4 has the meaning given herein before, and one of X and Y denotes a hydroxy group while the other denotes a suitable leaving group E as defined below,

and subsequent removal of the protecting group A.

Reactions of compounds of formula (VI) with compounds of formula (VII) are well known in the art. Typically, such alkylation reaction may be carried out in solvents like DMF, methanol, ethanol and isopropanol. Typical bases for this reaction are alkaline carbonates, sodium methylate, sodium hydride or lithium diisopropyl amide. The reaction temperatures may vary from 20°C to 150°C. Other preferred alkylation procedures make use of alkaline carbonates as bases in solvents like ketones, for example cesium carbonate in butanone at reflux temperature, or sodium hydride in DMF at room temperature. Suitable leaving groups "E" are those typically used in alkylation reactions and well known to the skilled artisan. Examples of such leaving groups are, among others, the anions of halogens, especially iodide, bromide or chloride, p-toluenesulfonate (tosylate), methanesulfonate (mesylate), trifluoromethansulfonate (triflate) or the azido group.

A protecting group "A" as mentioned herein is preferably, but not limited to tert-butoxycarbonyl (boc), propen-3-yl (allyl), triphenylmethyl (trityl) and silyl groups, e.g. tert.-butyl-dimethyl-silyl, triisopropyl-silyl.

Removal of a protecting group on a hetero atom depends on the nature of such group. Typical examples are the removal of a trityl group under acidic conditions,

for example with aqueous formic acid in THF under reflux or the removal of a tert-butoxycarbonyl group with trifluoroacetic acid in dichloromethane at room temperature or the removal of a substituted silyl group with tetrabutylammonium fluoride in aqueous THF at room temperature. An allyl group can smoothly be removed by treating the substrate with catalytic amounts of a palladium complex, e.g. $Pd(PPh_3)_4$ in dichloromethane in presence of an allyl-acceptor such as 1,3-dimethylbarbituric acid.

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

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

Inhibition of HER2 phosphorylation in Calu3 tumor cell line

$2x10^5$ Calu-3 (ATTC HTB-55) cells per well were plated in a 12-well plate. After 4 days cells were starved for 16h in Dulbecco's Modified Eagle Medium (DMEM)/0.5% Fetal Calf Serum (FCS) /1% Glutamine. During this 16h period cells were incubated with a solution of the test compound in dimethylsulfoxide(DMSO), so that the final concentration of the compound is 1 µM and the final volume of DMSO is 0.5%.Afterwards cells were lysed in lyses buffer containing 1% Triton®X-100, 10% Glycerol, 1mM Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA), 1.5mM $MgCl_2$, 150mM NaCl,

50mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer pH 7.5, 1mM Phenylmethylsulfonyl fluoride (PMSF), 10µg/mL Aprotinin (naturally occurring protein that is obtained and purified from cow's lungs) and 0.4 mm Orthovanadate (Na_3VO_4). Cell lysates were analyzed on a Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS PAGE) and after transfer to a nitrocellulose membrane detected with an antibody specifically recognizing the pY 1248 in HER-2 (phosphorylated tyrosine residue 1248 of human epidermal receptor 2). After incubation with an anti rabbit antibody coupled to POD (Peroxidase available from Biorad , Munich, Germany) signals were detected by chemiluminescence (ECL, Amersham). Inhibition of HER-2 phosphorylation is calculated as percentage of the control, which is treated with DMSO only. The percentage of the inhibition is calculated according to the following formula: Inhibition in % = 100 - (Phosphorylated-HER2-Signal of Test Sample * 100 / Phosphorylated-HER2-Signal DMSO-control). With all compounds a significant inhibition of HER2-phosphorylation was detected, which is exemplified by the compounds shown in Table 1. The reference compounds as used herein are:

Reference compound 1: 1-[4-(4-{2-[2-(4-Trifluoromethyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-phenyl)-butyl]-1H-[1,2,3]triazole (Example 4, p. 88, WO 01/77107).

Reference compound 2: 1-[2-(4-{2-[(E)-2-(4-Trifluoromethyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1*H*-[1,2,3]triazole (Example 2, p. 101, WO 03/059907).

Table 1:

	Control (DMSO)	Percent inhibition of HER2-phosphorylation (compound concentration 1 µM)
reference compound 1	0	52.3
reference compound 2	0	54.0
example 1	0	69.6
example 2	0	85.8
example 3	0	73.4
example 4	0	78.6

In vivo assay on tumor inhibition:

To generate primary tumors, Non-Small-Cell Lung Cancer (NSCLC) (e.g. Calu-3 (ATTC HTB-55) or A549 (ATTC CCL-185)) cells (4-5.0x10^6 in a volume of 100µl) are injected subcutaneously into the left flank of female SCID beige (Severe Combined Immunodeficient / beige mice available from Charles River, Sulzfeld, Germany) or BALB/c nude (BALB/c Nude Spontaneous Mutant Mice (homozygotes) available from Taconic Europe, Ry, Denmark) mice. The cells are thawed and expanded in vitro before use in the experiment. Mice are assigned to the treatment groups 14-21 days after cell injection. For grouping (n = 10-15 mice per group), the animals are randomized to get a similar mean primary tumor volume of ca. 100-150 mm^3 per group. The test compounds are administered orally once per day as a suspension in 7.5% gelatine 0.22% NaCl with an administration volume of 10 ml/kg based on actual body weights. Treatment is initiated one day after staging, and carried out until day 20-50, the final day of the study. The subcutaneous primary tumors are measured twice weekly, starting prior to randomisation, in two dimensions (length and width) using an electronic caliper. The volume of the primary tumor is calculated using the formula: V[mm^3] = (length [mm] x width [mm] x width [mm])/2. In addition, the body weight of all animals is recorded at least twice weekly. Finally, at the end of the study the tumors are explanted and weighed.

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

The above-mentioned pharmaceutical compositions can be obtained by processing the compounds according to this invention with pharmaceutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or it's salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for

the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

Preferred pharmaceutical compositions comprise the following:

a) **Tablet Formulation (Wet Granulation):**

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

Manufacturing Procedure:

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

b) Capsule Formulation:

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

Manufacturing Procedure:

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

c) Micro suspension

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

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

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

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses. Based on their HER-signalling pathway inhibition and their antiproliferative activity, said compounds are useful for preventing or treating proliferative diseases and conditions such as inflammatory diseases, e.g., rheumatoid arthritis, and in particular, oncological diseases such as cancer in humans or animals including, but not limited to, breast cancer, leukemia, ovarian cancer, bronchial or lung cancer, pancreatic cancer, and gastrointestinal cancer such as colon cancer, rectal cancer, and stomach cancer and said compounds are furthermore useful for the production of corresponding medicaments. The dosage depends on various factors such as manner of administration, species, age and/or individual state of health.

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

Examples:

Example 1

1-[2-(4-{2-[2-(E)-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) 1-Allyloxy-4-chloromethyl-benzene

7.67 g (67.0 mmol) methanesulfonyl chloride were given at 0°C to a solution of 10.0 g (60.9 mmol) (4-allyloxy-phenyl)-methanol and 9.34 ml (67.0 mmol) triethylamine in 35 ml dichloromethane and stirred at r.t. overnight. The mixture was poured in ice water, extracted with dichloromethane and the organic phase

dried over Na_2SO_4. After removal of solvents the residue was purified by chromatography on silica gel (ethyl acetate/n-heptane 1:5) to yield 3.12 g (28%) pale yellow oil.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.57(m, 2H, OCH_2), 4.72(s, 2H, CH_2Cl), 5.26(d, 1H, $=CH_2$), 5.39(d, 1H, $=CH_2$), 6.04(m, 1H, $CH=CH_2$), 6.95(d, 2H, 2'-/6'-H), 7.35(d, 2H, 3'-/5'-H).

ii) 1-[2-(4-Allyloxy-benzyloxy)-ethyl]-1H-[1,2,3]triazole

197 mg 8.21 mmol) 95% Sodium hydride were given at -50°C to a solution of 1.00 g (5.47 mmol) 1-allyloxy-4-chloromethyl-benzene and 619 mg (5.47 mmol) 2-(1H-[1,2,3]-triazol-1-yl)-ethanol in 9.0 ml DMF. The mixture was allowed to warm slowly to r.t., stirred overnight and 10 ml water added. The formed oil was collected with 10 ml dichloromethane, the aqueous phase extracted with 10 ml dichloromethane and the combined organic phases dried over Na_2SO_4.

Solvents were removed in vacuum and the residue purified by chromatography on silica gel (ethyl acetate / heptane 1:1) to yield 1.10 g (78%) yellow oil.

MS: M = 260.3 (API+), 258.3 (API-).

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.79(t, 2H, CH_2-CH_2-triazole), 4.39(s, 2H, OCH_2Ph), 4.54-4.59(m, 4H, OCH_2-vinyl, CH_2-triazole), 5.25(d, 1H, $=CH_2$), 5.38(d, 1H, $=CH_2$), 6.06(m, 1H, $CH=CH_2$), 6.89(d, 2H, 2'-/6'-H), 7.15(d, 2H, 3'-/5'-H), 7.16(s, 1H, triazole), 8.08(s, 1H, triazole).

iii) 4-(2-[1,2,3]Triazol-1-yl-ethoxymethyl)-phenol

A solution of 500 mg (1.93 mmol) 1-[2-(4-allyloxy-benzyloxy)-ethyl]-1H-[1,2,3]-triazole in 10 ml dichloromethane was added to a solution of 904 mg (5.79 mmol) 1,3-dimethylbarbituric acid and 58 mg (0.05 mmol) $Pd(PPh_3)_4$ in 20 ml dichloromethane and stirred for 4.5 h at 40°C. The mixture was extracted with 3 x 20 ml sat. $NaHCO_3$-solution and 8 ml water and the combined aqueous phases were reextracted with 2 x 10 ml dichloromethane. The organic extracts were combined and dried over $MgSO_4$. Solvents were distilled off and the residue

purified by chromatography on silica gel (ethyl acetate) to yield 248 mg (59%) of the title compound.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.77(t, 2H, CH_2-CH_2-triazole), 4.33(s, 2H, OCH_2Ph), 4.56(t, 2H, CH_2-triazole), 6.69(d, 2H, 2'-/6'-H), 7.03(d, 2H, 3'-/5'-H), 7.11(s, 1H, triazole), 8.07(s, 1H, triazole), 9.37(s, 1H, PhOH).

iv) 3-(4-Difluoromethoxy-phenyl)-acrylic acid

A mixture of 10.0 g (7.68 ml, 58.1 mmol) 4-difluoromethoxy-benzaldehyde, 6.65 g (63.9 mmol) malonic acid, 0.21 g (2.50 mmol) piperidine and 50 ml pyridine was kept at reflux temperature until carbon dioxide development ceased (3 h). After cooling to room temperature the reaction mixture was poured onto 200 g ice and 100 ml 6N HCl. The precipitate was isolated, washed with water and dried. Yield: 8.8 g (71%) 3-(4-Difluoromethoxy-phenyl)-acrylic acid.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.51(d, 1H, 2-H), 7.21(d, 2H, 3'-/5'-H), 7.32(t, 1H, $OCHF_2$), 7.59(d, 1H, 3-H), 7.77(d, 2H, 2'-/6'-H), 12.4(br, 1H, COOH)

v) 3-(4-Difluoromethoxy-phenyl)-acrylamide

To a suspension of 8.70 g (40.6 mmol) 3-(4-difluoromethoxy-phenyl)-acrylic acid in 60.0 ml tetrahydrofuran and 0.6 ml N,N-dimethylformamide a solution of 5.14 ml (60.9 mmol) oxalyl chloride in 10 ml tetrahydrofuran was added dropwise at 0°C within 10 min. Stirring was continued at 0-5°C for 30 min. and 2 h at room temperature thereafter. The resulting solution was cooled to 0-5°C again and then added within 15 min. to 150 ml of a 25% aqueous ammonia solution. The separating oil was collected and stirred for 30 min. with water. The precipitated amide was collected, washed with water and dried at 40°C in vacuo. 4.7 g (54%) 3-(4-Difluoromethoxy-phenyl)-acrylamide.

MS: M= 214.2 (API+).

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.57(d, 1H, 2-H), 7.10(br, 1H, NH), 7.21(d, 2H, 3'-/5'-H), 7.29(t, 1H, CHF_2), 7.45(d, 1H, 3-H), 7.53(br, 1H, NH), 7.63(d, 2H, 2'-/6'-H).

vi) 4-Chloromethyl-2-[2-(4-difluoromethoxy-phenyl)-vinyl]-oxazole

4.50 g (21.1 mmol) 3-(4-Difluoromethoxy-phenyl)-acrylamide, 3.20 g (25.2 mmol) 1,3-dichloroacetone and 45 ml toluene were kept at reflux temperature for 22 h with continuous removal of water by use of a Dean-Stark trap. After removal of solvents in vacuo, the residue was stirred with diethyl ether, the precipitation (some remaining starting material) sucked off and the filtrate evaporated to dryness. The residue was extracted three times with heptane, the heptane fractions evaporated and the residue dried in vacuo. 1.0 g (16%) 4-Chloromethyl-2-[2-(4-difluoromethoxy-phenyl)-vinyl]-oxazole.

MS: M = 286.2(API+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.70(s, 2H, CH_2Cl, 7.14(d, 1H, =CH), 7.22(d, 2H, Ar-H), 7.31(t, 1H, $OCHF_2$), 7.54(d, 1H, =CH), 7.80(d, 2H, Ar-H), 8.17(s, 1H, oxazole).

vii) 1-[2-(4-{2-[2-(E)-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

23 mg (0.91 mmol) 95% Sodium hydride were given to a solution of 200 mg (0.91 mmol) 4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol in 5.0 ml DMF and stirred for 15 min. 260 mg (0.91 mmol) 4-chloromethyl-2-[2-(4-difluoromethoxy-phenyl)-vinyl]-oxazole were added and stirring continued at r.t. for 12 h. After addition of 20 ml water the resulting precipitate was collected, washed with water (2x 10 ml), methanol/water 1:1 (2x 10 ml), a small amount of diethyl ether and dried in vacuo at 40°C to yield 256 mg (60%) of the product as beige powder.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.80(t, 2H, CH_2-CH_2-triazole), 4.40(s, 2H, OCH_2-Ph), 4.58(t, 2H, CH_2-triazole), 5.00(s, 2H, OCH_2-oxazole), 6.99(d, 2H, Ar-H), 7.09-7.25(m, 5H, Ar-H, vinyl-H) 7.14(d, 16.7 Hz, 1H, vinyl-H), 7.30 (t, 74.0 Hz, 1H, OCF_2H), 7.53(d, 16.7 Hz, 1H, vinyl-H), 7.72(s, 1H, triazole), 7.79 (d, 2H, Ar-$OCHF_2$), 8.16(s, 1H, triazole), 8.20(s, 1H, oxazole).

Example 2

1-[2-(4-{2-[2-(E)-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) 3-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acrylic acid

A mixture of 10.0 g (53.7 mmol) 2,2-difluoro-benzo[1,3]dioxole-5-carbaldehyde, 6.24 g (60.0 mmol) malonic acid, 0.46 g (5.40 mmol) piperidine and 40 ml pyridine was kept at reflux temperature until carbon dioxide development ceased (3 h). After cooling to room temperature the reaction mixture was poured onto 100 g ice and 30 ml 6N HCl. The precipitate was isolated, washed with water and dried. Yield: 8.60 g (70%) 3-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acrylic acid.

ii) 3-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acrylamide

To a suspension of 8.00 g (35.1 mmol) 3-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-acrylic acid in 40 ml tetrahydrofuran and 0.4 ml *N,N*-dimethyl formamide, 3.86 ml (45.0 mmol) oxalyl chloride was added dropwise at 0°C within 10 min. Stirring was continued at 0-5°C for 30 min. and 2 h at room temperature thereafter. The resulting solution was cooled to 0-5°C again and then added within 15 min. to 34 ml of an 25% aqueous solution of ammonia. After stirring for 30 min. the precipitated amide was collected, washed with water and dried at 40°C in vacuo. 7.20 g (90%) 3-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acrylamide were obtained.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.59(d, 1H, 2-H), 7.14(br, 1H, NH), 7.41-7.46(m, 3H, 3-H/7'-H/6'-H), 7.53(br, 1H, NH), 7.66(s, 1H, 4'-H).

iii) 4-Chloromethyl-2-[2-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazole

6.90 g (30.4 mmol) 3-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-acrylamide, 4.76 g (37.5 mmol) 1,3-dichloroacetone and 50 ml toluene were kept at reflux temperature for 48 h with continuous removal of water by applying a Dean-Stark trap. After removal of solvents in vacuo, the residue was treated with 60 ml of a 1:1 mixture of water/isopropanol. After filtration the precipitate was washed first with isopropanol, then with heptane. Drying at 40°C in vacuo gave 4-Chloromethyl-2-[2-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazole.

MS: M= 300.0 (API+).

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.70(s, 2H, CH_2Cl), 7.20(d, 1H, 2-H), 7.45(d, 1H, 7'-H), 7.55(d, 1H, 3-H),), 7.56(d, 1H, 6'-H), 7.92(s, 1H, 4'-H), 8.18(s, 1H, oxazole).

iv) **1-[2-(4-{2-[2-(E)-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole**

25 mg (1.00 mmol) 95% Sodium hydride were given to a solution of 219 mg (1.00 mmol) 4-(3-[1,2,3]triazol-1-yl-propoxy)-phenol in 5.0 ml DMF and stirred for 15 min. 300 mg (1.00 mmol) 4-chloromethyl-2-[2-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazole were added and stirring continued at r.t. for 12 h. After addition of 20 ml water the resulting precipitate was collected, washed with water (2x 10 ml), methanol/water 1:1 (2x 10 ml), and a small amount of diethyl ether and dried in vacuo at 40°C to yield 351 mg (73%) of a beige powder.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.82(t, 2H, CH_2-CH_2-triazole), 4.41(s, 2H, OCH_2-Ph), 4.59(t, 2H, CH_2-triazole), 5.02(s, 2H, OCH_2-oxazole), 7.00(d, 2H, 3'-/5'-H-Ar), 7.18(d, 2H, 2'-/6'-H-Ar) 7.20(d, 1H, vinyl-H), 7.45(d, 1H, ArO_2CF_2), 7.51-7.60(m, 2H, vinyl-H, ArO_2CF_2), 7.72(s, 1H, triazole), 7.92(d, 1H, ArO_2CF_2), 8.08(s, 1H, triazole), 8.20(s, 1H, oxazole).

Example 3

1-[2-(4-{2-[2-(E)-(4-Trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)- ethyl]-1H-[1,2,3]triazole

i) 3-(4-Trifluoromethylsulfanyl-phenyl)-acrylic acid

A mixture of 5.42 g (26.3 mmol) 4-trifluoromethylsulfanyl-benzaldehyde, 3.12 g (30.0 mmol) malonic acid, 0.26 g (3.0 mmol) piperidine and 12.0 ml pyridine was kept at reflux temperature until carbon dioxide development ceased (5 h). After cooling to room temperature, the reaction mixture was poured onto 50 g ice and 15 ml 6N HCl. The precipitate was isolated, washed with water and dried. Yield: 5.90 g (90%) 3-(4-Trifluoromethylsulfanyl-phenyl)-acrylic acid.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.65(d, 1H, 2-H), 7.63(d, 1H, 3-H), 7.74(d, 2H, 3'-/5'-H), 7.84(d, 2H, 2'-/6'-H), 12.7(br, 1H, COOH).

ii) 3-(4-Trifluoromethylsulfanyl-phenyl)-acrylamide

To a suspension of 5.24 g (21.1 mmol) 3-(4-trifluoromethylsulfanyl-phenyl)-acrylic acid in 30.0 ml tetrahydrofuran and 0.3 ml *N,N*-dimethylformamide a solution of 2.70 ml (32.0 mmol) oxalyl chloride in 5.0 ml tetrahydrofuran was added dropwise at 0°C within 20 min. Stirring was continued at 0-5°C for 30 min. and 3 h at room temperature thereafter. The resulting solution was cooled to 0-5°C again and then added within 15 min. to 100 ml of a 25% aqueous ammonia solution. After evaporation of the organic solvent, 200 ml water were added and the solution cooled. The precipitated amide was collected, washed with water and dried at 40°C in vacuo. Yield 4.62 g (89%) 3-(4-Trifluoromethylsulfanyl-phenyl)-acrylamide.

MS: M = 248.2(API+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.72(d, 1H, 2-H), 7.21(br, 1H, NH), 7.46(d, 1H, 3-H), 7.62(br, 1H, NH), 7.73(dd, 4H, Ar-H).

iii) 4-Chloromethyl-2-[2-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazole

4.45 g (18.0 mmol) 3-(4-Trifluoromethylsulfanyl-phenyl)-acrylamide, 2.80 g (22.2 mmol) 1,3-dichloroacetone and 50.0 ml toluene were kept at reflux temperature for 40 h with continuous removal of water by use of a Dean-Stark trap. After removal of solvents in vacuo, the residue was purified by chromatography on silica gel (eluent: heptane/ethyl acetate 1:1). All fractions containing the product were concentrated to a volume of 10 ml and the crystallized material isolated by filtration, washed with cold heptane and dried. Yield 2.02 g (35%) 4-Chloromethyl-2-[2-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazole.

MS: M = 320.1(API+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.71(s, 2H, CH_2Cl), 7.30(d, 1H, =CH), 7.59(d, 1H, =CH), 7.74(d, 2H, Ar-H), 7.89(d, 2H, Ar-H), 8.21(s, 1H, oxazole).

iv) 1-[2-(4-{2-[2-(E)-(4-Trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

25 mg (1.00 mmol) 95% Sodium hydride were given to a solution of 219 mg (1.00 mmol) 4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol in 5.0 ml DMF and stirred for 15 min. 304 mg (1.00 mmol) 4-Chloromethyl-2-[2-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazole were added and stirring continued at r.t. overnight. After addition of 20 ml water the resulting precipitate was washed twice with 10 ml water, 2 x 10 ml methanol, diethyl ether and dried at 45°C in vacuum. Yield: 301 mg (60%) pale beige powder.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.80(t, 2H, CH_2-CH_2-triazole), 4.40(s, 2H, OCH_2-Ph), 4.58(t, 2H, CH_2-triazole), 5.02(s, 2H, OCH_2-oxazole), 6.99(d, 2H, 3'-/5'-H-Ar), 7.18(d, 2H, 2'-/6'-H-Ar) 7.31(d, 1H, vinyl-H), 7.58(d, 1H, vinyl-H), 7.74(d, 2H, $ArSCF_3$), 7.72(s, 1H, triazole), 7.74(d, 2H, $ArSCF_3$), 8.08(s, 1H, triazole), 8.24(s, 1H, oxazole).

Example 4

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) 3-(4-Trifluoromethoxy-phenyl)-acrylic acid

A mixture of 5.00 g (3.80 ml, 26.3 mmol) 4-trifluoromethoxy-benzaldehyde, 3.10 g (30.0 mmol) malonic acid, 0.26 g (3.0 mmol) piperidine and 15.0 ml pyridine was kept at reflux temperature until carbon dioxide development ceased (3 h). After cooling to room temperature the reaction mixture was poured onto 50 g ice and 15 ml 6N HCl. The precipitate was isolated, washed with water and dried. Yield: 5.20 g (85%) 3-(4-Trifluoromethoxy-phenyl)-acrylic acid.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.57(d, 1H, 2-H), 7.40(d, 2H, 3'-/5'-H), 7.62(d, 1H, 3-H), 7.84(d, 2H, 2'-/6'-H), 12.5(br, 1H, COOH).

ii) 3-(4-Trifluoromethoxy-phenyl)-acrylamide

To a suspension of 4.90 g (21.1 mmol) 3-(4-Trifluoromethoxy-phenyl)-acrylic acid in 30.0 ml tetrahydrofuran and 0.3 ml *N,N*-dimethylformamide a solution of 2.70

ml (32.0 mmol) oxalyl chloride in 5.0 ml tetrahydrofuran was added dropwise at 0°C within 10 min. Stirring was continued at 0-5°C for 30 min. and 2 h at room temperature thereafter. The resulting solution was cooled to 0-5°C again and then added within 15 min. to 75 ml of a 25% aqueous ammonia solution. After stirring for 30 min. the precipitated amide was collected, washed with water and dried at 40°C in vacuo. 4.48 g (92%) 3-(4-Trifluoromethoxy-phenyl)-acrylamide.

MS: M = 232.2(API+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 6.63(d, 1H, 2-H), 7.16(br, 1H, NH), 7.42(d, 2H, 3'-/5'-H), 7.45(d, 1H, 3-H), 7.58(br, 1H, NH), 7.70(d, 2H, 2'-/6'-H).

iii) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole

4.28 g (18.5 mmol) 3-(4-Trifluoromethoxy-phenyl)-acrylamide, 2.80 g (22.2 mmol) 1,3-dichloroacetone and 30.0 ml toluene were kept at reflux temperature for 16 h with continuous removal of water by use of a Dean-Stark trap. After removal of solvents in vacuo, the residue was purified by chromatography on silica gel (eluent: heptane/ethyl acetate 20:1). All fractions containing the product were concentrated to a volume of 10 ml and the crystallized material isolated by filtration, washed with cold heptane and dried. 1.75 g (31%) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole.

MS: M = 304.2(API+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.71(s, 2H, CH_2Cl), 7.21(d, 1H, =CH), 7.40(d, 2H, Ar-H), 7.58(d, 1H, =CH), 7.87(d, 2H, Ar-H), 8.19(s, 1H, oxazole).

iv) 1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

25 mg (1.00 mmol) 95% Sodium hydride were given to a solution of 219 mg (1.00 mmol) 4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol in 5.0 ml DMF and stirred for 15 min. 304 mg (1.00 mmol) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole were added and stirring continued at r.t. overnight. After addition of 20 ml water the resulting precipitate was washed twice with 10 ml water,

2 x 10 ml methanol, diethyl ether and dried at 45°C in vacuum. Yield 352 mg (72%) colorless powder.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.80(t, 2H, CH_2-CH_2-triazole), 4.40(s, 2H, OCH_2-Ph), 4.58(t, 2H, CH_2-triazole), 5.01(s, 2H, OCH_2-oxazole), 6.99(d, 2H, 3'-/5'-H-Ar), 7.18(d, 2H, 2'-/6'-H-Ar) 7.21(d, 1H, vinyl-H), 7.40(d, 2H, $ArOCF_3$), 7.57(d, 1H, vinyl-H), 7.72(s, 1H, triazole), 7.87(d, 2H, $ArOCF_3$), 8.08(s, 1H, triazole), 8.22(s, 1H, oxazole).

Example 5

2-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-2H-[1,2,3]triazole

i) 2-[2-(4-Allyloxy-benzyloxy)-ethyl]-2H-[1,2,3]triazole

207 mg (8.21 mmol) 95% Sodium hydride were given at -50°C to a solution of 1.00 g (5.47 mmol) 1-allyloxy-4-chloromethyl-benzene and 619 mg (5.47 mmol) 2-(2H-[1,2,3]-triazol-2-yl)-ethanol in 10.0 ml DMF. The mixture was allowed to warm slowly to r.t., stirred overnight and 6 ml water added. The formed oil was collected with 10 ml dichloromethane, the aqueous phase extracted with 10 ml dichloromethane and the combined organic phases dried over Na_2SO_4.

Solvents were removed in vacuum and the residue purified by chromatography on silica gel (ethyl acetate / heptane 1:1) to yield 992 mg (70%) pale yellow oil.

MS: M = 282.3 (ESI+, M + Na^+).

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.86(t, 2H, CH_2-CH_2-triazole), 4.35(s, 2H, OCH_2Ph), 4.54(d, 2H, OCH_2-vinyl), 4.59(t, 2H, CH_2-triazole), 5.24(d, 1H, $=CH_2$), 5.37(d, 1H, $=CH_2$), 6.04(m, 1H, $CH=CH_2$), 6.88(d, 2H, 2'-/6'-H), 7.12(d, 2H, 3'-/5'-H), 7.77(s, 2H, triazole).

ii) 4-(2-[1,2,3]Triazol-2-yl-ethoxymethyl)-phenol

A solution of 950 mg (3.66 mmol) 2-[2-(4-allyloxy-benzyloxy)-ethyl]-2H-[1,2,3]-triazole in 20 ml dichloromethane was added to a solution of 1.71 g (11.0 mmol) 1,3-dimethylbarbituric acid and 104 mg (0.09 mmol) $Pd(PPh_3)_4$ in 40 ml

dichloromethane and stirred for 4.5 h at 40°C. The mixture was extracted with 3 x 40 ml sat. $NaHCO_3$-solution and 15 ml water and the combined aqueous phases were reextracted with 2 x 40 ml dichloromethane. The organic extracts were combined and dried over $MgSO_4$. Solvents were distilled off and the residue purified by chromatography on silica gel (ethyl acetate/ n-heptane 2:1) to yield 690 mg (86%) of the title compound.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.84(t, 2H, CH_2-CH_2-triazole), 4.29(s, 2H, OCH_2Ph), 4.58(t, 2H, CH_2-triazole), 6.68(d, 2H, 2'-/6'-H), 7.01(d, 2H, 3'-/5'-H), 7.77(s, 2H, triazole), 9.35(s, 1H, PhOH).

iii) **2-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-2H-[1,2,3]triazole**

25 mg (1.0 mmol) 95% Sodium hydride were given to a solution of 219 mg (1.00 mmol) 4-(2-[1,2,3]triazol-2-yl-ethoxymethyl)-phenol in 5.0 ml DMF and stirred for 15 min. 304 mg (1.00 mmol) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole were added and stirring continued at r.t. overnight. After addition of 20 ml water the resulting precipitate was washed twice with 10 ml water, 2 x 10 ml methanol, diethyl ether and dried at 45°C in vacuum. Yield 254 mg (52%) colorless powder.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.87(t, 2H, CH_2-CH_2-triazole), 4.36(s, 2H, OCH_2-Ph), 4.60(t, 2H, CH_2-triazole), 5.00(s, 2H, OCH_2-oxazole), 6.97(d, 2H, 3'-/5'-H-Ar), 7.14(d, 2H, 2'-/6'-H-Ar) 7.23(d, 1H, vinyl-H), 7.40(d, 2H, $ArOCF_3$), 7.56(d, 1H, vinyl-H), 7.70-7.86(m, 4H; 2H, triazole; 2H, $ArOCF_3$), 8.22(s, 1H, oxazole).

Example 6

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) **3-(Trifluoromethoxy-phenyl)-thioacrylamide**

A mixture of 60.0 g (274 mmol) 3-(4-trifluoromethoxy-phenyl)-acrylamide and 12.2 g (274 mmol) phosphorous pentasulfide in 2.0 l dioxane was stirred under reflux for 4 h. After evaporation, the residue was dissolved at 60°C in 100 ml

isopropanol and 200 ml water added. The precipitate was isolated by filtration, washed with isopropanol/water 1:2 and dried at 40°C in vacuo to yield 13.0 g (20%) of yellow coloured product.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 7.01(d, 1H, vinyl-H), 7.41(d, 2H, Ar-H), 7.64(d, 1H, vinyl-H), 7.73(d, 2H, Ar-H), 9.29(s, br, 1H, NH), 9.60(s, br, NH).

ii) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-thiazole

12.7 g (48.3 mmol) 3-(4-Trifluoromethoxy-phenyl)-acrylthioamide, 18.4 g (145 mmol) 1,3-dichloroacetone and 120 ml ethanol were refluxed for 4 h. After evaporation the residue was purified by chromatography on silica gel (ethyl acetate/isohexane 1:10) to yield 2.40 g 4-chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-thiazole as yellow solid.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 4.84(s, 2H, CH_2Cl), 7.40(d, 2H, Ar-H), 7.54(s, 2H, vinyl-H), 7.75(s, 1H, thiazole), 7.85(d, 2H, Ar-H).

iii) 1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

182 mg (7.00 mmol) 95% Sodium hydride were given to a solution of 1.50 g (7.00 mmol) 4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol in 7.0 ml DMF and stirred for 15 min. 2.06 g (7.00 mmol) 4-Chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-thiazole were added and stirring continued at r.t. overnight. After addition of 20 ml water the resulting precipitate was washed twice with 10 ml water, then with n-heptane and finally a little amount of diethyl ether and dried at 45°C in vacuum. Yield 2.4 g.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.82(t, 2H, CH_2-CH_2-triazole), 4.41(s, 2H, OCH_2-Ph), 4.58(t, 2H, CH_2-triazole), 5.18(s, 2H, OCH_2-thiazole), 7.00(d, 2H, 3'-/5'-H-Ar), 7.19(d, 2H, 2'-/6'-H-Ar) 7.37(d, 2H, $ArOCF_3$), 7.51(m, 2H, vinyl-H), 7.66, 7.69(2x s, 2x 1H, thiazole, triazole), 7.82(d, 2H, $ArOCF_3$), 8.04(s, 1H, triazole).

Example 7

1-[2-(4-{2-[2-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) 4-allyloxy-2-methyl-benzaldehyde

31.7 g (229 mmol) potassium carbonate and 9.51 g (57.3 mmol) potassium iodide were given to a solution of 15.6 g (115 mmol) 4-hydroxy-2-methyl-benzaldehyde and 55.4 g (458 mmol) allyl bromide in 500 ml 2-butanone and stirred for 16 h at 65°C. Solvents were distilled off and the residue distributed between ethyl acetate and 1 N sodium hydroxide. The organic layer was separated and the aqueous solution extracted once with ethyl acetate. The combined organic phases were dried and evaporated to give 19.8 g (98%) of 4-allyloxy-2-methyl-benzaldehyde.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.59 (s, 3H, CH_3), 4.67 (d, 2H, OCH_2-vinyl), 5.29 (d, 1H, =CH_2), 5.41 (d, 1H, =CH_2), 6.05 (m, 1H, CH=CH_2), 6.96 (d, 1H, 5-H), 6.74 (s, 1H, 3-H), 7.77 (d, 1H, 6-H), 10.07 (s, 1H, CHO).

ii) (4-allyloxy-2-methyl-phenyl)-methanol

8.50 g (224 mmol) lithium aluminium hydride were given to 250 ml THF and stirred for 20 min. A solution of 19.4 g (110 mmol) 4-allyloxy-2-methyl-benzaldehyde in 100 ml THF was added dropwise and stirring continued for 3 h. The reaction mixture was cooled to 0°C, carefully hydrolysed with 40 ml concentrated ammonium chloride solution, stirred for 60 min. and adjusted to pH = 5 with conc. hydrochloric acid. A formed salt precipitate was removed by filtration, washed with THF and the combined organic solutions evaporated. Chromatography of the residue on silica (n-heptane/ethyl acetate 1:3) gave 16.0 g (81%) (4-allyloxy-2-methyl-phenyl)-methanol as a slightly yellow oil.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.23 (s, 3H, CH_3), 4.40 (s, 2H, CH_2OH), 4.52 (d, 2H, OCH_2-vinyl), 4.88 (t, 1H, OH), 5.23 (d, 1H, =CH_2), 5.37 (d, 1H, =CH_2), 6.03 (m, 1H, CH=CH_2), 6.72 (d, 1H, 5-H), 6.74 (s, 1H, 3-H), 7.20 (d, 1H, 6-H).

iii) 1-allyloxy-4-chloromethyl-2-methyl-benzene

A solution of 16.0 g (89.6 mmol) (4-allyloxy-2-methyl-phenyl)-methanol in 270 ml dichloromethane and 1.5 ml DMF was cooled to 0°C. 7.80 ml (12.8 g, 108 mmol) thionyl chloride were added slowly and then stirred for 1 h at room temperature. Dichloromethane was distilled off, 300 ml toluene added and solvents removed in vacuo. The residue was taken up in 200 ml toluene and washed with concentrated sodium carbonate solution. The organic phase was dried and evaporated to give 17.5 g (99%) 1-allyloxy-4-chloromethyl-2-methyl-benzene as colored oil.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.34 (s, 3H, CH_3), 4.74 (d, 2H, OCH_2-vinyl), 4.55 (s, 2H, CH_2Cl), 5.25 (d, 1H, $=CH_2$), 5.38 (d, 1H, $=CH_2$), 6.02 (m, 1H, $CH=CH_2$), 6.75 (d, 1H, 5-H), 6.82 (s, 1H, 3-H), 7.29 (d, 1H, 6-H).

iv) 1-[2-(4-Allyloxy-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]triazole

1.122 g (46.7 mmol) 95% Sodium hydride were given at -50°C to a solution of 5.630 g (31.2 mmol) 1-allyloxy-4-chloromethyl-2-methyl-benzene and 3.525 g (31.2 mmol) 2-(1H-[1,2,3]-triazol-1-yl)-ethanol in DMF. The mixture was allowed to warm slowly to r. t., stirred for 5 hours. The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 and the solvent was distilled off under reduced pressure to yield 7.30 g (86%) 1-[2-(4-Allyloxy-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]triazole as yellow oil which was used without further purification.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.10 (s, 3H, CH_3), 3.80 (t, 2H, CH_2), 4.38 (s, 2H, CH_2), 4.52 (d, 2H, OCH_2-vinyl), 4.57 (t, 2H, CH_2), 5.23 (d, 1H, $=CH_2$), 5.37 (d, 1H, $=CH_2$), 6.02 (m, 1H, $CH=CH_2$), 6.69 (d, 1H, 5-H), 6.74 (s, 1H, 3-H), 7.10 (d, 1H, 6-H), 7.71 (s, 1H), 8.06 (s, 1H).

v) 3-Methyl-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol

A solution of 7.30 g (26.7. mmol) 1-[2-(4-Allyloxy-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]-triazole in 100 ml dichloromethane was added to a solution of 13.02 g (83.4 mmol) 1,3-dimethylbarbituric acid an 959 mg (0.8 mmol) $Pd(PPh_3)_4$ in 30 ml dichloromethane and stirred overnight at 40°C. The mixture was extracted with 3 x sat. $NaHCO_3$-solution. The combined aqueous phases were extracted with

dichloromethane. The combined organic extracts were dried over Na_2SO_4. Solvents were distilled off and the residue was purified by chromatography on silica gel (heptane/ ethyl acetate 1/1 to 0/1) to yield 3.30 g (53%) 3-Methyl-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol as a yellow solid melting at 92-93°C.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.05 (s, 3H, CH_3), 3.79 (t, 2H, CH_2), 4.33 (s, 2H, CH_2), 4.56 (t, 2H, CH_2), 6.50 (dd, 1H, 5-H), 6.55 (d, 1H, 3-H), 6.98 (d, 1H, 6-H), 7.70 (s, 1H), 8.05 (s, 1H), 9.25 (s, 1H, OH).

vi) 1-[2-(4-{2-[2-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]triazole

A mixture of 201 mg (0.86 mmol) 3-methyl-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol and 169 mg (0.52 mmol) cesium carbonate in 10 ml 2-butanone was stirred at 60°C for 30 minutes, then 246 mg (0.86 mmol) 4-chloromethyl-2-[2-(4-difluoromethoxy-phenyl)-vinyl]-oxazole and 143 mg (0.86 mmol) potassium iodide were added and stirring was continued overnight. After evaporation, the residue was mixed with aqueous NaOH (1N) and extracted with ethyl acetate. The combined extracts were dried, evaporated and the product purified on silica (ethyl acetate) to yield 242 mg (59%) 1-[2-(4-{2-[2-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-2-methyl-benzyloxy)-ethyl]-1H-[1,2,3]triazole as a white solid melting at 119-120°C

MS: M = 483.5 (ES+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.12 (s, 3H, CH_3), 3.81 (t, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.58 (t, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.80 (dd, 1H), 6.84(d, 1H), 7.13(d, 1H), 7.14 (d, 16.7 Hz, 1H), 7.21 (d, 2H), 7.31 (t, 74.5 Hz, 1H, CHF_2), 7.53 (d, 16.7 Hz, 1H), 7.71 (s, 1H), 7.79 (d, 2H), 8.07 (s, 1H), 8.18 (s, 1H).

Example 8

1-[2-(2-Methyl-4-{2-[2-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

A mixture of 201 mg (0.86 mmol) 3-methyl-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol and 169 mg (0.52 mmol) cesium carbonate in 10 ml 2-butanone was stirred at 60°C for 30 minutes, then 275 mg (0.86 mmol) 4-

chloromethyl-2-[2-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazole and 143 mg (0.86 mmol) potassium iodide were added and stirring was continued overnight. After evaporation, the residue was mixed with aqueous NaOH (1N) and extracted with ethyl acetate. The combined extracts were dried, evaporated and the product purified on silica (ethyl acetate) to yield 280 mg (63%) of the title as a white solid melting at 102°C

MS: M = 517.3 (ES+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.13 (s, 3H, CH_3), 3.82 (t, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.58 (t, 2H, CH_2), 5.00 (s, 2H, CH_2), 6.75-6.88 (m, 2H), 7.13(d, 1H), 7.33 (d, 16.2 Hz, 1H), 7.60 (d, 16.7 Hz, 1H), 7.67-7.79 (m, 3H), 7.86 (d, 2H), 8.07 (s, 1H), 8.23 (s, 1H).

Example 9

1-[2-(2-Methyl-4-{2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

A mixture of 201 mg (0.86 mmol) 3-methyl-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol and 169 mg (0.52 mmol) cesium carbonate in 10 ml 2-butanone was stirred at 60°C for 30 minutes, then 261 mg (0.86 mmol) 4-chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole and 143 mg (0.86 mmol) potassium iodide were added and stirring was continued overnight. After evaporation, the residue was mixed with aqueous NaOH (1N) and extracted with ethyl acetate. The combined extracts were dried, evaporated and the product purified on silica (ethyl acetate) to yield 208 mg (49%) of the title as a white solid melting at 84-85°C

MS: M = 501.6 (ES+)

^{1}H-NMR(400MHz, D_6-DMSO): δ= 2.12 (s, 3H, CH_3), 3.82 (t, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.58 (t, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.80 (d, 1H), 6.84 (s, 1H), 7.13(d, 1H), 7.21 (d, 16.7 Hz, 1H), 7.40 (d, 2H), 7.57 (d, 16.7 Hz, 1H), 7.71 (s, 1H), 7.86 (d, 3H), 8.07 (s, 1H), 8.21 (s, 1H).

Example 10

1-[2-(2-Fluoro-4-{2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

i) (4-allyloxy-2-fluoro-phenyl)-methanol

11.9 g (85.8 mmol) potassium carbonate and 0.357 g (2.15 mmol) potassium iodide were given to a solution of 6.10 g (42.9 mmol) 2-fluoro-4-hydroxymethylphenol and 20.8 g (172 mmol) allyl bromide in 250 ml 2-butanone and stirred for 32 h at 65°C. Solvents were distilled off and the residue distributed between ethyl acetate and 1 N sodium hydroxide. The organic layer was separated, dried and evaporated to give 4.27 g (55%) of (4-allyloxy-2-fluoro-phenyl)-methanol.

^{1}H-NMR(400MHz, $CDCl_3$): δ= 1.70(t, 1H, OH), 4.52(d, 2H, OCH_2-vinyl), 4.67(d, 2H, CH_2OH), 5.31(d, 1H, $=CH_2$), 5.41(d, 1H, $=CH_2$), 6.02(m, 1H, $CH=CH_2$), 6.63(d, 1H, 3-H), 6.70(d, 1H, 5-H), 7.29(d, 1H, 6-H).

ii) 1-allyloxy-3-fluoro-4-chloromethyl-benzene

A solution of 4.20 g (23.1 mmol) (4-allyloxy-2-fluoro-phenyl)-methanol in 80 ml dichloro-methane and 0.5 ml DMF was cooled to 0°C. 2.17 ml (3.57 g, 30.0 mmol) thionyl chloride were added slowly and then stirred for 1 h at room temperature. Dichloromethane was distilled off. The residue was taken up in 100 ml ethyl acetate and washed with concentrated sodium carbonate solution. The organic phase was dried and evaporated to give 4.47 g (97%) 1-allyloxy-3-fluoro-4-chloromethyl-benzene as coloured oil.

^{1}H-NMR(400MHz, $CDCl_3$): δ= 4.52(d, 2H, OCH_2-vinyl), 4.60(s, 2H, CH_2Cl), 5.31(d, 1H, $=CH_2$), 5.41(d, 1H, $=CH_2$), 6.03(m, 1H, $CH=CH_2$), 6.64(d, 1H, 2-H), 6.69(d, 1H, 6-H), 7.29(d, 1H, 5-H).

iii) 1-[2-(4-allyloxy-2-fluoro-benzyloxy)-ethyl]-1H-[1,2,3]triazole

816 mg (32.3 mmol) 95% Sodium hydride were given at -50°C to a solution of 4.32 g (21.5 mmol) 1-allyloxy-3-fluoro-4-chloromethyl-benzene and 2.51 g (22.2 mmol) 2-(1H-[1,2,3]-triazol-1-yl)-ethanol in 30 ml DMF. The mixture was allowed to

warm slowly to r.t., stirred overnight and 10 ml water added. The mixture was extracted twice with ethyl acetate, and the combined organic phases dried over Na_2SO_4. Solvents were removed in vacuum to yield 6.18 g 1-[2-(4-allyloxy-2-fluoro-benzyloxy)-ethyl]-1H-[1,2,3]triazole yellow oil that was used without further purification.

^{1}H-NMR(400MHz, $CDCl_3$): δ= 3.84(t, 2H, $C\underline{H}_2$-CH_2-triazole), 4.48(s, 2H, OCH_2Ph), 4.52(d, 2H, OCH_2-vinyl) 4.58(t, CH_2-triazole), 5.25(d, 1H, $=CH_2$), 5.38(d, 1H, $=CH_2$), 6.06(m, 1H, $C\underline{H}=CH_2$), 6.62(d, 1H, 3-H), 6.68(d, 1H, 5-H), 7.14(t, 1H, 6-H), 7.68(s, 1H, triazole), 7.69(s, 1H, triazole).

iv) 3-fluoro-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol

To a solution of 10.4 g (66.9 mmol) 1,3-dimethyl-pyrimidine-2,4,6-trione and 774 mg (0.67 mmol) tetrakis-(triphenylphosphine)-palladium in 100 ml dichloromethane was added dropwise a solution of 6.18 g (22.3 mmol) 1-[2-(4-allyloxy-2-fluoro-benzyloxy)-ethyl]-1H-[1,2,3]triazole in 30 ml dichloromethane and stirring was continued for 24 hours at 40°C. It was allowed to cool down over night. The reaction mixture was extracted with three 100 ml portions of sodium bicarbonate solution, the organic extract was dried, evaporated and purified by chromatography on silica (ethyl acetate / dichloromethane 3:7) to yield 2.97 g (56%) 3-fluoro-4-(2-[1,2,3]triazol-1-yl-ethoxymethyl)-phenol as oil.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.79(t, 2H, $OC\underline{H}_2$-CH_2-triazole), 4.38(s, 2H, $OC\underline{H}_2Ph$), 4.56(t, 2H, CH_2-triazole), 6.53(d, 1H, 2-H), 6.56(d, 1H, 6-H), 7.11(d, 1H, 5-H), 7.71(s, 1H, triazole), 8.05(s, 1H, triazole), 9.91(s, 1H, OH).

v) 1-[2-(2-fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole

A solution of 201 mg (0.847 mmol) 3-Fluoro-4-(2-[1,2,3]triazol-1-yl-ethoxylmethyl)-phenol in 5 ml dimethylformamide was treated with 22.5 mg (0.890 mmol) 95% sodium hydride and stirred at room temperature for 20 min, then 257 mg (0.847 mmol) 4-chloromethyl-2-[2-(4-trifluoromethoxy-phenyl)-vinyl]-oxazole were added and stirring continued for 14 h. After addition of water, the precipitate was isolated, washed thoroughly with water, twice with ether and

dried to give 1-[2-(2-fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

^{1}H-NMR(400MHz, D_6-DMSO): δ= 3.83(t, 2H, CH_2-CH_2-triazole), 4.45(s, 2H, OCH_2-Ph), 4.58(t, 2H, CH_2-triazole), 5.04(s, 2H, OCH_2-oxazole), 6.85(d, 1H, 5-H), 6.94(d, 1H, 3-H), 7.21(d, 1H, vinyl-H), 7.26(d, 1H, 6-H), 7.41(d, 2H, $ArOCF_3$), 7.57(d, 1H, vinyl-H), 7.71(s, 1H, triazole), 7.87(d, 2H, $ArOCF_3$), 8.07(s, 1H, triazole), 8.24(s, 1H, oxazole).

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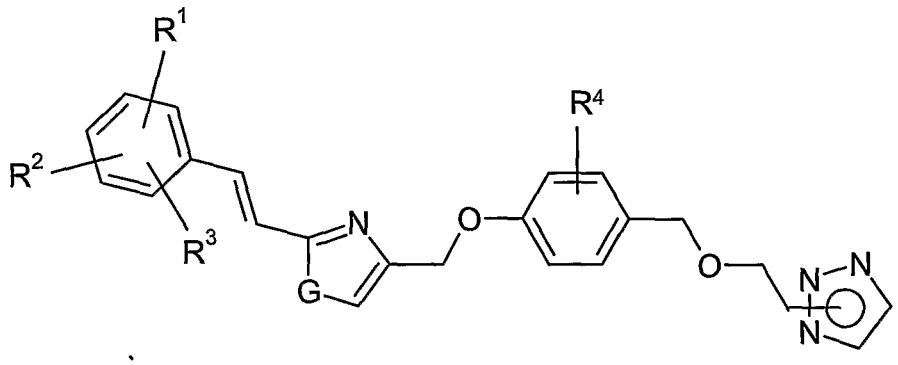
WO 98/03505

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Yarden, Y., and Ullrich, A., Annu. Rev. Biochem. 57 (1988) 443-478

Patent Claims

1. The compounds of formula (I)



formula I,

wherein

R^1 is -O-alkyl;
-S-alkyl;
-NH-alkyl;
all alkyl groups being optionally substituted with one or several halogen atoms;

R^2 is hydrogen; or
halogen; and

R^3 is hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form a 5 or 6 membered heterocyclic ring, being optionally once or several times substituted with halogen; and

R^3 is hydrogen; or
halogen;

G is oxygen; or
sulfur and

R^4 is hydrogen;
C_1-C_3 alkyl;
C_1-C_3 alkoxy; or
halogen; and

pharmaceutically acceptable salts thereof.

2. The compounds according to claim 1, wherein

R^1 is -O-CF_3; -O-CHF_2 or -S-CF_3;
R^2, R^3 and R^4 are all hydrogen; and
G is oxygen; and

pharmaceutically acceptable salts thereof.

3. The compounds according to claim 2:

1-[2-(4-{2-[2-(E)-(4-Trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)- ethyl]-1H-[1,2,3]triazole;

2-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-2H-[1,2,3]triazole; or

4-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium methanesulfonate;

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium *p*-toluenesulfonate; or

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium chloride;

1-[2-(4-{2-[2-(E)-(4-Trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole;

1-[2-(4-{2-[2-(E)-(4-Difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

4. The compounds according to claim 1, wherein

R^1 is -O-CF_3; -O-CHF_2 or -S-CF_3;
R^2 is halogen; and
R^3 and R^4 are hydrogen; and
pharmaceutically acceptable salts thereof.

5. The compounds according to claim 4:

1-[2-(4-{2-[2-(E)-(2-Fluoro-4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole; or
1-[2-(4-{2-[2-(E)-(2-Fluoro-4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)- ethyl]-1H-[1,2,3]triazole.

6. The compounds according to claim 1, wherein

R^1 and R^2 together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl;
R^3 and R^4 are hydrogen; and
pharmaceutically acceptable salts thereof.

7. The compound according to claim 6:

1-[2-(4-{2-[2-(E)-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

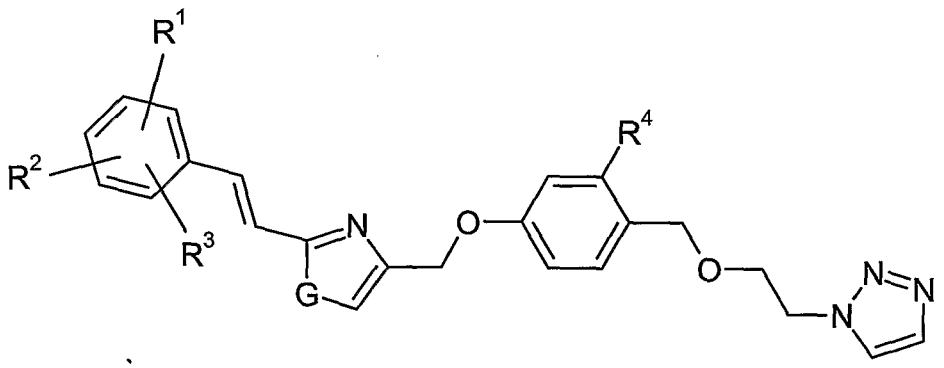
8. The compounds according to claim 1, wherein

R^1 and R^2 together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl;
R^3 is halogen;
R^4 is hydrogen; and
pharmaceutically acceptable salts thereof.

9. The compound according to claim 8:

1-[2-(4-{2-[2-(E)-(2,2,6-Trifluoro-benzo[1,3]dioxol-5-yl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole.

10. The compounds according to claim 1 with formula I-A,



formula I-A,

wherein

R^1 is -O-alkyl;
-S-alkyl;
-NH-alkyl;
all alkyl groups being optionally substituted with one or several halogen atoms;

R^2 is hydrogen; or
halogen; and

R^3 is hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form a 5 or 6 membered heterocyclic ring, being optionally once or several times substituted with halogen; and

R^3 is hydrogen; or
halogen;

G is oxygen; or
sulfur and

R^4 is fluorine; methyl; or methoxy; and

their pharmaceutically acceptable salts.

11. The compounds according to claim 10:

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole; or

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethylsulfanyl-phenyl)-vinyl]-oxazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole.

12. The compounds according to claim 10, wherein

R^1 is -O-alkyl;
-S-alkyl;
all alkyl groups being optionally substituted with one or several fluorine atoms;

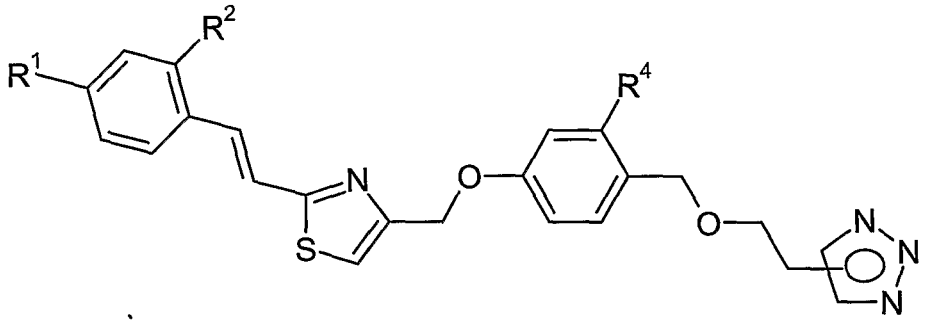
R^2 is hydrogen; and
R^3 is hydrogen; or alternatively

R^1 and R^2 together with the carbon atoms to which they are attached form 2,2-Difluoro-benzo[1,3]dioxolyl; and
R^3 is hydrogen; or

G is oxygen;
R^4 is hydrogen;
C_1-C_3 alkyl; or
fluorine; and

pharmaceutically acceptable salts thereof.

13. The compounds according to claim 1 with formula I-B,



formula I-B,

wherein
R^1 is -O-CF_3 or -O-CHF_2;
R^2 is hydrogen; or
halogen; and
R^4 is hydrogen; methyl; methoxy; or fluorine; and

their pharmaceutically acceptable salts.

14. The compounds according to claim 13:

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazole;

1-[2-(4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-difluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Fluoro-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methyl-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole;

1-[2-(2-Methoxy-4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole; or

4-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]-triazole.

15. The compounds according to claim 13:

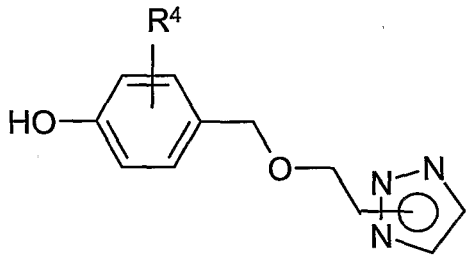
1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium methanesulfonate;

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium *p*-toluenesulfonate; or

1-[2-(4-{2-[2-(E)-(4-trifluoromethoxy-phenyl)-vinyl]-thiazol-4-ylmethoxy}-benzyloxy)-ethyl]-1H-[1,2,3]triazolium chloride.

16. The process for the manufacture of the compounds according to claim 1, wherein

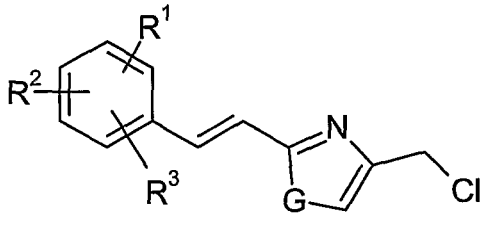
(a) the compound of formula (V)



formula (V),

wherein R^4 has the significance given,

is reacted with a compound of formula (IV)



formula (IV),

wherein R^1, R^2, R^3 and G have the significance given, to give the respective compound of formula (I);

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

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

17. A pharmaceutical composition, containing one or more compounds as claimed in any one of the claims 1 to 15 together with pharmaceutically acceptable excipients.

18. A pharmaceutical composition according to claim 17 for the inhibition of tumor growth.

19. The use of a compound in any one of claims 1 to 15 for the treatment of cancer.

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