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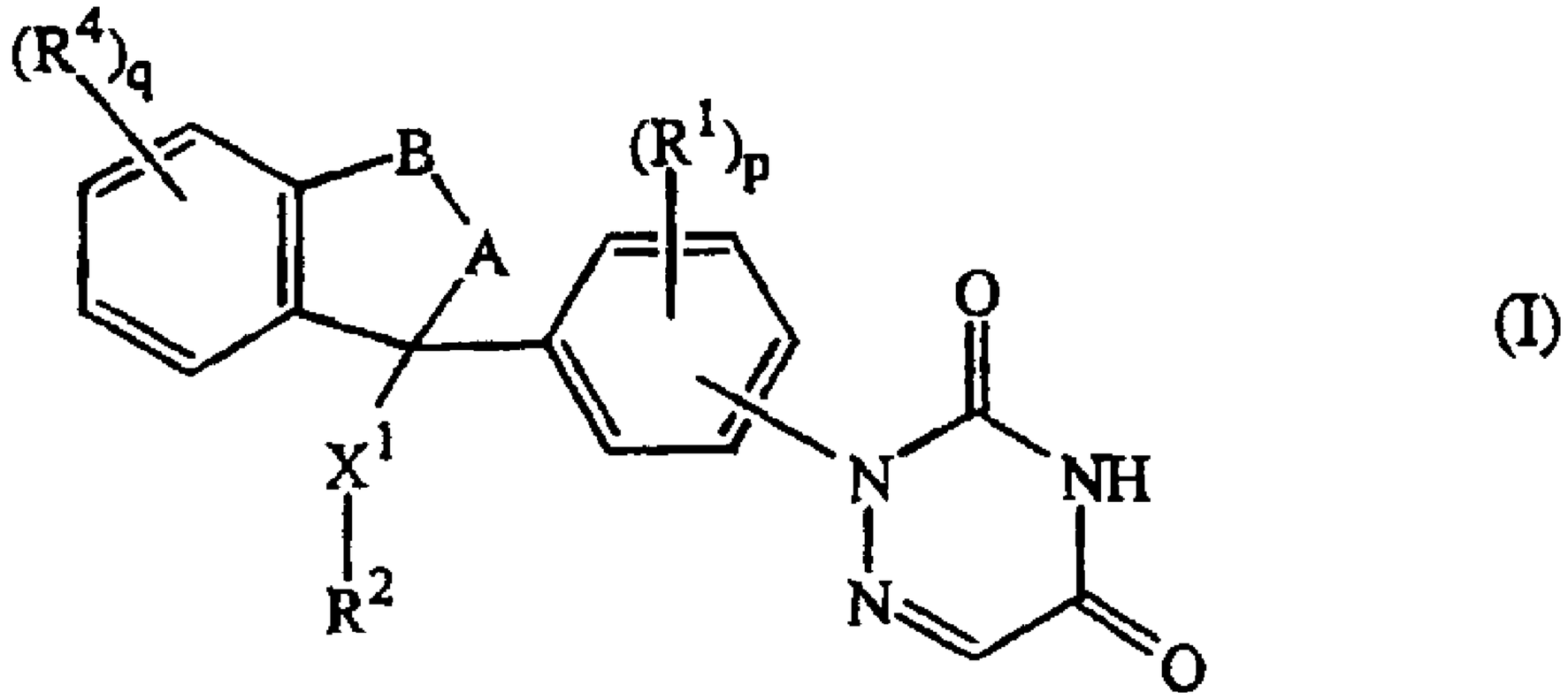

(I)

(57) Abrégé/Abstract:
The present invention is concerned with the compounds of formula (I) the N-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein p is 0 to 3; q is 0 to 4; -A-B- represents $-(CH_2)_r-$, $-(CH_2)_t-O-$, $-(CH_2)_t-S(=O)_u-$ or $-(CH_2)_t-NR^3-$; r is 2 to 4; t is 1 to 3; u is 0 to 2; X^1 is O, S, NR^3 or a direct bond; R^1 and R^4 are C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or substituted C_{1-4}alkyl; R^2 is aryl, Het^1, C_{3-7}cycloalkyl, cyano, optionally substituted C_{1-6}alkyl, $-C(=Q)-X^2-R^{15}$; R^3 is hydrogen or C_{1-4} alkyl; R^{15} is hydrogen, optionally substituted C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl; where X^2 is a direct bond, R^{15} may also be halo or Het^1; where X^2 is NR^5, R^{15} may also be hydroxy; where X^2 is C(=O)-NH-NH or NH-NH-C(=O), R^{15} may be replaced by R^{11}; Q is O, S or NR^3; X^2 is O, S, NR^5, C(=O)-NH-NH, NH-NH-C(=O) or a direct bond; R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl; R^6 is a sulfonyl or sulfinyl derivative; R^7 and R^8 are independently hydrogen, optionally substituted C_{1-4}alkyl, aryl, a carbonyl containing moiety, C_{3-7}cycloalkyl, $-Y-C_{1-4}$alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6; R^{11} is hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy, formyl, tri- haloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, $C(=O)NR^7R^8$, C_{1-4}alkanediyl-C(=O)-O-R^{14}, - C(=O)-O-R^{14}, $-Y-C_{1-4}$ alkanediyl-C(=O)-O-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3, Het^4 and $C(=O)Het^3$; aryl is optionally substituted phenyl; Het^1, Het^2, Het^3 and Het^4 are optionally substituted heterocycles; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

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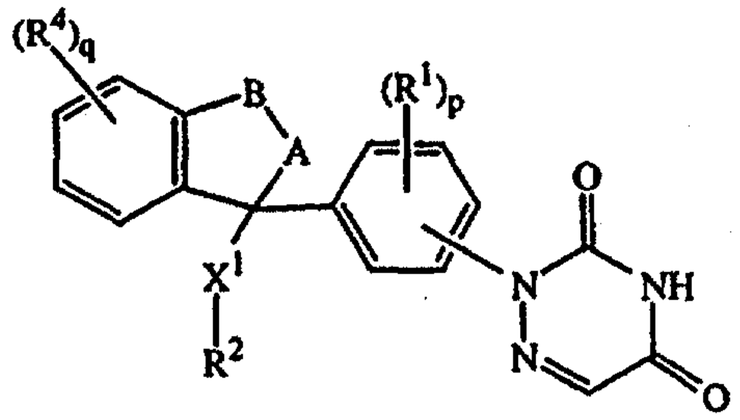
(54) Title: IL–5 INHIBITING 6–AZAURACIL DERIVATIVES

(57) Abstract

The present invention is concerned with the compounds of formula (I) the *N*–oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein p is 0 to 3; q is 0 to 4; –A–B– represents $–(CH_2)_r–$, $–(CH_2)_t–O–$, $–(CH_2)_t–S(=O)_u–$ or $–(CH_2)_t–NR^3–$; r is 2 to 4; t is 1 to 3; u is 0 to 2; X^1 is O, S, NR^3 or a direct bond; R^1 and R^4 are C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or substituted C_{1-4}alkyl; R^2 is aryl, Het^1, C_{3-7}cycloalkyl, cyano, optionally substituted C_{1-6}alkyl, $–C(=Q)–X^2–R^{15}$; R^3 is hydrogen or C_{1-4}alkyl; R^{15} is hydrogen, optionally substituted C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl; where X^2 is a direct bond, R^{15} may also be halo or Het^1; where X^2 is NR^5, R^{15} may also be hydroxy; where X^2 is C(=O)–NH–NH or NH–NH–C(=O), R^{15} may be replaced by R^{11}; Q is O, S or NR^3; X^2 is O, S, NR^5, C(=O)–NH–NH, NH–NH–C(=O) or a direct bond; R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl; R^6 is a sulfonyl or sulfinyl derivative; R^7 and R^8 are independently hydrogen, optionally substituted C_{1-4}alkyl, aryl, a carbonyl containing moiety, C_{3-7}cycloalkyl, $–Y–C_{1-4}$alkanediyl–C(=O)–O–R^{14}, Het^3 and R^6; R^{11} is hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, $C(=O)NR^7R^8$, C_{1-4}alkanediyl–C(=O)–O–R^{14}, $–C(=O)–O–R^{14}$, $–Y–C_{1-4}$alkanediyl–C(=O)–O–R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide–2–yl, Het^3, Het^4 and $C(=O)Het^3$; aryl is optionally substituted phenyl; Het^1, Het^2, Het^3 and Het^4 are optionally substituted heterocycles; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.



(I)

IL-5 INHIBITING 6-AZAURACIL DERIVATIVES

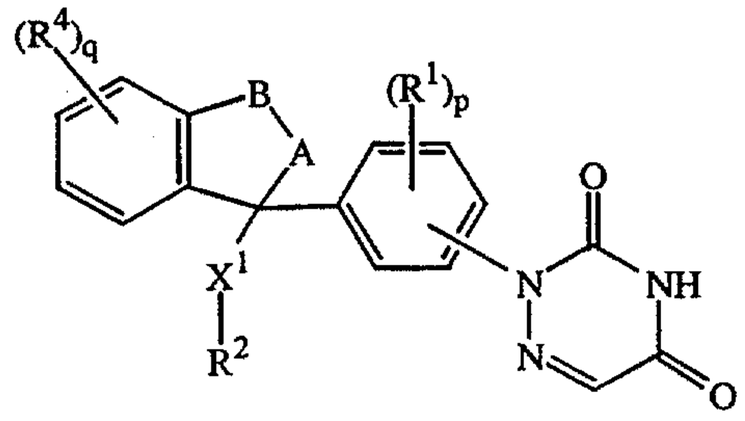
The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse reactions.

US 4,631,278 discloses α-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2*H*,4*H*)-diones, all having anti-protozoal activity, in particular, anti-coccidial activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. Unexpectedly, the 6-azauracil derivatives of the present invention prove to be potent inhibitors of the production of IL-5.

The present invention is concerned with the compounds of formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

p represents an integer being 0, 1, 2 or 3;

q represents an integer being 0, 1, 2, 3 or 4;

-A-B- represents $-(CH_2)_r-$, $-(CH_2)_t-O-$, $-(CH_2)_t-S(=O)_u-$ or $-(CH_2)_t-NR^3-$;

r represents 2, 3 or 4;

each t independently represents 1, 2 or 3;

u represents 0, 1 or 2;

X^1 represents O, S, NR^3 or a direct bond;

each R^1 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^4 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

R^2 represents aryl, Het^1, C_{3-7}cycloalkyl, cyano, C_{1-6}alkyl, $-C(=Q)-X^2-R^{15}$ or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy, Het^1thio and $-C(=Q)-X^2-R^{15}$;

each R^3 independently represents hydrogen or C_{1-4}alkyl;

each R^{15} independently represents hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl or C_{1-6}alkyl substituted with aryl, halo, hydroxy or Het^1;

where X^2 is a direct bond, R^{15} may also be halo or Het^1;

where X^2 is NR^5, R^{15} may also be hydroxy;

where X^2 is C(=O)-NH-NH or NH-NH-C(=O), R^{15} may be replaced by R^{11};

each Q independently represents O, S or NR^3;

each X^2 independently represents O, S, NR^5, C(=O)-NH-NH, NH-NH-C(=O) or a direct bond;

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di-(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkyl-sulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, amino-piperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, aminocarbonyl, arylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkyl-

carbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

each Y independently represents O, S, NR^3, or $S(O)_2$;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)NR^7R^8, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3, Het^4 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14} and R^6;

each R^{14} independently represents hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene, mono-or di(C_{1-4}alkyl)aminocarbonylmethylene, mono-or di(C_{3-7}cycloalkyl)aminocarbonylmethylene, azetidin-1-ylcarbonylmethylene, pyrrolidin-1-ylcarbonylmethylene, piperidin-1-ylcarbonylmethylene or homopiperidin-1-ylcarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, C(=O)NR^9R^{10}, C(=O)-O-R^{14}, R^6, -O-R^6, phenyl, Het^3, C(=O)Het^3 and C_{1-4}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl,

thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, $C(=O)$-O-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, $C(=O)$-O-R^{14}, -Y-C_{1-4}alkanediyl-$C(=O)$-O-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro,

bromo and iodo; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; 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, 2,2-dimethylethyl and the like; C_{1-6}alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; polyhaloC_{1-4}alkyl is defined as polyhalosubstituted C_{1-4}alkyl, in particular C_{1-4}alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC_{1-6}alkyl is defined as polyhalosubstituted C_{1-6}alkyl. The term C_{1-4}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{2-6}alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.

Het^1, Het^2, Het^3 and Het^4 are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het^1, Het^2, Het^3 and Het^4, for instance, pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

The heterocycles represented by Het^1, Het^2, Het^3 and Het^4 may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The pharmaceutically acceptable 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 latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-

acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and 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 *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het^1, Het^2 and Het^3 may be *N*-oxidized.

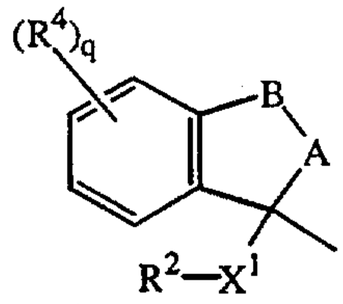
Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds

of formula (I) are obviously intended to be embraced within the scope of this invention.

The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

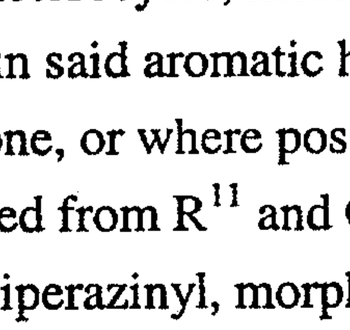
Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the  substituent; preferably in the para position.

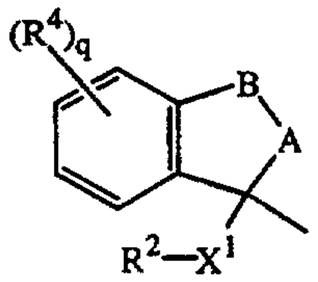
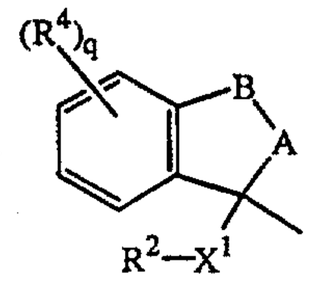
Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- q is 0 or 1;
- -A-B- is $-(CH_2)_r-$ or $-(CH_2)_t-O-$;
- X^1 is S, NR^3 or a direct bond; more in particular a direct bond;
- each R^1 independently is halo, polyhaloC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy or aryl, preferably, chloro or methyloxy, more preferably chloro;
- R^2 is Het^1, cyano, $-C(=Q)-X^2-R^{15}$ or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, $-C(=Q)-X^2-R^{15}$, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1oxy and Het^1thio; more in particular Het^1, cyano, $-C(=Q)-X^2-R^{15}$ or C_{1-6}alkyl substituted with Het^1;
- R^4 is hydrogen or halo;
- R^{15} is hydrogen or C_{1-6}alkyl, and when X^2 is a direct bond, R^{15} may also be halo, and when X^2 is C(=O)-NH-NH, R^{15} may also be phenyl;
- R^6 is C_{1-6}alkylsulfonyl or aminosulfonyl;
- R^7 and R^8 are each independently hydrogen, C_{1-4}alkyl, Het^3 or R^6;
- R^9 and R^{10} are each independently hydrogen, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, Het^3carbonyl, Het^3 or R^6;

- R^{11} is cyano, nitro, halo, C_{1-4}alkyloxy, formyl, NR^7R^8, $C(=O)NR^7R^8$, $-C(=O)-O-R^{14}$, aryl, arylcarbonyl, Het^3, Het^4 and $C(=O)Het^3$, more in particular aryl, $-C(=O)-O-R^{14}$,
- R^{14} is hydrogen or C_{1-4}alkyl;
- aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, $C(=O)-O-R^{14}$, $-O-R^6$, phenyl, $C(=O)Het^3$ and C_{1-4}alkyl substituted with hydroxy, C_{1-4}alkyloxy, $C(=O)-O-R^{14}$, Het^3 or NR^9R^{10}, more in particular phenyl optionally substituted with halo or C_{1-4}alkyl;
- Het^1 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with Het^2 or R^{11}; preferably Het^1 is oxadiazolyl or thiazolyl each independently and optionally substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with R^{11};
- Het^2 is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl;
- Het^3 is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkylcarbonyl, piperidinyl and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy and phenyl;
- Het^4 is thienyl.

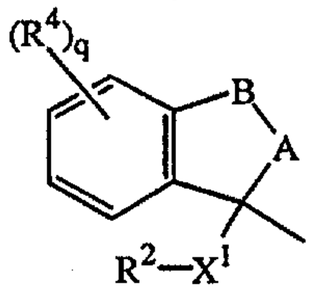
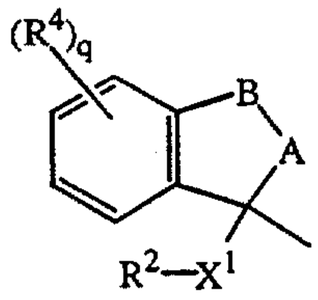
Special compounds are those compounds of formula (I) wherein p is 1 or 2 and each R^1 is chloro; more preferably p is 2 and the two chloro substituents are in the ortho positions relative to the 

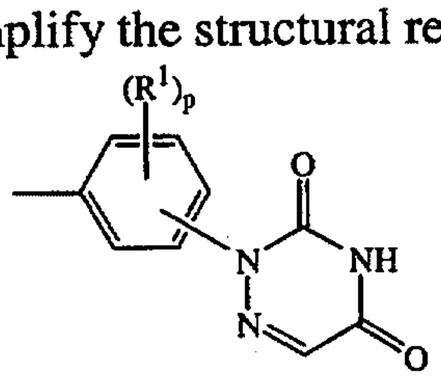
substituent.

Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the  substituent, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the  substituent.

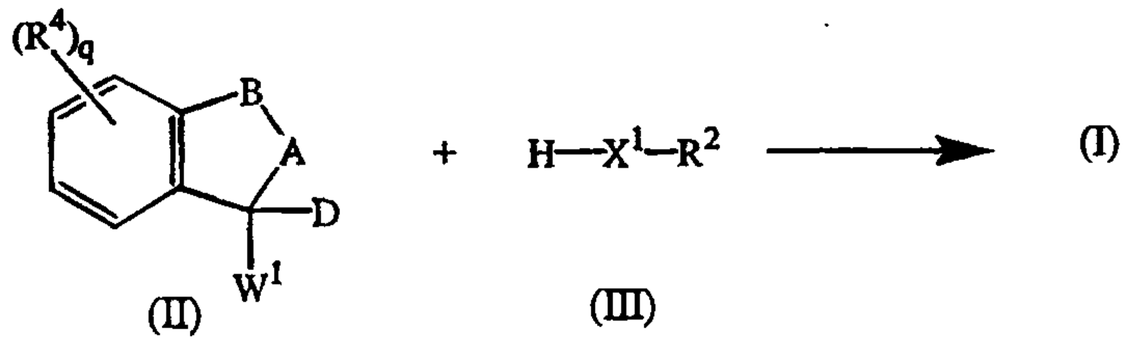
Other particular compounds are those compounds of formula (I) wherein X^1 is a direct bond and R^2 is cyano or a monocyclic heterocycle selected from thiazolyl and oxadiazolyl, wherein said monocyclic heterocycles each independently may optionally be substituted with one or two substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with R^{11}.

Other preferred compounds are those compounds of formula (I) wherein -A-B- is $(CH_2)_2$.

More preferred compounds are those compounds of formula (I) wherein $-X^1-R^2$ is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the  substituent, and p is 2 whereby both R^1 substituents are chloro positioned ortho relative to the  substituent.

In order to simplify the structural representation of the compounds of formula (I),  will hereinafter be represented by the symbol D.

Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) wherein W^1 is a suitable leaving group such as, for example, a halogen atom, with an appropriate reagent of formula (III).



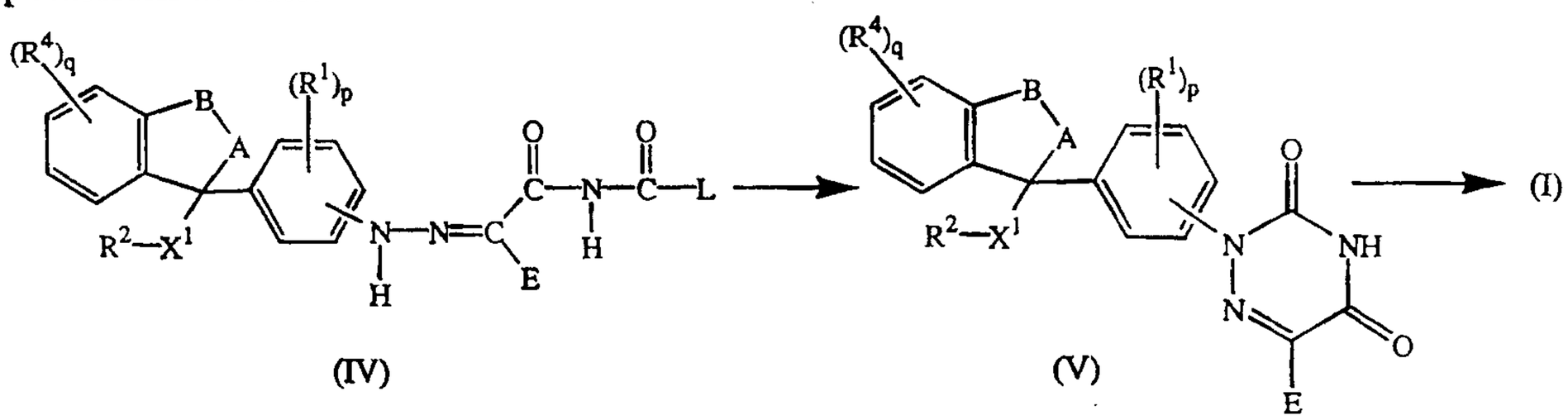
(II) (III) (I)

Said reaction may be performed in a reaction-inert solvent such as, for example, acetonitrile, *N*,*N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no additional reaction-inert solvent is required. The reaction is optionally carried out in the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium bicarbonate, sodiumethanolate and the like. Convenient reaction temperatures range between -70°C and reflux temperature.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

Some of the compounds and intermediates of the present invention can be prepared according to or analogous to the procedures described in EP-A-0,170,316, EP-A-0,232,932 and EP-A-1,000,040.

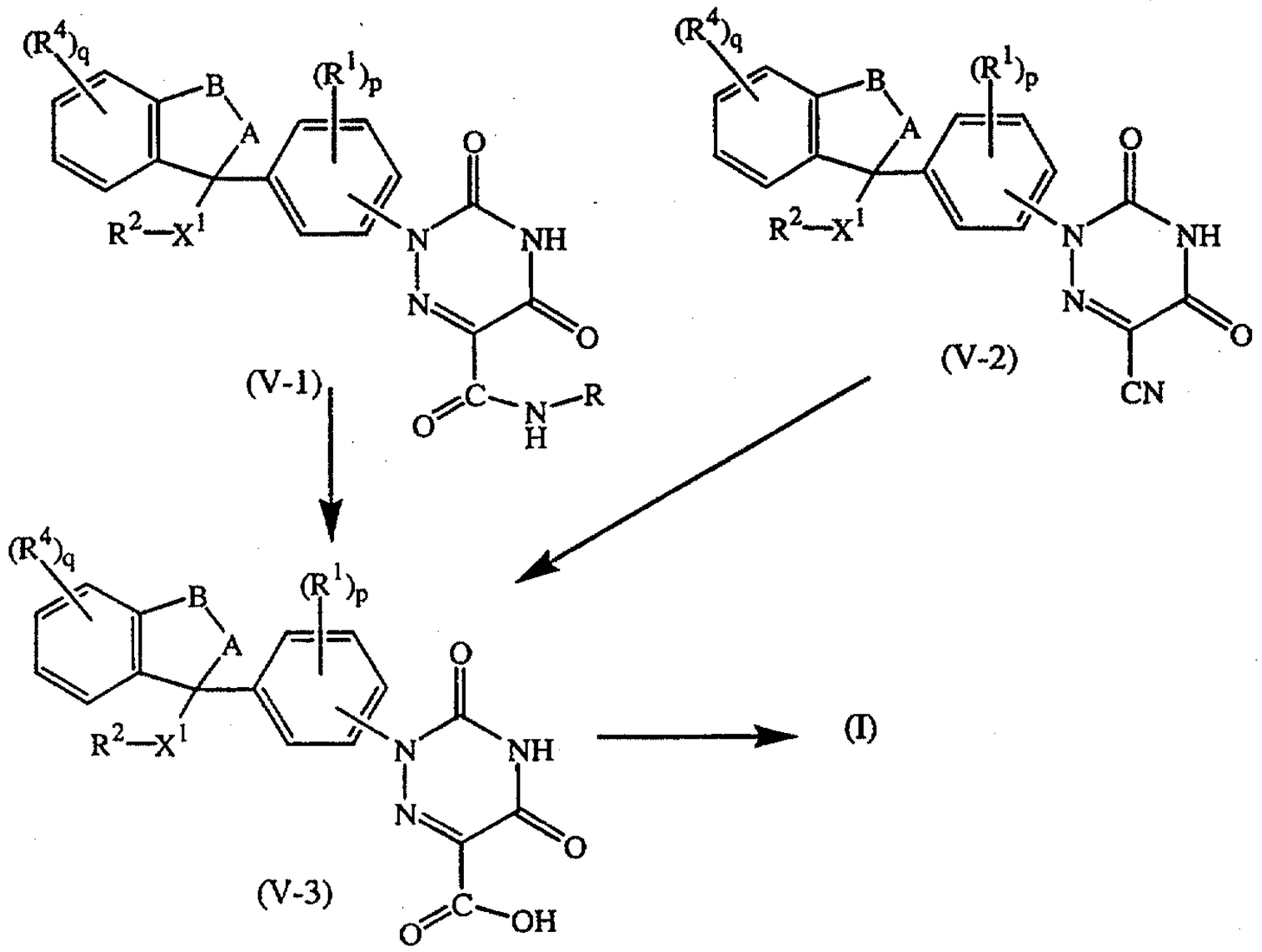
For instance, compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6}alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C_{1-6}alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V). The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.



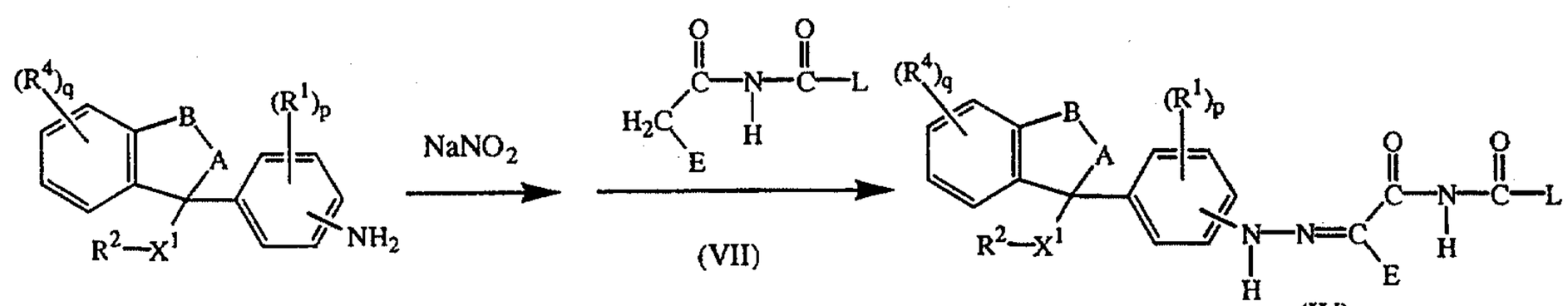
(IV) (V) (I)

Depending on its nature, E can be eliminated using various art-known elimination procedures. For example when E is an amide or a cyano moiety, it can be hydrolized to

a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated temperatures ranging up to reflux temperature.



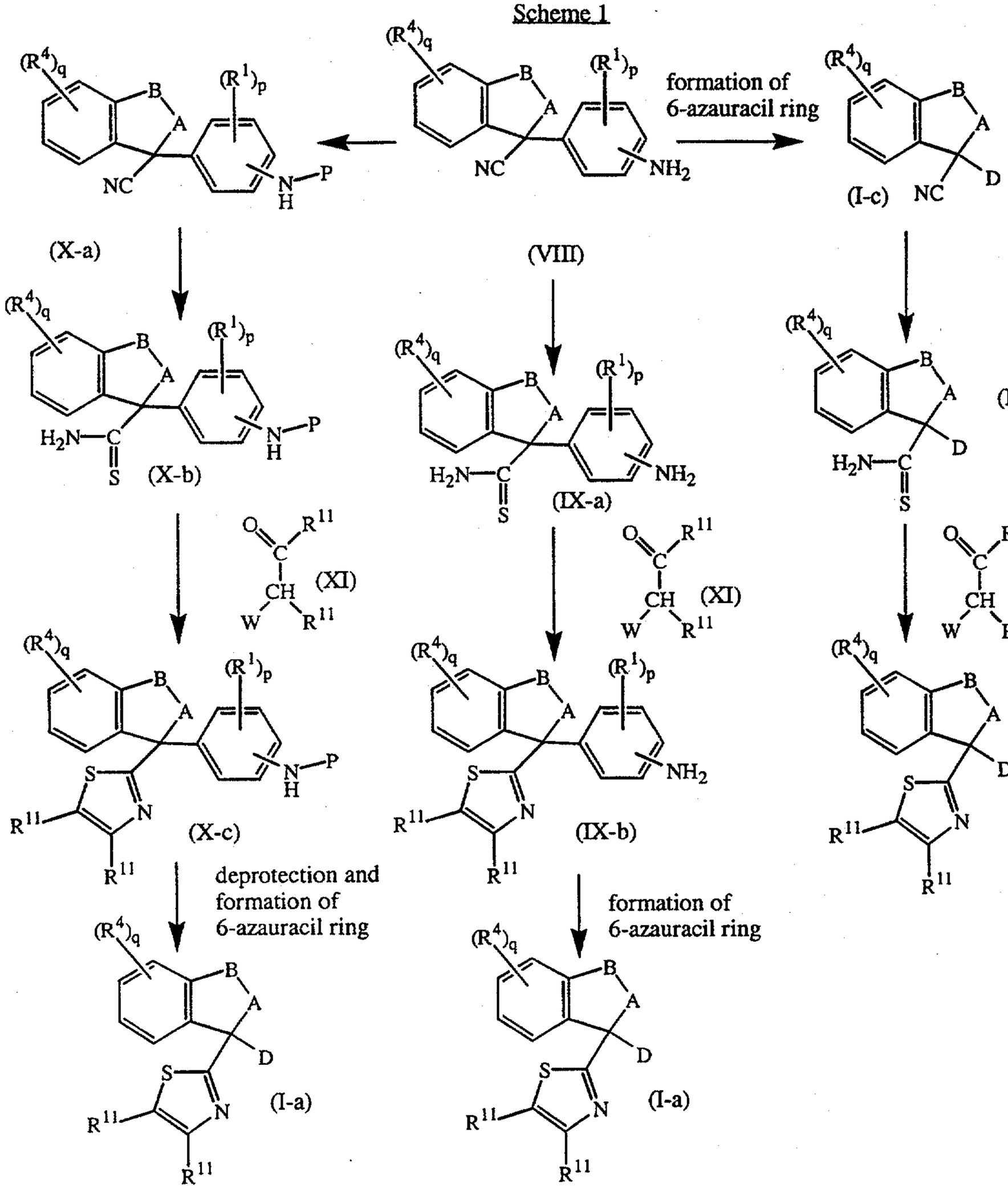
A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrite or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.



An interesting subgroup comprises those compounds of formula (I) wherein $-X^1-R^2$ is an optionally substituted 2-thiazolyl moiety, said compounds being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 depicts three possible ways to prepare compounds of formula (I-a).

Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XI) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

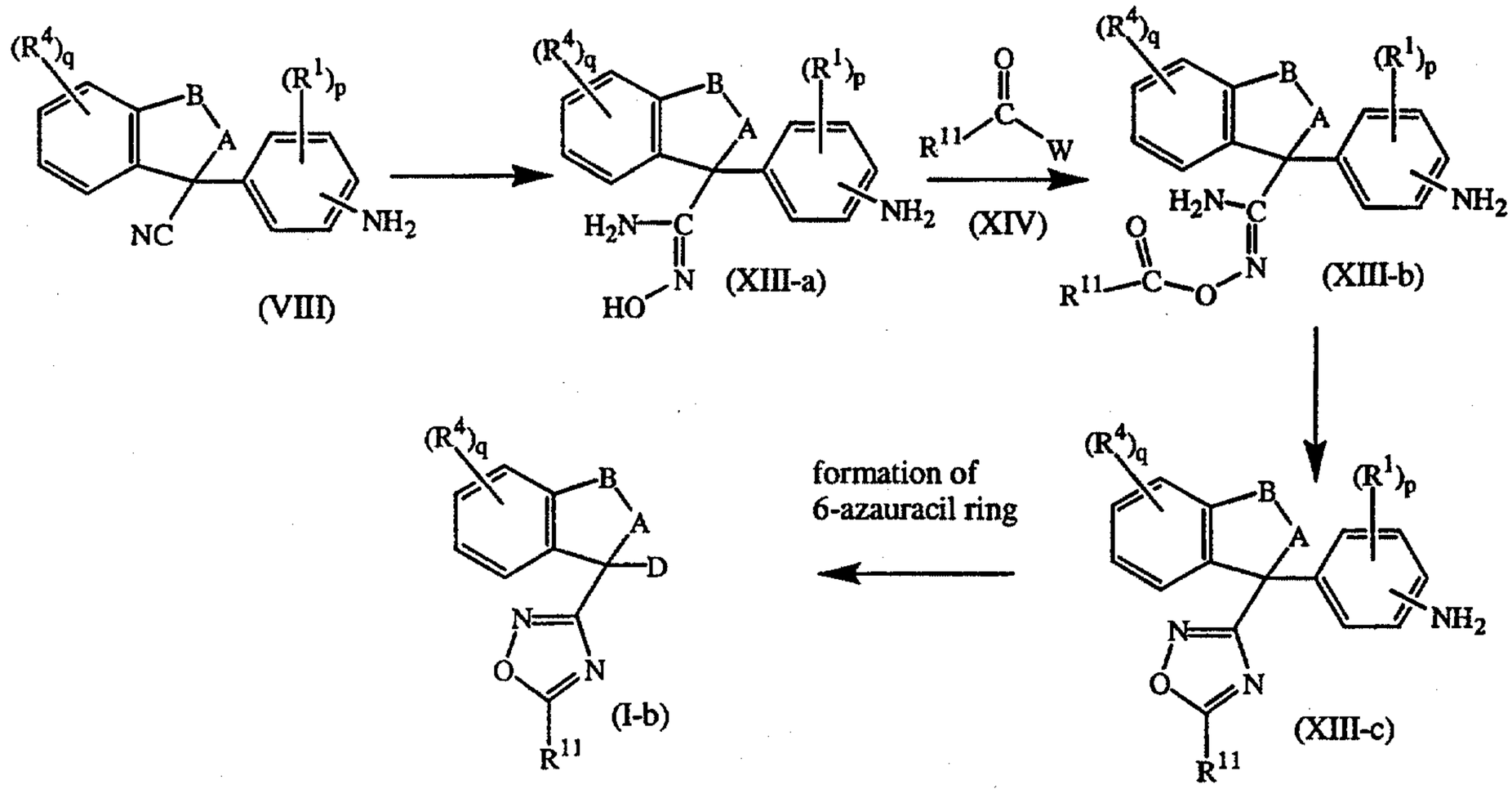
A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VIII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed compound of formula (I) wherein $-X^1-R^2$ is cyano, said compounds being represented by formula (I-c), with H_2S and further reacting the compound of formula (I) wherein $-X^1-R^2$ is a thioamide, said compounds being represented by formula (I-d), with an intermediate of formula (XI) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X^1-R^2$ is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b) can be prepared by reacting an intermediate of formula (VIII) as depicted in scheme 2.

Scheme 2

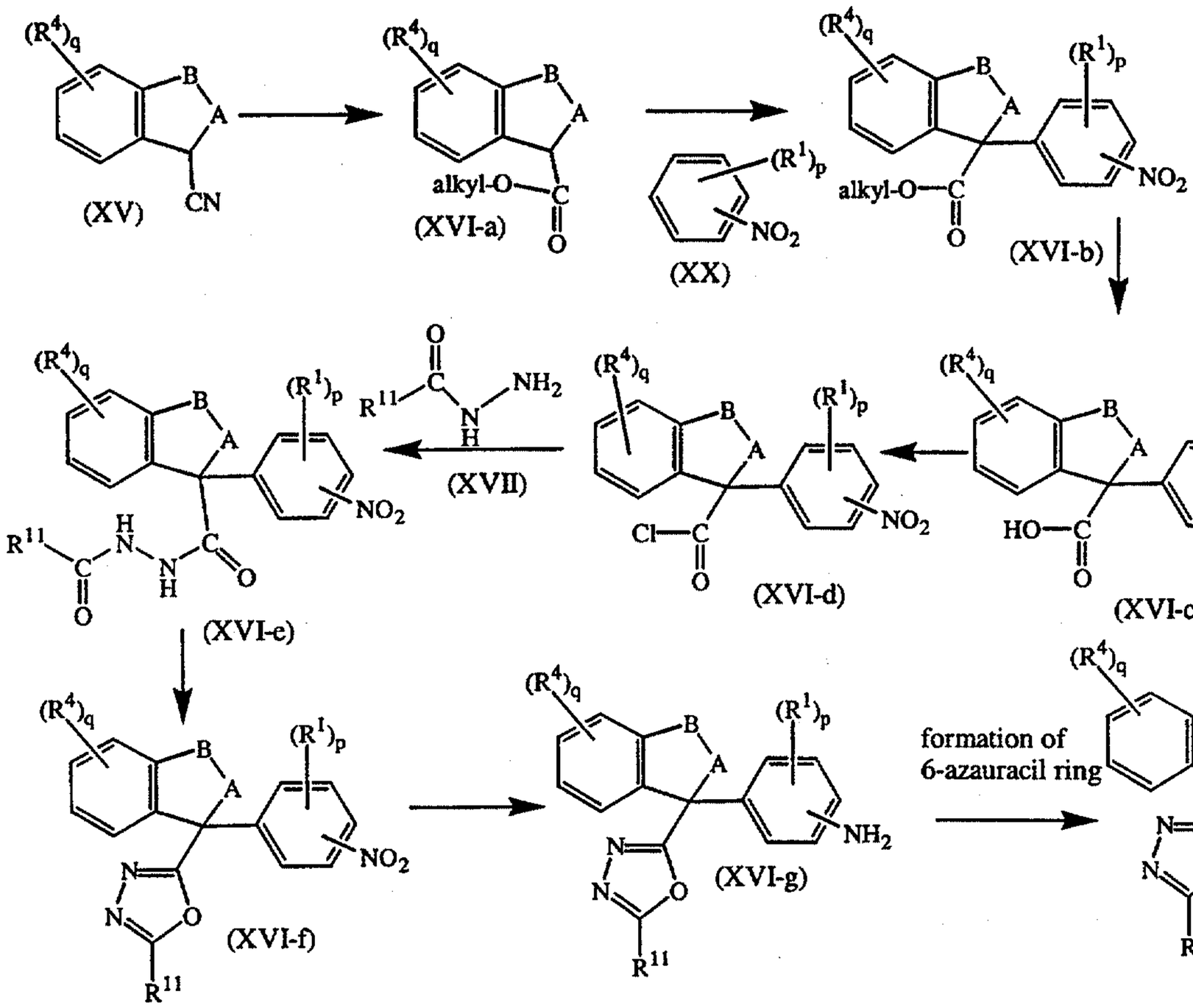


In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example, sodium methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N*,*N*-(1-methyl-ethyl)ethaneamine. The resulting intermediate of formula (XIII-b) is then cyclized to a 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

Still another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X^1-R^2$ is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

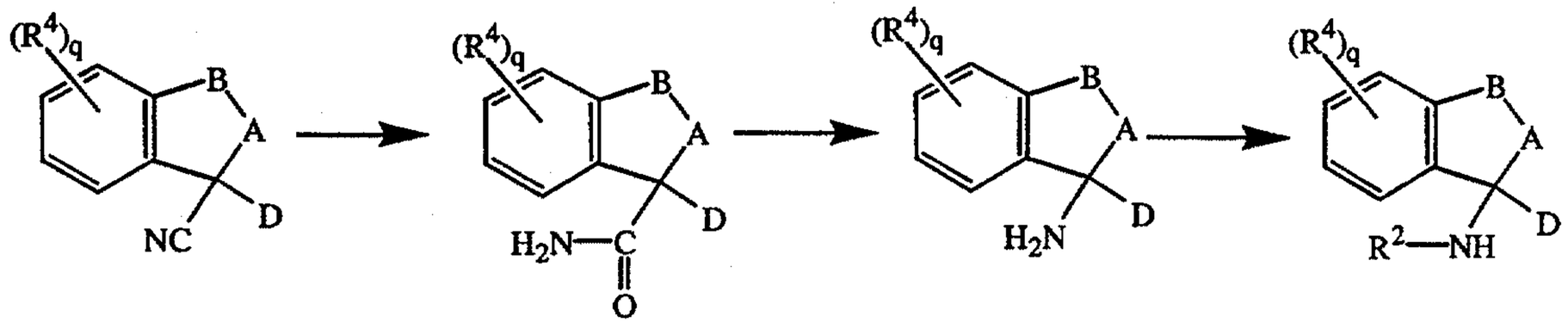
Scheme 3



The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid ester moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and an alcoholic solvent such as, for example, methanol and ethanol. The carboxylic acid ester derivative of formula (XVI-a) may further be reacted with an intermediate of formula (XX) in a reaction-inert solvent such as, for example, N,N-dimethylformamide, and in the presence of a base such as, for example, sodium hydride, thus obtaining an intermediate of formula (XVI-b) of which the ester may be converted into its corresponding carboxylic acid of formula (XVI-c). Said intermediate of formula (XVI-c) may be reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-d). Subsequently, the acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example *N*,*N*-(1-methylethyl)ethaneamine. The thus formed intermediate of formula (XVI-e) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-f) in the presence of phosphoryl chloride.As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-g) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X^1-R^2$ is $-NH-R^2$, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

Scheme 4

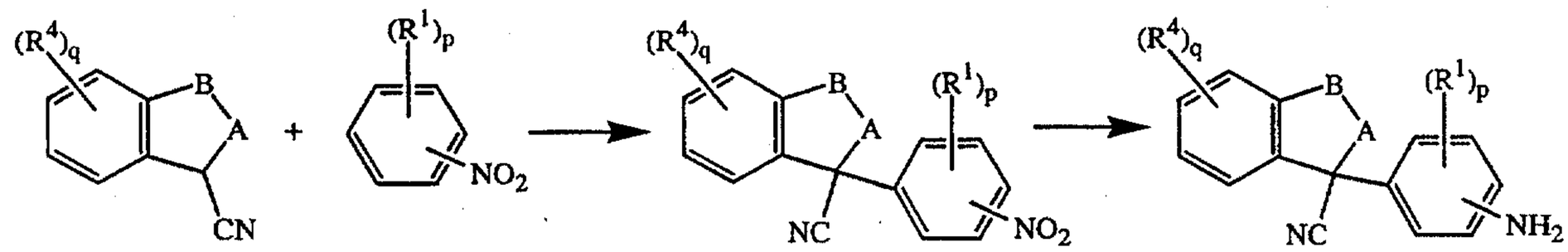


(XI-a) (XVIII-a) (XVIII-b) (I-c-1)

In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolized to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5



(XIX) (XX) (XV-a) (VIII)

An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, *N*,*N*-dimethylformamide, in the presence of a base such as, for example sodium hydride, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may be reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel.

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter.

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 3-phenyl-2-(phenylsulfonyl)oxaziridine or 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, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t-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.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically

isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angiitis, eosinophilic fasciitis, eosinophilic pneumonia, PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, *91*, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, Il-3, IL-4, IL-6, IL-10, γ-interferon (IFN-γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood of which the test results for IL-5 are presented in the experimental part hereinafter. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia

in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are orally active compounds.

In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dertmatitis, allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which 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 systemic administration such as oral, percutaneous, or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. 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 wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on 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 or as an ointment. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gellies, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. Application of said compositions may be by aerosol, e.g. with a propellent such as nitrogen, carbon dioxide, a freon, or without a propellent such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

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.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclo-dextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical

compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxy-C_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S.value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C-atom or tritium atom.

One particular group consists of those compounds of formula (I) containing a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I, ^{123}I, ^{125}I, ^{131}I; radioactive bromides, e.g. ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and radioactive fluorides, e.g. ^{18}F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.
The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.
When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

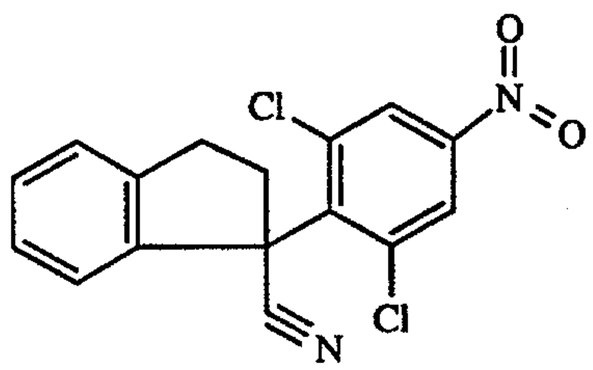
In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active

ingredient on a regimen of between two or four intakes per day.

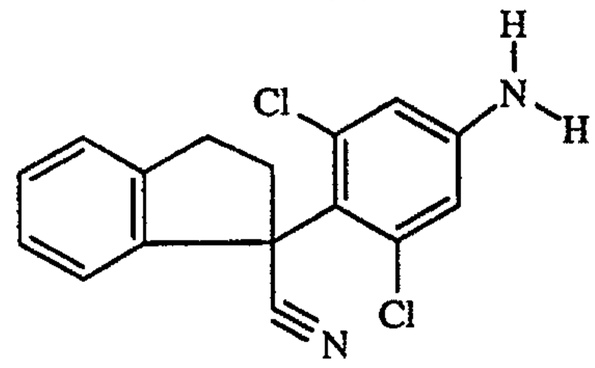
Experimental part

A. Preparation of the intermediate compounds

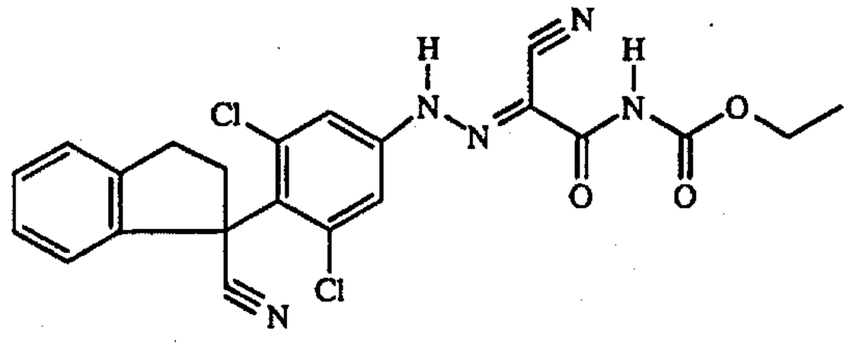
Example A1

a) Preparation of  intermediate (1)

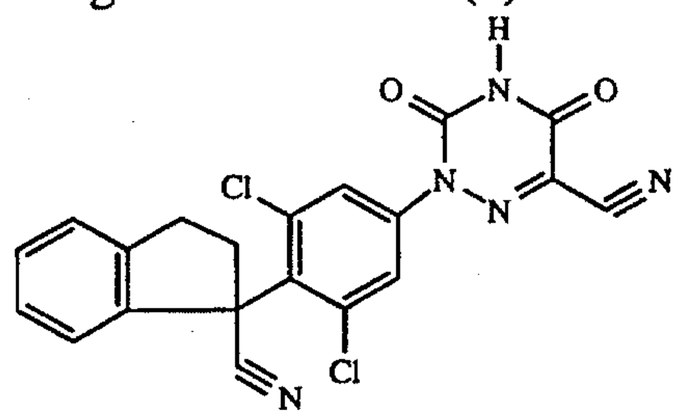
NaH (80% in oil; 0.0953 mol) was added portionwise at 0°C under N_2 flow to a solution of 2,3-dihydro-1*H*-Indene-1-carbonitrile (0.0733 mol) in *N*,*N*-dimethyl-formamide (100ml). The mixture was stirred for 30 minutes. A solution of 1,2,3-trichloro-5-nitrobenzene (0.11 mol) in *N*,*N*-dimethylformamide (50ml) was added dropwise while the temperature was kept below 5°C. The mixture was stirred at 0°C for 30 minutes. H_2O was added. The mixture was acidified with HCl 3N. The reaction was carried out again using the same quantities. Both mixtures were combined and ethyl acetate was added. The precipitate was filtered off, washed with ethylacetate and dried, to give residue 1 (2.1g). The filtrate was decanted. The organic layer was dried, filtered and the solvent was evaporated. The residue was taken up in diisopropyl ether. The precipitate was filtered off and dried, to give residue 2 (7.6g). The filtrate was evaporated. The residue (60g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 50/50). The pure fractions were collected and the solvent was evaporated, to give residue 3 (11.3g). Residue 1, 2 and 3 were combined, yielding 21g (44%) of intermediate (1).

b) Preparation of  intermediate (2)

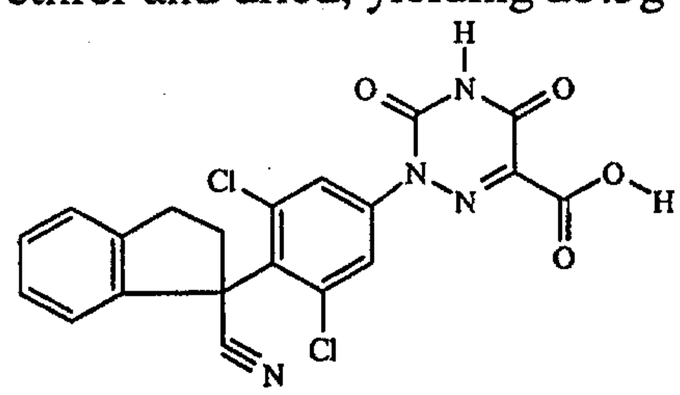
A mixture of intermediate (1) (0.063 mol) and $TiCl_3$ (15% in H_2O; 0.408 mol) in tetrahydrofuran (200ml) was stirred at room temperature overnight. H_2O was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layer was washed with K_2CO_3 10%, dried, filtered and the solvent was evaporated, yielding 18g (94%) of intermediate (2).

c) Preparation of  intermediate (3)

A mixture of $NaNO_2$ (0.059 mol) in H_2O (70ml) was added dropwise at 5°C to a solution of intermediate (2) (0.0593 mol) in acetic acid (130ml) and concentrated HCl (25ml). The mixture was stirred at 5°C for 30 min and then added dropwise at 5°C to a mixture of (cyanoacetyl)-carbamic acid ethyl ester (0.082 mol) and sodium acetate (180g) in H_2O (1800ml). The mixture was stirred at 5-10°C for 90 minutes. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 27.1g of intermediate (3).

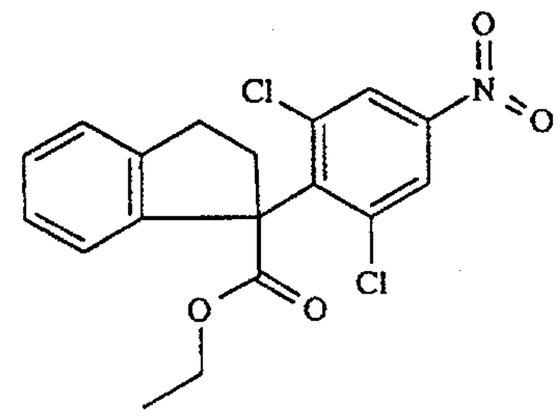
d) Preparation of  intermediate (4)

A mixture of intermediate (3) (0.0593 mol) and potassium acetate (0.0622 mol) in acetic acid (160ml) was stirred and refluxed for 3 hours and then cooled to room temperature. H_2O (300ml) was added. The precipitate was filtered off, washed with H_2O and diisopropyl ethrer and dried, yielding 25.3g of intermediate (4).

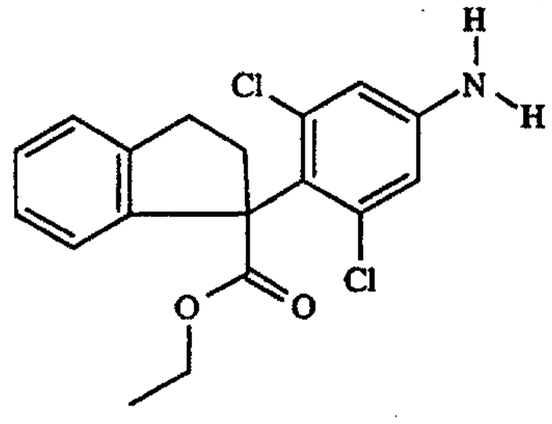
e) Preparation of  intermediate (5)

A mixture of intermediate (4) (0.0593 mol) in acetic acid (250ml) and HCl 12N (75ml) was stirred and refluxed for 3 hours, then cooled to room temperature and poured out into H_2O (600ml). The precipitate was filtered off, washed with H_2O and diisopropyl ether and dried, yielding 26.4g of intermediate (5).

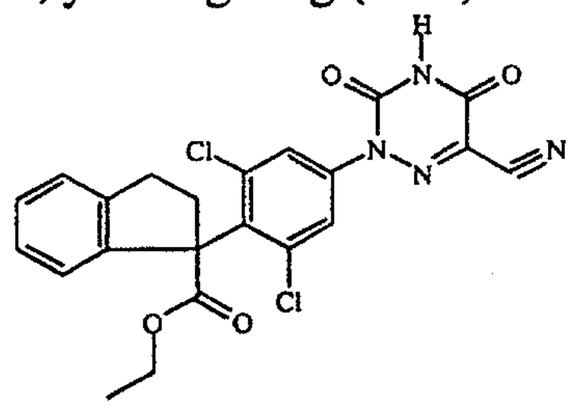
Example A2

a) Preparation of  intermediate (6)

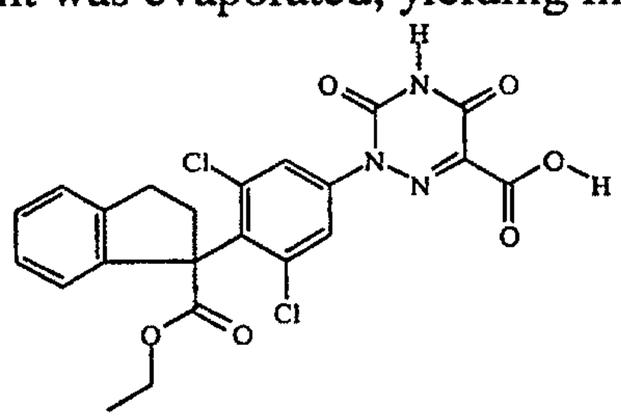
Analogous to the procedure described in example A.1.a.

b) Preparation of  intermediate (7)

A mixture of intermediate (6) (0.0144 mol) in methanol (50ml) and tetrahydrofuran (20ml) was hydrogenated under a 3 bar pressure for 75 minutes with Raney Nickel (5g) as a catalyst in the presence of thiophene (10 % in ethanol; 0.5ml). After uptake of H_2 (3 equivalents), the catalyst was filtered through celite, washed with CH_2Cl_2 and the filtrate was evaporated, yielding 4.6g (91%) of intermediate (7).

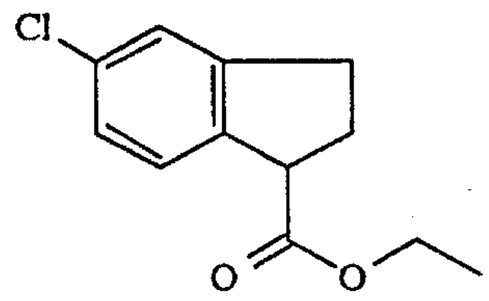
c) Preparation of  intermediate (8)

A mixture of intermediate (7) (0.013 mol) in acetic acid (42ml) and HCl (12 N; 3.6ml) was stirred at room temperature for 15 minutes and then cooled under N_2 flow to 10°C. A solution of $NaNO_2$ (0.013 mol) in H_2O (3ml) was added dropwise. The mixture was stirred at 10°C for 90 minutes. (Cyanoacetyl)-carbamic aicd, ethyl ester (0.0143 mol) and sodium acetate (0.0455 mol) were added. The mixture was stirred at room temperature for 1 hour. Sodium acetate (0.013 mol) was added again. The mixture was stirred at 110°C for 2 hours and allowed to cool to room temperature. H_2O was added. A gum was filtered off and taken up in CH_2Cl_2. The organic solution was dried, filtered and the solvent was evaporated, yielding intermediate (8).

d) Preparation of  intermediate (9)

Analogous to the procedure described in example A.1.e.

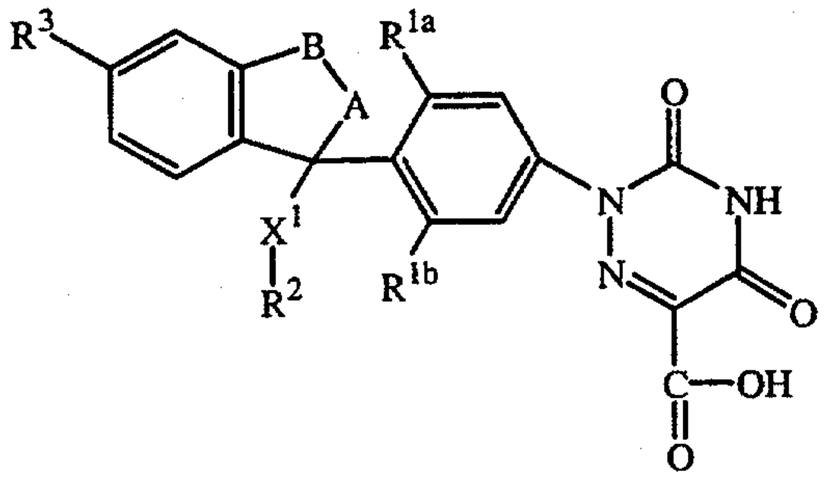
Example A3

Preparation of  intermediate (10)

A mixture of 5-chloro-2,3-dihydro-1*H*-indene-1-carbonitrile (0.118 mol), prepared according to the procedure described in J. Med. Chem., 1991, 34(4), 1307) in ethanol (90ml) and concentrated H_2SO_4 (28ml) was stirred and refluxed for 5 hours, poured out into H_2O and extracted with ethylacetate. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated, yielding 24.4g (92%) of intermediate (10).

The following intermediates were prepared according to the procedure described in example A2.

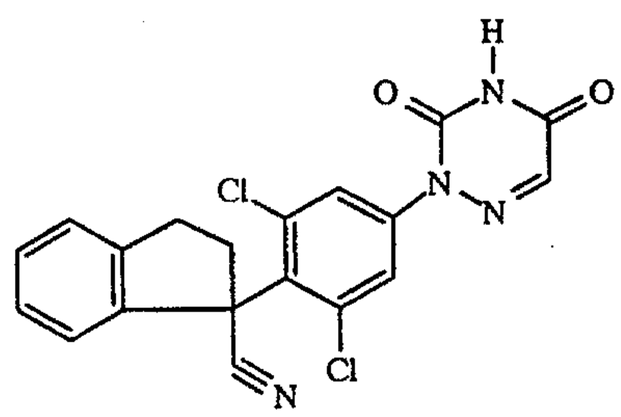
Table 1



Int. No.	B-A	X^1-R^2	R^{1a}	R^{1b}	R^3
11	-$(CH_2)_2$-	CN	H	H	H
12	-$(CH_2)_2$-	CN	OCH_3	H	H
13	-$(CH_2)_2$-	CN	Cl	H	H
14	-$(CH_2)_3$-	CN	Cl	H	H
15	-$(CH_2)_2$-	CN	Cl	Cl	Cl
16	-O-$(CH_2)_2$-	CN	Cl	Cl	H
17	-O-$(CH_2)_2$-	-C(=O)-OC_2H_5	Cl	Cl	H
18	-$(CH_2)_2$-	-C(=O)-OC_2H_5	Cl	Cl	Cl

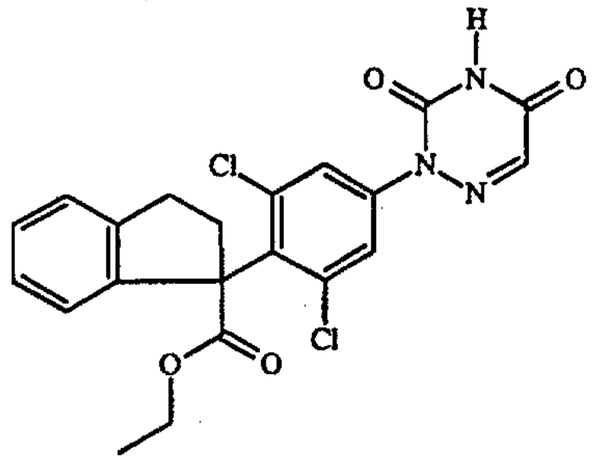
B. Preparation of the final compounds

Example B1

a) Preparation of  (compound 1)

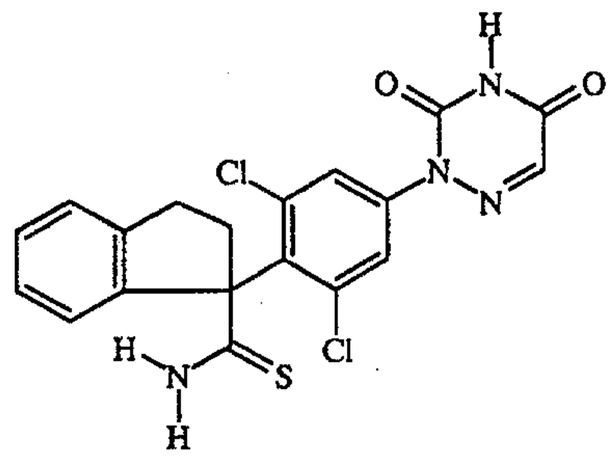
A mixture of intermediate (5) (0.0593 mol) in mercaptoacetic acid (40ml) was stirred at 175°C for 3 hours. The mixture was cooled to room temperature and poured out on ice. CH_2Cl_2 was added. The mixture was basified with K_2CO_3 10% and decanted. The

organic layer was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated. Part of this residue (1.2g) was crystallized from CH_2Cl_2. The precipitate was filtered off and dried, yielding 0.81g of compound (1).

b) Preparation of  (compound 2)

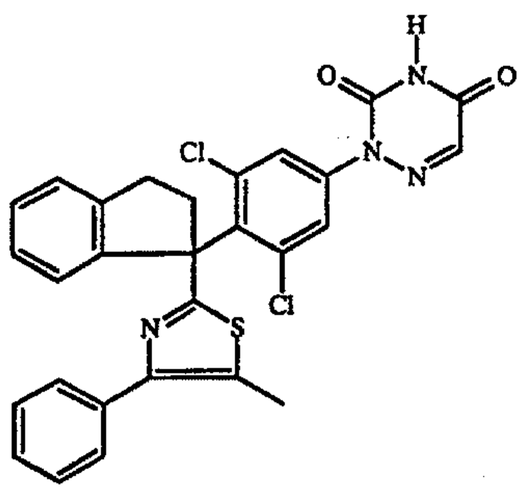
A mixture of intermediate (9) (0.0092 mol) and mercaptoacetic acid (0.77ml) in acetic acid (9ml) was stirred at 110°C for 18 hours, brought to room temperature and taken up in CH_2Cl_2. K_2CO_3 10% and K_2CO_3 solid were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98.5/1.5). The pure fractions were collected and the solvent was evaporated, yielding 0.85g (20%) of compound (2) (mp. 88°C).

Example B2

Preparation of  (compound 3)

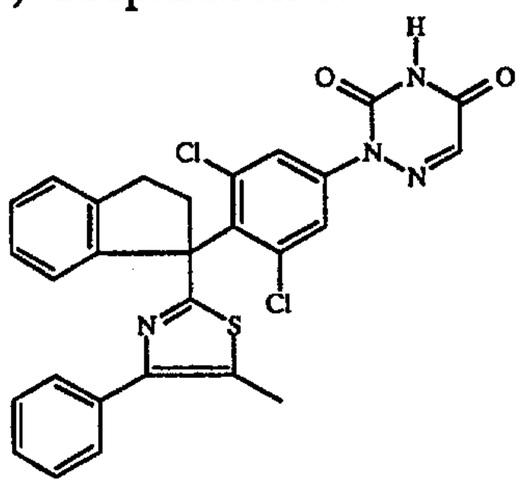
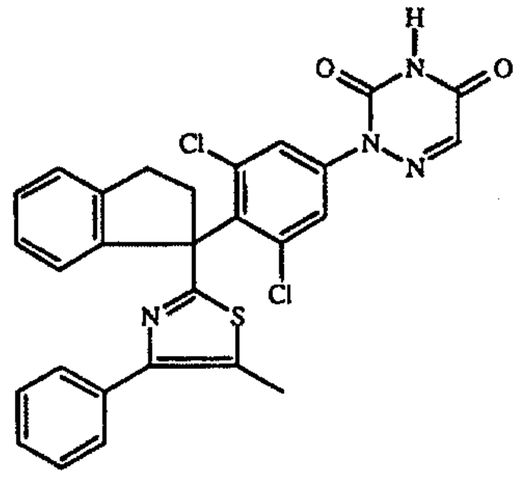
A mixture of compound (1) (0.00925 mol) and *N*,*N*-di(1-methylethyl)ethanamine (0.00925 mol) in pyridine (50ml) was stirred at 60°C. H_2S gas was bubbled through the mixture for 16 hours. The mixture was allowed to cool to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed twice with HCl 3N, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 1.5g (37%) of compound (3).

Example B3

a) Preparation of  (compound 4)

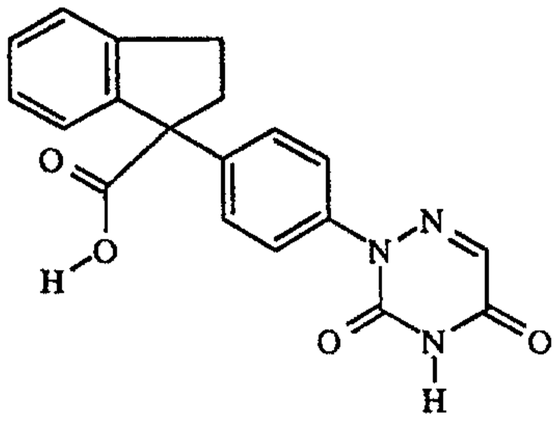
A mixture of compound (3) (0.00334 mol) and 2-bromo-1-phenyl-1-propanone (0.00401 mol) in ethanol (40ml) was stirred and refluxed for 3 hours. H_2O was added and the mixture was extracted twice with CH_2Cl_2. The combined organic layer was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH_2Cl_2, cyclohexane and diisopropyl ether. The precipitate was filtered off and dried, yielding 0.98g (53%) of compound (4) (mp. 237°C).

b) Preparation of

 (A) (compound 5) and  (B) (compound 6)

Compound (4) (0.0122 mol) was separated into its enantiomers by column chromatography (eluent: hexane/ethanol/acetic acid 75/25/0.1; column: CHIRACEL OD 20 μm). Two pure fractions were collected and their solvents were evaporated, yielding 2.6g of the (A) form (compound (5); mp. 122°C) and 2.3g of the (B) form (compound (6); mp. 138°C).

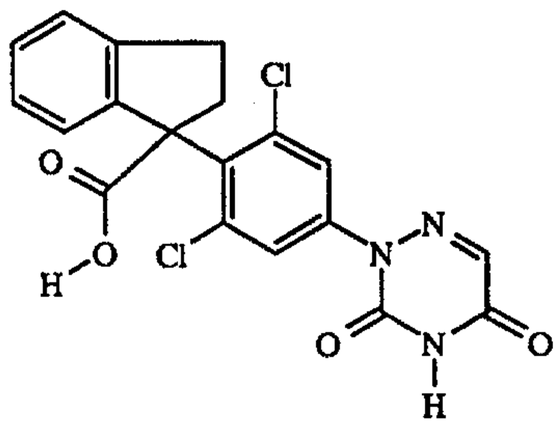
Example B4

Preparation of  (compound 7)

A mixture of compound (17) (0.0109 mol) in HCl 12N (100ml) and acetic acid (30ml) was stirred and refluxed for 3 days, then brought to room temperature and poured out

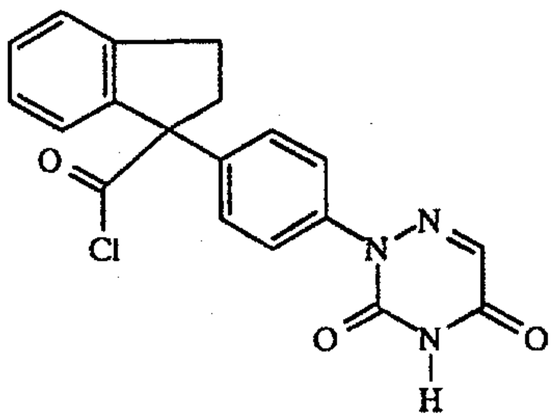
into H_2O. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2. The organic solution was dried, filtered and the solvent was evaporated, yielding 2.6g (68%) of compound (7).

Example B5

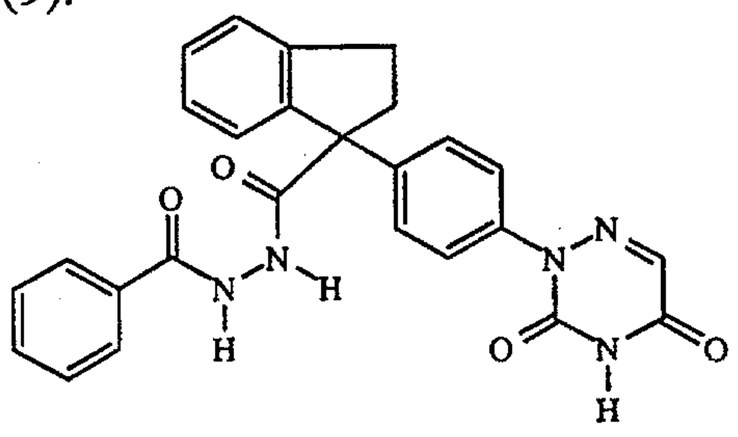
Preparation of  (compound 8)

A mixture of compound (2) (0.064 mol) in HBr in acetic acid (200ml) and aqueous HBr (140ml) was stirred and refluxed for 24 hours and then brought to room temperature. H_2O was added. The precipitate was filtered off, washed with H_2O and taken up in CH_2Cl_2 and a small amount of CH_3OH. The organic solution was dried, filtered and the solvent was evaporated, yielding 21.1g (78%) of compound (8).

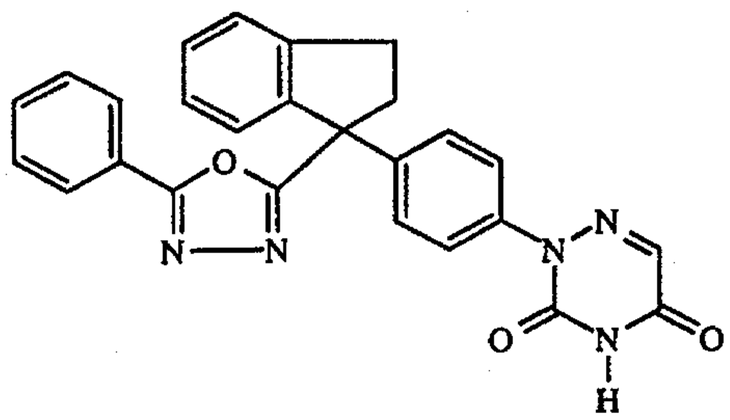
Example B6

a) Preparation of  (compound 9)

A mixture of compound (7) (0.00744 mol) in $SOCl_2$ (15ml) was stirred and refluxed for 90 minutes and then brought to room temperature. The solvent was evaporated, yielding compound (9).

b) Preparation of  compound (10)

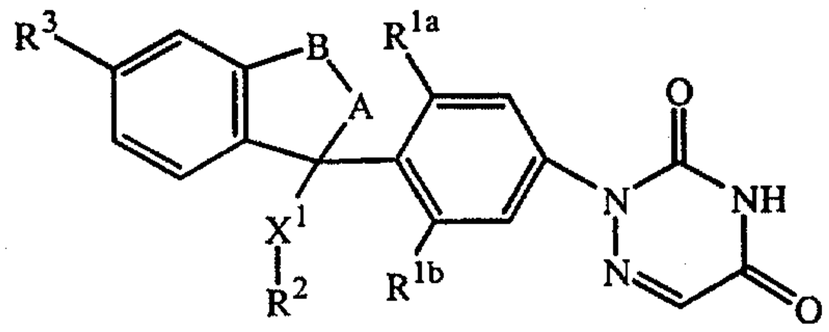
A mixture of compound (9) (0.00744 mol) in THF (30ml) was added dropwise at 10°C under N_2 flow to a solution of hydrazide benzoic acid (0.0082 mol) and *N,N*-diethyl-ethanamine (0.0298 mol) in CH_2Cl_2 (20ml). The mixture was brought to room temperature and stirred for 2 hours. H_2O was added. The mixture was acidified with HCl 3N and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 4g of compound (10).

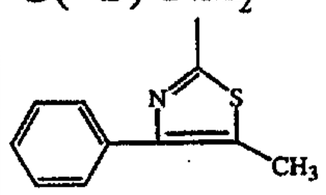
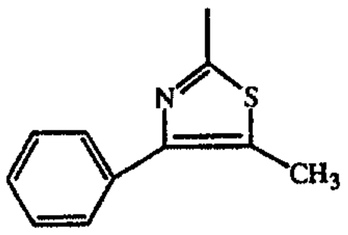
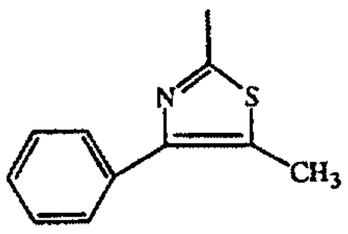
c) Preparation of  (compound 11)

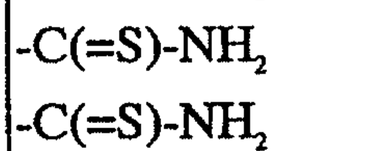
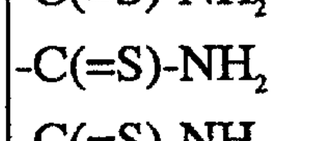
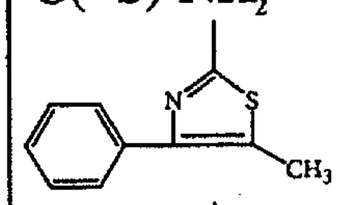
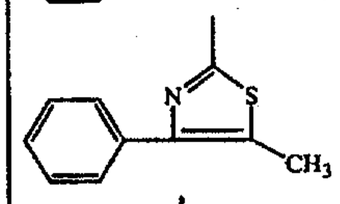
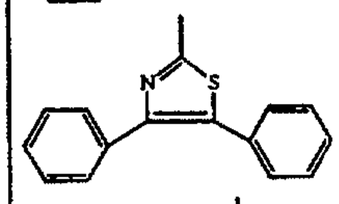
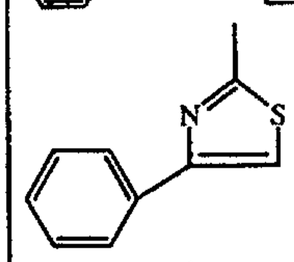
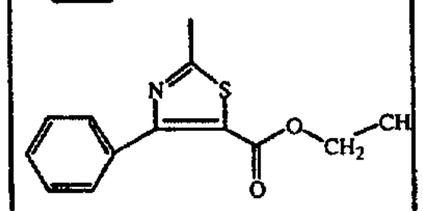
A mixture of compound (10) (0.00744 mol) in $POCl_3$ (20ml) was stirred and refluxed for 2 hours and then brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with H_2O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/ethyl acetate 60/40). The pure fractions were collected and the solvent was evaporated. The residue was taken up in diisopropyl ether. The precipitate was filtered off and dried, yielding 0.69g (20%) of compound (11) (mp. 128°C).

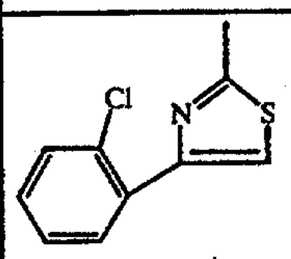
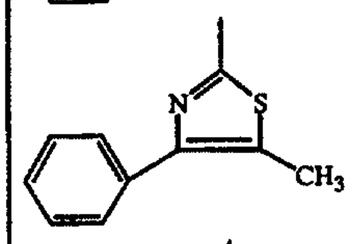
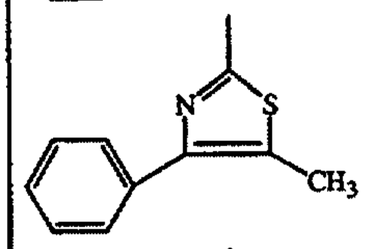
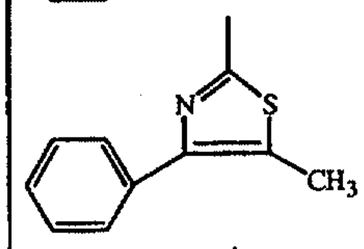
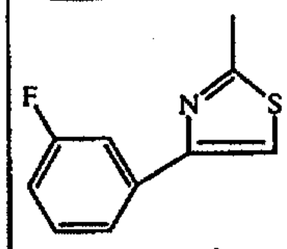
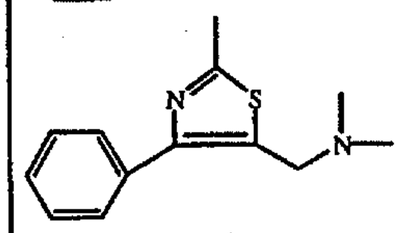
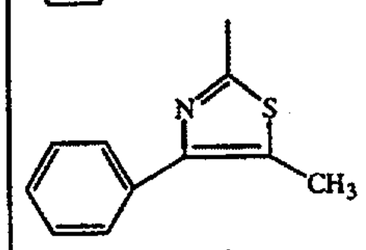
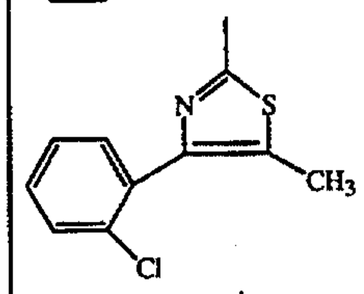
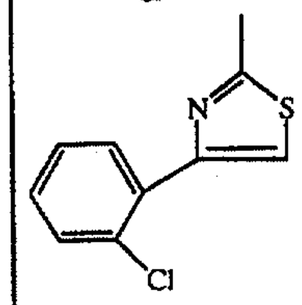
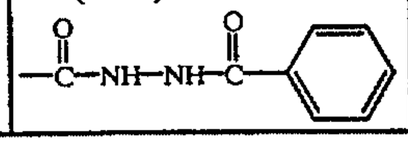
Table 2 lists the compounds that were prepared according to one of the above examples.

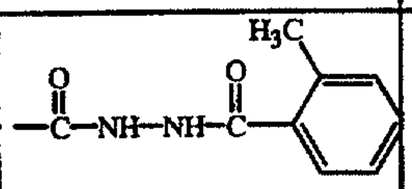
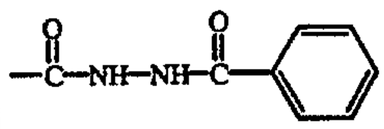
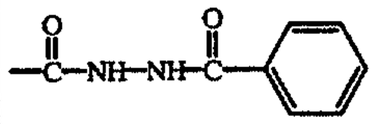
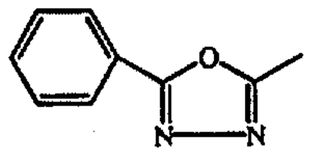
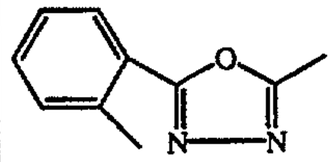
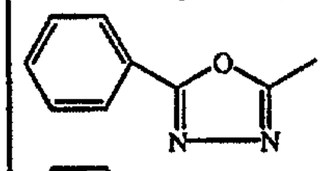
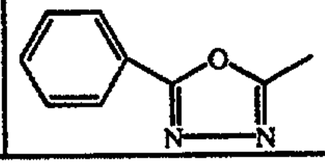
Table 2



Co. No.	Ex. No.	B-A	X^1-R^2	R^{1a}	R^{1b}	R^3	Physical data (mp. in °C)
1	B1a	$-(CH_2)_2-$	CN	Cl	Cl	H	>250°C
2	B1b	$-(CH_2)_2-$	$-C(=O)-O-C_2H_5$	Cl	Cl	H	88°C
3	B2	$-(CH_2)_2-$	$-C(=S)-NH_2$	Cl	Cl	H	
4	B3a	$-(CH_2)_2-$		Cl	Cl	H	237°C
5	B3b	$-(CH_2)_2-$		Cl	Cl	H	122°C; (A)
6	B3b	$-(CH_2)_2-$		Cl	Cl	H	138°C; (B)
7	B4	$-(CH_2)_2-$	$-C(=O)-OH$	H	H	H	

Co. No.	Ex. No.	B-A	X^1-R^2	R^{1a}	R^{1b}	R^3	Physical data (mp. in °C)
8	B5	$-(CH_2)_2-$	-C(=O)-OH	Cl	Cl	H	
9	B6a	$-(CH_2)_2-$	-C(=O)-Cl	H	H	H	
10	B6b	$-(CH_2)_2-$		H	H	H	
11	B6c	$-(CH_2)_2-$		H	H	H	128°C
12	B1a	$-(CH_2)_2-$	CN	Cl	Cl	Cl	240°C
13	B1a	$-O-(CH_2)_2-$	CN	Cl	Cl	H	
14	B1a	$-(CH_2)_3-$	CN	Cl	H	H	
15	B1a	$-O-(CH_2)_2-$	$-C(=O)-O-C_2H_5$	Cl	Cl	H	
16	B1a	$-(CH_2)_2-$	$-C(=O)-O-C_2H_5$	Cl	Cl	Cl	
17	B1b	$-(CH_2)_2-$	-CN	H	H	H	238°C
18	B1b	$-(CH_2)_2-$	-CN	OCH_3	H	H	250°C
19	B1b	$-(CH_2)_2-$	-CN	Cl	H	H	176°C
20	B2	$-(CH_2)_2-$	$-C(=S)-NH_2$	H	H	H	
21	B2	$-(CH_2)_2-$	$-C(=S)-NH_2$	Cl	H	H	
22	B2	$-(CH_2)_2-$	$-C(=S)-NH_2$	OCH_3	H	H	
23	B2	$-(CH_2)_2-$	$-C(=S)-NH_2$	Cl	Cl	Cl	
24	B2	$-O-(CH_2)_2-$	$-C(=S)-NH_2$	Cl	Cl	H	
25	B2	$-(CH_2)_3-$	$-C(=S)-NH_2$	Cl	H	H	
26	B3a	$-(CH_2)_2-$		H	H	H	208°C
27	B3a	$-(CH_2)_2-$		Cl	H	H	218°C
28	B3a	$-(CH_2)_2-$		Cl	Cl	H	202°C
29	B3a	$-(CH_2)_2-$		Cl	Cl	H	122°C
30	B3a	$-(CH_2)_2-$		Cl	Cl	H	130°C

Co. No.	Ex. No.	B-A	X^1-R^2	R^{1a}	R^{1b}	R^3	Physical data (mp. in °C)
31	B3a	$-(CH_2)_2-$		Cl	Cl	H	96°C
32	B3a	$-(CH_2)_2-$		OCH_3	H	H	184°C
33	B3a	$-(CH_2)_2-$		Cl	Cl	Cl	184°C
34	B3a	$-O-(CH_2)_2-$		Cl	Cl	H	170°C
35	B3a	$-(CH_2)_2-$		Cl	Cl	H	130°C
36	B3a	$-(CH_2)_2-$		Cl	Cl	H	150°C
37	B3a	$-(CH_2)_3-$		Cl	H	H	176°C
38	B3a	$-(CH_2)_2-$		Cl	Cl	Cl	156°C
39	B3a	$-(CH_2)_2-$		Cl	Cl	Cl	128°C
40	B5	$-O-(CH_2)_2-$	-C(=O)-OH	Cl	Cl	H	
41	B5	$-(CH_2)_2-$	-C(=O)-OH	Cl	Cl	Cl	
42	B6a	$-(CH_2)_2-$	-C(=O)-Cl	Cl	Cl	H	
43	B6a	$-O-(CH_2)_2-$	-C(=O)-Cl	Cl	Cl	H	
44	B6a	$-(CH_2)_2-$	-C(=O)-Cl	Cl	Cl	Cl	
45	B6b	$-(CH_2)_2-$		Cl	Cl	H	

Co. No.	Ex. No.	B-A	X^1-R^2	R^{1a}	R^{1b}	R^3	Physical data (mp. in °C)
46	B6b	$-(CH_2)_2-$		Cl	Cl	H	
47	B6b	$-O-(CH_2)_2-$		Cl	Cl	H	
48	B6b	$-(CH_2)_2-$		Cl	Cl	Cl	
49	B6c	$-(CH_2)_2-$		Cl	Cl	H	250°C
50	B6c	$-(CH_2)_2-$		Cl	Cl	H	160°C
51	B6c	$-O-(CH_2)_2-$		Cl	Cl	H	>250°C
52	B6c	$-(CH_2)_2-$		Cl	Cl	Cl	140°C

C. Pharmacological example

Example C.1 : *in vitro* inhibition of IL-5 production in human blood

Human whole blood stimulation

Peripheral blood from healthy male donors was drawn into heparinized syringes (12.5 U heparin/ml). Blood samples were three-fold diluted in RMPI 1640 medium (Life Technologies, Belgium) supplemented with 2 mM L-glutamine, 100 U/ml penicillin and 100 mg/ml streptomycin, and 300 ml fractions were distributed in 24-well multidisc plates. Blood samples were preincubated (60 minutes at 37°C) in a humidified 6% CO_2-atmosphere with 100 ml of drug solvent (final concentration 0.02% dimethylsulfoxide in RPMI 1640) or with 100 ml of an appropriate dose of test compound before being stimulated by the addition of 100 ml of phytohemagglutinin HA17 (Murex, UK) at a final concentration of 2 mg/ml. After 48 hours, cell-free supernatant fluids were collected by centrifugation and stored at -70°C until tested for the presence of IL-5.

IL-5 measurements

IL-5 measurements were conducted as described in Van Wauwe et al. (1996, Inflamm Res, *45*, 357-363) on page 358 using ELISA.

Table 3 lists the percentage inhibition of IL-5 production (column "% inh") at a test dose of 1×10^{-6} M for the compounds of the present invention.

Table 3

Co. No.	% inh.
1	70.5
2	63
4	89.33
5	88
6	91
10	16
12	74
17	7
18	16
19	30

Co. No.	% inh.
26	73
27	89
28	93
29	91
30	90
31	94
32	54
33	86
34	90
35	83

Co. No.	% inh.
36	89
37	85
38	75
39	90
49	80
50	52
51	79
52	84

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

Example D.1 : film-coated tablets

Preparation of tablet core

A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in CH_2Cl_2 (150 ml). Then there were added CH_2Cl_2 (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

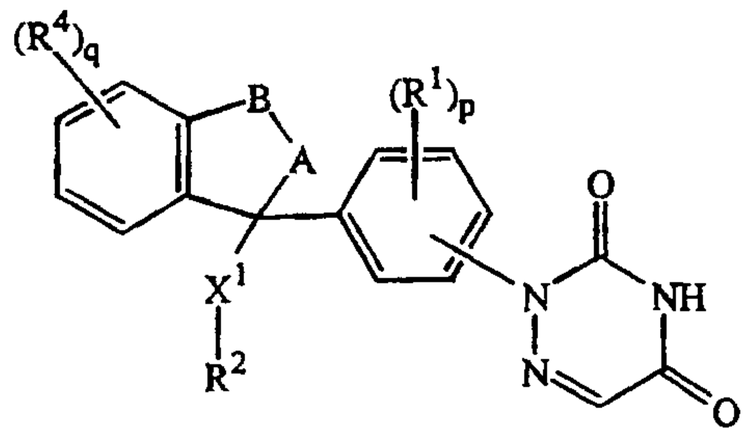
Example D.2 : 2% topical cream

To a solution of hydroxypropyl β-cyclodextrine (200 mg) in purified water is added A.I. (20 mg) while stirring. Hydrochloric acid is added until complete dissolution and

next sodium hydroxide is added until pH 6.0. While stirring, glycerol (50 mg) and polysorbate 60 (35 mg) are added and the mixture is heated to 70°C. The resulting mixture is added to a mixture of mineral oil (100 mg), stearyl alcohol (20 mg), cetyl alcohol (20 mg), glycerol monostearate (20 mg) and sorbate 60 (15 mg) having a temperature of 70°C while mixing slowly. After cooling down to below 25°C, the rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Claims

1. A compound of formula



(I)

an *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein:

p represents an integer being 0, 1, 2 or 3;

q represents an integer being 0, 1, 2, 3 or 4;

-A-B- represents $-(CH_2)_r-$, $-(CH_2)_t-O-$, $-(CH_2)_t-S(=O)_u-$ or $-(CH_2)_t-NR^3-$;

r represents 2, 3 or 4;

each t independently represents 1, 2 or 3;

u represents 0, 1 or 2;

X^1 represents O, S, NR^3 or a direct bond;

each R^1 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

each R^4 independently represents C_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, hydroxy, mercapto, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyloxy, aryl, cyano, nitro, Het^3, R^6, NR^7R^8 or C_{1-4}alkyl substituted with Het^3, R^6 or NR^7R^8;

R^2 represents aryl, Het^1, C_{3-7}cycloalkyl, cyano, C_{1-6}alkyl, $-C(=Q)-X^2-R^{15}$ or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1, Het^1oxy, Het^1thio and $-C(=Q)-X^2-R^{15}$;

each R^3 independently represents hydrogen or C_{1-4}alkyl;

each R^{15} independently represents hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl or C_{1-6}alkyl substituted with aryl, halo, hydroxy or Het^1;

where X^2 is a direct bond, R^{15} may also be halo or Het^1;

where X^2 is NR^5, R^{15} may also be hydroxy;

where X^2 is C(=O)-NH-NH or NH-NH-C(=O), R^{15} may be replaced by R^{11};

each Q independently represents O, S or NR^3;

each X^2 independently represents O, S, NR^5, C(=O)-NH-NH, NH-NH-C(=O) or a direct bond;

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;

each R^6 independently represents C_{1-6}alkylsulfonyl, aminosulfonyl, mono- or di-(C_{1-4}alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC_{1-6}alkylsulfonyl, C_{1-6}alkylsulfinyl, phenylC_{1-4}alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C_{1-4}alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4}alkyl)aminoC_{1-4}alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, dihydroxyC_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, aminocarbonyl, arylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxy-C_{1-4}alkyl-carbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het^3amino-carbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

each Y independently represents O, S, NR^3, or $S(O)_2$;

R^9 and R^{10} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, aminocarbonyl, phenylcarbonyl, Het^3carbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het^3aminocarbonyl, Het^3aminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 and R^6;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4}alkyloxy, formyl, trihaloC_{1-4}alkylsulfonyloxy, R^6, NR^7R^8, C(=O)NR^7R^8, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, aryl, aryloxy, arylcarbonyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyloxy, phthalimide-2-yl, Het^3, Het^4 and C(=O)Het^3;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, dihydroxyC_{1-4}alkyl, phenyl, phenylC_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-4}alkylcarbonyl, phenylcarbonyl, C_{1-4}alkylcarbonyloxyC_{1-4}alkylcarbonyl, hydroxyC_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonylcarbonyl, mono- or di(C_{1-4}alkyl)aminoC_{1-4}alkyl, phenylamino-carbonyl, phenylaminothiocarbonyl, C_{3-7}cycloalkyl, pyridinylC_{1-4}alkyl, C_{1-4}alkanediyl-C(=O)-O-R^{14}, -C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14} and R^6;

each R^{14} independently represents hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, aminocarbonylmethylene, mono-or di(C_{1-4}alkyl)aminocarbonylmethylene, mono-or di(C_{3-7}cycloalkyl)aminocarbonylmethylene, azetidin-1-ylcarbonylmethylene, pyrrolidin-1-ylcarbonylmethylene, piperidin-1-ylcarbonylmethylene or homopiperidin-1-ylcarbonylmethylene;

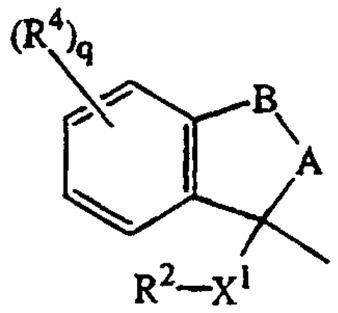
aryl represents phenyl optionally substituted with one, two or three substituents each independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkyloxy, formyl, polyhaloC_{1-4}alkyl, NR^9R^{10}, $C(=O)NR^9R^{10}$, C(=O)-O-R^{14}, R^6, -O-R^6, phenyl, Het^3, $C(=O)Het^3$ and C_{1-4}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, Het^3 or NR^9R^{10};

Het^1 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het^2, R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from Het^2 and R^{11};

Het^2 represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-b]thiazolyl; wherein said heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from R^{11} and C_{1-4}alkyl optionally substituted with one or two substituents independently selected from R^{11};

Het^3 represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, C(=O)-O-R^{14}, R^6 and C_{1-4}alkyl substituted with one or two substituents independently selected from hydroxy, C_{1-4}alkyloxy, phenyl, C(=O)-O-R^{14}, -Y-C_{1-4}alkanediyl-C(=O)-O-R^{14}, R^6 and $NR^{12}R^{13}$;

Het^4 represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl.

2. A compound as claimed in claim 1 wherein the 6-azauracil moiety is connected to the phenyl ring in the para position relative to the  substituent.

3. A compound as claimed in claims 1 or 2 wherein X^1 is a direct bond and R^2 is Het^1, cyano, $-C(=Q)-X^2-R^{15}$ or C_{1-6}alkyl substituted with one or two substituents selected from hydroxy, cyano, $-C(=Q)-X^2-R^{15}$, amino, mono- or di(C_{1-4}alkyl)-amino, C_{1-6}alkyloxy, C_{1-6}alkylsulfonyloxy, C_{1-6}alkyloxycarbonyl, C_{3-7}cycloalkyl, aryl, aryloxy, arylthio, Het^1oxy and Het^1thio.

4. A compound as claimed in any one of claims 1 to 3 wherein -A-B- is $-(CH_2)_r-$ or $-(CH_2)_t-O-$.

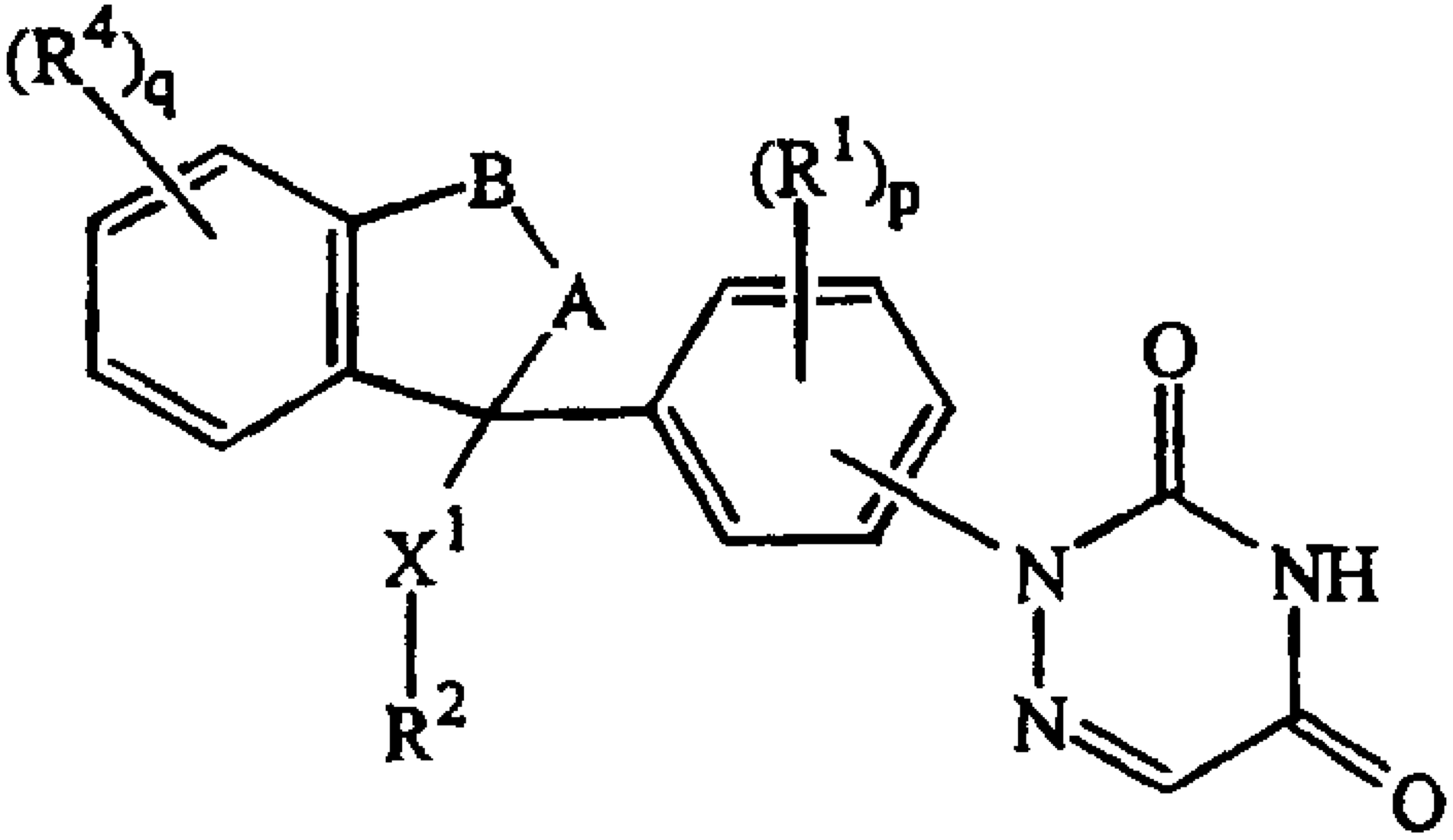
5. A compound as claimed in any one of claims 1 to 4 wherein p is 0, 1 or 2 and q is 0 or 1.

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

7. A process for preparing a composition as claimed in claim 6, wherein a pharmaceutically acceptable carrier is intimately mixed with a compound as defined in any one of claims 1 to 5.

8. A compound as claimed in any one of clams 1 to 5 for use as a medicine for treating eosinophil-dependent inflammatory diseases.

9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases/



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