Angiogenesis inhibiting thiadiazolyl pyridazine derivatives

This invention concerns novel 3-(3-substituted-1,2,4-thiadiazol-5-yl)pyridazine derivatives acting as angiogenesis inhibitors, and their preparation; it further relates to compositions comprising them, as well as their use as a medicine.

Angiogenesis, *i.e.* the formation of new vessels by endothelial cells, plays an important role in a variety of physiologic and pathophysiologic processes. The development of a vascular supply is essential for the growth. maturation and maintenance of normal tissues. It is also required for wound healing. Angiogenesis is critical for solid tumor growth and metastasis and is involved in a variety of other pathological conditions such as neovascular glaucoma, diabetic retinopathy, psoriasis and rheumatoid arthritis. These pathological states are characterized by augmented angiogenesis during which normally quiescent endothelial cells become activated. degrade extracellular matrix barriers, proliferate, and migrate to form new vessels. To control these angiogenesis dependent disorders, compounds with angiogenesis inhibitory properties would be very useful.

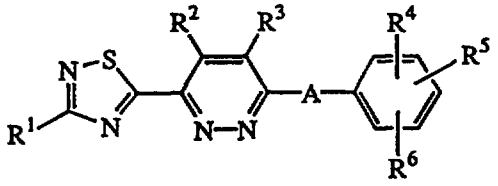
Several compounds inhibiting angiogenesis, also called angiostatics. angio-inhibitors or angiogenic antagonists, are disclosed in the art. For instance hydrocortisone is a well known angiogenesis inhibitor (Folkman et al., Science 230:1375, 1985' "A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment"; Folkman et al.. Science 221:719, 1983. "Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone").

EP-0,398,427, publised on November 22 1990, discloses antirhinoviral pyridazinames, and in EP-0,435,381, published on July 3 1991, pyridazinamines are described having antipicornaviral activity. EP-0,429,344, published on May 29 1991, discloses aminopyridazine derivatives as cholinergic agonists.

The compounds of the present invention differ from the prior art compounds by the fact that they are invariably substituted with a thiadiazolyl moiety and particularly by the fact that unexpectedly these compounds have angiogenesis inhibiting properties.

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This invention concerns compounds of formula



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

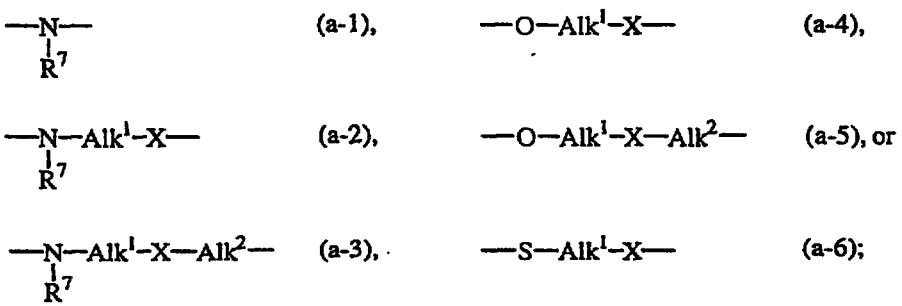
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1-NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 and R^3 are hydrogen, or taken together may form a bivalent radical of formula -CH=CH-CH=CH-;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

or when R^4 and R^5 are adjacent to each other they may be taken together to form a radical of formula -CH=CH-CH=CH-;

A is a bivalent radical of formula



(a-1), —O—Alk¹—X— (a-4),

(a-2), —O—Alk¹—X—Alk²— (a-5), or

(a-3), —S—Alk¹—X— (a-6);

wherein X is a direct bond, -O-, -S-, C=O, $-NR^8-$ or Het^2;

R^7 is hydrogen, C_{1-6}alkyl or Ar^2methyl;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2methyl;

Alk^1 is C_{1-6}alkanediyl;

Alk^2 is C_{1-4}alkanediyl;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

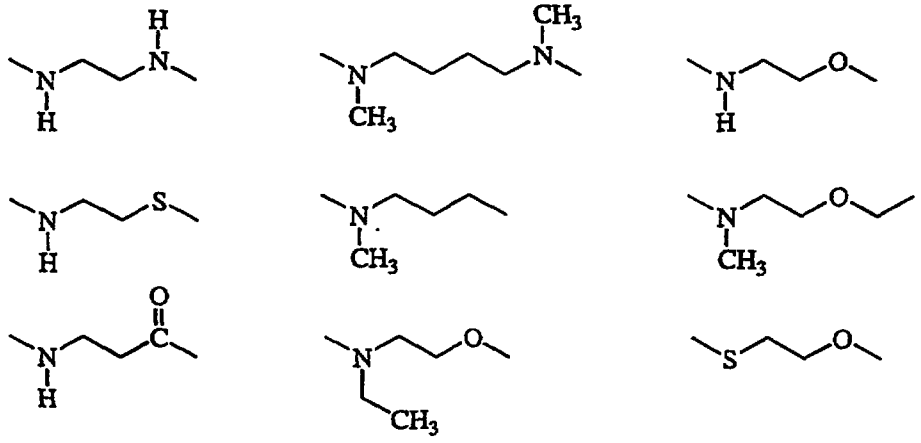
Ar^2 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het^2 is tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxane; a dioxane substituted with C_{1-6}alkyl; a dioxolane; or a dioxolane substituted with C_{1-6}alkyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C_{2-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-4}alkanediyl is meant to include C_{2-4}alkanediyl and methylene; and C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like. The term "C=O" refers to a carbonyl group.

Wherever in the compounds of the present invention the bivalent radical A is (a-2) or (a-3), the nitrogen of the $-NR^7-$ moiety is preferably linked to the pyridazinyl moiety of said compound. Analogously, wherever the bivalent radical A is (a-4), (a-5) or (a-6) the oxygen or sulfur atom is preferably linked to the pyridazinyl moiety. Examples of the bivalent radical A are for instance,



The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids.

The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formula (I), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one of the pyridazinyl nitrogens is *N*-oxidized.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to include also the pharmaceutically acceptable acid addition salts and all stereoisomeric forms.

A group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

a) R^1 is hydrogen, C_{1-6}alkyl, amino or di(C_{1-6}alkyl)amino;

b) R^2 and R^3 are hydrogen;

c) R^4, R^5 and R^6 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, C_{1-6}alkyloxycarbonyl or Het^1;

d) the bivalent radical A is (a-2) or (a-3) wherein R^7 is hydrogen or C_{1-6}alkyl, or A is (a-6) wherein X is O; Alk^1 in said radicals (a-2), (a-3) or (a-6) is preferably C_{2-4}alkanediyl.

A particular group of compounds are those compounds of formula (I) wherein R^1 is hydrogen, C_{1-4}alkyl or di(C_{1-4}alkyl)amino; R^2 and R^3 are hydrogen; R^4, R^5 and R^6 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy, trifluoromethyl, nitro, C_{1-4}alkyloxycarbonyl or Het^1; and the bivalent radical A is (a-2), (a-3), (a-4) or (a-6) wherein Alk^1 is preferably C_{2-4}alkanediyl.

A preferred group of compounds are those compounds of formula (I) wherein the bivalent radical A is (a-2), (a-4), or (a-6) wherein Alk^1 is C_{2-4}alkanediyl.

A more preferred group of compounds are those preferred compounds wherein Alk^1 is butanediyl.

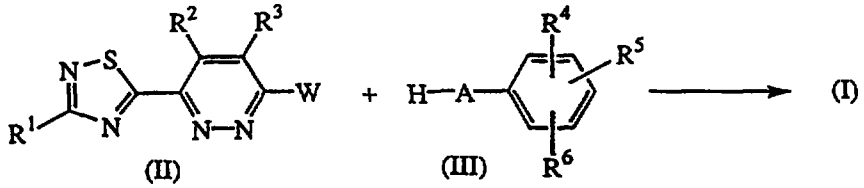
Most preferred are :

6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenoxy]butyl-3-pyridazinamine

N-methyl-6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenoxy]butyl]-3-pyridazinamine, and

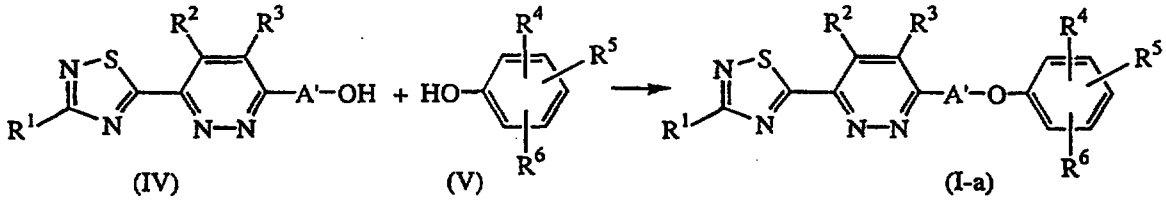
6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenylthio]butyl-3-pyridazinamine, and the pharmaceutically acceptable acid addition salts, the stereoisomeric forms, or the *N*-oxides thereof.

The compounds of the present invention can generally be prepared by reacting a pyridazine of formula (II) with an intermediate of formula (III).

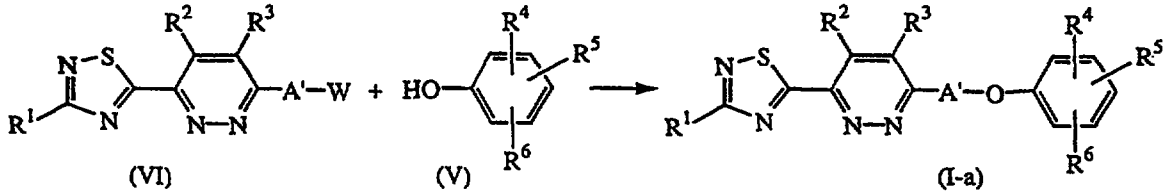


In the foregoing and following reaction schemes W represents an appropriate reactive leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo, or in some instances W may also be a sulfonyloxy group, e.g. methanesulfonyloxy, benzenesulfonyloxy, trifluoromethanesulfonyloxy and the like reactive leaving groups. Said reaction is performed following art-known procedures such as for instance stirring both reactants together in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, acetonitrile, methyl isobutylketone and the like, preferably in the presence of a base, e.g. sodium hydrogen carbonate, sodiumcarbonate or triethylamine. The reaction may conveniently be carried out at a temperature ranging between room temperature and the reflux temperature of the reaction mixture.

The compounds of formula (I) wherein the bivalent radical A' is a radical of formula (a-2), (a-4) or (a-6) wherein X is a direct bond, said compounds being represented by formula (I-a), can be prepared by condensing a phenol of formula (V) and an intermediate of formula (IV), e.g. by using the Mitsunobu reaction (Synthesis, 1, 1981). Said reaction is carried out in a reaction-inert solvent such as, e.g. THF, and in the presence of triphenylphosphine and diisopropryl azodicarboxylate (DIAD).



Further, the compounds of formula (I-a) can also be prepared following art-known *O*-alkylation reactions by reacting an intermediate of formula (VI), wherein W is a leaving group as defined above, with a phenol of formula (V) wherein A' is as defined above.



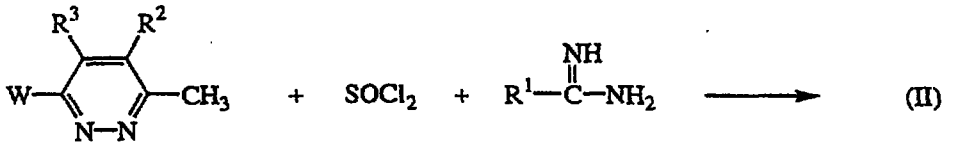
Said *O*-alkylation reaction can conveniently be carried out by mixing the reactants, optionally in a reaction-inert solvent. The addition of an appropriate base such as, e.g. sodium carbonate, sodium hydrogen carbonate, sodium hydroxide and the like, may optionally be used to pick up the acid which is formed during the course of the reaction. Further, it may be advantageous to convert the phenol of formula (V) first into a suitable salt form thereof such as, for example, an alkali or earth alkaline metal salt, by reacting (V) with an appropriate base as defined hereinabove and subsequently using said salt form in the reaction with the intermediate of formula (VI). Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said alkylation reaction under an inert atmosphere such as, for example, oxygen-free argon or nitrogen gas.

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions. For instance, compounds of formula (I) wherein the bivalent radical A is a radical of formula (a-2) to (a-6) wherein X is Het^2 and said Het^2 is a dioxane can be converted to the corresponding compounds of formula (I) wherein said X is C=O by hydrolysis under acidic conditions.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarbo-peroxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzene-carboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

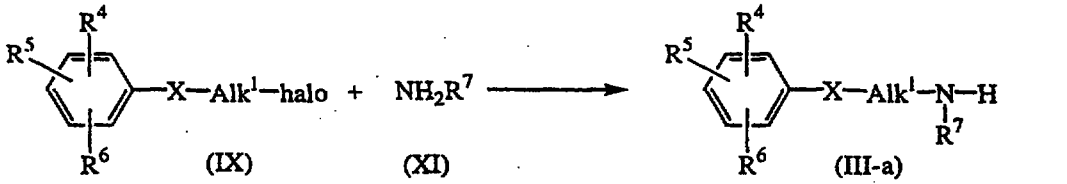
The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

Intermediates of formula (II) may be prepared by reacting compounds of formula (VII), wherein W is an appropriate leaving group as defined above, with an intermediate of formula (VIII), optionally added as its acid addition salt.

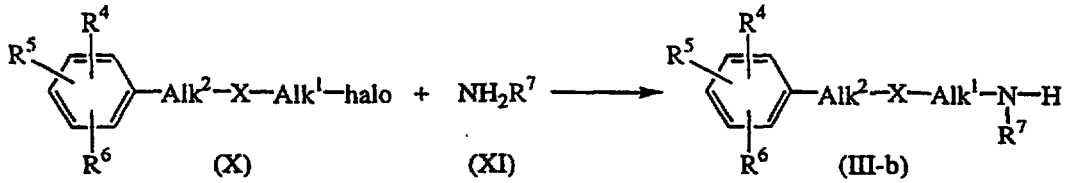


(VII) (VIII) (II)

Intermediates of formula (III) wherein the bivalent radical A represents a radical of formula (a-2), said intermediates represented by intermediates (III-a), or wherein said radical A represents a radical of formula (a-3), said intermediates represented by intermediates (III-b), can be prepared by reacting their corresponding halo analogues, *i.e.* intermediates (IX) or (X), with an intermediate of formula (XI).



(IX) (XI) (III-a)



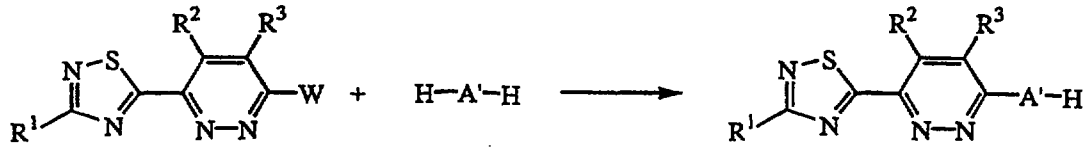
(X) (XI) (III-b)

Said reaction can be carried out by stirring an intermediate of formula (IX) or (X) with an intermediate of formula (XI) in a reaction-inert solvent such as, e.g. THF, in the presence of calciumoxide. Optionally, the temperature may be raised in a range between room temperature and the reflux temperature of the reaction mixture and, if desired, the reaction may be carried out in an autoclave at an increased pressure.

The intermediates of formula (IX) or (X) can also be reacted with an intermediate of formula (XI) wherein one of the hydrogen atoms on the nitrogen is replaced by an appropriate protecting group, such as, e.g. a benzyl group. If desired art-known

functional group transformations may be carried out before said protecting group is removed using art-known procedures such as, e.g. hydrogenation with palladium on carbon in the presence of hydrogen gas.

Intermediates of formula (IV), wherein A' represents a bivalent radical of formula (a-2), (a-4) or (a-6) wherein X is O, can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (XII) in a reaction-inert solvent such as, e.g. *N*,*N*-dimethylformamide, and optionally in the presence of a suitable base such as, e.g. sodium carbonate.



(II) (XII) (IV)

Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration. For instance, compounds of formula (I) wherein the bivalent radical A is a radical of formula (a-2) to (a-6) wherein Alk^1 is C_{2-6}alkanediyl can have a stereogenic center such as, e.g. compounds 88 and 89.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel CA, OA, OB, OC, OD, OF, OG, OJ and OK, and Chiralpak AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the

reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) have valuable pharmacological properties in that they inhibit angiogenesis, both *in vivo* and *in vitro*, as demonstrated in the pharmacological example C.1.

In view of their pharmacological activity, the compounds of formula (I), their pharmaceutically acceptable acid addition salts, stereochemically isomeric forms, or *N*-oxide forms thereof, are inhibitors of angiogenesis. Therefore, angiogenesis inhibitors are useful to control or treat angiogenesis dependent disorders such as, e.g. ocular neovascular diseases, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, hemangiomas, angiofibromas, psoriasis, osteoarthritis and rheumatoid arthritis. Also, angiogenesis inhibitors are useful to control solid tumor growth, such as, e.g. breast, prostate, melanoma, renal, colon, cervical cancer and the like; and metastasis.

Hence, the present invention discloses the compounds of formula (I) for use as a medicine as well as the use of these compounds of formula (I) for the manufacture of a medicament for treating angiogenesis dependent disorders.

In view of the usefulness of the subject compounds in the treatment or prevention of angiogenesis dependent disorders, the present invention provides a method of treating warm-blooded animals suffering from such disorders, said method comprising the systemic administration of a therapeutic effective amount of a compound of formula (I), a *N*-oxide or a pharmaceutically acceptable acid addition salt thereof.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.
To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual

pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose,

microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxy*galacto*sucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very good results. In the high-dosage formulations stronger flavours may be required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not

undergo any change or loss of taste and colour under the acidic conditions of the formulation.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as isotonizing, suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray, as a powder or in the form of drops.

Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 10 mg/kg body weight, and in particular from 0.01 mg/kg to 1 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.01 to 500 mg, and in particular 0.1 mg to 200 mg of active ingredient per unit dosage form.

The following examples are provided for purposes of illustration.

Experimental part

Hereinafter "DMF" means *N,N*-dimethylformamide, "DCM" means dichloromethane, "DIPE" means diisopropylether and "THF" means tetrahydrofuran.

A. Preparation of the intermediates

Example A.1

3-Chloro-6-methylpyridazine (0.3 mol) and thionyl chloride (400 g) were stirred and refluxed overnight. The solvent was evaporated. The residue was taken up in DCM (500 ml). The mixture was cooled to 0°C. 1-Imino-ethanamine hydrochloride (1:1) (33 g) was added. Then sodium hydroxide (50%, 80 ml) was added dropwise at 0°C. The mixture was allowed to warm to room temperature, then stirred for 1 hour, poured out into ice water, stirred for 30 minutes and filtered over dicalite. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was boiled in ethanol (800 ml), silica gel (20 g) and activated charcoal Norit (3 g). The mixture was filtered over dicalite and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent : DCM). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from ethanol. The precipitate was filtered off and dried, yielding : 18.3 g (29%) 3-chloro-6-(3-methyl-1,2,4-thiadiazol-5-yl)pyridazine (intermediate 1).

In a similar way, 3-chloro-6-(1,2,4-thiadiazol-5-yl)pyridazine (intermediate 2) and 5-(6-chloro-3-pyridazinyl)-*N,N*-dimethyl-1,2,4-thiadiazol-3-amine (intermediate 3) were prepared.

Example A.2

A mixture of 4-(4-bromobutoxy)-1,2-dichlorobenzene (0.03 mol), methylamine (20 g) and calciumoxide (7 g) in THF (100 ml) was stirred at 125°C overnight in an autoclave. The mixture was filtered over dicalite and the filtrate was evaporated. The residue was taken up in DIPE and the mixture was filtered over dicalite. The filtrate was converted into the hydrochloric acid salt (1:1) with HCl/2-propanol. The precipitate was filtered off and dried, yielding 6 g (70.3%) of 4-(3,4-dichlorophenoxy)-*N*-methyl-1-butanamine (intermediate 4, mp. 132°C).

Example A.3

A mixture of 1-bromo-3-(trifluoromethyl)benzene (0.1 mol), 1,6-hexanediamine (0.5 mol) and copper(I)oxide (1 g) was stirred for 5 hours at 140°C and left standing overnight. Water was added and the mixture was extracted with DCM. The organic layer was dried, filtered off and evaporated. The residue was purified on a glass filter

over silica gel (eluent : CH_2Cl_2/CH_3OH 98/2 to 90/10). The pure fractions were collected and evaporated. The oily residue was dissolved in DIPE and converted into the hydrochloric acid salt (1:2) in 2-propanol The precipitate was filtered off and dried, yielding 10 g (30%) of *N*-[3-(trifluoromethyl)phenyl]-1,6-hexanediamine dihydrochloride (intermediate 5).

In a similar way, *N*-phenyl-1,4-butanediamine dihydrochloride (intermediate 6) was prepared.

Example A.4

a) A mixture of 1-(4-bromobutoxy)-3-(trifluoromethyl)-benzene (0.11 mol) and benzylamine (0.6 mol) in dimethylacetamide (250 ml) was stirred at 80°C for 6 hours, then poured out into water and extracted with toluene. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:1) from DIPE. The precipitate was filtered off and dried. The residue was stirred in water. The precipitate was filtered off and dried, yielding 23.3 g (59%) of *N*-[4-[3-(trifluoromethyl)phenoxy]butyl]benzenemethaneamine hydrochloride (intermediate 7).

b) A mixture of intermediate 7 (0.03 mol) and paraformaldehyde (2 g) in methanol (150 ml) was hydrogenated with palladium on carbon (2 g) as a catalyst in the presence of thiophene (4%, 2 ml) and potassium acetate (4 g). After uptake of hydrogen gas (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in water and this mixture was extracted with DCM. The separated organic layer was dried, filtered, and the solvent evaporated. The residue was dissolved in DIPE and converted into the hydrochloric acid salt (1:1) with HCl/2-propanol. The precipitate was filtered off and dried, yielding 8.22 g (73%) of *N*-methyl-*N*-[4-[3-(trifluoromethyl)phenoxy]butyl]benzenemethanamine hydrochloride (intermediate 8).

c) A mixture of intermediate 8 (0.019 mol) in methanol (150 ml) was hydrogenated with palladium on carbon (10%, 2 g) as a catalyst. After uptake of hydrogen gas (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was converted into the free base with a NaOH solution. The aqueous solution was extracted with toluene. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:1) in DIPE. The precipitate was filtered off and dried, yielding 1.21 g (22.5%) of *N*-methyl-4-[3-(trifluoromethyl)phenoxy]-1-butanamine (intermediate 9).

Example A.5

A mixture of intermediate 1 (0.08 mol), 4-methylamino-1-butanol (0.11 mol) and sodium carbonate (10 g) in DMF (150 ml) was stirred at 60°C for 4 hours. The solvent was evaporated. The residue was taken up in DCM. The mixture was stirred, filtered over dicalite and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent : CH_2Cl_2/CH_3OH 100/0 to 97/3). The pure fractions were collected and the solvent was evaporated, yielding 22.2 g (100%) of 4-[methyl[6-(3-methyl-1,2,4-thiadiazol-5-yl)-3-pyridazinyl]amino]-1-butanol (intermediate 10).

B. Preparation of the final compounds

Example B.1

A mixture of intermediate 1 (0.02 mol), intermediate 9 (0.0212 mol) and sodium carbonate (0.03 mol) in DMF (60 ml) was stirred and heated at 60°C overnight. The mixture was evaporated, the residue was dissolved in a mixture of toluene and water and separated into its layers. The aqueous layer was extracted with toluene. The combined organic layer was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent : DCM). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanol. The precipitate was filtered off and dried, yielding 2.77 g (33%) of *N*-methyl-6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenoxy]butyl]-3-pyridazinamine (compound 52).

Example B.2

Diisopropryl azodicarboxylate (DIAD) (0.016 mol) in a small amount of THF was added dropwise to a mixture of intermediate 10 (0.008 mol), 4-trifluoromethyl-phenol (0.01 mol) and triphenylphosphine (0.016 mol) in THF (60 ml) while cooling on ice. The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent : DCM). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in DIPE and converted into the hydrochloric acid salt (1:1). The precipitate was filtered off and dried. This fraction was boiled in DIPE, filtered off and dried, yielding 1.31 g (36%) of *N*-methyl-6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[4-(trifluoromethyl)phenoxy]butyl]-3-pyridazinamine monohydrochloride (compound 55).

Example B.3

A mixture of compound (95) (0.0065 mol) in an aqueous solution of sulfuric acid (1%, 200 ml) was stirred and refluxed overnight. The reaction mixture was cooled and the precipitate was filtered off, washed with water and dried, yielding 3 g (100%) of 5-[[6-(3-methyl-1,2,4-thiadiazol-5-yl)-3-pyridazinyl]amino]-1-[3-(trifluoromethyl)-phenyl]-1-pentanone (compound 69).

Example B.4

a) A mixture of 3-chloro-6-cyano-pyridazine (0.03 mol) in triethylamine (12 ml) and DMF (50 ml) was stirred on an ice bath. Hydrogen sulfide was bubbled through the mixture for 20 minutes. The mixture was stirred overnight. Nitrogen gas was bubbled through the mixture for 1 hour. The mixture was poured out into water. The precipitate was filtered off, washed with water, dissolved in DMF and the solvent was evaporated, yielding 3 g (48%) of 6-mercapto-3-pyridazinecarbothioamide (intermediate 11).

b) A mixture of intermediate 11 (0.017 mol) in DMF (80 ml) was stirred at room temperature. Sodium hydride (50%, 0.02 mol) was added portionwise. The mixture was stirred for 30 minutes. A mixture of 1-(4-chlorobutoxy)-3-(trifluoromethyl)-benzene (0.02 mol) in DMF (20 ml) was added dropwise. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was stirred in DIPE (100 ml), filtered off and dried, yielding 3.1g (47%) of 6-[[4-[3-(trifluoromethyl)-phenoxy]butyl]thio]-3-pyridazinecarbothioamide (intermediate 12).

c) A mixture of intermediate 12 (0.009 mol) and *N,N*-dimethylacetamide dimethyl acetal (0.015 mol) in toluene (100 ml) was stirred and refluxed for 3 hours. The solvent was evaporated, yielding 4.1g (100%) of *N*-[1-(dimethylamino)ethylidene]-6-[[4-[3-(trifluoromethyl)phenoxy]butyl]thio]-3-pyridazinecarbothioamide (intermediate 13).

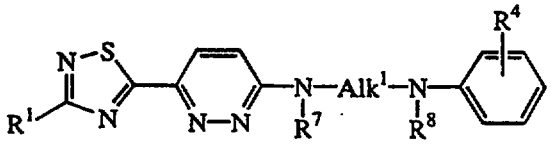
d) A mixture of intermediate 13 (0.009 mol) and pyridine (0.02 mol) in ethanol (80 ml) was stirred. A mixture of hydroxylamine-*O*-sulfonic acid (0.01 mol) in methanol (20 ml) was added. The mixture was stirred overnight. The solvent was evaporated. The residue was taken up in DCM. The organic solution was washed with a diluted NaOH solution and with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : DCM). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanol. The precipitate was filtered off and dried, yielding 1 g (26%) of 3-(3-methyl-1,2,4-thiadiazol-5-yl)-6-[[4-[3-(trifluoromethyl)phenoxy]butyl]thio]pyridazine (compound 94).

Example B.5

A mixture of compound (101) (0.0094 mol) in HCl (80 ml) was stirred and refluxed for 25 minutes. The mixture was cooled on ice, alkalized with a concentrated NH_4OH solution and extracted with DCM. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent : CH_2Cl_2/CH_3OH). The pure fractions were collected and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt with HCl/2-propanol. The mixture was allowed to crystallize out. The precipitate was filtered of and dried , yielding 1.1 g (2%) of compound (102).

Tables F.1 to F.5 list the compounds that were prepared according to one of the above examples and table F.6 lists both the experimental (column heading "exp.") and theoretical (column heading "theor.") elemental analysis values for carbon, hydrogen and nitrogen of the compounds as prepared in the experimental part hereinabove.

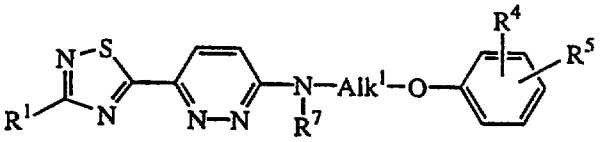
Table F.1 :



Co. No.	Ex. No.	R^1	R^4	R^7	R^8	Alk^1	Physical data
1	B.1	CH_3	H	H	H	$-(CH_2)_2-$	mp. 148.4°C
2	B.1	CH_3	H	H	H	$-(CH_2)_3-$	mp. 162.7°C
3	B.1	CH_3	H	H	H	$-(CH_2)_4-$	-
4	B.1	CH_3	H	H	H	$-(CH_2)_5-$	mp. 139.9°C
5	B.1	CH_3	H	H	H	$-(CH_2)_6-$	mp. 135.1°C
6	B.1	CH_3	3-CF_3	H	H	$-(CH_2)_2-$	-
7	B.1	CH_3	3-CF_3	H	H	$-(CH_2)_3-$	-
8	B.1	CH_3	3-CF_3	H	H	$-(CH_2)_6-$	mp. 121.9°C
9	B.1	CH_3	H	CH_3	H	$-(CH_2)_2-$	mp. 127.9°C
10	B.1	CH_3	H	CH_3	CH_3	$-(CH_2)_2-$	mp. 126.2°C
97	B.1	$(CH_3)_2N-$	3-CF_3	H	H	$-(CH_2)_6-$	HCl (1:2)
104	B.1	CH_3	3-CF_3	CH_3	H	$-(CH_2)_3-$	-
105	B.1	CH_3	3-CF_3	H	CH_3	$-(CH_2)_2-$	-
106	B.1	CH_3	3-CF_3	H	CH_3	$-(CH_2)_4-$	-

Co. No.	Ex. No.	R^1	R^4	R^7	R^8	Alk^1	Physical data
107	B.1	CH_3	3-CF_3	CH_3	CH_3	-$(CH_2)_2$-	-
108	B.1	CH_3	3-CF_3	H	H	-$(CH_2)_4$-	-
110	B.1	CH_3	3-CF_3	CH_3	$C_6H_5CH_2$-	-$(CH_2)_2$-	-
111	B.1	CH_3	3-CF_3	CH_3	CH_3	-$(CH_2)_4$-	HCl (1:2)
112	B.1	CH_3	3-CF_3	CH_3	H	-$(CH_2)_2$-	-
114	B.1	CH_3	3-CF_3	CH_3	H	-$(CH_2)_4$-	HCl (1:2)
115	B.1	CH_3	3-CF_3	H	CH_3	-$(CH_2)_5$-	-
116	B.1	CH_3	3-CF_3	CH_3	CH_3	-$(CH_2)_5$-	-
117	B.1	CH_3	3-CF_3	H	H	-$(CH_2)_5$-	-

Table F.2 :

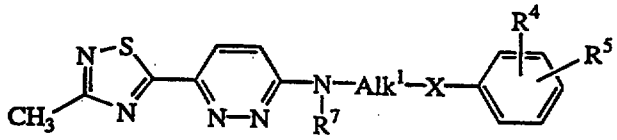


Co. No.	Ex. No.	R^1	R^7	Alk^1	R^4	R^5	Physical data
11	B.1	H	H	-$(CH_2)_4$-	3-CF_3	H	-
12	B.1	H	CH_3	-$(CH_2)_4$-	3-CF_3	H	-
13	B.1	CH_3	H	-$(CH_2)_4$-	H	H	mp. 186°C
14	B.1	CH_3	H	-$(CH_2)_4$-	4-Br	H	-
15	B.1	CH_3	H	-$(CH_2)_4$-	2-Cl	H	-
16	B.1	CH_3	H	-$(CH_2)_4$-	4-Cl	H	-
17	B.1	CH_3	H	-$(CH_2)_4$-	3-Cl	4-Cl	mp. 181°C
18	B.1	CH_3	H	-$(CH_2)_4$-	2-Cl	4-OCH_3	-
19	B.1	CH_3	H	-$(CH_2)_4$-	2-F	H	-
20	B.1	CH_3	H	-$(CH_2)_4$-	3-F	H	-
21	B.1	CH_3	H	-$(CH_2)_4$-	4-F	H	-
22	B.1	CH_3	H	-$(CH_2)_4$-	2-F	4-F	-
23	B.1	CH_3	H	-$(CH_2)_4$-	3-F	4-F	-
24	B.1	CH_3	H	-$(CH_2)_2$-	3-CF_3	H	-
25	B.1	CH_3	H	-$(CH_2)_3$-	3-CF_3	H	-
26	B.1	CH_3	H	-$(CH_2)_4$-	3-CF_3	H	-

Co. No.	Ex. No.	R^1	R^7	Alk^1	R^4	R^5	Physical data
27	B.2	CH_3	H	$-(CH_2)_5-$	3-CF_3	H	mp. 84-85°C
28	B.2	CH_3	H	$-(CH_2)_6-$	3-CF_3	H	-
29	B.1	CH_3	H	$-(CH_2)_4-$	2-$CH(CH_3)_2$	5-CH_3	-
30	B.1	CH_3	H	$-(CH_2)_4-$	3-OCH_3	H	mp. 152°C
31	B.1	CH_3	H	$-(CH_2)_4-$	4-OCH_3	H	mp. 172°C
32	B.2	CH_3	H	$-(CH_2)_4-$	3-OCH_3	4-OCH_3	-
33	B.2	CH_3	H	$-(CH_2)_4-$	$-COOCH_2CH_3$	H	-
34	B.1	CH_3	H	$-(CH_2)_4-$	3-NO_2	H	mp. 138°C
35	B.1	CH_3	CH_3	$-(CH_2)_4-$	H	H	mp. 106°C
36	B.1	CH_3	CH_3	$-(CH_2)_4-$	4-Br	H	-
37	B.1	CH_3	CH_3	$-(CH_2)_4-$	2-Cl	H	.HCl (1:1)
38	B.1	CH_3	CH_3	$-(CH_2)_4-$	4-Cl	H	-
39	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-Cl	4-Cl	-
40	B.2	CH_3	CH_3	$-(CH_2)_4-$	2-Cl	4-OCH_3	-
41	B.1	CH_3	CH_3	$-(CH_2)_4-$	2-F	H	.HCl (1:1)
42	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-F	H	.HCl (1:1)
43	B.1	CH_3	CH_3	$-(CH_2)_4-$	4-F	H	-
44	B.1	CH_3	CH_3	$-(CH_2)_4-$	2-F	4-F	.HCl (1:1)
45	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-F	4-F	-
46	B.2	CH_3	CH_3	$-(CH_2)_4-$	2-F	3-CF_3	.HCl (1:1)
47	B.2	CH_3	CH_3	$-(CH_2)_4-$	2-F	5-CF_3	-
48	B.2	CH_3	CH_3	$-(CH_2)_4-$	3-F	5-CF_3	.HCl (1:1)
49	B.2	CH_3	CH_3	$-(CH_2)_4-$	2-CF_3	H	.HCl (1:1)
50	B.1	CH_3	CH_3	$-(CH_2)_2-$	3-CF_3	H	-
51	B.1	CH_3	CH_3	$-(CH_2)_3-$	3-CF_3	H	.HCl (1:1)
52	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-CF_3	H	-
53	B.2	CH_3	CH_3	$-(CH_2)_4-$	3-CF_3	5-CF_3	-
54	B.2	CH_3	CH_3	$-(CH_2)_4-$	3-CF_3	4-NO_2	.HCl (1:1)
55	B.2	CH_3	CH_3	$-(CH_2)_4-$	4-CF_3	H	.HCl (1:1)
56	B.2	CH_3	CH_3	$-(CH_2)_4-$	2-NO_2	4-Br	-
57	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-NO_2	H	mp. 133°C
58	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-OCH_3	H	.HCl (1:1)
59	B.1	CH_3	CH_3	$-(CH_2)_4-$	4-OCH_3	H	mp. 122°C

Co. No.	Ex. No.	R^1	R^7	Alk^1	R^4	R^5	Physical data
60	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-OCH_3	4-OCH_3	mp. 135°C; .HCl (1:1)
61	B.1	CH_3	CH_3	$-(CH_2)_4-$	3-CH_3	H	mp. 121°C; .HCl (1:1)
62	B.1	CH_3	CH_3	$-(CH_2)_4-$	2-$CH(CH_3)_2$	5-CH_3	-
63	B.1	CH_3	CH_3CH_2-	$-(CH_2)_4-$	3-CF_3	H	-
64	B.1	CH_3	$CH_3(CH_2)_2-$	$-(CH_2)_4-$	3-CF_3	H	-
65	B.1	CH_3	$CH_3(CH_2)_3-$	$-(CH_2)_4-$	3-CF_3	H	-
66	B.2	CH_3	$C_6H_5CH_2-$	$-(CH_2)_4-$	3-CF_3	H	-
67	B.1	$(CH_3)_2N-$	H	$-(CH_2)_4-$	3-CF_3	H	-
68	B.1	$(CH_3)_2N-$	CH_3	$-(CH_2)_4-$	3-CF_3	H	.HCl (1:1)
98	B.1	H	H	$-(CH_2)_2-$	3-CF_3	H	-
99	B.1	H	CH_3	$-(CH_2)_2-$	3-CF_3	H	-
100	B.1	$(CH_3)_2N-$	CH_3	$-(CH_2)_2-$	3-CF_3	H	-
101	B.1	$C_6H_5CH_2$ -OCH_2	CH_3	$-(CH_2)_4-$	3-CF_3	H	-
102	B.5	HO-CH_2-	CH_3	$-(CH_2)_4$	3-CF_3	H	HCl
109	B.1	CH_3	CH_3	$-(CH_2)_4$	3-NH_2	H	HCl (1:2); H_2O (1:1)
113	B.1	CH_3	H	$-(CH_2)_4-$	3-NH_2	H	-

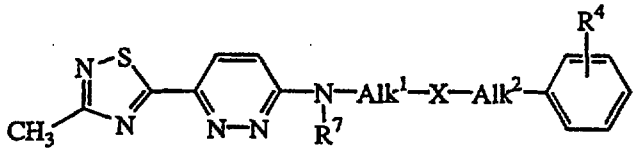
Table F.3 :



Co. No.	Ex. No.	R^7	Alk^1	X	R^4	R^5	Physical data
69	B.3	H	$-(CH_2)_4-$	C=O	3-CF_3	H	mp. 158°C
70	B.3	CH_3	$-(CH_2)_4-$	C=O	3-CF_3	H	mp. 104°C
71	B.1	H	$-(CH_2)_4-$	S	4-F	H	-
72	B.1	CH_3	$-(CH_2)_4-$	S	4-F	H	-
73	B.1	H	$-(CH_2)_4-$	S	3-CF_3	H	-
74	B.1	CH_3	$-(CH_2)_4-$	S	3-CF_3	H	.HCl (1:1)

Co. No.	Ex. No.	R^7	Alk^1	X	R^4	R^5	Physical data
75	B.1	H	$-(CH_2)_5-$	direct bond	4-F	H	-
76	B.1	CH_3	$-(CH_2)_5-$	direct bond	4-F	H	.HCl (1:1)
77	B.1	H	$-(CH_2)_5-$	direct bond	3-CF_3	H	mp. 134°C
78	B.1	CH_3	$-(CH_2)_5-$	direct bond	3-CF_3	H	.HCl (1:1)

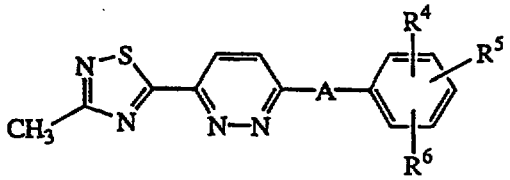
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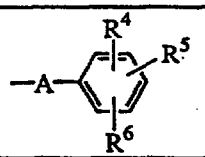
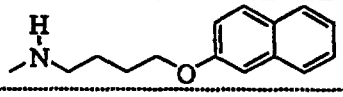
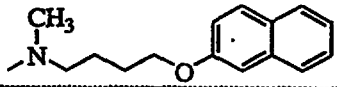
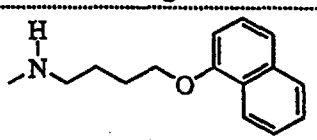


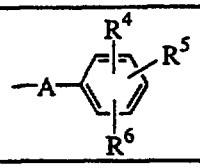
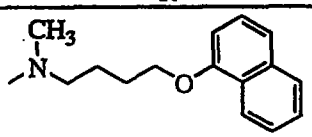
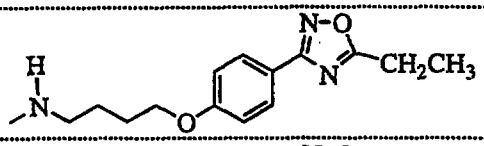
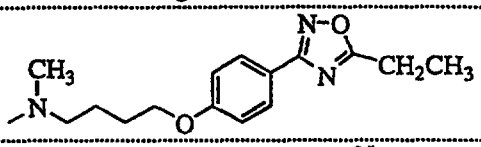
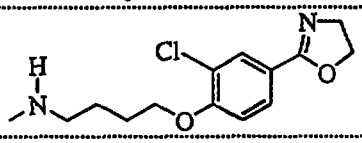
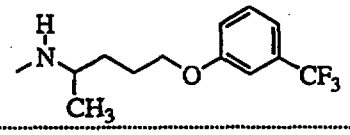
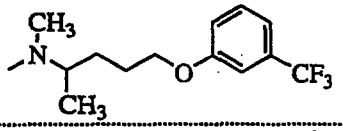
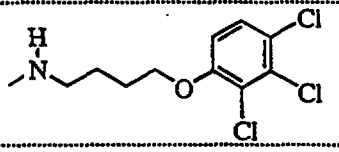
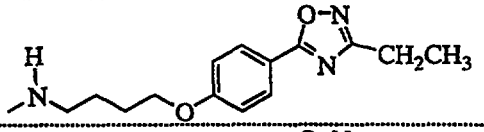
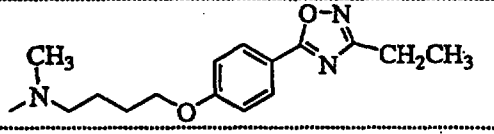
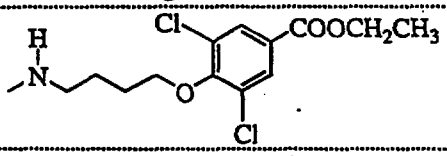
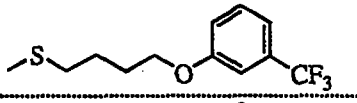
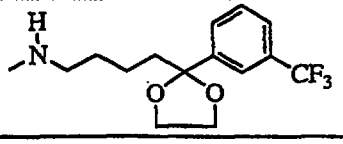
Co. No.	Ex. No.	R^7	- Alk^1-X-Alk^2	R^4
79	B.1	H	$-(CH_2)_3-O-CH_2^*-$	4-F
80	B.1	CH_3	$-(CH_2)_3-O-CH_2^*-$	4-F

* : CH_2 moiety is linked with phenyl bearing R^4

Table F.5 :



Co. No.	Ex. No.		Physical data
81	B.1		-
82	B.1		-
83	B.1		-

Co. No.	Ex. No.		Physical data
84	B.1		.HCl (1:1)
85	B.1		-
86	B.1		.HCl (1:1)
87	B.2		-
88	B.1		-
89	B.1		.HCl (1:1)
90	B.2		-
91	B.1		-
92	B.1		-
93	B.2		-
94	B.4		-
95	B.1		mp. 136°C

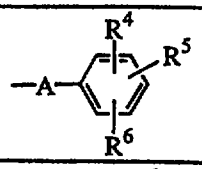
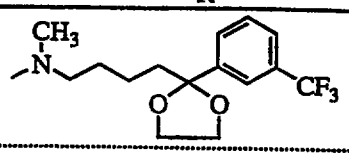
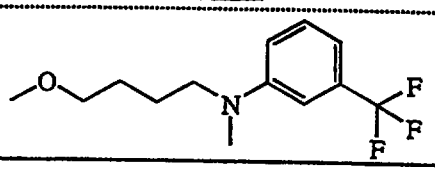
Co. No.	Ex. No.		Physical data
96	B.1		mp. 82°C
103	B.1		-

Table F.6 :

Co. No.	Carbon		Hydrogen		Nitrogen	
	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
3	59.7	59.98	5.9	5.92	24.59	24.69
6	50.22	50.52	3.85	3.97	22.19	22.09
7	51.75	51.77	4.30	4.34	21.59	21.31
11	51.70	51.64	4.12	4.08	18.00	17.71
12	52.40	52.80	4.57	4.43	16.92	17.10
14	48.33	48.58	4.18	4.32	16.60	16.66
15	53.95	54.32	4.91	4.83	18.87	18.63
16	53.90	54.32	4.61	4.83	18.71	18.63
18	53.11	53.26	4.86	4.97	17.24	17.25
19	56.78	56.81	5.04	5.05	19.97	19.48
20	56.71	56.81	5.03	5.05	19.75	19.48
21	56.73	56.81	5.02	5.05	19.77	19.48
22	53.38	54.10	4.42	4.54	18.89	18.56
23	52.43	54.10	4.37	4.54	18.27	18.56
24	50.15	50.39	3.57	3.70	18.25	18.36
25	51.84	51.64	3.76	4.08	17.74	17.71
26	52.70	52.80	4.39	4.43	17.51	17.10
28	54.91	54.91	5.05	5.07	16.15	16.01
29	63.00	63.45	6.75	6.85	17.60	17.62
32	57.13	56.84	5.74	5.77	17.60	17.44
33	57.83	58.09	5.43	5.61	17.15	16.94
36	49.93	49.77	4.65	4.64	16.36	16.12
37	50.74	50.71	4.88	4.96	16.58	16.43

Co. No.	Carbon		Hydrogen		Nitrogen	
	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
38	55.55	55.45	5.17	5.17	18.23	17.96
39	50.66	50.95	4.96	4.51	16.11	16.50
40	54.32	54.34	5.30	5.28	16.83	16.68
41	53.06	52.74	5.18	5.16	17.26	17.08
43	57.67	57.89	5.37	5.40	19.13	18.75
44	50.79	50.52	4.61	4.71	16.80	16.37
46	47.68	47.75	4.18	4.22	14.48	14.65
47	51.41	51.70	4.24	4.34	15.97	15.86
49	49.68	49.62	4.71	4.60	15.58	15.23
51	48.23	48.49	4.39	4.29	15.72	15.71
52	53.82	53.89	4.73	4.76	16.86	16.54
53	48.49	48.88	3.86	3.90	14.50	14.25
54	45.10	45.20	3.89	3.99	16.37	16.64
55	49.39	49.62	4.46	4.60	15.08	15.23
56	45.09	45.10	3.98	4.00	17.41	17.53
62	64.07	64.20	7.04	7.10	17.01	17.02
63	54.63	54.91	5.07	5.07	16.10	16.01
64	55.51	55.86	5.38	5.36	15.58	15.51
65	56.69	56.76	5.67	5.63	15.08	15.04
66	60.32	60.11	4.88	4.84	13.76	14.02
67	51.93	52.05	4.76	4.83	19.41	19.17
71	54.02	54.38	4.70	4.83	18.84	18.65
72	55.29	55.50	5.06	5.18	18.13	17.98
73	50.66	50.81	4.15	4.26	16.72	16.46
74	47.88	47.94	4.42	4.45	14.72	14.71
75	60.33	60.48	5.58	5.64	19.62	19.59
76	56.41	55.94	5.66	5.68	17.09	17.17
78	52.95	52.46	5.16	5.06	15.72	15.29
79	56.45	56.81	5.02	5.05	19.61	19.48
80	57.51	57.89	5.49	5.40	19.21	18.75
81	64.31	64.43	5.44	5.41	18.00	17.89
82	64.74	65.16	5.64	5.72	17.10	17.27
83	64.19	64.43	5.34	5.41	18.29	17.89
84	59.88	59.79	5.43	5.47	16.10	15.85
85	57.70	57.65	5.06	5.30	22.37	22.41
86	55.66	54.15	5.30	5.37	20.88	20.09

Co. No.	Carbon		Hydrogen		Nitrogen	
	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
87	53.74	53.99	4.69	4.76	19.00	18.89
88	53.50	53.89	4.74	4.76	16.58	16.54
90	45.93	45.91	3.56	3.63	15.79	15.75
91	57.64	57.65	5.23	5.30	22.56	22.41
92	58.28	58.52	5.52	5.58	21.65	21.71
93	49.40	49.80	4.30	4.39	14.02	14.52
94	50.76	50.69	4.00	4.02	13.50	13.14
98	48.85	49.04	3.12	3.29	19.44	19.06
99	50.14	50.39	3.65	3.70	18.24	18.36
100	50.73	50.94	4.57	4.51	19.84	19.80
102	48.30	47.95	4.42	4.45	14.59	14.72
103	53.53	53.89	4.68	4.76	16.39	16.54
104	52.71	52.93	4.57	4.69	20.62	20.58
105	52.20	51.77	4.31	4.34	21.89	21.31
106	53.90	54.02	4.91	5.01	19.92	19.89
107	51.31	52.93	4.48	4.69	19.74	20.58
108	52.65	52.93	4.58	4.69	20.64	20.58
109	47.18	46.86	5.61	5.68	17.85	18.21
110	59.42	59.49	4.66	4.78	17.37	17.34
111	47.10	47.16	5.07	4.95	16.16	16.50
112	51.64	51.77	4.30	4.34	21.26	21.31
113	57.33	57.28	5.93	5.66	23.97	23.58
114	47.33	46.07	4.50	4.68	17.38	16.96
115	55.09	55.03	5.47	5.31	19.33	19.25
116	49.11	48.19	5.06	5.20	16.38	16.06
117	54.29	54.02	4.76	5.01	19.87	19.89

C. Pharmacological examples

Example C.1

Angiogenesis inhibitory activity was measured *in vitro* using the rat aortic ring model of angiogenesis as described by Nicosia, R.F. and Ottinetti in "Laboratory Investigation", vol. 63, p. 115, 1990. The ability of compounds to inhibit microvessel formation was compared to vehicle-treated control rings. Quantitation (microvessel area) following eight days in culture was performed using an image analysis system, consisting of a light microscope, a CCD camera and an automated, custom-designed

image analysis program as described by Nissanov, J., Tuman, R.W., Gruver, L.M., and Fortunato, J.M. in "Laboratory Investigation", vol 73 (#5), p. 734, 1995. Compounds were tested at several concentrations for determination of inhibitory potency (IC_{50}'s). Several compounds, as listed in table C.1, have an IC_{50} value lower than 100 nM.

Table C.1 :

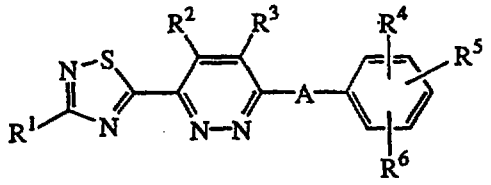
Co. No.	IC_{50}
1	$17.1x10^{-08}$
3	$4.57x10^{-08}$
4	$2.12x10^{-08}$
5	$1.64x10^{-08}$
6	$4.28x10^{-10}$
7	$4.54x10^{-08}$
8	$8.53x10^{-09}$
9	$1.79x10^{-08}$
10	$1.56x10^{-08}$
11	$9.08x10^{-08}$
14	$3.12x10^{-08}$
15	$1.34x10^{-09}$
16	$1.58x10^{-08}$
17	$1.28x10^{-08}$
20	$8.15x10^{-09}$
21	$4.84x10^{-08}$
22	$7.26x10^{-08}$
24	$1.33x10^{-09}$
25	$4.04x10^{-08}$
26	$3.97x10^{-09}$
27	$6.22x10^{-10}$
28	$1.76x10^{-09}$
29	$2.48x10^{-08}$
30	$6.31x10^{-09}$
35	$2.94x10^{-08}$
36	$5.30x10^{-09}$

Co. No.	IC_{50}
37	$1.32x10^{-09}$
38	$3.72x10^{-08}$
39	$1.71x10^{-08}$
40	$1.15x10^{-08}$
41	$2.56x10^{-09}$
42	$4.22x10^{-08}$
43	$2.78x10^{-09}$
44	$1.52x10^{-08}$
45	$2.00x10^{-09}$
46	$1.46x10^{-09}$
47	$1.25x10^{-08}$
48	$1.85x10^{-09}$
49	$3.12x10^{-10}$
50	$8.30x10^{-10}$
51	$9.38x10^{-09}$
52	$5.56x10^{-09}$
53	$7.33x10^{-09}$
54	$1.37x10^{-08}$
55	$3.62x10^{-09}$
56	$8.07x10^{-08}$
57	$5.11x10^{-08}$
61	$3.51x10^{-08}$
62	$5.53x10^{-09}$
63	$9.20x10^{-09}$
67	$3.24x10^{-08}$
70	$1.22x10^{-08}$

Co. No.	IC_{50}
71	$<1.00x10^{-10}$
72	$3.88x10^{-10}$
73	$2.86x10^{-09}$
74	$1.00x10^{-09}$
76	$1.15x10^{-09}$
77	$5.81x10^{-09}$
78	$2.80x10^{-10}$
82	$6.71x10^{-08}$
84	$1.74x10^{-08}$
86	$6.90x10^{-09}$
89	2.06x10-09
94	$4.71x10^{-09}$
95	$7.03x10^{-10}$
96	$5.08x10^{-10}$
97	$1.60x10^{-09}$
98	$3.07x10^{-09}$
100	$7.01x10^{-09}$
102	$2.08x10^{-09}$
103	$8.04x10^{-09}$
104	$2.03x10^{-08}$
105	$1.49x10^{-09}$
108	$3.79x10^{-08}$
110	$6.98x10^{-09}$
111	$1.87x10^{-09}$
112	$1.33x10^{-08}$

Claims

1. A compound of formula (I),



(I),

the *N*-oxide forms, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof, wherein

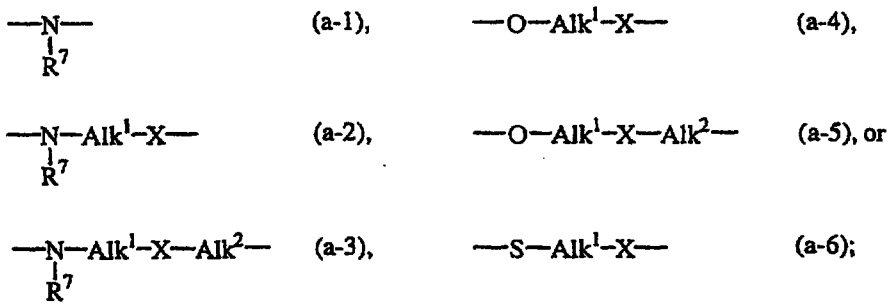
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, amino, mono- or di(C_{1-6}alkyl)amino, Ar^1, Ar^1-NH-, C_{3-6}cycloalkyl, hydroxymethyl or benzyloxymethyl;

R^2 and R^3 are hydrogen, or taken together may form a bivalent radical of formula -CH=CH-CH=CH-;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, nitro, amino, cyano, azido, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylthio, C_{1-6}alkyloxycarbonyl or Het^1;

or when R^4 and R^5 are adjacent to each other they may be taken together to form a radical of formula -CH=CH-CH=CH-;

A is a bivalent radical of formula



(a-1), (a-2), (a-3), (a-4), (a-5), or (a-6);

wherein X is a direct bond, -O-, -S-, C=O, -NR^8- or Het^2;

R^7 is hydrogen, C_{1-6}alkyl or Ar^2methyl;

R^8 is hydrogen, C_{1-6}alkyl or Ar^2methyl;

Alk^1 is C_{1-6}alkanediyl;

Alk^2 is C_{1-4}alkanediyl;

Ar^1 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;



Ar^2 is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trihalomethyl, amino or nitro;

Het^1 is a monocyclic heterocycle selected from oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl or oxazolinyl; and each monocyclic heterocycle may optionally be substituted on a carbon atom with C_{1-4}alkyl; and

Het^2 is tetrahydrofuran; a tetrahydrofuran substituted with C_{1-6}alkyl; a dioxane; a dioxane substituted with C_{1-6}alkyl; a dioxolane; or a dioxolane substituted with C_{1-6}alkyl.

2. A compound according to claim 1 wherein R^1 is hydrogen, C_{1-6}alkyl or di(C_{1-6}alkyl)amino; R^2 and R^3 are hydrogen; R^4, R^5 and R^6 are each independently selected from hydrogen, halo, C_{1-4}alkyl, C_{1-4}alkyloxy, trifluoromethyl, nitro, C_{1-6}alkyloxycarbonyl or Het^1; and the bivalent radical A is (a-2), (a-3), (a-4) or (a-6).

3. A compound according to claim 1 wherein the bivalent radical A is (a-2), (a-4), or (a-6) wherein Alk^1 is C_{2-4}alkanediyl.

4. A compound according to claim 3 wherein Alk^1 is butanediyl.

5. A compound according to claim 1 wherein the compound is 6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenoxy]butyl-3-pyridazinamine,
N-methyl-6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenoxy]-butyl]-3-pyridazinamine, or
6-(3-methyl-1,2,4-thiadiazol-5-yl)-*N*-[4-[3-(trifluoromethyl)phenylthio]butyl-3-pyridazinamine; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.

6. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

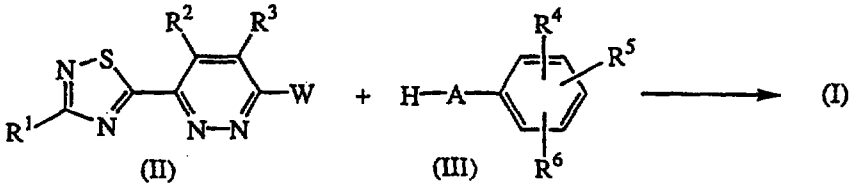
7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.

8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

9. Use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of angiogenesis dependent disorders.

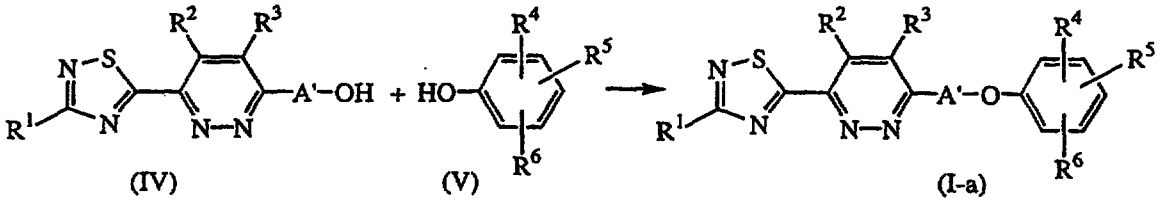
10. A process of preparing a compound as claimed in claim 1, wherein

a) an intermediate of formula (II) is reacted with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base;



(II) (III) (I)

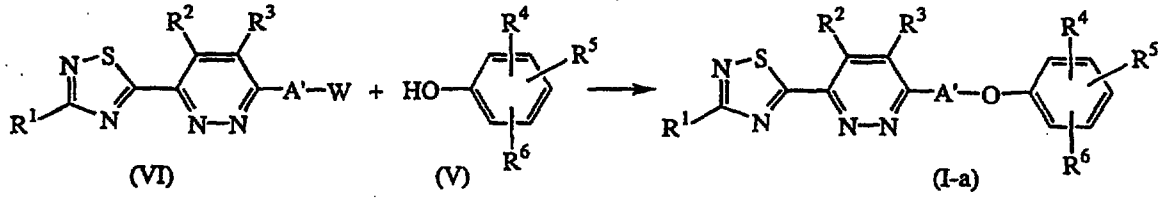
b) an intermediate of formula (IV), wherein the bivalent radical A' is a radical of formula (a-2), (a-4) or (a-6) wherein X is a direct bond, can be condensed with a phenol of formula (V) in a reaction-inert solvent and in the presence of DIAD, thereby yielding compounds of formula (I-a);



(IV) (V) (I-a)

wherein in the above reaction schemes the radicals R^1, R^2, R^3, R^4, R^5, R^6 and A are as defined in claim 1, and W is an appropriate leaving group;

c) an intermediate of formula (VI) is reacted with an intermediate of formula (V) in a reaction-inert solvent and, optionally in the presence of a suitable base;



(VI) (V) (I-a)

d) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted

into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

* C L M S *