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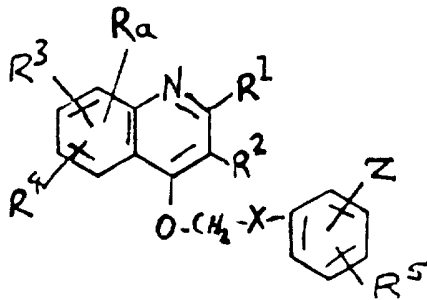
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(54) Title: NOVEL QUINOLINE DERIVATIVES

(57) Abstract:



wherein:
 R¹ is: H, alkyl, cycloalkyl, phenyl or alkyl containing fluoro, cycloalkyl, -OH, alkoxy or phenyl substituents;
 R² is: H, alkyl, cycloalkyl, cycloalkyl-alkyl, -COOH, -CN, alkoxy-carbonyl, -CN, -NO₂, phenyl or phenyl-alkyl;
 R³, R⁴ is: alkyl, alkoxy, fluoro-alkoxy, halogeno, -OH, -CF₃, -CN, -NH₂, alkanoylamino, alkylamino, dialkylamino, dialkylamino-alkyl, alkanoyl, carbamoyl, N-alkylcarbamoyl, di-(N-alkyl)carbamoyl, -COOH, alkoxy-carbonyl, alkylthio, alkylsulphonyl, alkylsulphonyl, and alkyl bearing an -NH₂, -OH or alkoxy substituent;
 or R³, R⁴ together form alkylonedioxy attached to adjacent C atoms;
 Ra, R⁵ is: H, alkyl, alkoxy, halogeno, CF₃, -CN, -NO₂;
 X is optional or is phenylene which may bear: alkyl, alkoxy, halogeno, -CF₃, -CN, -NO₂;
 Z is: 1H-tetrazol-5-yl, -CO.NH.(1H-tetrazol-5-yl), -CO.OR₆ or CO.NH.SO₂R₇ in which
 R₆ is: H or a non-toxic, biodegradable residue of a physiologically acceptable alcohol or phenol; and
 R₇ is: alkyl, cycloalkyl or phenyl which may bear alkyl, alkoxy, halogeno, -CN, -CF₃; or a non-toxic salt thereof; but not methyl 2-[(3-methoxycarbonylquinolin-4-yl)oxy]methyl]benzoate.
 The compounds are of value for treating hypertension and congestive heart failure

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(56) Documents cited: US 4 607 040
US 4 576 953

US 3 932 416

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NITROGEN COMPOUNDS

This invention concerns novel nitrogen compounds and, more particularly, novel quinoline derivatives which possess pharmacologically useful properties in antagonising at least in part one or more of the actions of the substances known as angiotensins, and in particular of that known as angiotensin II (hereinafter referred to as "AII"). The invention also concerns pharmaceutical compositions of the novel compounds for use in treating diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The invention also includes processes for the manufacture of the novel compounds and their use in treating one of the afore-mentioned diseases or medical conditions and for the production of novel pharmaceuticals for use in such medical treatments.

The angiotensins are key mediators of the renin-angiotensin-aldosterone system, which is involved in the control of homeostasis and fluid/electrolyte balance in many warm-blooded animals, including man. The angiotensin known as AII is produced by the action of angiotensin converting enzyme (ACE) from angiotensin I, itself produced by the action of the enzyme renin from the blood plasma protein angiotensinogen. AII is a potent spasmogen especially in the vasculature and is known to increase vascular resistance and blood pressure. In addition, the angiotensins are known to stimulate the release of aldosterone and hence result in vascular congestion and hypertension via sodium and fluid retention mechanisms. Hitherto there have been a number of different approaches to pharmacological intervention in the renin-angiotensin-aldosterone system for therapeutic control of blood pressure and/or fluid/electrolyte balance, including, for example, inhibiting the actions of renin or ACE. However, there remains a continuing need for an alternative approach because of the side-effects and/or idiosyncratic reactions associated with any particular therapeutic approach.

Certain substituted imidazoles and benzimidazoles described in European Patent Application, publication no. 253310 A2 and U.S.

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Patent no. 4880804 respectively are known to inhibit the action of angiotensin II, as too are certain substituted pyrroles, pyrazoles and triazoles described in European Patent Application, publication no. 323841 A2. Also certain structurally related quinoline derivatives described in European Patent Application, publication no. 348155 A1 are known to be antagonists of leukotriene D₄. In addition, a structurally related compound, methyl 2-[(3-methoxycarbonylquinolin-4-yloxy)methyl]benzoate, is described in J. Chem. Soc., Perkin Trans. 1, 1972, 1803-8 but without indication of any useful pharmacological properties.

We have now discovered that the compounds of the invention (set out below) surprisingly antagonise one or more of the actions of the substances known as angiotensins (and in particular of AII) and thus minimise the physiological effects associated with their presence in warm-blooded animals (including man) and this is the basis of the invention.

According to the invention there is provided a quinoline derivative of the formula I (set out hereinafter, together with the other chemical formulae identified by Roman numerals) wherein R¹ is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, hydroxy, (1-4C)alkoxy or phenyl substituent; R² is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, cyano, nitro, phenyl or phenyl(1-4C)alkyl; R³ and R⁴ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, fluoro(1-4C)alkoxy, halogeno, hydroxy, trifluoromethyl, cyano, nitro, amino, (1-4C)alkanoylamino, alkylamino and dialkylamino of up to 6 carbon atoms, dialkylamino-alkyl of 3 to 8 carbon atoms, (1-4C)alkanoyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, carboxy, (1-4C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, and substituted (1-4C)alkyl, the latter bearing an amino, hydroxy or (1-4C)alkoxy substituent; or R³ and R⁴ together form (1-4C)alkylenedioxy attached to adjacent carbon atoms of the benzene moiety of formula I; R⁵ and R⁶ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; A is methylene; X is

phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro, or X is a direct bond between the adjacent phenyl group and moiety A; Z is 1H-tetrazol-5-yl, -CO.NH.(1H-tetrazol-5-yl) or a group of the formula -CO.OR⁶ or -CO.NH.SO₂.R⁷ in which R⁶ is hydrogen or a non-toxic, biodegradable residue of a physiologically acceptable alcohol or phenol, and R⁷ is (1-6C)alkyl, (3-8C)cycloalkyl or phenyl; and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof; but excluding methyl 2-[(3-methoxycarbonylquinolin-4-yloxy)-methyl]benzoate.

It will be appreciated that, depending on the nature of the substituents, certain of the formula I compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that this invention concerns any form of such a compound of formula I which possesses the afore-mentioned useful pharmacological properties, it being well known how to make optically active forms, for example by synthesis from suitable chiral intermediates, and how to determine their pharmacological properties, for example by use of the standard tests described hereinafter.

It is to be understood that generic terms such as "alkyl" include both straight and branched chain variants when the carbon numbers permit. However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named where intended. The same convention applies to other radicals.

A particular value for R¹ or R² when it is alkyl is, for example, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl or hexyl; and when it is cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

A particular value for R¹ when it is alkyl bearing one or more fluoro substituents is, for example, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; and when it is alkyl bearing a hydroxy, cycloalkyl, (1-4C)alkoxy or phenyl substituent is, for example, hydroxymethyl, 1-hydroxyethyl,

2-hydroxyethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl or 2-phenylethyl.

A particular value for R^2 when it is cycloalkyl-alkyl is, for example, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl or 2-cyclopentyl-ethyl; when it is phenylalkyl is, for example, benzyl, 1-phenylethyl or 2-phenylethyl; and when it is alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl.

Appropriate values for R^3 , R^4 , R^5 or R_a , or for an optional substituent which may be present when X is phenylene, as defined above, include by way of example:-

for alkyl: methyl and ethyl; for alkoxy: methoxy and ethoxy; for fluoroalkoxy: trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy and 3,3,3-trifluoropropoxy; for halogeno: fluoro, chloro, bromo and iodo; for alkanoylamino: formamido, acetamido and propanamido; for alkylamino: methylamino, ethylamino and butylamino; for dialkylamino: dimethylamino, diethylamino and dipropylamino; for dialkylamino-alkyl: dimethylaminomethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl and 3-(diethylamino)propyl; for alkanoyl: formyl, acetyl and butyryl; for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl; for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkylthio: methylthio, ethylthio and butylthio; for alkylsulphinyl: methylsulphinyl, ethylsulphinyl and butylsulphinyl; and for alkylsulphonyl: methylsulphonyl, ethylsulphonyl and butylsulphonyl; for alkyl bearing an amino, hydroxy or alkoxy substituent: hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, 2-methoxyethyl and 2-ethoxyethyl; and alkylenedioxy: methylenedioxy and ethylenedioxy.

A particular value for R^6 when it is a non-toxic, biodegradable residue of a physiologically acceptable alcohol or phenol is, for example, a residue derived from a (1-6C)alkanol such as methanol or ethanol, or phenol, glycerol or the like.

A particular value for R^7 when it is alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl or pentyl; and when it is cycloalkyl is, for example, cyclobutyl, cyclopentyl or cyclohexyl.

Particular values for optional substituents which may be

present on one or more phenyl moieties include, by way of example, for halogeno: fluoro, chloro and bromo; for alkyl: methyl and ethyl; and for alkoxy: methoxy and ethoxy.

A specific value for X which is of particular interest is, for example, p-phenylene.

A preferred value for R⁶ or R⁵ is, for example, hydrogen and for R¹ is, for example, methyl, ethyl or propyl.

A preferred value for A is, for example, when it is methylene.

A preferred group of compounds of the invention comprises those compounds of the formula Ia (set out hereinafter) wherein R¹, R², R³, R⁴ and R⁵ have any of their meanings as defined above and Z¹ is carboxy, 1H-tetrazol-5-yl or benzenesulphonamido, the latter optionally containing one or two substituents independently selected from halogeno (such as fluoro, chloro or bromo), (1-4C)alkyl (such as methyl or ethyl), (1-4C)alkoxy (such as methoxy or ethoxy), cyano, nitro and trifluoromethyl; together with the non-toxic salts thereof.

A preferred value for Z or Z¹ is, for example, carboxy or 1H-tetrazol-5-yl, which latter is especially preferred and, in particular, when it is attached ortho to the group X.

A particularly preferred combination of values in any of the above definitions is wherein the quinoline moiety together with the attached substituents R¹, R², R³ and R⁴, and Ra when present, has any of the following values:- 2-methylquinoline, 2-ethylquinoline, 2-ethyl-6-methoxyquinoline, 6,7-dimethoxy-2-ethylquinoline, 2-ethyl-5,6,7-trimethoxyquinoline, 2-ethyl-6-hydroxyquinoline, 2-ethyl-6-methylthioquinoline, 2-ethyl-7-hydroxymethylquinoline, 2-ethyl-6-(2-fluoroethoxy)quinoline, 2-ethyl-6-(2,2,2-trifluoroethoxy)-quinoline, 2-ethyl-6-carboxamidoquinoline, 2-ethyl-6-fluoroquinoline, 2-ethyl-6-isopropoxyquinoline or 6-aminomethyl-2-ethylquinoline; and in which the substituent O.A.X- is attached at the 4-position of the quinoline ring.

Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples. Of these compounds, those described in Examples 7, 25, 33, 36, 38 and 47 are particularly preferred and are provided, together with their non-toxic salts, as a further feature of

the invention.

Although all of the formula I compounds can form salts with suitable acids, it will be appreciated that those compounds of formula I wherein Z is other than an ester group or in which R³ or R⁴ is a carboxy group can form salts with bases as well as with acids. Particularly suitable non-toxic salts for such compounds therefore also include, for example, salts with bases affording physiologically acceptable cations, for example, alkali metal (such as sodium and potassium), alkaline earth metal (such as magnesium and calcium), aluminium and ammonium salts, as well as salts with suitable organic bases, such as with ethanolamine, methylamine, diethylamine or triethylamine, as well as salts with acids forming physiologically acceptable anions, such as salts with mineral acids, for example with hydrogen halides (such as hydrogen chloride and hydrogen bromide), sulphuric and phosphoric acid, and with strong organic acids, for example with p-toluenesulphonic and methanesulphonic acids.

The compounds of formula I may be obtained by standard procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise:

a) For those compounds in which Z is carboxy (that is in which Z is a group of the formula $-CO.OR^6$ in which R⁶ is hydrogen), a carboxylic acid derivative of the formula II, in which Q is a protected carboxy group selected from (1-6C)alkoxycarbonyl (especially methoxy-, ethoxy-, propoxy- or t-butoxy-carbonyl), phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy.

The conversion may be carried out, for example by hydrolysis, conveniently in the presence of a suitable base such as an alkali metal hydroxide, for example, lithium, sodium or potassium hydroxide. The hydrolysis is generally carried out in the presence of a suitable aqueous solvent or diluent, for example in an aqueous (1-4C)alkanol, such as aqueous methanol or ethanol. However, it may also be performed in a mixture of an aqueous and non-aqueous solvent such as water and toluene using a conventional quaternary ammonium phase transfer catalyst. The hydrolysis is generally performed at a

temperature in the range, for example, 0 - 120°C, depending on the reactivity of the group Q. In general, when Q is carbamoyl, temperatures in the range, for example, 40 - 120°C are required to effect the hydrolysis.

Alternatively, when Q is benzyloxycarbonyl, the conversion may also be performed by hydrogenolysis, for example using hydrogen at 1-3 bar in the presence of a suitable catalyst, such as palladium on charcoal or on calcium sulphate, in a suitable solvent or diluent such as a (1-4C)alkanol (typically ethanol or 2-propanol) and at a temperature in the range, for example, 0 - 40°C.

Further, when Q is t-butoxycarbonyl, the conversion may also be carried out by hydrolysis at a temperature in the range, for example, 0 - 100°C, in the presence of a strong acid catalyst, such as trifluoroacetic acid. The hydrolysis may either be performed in an excess of the acid or in the presence of a suitable diluent such as tetrahydrofuran, t-butyl methyl ether or 1,2-dimethoxyethane.

b) For those compounds of formula I wherein Z is tetrazolyl, a compound of the formula III in which L is a suitable protecting group; such as trityl or benzhydryl, affixed to a nitrogen of the tetrazolyl moiety, is deprotected.

The reaction conditions used to carry out the deprotection necessarily depend on the nature of the group L. As an illustration, when it is trityl or benzhydryl, the decomposition conditions include, for example, acid catalysed hydrolysis in a mineral acid (such as aqueous hydrochloric acid), conveniently in an aqueous solvent (such as aqueous dioxan or 2-propanol). Alternatively, a trityl or benzhydryl group may be removed by hydrogenolysis, for example as described in (a) above for conversion of a benzyloxycarbonyl to a carboxy.

c) A quinolone of the formula IV wherein R¹ is other than hydrogen is alkylated with a compound of the formula V wherein Hal. stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The reaction is generally carried out in the presence of a

suitable base, for example, an alkali metal alkoxide such as sodium methoxide or sodium ethoxide or an alkali metal hydride such as sodium hydride or an organic base such as diisopropylethylamine and in a suitable solvent or diluent, for example, a (1-4C)alkanol such as methanol or ethanol when an alkali metal alkoxide is used, or in a polar solvent such as N,N-dimethylformamide and at a temperature in the range, for example, 10 - 100°C. Alternatively, a quaternary ammonium hydroxide may be used in a mixture of an aqueous and non-aqueous solvent such as water and dichloromethane. In carrying out process (c), when in the starting material Z is an acidic group, about two molecular equivalents of a suitable base is generally required, whereas when Z is a non-acidic group the presence of one molecular equivalent of a suitable base is generally sufficient.

Procedure (c) is particularly suitable for the production of those compounds of the formula I in which Z is a group of the formula $-\text{CO.OR}^6$ in which R^6 is other than hydrogen, for example wherein R^6 is (1-6C)alkyl, benzyl or phenyl, which compounds are also starting materials of formula II for the reaction described in (a) above. Similarly, using an analogous procedure, but starting with the appropriate halomethyl tetrazolyl derivative of the formula VI, the starting materials of the formula III may be obtained for procedure (b).

The majority of the quinolones of formula IV are already known and the remainder can be made by analogy therewith using standard procedures of organic chemistry well known in the art, for example as described in standard works of heterocyclic chemistry such as that edited by Elderfield. The necessary compounds of the formula V (and also of formula VI) may be made by standard procedures such as those which are illustrated in Scheme 1 for compounds in which X is phenylene.

d) A halogenoquinoline of the formula VII wherein Y^1 is a halogeno group (such as chloro, bromo or iodo) is reacted with an alcohol of the formula VIII.

The reaction is generally carried out in the presence of a suitable base, for example an alkali metal alkoxide such as sodium

methoxide or ethoxide or an alkali metal hydride such as sodium hydride and in a suitable solvent or diluent, for example a (1-4C)alkanol such as methanol or ethanol when an alkali metal alkoxide is used, or a polar solvent such as N,N-dimethylformamide. Alternatively, an alcohol of the formula VIII may be used in the form of its preformed alkali metal salt (when Z is a non-acidic group) or di-alkali metal salt (when Z is an acidic group). The reaction is usually performed at a temperature in the range of 40 to 120°C. Alternatively, the reaction may in preference be carried out with a formula VIII compound in the presence of an acid catalyst such as p-toluenesulphonic acid, instead of under basic conditions, and in the presence of an inert solvent or diluent such as toluene.

The haloquinolines of the formula VII may be obtained, for example, by halogenation of the corresponding quinolones of formula IV, for example, by reaction with phosphorus oxychloride in the absence of a solvent, or in the presence of an inert solvent or diluent such as toluene or dioxane, and at a temperature in the range 60 to 110°C. The alcohols of the formula VIII are in general known or can be prepared by standard procedures well known in the art.

Whereafter, those compounds of formula I wherein Z is 1H-tetrazol-5-yl may be obtained by stepwise conversion of a compound of the formula I wherein Z is a group of the formula $-CO.OR^6$ into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide such as an alkali metal azide, preferably in the presence of an ammonium halide, and preferably in the presence of a suitable polar solvent such as N,N-dimethylformamide and at a temperature in the range, for example, 50 to 160°C.

Whereafter, those compounds of the formula I wherein Z is $-CO.NH.(1H-tetrazol-5-yl)$, a group of the formula $-CO.NH.SO_2R^7$ or a group of the formula $-CO.OR^6$ in which R^6 is other than hydrogen, may be obtained, for example, by reacting a carboxylic acid of the formula I in which Z is carboxy (or a reactive derivative of said acid) with 5-aminotetrazole, a sulphonamide of the formula $NH_2.SO_2R^7$ or a salt thereof (for example, an alkali metal salt), or a hydroxy compound of the formula $HO.R^6$ or with a salt thereof (for example, an alkali metal thereof). Suitable reactive derivatives include, for example the chloride, bromide, azide, anhydride and mixed anhydride with formic or

acetic acid of the carboxylic acid of formula I as defined above. When the free acid form is used, the reaction is generally carried out in the presence of a suitable dehydrating agent such as dicyclohexylcarbodiimide or 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide in the presence of a base such as triethylamine or pyridine. When a reactive derivative is used, either the reaction is carried out in the presence of a base such as mentioned above, or, for the preparation of a compound of the formula I wherein Z is a group of the formula $-CO.NH.SO_2R^7$ or a group of the formula $-CO.OR^6$, the sulphonamide or hydroxy compound is used in the form of a salt, such as its alkali metal salt (in particular the lithium, sodium or potassium salt thereof). The reaction is generally performed in the presence of a suitable diluent or solvent such as dioxan, *t*-butyl methyl ether or tetrahydrofuran and at a temperature in the range, for example, 0 - 60°C.

Whereafter, when a non-toxic salt of a compound of formula I is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically acceptable cation, or with the appropriate acid affording a physiologically acceptable anion, or by any other conventional salt formation procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula I in which Z is an acidic group may be resolved, for example by reaction with an optically active form of a suitable organic base, for example, ephedrine, N,N,N-trimethyl-(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

Certain of the intermediates defined herein are novel, for example the compounds of the formula II, III and IV, and are provided as a further feature of the invention.

As stated above, the compounds of formula I will have

beneficial pharmacological effects in warm-blooded animals (including man) in diseases and medical conditions where amelioration of the vasoconstrictor and fluid retaining properties of the renin-angiotensin-aldosterone system is desirable, at least in part by antagonism of one or more of the physiological actions of AII. The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role.

The antagonism of one or more of the physiological actions of AII and, in particular, the antagonism of the interaction of AII with the receptors which mediate its effects on a target tissue, may be assessed using one or more of the following, routine laboratory procedures:

Test A: This in vitro procedure involves the incubation of the test compound initially at a concentration of 100 micromolar (or less) in a buffered mixture containing fixed concentrations of radiolabelled AII and a cell surface membrane fraction prepared from a suitable angiotensin target tissue. In this test, the source of cell surface membranes is the guinea pig adrenal gland which is well known to respond to AII. Interaction of the radiolabelled AII with its receptors (assessed as radiolabel bound to the particulate membrane fraction following removal of unbound radiolabel by a rapid filtration procedure such as is standard in such studies) is antagonized by compounds which also bind to the membrane receptor sites and the degree of antagonism (observed in the test as displacement of membrane-bound radioactivity) is determined readily by comparing the receptor-bound radioactivity in the presence of the test compound at the specified test concentration with a control value determined in the absence of the test compound. Using this procedure compounds showing at least 50% displacement of radiolabelled AII binding at a concentration of 10^{-4} M are retested at lower concentrations to determine their potency. For determination of the IC_{50} (concentration for 50% displacement of radiolabelled AII binding), concentrations of the test compound are ordinarily chosen to allow testing over at least

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four orders of magnitude centred about the predicted approximate IC_{50} , which latter is subsequently determined from a plot of percentage displacement against concentration of the test compound.

In general, compounds of formula I as defined above wherein Z is an acidic group show significant inhibition in Test A at a concentration of 50 micromolar or much less.

Test B: This in vitro test involves the measurement of the antagonistic effects of the test compound against AII-induced contractions of isolated rabbit aorta, maintained in a physiological salt solution at 37°C. In order to ensure that the effect of the compound is specific to antagonism of AII, the effect of the test compound on noradrenaline-induced contractions may also be determined in the same preparation.

In general, compounds of formula I as defined above wherein Z is an acidic group show significant inhibition in Test B at a final concentration of 50 micromolar or much less. [Note: Compounds of formula I wherein Z is a group of the formula $-CO.OR^6$ in which R^6 is other than hydrogen in general show only weak activity in the in vitro Tests A or B.]

Test C: This in vivo test involves using terminally-anaesthetised or conscious rats in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure. The AII antagonistic effects of the test compound following oral or parenteral administration, are assessed against angiotensin II-induced pressor responses. To ensure that the effect is specific, the effect of the test compound on vasopressin-induced pressor responses may also be determined in the same preparation.

The compounds of formula I generally show specific AII-antagonist properties in Test C at a dose of 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

Test D: This in vivo test involves the stimulation of endogenous AII biosynthesis in a variety of species including rat, marmoset and dog by introducing a diet of low sodium content and giving appropriate daily doses of a saluretic known as frusemide. The test compound is then administered orally or parenterally to the animal in which an arterial catheter has been implanted under anaesthesia for the

measurement of changes in blood pressure.

In general compounds of formula I will show AII-antagonist properties in Test D as demonstrated by a significant reduction in blood pressure at a dose of 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

By way of illustration of the angiotensin II inhibitory properties of compounds of formula I, the compound of example 7 gave the following results in tests A, B and C described above:-

In test A: an average IC_{50} of $1.7 \times 10^{-8} M$;

In test B an average pA_2 of 8.95;

In test C: ED_{50} of 0.5 mg/kg (i.v. administration).

The compounds of formula I will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals (including man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or a salt thereof as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

The compounds of formula I may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove.

In general a compound of formula I (or a pharmaceutically acceptable salt thereof as appropriate) will generally be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being

treated according to principles well known in the medical arts.

In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula I are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle. In general for such treatment, the compounds of the formula I will generally be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula I are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of AII in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

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

- (i) concentrations and evaporations were carried out by rotary evaporation in vacuo;
- (ii) operations were carried out at room temperature, that is in the range 18-26°C;
- (iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;
- (iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;
- (v) ^1H NMR spectra were normally determined at 200 MHz in CDCl_3 using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet;
- (vi) ^{13}C NMR spectra were normally determined at 100 MHz in CDCl_3 or d_6 -dimethylsulphoxide (d_6 -DMSO) using the solvent signal as internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS;
- (vii) all end-products had satisfactory microanalyses; and
- (viii) the term " ^1H -tetrazol-5-yl" stands for " ^1H -1,2,3,4-tetrazol-5-yl".

Example 1

1.25M sodium hydroxide solution (2.4 ml) was added to a solution of methyl 4'-[(2-ethylquinolin-4-yloxy)methyl]biphenyl-2- carboxylate (A) (380 mg) in ethanol (5 ml). The solution was heated under reflux for 2 hours and then volatile material was removed by evaporation. The residue was dissolved in water (30 ml) and the solution acidified to pH 4 with 2M hydrochloric acid. The precipitated solid was a collected, dried under high vacuum and recrystallised from ethanol to give 4'-[(2-ethylquinolin-4-yloxy)methyl]biphenyl-2-carboxylic acid (254 mg), as white crystals, m.p. 204-205°C;

NMR (d_6 -dimethylsulphoxide (d_6 -DMSO)): 1.34(t,3H), 2.9(q,2H), 5.42(s,2H), 7.1(s,1H), 7.38-7.78(complex m,10H), 7.88(d,1H), 8.15(dd,1H), 12.74(br,1H); mass spectrum (negative fast atom bombardment [-ve FAB], DMSO/glycerol (GLY): 382 (M-H)⁻, 172; microanalysis found: C,78.0; H,5.4; N,4.05; $C_{25}H_{21}NO_3$ requires: C,78.3; H,5.5; N,3.7%.

The starting material (A) was obtained as follows:-

(i) A 1.6M solution of butyllithium in hexane (24.0 ml) was added dropwise to a stirred solution of 4-bromotoluene (6.0 g) in dry tetrahydrofuran (THF) (50 ml) at -78°C under an atmosphere of argon. The temperature was maintained at -78°C for 20 minutes and then a 1M solution of anhydrous zinc chloride in ether (38.6 ml) was added. The solution was kept at -78°C for 15 minutes, and then tetrakis (triphenylphosphine)palladium (60 mg) in THF (5 ml) was added, followed by methyl-2-iodobenzoate (6.1 g) in THF (10 ml). The solution was allowed to reach ambient temperature over 1 hour, then heated under reflux for 5 hours. The solvent was removed by evaporation and the residue was dissolved in chloroform (150 ml). The solution was washed with a solution of ethylene diaminetetracetic acid (10 g) in water (100 ml) and the aqueous layer was re-extracted with chloroform (100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:9 v/v) to give methyl 4'-methylbiphenyl-2-carboxylate (B) as a colourless oil (4.4 g); NMR: 2.4(s,3H), 3.65(s,3H), 7.2(s,4H), 7.35(m,3H), 7.5(m,1H),

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7.8(d,1H).

(ii) N-Bromosuccinimide (8.1 g) and azo(bisisobutyronitrile) (130 mg) were added to a solution of compound (B) (9.3 g) in carbontetrachloride (300 ml). The mixture was heated under reflux for 4 hours and then cooled to ambient temperature. Insoluble material was removed by filtration and the filtrate concentrated. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:9 v/v) to give methyl 4'-(bromomethyl)biphenyl-2-carboxylate (C) as a solid (10.9 g), m.p. 48-50°C; NMR: 3.65(s,3H), 4.55(s,2H), 7.25-7.60 complex (m,7H), 7.85(d,1H).

(iii) Sodium hydride (60% dispersion in mineral oil; 60 mg) was added to a stirred solution of 2-ethyl-4-quinolone (260 mg) prepared by the method described in Org. Syn., 1955, Coll. Vol. III, p.374 and p593), in N,N-dimethylformamide (DMF)(2.5 ml). The mixture was stirred until evolution of hydrogen had ceased and then a solution of the bromomethyl compound (C) (460 mg) in DMF (1 ml) was added. The reaction mixture was stirred for 16 hours. The solvent was removed by evaporation and the residue was partitioned between water (10 ml) and ethyl acetate (2 x 5 ml). The organic phase was washed with water, followed by saturated sodium chloride solution and dried (MgSO₄). The solvent was evaporated and the residue purified by flash chromatography, eluting with ethyl acetate/dichloromethane (1:4 v/v) to give methyl 4'-[(2-ethylquinolin-4-yloxy)methyl]biphenyl-2-carboxylate (A) as a solid (385 mg), m.p. 132-134°C; NMR: 1.41(t,3H), 2.97(q,2H), 3.68(s,3H), 5.34(s,2H), 6.77(s,1H), 7.44-7.7(complex m,9H), 7.87(dd,1H), 8.0(d,1H), 8.26(dd,1H); mass spectrum (positive chemical ionisation [+ve CI]: 398 (M+H)⁺, 225, 174; ¹³C NMR: (benzylic CH₂) 69.73.

Examples 2-4

Using a similar procedure to that described in Example 1, but starting from the appropriate ester of the formula II in which Q is a methoxycarbonyl group the following compounds were obtained:-

(Example 2): 4'-[(2-Methylquinolin-4-yloxy)methyl]biphenyl-2-carboxylic acid hydrochloride, m.p. 184-186°C; NMR (d₆-DMSO):

2.93(s,3H), 5.67(s,2H), 7.38-7.72(m,8H), 7.77(dd,1H), 7.84(dd,1H), 8.08(dt,1H), 8.29(d,1H), 8.33(d,1H); mass spectrum (-ve FAB, DMSO/m-nitrobenzyl alcohol)(NBA): 368 (M-H)⁻; microanalysis found: C,71.2; H,5.0; N,3.6; Cl, 8.6%, C₂₄H₁₉NO₃·HCl requires: C,71.0; H,5.0; N,3.5; Cl,8.7%; starting from methyl 4'-[(2-methylquinolin-4-yloxy)-methyl]biphenyl-2-carboxylate, obtained as a solid, m.p. 146 °C; NMR: 2.71(s,3H), 3.67(s,3H), 5.33(s,2H), 6.74(s,1H), 7.3-7.6(complex m,8H), 7.68(dt,1H), 7.87(dd,1H), 7.98(d,1H), 8.23(dd,1H); itself obtained from 2-methyl-4-quinolone, using analogous procedures to those described in Example 1;

(Example 3): 4'-[(2-Propylquinolin-4-yloxy)methyl]biphenyl-2-carboxylic acid^{*}, m.p. 198-200°C; NMR (d₆-DMSO): 0.97(t,3H), 1.8(m,2H), 2.85(t,2H), 5.43(s,2H), 7.08(s,1H), 7.35-7.65(complex m,8H), 7.73(dt,2H),7.87(d,1H), 8.15(dd,1H), 12.7(br s,1H); mass spectrum (-ve FAB, DMSO/GLY): 396 (M-H)⁻, 186; microanalysis, found: C,77.5; H,6.0; N,3.5%; C₂₆H₂₃NO₃·0.33C₂H₅OH requires: C,77.8; H,6.1; N,3.4%; starting from methyl 4'-[(2-propylquinolin-4-yloxy)methyl]-biphenyl-2-carboxylate, obtained as a viscous oil; NMR: 1.03(t,3H), 1.87(m,2H), 2.94(t,2H), 3.68(s,3H), 5.36(s,2H), 6.75(s,1H), 7.34-7.6(complex m,8H), 7.68(dt,1H), 7.85(dd,2H), 8.03(d,1H), 8.25(dd,1H); ¹³C NMR (CDCl₃): (benzylic CH₂) 69.8; itself obtained from 2-propyl-4-quinolone using analogous procedures to those described in Example 1; [^{*}Note: 1M aqueous citric acid solution was used in place of 2M hydrochloric acid in the work-up procedure].

(Example 4): 4'-[(2-Butylquinolin-4-yloxy)methyl]biphenyl-2-carboxylic acid, m.p. 148°C; NMR (d₆-DMSO): 0.93(t,3H), 1.38(m,2H), 1.8(m,2H), 2.95(t,2H), 5.5(s,2H), 7.25(s,1H), 7.33-7.68(complex m,8H), 7.7-7.85(m,2H), 7.98(d,1H), 8.2(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 410 (M-H)⁻, 200; microanalysis found: C,77.1; H,6.1; N,3.1%; C₂₇H₂₅NO₃·0.5H₂O requires: C,77.1; H,6.2; N,3.3%; starting from methyl 4'-[(2-butylquinolin-4-yloxy)methyl]biphenyl-2-carboxylate obtained as viscous oil; NMR: 0.97(t,3H), 1.45(m,2H), 1.78(m,2H), 2.94(t,2H), 3.68(s,3H), 5.35(s,2H), 6.76(s,1H), 7.35-7.6(complex m,8H), 7.69(dt,1H), 7.88(dd,1H), 8.0(d,1H), 8.25(dd,1H); mass spectrum (+ve CI): 426 (M+H)⁺, 225, 202; itself obtained from 2-butyl-4-quinolone using analogous procedures to those described in Example 1.

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The starting materials, 2-methyl-4-quinolone and 2-propyl-4-quinolone, were obtained as described in Org. Syn., 1955 Coll. Vol. III, page 374 and page 593. 2-Butyl-4-quinolone was obtained using an analogous procedure, starting from ethyl 3-oxo-heptanoate and had the following NMR spectrum: 0.88(t,3H), 1.34(m,2H), 1.7(m,2H), 2.7(t,2H), 6.27(s,1H), 7.34(t,1H), 7.6(dt,1H), 7.78(d,1H), 8.36(d,1H), 11.8(br s, 1H).

Example 5

5M Aqueous sodium hydroxide solution (2 ml) was added to a solution of methyl 4-[(2-propylquinolin-4-yloxy)methyl]benzoate (A) (500 mg) in methanol (5 ml). the solution was allowed to stand for 16 hours. Water (50 ml) was added and the mixture heated to dissolve the solid precipitate. The solution was filtered and the filtrate acidified to pH4 with 1M aqueous citric acid solution. The precipitated solid was collected by filtration and dried under high vacuum to give 4-[(2-propylquinolin-4-yloxy)methyl]benzoic acid (347 mg), as a white powder, m.p. 225-227°C; NMR (d_6 -DMSO): 0.95(t,3H), 1.7-1.9(m,2H), 2.84(t,2H), 5.5(s,2H), 7.05(s,1H), 7.5(dt,1H), 7.7(m,3H), 7.88(d,1H), 8.0(d,1H), 8.15(dd,1H), 12.9(br,1H); mass spectrum (-ve FAB, DMSO/Gly); 32) (M-H)⁻, 186; microanalysis found: C,73.9; H,5.9; N,4.2%; $C_{20}H_{19}NO_3 \cdot 0.25H_2O$ requires; C,73.7; H,6.0; N,4.3%.

The starting ester (A) was obtained from 2-propyl-4-quinolone (561 mg) and methyl 4-(bromomethyl)benzoate (700 mg) together with appropriate amount to the other necessary agents and solvents, using a similar procedure to that described in Example 1, part (iii) and purification by flash chromatography eluting with a mixture of methanol and dichloromethane (1:9 v/v), as a solid (540 mg), m.p. 62-65°C; NMR: 1.0(t,3H), 1.83(m,2H), 2.9(t,2H), 3.95(s,3H), 5.37(s,2H), 6.69(s,1H), 7.46(dt,1H), 7.58(d,2H), 7.67(dt,1H), 8.0(d,1H), 8.1(d,2H), 8.2(dd,1H).

Example 6

4-[(2-Propylquinolin-4-yloxy)methyl]benzoic acid (240 mg) was added to a mixture of benzene sulphonamide (120 mg),

4-dimethylaminopyridine (90 mg) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (150 mg) in dichloromethane (20 ml) and the mixture stirred overnight. Chloroform (20 ml) was added the mixture was washed successively with 1M citric acid solution (10 ml), water (2 x 10 ml), saturated sodium chloride solution (5 ml) and then dried (MgSO_4). The solvent was removed by evaporation and the residue triturated with methanol to give 4-[(2-propylquinolin-4-yloxy)methyl]-N-phenylsulphonylbenzamide as a white powder (160 mg), m.p. 140 °C (dec.); NMR (d_6 -DMSO): 0.95(t,3H), 1.79(m,2H), 2.88(t,2H), 5.5(s,2H), 7.14(s,1H), 7.5-7.7(m,6H), 7.78(dt,1H), 7.87-8.02(m,5H), 8.18(dd,1H); mass spectrum (-ve FAB, DMSO/Gly): 495 (M-H)⁻; microanalysis found: C,66.1; H,5.4; N,5.8%; $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_4 \cdot 0.5\text{H}_2\text{O}$ requires: C,66.5; H,5.3; N,6.0%.

Example 7

A mixture of 2-methyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline (A) (890 mg) and a 7.5M solution of hydrogen chloride dioxane (10 ml) and water (1 ml) was allowed to stand for 72 hours. Volatile material was removed by evaporation and the residue was triturated with ether (2 x 50 ml). The ether was decanted off and the solid residue crystallised from isopropanol to give 2-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride (370 mg), as a white solid, m.p. 188-190°C; NMR (d_6 -DMSO): 2.92(s,3H), 5.63(s,2H), 7.21(d,2H), 7.56-7.87(m,8H), 8.07(dt,1H), 8.28(dd,1H), 8.32(dd,1H); mass spectrum [-ve FAB, DMSO/NBA]: 392 (M-H)⁻, 158; microanalysis found: C,66.0; H,4.6; N,15.5%; $\text{C}_{24}\text{H}_{19}\text{N}_5\text{O} \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ requires: C,65.7; H,4.8; N,16.0%.

The starting material (A) was obtained as follows:-

Sodium hydride (60% dispersion in mineral oil; 90 mg) was added to a stirred solution of 2-methyl-4-quinolone (340 mg) in DMF (10 ml). The mixture was stirred until evolution of hydrogen had ceased and a solution of 5-2-(4'-bromomethylbiphenyl)-2-triphenylmethyl-2H tetrazole (1.2 g) (obtained as described in European Patent 0291969) in DMF (5 ml) was added. The mixture was stirred for 16 hours. The solvent was removed by evaporation and the

residue partitioned between water (20 ml) and dichloromethane (2 x 10 ml). The organic layer was washed with saturated sodium chloride solution (5 ml) and dried ($MgSO_4$). The solvent was removed by evaporation and the resultant oil was purified by flash chromatography, eluting with methanol/dichloromethane (1:99 v/v) to give 2-methyl-4-[2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethoxy]quinoline (A) (890 mg) as a white solid m.p. 168-170 °C (dec.); NMR: 2.7(s,3H), 5.14(s,2H), 6.7(s,1H), 6.9(dd,6H), 7.15-7.55(complex m,17H), 7.65(dt,1H), 7.95(m,2H), 8.1(dd,1H).

Example 8

Using an analogous procedure to that described in Example 7 but starting from 2-propyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline (A), there was obtained 2-propyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 178-180°C; NMR (d_6 -DMSO): 0.98(t,3H), 1.88(m,2H), 3.08(t,2H), 5.6(s,2H), 7.2(d,2H), 7.5-7.85(complex m,8H), 8.02(dt,1H), 8.2(d,1H), 8.28(dd,1H); mass spectrum (-ve FAB, DMSO/NBA): 420(M-H)⁻; microanalysis found: C,67.9; H,5.2; N,14.9%; $C_{26}H_{23}N_5O.HCl$ requires C,68.2; H,5.3; N,15.3%.

The starting material (A) was obtained as white solid, m.p. 150-152°C; NMR: 1.05(t,3H), 1.88(m,2H), 2.92(t,2H), 5.2(s,2H), 6.73(s,1H), 6.94(dd,6H), 7.15-7.58(complex m,17H), 7.68(dt,1H), 8.0(m,2H), 8.12(dd,1H), ¹³C NMR ($CDCl_3$): (benzylic CH_2) 69.67; starting from 2-propyl-4-quinolone using a similar procedure to that described in Example 7.

Examples 9-29

Using an analogous procedure to that described in Example 7, but starting from the appropriate triphenylmethyl tetrazoles (III), the following compounds of formula I were obtained in yields of 70-90%:-

(Example 9): 5-Cyano-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methoxy]quinoline hydrochloride, m.p. 240°C (dec); NMR (d_6 -DMSO): 1.40(t,3H), 3.16(q,2H), 5.57(s,2H), 7.17(d,2H), 7.50-7.75(m,7H),

8.10(t,1H), 8.32(d,1H), 8.62(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 431 (M-H)⁻; microanalysis, found: C,65.2; H,4.5; N,16.6; H₂O, 2.0%;

C₂₆H₂₀N₆O.HCl.0.5H₂O requires: C,64.9; H,4.8; N,16.8; H₂O, 1.8%;

(Example 10): 2-Ethyl-6-trifluoromethyl-4-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 188-190°C; NMR (d₆-DMSO): 1.43(t,3H), 3.20(q,2H), 5.67(s,2H), 7.20(d,2H),

7.55-7.73(m,7H), 8.30(d,1H), 8.48(d,2H); mass spectrum (-ve FAB, DMSO/GLY): 474 (M-H)⁻; microanalysis, found: C,60.6; H,3.9; N,13.3%;

C₂₆H₂₀N₅OF₃.HCl requires: C,61.0; H,4.1; N,13.7%;

(Example 11): 2-Ethyl-8-trifluoromethyl-4-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline^{*}, m.p. 110-113°C; NMR (CDCl₃):

1.42(t,3H), 3.05(q,2H), 5.37(s,2H), 6.85(s,1H), 7.28-7.62(m,8H),

8.03(d,1H), 8.14(dd,1H), 8.43(d,1H); mass spectrum (-ve FAB,

DMSO/GLY): 474 (M-H)⁻; microanalysis, found: C,64.6; H,4.4; N,13.3%;

C₂₆H₂₀N₅OF₃.0.67 dioxane requires C,64.5; H,4.7; N,13.1%. *Isolated as free base;

(Example 12): 2-Ethyl-6-methoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 213-215°C; NMR (d₆-DMSO):

1.41(t,3H), 3.12(q,2H), 3.95(s,3H), 5.68(s,2H), 7.20(d,2H),

7.50-7.76(m,9H), 8.21(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 436

(M-H)⁻; microanalysis, found: C,66.1; H,5.0; N,14.6%; C₂₆H₂₃N₅O₂.HCl. requires C,65.9; H,5.1; N,14.8%;

(Example 13): 2-Ethyl-8-methoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 125-127°C; NMR (d₆-DMSO):

1.40(t,3H), 3.24(q,2H), 4.14(s,3H), 5.66(s,2H), 7.21(d,2H),

7.50-7.84(m,10H); mass spectrum (-ve FAB, DMSO/GLY): 436 (M-H)⁻;

microanalysis, found: C,63.7; H,5.8; N,13.5%;

C₂₆H₂₃N₅O₂.HCl.0.5H₂O.0.5dioxane requires C,63.8; H,5.3; N,13.3%.

(Example 14): 2-Ethyl-5,7-dimethoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 203-205°C; NMR (d₆-DMSO):

1.40(t,3H), 3.07(q,2H), 3.91(s,3H), 3.94(s,3H), 5.56(s,2H),

6.80(d,1H), 7.21(d,2H), 7.31(s,2H), 7.51(d,2H), 7.56-7.62(m,2H),

7.68-7.75(m,2H); mass spectrum (-ve FAB, DMSO/GLY): 466(M-H)⁻;

microanalysis, found: C,63.6; H,5.3; N,12.9; H₂O, 1.0%;

C₂₇H₂₅N₅O₃.HCl.0.25H₂O.0.25dioxane requires C,63.5; H,5.2; N,13.2%;

H₂O, 0.9%;

(Example 15): 2-Ethyl-6,7-dimethoxy-4-[(2'-(1H-tetrazol-5-yl)-

biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 272°C (decomp);
NMR (d_6 -DMSO): 1.40(t,3H), 3.10(q,2H), 3.95(s,3H), 3.98(s,3H),
5.65(s,2H), 7.20(d,2H), 7.43(d,2H), 7.53-7.74(m,7H); mass spectrum
(-ve FAB, DMSO/GLY): 466(M-H)⁻; microanalysis, found: C,62.7; H,5.1;
N,13.5; H₂O, 2.5%; C₂₇H₂₅N₅O₃·HCl·0.75H₂O requires C,62.7; H,5.1;
N,13.5; H₂O, 2.6%;

(Example 16): 2-Ethyl-5,8-dimethoxy-4-[(2'-(1H-tetrazol-5-yl)-
biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 171°C (decomp.);
NMR (d_6 -DMSO): 1.39(t,3H), 3.22(q,2H), 3.90(s,3H), 4.09(s,3H),
5.62(s,2H), 7.19-7.28(m,3H), 7.51-7.77(m,8H); mass spectrum (-ve FAB,
DMSO/GLY): 466 (M-H)⁻; microanalysis, found: C,61.3; H,5.4; N,12.9;
H₂O, 5.8%; C₂₇H₂₅N₅O₃·HCl·1.5H₂O requires C,61.1; H,5.3; N,13.2; H₂O,
5.1%;

(Example 17): 2-Ethyl-5,6,7-trimethoxy-4-[(2'-(1H-tetrazol-5-yl)-
biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 181-182°C; NMR
(d_6 -DMSO): 1.42(t,3H), 3.10(q,2H), 3.68(s,3H), 3.87(s,3H), 4.00(s,3H),
5.55(s,2H), 7.20(d,2H), 7.42(s,1H), 7.53-7.62(m,5H), 7.68-7.74(m,2H);
mass spectrum (-ve FAB, DMSO/GLY): 496 (M-H)⁻; microanalysis, found:
C,60.6; H,5.1; N,12.6; H₂O, 2.9%; C₂₈H₂₇N₅O₄·HCl·H₂O requires C,60.9;
H,5.3; N,12.7; H₂O, 3.3%;

(Example 18): 7-Cyano-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-
methoxy]quinoline hydrochloride, m.p. 160-163°C; NMR (d_6 -DMSO):
1.43(t,3H), 3.17(q,2H), 5.64(s,2H), 7.20(d,2H), 7.55(d,2H),
7.58-7.72(m,5H), 8.08(d,1H), 8.40(d,1H), 8.76(s,1H); mass spectrum
(-ve FAB, DMSO/GLY): 431 (M-H)⁻; microanalysis, found: C,64.3; H,4.9;
N,16.6%; C₂₆H₂₀N₆O·HCl·H₂O·0.1dioxane requires C,64.1; H,4.8; N,17.0%;

(Example 19): 2-Ethyl-7-methoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-
4-yl)methoxy]quinoline hydrochloride, m.p. 172-174°C; NMR(d_6 -DMSO):
1.44(t,3H), 3.15(q,2H), 3.97(s,3H), 5.64(s,2H), 7.21(d,2H),
7.38-7.77(m,9H), 8.20(d,1H); mass spectrum (-ve FAB, DMSO/GLY):
436(M-H)⁻; microanalysis, found: C,63.8; H,5.5; N,13.8; H₂O, 3.5%;
C₂₆H₂₃N₅O₂·HCl·H₂O requires C,63.5; H,5.3; N,14.2; H₂O, 3.7%;

(Example 20): 6-Carbomethoxy-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)-
biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 202-204°C; NMR
(d_6 -DMSO): 1.50(t,3H), 3.28(q,2H), 4.00(s,3H), 5.74(s,2H), 7.29(d,2H),
7.56-7.82(m,7H), 8.48-8.55(m,2H), 8.82(s,1H); mass spectrum (-ve FAB,
DMSO/GLY): 464 (M-H)⁻; microanalysis, found: C,64.6; H,4.7; N,13.8%;

$C_{27}H_{23}N_5O_3 \cdot HCl$ requires C, 64.6; H, 4.8; N, 14.0%;

(Example 21): 2-Ethyl-5-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methoxy]quinoline hydrochloride, m.p. 168-169°C (dec.); NMR (d_6 -DMSO): 1.42(t, 3H), 2.75(s, 3H), 3.17(q, 2H), 5.61(s, 2H), 7.20(d, 2H), 7.54-7.71(m, 8H), 7.89(t, 1H), 8.19(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 420 (M-H)⁻; microanalysis, found: C, 65.8; H, 5.4; N, 14.0; H₂O, 3.0%; $C_{26}H_{23}N_5O \cdot HCl \cdot 0.75H_2O \cdot 0.33 EtOAc$ requires C, 65.6; H, 5.6; N, 14.0; H₂O, 2.7%;

(Example 22): 2-Ethyl-7-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 213-215°C (dec.); NMR (d_6 -DMSO): 1.43(t, 3H), 2.59(s, 3H), 3.19(q, 2H), 5.65(s, 2H), 7.22(d, 2H), 7.54-7.75(m, 8H), 8.09(s, 1H), 8.19(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 420 (M-H)⁻; microanalysis, found: C, 68.5; H, 5.3; N, 15.3%; $C_{26}H_{23}N_5O \cdot HCl$ requires C, 68.2; H, 5.3; N, 15.3%;

(Example 23): 2,6-Dimethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methoxy]quinoline hydrochloride, m.p. 200-202°C (dec.); NMR (d_6 -DMSO): 2.56(s, 3H), 2.89(s, 3H), 5.62(s, 2H), 7.22(d, 2H), 7.54-7.72(m, 7H), 7.91(dd, 1H), 8.06(s, 1H), 8.18(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 406 (M-H)⁻; microanalysis, found: C, 67.1; H, 4.8; N, 15.4%; $C_{25}H_{21}N_5O \cdot HCl \cdot 0.25H_2O$ requires C, 67.0; H, 5.0; N, 15.6%;

(Example 24): 2,8-Dimethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methoxy]quinoline hydrochloride, m.p. 193-195°C (dec.); NMR (d_6 -DMSO): 2.82(s, 3H), 2.99(s, 3H), 5.63(s, 2H), 7.21(d, 2H), 7.53-7.72(m, 8H), 7.89(d, 1H), 8.16(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 406 (M-H)⁻; microanalysis, found: C, 67.5; H, 5.0; N, 15.6%; $C_{25}H_{21}N_5O \cdot HCl$ requires C, 67.6; H, 5.0; N, 15.8%;

(Example 25): 2-Ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]-quinoline hydrochloride, m.p. 178-181°C (dec.); NMR (d_6 -DMSO): 1.48(t, 3H), 3.22(q, 2H), 5.68(s, 2H), 7.23(d, 2H), 7.5-7.8(m, 7H), 7.83(t, 1H), 8.08(t, 1H), 8.32(t, 2H); ¹³C NMR: (benzylic CH₂) 71.9; mass spectrum (-ve FAB, DMSO/GLY): 406 (M-H)⁻; microanalysis, found: C, 68.0; H, 5.1; N, 15.8%; $C_{25}H_{21}N_5O \cdot HCl$ requires C, 67.6; H, 5.0; N, 15.8%.

(Example 26): 6,8-Dimethyl-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 195-197°C (dec.); NMR (d_6 -DMSO): 1.4(t, 3H), 2.5(s, 3H), 2.81(s, 3H), 3.34(q, 2H), 5.65(s, 2H), 7.22(d, 2H), 7.54-7.72(m, 8H), 7.89(s, 1H); mass spectrum (-ve FAB, DMSO/GLY): 434 (M-H)⁻; microanalysis, found: C, 68.7; H, 5.6; N, 14.8%;

$C_{27}H_{25}N_5O.HCl$ requires C, 68.7; H, 5.5; N, 14.9%;

(Example 27): 6-Chloro-2-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride m.p. 197-198°C (dec.); NMR (d_6 -DMSO): 2.9(s, 3H), 5.61(s, 2H), 7.22(d, 2H), 7.53-7.77(m, 7H), 8.08(dd, 1H), 8.21-8.28(m, 2H); ^{13}C NMR: (benzylic CH_2) 72; mass spectrum (-ve FAB, DMSO/GLY): 426 (M-H)⁻; microanalysis, found: C, 62.2; H, 4.1; N, 15.1; Cl, 15.0%; $C_{24}H_{18}N_5ClO.HCl$ requires C, 62.1; H, 4.1; N, 15.1; Cl, 15.3%;

(Example 28): 7-Chloro-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride m.p. 170-172°C (dec.); NMR (d_6 -DMSO): 1.43(t, 3H), 3.18(q, 2H), 5.64(s, 2H), 7.21(d, 2H), 7.5-7.75(m, 7H), 7.81(dd, 1H), 8.29(d, 1H), 8.40(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 440 (M-H)⁻; microanalysis, found: C, 61.8; H, 4.3; N, 14.2; Cl, 14.3; H_2O , 2.1%; $C_{25}H_{20}N_5ClO.HCl.0.5H_2O$ requires C, 61.6; H, 4.5; N, 14.4; Cl, 14.6; H_2O , 1.8%; and

(Example 29): 8-Chloro-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride m.p. 146-148°C (dec.); NMR (d_6 -DMSO): 1.38(t, 3H), 3.08(q, 2H), 5.52(s, 2H), 7.19(d, 2H), 7.38(t, 1H), 7.51-7.75(m, 7H), 8.02(d, 1H), 8.18(dd, 1H); mass spectrum (-ve FAB, DMSO/GLY): 440(M-H)⁻; microanalysis, found: C, 60.8; H, 4.6; N, 14.1%; $C_{25}H_{20}N_5ClO.HCl.H_2O$ requires C, 60.5; H, 4.6; N, 14.1%.

The necessary starting materials of formula III were obtained in yields of 20-70% using an analogous procedure to that described in Example 7 but starting from the appropriate quinolines of formula IV. The compounds of formula III had the following properties:

(9): 5-Cyano-2-ethyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline, isolated as a foam; NMR (d_6 -DMSO): 1.34(t, 3H), 2.96(q, 2H), 5.55(s, 2H), 6.82-6.93(m, 6H), 7.14(d, 2H), 7.25-7.36(m, 9H), 7.40-7.65(m, 6H), 7.80(dd, 1H), 7.93(t, 1H), 8.16(d, 1H), 8.30(d, 1H);

(10): 2-Ethyl-6-trifluoromethyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline, isolated as a foam; NMR: 1.55(t, 3H), 3.12(q, 2H), 5.35(s, 2H), 6.91(s, 1H), 7.05-7.10(m, 6H), 7.33-7.45(m, 13H), 7.52-7.69(m, 3H), 7.99(dd, 1H), 8.10(dd, 1H), 8.24(d, 1H), 8.64(s, 1H);

- (11): 2-Ethyl-8-trifluoromethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.45(t,3H), 3.01(q,2H), 5.19(s,2H), 6.80(s,1H), 6.88-7.0(m,6H), 7.18-7.55(m,17H), 8.05(dd,2H), 8.32(d,1H); ¹³C NMR: (benzylic CH₂) 69.96;
- (12): 2-Ethyl-6-methoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.37(t,3H), 2.90(q,2H), 3.80(s,3H), 5.19(s,2H), 6.70(s,1H), 6.91-6.97(m,6H), 7.19-7.35(m,14H), 7.42-7.52(m,4H), 7.89-7.95(m,2H); ¹³C NMR: (benzylic CH₂) 69.72;
- (13): 2-Ethyl-8-methoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR (d₆-DMSO): 1.33(t,3H), 2.88(q,2H); 3.93(s,3H), 5.31(s,2H), 6.81-6.92(m,6H); 7.10-7.12(m,4H), 7.25-7.70(m,15H), 7.85(d,2H);
- (14): 2-Ethyl-5,7-dimethoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.39(t,3H), 2.89(q,2H), 3.87(s,3H), 3.93(s,3H), 5.14(s,2H), 6.46(d,1H), 6.58(s,1H), 6.86-6.95(m,6H), 7.01(d,1H), 7.16-7.29(m,11H), 7.35-7.52(m,5H), 7.91-7.95(m,1H); ¹³C NMR: (benzylic CH₂) 69.63;
- (15): 2-Ethyl-6,7-dimethoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 211°C (decomp.); NMR (d₆-DMSO): 1.39(t,3H), 2.90(q,2H), 3.87(s,3H), 4.03(s,3H), 5.20(s,2H), 6.65(s,1H), 6.94-7.00(m,6H), 7.19-7.33(m,13H), 7.39-7.55(m,5H), 7.94(dd,1H); ¹³C NMR: (benzylic CH₂) 69.72;
- (16): 2-Ethyl-5,8-dimethoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 94-97°C; NMR (CDCl₃): 1.41(t,3H), 3.04(q,2H), 3.85(s,3H), 4.04(s,3H), 5.18(s,2H), 6.75(d,2H), 6.88-6.98(m,7H), 7.18-7.29(m,11H), 7.37-7.56(m,5H), 7.91-7.96(m,1H); ¹³C NMR: (benzylic CH₂) 69.85;
- (17): 2-Ethyl-5,6,7-trimethoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 90-95°C; NMR: 1.39(t,3H), 2.90(q,2H), 3.78(s,3H), 3.96(s,3H), 4.00(s,3H), 5.19(s,2H), 6.63(s,1H), 6.92-6.98(m,6H), 7.18-7.56(m,17H), 7.91-7.95(m,1H); ¹³C NMR: (benzylic CH₂) 70.26;
- (18): 7-Cyano-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline*, m.p. 172-175°C; NMR (d₆-DMSO): 1.33(t,3H), 2.94(q,2H), 5.36(s,2H), 6.81-6.90(m,6H), 7.18(d,2H),

7.25-7.36(m,10H), 7.43(d,2H), 7.47-7.70(m,4H), 7.85(dd,1H),
8.13(d,1H), 8.39(d,1H);

[*Note: Prepared by alkylation of a 70:30 mixture of 7-cyano-2-ethyl-4-quinolone and 5-cyano-2-ethyl-4-quinolone and purified by flash chromatography using ethyl acetate/dichloromethane (2:98 v/v) as eluant.]

(19): 2-Ethyl-7-methoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline*, m.p. 159-161°C; NMR: 1.39(t,3H), 2.92(q,2H), 3.93(s,3H), 5.12(s,2H), 6.62(s,1H), 6.90-6.95(m,7H), 7.21-7.55(m,17H), 7.95-7.80(m,2H); ¹³C NMR: (benzylic CH₂) 69.69;

[*Note: Prepared by alkylation of a 80:20 mixture of 2-ethyl-7-methoxy-4-quinolone and 2-ethyl-5-methoxy-4-quinolone and purified by flash chromatography using ethyl acetate/hexane (50:50 v/v) as eluant.]

(20): 6-Carbomethoxy-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 179-181°C; NMR (d₆-DMSO): 1.33(t,3H), 2.89(q,2H), 3.85(s,3H), 5.39(s,2H), 6.81-6.95(m,6H), 7.12-7.23(m,3H), 7.24-7.38(m,9H), 7.43(d,2H), 7.50-7.69(m,3H), 7.82(dd,1H), 7.95(d,1H), 8.17(dd,1H), 8.76(d,1H);

(21): 2-Ethyl-5-methyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl]methoxy)quinoline; m.p. 179-181°C (dec.); NMR: 1.38(t,3H), 2.78(s,3H), 2.90(m,2H), 5.15(s,2H), 6.69(s,1H), 6.9-6.98(m,6H), 7.13-7.34(m,13H), 7.4-7.57(m,5H), 7.85(d,1H), 7.94(dd,1H); ¹³C NMR: (benzylic CH₂) 70.27; microanalysis, found: C,79.3; H,5.9; N,10.5%; C₄₅H₃₇N₅O.H₂O requires C,79.3; H,5.7; N,10.3%;

(22): 2-Ethyl-7-methyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 205-206°C (dec.); NMR: 1.39(t,3H), 2.52(s,3H), 2.94(q,2H), 5.14(s,2H), 6.66(s,1H), 6.90-6.95(m,6H), 7.17-7.32(m,14H), 7.39-7.43(m,3H), 7.79(s,1H), 7.96-8.02(m,2H); ¹³C NMR: (benzylic CH₂) 69.69; microanalysis, found C,81.6; H,5.9; N,10.6%; C₄₅H₃₇N₅O requires C,81.4; H,5.6; N,10.6%;

(23): 2,6-Dimethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 2.41(s,3H), 2.69(s,3H), 5.15(s,2H), 6.67(s,1H), 6.91-6.95(m,6H), 7.22-7.25(m,13H), 7.44-7.51(m,4H), 7.89-7.99(m,3H);

(24): 2,8-Dimethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl]methoxy)quinoline; m.p. 175-177°C (dec.); NMR:

2.7(s,3H), 2.78(s,3H), 5.14(s,2H), 6.69(s,1H), 6.87-6.95(m,6H), 7.15-7.3(m,14H), 7.38-7.54(m,4H), 7.94-8.02(m,2H); microanalysis, found: C,81.6; H,5.2; N,10.9%; $C_{44}H_{35}N_5O$ requires C,81.3; H,5.4; N,10.8%;

(25): 2-Ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 173-174°C (dec.); NMR: 1.4(t,3H), 2.96(q,2H), 5.16(s,2H), 6.73(s,1H), 6.9-6.94(m,6H), 7.18-7.32(m,13H), 7.33-7.55(m,4H), 7.67(dt,1H), 7.99(m,2H), 8.11(d,1H); microanalysis, found: C,81.1; H,5.4; N,10.9%; $C_{44}H_{35}N_5O$ requires C,81.4; H,5.4; N,10.8%;

(26): 6,8-Dimethyl-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 183-185°C (dec.); NMR: 1.4(t,3H), 2.37(s,3H), 2.76(s,3H), 2.95(q,2H), 5.13(s,2H), 6.68(s,1H), 6.90-6.95(m,6H), 7.17-7.35(m,13H), 7.43-7.50(m,4H), 7.76(s,1H), 7.95(m,1H);

(27): 6-Chloro-2-methyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl]methoxy)quinoline; m.p. 182-184°C (dec.); NMR: 2.68(s,3H), 5.15(s,2H), 6.75(s,1H), 6.87-6.97(m,6H), 7.15-7.35(m,13H), 7.4-7.62(m,4H), 7.9(d,1H), 7.98(m,1H), 8.08(d,1H);

(28): 7-Chloro-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl]methoxy)quinoline; m.p. 176-178°C (dec.); NMR: 1.53(t,3H), 3.08(q,2H), 5.29(s,2H), 6.86(s,1H), 7.02-7.10(m,6H), 7.32-7.48(m,14H), 7.52-7.70(m,3H), 8.08-8.18(m,3H); ^{13}C NMR (benzylic CH_2) 70.01;

(29): 8-Chloro-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl]methoxy)quinoline; m.p. 156-158°C (dec.); NMR: 1.42(t,3H), 3.05(q,2H), 5.16(s,2H), 6.8(s,1H), 6.87-6.98(m,6H), 7.15-7.33(m,14H), 7.38-7.55(m,3H), 7.78(dd,1H), 7.95-8.06(m,2H).

Using an analogous procedure to that described in Org. Syn., 1955, Coll. Vol. III, pages 374 and 593, the following quinolones of formula IV were obtained in yields of 20-60%:-

2-Ethyl-6-trifluoromethyl-4-quinolone, m.p. 288-289 °C;

2-Ethyl-8-trifluoromethyl-4-quinolone, m.p. 162-163 °C;

5-Cyano-2-ethyl-4-quinolone, m.p.250 °C (dec.);

7-Cyano-2-ethyl-4-quinolone, (isolated as a 70:30 mixture of 7-CN and

5-CN isomers);

2-Ethyl-6-methoxy-4-quinolone, m.p. 210-212 °C;

2-Ethyl-7-methoxy-4-quinolone, (isolated as an 80:20 mixture of 7-OMe and 5-OMe isomers);

2-Ethyl-8-methoxy-4-quinolone, m.p. 196-198 °C;

2-Ethyl-5,7-dimethoxy-4-quinolone, m.p. 242-244 °C;

2-Ethyl-5,8-dimethoxy-4-quinolone, m.p. 196-198 °C;

2-Ethyl-6,7-dimethoxy-4-quinolone, m.p. 284-287 °C;

2-Ethyl-5,6,7-trimethoxy-4-quinolone, m.p. 226-228 °C;

Methyl 2-ethyl-4-hydroxyquinol-6-ylcarboxylate, 245 °C (dec.);

2-Ethyl-5-methyl-4-quinolone, m.p. 264-266°C*;

2-Ethyl-7-methyl-4-quinolone, m.p. 242-244°C*;

2-Ethyl-6,8-dimethyl-4-quinolone, m.p. 264-266°C; and

8-Chloro-2-ethyl-4-quinolone, m.p. 183-184°C.

7-chloro-2-ethyl-4-quinolone (isolated as a 43.5:56.5) mixture of 7-Cl and 5-Cl isomers).

[* Note: these compounds were separated by flash chromatography on silica, eluting with methanol/dichloromethane (1:9 v/v) as eluant.]

2,6-Dimethyl-4-quinolone and 2,8-dimethyl-4-quinolone were obtained as described in Ann. Chem., 1982, 1656-1676.

6-Chloro-2-methyl-4-quinolone was obtained as described in Synthesis, 1987, 482-3.

Example 30

2M Aqueous sodium hydroxide solution (3.8 ml) was added to a solution of 6-carbomethoxy-2-ethyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline in methanol (10 ml) and dioxane (15 ml). The solution was heated to reflux for 1 hour, cooled, and the solvent removed by evaporation. Water (40 ml) was added and the solution extracted with ethyl acetate (40 ml). The aqueous phase was acidified with concentrated hydrochloric acid (2 ml) and the resulting suspension dissolved in dioxane (20 ml). The solution was stirred for 1 hour then evaporated to a yellow gum. Crystallisation from methanol gave 6-carboxy-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride (0.24 g)

as a white powder, m.p. 161-164°C; NMR (d_6 -DMSO): 1.45(t,3H), 3.24(q,2H), 5.68(s,2H), 7.24(d,2H), 7.53-7.76(m,7H), 8.47(d,2H), 8.77(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 450 (M-H)⁻; microanalysis, found: C,61.3; H,4.9; N,13.3; H₂O, 1.7%; C₂₆H₂₁N₅O₃.HCl.MeOH.0.5H₂O requires C,61.3; H,5.1; N,13.2; H₂O, 1.7%.

Example 31

Using an analogous procedure to that described in Example 7, but starting from 2-ethyl-6-(tert-butyldimethylsilyloxy)-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, itself isolated as a foam [NMR: 0.25(s,6H), 1.02(s,9H), 1.38(t,3H), 2.94(q,2H), 5.20(s,2H), 6.68(s,1H), 6.88-6.98(m,6H), 7.17-7.34(m,14H), 7.40-7.60(m,4H), 7.89-8.00(m,2H); ¹³C NMR: (benzylic CH₂) 69.52] starting from 2-ethyl-6-(tert-butyldimethylsilyloxy)-4-quinolone, there was obtained 2-ethyl-6-hydroxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 189-191°C; NMR (d_6 -DMSO): 1.42(t,3H), 3.14(q,2H), 5.61(s,2H), 7.22(d,2H), 7.49-7.72(m,9H), 8.20(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 422 (M-H)⁻; microanalysis, found: C,62.7; H,4.8; N,14.4; H₂O, 4.4%; C₂₅H₂₁N₅O₂.HCl.H₂O requires C,62.8; H,4.8; N,14.6; H₂O, 3.8%.

Examples 32-54

Using an analogous procedure to that described in Example 7, but starting from the appropriate triphenylmethyl tetrazole (III), the following compounds of formula I were obtained in yields of 70-90%:-

(Example 32): 2-Ethyl-6-methylthio-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 156-158°C; NMR (d_6 -DMSO): 1.40(t,3H), 2.62(s,3H), 3.17(q,2H), 5.66(s,2H), 7.20(d,2H), 7.51-7.70(m,7H), 7.90-7.95(m,2H), 8.25(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 452 (M-H)⁻; microanalysis, found: C,63.2; H,4.8; N,13.7%; C₂₆H₂₃N₅OS.HCl.0.25.H₂O requires C,63.2; H,4.8; N,14.2%;

(Example 33): 2-Ethyl-7-hydroxymethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 228-230°C; NMR (d_6 -DMSO): 1.41(t,3H), 3.15(q,2H), 5.06(s,2H), 5.62(s,2H), 7.20(d,2H), 7.55(d,2H), 7.56-7.62(m,3H), 7.65-7.72(m,2H), 7.99(d,2H), 8.12-8.20(m,1H); mass spectrum (-ve FAB, DMSO/GLY): 436 (M-H)⁻;

microanalysis, found: C, 65.7; H, 5.1; N, 14.8%; $C_{26}H_{23}N_5O_2 \cdot HCl$ requires C, 65.9; H, 5.1; N, 14.8%;

(Example 34): 2-Ethyl-6-methylsulphonyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 149-151°C; NMR (d_6 -DMSO): 1.40(t, 3H), 3.11(q, 2H), 3.30(s, 3H), 5.59(s, 2H), 7.20(d, 2H), 7.53-7.70(m, 7H), 8.20(d, 1H), 8.33(dd, 1H), 8.67(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 484 (M-H)⁻; microanalysis, found: C, 58.3; H, 5.0; N, 12.2%; $C_{26}H_{23}N_5O_3 \cdot HCl \cdot H_2O$ requires C, 57.8; H, 4.9; N, 13.0%;

(Example 35): 2-Ethyl-6,7-methylenedioxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 174-175°C; NMR (d_6 -DMSO): 1.40(t, 3H), 3.11(q, 2H), 5.62(s, 2H), 6.35(s, 2H), 7.19(d, 2H), 7.45-7.76(m, 9H); mass spectrum (-ve FAB, DMSO/GLY): 450 (M-H)⁻; microanalysis, found: C, 61.6; H, 4.8; N, 13.2; H₂O, 4.3%; $C_{26}H_{21}N_5O_3 \cdot HCl \cdot 1.2H_2O$ requires C, 61.3; H, 4.8; N, 13.7; H₂O, 4.2%;

(Example 36): 2-Ethyl-6-(2-fluoroethoxy)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 161-163°C; NMR (d_6 -DMSO): 1.40(t, 3H), 3.12(q, 2H), 4.32-4.55(m, 2H), 4.66-4.98(m, 2H), 5.64(s, 2H), 7.20(d, 2H), 7.50-7.81(m, 9H), 8.24(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 468 (M-H)⁻; microanalysis, found: C, 63.1; H, 4.9; N, 12.9; H₂O, 1.7%; $C_{27}H_{24}N_5O_2F \cdot HCl \cdot 0.5H_2O$ requires C, 63.0; H, 4.8; N, 13.6; H₂O, 1.8%;

(Example 37): 7-Carboethoxy-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 226-228°C; NMR (CD_3CN/CF_3CO_2H): 1.55(t, 3H), 1.62(t, 3H), 3.31(q, 2H), 4.60(q, 2H), 5.75(s, 2H), 7.42(d, 2H), 7.52(s, 1H), 7.70(d, 2H), 7.73-7.78(m, 2H), 7.85-7.91(m, 2H), 8.44(dd, 1H), 8.60(d, 1H), 8.78(d, 1H); mass spectrum (-ve FAB, DMSO/GLY): 479 (M-H)⁻; microanalysis, found: C, 64.7; H, 5.0; N, 13.4; H₂O, 0.4%; $C_{28}H_{25}N_5O_3 \cdot HCl \cdot 0.1H_2O$ requires C, 64.9; H, 5.1; N, 13.5; H₂O, 0.3%;

(Example 38): 2-Ethyl-6-(2,2,2-trifluoroethoxy)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 140-141°C; NMR (d_6 -DMSO): 1.41(t, 3H), 3.14(q, 2H), 5.03(q, 2H), 5.68(s, 2H), 7.20(s, 2H), 7.52-7.75(m, 8H), 7.85(dd, 1H), 8.28(d, 1H), mass spectrum (-ve FAB, DMSO/GLY): 504 (M-H)⁻; microanalysis, found: C, 58.0; H, 4.7; N, 12.4; H₂O, 2.6%; $C_{27}H_{22}N_5O_2F_3 \cdot HCl \cdot H_2O$ requires C, 57.9; H, 4.3; N, 12.5; H₂O, 3.2%;

(Example 39): 6-Carboxamido-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)-

biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 178-180°C; NMR (d_6 -DMSO): 1.44(t,3H), 3.21(q,2H), 5.69(s,2H), 7.22(d,2H), 7.57-7.75(m,6H), 8.36(d,1H), 8.46(dd,2H), 8.76(d,1H); mass spectrum (+ve FAB, DMSO/GLY): 451 (M+H)⁺; microanalysis, found: C,62.4; H,5.1; N,16.1; H₂O, 1.7%; C₂₆H₂₂N₆O₂·HCl·0.25H₂O·0.4CH₃OH requires C,62.3; H,5.0; N,16.5; H₂O, 1.8%;

(Example 40): 2-Ethyl-6-trifluoromethoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 180-182°C; NMR (d_6 -DMSO): 1.43(t,3H), 3.18(q,2H), 5.65(s,2H), 7.20(d,2H), 7.52-7.73(m,7H), 8.03-8.15(m,2H), 8.41(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 490 (M-H)⁻; microanalysis, found: C,59.0; H,3.6; N,13.2%; C₂₆H₂₀N₅O₂F₃·HCl requires C,59.1; H,4.0; N,13.3%;

(Example 41): 6-Cyano-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 153-155°C; NMR (d_6 -DMSO): 1.41(t,3H), 3.15(q,2H), 5.62(s,2H), 7.20(d,2H), 7.53-7.75(m,7H), 8.22-8.39(m,2H), 8.79(s,1H); mass spectrum (+ve FAB, DMSO/GLY): 433 (M+H)⁺; microanalysis, found: C,66.9; H,4.3; N,17.6%; C₂₆H₂₀N₆O·HCl requires C,66.6; H,4.5; N,17.9%;

(Example 42): 2-Ethyl-6-formyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 142-144°C; NMR (d_6 -DMSO): 1.45(t,3H), 3.20(q,2H), 5.70(s,2H), 7.22(d,2H), 7.52-7.75(m,7H), 8.34-8.49(m,2H), 8.85(s,1H), 10.22(s,1H); mass spectrum (+ve FAB, DMSO/NBA): 436 (M+H)⁺; microanalysis, found: C,65.0; H,4.6; N,14.4%; C₂₆H₂₁N₅O₂·HCl·0.5H₂O requires C,64.9; H,4.8; N,14.6%;

(Example 43): 6-Dimethylamino-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline dihydrochloride, m.p. 206-209°C; NMR (d_6 -DMSO): 1.40(t,3H), 3.07(s,6H), 3.12(q,2H), 5.63(s,2H), 7.05(d,1H), 7.21(d,2H), 7.45(s,1H), 7.51(s,1H), 7.55-7.65(m,3H), 7.66-7.75(m,3H), 8.23(d,1H); mass spectrum (+ve FAB, DMSO/NBA): 451 (M+H)⁺; microanalysis, found: C,61.8; H,5.4; N,16.0; Cl,13.2%; C₂₇H₂₆N₆O·2HCl requires C,61.9; H,5.4; N,16.1; Cl,13.6%;

(Example 44): 2-Ethyl-6-nitro-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 149-152°C; NMR (d_6 -DMSO): 1.45(t,3H), 3.18(q,2H), 5.66(s,2H), 7.22(d,2H), 7.54-7.75(m,7H), 8.45(d,1H), 8.68(dd,1H), 8.95(d,1H); mass spectrum (+ve FAB, DMSO/NBA): 453 (M+H)⁺; microanalysis, found: C,59.3; H,4.5; N,16.8; H₂O, 3.9%; C₂₅H₂₀N₆O₃·HCl·H₂O requires C,59.2; H,4.5; N,16.6; H₂O,

3.6%;

(Example 45): 6-Cyano-2-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 280-282°C; NMR (d_6 -DMSO): 2.90(s,3H), 5.63(s,2H), 7.21(d,2H), 7.57-7.79(m,8H), 8.25-8.41(m,2H), 8.79(s,1H); mass spectrum (-ve FAB, DMSO/GLY): 417 (M-H)⁻; microanalysis, found: C,66.0; H,4.5; N,17.8%; $C_{25}H_{18}N_6O.HCl$ requires C,66.0; H,4.2; N,18.5%;

(Example 46): 2-Ethyl-6-fluoro-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 185-186°C; NMR (d_6 -DMSO): 1.44(t,3H), 3.20(q,2H), 5.67(s,2H), 7.20(d,2H), 7.50-7.78(m,7H), 7.93-8.08(m,2H), 8.36-8.49(m,1H); mass spectrum (-ve FAB, DMSO/GLY): 424 (M-H)⁻; microanalysis, found: C,64.7; H,4.4; N,14.8%; $C_{25}H_{20}N_5FO.HCl$ requires: C,65.0; H,4.6; N,15.2%;

(Example 47): 2-Ethyl-6-isopropoxy-4-[(2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 177-180°C (dec); NMR (d_6 -DMSO): 1.36(d,6H), 1.4(t,3H), 3.16(q,2H), 4.83(m,1H), 5.66(s,2H), 7.20(d,2H), 7.48-7.65(m,6H), 7.65-7.75(m,3H), 8.28(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 464 (M-H)⁻; microanalysis, found: C,66.2; H,6.1; N,13.8; H_2O ,0.2%; $C_{28}H_{27}N_5O_2.HCl.0.1(CH_3)_2CHOH.0.25H_2O$ requires C,66.3; H,5.7; N,13.7; H_2O ,0.9%;

(Example 48): 5-Chloro-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 189-190°C (dec); NMR (d_6 -DMSO): 1.41(t,3H), 3.14(q,2H), 5.63(s,2H), 7.19(d,2H), 7.50-7.63(m,5H), 7.63-7.74(m,2H), 7.84(d,1H), 7.94(t,1H), 8.28(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 440 (M-H)⁻; microanalysis, found: C,62.8; H,4.2; N,14.7%; $C_{25}H_{20}N_5ClO.HCl$ requires C,62.8; H,4.4; N,14.6%;

(Example 49): 2-Trifluoromethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline, m.p. 187-190°C (dec); NMR (d_6 -DMSO): 5.53(s,2H), 7.20(d,2H), 7.50-7.80(m,8H), 7.90(dt,1H), 8.12(d,1H), 8.28(dd,1H), 13.0(brs,1H); mass spectrum (-ve FAB, DMSO/GLY): 446 (M-H)⁻; microanalysis, found: C,64.3; H,3.3; N,15.5%; $C_{24}H_{16}N_5F_3O$ requires C,64.4; H,3.6; N,15.7%;

(Example 50): 2-Methoxymethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 169-171°C; NMR (d_6 -DMSO): 3.50(s,3H), 4.98(s,2H), 5.67(s,2H), 7.22(d,2H), 7.54-7.74(m,7H), 7.84(t,1H), 8.08(t,1H), 8.32-8.38(m,2H); mass spectrum (-ve FAB,

DMSO/GLY): 422 (M-H)⁻; microanalysis, found; C,65.2; H,4.8; N,15.2%;
C₂₅H₂₁N₅O₂.HCl requires C,65.3; H,4.8; N,15.2%;

(Example 51): 2-Ethoxymethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 164-166°C; NMR (d₆-DMSO): 1.25(t,3H), 3.68(q,2H), 4.99(s,2H), 5.68(s,2H), 7.21(d,2H), 7.54-7.72(m,7H), 7.84(t,1H), 8.08(t,1H), 8.34(d,2H); mass spectrum (-ve FAB, DMSO/GLY): 436(M-H)⁻; microanalysis, found; C,65.6; H,5.2; N,14.4%; C₂₆H₂₃N₅O₂.HCl requires C,65.9; H,5.1; N,14.8%;

(Example 52): 2,3-Dimethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 155-156°C (dec); NMR (d₆-DMSO): 2.35(s,3H), 2.95(s,3H), 5.38(s,2H), 7.16(d,2H), 7.47(d,2H), 7.53-7.76(m,4H), 7.85(t,1H), 8.05(dt,1H), 8.19(d,1H), 8.38(d,1H); mass spectrum (+ve FAB, DMSO/NBA): 408 (M+H)⁺; microanalysis, found: C,66.8; H,4.9; N,15.3%; C₂₅H₂₁N₅O.HCl.0.25CH₃OH requires C,67.1; H,5.1; N,15.5%;

(Example 53): 2-(3,3,3-Trifluoropropyl)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 204-206°C (dec); NMR (d₆-DMSO): 2.92-3.14(m,2H), 3.40-3.51(m,2H), 5.64(s,2H), 7.21(d,2H), 7.50-7.64(m,4H), 7.65-7.87(m,4H), 8.08(t,1H), 8.25-8.35(m,2H); mass spectrum (+ve FAB, DMSO/NBA): 476 (M+H)⁺; microanalysis, found: C,60.8; H,3.9; N,13.7%; C₂₆H₂₀N₅F₃O.HCl requires C,61.0; H,4.1; N,13.7%;

(Example 54): 2-Hydroxymethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, m.p. 199-201°C (dec); NMR (d₆-DMSO): 5.07(s,2H), 5.66(s,2H), 7.22(d,2H), 7.53-7.63(m,4H), 7.65-7.75(m,3H), 7.83(t,1H), 8.09(t,1H), 8.32(d,1H), 8.39(d,1H); mass spectrum (-ve FAB, DMSO/GLY): 408 (M-H)⁻; microanalysis, found: C,64.2; H,4.7; N,15.5%; C₂₄H₁₉N₅O₂.HCl requires C,64.6; H,4.5; N,15.7%;

The necessary starting materials of formula III used in Examples 32-53 were obtained in yields of 20-70% using an analogous procedure to that described in Example 7 but starting from the appropriate quinolones of formula IV. The compounds of formula III had the following properties:-

(32): 2-Ethyl-6-methylthio-4-[(2'-(2-triphenylmethyl-2H-tetrazol-

-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 164-166°C; NMR: 1.37(t,3H), 2.50(s,3H), 2.92(q,2H), 5.19(s,2H), 6.70(s,1H), 6.91-6.95(m,6H), 7.19-7.34(m,14H), 7.44-7.60(m,4H), 7.89-7.99(m,2H); ¹³C NMR: (benzylic CH₂) 69.82;

(33): 2-Ethyl-7-hydroxymethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 99-102°C; NMR(d₆-DMSO): 1.29(t,3H), 2.82(q,2H), 5.10(s,2H), 5.31(s,2H), 6.84-6.93(m,6H), 7.02(s,1H), 7.15(d,2H), 7.27-7.38(m,9H), 7.44(d,2H), 7.48-7.83(m,7H);

(34): 2-Ethyl-6-methylsulphonyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.19(t,3H), 2.76(q,2H), 2.89(s,3H), 5.03(s,2H), 6.61(s,1H), 6.72-6.77(m,6H), 7.00-7.12(m,13H), 7.22-7.35(m,3H), 7.74-7.78(m,1H), 7.85-7.98(m,2H), 8.67(s,1H); ¹³C NMR: (benzylic CH₂) 70.52;

(35): 2-Ethyl-6,7-methylenedioxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR 1.38(t,3H), 2.90(q,2H), 5.15(s,2H), 6.09(s,2H), 6.65(s,1H), 6.88-6.98(m,6H), 7.16-7.55(m,19H), 7.96-8.03(m,1H); ¹³C NMR (benzylic CH₂) 69.75;

(36): 2-Ethyl-6-(2-fluoroethoxy)-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 173-175°C; NMR: 1.30(t,3H), 2.84(q,2H), 4.03-4.19(m,2H), 4.51-4.74(m,2H), 5.11(s,2H), 6.64(s,1H), 6.85-6.90(m,6H), 7.12-7.46(m,18H), 7.85-7.89(m,2H); ¹³C NMR: (benzylic CH₂) 69.93;

(37): 7-Carboethoxy-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 160-163°C; NMR (d₆-DMSO): 1.33(t,3H), 1.38(t,3H), 2.92(q,2H), 4.38(q,2H), 5.35(s,2H), 6.84-6.89(m,6H), 7.16(d,2H), 7.21(s,1H), 7.29-7.31(m,9H), 7.42(d,2H), 7.52-7.65(m,3H), 7.83-7.89(m,2H), 8.10(d,1H), 8.46(d,1H);

(38): 2-Ethyl-6-(2,2,2-trifluoroethoxy)-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 147-149°C; NMR: 1.40(t,3H), 2.95(q,2H), 4.38(q,2H), 5.21(s,2H), 6.73(s,1H), 6.92-7.00(m,6H), 7.21-7.55(m,18H), 7.93-8.00(m,2H); ¹³C NMR: (benzylic CH₂) 70.00;

(39): 6-Carboxamido-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.31(t,3H), 2.87(q,2H), 5.38(s,2H), 6.82-6.89(m,6H), 7.13(d,2H), 7.31-7.34(m,9H), 7.45(d,2H), 7.54-7.63(m,3H), 7.80-7.94(m,3H),

- 8.14(dd,1H), 8.70(d,1H);
(40): 2-Ethyl-6-trifluoromethoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 144-146°C; NMR: 1.38(t,3H), 2.95(q,2H), 5.18(s,2H), 6.75(s,1H), 6.90-6.97(m,6H), 7.20-7.32(m,13H), 7.39-7.55(m,4H), 7.95-8.05(m,3H); ¹³C NMR: (benzylic CH₂) 70.22;
(41): 6-Cyano-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 178-179°C; NMR (d₆-DMSO): 1.33(t,3H), 2.92(q,2H), 5.36(s,2H), 6.80-6.90(m,6H), 7.16-8.02(m,20H), 8.42(s,1H);
(42): 2-Ethyl-6-formyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 164-166°C; NMR (d₆-DMSO): 1.34(t,3H), 2.92(q,2H), 5.40(s,2H), 6.85-6.91(m,6H), 7.17-7.33(m,13H), 7.46-7.66(m,4H), 7.82(dd,1H), 8.05(dq,2H), 8.59(d,1H), 9.91(s,1H);
(43): 6-Dimethylamino-2-ethyl-4-([2'-2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR (d₆-DMSO): 1.28(t,3H), 2.83(q,2H), 2.94(s,6H), 5.35(s,2H), 6.82-6.94(m,6H), 6.98(s,1H), 7.08(d,1H), 7.15(d,2H), 7.27-7.40(m,9H), 7.41-7.70(m,6H), 7.72-7.84(m,2H);
(44): 2-Ethyl-6-nitro-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR (d₆-DMSO): 1.34(t,3H), 2.94(q,2H), 5.42(s,2H), 6.84-6.89(m,6H), 7.18(d,2H), 7.30-7.36(m,9H), 7.42-7.65(m,6H), 7.84(d,1H), 8.07(d,1H), 8.41(dd,1H), 8.88(d,1H);
(45): 6-Cyano-2-methyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, m.p. 188°C (dec.); NMR (d₆-DMSO): 2.65(s,3H), 5.35(s,2H), 6.82-6.89(m,6H), 7.16-7.34(m,13H), 7.43-7.67(m,4H), 7.86(dd,1H), 7.98(s,2H), 8.42(s,1H);
(46): 2-Ethyl-6-fluoro-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 183-184°C; NMR: 1.40(t,3H), 2.95(q,2H), 5.18(s,2H), 6.75(s,1H), 6.87-6.98(m,6H), 7.17-7.35(m,13H), 7.36-7.58(m,4H), 7.70(dd,1H), 7.93-8.05(m,2H); microanalysis, found: C,78.8; H,5.1; N,10.5%; C₄₄H₃₄N₅FO requires C,79.1; H,5.1; N,10.5%;
(47): 2-Ethyl-6-isopropoxy-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as a foam; NMR: 1.35(d,6H), 1.38(t,3H), 2.90(q,2H), 4.64(m,1H), 5.19(s,2H), 6.69(s,1H), 6.90-6.98(m,6H), 7.15-7.35(m,14H), 7.38-7.55(m,4H),

7.92(d,1H), 7.95(dd,1H);

(48): 5-Chloro-2-ethyl-4-([2'-(triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 180-181°C (dec.); NMR (d_6 -DMSO): 1.3(t,3H), 2.85(q,2H), 5.35(s,2H), 6.80-6.92(m,6H), 7.13(t,3H), 7.23-7.37(m,9H), 7.40-7.67(m,7H), 7.74-7.88(m,2H);

(49): 2-Trifluoromethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as an amorphous solid; NMR (d_6 -DMSO): 5.48(s,2H), 6.8-6.94(m,6H), 7.19(d,2H), 7.24-7.38(m,9H), 7.4-7.69(m,7H), 7.8-7.94(m,2H), 8.07-8.17(m,2H); ^{13}C NMR: (benzylic CH_2) 70.45;

(50): 2-Methoxymethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 174-176°C; NMR: 3.52(s,3H), 4.73(s,2H), 5.19(s,2H), 6.89-6.94(m,6H), 7.06(s,1H), 7.18-7.30(m,13H), 7.30-7.53(m,4H), 7.69(dt,1H), 7.98(m,2H), 8.14(dd,1H); microanalysis, found: C,78.7; H,5.2; N,10.4%; $C_{44}H_{35}N_5O_2 \cdot 0.25H_2O$ requires C,78.9; H,5.3; N,10.5%;

(51): 2-Ethoxymethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 156-158°C; NMR: 1.29(t,3H), 3.66(q,2H), 4.77(s,2H), 5.20(s,2H), 6.90-6.94(m,6H), 7.09(s,1H), 7.18-7.29(m,13H), 7.30-7.53(m,4H), 7.68(dt,1H), 7.96-8.03(m,2H), 8.14(dd,1H); microanalysis, found: C,79.0; H,5.5; N,10.3%; $C_{45}H_{37}N_5O_2$ requires C,79.5; H,5.5; N,10.3%;

(52): 2,3-Dimethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 170-172°C; NMR: 2.37(s,3H), 2.73(s,3H), 4.95(s,2H), 6.90-6.99(m,6H), 7.18-7.35(m,13H), 7.37-7.58(m,4H), 7.64(dt,1H), 7.95-8.07(m,3H);

(53): 2-(3,3,3-Trifluoropropyl)-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, isolated as an amorphous solid, m.p. 182-184°C; NMR (d_6 -DMSO): 2.7-3.0(m,2H), 3.05-3.20(m,2H), 5.32(s,2H), 6.80-6.90(m,6H), 7.12-7.65(m,18H), 7.70(dt,1H), 7.87(dt,2H), 8.03(d,1H);

The starting material used in Example 54 was obtained as follows:-

(i) Using an analogous procedure to that described in Example 7 but starting from the appropriate quinolone of formula IV, there was thus obtained 2-ethoxycarbonyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-

5-yl)biphenyl-4-yl]methoxy)quinoline; m.p. 146-147°C (dec.); NMR: 1.51(t,3H), 4.57(q,2H), 5.23(s,2H), 6.89-6.94(m,6H), 7.18-7.30(m,13H), 7.40-7.53(m,4H), 7.68(s,1H), 7.75(dt,1H), 8.0(m,1H), 8.17(d,1H), 8.26(d,1H).

(ii) Lithium borohydride (11 mg) was added to a solution of 2-ethoxycarbonyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline (346 mg) in tetrahydrofuran (4 ml) and the mixture stirred for 18 hours. Water (20 ml) was added to the mixture and a white solid precipitated. The solid was collected by filtration, dissolved in ethyl acetate and the solution dried (MgSO₄). The solvent was removed by evaporation and the residue crystallised from ethyl acetate/hexane to give 2-hydroxymethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline (213 mg), as a white crystalline solid, m.p. 183-185°C (dec.); NMR: 4.85(s,2H), 5.18(s,2H), 6.70(s,1H), 6.85-6.98(m,6H), 7.15-7.35(m,13H), 7.35-7.58(m,4H), 7.70(dt,1H), 7.95-8.08(m,2H), 8.15(d,1H); microanalysis, found: C,78.7; H,4.7; N,10.7%; C₄₃H₃₃N₅O₂ requires C,79.2; H,5.1; N,10.7%.

Example 55

Using an analogous procedure to that described in Example 7, but starting from 6-(tert-butyloxycarbonyl)aminomethyl-2-ethyl-4-([2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methoxy)quinoline, itself isolated as a foam [NMR: 1.40(t,3H), 1.45(s,9H), 2.96(q,2H), 4.37(d,2H), 4.83(brs,1H), 5.18(s,2H), 6.89-6.99(m,6H), 7.18-7.35(m,14H), 7.40-7.55(m,3H), 7.62(dd,1H), 7.92-8.02(m,3H); ¹³C NMR: (benzylic CH₂) 70.02] starting from 6-(tert-butyloxycarbonyl)-aminomethyl-2-ethyl-4-quinolone, there was thus obtained 6-aminomethyl-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]-quinoline dihydrochloride, m.p. 150-153°C; NMR (d₆-DMSO): 1.45(t,3H), 3.20(q,2H), 4.22-4.33(m,2H), 5.69(s,2H), 7.23(d,2H), 7.52-7.75(m,7H), 8.17(dd,1H), 8.34-8.46(m,2H), 8.62(brs,2H); mass spectrum (+ve FAB, DMSO/NBA): 437 (M+H)⁺; microanalysis, found: C,57.9; H,5.7; N,14.4; Cl,14.5; H₂O, 3.7%; C₂₆H₂₄N₆O.2.25HCl.1.25H₂O.0.25(C₂H₅)₂O requires C,57.9; H,5.5; N,15.0; Cl,14.3; H₂O, 4.0%.

Using an analogous procedure to that described in Org. Syn.,

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1955, Coll. Vol. III, pages 374 and 593, the following quinolones used in Examples 31, 32, 35-47 and 49-54 may be obtained in yields of 20-60%:-

- 2-Ethyl-6-(tert-butyldimethylsilyloxy)-4-quinolone, m.p. 197-198°C;
- 2-Ethyl-6-methylthio-4-quinolone, m.p. 196-199°C;
- 2-Ethyl-6,7-methylenedioxy-4-quinolone, m.p. 250°C (dec.);
- 2-Ethyl-6-(2-fluoroethoxy)-4-quinolone, m.p. 267-269°C;
- 7-Carboethoxy-2-ethyl-4-quinolone, m.p. 220-223°C;
- 2-Ethyl-6-(2,2,2-trifluoroethoxy)-4-quinolone, m.p. 260°C (dec.);
- 6-Carboxamido-2-ethyl-4-quinolone, m.p. >300°C;
- 2-Ethyl-6-trifluoromethoxy-4-quinolone, m.p. 258-260°C;
- 6-Cyano-2-ethyl-4-quinolone, m.p. 290°C (dec.);
- 2-Ethyl-6-formyl-4-quinolone, m.p. 285°C (dec.);
- 6-Dimethylamino-2-ethyl-4-quinolone, m.p. 237-239°C;
- 2-Ethyl-6-nitro-4-quinolone, m.p. >280°C;
- 6-Cyano-2-methyl-4-quinolone, m.p. 297-8°C;
- 2-Ethyl-6-fluoro-4-quinolone, m.p. 243-245°C;
- 2-Ethyl-6-isopropoxy-4-quinolone, m.p. 174-177°C;
- 2-Trifluoromethyl-4-quinolone, m.p. 210-212°C;
- 2-Methoxymethyl-4-quinolone, m.p. 186-188°C;
- 2-Ethoxymethyl-4-quinolone, m.p. 146°C;
- 2,3-Dimethyl-4-quinolone, m.p. >300°C;
- 2-Ethoxycarbonyl-4-quinolone, m.p. 214-215°C;
- 2-(3,3,3-Trifluoropropyl)-4-quinolone, m.p. 240-242°C.

2-Ethyl-7-hydroxymethyl-4-quinolone used in Example 33 was obtained as follows:-

Lithium aluminium hydride (0.6 g) was added to a solution of 7-carboethoxy-2-ethyl-4-quinolone (2.65 g) in THF (200 ml) and the resulting suspension stirred for 2 hours at ambient temperature. Water (100 ml) was slowly added, followed by ethyl acetate (100 ml). The suspension was filtered and washed with ethyl acetate (100 ml). The phases of the filtrate were separated and the aqueous layer re-extracted with ethyl acetate (100 ml). The combined organic phases were dried ($MgSO_4$) and evaporated to give a solid which on recrystallisation from ethyl acetate gave 2-ethyl-7-hydroxymethyl-4-quinolone as a white powder, m.p. 254-257°C.

2-Ethyl-6-methylsulphonyl-4-quinolone used in Example 34 was obtained as follows:-

Oxone (920 mg) was added to a solution of 2-ethyl-6-methylthio-4-quinolone (220 mg) in methanol (10 ml) and water (1 ml). The suspension was stirred at ambient temperature for 1 hour then evaporated to give a yellow solid. Saturated sodium bicarbonate solution (10 ml) was added and the resulting precipitate collected by filtration and dried to give 2-ethyl-6-methylsulphonyl-4-quinolone (150 mg) as a light yellow powder, m.p. 283°C.

5-Chloro-2-ethyl-4-quinolone used in Example 48 was obtained as follows:-

A mixture of 4-benzyloxy-5-chloro-2-ethyl quinoline (A) (1.8 g) and a solution of hydrogen bromide in acetic acid (45% v/v; 30 ml) was heated at 100°C for 4 hours. The mixture was diluted with ice/water and basified to pH 9 with 5M aqueous sodium hydroxide solution, when a solid precipitated. The mixture containing the solid precipitate was extracted with ethyl acetate (50 ml), and the solid was then collected by filtration. The solid was purified by flash chromatography, eluting with methanol/dichloromethane (4:96 v/v) to give 5-chloro-2-ethyl-4-quinolone as a white solid, m.p. 236-239°C; NMR (d_6 -DMSO): 1.25(t,3H), 2.58(q,2H), 5.89(s,1H), 7.2(dd,1H), 7.42-7.53(m,2H), 11.4(brs,1H); microanalysis, found: C,63.2; H,4.8; N,6.6%; $C_{11}H_{10}NClO$ requires C,63.6; H,4.8; N,6.8%.

The starting material (A) was obtained as follows:-

Sodium hydride (60% dispersion in mineral oil; 1.95 g) was added to a stirred solution of a mixture of 7-chloro-2-ethyl-4-quinolone and 5-chloro-2-ethyl-4-quinolone (43.5:56.5, 10 g) in DMF (100 ml). The mixture was stirred until evolution of hydrogen had ceased and benzylbromide (8.25 g) was added. The mixture was stirred for 18 hours. The solvent was removed by evaporation and the residue partitioned between water (80 ml) and dichloromethane (2 x 100 ml). The organic layer was washed with saturated sodium chloride solution (50 ml) and dried ($MgSO_4$). The solvent was removed by evaporation and the resultant yellow oil was purified by flash chromatography, eluting with increasing concentration of ethyl acetate in dichloromethane.

The product was eluted with ethyl acetate/dichloromethane (10:90 v/v) to give 4-benzyloxy-5-chloro-2-ethylquinoline as a white solid (2.6 g), m.p. 78-80°C; NMR: 1.39(t,3H), 2.94(q,2H), 5.38(s,2H), 6.72(s,1H), 7.30-7.55(m,6H), 8.0(d,1H), 8.13(d,1H).

6-(tert-butyloxycarbonyl)aminomethyl-2-ethyl-4-quinolone used in Example 55 was obtained as follows:-

Cobalt (II) chloride (2.87 g) was added to a suspension of 2-ethyl-6-cyano-4-quinolone (1.2 g) in methanol (100 ml). Sodium borohydride (2.24 g) was added in small portions to the resulting purple suspension and the mixture stirred for 2 hours during which time a colloidal precipitate appeared. Excess borohydride was destroyed by careful acidification with 2M hydrochloric acid and the mixture was then made basic with 1M sodium hydroxide solution. Di-tert-butyl dicarbonate (1.32 g) was added to the resulting slurry and stirring was continued for 1 hour. The slurry was filtered through diatomaceous earth and washed with methanol (100 ml). The filtrate was evaporated and the residue was extracted with dichloromethane, dried (MgSO₄) and evaporated to give a cream foam. Trituration with diethyl ether gave 6-(tert-butyloxycarbonyl)-aminomethyl-2-ethyl-4-quinolone (1.2 g) as a cream powder, m.p. 228°C (dec.).

Example 56

Using an analogous procedure to that described in Example 7, but starting from 4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-yl)methoxy]quinoline (A), there was obtained in 60% yield 4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline hydrochloride, as a white solid, m.p. 162-164°C; NMR (d₆-DMSO): 5.7(s,2H), 7.2(d,2H), 7.45-7.8(complex m,7H), 7.9(t,1H), 8.1(dt,1H), 8.3(dt,2H), 9.2(dd,1H); mass spectrum (-ve FAB, DMSO/GLY): 378 (M-H)⁻; microanalysis, found: C,66.6; H,4.2; N,16.4%; C₂₃H₁₇N₅O.HCl requires: C,66.4; H,4.3; N,16.8%.

The starting material (A) was obtained as follows:-

(i) Powdered potassium acetate (17.5 g) was added to a solution of 5-[2-(4'-bromomethylbiphenyl)]-2-triphenylmethyl-2H-tetrazole (50

g) (obtained as described in European Patent Application, Publication No. 0291969) and 1,4,7,10,13,16-hexaoxacyclooctadecane (100 mg) in 1,2-dimethoxyethane (DME) (600 ml), and the mixture was heated under reflux for 20 hours. Insoluble material was removed by filtration, and the residue triturated with a mixture of ethyl acetate and hexane (1:4 v/v) to give 5-[2-[4'-acetoxymethylbiphenyl]-2-triphenylmethyl-2H-tetrazole (B) (41.8 g), as a cream powder, m.p. 119-121°C; NMR (CDCl₃): 2.1(s,3H), 5.0(s,2H), 6.8-6.95(complex m,8H), 7.2-7.55(complex m,14H), 7.9-8.0(m,1H).

(ii) A solution of compound (B) (41.8 g) in tetrahydrofuran (THF) (200 ml) was added over a period of 40 minutes to a suspension of lithium borohydride (4.1 g) in THF (400 ml) stirred at 0°C under an atmosphere of argon. The mixture was stirred at ambient temperature for 20 hours and then cooled to 0°C. 20% Aqueous citric acid solution (40 ml) was added and the mixture was diluted with saturated sodium chloride solution (600 ml). The mixture was extracted with ethyl acetate (2 x 500 ml) and the extracts were washed with water (500 ml) and saturated sodium chloride solution (500 ml). The extracts were dried (MgSO₄) and volatile material removed by evaporation. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (2:3 v/v), to give 5-[2-(4'-hydroxymethylbiphenyl)]-2-triphenylmethyl-2H-tetrazole (C) (17.4 g), as a white solid, m.p. 168-169°C (after recrystallisation from a mixture of ethyl acetate and hexane (1:9 v/v)); NMR (CDCl₃): 4.6(s,2H), 6.85-7.0(m,6H), 7.2-7.5(complex m,16H), 7.9-8.0(m,1H).

(iii) Sodium hydride (60% dispersion in mineral oil; 80 mg) was added to a stirred solution of compound (C) (0.99 g) in DMF (10 ml). The mixture was stirred until evolution of hydrogen ceased and then 4-chloroquinoline (0.33 g) was added. The mixture was stirred for 24 hours, poured into water (100 ml) and extracted with ethyl acetate (2 x 50 ml). The extracts were washed with water (40 ml) and saturated sodium chloride solution (40 ml) and then dried (MgSO₄). Volatile material was removed by evaporation and the residue purified by flash chromatography, eluting with ethyl acetate/hexane (1:1 v/v), to give 4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methoxy]-quinoline (A) (0.80 g), as a foam; NMR (CDCl₃): 5.2(s,2H), 6.8(d,1H), 6.85-6.95(m,6H), 7.15-7.55(complex m,17H), 7.7(t,1H), 7.95-8.25(m,3H),

8.7(d,1H).

Example 57 (Note: all parts by weight)

The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) Capsule (for oral administration)

| | |
|---------------------|-------|
| Active ingredient * | 20 |
| Lactose powder | 578.5 |
| Magnesium stearate | 1.5 |

b) Tablet (for oral administration)

| | |
|--------------------------------|------|
| Active ingredient * | 50 |
| Microcrystalline cellulose 400 | |
| Starch (pregelatinised) | 47.5 |
| Magnesium stearate | 2.5 |

c) Injectable Solution (for intravenous administration)

| | |
|-------------------------------------|------------|
| Active ingredient * | 0.05 - 1.0 |
| Propylene glycol | 5.0 |
| Polyethylene glycol (300) 3.0 - 5.0 | |
| Purified water | to 100% |

d) Injectable Suspension (for intramuscular administration)

| | |
|-----------------------|------------|
| Active ingredient * | 0.05 - 1.0 |
| Methylcellulose | 0.5 |
| Tween 80 | 0.05 |
| Benzyl alcohol | 0.9 |
| Benzalkonium chloride | 0.1 |
| Purified water | to 100% |

Note: the active ingredient * may typically be an Example described hereinbefore and will conveniently be present as a pharmaceutically acceptable acid-addition salt, such as the hydrochloride salt. Tablets and capsules formulations may be coated in conventional manner

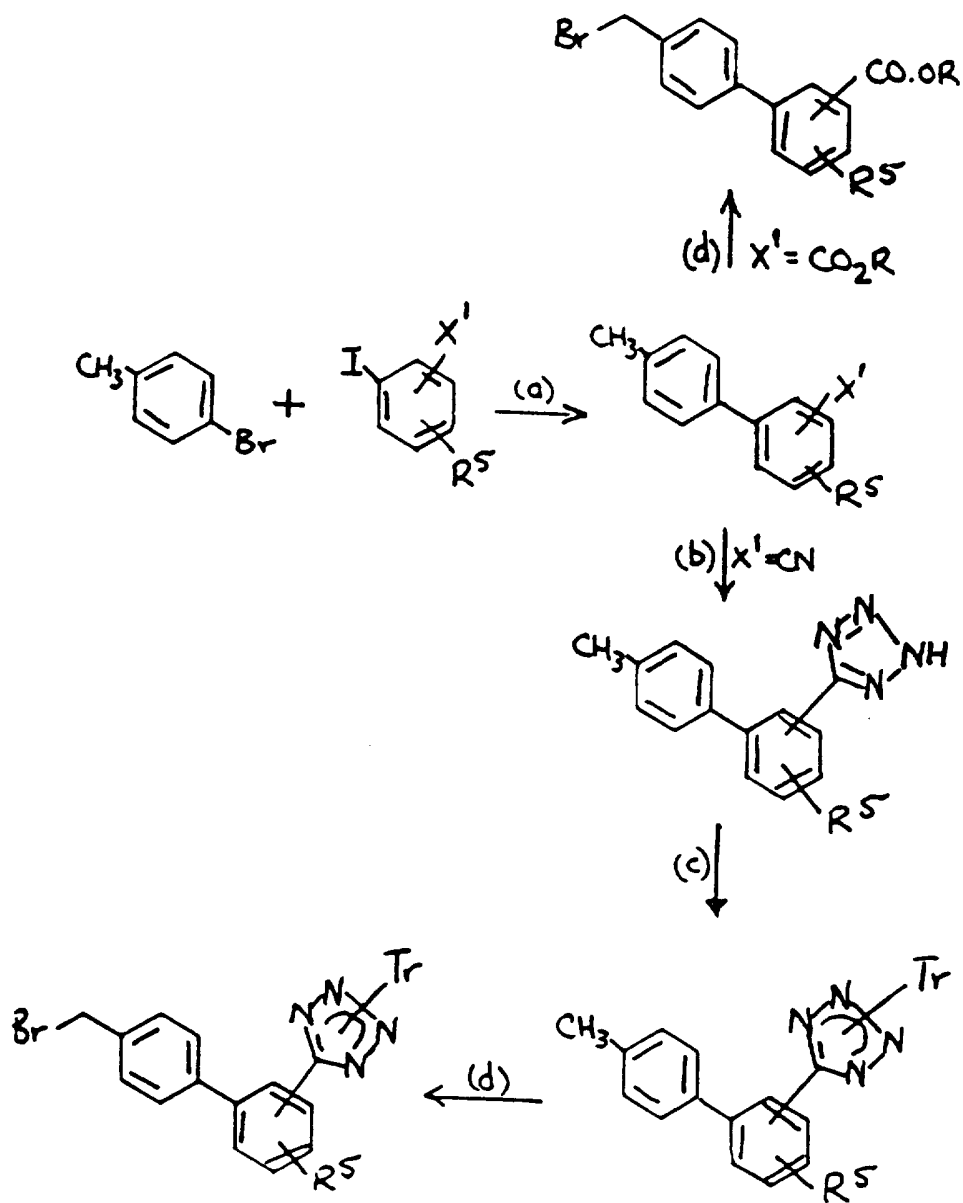
in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.

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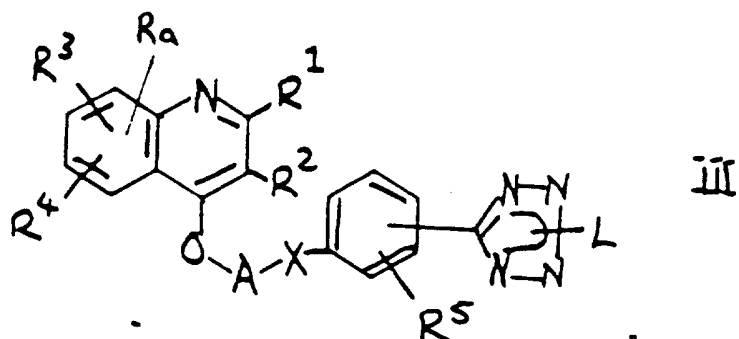
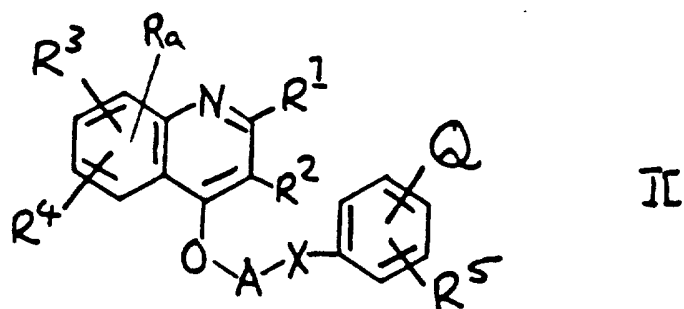
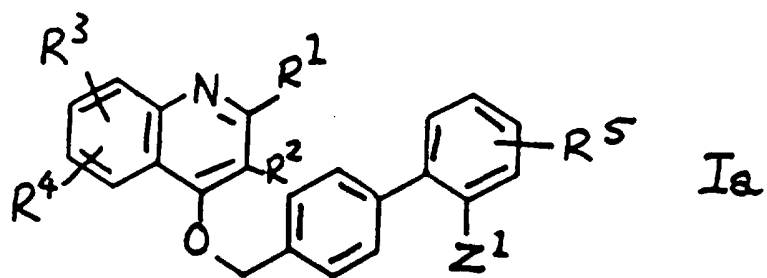
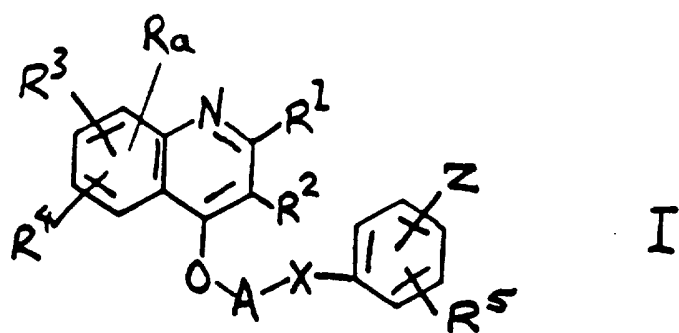
Scheme 1



Note: R = lower alkyl, benzyl, phenyl; Tr = triphenylmethyl (trityl)

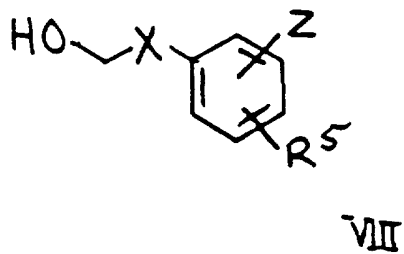
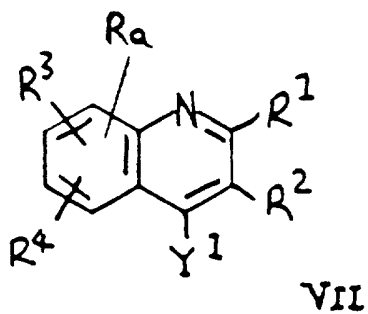
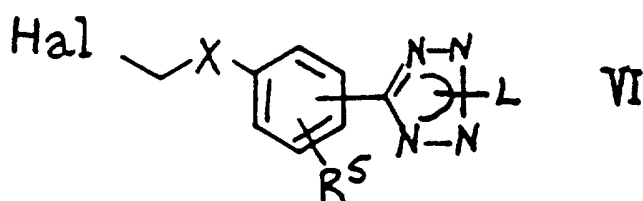
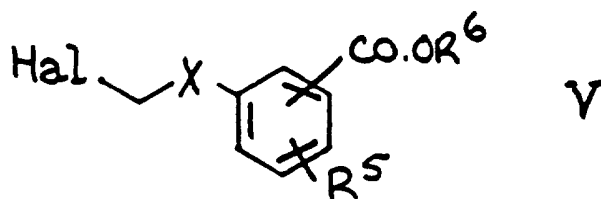
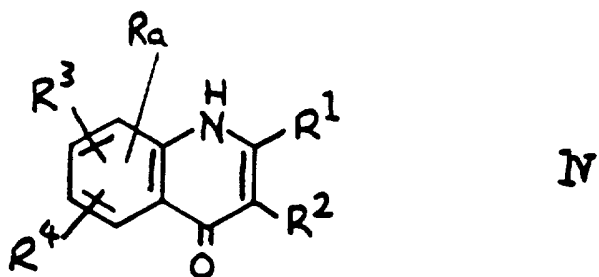
Reagents: a) BuLi/THF; ZnCl₂/Et₂O; Pd(Ph₃P)₄
b) Bu₃Sn.N₃/toluene; HCl/toluene
c) Tr.Cl/Et₃N/CH₂Cl₂
d) N-bromosuccinimide/azoisobutyronitrile/CCl₄

Chemical Formulae



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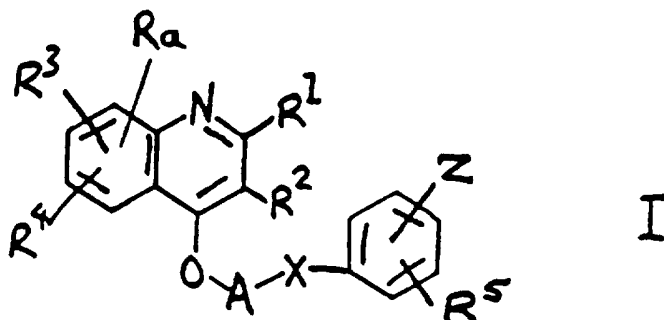
Chemical Formulae
(continued)



CLAIMS

What we claim is :-

1. A quinoline derivative of the formula I



wherein R¹ is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, hydroxy, (1-4C)alkoxy or phenyl substituent; R² is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, carboxy, (1-4C)alkoxycarbonyl, cyano, nitro, phenyl or phenyl(1-4C)alkyl; R³ and R⁴ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, fluoro(1-4C)alkoxy, halogeno, hydroxy, trifluoromethyl, cyano, nitro, amino, (1-4C)alkanoylamino, alkylamino and dialkylamino of up to 6 carbon atoms, dialkylamino-alkyl of 3 to 8 carbon atoms, (1-4C)alkanoyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, carboxy, (1-4C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, and substituted (1-4C)alkyl, the latter bearing an amino, hydroxy or (1-4C)alkoxy substituent; or R³ and R⁴ together form (1-4C)alkylenedioxy attached to adjacent carbon atoms of the benzene moiety of formula I; Ra and R⁵ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; A is methylene; X is phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro, or X is a direct bond between the adjacent phenyl group and moiety A; Z is 1H-tetrazol-5-yl, -CO.NH.(1H-tetrazol-5-yl) or a group of the formula -CO.OR⁶ or -CO.NH.SO₂.R⁷ in which R⁶ is hydrogen or a non-toxic, biodegradable residue of a physiologically acceptable alcohol or

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phenol, and R⁷ is (1-6C)alkyl, (3-8C)cycloalkyl or phenyl; and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof; but excluding methyl 2-[(3-methoxycarbonylquinolin-4-yloxy)-methyl]benzoate.

2. A compound as claimed in claim 1 wherein R¹ is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl, or 2-phenylethyl; R² is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentyl-ethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, cyano, nitro, phenyl, benzyl, 1-phenylethyl or 2-phenylethyl; R³ and R⁴ are independently selected from hydrogen, methyl, ethyl, methoxy, ethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, cyano, nitro, amino, formamido, acetamido, propanamido, methylamino, ethylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dimethylaminomethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-(diethylamino)propyl, formyl, acetyl, butyryl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, methylthio, ethylthio, butylthio, methylsulphinyl, ethylsulphinyl, butylsulphinyl, methylsulphonyl, ethylsulphonyl, butylsulphonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, 2-methoxyethyl and 2-ethoxyethyl; or R³ and R⁴ together form methylenedioxy or ethylenedioxy attached to adjacent carbon atoms of the benzene moiety of formula I; R_a and R⁵ are independently selected from hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, cyano and nitro; X is phenylene optionally bearing a substituent selected from methyl,

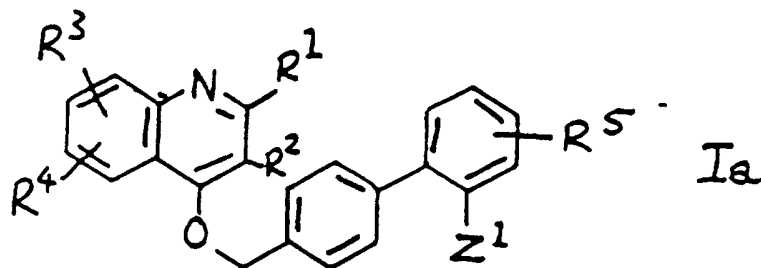
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ethyl, methoxy, ethoxy, fluoro, chloro, bromo, iodo, trifluoromethyl, cyano and nitro, or X is a direct bond between the adjacent phenyl group and moiety A; R⁶ is hydrogen or a residue derived from a (1-6C)alkanol, or phenol or glycerol; and R⁷ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclobutyl, cyclopentyl, cyclohexyl or phenyl; and wherein any of said phenyl moieties may be unsubstituted or bear one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, cyano and trifluoromethyl.

3. A compound as claimed in claim 1 wherein R¹ is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl; R³, R⁴ and R⁵ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; and Ra is hydrogen.

4. A compound as claimed in claim 1 wherein R³ and R⁴ are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, fluoro(1-4C)alkoxy, halogeno, trifluoromethyl, cyano, nitro, amino, (1-4C)alkanoylamino, alkylamino and dialkylamino of up to 6 carbon atoms, dialkylamino-alkyl of 3 to 8 carbon atoms, (1-4C)alkanoyl, carbamoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, carboxy, (1-4C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, and substituted (1-4C)alkyl, the latter bearing an amino, hydroxy or (1-4C)alkoxy substituent; or R³ and R⁴ together form (1-4C)alkylenedioxy attached to adjacent carbon atoms of the benzene moiety of formula I; and Ra is hydrogen.

5. A compound of the formula Ia



wherein R¹, R², R³ and R⁴ have any of their meanings as defined in any of claims 1-4, R⁵ is hydrogen and Z¹ is carboxy or 1H-tetrazol-5-yl; together with the non-toxic salts thereof.

6. A compound as claimed in any of claims 1, 2 and 5 wherein the quinoline moiety together with the attached substituents R¹, R², R³ and R⁴, and Ra when present, is selected from 2-methylquinoline, 2-ethylquinoline, 2-ethyl-6-methoxyquinoline, 6,7-dimethoxy-2-ethylquinoline, 2-ethyl-5,6,7-trimethoxyquinoline, 2-ethyl-6-hydroxyquinoline, 2-ethyl-6-methylthioquinoline, 2-ethyl-7-hydroxymethylquinoline, 2-ethyl-6-(2-fluoroethoxy)quinoline, 2-ethyl-6-(2,2,2-trifluoroethoxy)quinoline, 2-ethyl-6-carboxamidoquinoline, 2-ethyl-6-fluoroquinoline, 2-ethyl-6-isopropoxyquinoline and 6-aminomethyl-2-ethylquinoline; and in which the substituent O.A.X- is attached at the 4-position of the quinoline ring.

7. A compound of the formula I selected from :-
2-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
6,8-dimethyl-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-6-methylthio-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-7-hydroxymethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-6-(2-fluoroethoxy)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-6-(2,2,2-trifluoroethoxy)-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
6-carboxamido-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
6-cyano-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-6-fluoro-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-6-isopropoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline; and

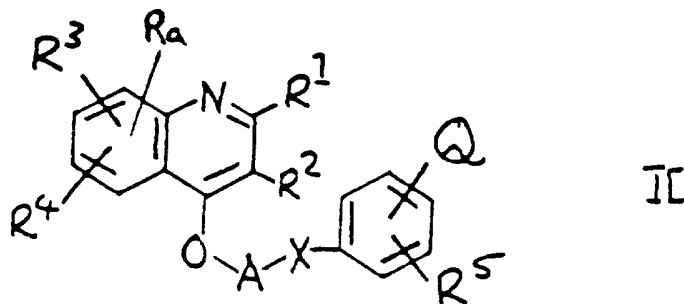
6-aminomethyl-2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]-quinoline;
and the non-toxic salts thereof.

8. A compound of the formula I selected from:-
2-methyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline;
2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]quinoline; and
2-ethyl-6-isopropoxy-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methoxy]-
quinoline; and the non-toxic salts thereof.

9. A salt as claimed in any one preceding claim which is selected from salts with acids forming physiologically acceptable anions and, for those compounds of formula I which are acidic, alkali metal, alkaline earth metal, aluminium and ammonium salts, and salts with organic bases affording physiologically acceptable anions.

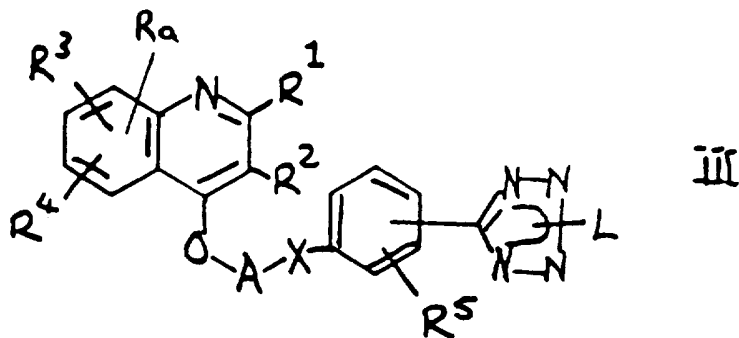
10. A process for the manufacture of a compound of formula I or a non-toxic salt thereof, as claimed in claim 1, 5, 7 or 8 which is characterised in that:-

(a) For those compounds in which Z is carboxy, a carboxylic acid derivative of the formula II



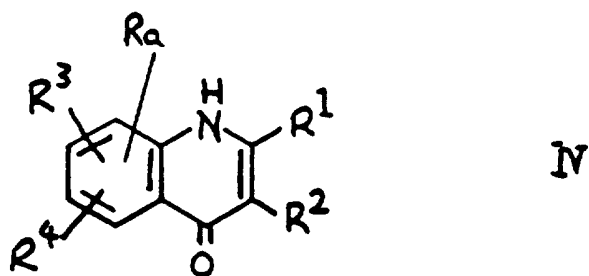
in which Q is a protected carboxy group selected from (1-6C)alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy;

(b) For those compounds of formula I wherein Z is tetrazolyl, a compound of the formula III

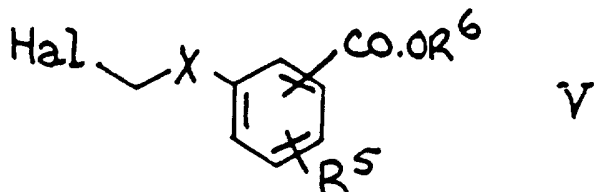


which L is a suitable protecting group affixed to a nitrogen of the triazolyl moiety, is deprotected;

A quinolone of the formula IV

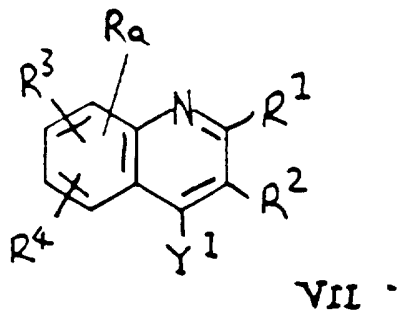


when R¹ is other than hydrogen is alkylated with a compound of the formula V

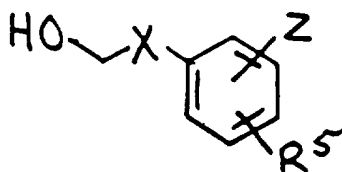


wherein Hal. stands for a suitable leaving group; or

A halogenoquinoline of the formula VII



wherein Y¹ is a halogeno group is reacted with an alcohol of the formula VIII



VII

whereafter: when a compound of the formula I is required wherein Z is 1H-tetrazol-5-yl, a compound of the formula I wherein Z is a group of the formula $-CO.OR^6$ is converted into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide;

when a compound of the formula I is required wherein Z is a group of the formula $-CO.NH.SO_2R^7$ or a group of the formula $-CO.OR^6$ in which R^6 is other than hydrogen, a carboxylic acid of the formula I in which Z is carboxy (or a reactive derivative of said acid) is reacted with a sulphonamide of the formula $NH_2.SO_2R^7$ or a hydroxy compound of the formula $HO.R^6$, or with a salt thereof;

when a non-toxic salt of a compound of formula I is required, it is obtained by reaction with the appropriate acid or base affording a physiologically acceptable ion, or by any other conventional salt formation procedure; and

when an optically active form of a compound of formula I is required, one of the aforesaid processes (a)-(d) is carried out using an optically active starting material, or the racemic form of a compound of formula I in which Z is an acidic group is resolved by reaction with an optically active form of a suitable organic base followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, and liberation of the required optically active form of said compound of formula I by conventional treatment with acid;

and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , Ra, A, X and Z have any of the meanings defined in any of claims 1-6 unless otherwise stated.

11. A pharmaceutical composition which comprises a compound of the formula I or Ia, or a non-toxic salt thereof, as claimed in any of claims 1 to 9, together with a pharmaceutically acceptable diluent or

carrier.

12. A compound of the formula II wherein R^1 , R^2 , R^3 , R^4 , R^5 , Ra, A and X have any of the meanings defined in any of claims 1-6, and Q is a protected carboxy group selected from (1-6C)alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl and carbamoyl.

13. A compound of formula III wherein R^1 , R^2 , R^3 , R^4 , R^5 , Ra, A and X have any of the meanings defined in any of claims 1-6, and L is a protecting group.

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Noted this 10th day of August 1990.


PATENT AGENT FOR THE APPLICANT