PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 453/02, A61K 31/435 — A1

(11) International Publication Number: **WO 94/14803**

(43) International Publication Date: 7 July 1994 (07.07.94)

(21) International Application Number: PCT/GB93/02614

(22) International Filing Date: 21 December 1993 (21.12.93)

(30) Priority Data:

9226574.3	21 December 1992 (21.12.92)	GB
9226576.8	21 December 1992 (21.12.92)	GB

(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; Imperial Chemical House, 9 Millbank, London SW1P 3JP (GB).

(72) Inventors; and

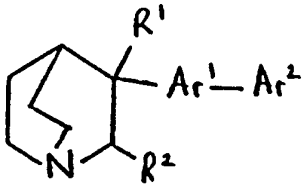
(75) Inventors/Applicants *(for US only)*: BROWN, George, Robert [GB/GB]; 11 Church Road, Wilmslow, Cheshire SK9 6HH (GB). MALLION, Keith, Blakeney [GB/GB]; 4 Aylesby Close, Knutsford, Cheshire WA16 8AE (GB).

(74) Agent: BILL, Kevin; ICI Group Patents Services Dept., PO Box 6, Shire Park, Bessemer Road, Welwyn Garden City, Hertfordshire AL7 1HD (GB).

(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: QUINUCLIDINE DERIVATIVES AS SQUALENE SYNTHASE INHIBITORS



(I)

(57) Abstract

Compounds of formula (I) in which R^1 is hydrogen or hydroxy; R^2 is hydrogen; or R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond; Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety; or Ar^1 is a heterocyclic moiety and Ar^2 is a phenyl moiety; and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives; provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms; when Ar^1 and Ar^2 are both hydrogen, Ar^2 is not an oxadiazole moiety; and their pharmaceutically acceptable salts are inhibitors of squalene synthase and hence useful in treating medical conditions in which a lowering of cholesterol is beneficial. Processes preparing these derivatives, pharmaceutical compositions containing them are also described together with their use in medicine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

QUINUCLIDINE DERIVATIVES AS SQUALENE SYNTHASE INHIBITORS

This invention concerns heterocyclic derivatives which are useful in inhibiting squalene synthase, processes for their preparation and pharmaceutical compositions containing them. The present invention is also concerned with methods of using such heterocyclic derivatives in treating diseases and medical conditions where inhibition of squalene synthase is desirable, for example in treating diseases or medical conditions such as hypercholesterolemia and atherosclerosis.

Several different classes of compounds have been reported to possess the capability of being able to lower cholesterol levels in blood plasma. For example agents which inhibit the enzyme HMG CoA reductase, which is essential for the production of cholesterol, have been reported to reduce levels of serum cholesterol. Illustrative of this class of compounds is the HMG CoA reductase inhibitor known as lovastatin which is disclosed in US Patent No 4,231,938. Other agents which are reported to lower serum cholesterol include those which act by complexing with bile acids in the intestinal system and which are hence termed "bile acid sequestrants". It is believed that many of such agents act by sequestering bile acids within the intestinal tract. This results in a lowering of the levels of bile acid circulating in the enteroheptatic system and promoting replacement of bile acids by synthesis in the liver from cholesterol, which results in an upregulation of the hepatic LDL receptor and hence in a lowering of circulating blood cholesterol levels.

Squalene synthase (also referred to in the art as squalene synthetase) is a microsomal enzyme which catalyses the first committed step of cholesterol biosynthesis. Two molecules of farnesyl pyrophosphate (FPP) are condensed in the presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) to form squalene. The inhibition of this committed step to cholesterol should leave unhindered biosynthetic pathways to ubiquinone, dolichol and isopentenyl t-RNA. Elevated cholesterol levels are known to be one of the main risk factors for ischaemic cardiovacsular disease. Thus, an agent which inhibits squalene synthase should be useful in treating diseases and medical conditions in which a reduction in the levels of cholesterol is desirable, for example hypercholesterolemia and atherosclerosis.

Thus far, the design of squalene synthase inhibitors has concentrated on the preparation of analogues of the substrate farnesyl pyrophosphate (FPP), and hence on compounds which contain phosphorus groups. For example, the preparation of phosphorous-containing squalene synthase inhibitors is reported in published European Patent Application No. 409,181; and the preparation of isoprenoid (phosphinylmethyl)phosphonates as inhibitors of squalene synthase is reported by Biller et al, J. Med. Chem., 1988, 31, 1869. Various quinuclidine derivatives have been reported in, for example, EP 307,142 and EP 316,718 to be muscarinic agonists. Recently certain quinuclidine derivatives have been reported (WO 92/15579 and US 5,135,935) to inhibit squalene synthase.

The present invention is based on the discovery that certain heterocyclic derivatives are inhibitors of squalene synthase, and are hence useful in treating diseases and medical conditions in which inhibition of squalene synthase is desirable.

According to the present invention there is provided a compound of formula I (formula set out hereinafter together with the other chemical formulae referred to herein), or a pharmaceutically acceptable salt thereof, wherein:
R^1 is hydrogen or hydroxy;
R^2 is hydrogen; or
R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;
Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety; or
Ar^1 is a heterocyclic moiety and Ar^2 is a phenyl moiety;
and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives;
provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or

two nitrogen atoms; when R^1 and R^2 are both hydrogen, Ar^1 is not an oxadiazole moiety; and excluding the compound 3-[5-(3-phenyl-1,2,4-thiadiazol)-yl]quinuclidine and its pharmaceutically acceptable salts.

It will be understood that when formula I compounds contain a chiral centre, the compounds of the invention may exist in, and be isolated in, optically active or racemic form. The invention includes any optically active or racemic form of a compound of formula I which possesses the beneficial pharmacological effect of inhibiting squalene synthase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by, resolution of a racemic form, by synthesis from optically active starting materials or by asymmetric synthesis.

It will also be understood that, insofar as certain of the compounds of the formula I may exhibit the phenomenon of tautomerism, for example a compound of formula I in which Ar^2 bears a hydroxy substituent, the present invention includes any tautomeric form of a compound of formula I which possesses the beneficial pharmacological effect of inhibiting squalene synthase.

It is also to be understood that generic terms such as "alkyl" include both the straight chain and branched chain groups such as butyl and tert-butyl. However, when a specific term such as "butyl" is used, it is specific for the straight chain or "normal" butyl group, branched chain isomers such as "t-butyl" being referred to specifically when intended.

It will also be appreciated that oxime derivatives of the (1-6C)alkanoyl group will comprise aldoximes and ketoximes of formula -C(Ra)=NOH (Ra is H or alkyl), and the O-alkyl ethers of these oximes will have the formula -C(Ra)=NORb (Ra is H or alkyl, and Rb is alkyl).

It will be appreciated that when R^1 and R^2 are joined so that CR^1-CR^2 is a double bond, the quinuclidine ring in formula I will comprise the 2,3-dehydroquinuclidine moiety shown in formula Ia.

When Ar^2 is a heterocyclic moiety, Ar^2 encompases monocyclic aromatic heterocycles which contains (in addition to carbon atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur; bicyclic aromatic heterocycles of about 8 to 10 ring atoms and containing

(in addition to carbon atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, and in particular, benz-derivatives of said monocyclic aromatic heterocycles, as well as bicyclic heterocycles which consist of a non-aromatic 5-membered or 6-membered heterocyclic ring containing (in addition to carbon atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur fused to a benzene ring; but does not encompass heteroaryl moieties which consist of an aromatic 6-membered ring containing one or two nitrogen atoms as ring atoms.

It will be appreciated that Ar^2 may be attached to Ar^1 through any available ring atom.

Suitable values for Ar^2, when a heterocyclic moiety, will therefore include, for example, an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, and an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur which is fused to a benzene ring.

When Ar^1 is a heterocyclic moiety, Ar^1 encompasses monocyclic aromatic heterocycles which contain (in addition to carbon atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur; bicyclic aromatic heterocycles of about 8 to 10 ring atoms and containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, and in particular, benz-derivatives of said monocyclic aromatic heterocycles; as well as bicyclic heterocycles which consist of a non-aromatic 5-membered or 6-membered heterocyclic ring containing (in addition to carbom atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur fused to a benzene ring. It will be appreciated that the heterocyclic moiety may be attached to Ar^2 and the quinuclidine moiety through any available ring atom.

Suitable values for Ar^1, when Ar^1 is a heterocyclic moiety, will therefore include, for example, an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitogen, oxygen and sulphur, and an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur which is fused to a benzene ring; a

non-aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur fused to a benzene ring.

Suitable values for Ar^1, when Ar^1 is a phenylene moiety, include 1,2-phenylene, 1,3-phenylene and 1,4-phenylene.

A particular value for an optional substituent which may be present on Ar^1 or Ar^2 is, for example,

for alkyl;	(1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or sec-butyl;
for alkenyl;	(2-4C)alkenyl, such as allyl, prop-2-enyl, but-2-enyl or 2-methyl-2-propenyl;
for alkynyl;	(2-4C)alkynyl, such as prop-2-ynyl or but-2-ynyl;
for alkoxy;	(1-4C)alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy;
for alkylamino;	(1-4C)alkylamino, such as methylamino, ethylamino, propylamino or butylamino;
for di-alkylamino;	di-[(1-4C)alkylamino, such as dimethylamino, diethylamino, methylpropylamino or dipropylamino;
for alkylcarbamoyl;	N-methylcarbamoyl, N-ethylcarbamoyl or N-propylcarbamoyl;
for di-alkylcarbamoyl;	N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl;
for alkoxycarbonyl;	methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl;
for alkylthio;	methylthio, ethylthio, propylthio, isopropylthio or butylthio;
for alkylsulphinyl;	methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl or butylsulphinyl;
for alkylsulphonyl;	methylsulphonyl, ethylsulphonyl, propylsulphonyl, isoproylsulphonyl or butylsulphonyl;
for halogeno;	fluoro, chloro, bromo or iodo;

for halogenoalkyl;	halogenoalkyl containing one, two or three halo groups selected from fluoro, chloro, bromo and iodo and an alkyl group selected from methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl and sec-butyl, (in particular fluoromethyl, difluoromethyl or trifluoromethyl);
for alkylureido;	N'-methylureido, N'-ethylureido, N'-prpoylureido, N'-isopropylureido or N'-butylureido;
for alkanoyl;	formyl, acetyl, propionyl and butyryl;
for O-(1-6C)alkyl ethers of alkanoyl oximes;	methyl, ethyl, propyl, isopropyl and butyl esters of said oximes; and
for alkanoylamino;	formamido, acetamido, propionamido, iso-propionamido, butyramido or iso-butyramido.

In particular, when R^1 and R^2 are both hydrogen, Ar^1 is not an oxadiazole or a thiadiazole moiety.

A particular value for Ar^1 when Ar^1 is a phenylene moiety is, for example, 1,3-phenylene or 1,4-phenylene.

Particular values for Ar^2 when Ar^2 is a heterocyclic moiety include, for example, furyl, pyrrolyl, thienyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzfuranyl, quinolyl, isoquinolyl, benzimidazolyl, indolyl, benzthiazolyl, benzdioxanyl (such as 1,4-benzdioxanyl), benzdioxolyl (such as 1,3-benzdioxolyl) and 2,3-dihydrobenzfuranyl.

Particular values for Ar^1 when Ar^1 is a hetrocyclic moiety include, for example, furyl, pyrrolyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzfuranyl, quinolyl, isoquinolyl, benzimidazolyl, indolyl, benzthiazolyl, benzdihydrofuranyl, benzdioxanyl (such as 1,4-benzdioxanyl) and benzdioxolyl (such as 1,3-benzdioxolyl).

More particular values for Ar^1 and Ar^2 when they represent a heterocyclic moiety include, for example, pyrrolyl, quinolyl,

oxadiazolyl, oxazolyl, thienyl, thiazolyl, furyl, pyridyl, benzthiazolyl, benzoxazolyl, benzimidazolyl and benzdioxolyl.

Values of particular interest for Ar^1 when Ar^1 is a heterocyclic moiety include, for example, pyridyl and thiazolyl (especially pyridyl).

Values of particular interest for Ar^2 when Ar^2 is a heterocyclic moiety include, for example, pyrrolyl, quinolyl, oxadiazolyl, oxazolyl, thienyl, thiazolyl, furyl, pyridyl, benzthiazolyl, benzoxazolyl, benzimidazolyl and benzdioxolyl, especially pyrrolyl, quinolyl, oxadiazolyl, oxazolyl, thiazolyl, benzthiazolyl and benzdioxolyl (more especialy oxadiazolyl or quinoyl).

In general, it is preferred that Ar^1 is optionally unsubstituted or substituted by one, two or three substituents independently selected from those mentioned above; and that Ar^2 is optionally unsubstituted or substituted by one, two or three substituents from those mentioned above.

In a particular embodiment, one or both of Ar^1 and Ar^2 may optionally bear one or more substituents selected from halogeno, hydroxy, nitro, (1-6C)alkyl, (2-6C)alkenyl, (1-6C)alkoxy, (1-6C)alkanoylamino, halogeno-(1-6C)alkyl, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oximes.

In general it is preferred, for example, that R^1 is hydroxy and R^2 is hydrogen.

In general it is preferred, for example, that when Ar^1 is phenylene , Ar^1 is 1,4-phenylene.

It is generally preferred, for example, that when Ar^1 or Ar^2 is a heterocyclic moiety, it is an aromatic 5-membered or 6-membered heterocyclic ring containing (in addition to carbon atoms) one, two or three heteroatoms selected from nitrogen, oxygen and sulphur which is optionally fused to a benzene ring.

It is generally preferred, for example, that when Ar^1 is a heterocyclic moiety Ar^1 is a pyridyl moiety.

It is generally preferred, for example, that when Ar^2 is a heterocyclic moiety Ar^1 is an oxadiazole or quinolyl moiety.

Specific values for R^1/R^2 include when R^1 is hydroxy annd R^2 is hydrogen.

Specific values for -Ar^1-Ar^2 include, for example, a 2-phenylpyrid-5-yl, 2-phenylthiazol-5-yl, 3-phenylpyrid-6-yl, 4-(2,5-dimethylpyrrol-1-yl)phenyl, 4-(1-pyrrolyl)phenyl, 4-(2-quinolyl)phenyl, 4-(2-benzthiazolyl)phenyl, 4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl, 4-(2-benzoxazolyl)phenyl, 4-(2-methyloxazol-5-yl)phenyl, 4-(1-meythl-benzimidazol-2-yl)phenyl, 4-(2-thienyl)phenyl, 4-(2-thiazolyl)phenyl, 4-(3,4-methylenedioxyphenyl)phenyl, 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl, 4-(3-quinolyl)phenyl, 4-(3-thienyl)phenyl or a 4-(3-furyl)phenyl moiety.

Further values of interest for Ar^2 when Ar^2 is a heterocyclic moiety include, for example, 2-thienyl, 1-imidazolyl, 1-pyrrolyl, 2-imidazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-3-yl, 3-quinolyl, 2-quinolyl, 1-isoquinolyl, 2-thiazolyl, 3-isoquinolyl, 1-benzimidazolyl, 2-benzthiazolyl, 5-oxadiazoyl, 2-indolyl and 3-indolyl, which may optionally bear one or two substituents independently selected from fluoro, chloro, bromo, iodo, hydroxy, nitro, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, allyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, acetamido, propionamido, iso-propionamido, fluoromethyl, difluoromethyl, trifluoromethyl, formyl, acetyl, propionyl, butyryl and oxime derivatives of the last four groups and O-methyl, ethyl, propyl, isopropyl and butyl ethers of said oximes.

Further values of interest for Ar^1 when Ar^1 is a phenylene moiety include, for example, an unsubstituted 1,4-phenylene moiety and a 1,4-phenylene moiety having one or two substituents independently selected from fluoro, chloro, bromo, iodo, hydroxy, nitro, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, allyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, acetamido, propionamido, iso-propionamido, fluoromethyl, difluoromethyl, trifluoromethyl, formyl, acetyl, propionyl, butyryl and oxime derivatives of the last four groups and O-methyl, ethyl, propyl, isopropyl and butyl ethers of said oximes.

In a specific embodiment Ar^1 is an unsubstituted 1,4-phenylene moiety Ar^2 is an optionally substituted heterocyclic moiety (as hereinbefore defined).

A particular value for Ar^1 when R^1 and R^2 are both hydrogen is a 6-membered monocyclic heteroaryl moiety, or a bicyclic heteroaryl moiety of about 8 to 10 ring atoms.

Specific values for Ar^1 include, for example, thienyl, pyridyl, thiazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzthiazolyl, oxadiazoyl and indolyl which may optionally bear one or two substituents independently selected from fluoro, chloro, bromo, iodo, hydroxy, nitro, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, allyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, acetamido, propionamido, iso-propionamido, fluoromethyl, difluoromethyl, trifluoromethyl, formyl, acetyl, propionyl, butyryl and oxime derivatives of the last four groups and O-methyl, ethyl, propyl, isopropyl and butyl ethers of said oximes.

Specific values for Ar^2 include, for example, an unsubstituted phenyl moiety and a phenyl moiety having one or two substituents independently selected from fluoro, chloro, bromo, iodo, hydroxy, nitro, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, allyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, acetamido, propionamido, iso-propionamido, fluoromethyl, difluoromethyl, trifluoromethyl, formyl, acetyl, propionyl, butyryl and oxime derivatives of the last four groups and O-methyl, ethyl, propyl, isopropyl and butyl ethers of said oximes.

In a specific embodiment Ar^1 is unsubstituted and Ar^2 optionally substituted by one or two substituents independently selected from fluoro, chloro, bromo, iodo, hydroxy, nitro, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, allyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, acetamido, propionamido, iso-propionamido, fluoromethyl, difluoromethyl, trifluoromethyl, formyl, acetyl, propionyl, butyryl and oxime derivatives of the last four groups and O-methyl, ethyl, propyl, isopropyl and butyl ethers of said oximes.

In one embodiment of the present invention, R^1 and R^2 are both hydrogen; and Ar^1 and Ar^2 have any of the meanings defined above.

In a further embodiment of the present invention, R^1 is hydroxy; R^2 is hydrogen; and Ar^1 an Ar^2 have any of the meanings defined above.

In a further embodiment of the present invention, R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond; and Ar^1 and Ar^2 have any of the meanings defined above.

In a particular aspect of the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen; or

R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;

Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur; and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl èthers of said oxime derivatives;

provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms.

Particular, preferred and specific values are the appropriate values mentioned above.

In a further aspect of the present invention of there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein;

R^1 is hydrogen or hydroxy;

R^2 is hydrogen; or

R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;

Ar^1 is a heterocyclic moiety;

Ar^2 is phenyl;

and wherein one or both of Ar^1 and Ar^2 may optionally be unsubstituted or may bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives; provided that when R^1 and R^2 are both hydrogen, then Ar^1 is not an oxadiazole moiety; and excluding the compound 3-[5-(3-phenyl-1,2,4-thiadiazol)-yl]quinuclidine and its pharmaceutically acceptable salts.

Particular, preferred and specific values are the appropriate values mentioned above. In particular when R^1 and R^2 are both hydrogen, then Ar^1 is not an oxadiazole moiety or a thiadiazole moiety.

Thus, in an embodiment of the present invention of particular interest there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof wherein R^1 is hydroxy, R^2 is hydrogen, Ar^1 is a phenylene moiety, Ar^2 is a heterocyclic moiety containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur; and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives; provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms.

Particular, preferred and specific values are the appropriate values mentioned above.

In further embodiment of interest the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein; R^1 is hydroxy; R^2 is hydrogen; Ar^1 is a heterocyclic moiety; Ar^2 is phenyl; and wherein one or both of Ar^1 and Ar^2 may optionally be unsubstituted or may bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylamino,

di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives.

Particular, preferred and specific values are the appropriate values mentioned above.

In a further embodiment of interest there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof wherein R^1 is hydroxy, R^2 is hydrogen, Ar^1 is a 1,4-phenylene moiety, Ar^2 is a 5- or 6-membered heteroaryl moiety containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, which moiety may optionally be fused to a benzene ring;
and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives; provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms.

Particular, preferred and specific values are the appropriate values mentioned above.

In a specific embodiment of the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein;
R^1 is hydroxy; R^2 is hydrogen; Ar^1 is 1,4-phenylene and Ar^2 is pyrrolyl, benzthiazolyl, oxadiazolyl or quinolyl, and Ar^1 and Ar^2 are optionally substituted as defined above.

In a further embodiment of the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein;
R^1 is hydroxy;

R^2 is hydrogen;
Ar^1 is a 5-membered or 6-membered heteroaryl moiety containing one or two heteroatoms selected from nitrogen, oxygen and sulphur;
Ar^2 is phenyl;
and wherein one or both of Ar^1 and Ar^2 may optionally be unsubstituted or may bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives.

Particular, preferred and specific values are the appropriate values mentioned above.

In a specific embodiment of the present invention R^1 is hydroxy, R^2 is hydrogen, Ar^1 is a 5-membered or 6-membered heteroaryl moiety having one or two heteroatoms selected from nitrogen, oxygen and sulphur; and Ar^2 is a phenyl moiety which may optionally be unsubstituted or may bear one, two or three substituents independently selected from halogeno, hydroxy, nitro, (1-6C)alkyl, (2-6C)alkenyl, (1-6C)alkoxy, (1-6C)alkanoylamino, halogeno-(1-6C)alkyl, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oximes.

Particular, preferred and specific values are the approriate values mentioned above.

Compounds of the invention which are of particular interest include the compounds described in the accompanying Examples (and their pharmaceutically-acceptable salts), and are hence provided as a further feature of the present invention. In particular the present invention provides a compound as described in Example 5,12,13,16 or 21 (or a pharmaceutically acceptable salts thereof).

A suitable pharmaceutically-acceptable salt of the present invention comprises an acid-addition salt derived from an inorganic or organic acid which provides a pharmaceutically-acceptable anion. Thus, examples of salts of the present invention include acid-addition salts with hydrochloric, hydrobromic, nitric, sulphuric, phosphoric,

trifluoroacetic, citric, tartaric, succinic, maleic, fumaric or acetic acid. In addition, suitable pharmaceutically-acceptable salts include [where the compound of formula I is sufficiently acidic, for example where the compound of formula I bears an acidic substituent such as carboxy] those formed with a base which affords a pharmaceutically acceptable cation. Suitable bases include an alkali metal salt (such as a sodium or potassium salt), an alkaline earth metal salt (such as a calcium or magnesium salt), an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation such as a salt with methylamine, dimethylamine, triethylamine, piperidine or morpholine.

The compounds of the present invention may be obtained by standard procedures of organic chemistry already known to be applicable to the preparation of structurally analogous compounds. Such procedures for the preparation of the compounds of formula I, or pharmaceutically acceptable salts thereof, are provided as a further feature of the present invention and are illustrated by the following preferred processes in which the various generic radicals, for example, R^1, R^2, Ar^1 and Ar^2 have any of the meanings defined hereinbefore, and in which Ar^1 and Ar^2 may be unsubstituted or substituted as hereinbefore defined.

(a) For those compounds of formula I in which R^1 is hydroxy and R^2 is hydrogen, reacting a compound of formula Ar^2-Ar^1-M in which M is a metal atom or a derivative thereof, with quinuclidin-3-one.

Suitable values for M include, for example, magnesium and lithium. In the case where M is magnesium it is conveniently present in the form of a derivative such as the group -MgX where X is a halogeno atom, such as iodo or bromo, so that the compound of formula Ar^2-Ar^1-M is a "Grignard Reagent". The reaction is generally carried out in an inert solvent, such as dry diethyl ether or dry tetrahydrofuran, and at a temperature from about ambient temperature to the reflux temperature of the reaction mixture.

The compounds of formula Ar^2-Ar^1-M may be prepared by reacting a compound of formula Ar^2-Ar^1-hal in which "hal" is a halogeno atom such as iodo or bromo with the appropriate metal. For example in the case where M is the group -MgX, the compound of formula Ar^2-Ar^1-hal may be reacted with magnesium turnings as is well known in the art. The desired

Grignard Reagent may also be prepared by a transmetallation reaction, for example by reaction of a compound of formula Ar^2-Ar^1-hal with a Grignard Reagent such as MeMgBr. Where M is a metal atom such as lithium, the compound of formula Ar^2-Ar^1-M may be prepared by reaction of a compound of formula Ar^2-Ar^1-hal with lithium in an inert solvent such as dry ether or tetrahydrofuran at a temperature below 0°C, such as at about -70°C. Alternatively, the compound of formula Ar^2-Ar^1-hal may be treated with an alkyl lithium compound such as sec-butyl lithium.

The compounds of formula Ar^2-Ar^1-hal may be prepared from compounds of formula H_2N-Ar^1-hal in which "hal" is a halogen atom such as iodo or bromo. The compound of formula H_2N-Ar^1-hal is treated with sodium nitrite and concentrated hydrochloric acid with cooling as described in Example 1 part(a) to generate a diazonium salt which is then treated with the compound, Ar^2, in the presence of a base such as sodium hydroxide to give the compound of formula Ar^2-Ar^1-hal. Positional isomers may be separated using conventional techniques such as column chromatography.

Alternatively, the compounds of formula Ar^2-Ar^1-hal may be prepared by reaction of the appropriate compound of formula Ar^2-X in which X is a leaving group such as halogen (for example, bromo) or trifluoromethanesulphonyloxy, with the appropriate compound of formula hal-Ar^1-$B(L^1)L^2$ in which "hal" is halogen such as bromo and L^1 and L^2 are suitable ligands such as hydroxy. The reaction will be carried out in the presence of a catalyst such as tetrakis(triphenylphosphine)-palladium(0). Suitable reaction conditions are those mentioned in (b) below. Similarly, compounds of formula Ar^2-Ar^1-hal may be prepared by reaction of a compound of formula Ar^2-$B(L^1)L^2$ with a compound of formula X-Ar^1-hal.

Compounds of formula Ar^2-Ar^1-hal may also be prepared by other methods well known to those skilled in the art. For example, when Ar^2 is pyrrole, by reaction with a 2,5-diethoxytetrahydrofuran with a compound of formula hal-Ar^1-NH_2.

(b) Reacting a compound of formula II wherein L^1 and L^2 are suitable ligands with a compound of formula Ar^2-X, in which X represents a leaving group, in the presence of a catalyst.

Suitable values for X include, for example, halogen such as bromo or iodo, and a trifluoromethanesulphonyloxy group. Suitable values for the ligands L^1 and L^2 present on the boron atom include groups independently selected from hydroxy, (1-4C)alkoxy (such as methoxy or ethoxy) and (1-6C)alkyl (such as methyl, ethyl, propyl or butyl). The groups L^1 and L^2 may, together with the boron atom to which they are attached, form a boroxin ring. The groups L^1 and L^2 may be joined together to define an -oxyalkyleneoxy- group so that L^1 and L^2 together with the boron atom define a cyclic borate ester group. A particularly suitable leaving group is the group $-B(OH)_2$.

Suitable catalysts include, for example, a catalyst selected from a palladium (0), palladium (II), nickel (0) and nickel (II) catalyst. Particular catalysts include, for example, tetrakis-(triphenylphosphine)nickel(0), bis(triphenylphosphine)nickel(II) chloride, nickel(II)chloride, palladium(II)chloride, bis(triphenylphosphine)palladium(II)chloride, bis(triphenylphosphine)phenylpalladium iodide and tetrakis(triphenylphosphine)palladium(0). A radical initiator, for example, azo(bisisobutyronitrile) may also be present.

The process is generally performed in the presence of a suitable solvent or diluent, for example, a hydrocarbon, such as toluene or xylene, or an ether such as dioxan or tetrahydrofuran, and at a temperature in the range, for example, 20-150°C.

Compounds of formula II may be prepared by reaction of a compound of formula $RO\text{-}BL^1(L^2)$, such as a compound of formula $B(OR)_3$, wherein R is (1-6C)alkyl with a Grignard Reagent or aryllithium compound derived from a compound of formula IIIa in which X is halogen such as bromo in an analogous manner to the preparation of compounds of formula $Ar^2\text{-}B(L^1)L^2$ mentioned below.

Alternatively, compounds of formula II in which R^1 is hydroxy and R^2 is hydrogen may be prepared by reaction of quinuclidin-3-one with a Grignard Reagent or aryllithium compound derived, using standard procedures such as those mentioned in (a) above, from a compound of formula $hal\text{-}Ar^1\text{-}B(L^1)L^2$ in which "hal" represents halogen such as bromo or iodo and L^1 and L^2 are as defined above, and in which they are preferably joined together so that L^1 and L^2 together to form an

oxyalkyleneoxy group in which the alkylene moiety may bear one or more alkyl groups. The compounds of formula hal-Ar^1-$B(L^1)L^2$ in which R^1 is hydroxy and R^2 is hydrogen may be converted into those in which R^1 and R^2 are both hydrogen or R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond using standard procedures such as those mentioned under (d), (e), (f) or (g) below.

(c) Reacting a compound of formula III in which X is a suitable leaving group with a compound of formula hal-Ar^1-$B(L^1)L^2$ in which L^1 and L^2 are suitable ligands in the presence of a catalyst.

Suitable values for X, L^1 and L^2, suitable catalysts and suitable reaction conditions are those mentioned under (b) above.

The compounds of formula hal-Ar^1-$B(L^1)L^2$ may be prepared by reaction of a boron compound of formula RO-$BL^1(L^2)$ in which L^1 and L^2 are alkyl or alkoxy groups as defined above. Thus, for example, a compound of formula $B(OR)_3$ wherein R is a (1-6C)alkyl group may be reacted with a Grignard Reagent or aryllithium compound derived, using standard procedures such as those mentioned in (a) above, from a compound of formula Ar^2-hal wherein "hal" represents a halogeno atom such as bromo or iodo. The reaction is generally carried out in a solvent such as tetrahydrofuran or diethyl ether, or a mixture thereof, and at a temperature of -78°C to 25°C. The compounds of formula V wherein the ligands attached to boron are alkoxy may be converted to those in which the ligands are hydroxy by hydrolysis using standard techniques. The boroxin compounds may be prepared from the latter by dehydration using standard procedures.

The compounds of formula III in which R^1 is hydroxy and R^2 is hydrogen may be prepared by reaction of quinuclidin-3-one with a aryllithium compound derived, using procedures such as those analogous to those mentioned under (a) above, from a compounds of formula hal-Ar^1-X in which "hal" represents a halogen atom such as bromo or iodo and X is as defined above. The compounds of formula III in which R^1 is hydroxy and R^2 is hydrogen may be converted into compounds of formula III in which R^1 and R^2 are both hydrogen using standard procedures such as those

mentioned in (d) or (g) below, and into compounds in which R^1 and R^2 are joined so that CR^1-CR^2 is a double bond using standard procedures such as those mentioned in (e) or (f) below.

(d) For those compounds of formula I in which R^1 and R^2 are both hydrogen, reducing a compound of formula I in which R^1 and R^2 are joined together so that -CR^1-CR^2 is a double bond.

The reduction may be carried out, for example, by catalytic hydrogenation, or by reaction with a suitable reducing agent. Suitable reaction conditions include, for example, catalytic hydrogenation using a catalyst which comprises a noble metal. Particular catalysts include palladium, platinum, nickel and supported catalysts such as Pd/C. The reduction is conveniently carried out in a solvent of, for example, an alcohol such as ethanol, and at (or near) ambient temperature and optionally under pressure.

Further suitable reaction conditions include, for example, reduction with a borane such as diborane. The reaction is generally carried out in an inert solvent of, for example, tetrahydrofuran or methyl t-butyl ether at, for example, a temperature of 0 to 60°C. It may be preferable to cool the reaction below ambient temperature (eg. to about 0°C) during the reduction. The borane generated may be hydrolysed by treatment with an organic acid such as acetic acid.

(e) For those compounds of formula I in which R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond, dehydrating a compound of formula I in which R^1 is hydroxy.

The dehydration may be carried out using an acid such as sulphuric acid (for example, concentrated sulphuric acid), or p-toluene sulphonic acid. The reaction may conveniently be carried out with heating. For example, the reaction may be carried out using p-toluene sulphonic acid in a hydrocarbon solvent of, for example, toluene or xylene at ambient temperature to reflux, and preferably at reflux. The dehydration may also be carried out using trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature from ambient temperature to the reflux temperature of the reaction mixture.

(f) For compounds of formula I in which R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond, treating a compound of formula IV in which X is a leaving group with a base.

Suitable values for X include, for example, halogeno such as chloro, bromo or iodo, or a sulphonyloxy group such as methanesulphonyloxy or toluenesulphonyloxy. Suitable bases include alkali metal hydroxides (such as potassium or sodium hydroxide), and alkali metal alkoxides (such as potassium t-butoxide or sodium ethoxide).

The reaction may conveniently be carried out in the presence of a solvent, preferably a polar organic solvent. Suitable solvents include, for example, an alcohol (such as ethanol), or an aprotic solvent such as dimethylformamide or N-methyl pyrrolidone. The reaction may be carried out at ambient temperature or at an elevated temperature such as at temperature between ambient and the reflux temperature of the reaction mixture.

The compounds of formula IV may be prepared, for example, from compounds of formula I in which R^1 is hydroxy and R^2 is hydrogen using methods well known in the art. For example, compounds of formula IV in which X is halogen may be prepared by reaction of formula I in which R^1 is hydroxy with the appropriate phosphorus halide (for example PCl3, PBr_3 or PI_3) or, where X is chloro, by reaction with thionyl chloride. Compounds of formula IV in which X is methanesulphonyloxy or toluenesulphonyloxy may be prepared by reaction of the compound of formula I in which R^1 is hydroxy with mesyl chloride or tosyl chloride respectively.

(g) For those compounds of formula I in which R^1 and R^2 are both hydrogen, by dehydroxylation of a compound of formula I in which R^1 is hydroxy.

The reaction may be carried out by catalytic hydrogenation. Suitable reaction conditions include those mentioned under (d) above. The reaction may also be carried out using, for example, trifluoroacetic acid and Et_3SiH, conveniently at a temperature between ambient temperature and the reflux temperature of the reaction mixture (eg. at about 50°C).

It will be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein. Suitable protecting groups for hydroxy include, for example, silyl groups such as trimethylsilyl or t-butyldimethylsilyl, tetrahydropyranyl and esterifying groups such as a methyl or ethyl ester; and for amino groups include benzyloxycarbonyl and t-butoxycarbonyl. Carboxy groups may be protected in a reduced form such as in the form of the corresponding protected alcohol, which may be subsequently oxidised to give the carboxy group. The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

It will also be appreciated that the preferred process for preparing a particular compound of formula I will depend upon the nature of the various radicals. Similarly, the preferred choice of reagent will depend upon the nature of the various radicals present. For example, when it is required to reduce a particular compound the reducing agent will generally be selected to be one which does not interfere with other groupings present.

It will also be appreciated that certain of the various optional substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acylhalide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with the appropriate acid (which affords a physiologically acceptable anion), or with the appropriate base (which affords a physiologically acceptable cation), or by any other conventional salt formation procedure.

As mentioned previously, the compounds of the formula I (and their pharmaceutically-acceptable salts) are inhibitors of the enzyme squalene synthase. Thus the compounds of the present invention are capable of inhibiting cholesterol biosynthesis by inhibition of de novo squalene production.

The beneficial pharmacological properties of the compounds of the present invention may be demonstrated using one or more of the following techniques.

(a) Inhibition of Squalene synthase

In this test, the ability of a compound to prevent the formation of squalene from a radioactive substrate (tritiated farnesyl pyrophosphate) is assessed.

The test compound is incubated at a concentration of 25 micromolar in 200µl of a buffered solution containing potassium phosphate (50mM), $MgCl_2$ (4.95mM), KF (9.9mM), NADPH (0.9mM) and rat liver microsomal protein (20µg). Rat liver microsomes are prepared by the method described in published European Patent Application No. 324,421 and stored in liquid nitrogen prior to assay. Assay vials are kept at 37°C throughout the incubation.

The reaction is started with the addition of the substrate (1-[^{3}H]-farnesyl pyrophosphate), final concentration 20µM, and stopped after 15 minutes reaction time with the addition of 50µl of 4% KOH. The

reaction products are separated from unreacted substrate after application to a C-18 octadecyl 1ccBond column (Analytichem Int product No. 617101). An aqueous fraction is eluted with 250µl of 0.1M KOH. Squalene is then eluted with 1.0 ml 10% ethylacetate in hexane and radioactivity determined. The difference in radioactivity in the presence and absence of the test compound is used to determine the level of inhibition. If the test compound inhibits at greater than about 70% at 25 micromolar, it is generally re-tested at 25 and 2.5 micromolar. The IC_{50} (concentration which results in a 50% inhibition of squalene production), of the test compound can be determined by testing the compound at several, for example five, concentrations predicted from the two concentration results. The IC_{50} can then be determined from a plot of percentage inhibition against concentration of test compound.

In general, compounds of formula I show significant inhibition in the above test at a concentration in the range of about 0.001 to 25µM.

By way of illustration of the squalene synthase inhibitory properties of the compound of formula I, described in Example 3 below gave an inhibition of about 71% at a concentration of 2.5µM; and the compound described in Example 16 below gave an inhibition of about 91% at a concentrationm of about 2.5µM.

(b) Acute rat cholesterol synthesis assay.

This is an acute in vivo test in the rat to measure de novo hepatic cholesterol synthesis from exogenously administered ^{14}C-acetate.

Female rats (35 - 55 g) are housed in reverse lighting conditions (red light from 0200h - 1400h) for a period of about 2 weeks prior to test. Animals are allowed free access to chow and drinking water throughout this period. At test, animals should weigh 125 - 150 g.

Test compounds may be administered by oral gavage, dissolved or suspended in 0.5% polysorbate, or by ip or iv dosing. Control animals receive vehicle alone. After 1 hour the rats are injected ip with 25µCi [2-^{14}C]-acetate (NEN DUPONT. specific activity, 45-60mCi/mmol NEC-085H, or AMERSHAM specific activity, 50-60mCi/mmol CFA 14) in a volume of 0.25 ml saline (100µCi/ml). After a further hour, rats are terminally anaesthetised with halothane and a blood sample obtained from the abdominal vena cava.

1ml of plasma is lyophilised and then saponified in 2ml ethanolic KOH (1 part 33% KOH, 9 parts ethanol) at 75°C for 2 hours. After addition of an equal quantity of water, non-saponifiable lipids are extracted with two 5ml volumes of hexane. The hexane extracts are evaporated to dryness and the residues dissolved in ethanol to determine cholesterol specific radioactivity. ED_{50} values can be determined in the standard way.

In general, compounds of formula I show activity in the range of about 0.1 to 100 mg/kg.

By way of illustration, the compound of formula I described in Example 3 gave a 74% reduction in the rate of cholesterol biosynthesis and an ED_{50} of about 14 mg/kg; the compound described in Example 12 gave an ED_{50} of about 3.8mg/kg and the compoud described in Example 6 gave an ED_{50} of about 4.5mg/kg.

In an alternative in vivo test, de novo hepatic cholesterol synthesis from exogenously administered ^{3}H-mevalonolactone is measured. The above procedure is used but with ^{3}H-mevalonolactone (2.6μCi) administered in place of ^{14}C-acetate and the test compound is generally administered as a solution or suspension in 10% dimethylsulphoxide in 0.5% hydroxypropylmethylcellulose.

No overt toxicity was detected when compounds of the formula I were administered at several multiples of their minimum inhibitory dose or concentration.

As mentioned above, the compounds of the present invention are squalene synthase inhibitors and hence possess the property of inhibiting cholesterol biosynthesis. Thus the compounds of the present invention will be useful in treating diseases or medical conditions in which an inhibition of squalene synthase is desirable, for example those in which a lowering of the level of cholesterol is blood plasma is desirable. In particular, the compounds of the present invention will be useful in treating hypercholesterolemia and/or ischaemic diseases associated with atheromatous vascular degeneration such as atherosclerosis. The compounds of the present invention will also be useful in treating fungal infections.

Thus according to a further feature of the present invention there is provided a method of inhibiting squalene synthase in a

warm-blooded animals (such as man) requiring such treatment, which method comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically-acceptable salt thereof,

wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen; or

R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;

Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety; or

Ar^1 is a heterocyclic moiety and Ar^2 is a phenyl moiety;

and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives;

provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms; and that when R^1 and R^2, are both hydrogen, Ar^1 is not an oxadiazole moiety.

In particular, the present invention provides a method of inhibiting cholesterol biosynthesis, and more particularly to a method of treating hypercholesterolemia and atheromatous vascular degeneration (such as atherosclerosis).

Thus the present invention also provides the use of a compound of formula I (as herein defined), or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for treating diseases or medical conditions in which a lowering of the level of cholesterol in blood plasma is desirable (such as hypercholesterolemia and atherosclerosis).

When used in the treatment of diseases and medical conditions in which an inhibition of cholesterol biosynthesis is desired, for example in the treatment of hypercholesterolemia or atherosclerosis, it is envisaged that a compound of formula I (or a pharmaceutically acceptable salt thereof) will be administered orally, intravenously, or

by some other medically acceptable route so that a dose in the general range of, for example, 0.01 to 50 mg per kg body weight is received. However it will be understood that the precise dose administered will necessarily vary according to the nature and severity of the disease, the age and sex of the patient being treated and the route of administration.

In general, the compounds of formula I (or a pharmaceutically-acceptable salt thereof) will usually be administered in the form of a pharmaceutical composition, that is together with a pharmaceutically acceptable diluent or carrier, and such a composition is provided as a further feature of the present invention.

A pharmaceutical composition of the present invention may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or suspensions for oral administration, in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for parenteral administration such as by intravenous or intramuscular injection.

A composition may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with a coating, such as an enteric coating (for example, one based on cellulose acetate phthalate), to minimise dissolution of the active ingredient of formula I (or a pharmaceutically-acceptable salt thereof) in the stomach or to mask unpleasant taste.

The compounds of the present invention may, if desired, be administered together with (or sequentially to) one or more other pharmacological agents known to be useful in the treatment of cardiovascular disease, for example, together with agents such as HMG-CoA reductase inhibitors, bile acid sequestrants, other hypocholesterolaemic agents such as fibrates, for example gemfibrozil, and drugs for the treatment of coronary heart disease. As a further example, the compounds of the present invention may, if desired, be administered together with (or sequentially to) an angiotensin converting enzyme (ACE) inhibitor, such as captopril, lisinopril, zofenopril or enalapril.

Compounds which inhibit squalene synthase have also found utility as antifungal agents. Thus the present invnetion also provides a method of treating fungal infections comprising adimistering a compound

of formula I, or a non-toxic salt thereof, to an organism in need of such treatment.

In particular, the present invention also provides a method of treating fungal infections which comprises administration to an a warm blooded animal, such as man, in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

When used as anti-fungal agents the compounds may be formulated in a variety of ways, the nature of such formulation depending on whether the use is for controlling pathogens infecting mammals such as man, or in agriculture such as in soil or plants, or some other object. For medical applications, the compounds of the present invention may, in addition to the formulations mentioned above, be adapted for topical administration and such a composition is provided as a further feature of the present invention. Such compositions may be in a variety of forms, for example creams or lotions.

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

(i) 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 or medium pressure liquid chromatography (MPLC) was performed on silica gel (Merck Kieselgel Art.9385, obtained from E Merck, Darmstadt, Germany);

(iv) yields are given for illustration only and are not necessarily the maximum attainable by diligent process development;

(v) proton NMR spectra were normally determined at 200 MHz using tetramethylsilane (TMS) as a 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) all end-products were characterised by microanalysis, NMR and/or mass spectroscopy; and

(vii) conventional abbreviations are used for individual radicals and recrystallisation solvents, for example, Me = methyl, Et = ethyl, Pr = Propyl, Pr^i = isopropyl, Bu = butyl, Bu^i = isobutyl, Ph = phenyl; EtOAc = ethyl acetate, Et_2O = ether, MeCN = acetonitrile, MeOH = methanol, EtOH = ethanol, Pr^iOH = 2-propanol, H_2O = water.

EXAMPLE 1

A solution of sec-butyllithium in cyclohexane (29 ml, 1.3M) was added dropwise with stirring to a solution of 1-(4-bromophenyl)-2,5-dimethylpyrrole (9.06 g) in dry tetrahydrofuran (120 ml) under an atmosphere of argon at -78°C. The mixture was stirred for 5 minutes and a solution of quinuclidin-3-one (4.3 g) in dry tetrahydrofuran (30 ml) added over a period of 7 minutes. Stirring was continued at -78°C for 30 minutes and the mixture was then allowed to reach room temperature over a period of 2 hours. Water (200 ml) was then added to the reaction mixture whilst keeping the reaction temperature below 10°C. The mixture was extracted with ethyl acetate, the ethyl acetate phase separated, dried (Na_2SO_4) and evaporated to yield a residue which was purified by medium pressure column chromatography on alumina (ICN Alumna N 32-63), eluting with ethyl acetate. The product was further purified by crystallisation from ethyl acetate to give **3-[4-(2,5-dimethylpyrrol-1-yl]phenyl)-quinuclidin-3-ol** (5.0 g) as a colourless solid, m.p. 215-216°C; microanalysis, found: C, 76.9; H, 8.2; N, 9.2%; $C_{19}H_{24}N_2O$ requires: C, 77.0; H, 8.2; N, 9.4%; NMR ($[CD_3]_2SO/CD_3COOD$): 1.5-1.6(1H, m), 1.7-1.9(2H, m), 2.4(2H, s), 2.55(6H, s), 3.1-3.3(4H, m), 3.4-3.5(1H, d), 3.85-3.95(1H, d), 5.8(2H, s), 7.3-2H, d) and 7.7(2H, d): m/Z 297 (M+H).

The preparation of 1-(4-bromophenyl)-2,5-dimethylpyrrole is described in, for example, J.Chem.Soc. Perkin 1, (1984), 2801.

EXAMPLE 2

Using a similar procedure to that in Example 1 but using 1-(4-bromophenyl)pyrrole as starting material (in place of 1-(4-bromophenyl)-2,5-dimethylpyrrole) there was obtained **3-[4-(pyrrol-1-yl)phenyl]quinuclidin-3-ol** (10% yield), m.p. 176-177°C,

microanalysis, found: C, 75.8; H, 7.6; N, 9.9%; $C_{17}H_{20}N_2O$ requires: C, 76.1; H, 7.5; N, 10.4%; NMR ($[CD_3]_2SO$), 1.2-1.5(3H, m), 1.9-2.0(1H, s), 2.1-2.2(1H, m), 2.6-2.8(4H, m), 2.8-2.9(1H, d), 3.3-3.4(1H, d of d), 5.1(1H, s), 6.25(2H, d of t), 7.3(2H, d of d) and 7.5-7.6(4H, m): m/Z 269 (M+H).

The preparation of 1-(4-bromophenyl)pyrrole is described in, for example, Australian Journal of Chemistry, (1966), 19, 289.

EXAMPLE 3

A solution of tert-butyl lithium in pentane (2.4 ml, 1.7M) was added dropwise with stirring to a solution of 2-(4-bromophenyl)quinoline (566 mg) in dry tetrahydrofuran (30 ml) under an atmosphere of argon at -78°C. The reaction mixture was stirred for 0.5 hours and a solution of quinuclidin-3-one (225 mg) in tetrahydrofuran (8 ml) was then added dropwise over a period of 10 minutes. Stirring was continued at -78°C for 2.5 hours and the mixture was then allowed to reach 0°C over a period of 2 hours. Water (100 ml) and 2M aqueous sodium hydroxide solution (2 ml) were added. The mixture was extracted with ethyl acetate, the ethyl acetate phase separated, dried (Na_2SO_4) and evaporated to give a colourless solid which was purified by crystallisation from propan-2-ol to give **3-[4-(2-quinolyl)phenyl)quinuclidin-3-ol** (286 mg) as a colourless solid, m.p. 228-230°C; microanalysis, found: C, 79.6; H, 69.0; N, 8.10%; $C_{22}H_{22}N_2O$ requires: C, 80.0; H, 6.71; N, 8.48%; NMR [$(CD_3)_2SO$]: 1.22-1.52(3H, m), 1.95-2.02(1H, m), 2.10-2.25(1H, m), 2.60-2.94(5H, m), 3.44(1H, d), 5.21(1H, s), 7.50-7.86(4H, m), 7.95-8.35(3H, m), 8.24(2H, d) and 8.44(1H, d): m/Z 331 (M+H).

The preparation of 2-(4-bromophenyl)quinoline is described in, for example, CA 72, 31573e and J.Inst.Chem., Calcutta, (1969), 41, 138-141.

EXAMPLE 4

A solution of sec-butylithium in cyclohexane (5.0 ml, 1.3M) was added dropwise with stirring to a solution of 2-(4-bromophenyl)-benzothiazole (1.60 g) in tetrahydrofuran (25 ml) under an atmosphere of argon at -78°C. The reaction mixture was stirred for 15 minutes and a

solution of quinuclidine-3-one (625 mg) in tetrahydrofuran (10 ml) was then added over a period of 6 minutes. Stirring was continued at -78°C for 2 hours and the mixture was then allowed to reach room temperature over a period of 16 hours. 1M Aqueous hydrochloric acid solution (100 ml) was added whilst keeping the reaction temperature below 10°C. The aqueous phase was washed with ethyl acetate (1 x 50 ml) before the addition of excess sodium hydroxide solution (density 1.35 g/cm^3) to pH14. The mixture was extracted with ethyl acetate, the ethyl acetate phase separated, dried (Na_2SO_4) and evaporated to give a colourless solid which crystallised from ethyl acetate to give **3-[4-(benzothiazol-2-yl)-phenyl)quinuclidin-3-ol** (260 mg), m.p. 215.5-216°C; microanalysis, found: C, 71.3; H, 6.0; N, 8.10%; $C_{20}H_{20}N_2OS$ requires: C, 71.4; H, 5.99; N, 8.33%; NMR ($[CD_3]_2SO$): 1.20-1.56(3H, m), 1.98(1H, bs), 2.08-2.28(1H, m), 2.60-3.00(5H, m), 3.41(1H, d), 5.31(1H, s), 7.40-7.60(2H, m), 7.71(2H, d), 8.05(3H, d) and 8.13(1H, d of d); m/Z 337 (M+H).

The preparation of 2-(4-bromophenyl)benzothiazole is described in, for example, Cancer Res., (1968), 28, 2539-2544.

EXAMPLE 5

A solution of sec-butyllithium in cyclohexane (13 ml, 1.3M) was added dropwise with stirring to a solution of 5-(4-iodophenyl)-3-methyl-1,2,4-oxadiazole (505 mg) in dry tetrahydrofuran (10 ml) under an atmosphere of argon at -78°C. The mixture was stirred for 10 minutes and a solution of quinuclidin-3-one (200 mg) in dry tetrahydrofuran (5 ml) was then added over a period of 6 minutes. Stirring was continued at -78°C for 3 hours and the mixture was then allowed to reach room temperature over a period of 16 hours. The mixture was added to ice and extracted with ethyl acetate, the ethyl acetate phase separated, dried (Na_2SO_4) and evaporated to give a residue which was crystallised from ethyl acetate to give **3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-quinuclidin-3-ol** (58 mg) as a colourless solid, m.p. 213-214°C; microanalysis, found: C, 64.00; H, 6.40; N, 13.3%; $C_{16}H_{19}N_3O_2 1.0H_2O$ requires: C, 63.6; H, 6.80; N, 13.7%; NMR ($[CD_3]_2SO$): 1.20-1.50(3H, m), 1.97(1H, bs), 2.02-2.22(1H, m), 2.41(3H, s), 2.60-3.00(5H, m), 3.41(1H, d), 5.34(1H, s), 7.75(2H, d) and 8.04(2H, d); m/Z 286 (M+H).

The starting 5-(4-iodophenyl)-3-methyl-1,2,4-oxadiazole was prepared by the following method:

Acetamide oxime hydrochloride (1.5 g) was added portionwise to sodium hydride (1.18g; 60% dispersion in oil) in dry tetrahydrofuran (40 ml) at 0-5° under an atmosphere of argon. 4Å molecular sieves (1 g) were added.

After 1 hour, a solution of ethyl-4-iodo benzoate (3.73 g) in tetrahydrofuran (10 ml) was added. The reaction mixture was heated for 3 hours at 60-65°. The reaction mixture was cooled to 0°C and water (50 ml) added. The mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with saturated brine solution, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel (Merck Art no 9385) using a 7:3 (v/v) mixture of hexane and ethyl acetate as eluent to give 5-(4-iodophenyl)-3-methyl-1,2,4-oxadiazole (1.12 g) as a colourless solid; microanalysis: C, 38.2; H, 2.5; N, 9.5%; $C_9H_7IN_2O$ requires C, 37.8; H, 2.47; N, 9.8%; NMR ($[CD_3]_2SO$): 2.41(3H, s), 7.77-7.90(2H, d) and 7.95-8.08(2H, d); m/Z 287 (M+H).

EXAMPLE 6

In a similar manner to Example 4, but using 2-(4-bromophenyl)benzoxazole as starting material in place of 2-(4-bromophenyl)benzothiazole, there was obtained 3-[4-(benzoxazol-2-yl)phenyl]quinuclidin-3-ol as a solid, m.p. 255.5-256°C; microanalysis, found: C, 74.6; H, 6.20; N, 8.50%; $C_{20}H_{20}N_2O_2$ requires: C, 75.0; H, 6.30; N, 8.74; NMR($[CD_3]_2SO$): 1.40(3H,m), 2.00(1H,m), 2.81(1H,m), 2.60-3.00(5H,m), 3.45(1H,d), 5.35(1H,s), 7.45(2H,m), 7.80(4H,m) and 8.18(2H,d); m/z 321 (M+H).

The 2-(4-bromophenyl)benzoxazole used as starting material was prepared as follows.

Thionyl chloride (7.3ml) was added dropwise to a stirred suspension of 4-bromobenzoic acid (17.6g) in N-methylpyrrolidinone (50ml) at 10°C over a period of 20 minutes under an atmosphere of argon. The mixture was stirred at ambient temperature for 0.5 hours. 2-aminophenol (9.1g) was added. The mixture was then heated at 105°C for 0.5 hours and

then at 145°C for 3 hours. The reaction mixture was cooled to 40° and then poured into a vigorously stirred mixture of ice (50g), water(50ml) and 40% sodium hydroxide solution (25ml). The mixture was stirred for 0.5 hours. The solid precipitate was collected by filtration and washed with water. The solid was stirred in ethyl acetate (300ml) and the mixture filtered. The filtrate was evaporated to give a solid which was purified by chromatography on silica gel (Merck Art 7734) using a 4:1 (v/v) mixture of hexane/ethyl acetate as eluent to give 2-(4-bromophenyl)benzoxazole (11.5g) as a solid, m.p. 157.5°C; NMR ($CDCl_3$): 7.38(2H,m), 7.57(1H,m), 7.67(2H,m), 7.76(1H,m) and 8.12(2H,m); m/z 274 (M+H).

EXAMPLE 7

In a similar manner to Example 4, but using 2-(4-bromophenyl)-5-methyloxazole in place of 2-(4-bromophenylbenzothiazole, there was obtained 3-[4-(5-methyloxazol-2-yl)phenyl]quinuclidin-3-ol as a solid, m.p 189-190°C; microanalysis, found: C, 71.5; H, 7.30; N, 9.60%; $C_{17}H_{20}N_2O_2$ requires: C, 71.8; H, 7.09; N, 9.85%; NMR($[CD_3]_2SO$): 1.18-1.50(3H,m), 1.92(1H,m), 2.05-2.23(1H,m), 2.38(3H,s), 2.60-2.95(5H,m), 3.36(1H,d), 5.21(1H,s), 6.96(1H,d), 7.65(2H,d) and 7.91(2H,d); m/z 285 (M+H).

The 2-(4-bromophenyl)-5-methyl oxazole used as starting material was prepared as follows.

A solution of propargylamine (3.55g) in ethyl acetate (25ml) was added to a stirred mixture of 4-bromobenzoyl chloride (14.2g) and sodium carbonate (10.6g) in ethyl acetate (100ml) over a period of 0.25 hours at 25°C. The mixture was heated at reflux for 1 hour. The mixture was cooled to ambient temperature and water (200ml) and ethyl acetate (100ml) were added. The ethyl acetate phase was separated, washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was crystallised from ethyl acetate to give 4-bromobenzoyl-N-propargylamide (8.9g) as a solid, m.p. 281.8°; NMR($[CD_3]_2SO$): 3.10(1H,m), 4.05(2H,m), 7.69(2H,m), 7.80(2H,m) and 9.00(1H,m); m/z 238 (M+H).

Mercuric acetate (40mg) was added to a mixture of 4-bromobenzoylpropargyl amide (3.57g) in acetic acid (30ml) and the

mixture heated at reflux for 1.25 hours. The mixture was cooled to ambient temperature and the acetic acid was removed by evaporation. The residue was purified by chromatography on silica gel (Merck Art No 7734) using a 7:3 (v/v) mixture of hexane/ethyl acetate as eluent to give 2-(4-bromophenyl)-5-methyl-oxazole (2.75g) as a pale yellow solid, m.p. 66.8°C; NMR($CDCl_3$): 2.40(3H,s), 6.81(1H,d), 7.52(2H,m) and 7.82(2H,m); m/z 238(M+H).

EXAMPLE 8

In a similar manner to Example 4 but using N'-methyl-2-(4-bromophenyl)benzimidazole as starting material in place of 2-(4-bromophenyl)benzothiazole, there was obtained 3-[4-(N'-methylbenzimidazol-2-yl)phenyl]quinuclidin-3-ol as a solid, m.p. 243-5°C; microanalysis, found: C, 73.50; H, 6.90; N, 11.9%; $C_{21}H_{23}N_3O$ 0.5 H_2O requires: C, 73.70; H, 7.0; N, 12.2%; NMR($[CD_3]_2SO$): 1.25-1.58(3H,m), 2.02(1H,bs), 2.10-2.25(1H,m), 2.40-3.00(5H,m), 3.45(1H,d), 3.88(3H,s), 5.30(1H,s), 7.18-7.32(2H,m), 7.52-7.75(4H,m) and 7.82(2H,d); m/z 334 (M+H).

The N'-methyl-2-(4-bromophenyl)benzimidazole used as starting material was prepared as follows.

A solution of 4-bromobenzaldehyde (1.85g) in ethanol (5ml) was added to a solution of 2-N-methylaminoaniline (1.22g) in ethanol. The reaction mixture was stirred for 2 hours at room temperature. Nitrobenzene (6ml) was added and the reaction mixture was heated to 210°C (ethanol was removed during this period) and then heated at 210°C for 2 minutes. The reaction mixture was cooled to ambient temperature and ethyl acetate (50ml) and 2N aqueous hydrochloric acid (100ml) were added. N'-methyl-2-(4-bromophenyl)benzimidazole was precipiated as its hydrochloride salt and was collected by filtration. The crude hydrochloride salt was suspended in water (25ml) and basified with 2M aqueous sodium hydroxide solution. This aqueous solution was extracted with ethyl acetate. The ethyl actetate phase was separated, washed with brine (2 x 25ml), dried ($MgSO_4$) and evaporated. The residue was purified by medium pressure chromatography on silica gel using a 1:1 (v/v) mixture of hexane/ethyl acetate as eluent to give N'-methyl-2-(4-bromophenyl)benzimidazole (1.45g) as a solid, m.p.

112-114°C; microanalysis, found: C, 58.30; H, 3.90; N, 10.00%; $C_{14}H_{11}N_2Br$ requires: C, 58.60; H, 3.86; N, 9.76%; NMR($CDCl_3$): 3.85(3H,s), 7.25-7.42(3H,m), 7.65(4H,s) and 7.75-7.86(1H,m).

EXAMPLE 9

Saturated sodium hydrogen carbonate solution (10ml) was added to a stirred solution of 3-(4-bromophenyl)-3-hydroxyquinuclidine (490mg), thiophene-2-boronic acid (320mg) and tetrakis triphenylphosphine palladium [0] (20mg) in dimethoxyethane (25ml) at ambient temperature and under an atmosphere of argon. The mixture was heated at reflux for 1.5 hours and then cooled to ambient temperature. Water (100ml) was added and the mixture extracted with ethyl acetate. The ethyl acetate phase was separated and extracted with 2M aqueous hydrochloric acid. The aqueous acid extract was basified to pH12 with 8M aqueous sodium hydroxide solution and then extracted with ethyl acetate. The ethyl acetate phase was washed with saturated brine, dried ($MgSO_4$) and evaporated. The residue was recrystallised from ethyl acetate to give 3-(4-(thien-2-yl)phenyl]quinuclidin-3-ol (301mg) as a grey solid, m.p. 165-8°C; microanalysis, found: C, 69.7; H, 6.70; N, 4.70%, $C_{17}H_{19}NOS.0.5H_2O$ requires: C, 69.6; H, 6.80, N, 4.70%; NMR($[CD_3]_2SO$): 1.20-1.50(3H,m), 1.92(1H,m), 2.05-2.23(1H,m), 2.60-2.97(5H,m), 3.32(1H,d), 5.22(1H,s), 7.08-7.15(1H,m) and 7.42-7.65(6H,m); m/z 286(M+H).

The boronic acid used as starting material was prepared as follows.

A solution of borane in tetrahydrofuran (40ml, 1M) was added at 0°C, with stirring, to magnesium turnings (288mg) over a period of 0.33 hours whilst under an atmosphere of argon. 2-Bromothiophene (1.63g) was then added to the reaction mixture over a period of 0.25 hours and the resulting mixture stirred at room temperature for 16 hours. The mixture was added slowly, with stirring, to ice-water (250ml). Aqueous 2M hydrochloric acid was added to give a pH 1 solution. The aqueous mixture was extracted with diethyl ether, the ether phase was separated, washed with saturated brine, dried ($MgSO_4$) and evaporated. There was thus obtained thiophene-2-boronic acid (710mg) as a colourless solid; m/z 129 (M+H).

EXAMPLE 10

A solution of sec-butyllithium in cyclohexane (7.5ml, 1.3M) was added dropwise over a period of 10 minutes to a solution of 4-bromophenylboronic acid [N-methyl-O;O'-diethanolamine]ester (1.42g) in dry tetrahydrofuran (25ml) under an atmosphere of argon at -100°C. The mixture was stirred for 30 minutes and a solution of quinuclidin-3-one (0.625g) in dry tetrahydrofuran (10ml) was then added over a period of 10 minutes whilst maintaining the temperature at -100°C. The reaction mixture was stirred for 1 hour at -100°C, allowed to warm to ambient temperature and then stirred at ambient temperature for a further 2 hours. An aqueous solution of ammonium chloride (0.55g) in water (5ml) was added and the mixture stirred for 0.5 hours. The tetrahydrofuran was then removed by evaporation. Toluene (20ml) and saturated sodium carbonate solution (10ml) were added to the residue. A solution of 2-bromothiazole (870mg) in absolute alcohol (10ml) was added to the mixture at 25°C whilst under an atmosphere of argon. Tetrakis triphenylphosphine palladium [0] (100mg) was added and the mixture heated at reflux for 4 hours. After cooling to ambient temperature, ice and 2M aqueous hydrochloric acid were added and the mixture washed with ethyl acetate. The aqueous phase was basified with 10M aqueous sodium hydroxide solution and then extracted with dichloromethane. The dichloromethane phase was separated, washed with saturated brine solution, dried ($MgSO_4$) and evaporated. The residue was triturated with ethyl acetate to give 3-[4-(thiazol-2-yl)phenyl]quinuclidin-3-ol (120mg) as a solid, m.p. 218-219°C; microanalysis, found: C, 65.0; H, 6.40; N, 9.40%, $C_{16}H_{18}NO_2S$ 0.5 H_2O requires: C, 65.0; H, 6.40; N, 9.50%; NMR($[CD_3]_2SO$): 1.20-1.52(3H,m), 1.93(1H,m), 2.02-2.22(1H,m), 2.53-2.95(5H,m), 3.40(1H,d), 5.22(1H,s), 7.62(2H,d), 7.75(1H,d) and 7.90(3H,m); m/z 289(M+H).

EXAMPLE 11

Using a similar procedure to that in Example 1, but using 4-(4-bromophenyl)-1,2-methylenedioxybenzene as starting material (in place of 1-(4-bromophenyl)-2,5-dimethylpyrrole) there was obtained 3-[4-(3,4-methylenedioxyphenyl)phenyl]quinuclidin-3-ol (18% yield) as a

solid, m.p. 167-169°C; microanlaysis, found: C, 74.0; H, 6.6; N, 4.1%; $C_{20}H_{21}NO_3$ requies: C, 74.3; H, 6.6; N, 4.3%; NMR:$(CD_3]_2SO/CD_3COOD)$: 1.4-1.8(3H,m), 2.3(2.5(2H,m), 3.1-3.3(4H,m), 3.4-3.9(2H,d of d), 6.1(2H,s), 7.0(1H,d), 7.1-7.2(1H, d of d), 7.2-7.3(1H,d), and 7.6(4H,s); m/z 324 (M+H).

The 4-(4-bromophenyl-1,2-methylene dioxybenzene used as starting material was prepared as follows.

A 2M aqueous solution of sodium carbonate (12ml) was added to a stirred mixture of 4-bromo-1,2-methylenedioxybenzene (2.01g), 4-bromophenylboronic acid and tetrakis triphenylphosphine palladium (175mg) in toluene (60ml) under an argon atmosphere. The reaction mixture was heated at 70°C for 4 hours and then cooled to ambient temperature. The mixture was filtered and the filtrate was extracted with ethyl acetate. The ethyl acetate phase was separated, dried ($MgSO_4$) and evaporated.

The residue was purified by medium pressure column chromatography on silica gel using 5% ethyl acetate/hexane as eluent to give, after crystallisation from hexane, 4-(4-bromophenyl) 1,2-methylenedioxybenzene (385mg) as a colourless solid, m.p. 97-99°C; microanalysis, found: C, 56.7; H, 3.3%; $C_{13}H_9BrO_2$ requires: C, 56.3; H, 3.3%; NMR:$(CDCl_3)$: 6.0(2H,s), 6.8-6.9(1H,d), 7.0(2H,m) and 7.3-7.5(4H, d of d); m/z 278(M+H).

EXAMPLE 12

A solution of sec-butyllithium in cyclohexane (22.5ml, 1.3M) was added slowly to a solution of 4-bromophenyl boronic acid-N-methyl-O:O diethanolamino ester (Tet. Let. 30, (51), 7194, 1989) (3.3g) in freshly distilled tetrahydrofuran (30ml) under an atmosphere of argon and at a temperature of -100°C.

The reaction mixture was stirred at -100°C for a further 30 minutes. A solution of quinculidin-3-one (1.45g) in freshly distilled tetrahydrofuran (6ml) was added and the reaction mixture was stirred at -100°C for 15 minutes. The reaction mixture was allowed to warm to ambient temperature and was then stirred at ambient temperature for 2 hours. A solution of ammonium chloride (1.15g) in water (10ml) was then

added to the mixture. The mixture was stirred for 5 minutes and the solvent was then evaporated to give a green oil. Toluene (30ml), saturated aqueous sodium carbonate solution (15ml) and a solution of 3-bromoquinoline (2.44g) in absolute alcohol (15ml) were added to the residue. The reaction vessel was purged with argon and tetrakistriphenylphosphinepalladium [0] (200mg) was then added to the mixture. The mixture was then heated at reflux with stirring for 4 hours. The mixture was cooled to ambient temperature and the solvent evaporated. Ice followed by 2M aqueous hydrochloric acid were added to the residue and the mixture was extracted with ethyl acetate (3 x 50ml)

The aqueous phase was treated with ice, basified with aqueous sodium hydroxide solution (density 1.35g/cm^3) and extracted with ethyl acetate (4 x 70ml). The ethyl acetate extracts were combined, dried ($MgSO_4$) and evaported. The residue was triturated with hot ethyl acetate and the mixture cooled to give 3-[4-quinol-3-ylphenyl]quinculidin-3-ol as a solid (46% yield), m.p. 220-221°C, microanalysis: found: C, 79.2; H, 6.6; N, 8.3%; $C_{22}H_{22}N_2O$ 0.25H_2O requires: C, 78.9; H, 6.7; N, 8.4%; NMR([CD_3]$_2$SO): 1.2-1.5(3H,m), 2.0(1H,br.s), 2.1-2.2(1H,m), 2.6-2.8(4H,m), 2.95(1H,d), 3.45(1H,d), 5.2(1H,s), 7.6-7.8(4H,m), 7.85(2H,d), 8.05(2H,d), 8.6(1H,d) and 9.3(1H,d); m/z 331(M+H).

EXAMPLE 13

A solution of sec-butyllithium in cyclohexane (4.2ml, 1.3M) was added slowly to a stirred solution of 3-[4-iodophenyl]-5-methyl-1,2,4-oxadiazole (1.43g) in freshly distilled tetrahydrofuran (20ml) -100°C and under an atmosphere of argon. The reaction mixture was stirred at -100°C for 10 minutes. A solution of quinculidin-3-one (625mg) in freshly distilled tetrahydrofuran (7ml) was added.

The mixture was stirred at -100°C for 30 minutes, allowed to warm to ambient temperature and then stirred at ambient temperature for a further 2 hours. The solvent was removed by evaporation. 2M aqueous hydrochloric acid (20ml) was added and the mixture was extracted with ethyl acetate [3 x 20ml]. The aqueous phase was then basified with aqueous sodium hydroxide solution and the mixture extracted with ethyl acetate [6 x 30ml). The ethyl acetate extracts were combined, dried

($MgSO_4$) and evaporated. The residue was purified by preparative thin layer chromatography on silica gel plates (40 x 20 x 0.5mm; Schliecher and Schull G 1505/LS 254) using a mixture of methanol [100 parts] and ammonia (density, 0.88g/cm^3) [2 parts] to give 3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]quinuclidin-3-ol (9% yield); microanalysis, found: C, 67.0; H, 6.3; N, 14.6%; $C_{16}H_{19}N_3O_2$ requires: C, 67.3; H, 6.7; N; 14.7%; NMR($[CD_3]_2SO$): 1.2-1.5(3H,m), 2.0(1H br.s), 2.1-2.2(1H,m), 2.7(3H,s), 2.6-2.8(4H,m), 2.95(1H,d), 3.45(1H,d), 5.3(1H,s), 7.7(2H,d) and 7.95(2H,d), m/z 286 (M+H).

EXAMPLE 14

A mixture of 3-(4-bromophenyl)quinuclidin-3-ol (0.57g), 3-thienyl boronic acid (CA 52:1136g) (0.465g), tetra kis(triphenylphosphine) palladium (0) (25mg), 1,2-dimethoxy ethane (25ml) and saturated sodium bicarbonate solution (10ml) was heated at 80°C for 17 hours under an atmosphere of argon. The reaction mixture was evaporated and the residue partitioned between water (25ml) and ethyl acetate (4 x 30ml). The organic extracts were combined, washed with 2M aqueous sodium hydroxide solution (3 x 25ml), water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica-gel using a 90:10 (v/v) mixture of methylene chloride/methanol as eluent to give a foam (0.5g) which was crystallised from ethyl acetate to give 3-[4-(3-thienyl)phenyl]quinuclidin-3-ol as a solid, m.p. 163-5°C; microanalysis, found: C, 70.2; H, 6.8; N, 4.8%; $C_{17}H_{19}NOS$ 0.05 CH_2Cl_2 requires: C, 70.4; H, 6.6; N, 4.8%; NMR ($[CD_3]_2SO$): 1.15-2.22 (5H,m), 2.55-3.41(6H,m), 5.10(1H,br s), 7.50-7.7(6H,m) and 7.80(1H,d of d); m/z 286(M+H).

The 3-(4-bromophenyl)quinuclidin-3-ol was prepared as follows.

A suspension of magnesium turnings (12.0g) in anhydrous ether (500ml) was treated with a few crystals of iodine and dropwise with a solution of 1,4-dibromobenzene (118g) in anhydrous ether (300ml). Stirring was continued for 1 hour until the Grignard reagent had completely formed. The mixture was cooled to 5°C and a solution

of 3-quinuclidone (56.2g) in tetrahydrofuran (150ml) was added portionwise. After stirring for a further 2 hours at room temperature, the reaction mixture was poured onto ice (300g) and a saturated solution of ammonium chloride (500ml). The mixture was extracted with ether (4 x 200ml). The ether extracts were combined, dried ($MgSO_4$), and evaporated. The solid residue was triturated with ethyl acetate to give 3-(4-bromopenyl)quinuclidin-3-ol as a solid, m.p. 188-191°C; NMR ($[CD_3]_2SO$): 1.1-1.50(3H,m), 1.87(1H,m), 2.13(1H,m), 2.55-2.83(4H,m), 2.84-2.90(1H,d), 3.25-3.40(1H, d of d), 5.18(1H,s), and 7.4-7.55(4H,m).

EXAMPLE 15

In a similar manner to that described in Example 14 but using 3-furylboronic acid as starting material there was obtained 3-[4-(3-furyl)phenyl]quinuclidin-3-ol as a solid, m.p. 174-7°C; microanalysis, found: C, 73.4; H, 7.0; N, 5.0; H_2O 0.17% $C_{17}H_{19}NO_2$ 0.1 CH_2Cl_2 0.05 H_2O requires: C, 73.2, H, 6.9, N, 5.0%; H_2O 0.3% NMR ($[CD_3]_2SO$): 1.15-2.14(5H,m), 2.6-3.6(6H,m), 5.12(1H,br s), 6.92(1H, d of d), 7.48-7.58(4H,m), 7.7(1H, d of d) and 8.13(1H, d of d); m/z 270(M+H).

3-furylboronic acid is reported in J. Het. Chem., 12, (1975), 195; 13, (1976), 1265 and Bull. Soc. Chim. (France), (1976), 1999.

EXAMPLE 16

A solution of tert-butyl lithium in pentane (9 ml, 1.3 M) was added slowly to a stirred solution of 5-bromo-2-phenylpyridine (1.41g) in dry tetrahydrofuran (15 ml) at -100°C under an atmosphere of argon. The reaction mixture was stirred at -100°C for 15 minutes. A solution of quinuclidin-3-one (0.75 g) in dry tetrahydrofuran (10 ml) was added and the reaction mixture was stirred at -100°C for 15 minutes and then at room temperature for 30 minutes. Ice/water (50 ml) was added to the reaction mixture, the tetrahydrofuran removed by evaporation and the resulting mixture was extracted with ethyl acetate (4 x 80 ml). The

ethyl acetate extracts were combined, dried ($MgSO_4$) and evaporated to give a solid which was collected by filtration and washed with cold ethyl acetate to give 3-[2-phenylpyrid-5-yl]quinuclidin-3-ol as a solid (840 mg), m.p. 214-215°C; micro-analysis, found: C,72.8; H,6.6; N, 9.5%; $C_{18}H_{20}N_2O.H2O$ requires C, 72.5; H, 6.7; N, 9.4%; NMR ($[CD_3]_2SO$): 1.1-1.6(3H, m), 1.65 (2H, s), 2.1-2.3(1H, m), 2.6-2.7(2H, m), 2.9-3.0(1H, d), 3.4-3.5(1H, d), 5.2-5.5(1H, br s), 7.4-7.75(3H, m), 7.9-8.1(4H, m), 8.8(1H, s); m/Z 281 (M+H).

The 5-bromo-2-phenylpyridine used as starting material was prepared as follows:-

Tetrakistriphenylphosphine palladium [0] (200 mg) was added portionwise to a stirred, two phase solution of phenyl boric acid (1.22 g), 2,5-dibromopyridine (2.37 g), toluene (10 ml), absolute ethanol (5 ml) and saturated sodium carbonate (5 ml) under an atmosphere of argon. The reaction mixture was then heated at reflux for a period of four hours. The reaction mixture was then poured into 2N aqueous hydrochloric acid solution and the resulting mixture extracted with ethyl acetate (3 x 30 ml). The ethyl acetate extracts were combined, dried ($MgSO_4$) and evaporated to give a yellow wax which was purified by gravity chromatography on silica gel using a 10:90 (v/v) mixture of ethyl acetate and pentane as eluents to give 5-bromo-2-phenylpyridine; microanalysis, found: C, 53.7; H, 3.2; N, 5.7%; $C_{11}H_8NBr.2/3H_2O$ requires C, 53.6; H, 3.4; N, 5.7%; NMR ($[CD_3]_2SO$): 7.4-7.5(3H, s), 7.95(1H, d), 8.05-8.1(3H, m) and 8.8(1H, d); m/Z 233.

EXAMPLE 17

A solution of sec-butyllithium in cyclohexane (5.0 ml, 1.3M) was added dropwise to a solution of 2-(4-bromophenyl)thiazole (1.22 g) in dry tetrahydrofuran (25 ml) under an atmosphere of argon at -78°C. The mixture was stirred for 20 minutes and a solution of quinuclidin-3-one (625 mg) in dry tetrahydrofuran (10 ml) was added over a period of 12 minutes. Stirring was continued at -78°C for 2 hours and the mixture allowed to reach room temperature over a period of 16 hours. 1M Aqueous hydrochloric acid solution (150 ml) was added to the reaction mixture whilst keeping the temperature below 10°C. The aqueous phase was

washed with ethyl acetate (2 x 40 ml) and then basified to pH14 by addition of excess aqueous sodium hydroxide solution (density 1.35 g/cm^3). The mixture was extracted with ethyl acetate. The ethyl acetate phase was separated, dried (Na_2SO_4) and evaporated to give an oil. Trituration of the oil with a 1:1 v/v mixture of ether and hexane and then with ethyl acetate gave a colourless solid. Crystallisation from ethyl acetate gave **3-[(2-(4-bromophenyl)thiazol-5-yl]quinuclidin-3-ol** as a colourless solid (98 mg), m.p. 169.5-170°C; NMR ($[CD_3]_2SO$): 1.28-1.58(3H, m), 1.91(1H, m), 2.00-2.20(1H, m), 2.60-2.90(4H, m), 2.95(1H, d), 3.38(1H, d), 5.88(1H, s), 7.64-7.72(2H, d) and 7.82-7.89(3H, d plus s); m/Z 365 (M+H).

The preparation of 2-(4-bromophenyl)thiazole is described in, for example, Helv. Chim. Acta., (1950), 33, 1271.

EXAMPLE 18

Using a similar procedure to that in Example 2 but using 2-phenylthiazole as starting material in place of 2-(4-bromophenyl)thiazole there was obtained **3-(2-phenylthiazol-5-yl)quinuclidin-3-ol** as a solid, m.p. 168-168.5°C, microanalysis, found: C, 67.0; H, 6.40; N, 9.60%; $C_{16}H_{18}N_2OS$ requires: C, 67.1; H, 6.34; N, 9.78%; NMR ($[CD_3]_2SO$): 1.30-1.58(3H, m), 1.91(1H, bs), 2.02-2.18(1H, m), 2.57-2.90(4H, m), 2.95(1H, d), 3.37(1H, d), 5.85(1H, m), 7.43-7.53(3H, m), 7.83(1H, s) and 7.85-7.95(2H, m); m/Z 287 (M+H).

EXAMPLE 19

A mixture of p-toluene sulphonic acid (790 mg) and 3-(2-phenylthiazol-5-yl)quinuclidin-3-ol (527 mg) in toluene (50 ml) was heated under reflux for 1 hour using a Dean and Stark water separator. After cooling, the toluene phase was washed with saturated aqueous sodium hydrogen carbonate solution. The toluene was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on alumina (Fluka Alumina 507C) using a 9:1 (v/v) mixture of ethyl acetate and methanol as eluent to give **3-(2-phenylthiazol-5-yl)-2,3-dehydroquinuclidine** as a colourless solid (468 mg), m.p. 96-97°C, microanalysis, found: C, 71.3; H, 6.10; N, 10.1%; $C_{16}H_{16}N_2S$ requires: C,

71.3; H, 6.01; N, 10.4%; NMR: ($[CD_3]_2SO$): 1.42-1.58(2H, m), 1.70-1.83(2H, m), 2.43-2.60(2H, m), 2.88-3.03(2H, m), 3.18(1H, d), 6.80(1H, m), 7.45-7.55(3H, m), 7.87-7.95(2H, m) and 8.0(1H, s); m/Z 269 (M+H).

EXAMPLE 20

3-(2-phenylthiazol-5-yl)-2,3-dehydroquinuclidine (260 mg) in absolute ethanol (25 ml) was hydrogenated at atmospheric pressure and ambient temperature for 18 hours over a catalyst of 10% palladium on carbon (50 mg). The catalyst was removed by filtration and the alcohol evaporated. The residue was purified by column chromatography on alumina (Fluka Alumina 507C) using a 19:1 (v/v) mixture of ethyl acetate and methanol as eluent to give, **3-(2-phenylthiazol-5-yl)quinuclidine** as a colourless solid (170 mg), m.p. 51.5-52°C; microanalysis, found: C, 70.80; H, 6.70; N, 10.2%; $C_{16}H_{18}N_2S$ requires: C, 71.1; H, 6.71; N, 10.4%; NMR ($[CD_3]_2SO$): 1.30-1.49(1H, m), 1.55-1.77(3H, m), 1.91(1H, m), 2.62-2.95(5H, m), 3.20-3.40(2H, m), 7.42-7.52(3H, m), 7.72(1H, s) and 7.85-7.92(2H, m); m/Z 271 (M+H).

EXAMPLE 21

A mixture of 3-[5-bromopyrid-2-yl]quinuclidin-3-ol (566mg) and phenylboronic acid (244mg) was dissolved in a mixture of toluene (17 ml), saturated sodium carbonate solution (8.5ml) and absolute alcohol (8.5ml) to give a colourless two phase solution. The reaction vessel was then purged with argon, and tetrakistriphenylphosphine palladium[0] (50mg) was added. The mixture was then heated at reflux, with stirring, for a period of six hours. The solvent was removed by evaporation and saturated sodium carbonate solution was added to the residue. The mixture was extracted with dichloromethane (3 x 50ml). The dichloromethane extracts were combined, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (Merck Art 7734) using methanol as eluent to give **3-[5-phenylpyrid-2-yl]-quinuclidin-3-ol** (62% yield) as a solid, m.p. 210-212°C; microanalysis, found: C, 74.1; H, 70.1; N, 9.4%; $C_{18}M_{20}N_2O$ 0.67 H_2) requires: C, 74.0; H, 7.3; N, 9.6%; NMR ($[CD_3]_2SO$): 1.1-1.6(3H,m), 1.95(2H,s), 2.05-2.20(1H,m), 2.6-2.8(2H,m), 2.9-3.0(1H,d), 3.3-3.4(1H,d),

5.3-5.45(1H,br.s), 7.4-7.55(3H,m), 7.85-7.95(2H,m), 8.0-8.1(2H,m), 8.8(1H,m); m/z 281(M+H).

The 3-[5-bromopyrid-2-yl]quinuclidin-3-ol used as starting material was prepared as follows.

A solution of sec-butyl lithium in cyclohexane (7.7ml, 1.3M) was added very slowly to a solution of 2,5-dibromopyridine (2.36g) in freshly distilled (from CaH_2) tetrahydrofuran (30ml) at -100°C and under an atmosphere of argon. The mixture was stirred at -100°C for a period of 5 minutes and a solution of quinuclidin-3-one (1.25g) in freshly distilled (from CaH_2) tetrahydrofuran (10ml) was then added.

The reaction mixture was stirred at -100°C for 30 minutes, allowed to warm to ambient temperature and then stirred at ambient temperature for a further 2 hours. Saturated sodium carbonate solution (50ml) was then added and the mixture was stirred for 10 minutes. The mixture was extracted with ethyl acetate (3 x 50ml). The ethyl acetate extracts were combined, dried ($MgSO_4$) and evaporated. The residue gave a yellow wax (1.6gm) on standing which was triturated with boiling ethyl acetate. On cooling there was obtained 3-[5-bromopyrid-2-yl]-quinuclidin-3-ol (820mg) as a white solid, m.p. 169 -70; microanalysis, found: C, 51.3; H, 5.5; N, 9.7%; $C_{12}H_{15}N_2O$ Br requires: C, 50.9; H,5.4; N, 9.9%. NMR($[CD_3]_2SO$): 1.1-1.3(1H,m); 1.3-1.6(2H,m); 1.95(2H,bs), 2.05-2.2(1H,m); 2.6-2.8(2H,m); 2.9-3.0(1H,d); 3.3-3.4(1H,d); 5.4(1H,s); 7.55-7.6(1H,d); 7.8-7.9(1H,dd); 8.5(1H,d); m/z 283/285(M+H).

EXAMPLE 22

Illustrative pharmaceutical dosage forms suitable for presenting the compounds of the invention for therapeutic or prophylactic use include the following tablet and capsule formulations, which may be obtained by conventional procedures well known in the art of pharmacy and are suitable for therapeutic or prophylactic use in humans:-

(a) Tablet I

	mg/tablet
Compound Z*	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v aqueous paste)	0.75
Magnesium stearate	1.0

(b) Tablet II

	mg/tablet
Compound Z*	50
Lactose Ph. Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(c) Tablet III

	mg/tablet
Compound Z*	100
Lactose Ph. Eur.	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(d) Capsule

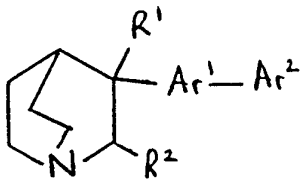
	mg/capsule
Compound Z*	10
Lactose Ph.Eur.	488.5
Magnesium stearate	1.5

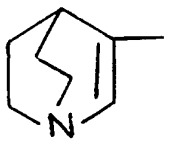
Note

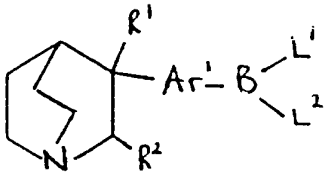
* The active ingredient Compound Z is a compound of formula I, or a salt thereof, for example a compound of formula I described in any of the preceding Examples.

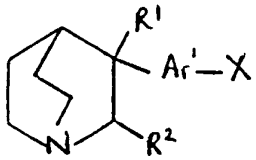
The tablet compositions (a) - (c) may be enteric coated by conventional means, for example, with cellulose acetate phthalate

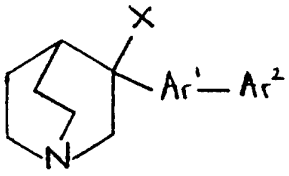
CHEMICAL FORMULAE

I 

Iq 

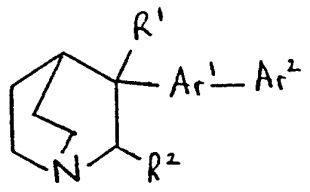
II 

III 

IV 

CLAIMS

1. A compound of formula I:

I 

or a pharmaceutically acceptable salt thereof, wherein:
R^1 is hydrogen or hydroxy;
R^2 is hydrogen; or
R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;
Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety; or
Ar^1 is a heterocyclic moiety and Ar^2 is a phenyl moiety;
and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives;
provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms; when R^1 and R^2 are both hydrogen, Ar^1 is not an oxadiazole moiety; and excluding the compound 3-[5-(3-phenyl-1,2,4-thiadiazol)-yl]quinuclidine and its pharmaceutically acceptable salts.

2. A compound as claimed in any one of the preceeding claims wherein Ar may optionally be unsubstituted or may bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, (1-6C)alkyl, (2-6C)alkenyl, (1-6C)alkoxy, (1-6C)alkanoyl and oxime

derivatives thereof and O-(1-6C)alkyl ethers of said oximes, halogeno(1-6C)alkyl and (1-6C)alkanoylamino.

3. A compound as claimed in claim 1 or 2 wherein Ar^1 is a 1,4-phenylene moiety and Ar^2 is a heterocyclic moiety selected from a pyrrolyl, quinolyl, oxadiazolyl, oxazolyl, thienyl, thiazolyl, furyl, pyridyl, benzthiazolyl, benzoxazolyl, benzimidazolyl and benzdioxolyl, especially pyrrolyl, quinolyl, oxadiazolyl, oxazolyl, thiazolyl, benzthiazolyl and a benzdioxolyl moiety.

4. A compound as claimed in claim 1,2, or 3 wherein Ar^1 is selected from a pyridyl and thiazolyl moiety.

5. A compound as claimed in any one of the preceeding claims wherein R^1 is hydroxy and R^2 is hydrogen.

6. A compound as claimed in any one of the preceeding claims wherein $-Ar^1-Ar^2$ is selected from a 2-phenylpyrid-5-yl, 2-phenylthiazol-5-yl, 3-phenylpyrid-6-yl, 4-(2,5-dimethylpyrrol-1-yl)phenyl, 4-(1-pyrrolyl)phenyl, 4-(2-quinolyl)phenyl, 4-(2-benzthiazolyl)phenyl, 4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl, 4-(2-benzoxazolyl)phenyl, 4-(2-methyloxazol-5-yl)phenyl, 4-(1-meythl-benzimidazol-2-yl)phenyl, 4-(2-thienyl)phenyl, 4-(2-thiazolyl)phenyl, 4-(3,4-methylenedioxyphenyl)phenyl, 4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl, 4-(3-quinolyl)phenyl, 4-(3-thienyl)phenyl and a 4-(3-furyl)phenyl moiety.

7. A compound of formula I, or a pharmaceutically acceptable salt thereof, wherein:
R^1 is hydroxy; R^2 is hydrogen; Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur;
and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more

substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives;
provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms.

8. A compound as claimed in claim 6 wherein Ar^1 is a 1,4-phenylene moiety and Ar^2 is selected from an oxadiazole and a quinolyl moiety.

9. A compound of formula I, or a pharmaceutically acceptable salt thereof, wherein;
R^1 is hydroxy; R^2 is hydrogen; Ar^1 is a heterocyclic moiety;
Ar^2 is phenyl; and wherein one or both of Ar^1 and Ar^2 may optionally be unsubstituted or may bear one or more substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno-(1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives.

10. A compound as claimed in claim 8 wherein Ar^2 is a pyridyl moiety.

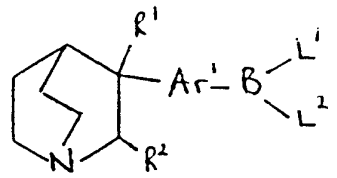
11. A compound as claimed in claim 1 which is selected from
3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)quinuclidin-3-ol
3-[4-quinol-3-ylphenyl]quinculidin-3-ol
3-[4-(5-methyl-1,2,4- oxadiazol-3-yl)phenyl]quinuclidin-3-ol
3-[2-phenylpyrid-5-yl]quinuclidin-3-ol

3-[5-phenylpyrid-2-yl]quinuclidin-3-ol
and pharmaceutically acceptable salts thereof

12. A process for preparing a compound of formula I, or a pharmaceuticaly acceptable salt thereof, as claimed in claim 1 which process is selected from:

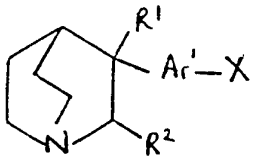
(a) for those compounds of formula I in which R^1 is hydroxy and R^2 is hydrogen, reacting a compound of formula Ar^2-Ar^1-M in which M is a metal atom or a derivative thereof, with quinuclidin-3-one;

(b) reacting a compound of formula II:

II 

wherein L^1 and L^2 are suitable ligands with a compound of formula Ar^2-X, in which X represents a leaving group, in the presence of a catalyst;

(c) reacting a compound of formula III:

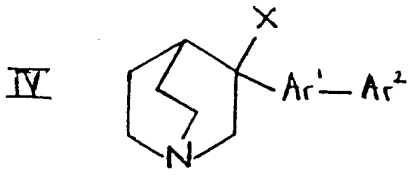
III 

in which X is a suitable leaving group with a compound of formula hal-Ar^1-$B(L^1)L^2$ in which L^1 and L^2 are suitable ligands in the presence of a catalyst;

(d) for those compounds of formula I in which R^1 and R^2 are both hydrogen, reducing a compound of formula I in which R^1 and R^2 are joined together so that -CR^1-CR^2 is a double bond;

(e) for those compounds of formula I in which R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond, dehydrating a compound of formula I in which R^1 is hydroxy;

(f) for compounds of formula I in which R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond, treating a compound of formula IV:



in which X is a leaving group with a base; and

(g) for those compounds of formula I in which R^1 and R^2 are both hydrogen, by dehydroxylation of a compound of formula I in which R^1 is hydroxy;

and whereafter, when a pharmaceutically-acceptable salt of a compound of the formula I is required, reacting a compound of formula I with an acid which affords a physiologically acceptable anion, or with a base which affords a physiologically acceptable cation.

13. A pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof thereof, as claimed in any one of claims 1 to 9 together with a pharmaceutcially acceptable diluent or carrier.

14. A method of inhibiting squalene synthase in a warm-blooded animals (such as man) requiring such treatment, which method comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically-acceptable salt thereof,
wherein:
R^1 is hydrogen or hydroxy;
R^2 is hydrogen; or
R^1 and R^2 are joined together so that CR^1-CR^2 is a double bond;
Ar^1 is a phenylene moiety and Ar^2 is a heterocyclic moiety; or
Ar^1 is a heterocyclic moiety and Ar^2 is a phenyl moiety;
and wherein one or both of Ar^1 and Ar^2 may optionally bear one or more

substituents independently selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino N-(1-6C)alkylcarbamoyl, di-N,N-[(1-6C)alkyl]carbamoyl, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno (1-6C)alkyl, (1-6C)alkanoylamino, ureido, N'-(1-6C)alkylureido, (1-6C)alkanoyl and oxime derivatives thereof and O-(1-6C)alkyl ethers of said oxime derivatives;
provided that Ar^2 is not a 6-membered heteroaryl moiety containing one or two nitrogen atoms; and that when R^1 and R^2, are both hydrogen, Ar^1 is not an oxadiazole moiety.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 93/02614

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D453/02 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 135 935 (MERCK & CO. , INC.) 4 August 1992 cited in the application * complete document * ---	1,13
X	EP,A,0 307 142 (MERCK SHARP & DOHME LTD.) 15 March 1989 * examples 3,5,7-9,12,16,18,39 * ---	1
A	WO,A,92 15579 (RHONE-POULENC RORER INTERNATIONAL INC.) 17 September 1992 cited in the application see claims ---	1,13
P,A	WO,A,93 24486 (ZENECA LTD.) see claims --- -/--	1,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1994	23. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 93/02614

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO,A,93 09115 (IMPERIAL CHEMICAL INDUSTRIES PLC) 13 May 1993 see claims	1,13

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/02614

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

formation on patent family members

Inter nal Application No
PCT/GB 93/02614

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5135935	04-08-92	NONE		
EP-A-0307142	15-03-89	AU-A-	2207388	16-03-89
		JP-A-	1104070	21-04-89
WO-A-9215579	17-09-92	AU-A-	1752792	06-10-92
WO-A-9324486	09-12-93	NONE		
WO-A-9309115	13-05-93	AU-A-	2783392	07-06-93
		CA-A-	2081674	01-05-93
		EP-A-	0569564	18-11-93