Synthesis and Activity of a Novel Series of 3-Biarylquinuclidine Squalene Synthase Inhibitors[1]

George R. Brown,* David S. Clarke, Alan J. Foubister, Susan Freeman, Peter J. Harrison,† Michael C. Johnson, Keith B. Mallion, John McCormick, Fergus McTaggart, Alan C. Reid, Graham J. Smith, and Melvyn J. Taylor

Cardiovascular and Muscoskeletal Department, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

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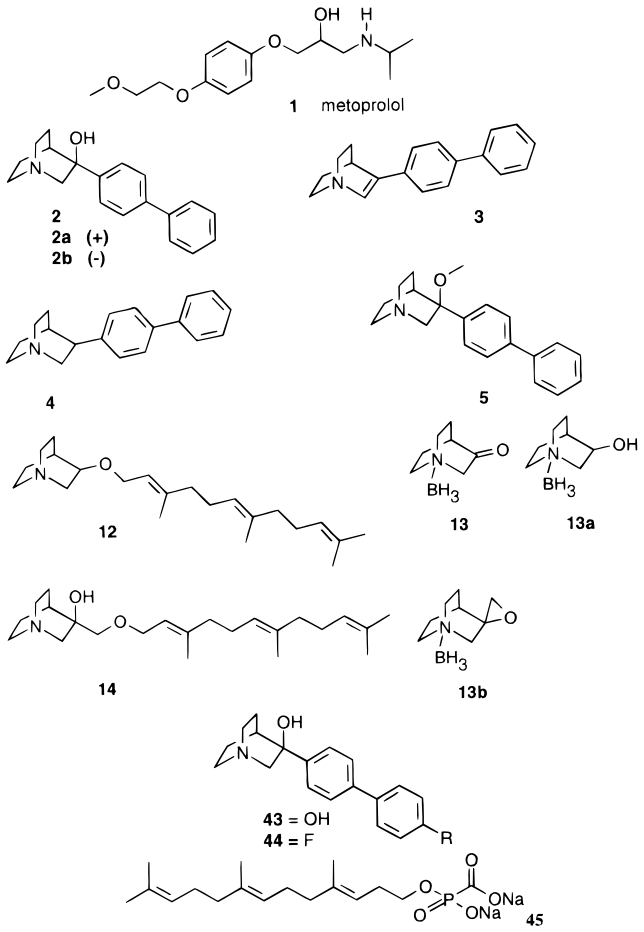
Quinuclidines with a 3-biaryl substituent are a new class of potent, orally active squalene synthase (SQS) inhibitors. Variants around these rigid structures indicate key structural requirements for cationic SQS inhibitors. Thus the lower *in vitro* potency found for quinuclidines bearing 3-substituents, which did not overlay the biphenyl group of 3-(biphenyl-4-yl)-3-hydroxyquinuclidine (**2**) (IC_{50} = 16 nM, rat microsomal SQS), implied a directional requirement for the 3-substituent. Similarly, the lower potency of the 3-terphenyl analogue **6** (IC_{50} = 370 nM) indicated size constraints for this substituent. In compounds with a linking group between the quinuclidine and biphenyl ring, linking groups of lower lipophilicity were less well tolerated (e.g., **17**, CH_2CH_2, IC_{50} = 5 nM vs **19**, NHCO, IC_{50} = 1.2 μM). Replacement of the distal phenyl ring of **2** with a more polar pyridine heterocycle caused a reduction in *in vitro* potency. In general, good *in vivo* activity in the rat was restricted to 3-hydroxy analogues, with the 3-[4-(pyrid-4-yl)phenyl] derivative **39** (IC_{50} = 161 nM) showing the best inhibition (following oral dosing) of cholesterol biosynthesis from mevalonate (ED_{50} = 2.7 mg/kg).

Raised levels of plasma LDL cholesterol are widely accepted[2] to be a risk factor for human coronary heart disease. Although patients have benefitted from cholesterol-lowering regimes, clear evidence for a reduction in patient mortality had been lacking. Recently, however, the Scandinavian 4S clinical study with the HMGCoA reductase inhibitor simvastatin has reported[3] an improvement in the survival of patients with existing coronary disease. This study has thus added impetus to the search for novel hypocholesterolemic agents which would give a greater reduction in cholesterol levels than is currently available from the HMGCoA reductase inhibitor class of drugs and hence the prospect of more effective treatment of coronary disease.

Plasma LDL cholesterol levels are lowered when there is a temporary interruption of cholesterol biosynthesis, which causes upregulation of hepatic LDL receptors and a consequent removal of LDL cholesterol from the blood plasma. Indirect clinical precedent supporting this hypothesis is found for the HMGCoA reductase inhibitor class of drugs,[4] and as part of efforts to find new hypocholesterolemic agents, the inhibition of other steps of the biosynthesis pathway has been investigated. Inhibition of squalene synthase (SQS) has been postulated to be advantageous, and potent *in vitro* inhibitors have been discovered.[5] The most effective *in vivo* inhibitors of SQS are, however, the polyanionic natural products[6] (termed squalestatins or zaragozic acids) and the substituted bisphosphonates.[7] Both of these inhibitor series have been reported[8] to have poor oral bioavailability in animals and to display potentially toxic actions. Our search for an alternative series of inhibitors led to the discovery of weak *in vitro* inhibition (IC_{50} = 14 μM) in a rat liver microsomal SQS assay for the β-adrenergic receptor-blocking drug metoprolol (**1**; Chart 1). Further directed screening of related compounds from the Zeneca compound collection with either similar chemical structure or similar β-receptor antagonist properties afforded little inhibitory activity, indicating the discriminating nature of the SQS enzyme. However, a quinuclidine derivative, **2** (which was originally designed as a rigid conformer of the "ethanolamine"

Chart 1



† Deceased.

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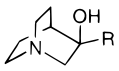
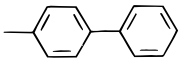
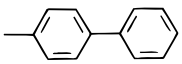
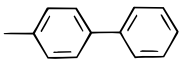
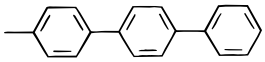
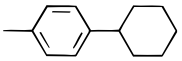
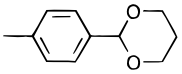
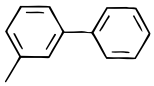
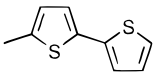
Table 1. *In Vitro* Activities of Substituted 3-Hydroxyquinuclidines



Compound	R	mp °C	IC_{50} rat microsomal SQS (n = 2) nM	Formula[a]
2		174-175	16	$C_{19}H_{21}NO\ 0.1H_2O$
2a (+)		158-159	7	$C_{19}H_{21}NO\ 0.1H_2O$
2b (-)		159-160	121	$C_{19}H_{21}NO\ 0.1H_2O$
3	See Chart 1	269-270[b]	18	$C_{19}H_{19}N.HCl$
4	See Chart 1	248-249[b]	11	$C_{19}H_{21}N.HCl$
5	See Chart 1	227-229[b]	>2.5 μM	$C_{20}H_{23}NO.HCl.0.4\ H_2O$
6		214-215	370	$C_{25}H_{25}NO.0.5\ H_2O$
7		165-167	>2.5 μM	$C_{13}H_{17}NO$
8		172-173	190	$C_{19}H_{27}NO$
9		215-217	>2.5 μM	$C_{17}H_{23}NO_3$
10		165-166	60	$C_{19}H_{21}NO.0.1\ H_2O$
11		205-206	2.5 μM	$C_{15}H_{17}NOS_2$
12	See Chart 1	oil	70	$C_{22}H_{37}NO$
14	See Chart 1	oil	60	$C_{23}H_{39}NO_2$
45	Squibb 32377[c]	oil	30μM	

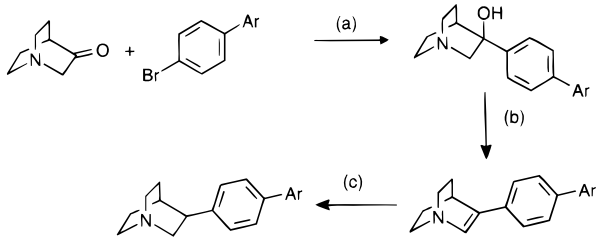
[a] All new compounds analyzed correctly (±0.4%) for C,H,N and afforded ^{1}H-NMR data consistent with the structures assigned. [b] HCl salt. [c] Squibb 32377 used as standard SQS inhibitor; lit.[5b] IC_{50} = 9 μM.

class[9] of β-adrenergic receptor-blocking drugs), was identified as a potent SQS inhibitor (IC_{50} = 16 nM). A program of work was instituted to give further insight into the structure−activity relationship around 3-biarylquinuclidines as SQS inhibitors, and the synthesis and inhibitory properties are now described for this novel[10] series of cationic SQS inhibitors.

Chemistry

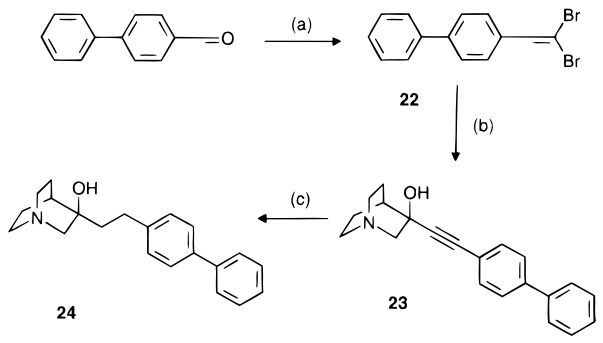
Compounds **2** and **6**−**11** (Table 1) were prepared by reaction of quinuclidin-3-one and the appropriate bromoaryl compound in the presence of ^{s}BuLi (general procedure A, Scheme 1). The enantiomers **2a**,**b** were obtained by chromatography of **2** on a chiral column. Dehydration of **2** in refluxing PhMe in the presence of 4-toluenesulfonic acid afforded **3**, which was hydrogenated over Pd/C catalyst to give **4**. Reaction of the known[11] quinuclidin-3-one (*N*-*B*) borane **13** with the Grignard reagent from 4-(4-bromophenyl)benzene followed by methylation with MeI in the presence of NaH and subsequent deprotection of the nitrogen atom with HCl gave the methyl ether **5** (in general, alkylation reactions of OH-substituted quinuclidines proceeded in poor yield, unless the quinuclidine ring nitrogen atom was protected as a borane complex). In a similar manner 3-hydroxyquinuclidine (*N*-*B*) borane[12] **13a** was allowed to react with farnesyl bromide in the presence of NaH to give **12** (Chart 1) after deprotection with HCl. Farnesol was treated with NaH before reaction with the quinuclidine spiro-oxirane (*N*-*B*) borane[13] **13b** (Chart 1) to give **14** after deprotection with HCl. The *E* and *Z* olefins **15** and **16** were separated by column chromatography after Wittig reaction between 3-formylquinuclidine[14] and [(4-biphenylyl)methyl]triphenylphosphonium chloride in the presence of KO^{t}Bu. Catalytic transfer hydrogenation of **15**, with HCO_2NH_4 in the presence of 10% Pd/C, gave the ethyl derivative **17**. 4-Phenylbenz-

Scheme 1. General Procedure A[a]



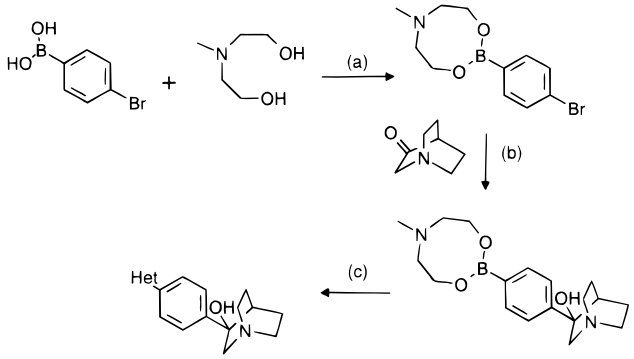
[a] (a) ^{s}BuLi, THF, −70 °C; (b) *p*-TSA, PhMe; (c) H2, Pd/C.

Scheme 2[a]



[a] (a) CBr_4, PPh_3, Zn; (b) ^{n}BuLi, THF; (c) $CH_3CO_2NH_4$, Pd/C.

Scheme 3. General Procedure B[a]



[a] (a) THF; (b) ^{s}BuLi, THF, quinuclidin-3-one; (c) HetBr, NH_4Cl, $Pd(PPh_3)_4$, Na_2CO_3.

aldehyde was allowed to react with 3-aminoquinuclidine, and the resulting imine **18** was reduced with $NaBH_4$ to give **19**. Acylation of 3-aminoquinuclidine with 4-phenylbenzoyl chloride and 4-phenylbenzenesulfonyl chloride gave **20** and **21**, respectively.

Reaction[15] of 4-phenylbenzaldehyde (Scheme 2), CBr_4, PPh_3, and zinc dust gave 1-(biphenyl-4-yl)-2,2-dibromoethylene (**22**), which on treatment with ^{n}BuLi and quinuclidin-3-one afforded the ethynyl derivative **23**. Reduction of **23** with HCO_2NH_4 in the presence of 10% Pd/C gave the ethyl-linked derivative **24**. Compounds **25** and **26** were prepared by reaction of quinuclidin-3-one and trimethylsulfoxonium iodide with 4-phenylphenol or 4-phenylthiophenol (respectively) in the presence of NaOH and ^{n}Bu$_4$HSO$_4$. Oxidation of **26** with $NaIO_4$ gave the sulfoxide **27** and with potassium peroxymonosulfate the sulfone **28**. Wadsworth−Emmons reaction of quinuclidin-3-one with diethyl [(biphenyl-4-yl)methyl]-phosphonate in the presence of KO^{t}Bu and reduction of the product with HCO_2NH_4 in the presence of Pd/C afforded **29**. The thio-linked quinuclidine **30** was prepared from 3-chloroquinuclidine and 4-phenylthiophenol in the presence of NaH, and subsequent oxidation (as for the preparation of **28**) gave the sulfone **31**. Reaction of the Li derivative prepared from 4-bromobiphenyl with 3-formylquinuclidine gave a separable mixture of the diastereoisomeric pairs **32** and **33**. Reaction of thiophene-2-boronic acid and 3-(4-bromophenyl)-3-hydroxyquinuclidine with $(PPh_3)_4$ Pd as catalyst gave **34**.

The known[16] (4-bromophenyl)boronic acid *N*-methyl-*O*,*O*-diethanolamine ester was prepared *in situ* and allowed to react with quinuclidin-3-one (general procedure B, Scheme 3) in the presence of ^{s}BuLi, and the product was reacted in the presence of $(PPh_3)_4$Pd with 2-bromothiazole, 3-bromoquinoline, and 2-bromopyrimidine to afford respectively **35**, **40**, and **41** (Table 3). Compounds **36**−**39** were prepared from the appropriate biaryl bromide and quinuclidin-3-one using general procedure A. When 2-phenylthiazole (instead of a bromo derivative) was reacted with quinuclidin-3-one using general procedure A, **42** resulted. Compounds **43** and **44** (Chart 1) were prepared by general procedure A using respectively 4-bromo-4′-[(*tert*-butyldimethylsilyl)oxy]biphenyl and 4-bromo-4′-fluorobiphenyl as starting materials. Spectroscopic data are provided as Supporting Information for compounds, which do not appear in the Experimental Section in detail (i.e., those prepared by the general procedures).

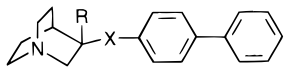
Biological Results and Discussion

The structural requirements for inhibitory activity were examined by variation of (a) the quinuclidine ring, (b) the biaryl rings, (c) a linking group between the 3-biaryl substituent and the quinuclidine ring, and (d) the biaryl ring with a selection of heteroaromatic rings. Thus the inhibitory potency *in vitro* in the rat microsomal SQS assay was retained following modifications to the quinuclidine ring of **2** (Table 1), as shown by the dehydro and desoxy examples **3** and **4**. The hydroxyl group in **2** was not essential for potent *in vitro* enzyme inhibition, however, as **2** and **4** were equipotent as SQS inhibitors. The methyl ether **5** was a much less potent inhibitor, and this result implied a steric impediment to activity at the 3-position of the quinuclidine ring. Both the enantiomers of **2** displayed inhibitory activity, although the (+)-enantiomer **2a** was found to be more potent.

In anticipation that the biaryl group was binding to a lipophilic region of the enzyme, an additional phenyl ring was introduced onto **2**, which led to a reduction in potency (as in **6**), but an even greater reduction in potency was observed when the distal phenyl ring was not present, as in **7**. When the distal phenyl ring was replaced by a saturated ring, e.g., cyclohexyl **8** or dioxanyl **9**, inhibitory potency was also reduced relative to **2**, and thus the best inhibitory activity was found in compounds with planar biaryl substitution. The biaryl quinuclidines **10** and **11**, however, were also found to be less active than **2**, which implies that there is also a directional requirement for the rigid biaryl side chain. The more marked loss of inhibitory potency found for **11**, against **10** (2.5 μM vs 60 nM), may reflect the coplanarity of the thiophene rings in **11**. These test results for compounds **6**−**11** thus suggest that among the ring variations examined, the 4-biphenyl group is optimal for potent inhibitory activity, for both the size and the planarity and in the directional requirement of the substituent in relation to the rigid quinuclidine ring system.

When compounds were synthesized (Table 2) with a link group inserted between the biaryl residue and the quinuclidine ring, the 4-biphenyl group was chosen for all analogues, so that the different link groups could be compared. In the two-atom-linked compounds, a two-carbon link (**15** and **17**) produced very potent SQS inhibitors, but the cis olefin **16** was of lower potency (supporting the above hypothesis that there is a directional requirement of the biaryl substituent for high inhibitory potency). Quinuclidines **19**−**21** (CLOGP range 3.5−4.2) contain less lipophilic linking groups

Table 2. *In Vitro* Activities of Bridged Quinuclidines



compd	R	X	mp (°C)	IC_{50} rat microsomal SQS ($n = 2$; nM)	formula[a]
15	H		>300[b]	4	$C_{21}H_{23}N{\cdot}HCl{\cdot}H_2O$
16	H		216−217[b]	580	$C_{21}H_{23}N{\cdot}HCl{\cdot}0.25H_2O$
17	H	CH_2CH_2	223−224[b]	5	$C_{21}H_{25}N{\cdot}HCl$
19	H	NHCH2	180−181[b]	140	$C_{20}H_{24}N_2{\cdot}2HCl{\cdot}H_2O$
20	H	NHCO	183−185	1.2 μM	$C_{20}H_{22}N_2O{\cdot}0.25H_2O$
21	H	$NHSO_2$	77−78	>2.5 μM	$C_{19}H_{22}N_2O_2S{\cdot}0.5EtOAc$
23	OH	C≡C	217−218	3	$C_{21}H_{21}NO$
24	OH	CH_2CH_2	224−225[b]	7	$C_{21}H_{25}NO{\cdot}HCl{\cdot}0.3H_2O$
25	OH	CH_2O	132−133	13	$C_{20}H_{23}NO_2{\cdot}0.2H_2O$
26	OH	CH_2S	145−147[b]	8	$C_{20}H_{23}NOS{\cdot}HCl{\cdot}H_2O$
27	OH	CH_2SO	157−162	>2.5 μM	$C_{20}H_{23}NO_2S{\cdot}0.5H_2O$
28	OH	CH_2SO_2	203−205	>2.5 μM	$C_{20}H_{23}NO_3S{\cdot}0.25H_2O$
29	H	CH_2	283−287[b]	27	$C_{20}H_{23}NO_3S$
30	H	S	72−77	21	$C_{19}H_{21}NS$
31	H	SO_2	126−127	>2.5 μM	$C_{19}H_{21}NO_2S{\cdot}0.5H_2O$
32	H	CHOH	182−184	2.5 μM	$C_{20}H_{23}NO{\cdot}0.4H_2O$
33	H	CHOH	213−214	2.5 μM	$C_{20}H_{23}NO{\cdot}0.65H_2O$

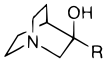
[a] All new compounds analyzed correctly (±0.4%) for C,H,N and afforded ^{1}H-NMR data consistent with the structures assigned. [b] HCl salt.

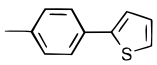
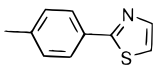
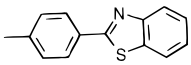
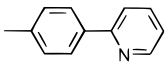
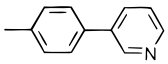
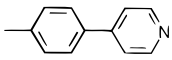
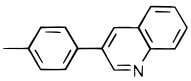
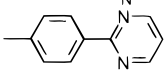
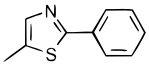
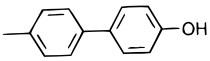
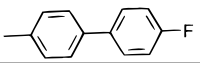
(e.g., NHCO), and here inhibitory potency was well below that of **15** and **17** (CLOGP = 5.2, 5.5) with the sulfonamide group affording a compound, **21** (CLOGP = 3.5), only showing inhibition at micromolar concentrations. When the two-atom-linked 3-biphenylylquinuclidines also had a 3-hydroxy substituent, the overall CLOGP values were lowered due to the presence of the OH group, but comparisons of inhibitory potencies within this less lipophilic series revealed the same trend between IC_{50} values and CLOGP as found for the non-hydroxy quinuclidines (**24**, IC_{50} = 7 nM, CLOGP = 4.3 vs **28**, IC_{50} > 2.5 μM, CLOGP = 2.7). The quinuclidines with a single link atom also showed this trend between the nature of the linking group and enzyme inhibitory potency (**29** and **30**, CLOGP = 5.0, 6.5 vs **31** and **32**, CLOGP = 3.3). Thus within a series of quinuclidine SQS inhibitors, the less lipophilic linking groups (Table 2) lowered the *in vitro* inhibitory potency. These results may be explained by the hypothesis that the 3-biaryl substituent in these quinuclidine SQS inhibitors was acting as a mimic of a farnesyl chain subunit, where a polar function would be expected to be less well tolerated in a lipophilic region of the active site (see below).

Introduction of heteroaromatic rings in place of the distal phenyl ring of **2** (Table 3) did not afford an *in vitro* structure−activity relationship based on CLOGP values. Greatest *in vitro* potency was found for the thiophene **34** and the thiazole ring-containing **35**, **36**, and **42**, whereas the more polar nitrogen-substituted ring systems present in **37**−**40** were apparently less well accepted at the inhibitory site. Unexpectedly the pyrimidine **41** was a potent SQS inhibitor.

Analysis of how these new SQS inhibitors might be acting *in vitro* was based on consideration of the enzyme mechanism.[17] SQS assembles two molecules of farnesyl pyrophosphate (FPP) into squalene in two distinct steps. The first of these requires the transfer of a farnesyl residue from one FPP onto the C(2)−C(3) double bond of the other to give presqualene pyrophosphate (PSPP). This in turn is converted into squalene by rearrangements that are terminated by the transfer of hydride from the NADPH cofactor. Both steps have been envisaged[17] to involve a cyclopropyl carbocationic intermediate. Ammonium,[18] amidinium,[19] and sulfonium[20] inhibitors of SQS have been described which potentially mimic such putative carbocationic intermediates, but with the exception of certain farnesylamine

Table 3. *In Vitro* Activities of 3-Heteroarylquinuclidines



Compound	R	mp °C	IC_{50} rat microsomal SQS (n = 2) nM	Formula[a]
34		165-166	40	$C_{17}H_{19}NOS.\ 0.5\ H_2O$
35		218-219	30	$C_{16}H_{18}N_2OS.\ 0.5\ H_2O$
36		215-216	6	$C_{20}H_{20}N_2OS$
37		237-238	240	$C_{18}H_{20}N_2O.\ 0.25\ H_2O$
38		172-173	270	$C_{18}H_{20}N_2O.\ 0.5\ H_2O$
39		127-130	161	$C_{18}H_{20}N_2O.\ H_2O$
40		220-221	200	$C_{22}H_{22}N_2O.\ 0.25\ H_2O$
41		246-247	30	$C_{17}H_{19}N_3O.\ 0.25\ H_2O$
42		168-169	60	$C_{16}H_{18}N_2OS$
43		270-271	132	$C19H_{12}NO_2.0.6H_2O$
44		172-173	18	$C_{19}H_{20}FNO.0.25H_2O$

[a] All new compounds analysed correctly (±0.4%) for C,H,N and afforded ^{1}H-NMR data consistent with the structures assigned.

derivatives,[21] SQS inhibitory activity has been low (micromolar). The potent (nM) quinuclidine SQS inhibitors (pK_a for **2** = 9.1) described above may also inhibit the enzyme by acting as carbocation mimics for either the first or second step of the FPP to squalene conversion. Thus in the phosphate buffer used in the *in vitro* test, ion pair formation may occur between the quinuclidine inhibitors and phosphate/pyrophosphate ions. The biarylquinuclidines also conform to Biller's hypothesis[22] (regarding phosphonate SQS inhibitors) that aryl units may act as isosteres for isoprenyl subunits in the farnesyl chain because the 4-biphenyl group was an optimal 3-substituent. This hypothesis may account for the poor inhibitory potency seen with quinuclidines containing less lipophilic link groups (Table 2) and of compounds with a distal phenyl ring replaced by the more polar pyridine ring (**37**−**39**, IC_{50} range 161−240 nM). The farnesyl compounds **12** and **14** were prepared to examine the hypothesis further and found to be good *in vitro* SQS inhibitors (IC_{50} = 70 and 50 nM, respectively) but with a lower potency than **2**. In fully extended conformations, however, **12** and **14** would overlay more optimally with the biphenyl-3-yl compound **10**, which has a similar inhibitory potency.

Oral dosing of compound **2** to rats gave an ED_{50} for inhibition of cholesterol biosynthesis (from mevalonate) of 7 mg/kg (95% confidence limits, 3.6−13.6), but the more potent enantiomer *in vitro* (**2a**) had the same potency *in vivo* as **2**. This finding of *in vivo* activity for the potentially cationic quinuclidine SQS inhibitors (e.g., **2**) contrasts with its lack in some earlier series of inhibitors that are referenced above. Recently, however, an oxypropylamine series of inhibitors[23] and further quinuclidines in the patent literature[10] have been claimed to afford significant activity following oral dosing to rats. In anticipation that **2** and related biphenyl derivatives might be hydroxylated *in vivo*, the 4-hydroxy derivative **43** (Chart 1) and the corresponding 4-fluoro derivative **44** were tested in rats by oral dosing. Although **43** exhibited a lower *in vitro* potency (IC_{50} = 132 nM) than **2**, the putative metabolite possessed similar activity *in vivo* (ED_{50} = 12 mg/kg). *In vitro* potency was restored (18 nM vs 16 nM for **2**) in the fluoro analogue **44**, for which metabolism analogous to that of **2** is blocked, and this compound showed an identical oral ED_{50} in rats with that of **2**. Thus while the presence of an OH group in **43** clearly reduces *in vitro* potency, *in vivo* activity is unaffected. Other compounds in Table 1 (**3**−**14**) afforded ED_{50} values which were >10 mg/kg, and this also applied to compounds without a 3-OH group in Table 2, i.e., **15**−**20** and **29**−**33**. The 3-hydroxy derivatives **23**−**26** were less active having ED_{50} values in the range 35−50 mg/kg, but good oral activity was discovered among the heterocyclic analogues of **2** (Table 3). The potent *in vitro* inhibitors (such as **34**−**36** and **43**; Table 3**)** had ED_{50} values which were >10 mg/kg, but despite their lower *in vitro* inhibitory potency, the pyridyl ring-containing analogues **37**−**41** had an ED_{50} range of 2−16 mg/kg. In particular **39** was the most potent compound *in vivo*, with an ED_{50} of 2.7 mg/kg (95% confidence limits, 1.4−5.2).

In conclusion 3-biarylquinuclidines are potent inhibitors of rat microsomal SQS and may (compared to other more flexible cationic SQS inhibitors) provide useful information on the structural requirements for the acceptance of cationic inhibitors at the enzyme active site. Thus the lipophilic biaryl side chain in the most potent *in vitro* inhibitors is rigidly held in relation to the protonated quinuclidine nitrogen atom. The lower *in vitro* potency found for compounds bearing 3-substituents which do not overlay the biphenyl group of **2** implied a directional requirement for the lipophilic biaryl group. In compounds with a linking group between the quinuclidine and biaryl rings, the presence of a less lipophilic linking group moderated the SQS inhibitory potency and replacement of the distal phenyl rings of **2** with a more polar pyridine heterocycle gave a reduction in *in vitro* potency. Good *in vivo* activity was restricted to 3-hydroxy analogues, with the pyridyl derivative **39** showing the best inhibition of rat *in vivo* cholesterol biosynthesis.

Experimental Section

Melting points were determined with a Buchi apparatus and are uncorrected. The ^{1}H-NMR spectra were determined with a Bruker AM (200 MHZ) spectrometer (with $SiMe_4$ as an internal standard), and mass spectra were measured on a MS902 Kratos (AEI) instrument. Optical rotations were measured on a Perkin Elmer 241 polarimeter and elemental analyses determined on a Perkin Elmer series II-2400 analyzer. Reactions were carried out under an atmosphere of argon, and column chromatography was on E. Merck silica gel (Kieselgel 60, 230−400 mesh). Solvents were dried over $MgSO_4$ before evaporation. Sodium hydride was 60% dispersion in mineral oil.

General Procedure A: Preparation of 3-Biaryl-3-hydroxyquinuclidines 2 and 6−11. 3-(Biphenyl-4-yl)-3-hydroxyquinuclidine (2). ^{s}BuLi in cyclohexane (100 mL, 130 mmol) was added to a stirred solution of 4-bromobiphenyl (25 g, 107 mmol) in dry THF (240 mL) at −78 °C. The mixture was stirred for 5 min, and a solution of quinuclidin-3-one (12 g, 96 mmol) in dry THF (100 mL) was added during 20 min. Stirring was continued at −78 °C for 30 min and the mixture allowed to reach room temperature over 2 h; 2 M HCl (225 mL) was added below 10 °C and the aqueous layer washed with Et_2O (2 × 300 mL) before the addition of excess 10 M NaOH to pH 14. The mixture was extracted with EtOAc which had been heated to 50 °C and the extract allowed to cool, dried, and evaporated to give a colorless solid, which crystallized from EtOAc to give **2** (11.0 g, 41%): mp 165−166 °C; ^{1}H-NMR ($CDCl_3/CD_3CO_2D$) δ 1.7−1.9 (m, 3H), 2.5 (m, 1H), 2.5−2.7 (m, 1H), 3.2−3.5 (m, 4H), 3.7 (d, 1H, J = 13.6 Hz), 4.0 (d, 1H, J = 13.6 Hz), 7.3−7.7 (m, 9H); EI-MS m/z 279 (M^+). Anal. ($C_{19}H_{21}NO\cdot0.1H_2O$) C, H, N.

(+)- and (−)-3-(Biphenyl-4-yl)-3-hydroxyquinuclidine (2a,b). The racemate **2** (18 mg, 0.06 mmol) was resolved by chromatography on a chiral cell OD (250 × 4.6 mm i.d. column) using a 70:30:0.2 mixture (by volume) of *n*-hexane−^{i}PrOH−Et_2NH as eluant at a flow rate of 1 mL/min, to give the separate enantiomers which were crystallized from butan-2-one to give as crystalline solids: **2a** (8 mg, 88%, retention time 8.81 min) mp 158−159 °C, $[\alpha]^{22}_D$ = +32.0° (c = 3.4 mg/mL in MeOH), and **2b** (7.8 mg, 86%, 9.86 min) mp 159−160 °C, $[\alpha]^{22}_D$ = −31.2° (c = 3.3 mg/mL in MeOH).

3-(Biphenyl-4-yl)-2,3-dehydroquinuclidine Hydrochloride (3). 4-Toluenesulfonic acid (9.76 g, 54 mmol) and **2** (4.7 g, 16.8 mmol) were heated under reflux in PhMe (300 mL) for 2 h using a Dean−Stark water separator. The PhMe was evaporated and the residue dissolved in 1 M NaOH (125 mL). The aqueous mixture was extracted with EtOAc and the EtOAc layer washed with brine, dried, and concentrated to 60 mL. Excess of saturated ethereal HCl was added, and the precipitated solid crystallized from MeOH−EtOAc to give, as a colorless solid, **3** (3.7 g, 74%): mp 263−265 °C; ^{1}H-NMR (DMSO-d_6) δ 1.6−1.8 (m, 2H), 1.95−2.15 (m, 2H), 2.9−3.1 (m, 2H), 3.5−3.7 (m, 3H), 7.1 (d, 1H, J = 2.0 Hz), 7.3−7.5 (m, 3H),

7.6−7.8 (m, 6H); EI-MS *m/z* 262 (M + H). Anal. ($C_{19}H_{19}N$·HCl) C, H, N.

3-(Biphenyl-4-yl)quinuclidine Hydrochloride (4). **3** (260 mg, 0.87 mmol) in EtOH (25 mL) was hydrogenated at atmospheric pressure for 4 h over 10% Pd/C catalyst (30 mg). The catalyst was filtered and the EtOH evaporated. The residue was crystallized from MeOH−EtOAc to give, as a colorless solid, **4** (175 mg, 58%): mp 248-249 °C; ^{1}H-NMR (DMSO-d_6) δ 1.6−1.8 (m, 1H), 1.9−2.2 (m, 3H), 3.1−3.8 (m, 8H), 7.3−7.7 (m, 9H); EI-MS *m/z* 264 (M + H). Anal. ($C_{19}H_{21}N$·HCl·1.5H_2O) C, H, N.

3-(Biphenyl-4-yl)-3-methoxyquinuclidine Hydrochloride (5). 4-Bromobiphenyl (1.68 g, 7.2 mmol) was added to stirred Mg turnings (with a crystal of I_2) in Et_2O (8 mL) and the mixture heated to reflux for 1.5 h. **13**[11] (1.0 g, 7.2 mmol) in THF (10 mL) was added at room temperature and the mixture heated under reflux for 1 h. After cooling, H_2O (15 mL) was added and the mixture extracted with EtOAc. The EtOAc layer was washed with H_2O, dried, and evaporated to a solid which was triturated with CH_2Cl_2 (10 mL), and the borane complex of **2** (0.4 g, 19%) was collected. The complex (382 mg, 1.3 mmol) in DMF (3 mL) was added to NaH (31.2 mg, 1.3 mmol) in DMF (0.5 mL) followed by MeI (369 mg, 2.6 mmol) and stirring continued for 3 h. H_2O (30 mL) was added and the mixture extracted with EtOAc. The EtOAc layer was washed with H_2O, dried, and evaporated and the residue triturated in CH_2Cl_2−hexane (1:1) and filtered; the filtrate was evaporated to give the borane complex of **5** (133 mg, 33%). This complex (133 mg) in acetone (5 mL) was treated with EtOH/HCl to pH 1, and after 30 min the mixture was concentrated to 2 mL and Et_2O (4 mL) added. The resulting precipitate was collected to give, as a colorless solid, **5** (97 mg, 68%): mp 227−229 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40−1.62 (m, 1H), 1.72−2.0 (m, 2H), 2.10−2.29 (m, 1H), 2.80 (m, 1H), 2.88 (s, 3H), 3.1−3.36 (m, 4H), 3.52−3.8 (m, 2H), 7.3−7.63 (m, 5H), 7.72 (t, 4H, J = 8.4 Hz); EI-MS *m/z* 294 (M + H). Anal. ($C_{20}H_{23}NO$·HCl·0.4H_2O) C, H, N.

3-(Farnesyloxy)quinuclidine (12). **13a**[12] (1.4 g, 10 mmol) was added to NaH (414 mg, 11 mmol) in DMF (10 mL), farnesyl bromide (2.7 mL, 10 mmol) in DMF (3 mL) added at 5 °C, and the mixture stirred for 3 h at ambient temperature. The mixture was poured onto H_2O (130 mL) and extracted with EtOAc. The EtOAc layer was washed with H_2O, dried, and evaporated to a residue, which was purified by chromatography on silica gel eluting with pentane−EtOAc (19:1) to give an oil (2.65 g, 77%). The oil (2.0 g) in acetone (35 mL) was treated with EtOH/HCl to pH 1 and stirred for 20 h. The acetone was evaporated and the residue partitioned between Et_2O and H_2O. The aqueous phase was made alkaline to pH 11 with 10 M NaOH and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and evaporated to give, as an oil, **12** (1.55 g, 80%); ^{1}H-NMR ($CDCl_3$) δ 1.22−1.48 (m, 2H), 1.55−1.78 (m, 12H), 1.85 (m, 1H), 1.9−2.2 (m, 9H), 2.60−3.0 (m, 5H), 3.03−3.18 (m, 1H), 3.48 (m, 1H), 3.85−4.07 (m, 2H), 5.08 (m, 2H), 5.35 (m, 1H); EI-MS *m/z* 362 (M + H). Anal. ($C_{22}H_{37}NO$) C, H, N.

3-[(Farnesyloxy)methyl]-3-hydroxyquinuclidine (14). Compound **14** was prepared in a similar manner to **25**, by opening the known[13] intermediate borane-protected epoxide **13b** *in situ* with farnesol sodium salt and deprotection to give, as an oil, **14** (50%); ^{1}H-NMR ($CDCl_3$) δ 1.15−1.37 (m, 1H), 1.50 (m, 1H), 1.57 (s, 6H), 1.65 (s, 6H), 1.82−2.2 (m, 11H), 2.45−3.0 (m, 7H), 3.21 (d, 1H, J = 8.3 Hz), 3.37 (d, 1H, J = 8.3 Hz), 4.0 (d, 2H, J = 6.3 Hz), 5.07 (m, 2H), 5.31 (m, 1H); EI-MS *m/z* 362 (M + H). Anal. ($C_{23}H_{39}NO_2$) C, H, N.

***(E)*- and *(Z)*-3-[(4-Phenyl)styr-2-yl]quinuclidine Hydrochloride (15 and 16).** KO^{t}Bu (1.12 g, 10 mmol) was added to a stirred suspension of [(4-biphenylyl)methyl]triphenylphosphonium chloride (4.4 g, 9.4 mmol) in THF (60 mL). The mixture was stirred for 30 min and cooled to −40 °C before a solution of 3-formylquinuclidine[14] (570 mg, 4.1 mmol) in THF (5.0 mL) was added over 10 min. The mixture was stirred at ambient temperature for 16 h before the THF was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with H_2O, dried, and evaporated and the residue purified by flash column chromatography on silica gel eluting with 10% MeOH−CH_2Cl_2 followed by MeOH−CH_2Cl_2−0.880 ammonia (10:90:0.1) to give **16** as free base (R_f = 0.72), which was dissolved in EtOH and an excess of ethereal HCl. Et_2O was added until crystallization began to give, as a colorless solid, **16** (90 mg, 7%): mp 216−217 °C; ^{1}H-NMR (D_2O) δ 1.8−2.15 (m, 5H), 2.15−2.4 (m, 1H), 3.02−3.6 (m, 6H), 5.89−6.0 (m, 1H), 6.3−6.7 (d, 1H, J = 12 Hz), 7.3−7.4 (d, 2H, J = 7.0 Hz), 7.4−7.6 (m, 3H), 7.6−7.8 (t, 4H); EI-MS *m/z* 290 (M + H). Anal. ($C_{21}H_{23}N$·HCl·0.25H_2O) C, H, N.

Further elution with the above eluant gave **15** as free base (R_f = 0.6), which was converted to the hydrochloride salt as above to give **15** (65 mg, 5%): mp >300 °C; ^{1}H-NMR (D_2O) δ 1.8−2.2 (m, 5H), 2.8−3.0 (m, 1H), 3.1−3.22 (m, 1H), 3.3−3.7 (m, 5H), 6.25−6.4 (m, 1H), 6.5−6.6 (d, 1H, J = 14.4 Hz), 7.43−7.6 (m, 5H), 7.6−7.78 (m, 4H); EI-MS *m/z* 290 (M + H). Anal. ($C_{21}H_{23}N$·HCl·H_2O) C, H, N.

3-[(Biphenyl-4-yl)eth-2-yl]quinuclidine Hydrochloride (17). Pd/C (10%, 40 mg) was added to a stirred solution of HCO_2NH_4 (250 mg, 4 mmol) and **15** (243 mg, 0.75 mmol) in MeOH (10 mL) and the mixture heated at 60 °C with stirring for 1 h. A further quantity of HCO_2NH_4 (500 mg, 8 mmol) was added and the mixture heated at 60 °C for a further 1 h. The mixture was cooled and filtered through diatomaceous earth, and the residues were washed with MeOH. The MeOH filtrates were evaporated, and the residue was partitioned between 4 M NaOH and CH_2Cl_2. The CH_2Cl_2 layer was separated, dried, and evaporated to give an oil, which was purified by flash column chromatography on silica gel, eluting with MeOH−CH_2Cl_2−0.880 ammonia (10:90:0.1). The product was dissolved in acetone and an excess of ethereal HCl added followed by sufficient Et_2O to cause crystallization, as a colorless solid, of **17** (115 mg, 47%): mp 223−224 °C; ^{1}H-NMR (D_2O) δ 1.6−2.1 (m, 8H), 2.5−2.65 (t, 2H, J = 8.3 Hz), 2.75−2.9 (m, 1H), 3.1−3.5 (m, 5H), 7.22−7.32 (d, 2H, J = 7.0 Hz), 7.32−7.52 (m, 3H), 7.55−7.65 (d, 2H, J = 8.3 Hz), 7.65−7.75 (d, 2H, J = 8.3 Hz); EI-MS *m/z* 292 (M + H). Anal. ($C_{21}H_{25}N$·HCl) C, H, N.

3-[[(Biphenyl-4-yl)methyl]amino]quinuclidine Hydrochloride (19). 4-Phenylbenzaldehyde (160 mg, 0.88 mmol) and 3-aminoquinuclidine (110 mg, 0.87 mmol) were heated under reflux in PhMe (50 mL) for 2 h using a Dean−Stark water separator, and the PhMe was evaporated. The residue was purified by medium pressure column chromatography on alumina (ICN Alumina N 32-63), eluting with EtOAc to give 3-[[(biphenyl-4-yl)methylene]amino]quinuclidine, as a colorless solid (**18**; 150 mg, 60%): mp 82−84 °C; ^{1}H-NMR ($CDCl_3$) δ 1.35−1.5 (m, 1H), 1.6−1.8 (m, 3H), 2.2−2.3 (m, 1H), 2.8−3.0 (m, 4H), 3.0−3.2 (m, 2H), 3.4−3.5 (m, 1H), 7.3−7.5 (m, 3H), 7.55−7.65 (m, 4H), 7.8 (d, 2H, J = 8.3 Hz), 8.3 (s, 1H); EI-MS *m/z* 291 (M + H).

$NaBH_4$ (260 mg, 7 mmol) was added to a stirred solution of **18** (990 mg, 3.4 mmol) in MeOH (50 mL) and the mixture stirred for 2 h. The MeOH was evaporated and the residue dissolved in 1 M HCl (12 mL). The aqueous solution was washed with Et_2O (3 × 25 mL) before the addition of excess 10 M NaOH to pH 14. The mixture was extracted with Et_2O and the extract dried and evaporated. An excess of saturated ethereal HCl was added to precipitate a solid which was crystallized from MeOH−EtOAc to give, as a colorless solid, **19** (820 mg, 74%): mp 180−181 °C; ^{1}H-NMR (DMSO-d_6) δ 1.7−2.0 (m, 3H), 2.2−2.4 (m, 1H), 2.6 (s, 1H), 3.1−3.8 (m, 8H), 4.2 (s, 2H), 7.3−7.5 (m, 3H), 7.6−7.8 (m, 6H); EI-MS *m/z* 293 (M + H). Anal. ($C_{20}H_{24}N_2$·2HCl·H_2O) C, H, N.

3-[(Biphenyl-4-yl)carbamoyl]quinuclidine (20). Et_3N (2.44 mL, 17.5 mmol) was added dropwise to 4-biphenylcarbonyl chloride (1.0 g, 4.6 mmol) and 3-aminoquinuclidine dihydrochloride (1.0 g, 5.0 mmol) in CH_2Cl_2 (10 mL). After 18 h the precipitate was collected and dissolved in H_2O; 2 M NaOH was added to pH 9 and the mixture extracted with EtOAc. The extracts were dried and evaporated and the residue crystallized from EtOAc−hexane to give **20** (450 mg, 32%): mp 183−185 °C; ^{1}H-NMR ($CDCl_3$) δ 1.53 (m, 1H), 1.76 (m, 3H), 2.08 (m, 1H), 2.69 (d, 1H, J = 12.6 Hz), 2.9 (m, 4H), 3.45 (m, 1H), 4.2 (m, 1H), 6.35 (d, 1H, J = 6.3 Hz), 7.4 (m, 3H), 7.6 (m, 4H), 7.85 (d, 2H, J = 6.3 Hz). Anal. ($C_{20}H_{22}N_2O$·0.25H_2O) C, H, N.

3-(Biphenylsulfonamido)quinuclidine (21). 4-Biphenylsulfonic acid (0.6 g, 2.56 mmol) and $SOCl_2$ (1.53 g, 12.8 mmol) were heated under reflux for 18 h, and the mixture was evaporated. The residue in CH_2Cl_2 (6 mL) was added to a mixture of 3-aminoquinuclidine dihydrochloride (0.56 g, 2.81 mmol) and Et_3N (2.0 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred for 3 h and evaporated. The residue was shaken with 1 M NaOH (25 mL) and EtOAc (75 mL) and the EtOAc layer washed with brine, dried, and evaporated. The residue was chromatographed on alumina (ICN Alumina N 32-63), eluting with EtOAc to give **21** (320 mg, 37%): mp 77−78 °C; ^{1}H-NMR ($CDCl_3$) δ 1.3−1.85 (m, 5H), 2.40−2.85 (m, 5H), 3.1 (m, 1H), 3.38 (m, 1H), 4.8−5.25 (m, 1H), 7.45 (m, 3H), 7.6 (m, 2H), 7.7 (m, 2H), 7.92 (m, 2H). Anal. ($C_{19}H_{22}N_2O_2S$·0.5EtOAc) C, H, N.

3-[(Biphenyl-4-yl)ethynyl]-3-hydroxyquinuclidine (23). CBr_4 (25.2 g, 76 mmol)[20] was added to PhP_3 (26.2 g, 100 mmol) in dry CH_2Cl_2 (600 mL) and the mixture stirred for 15 min. Zn dust (6.5 g, 100 mmol) was added in one portion and the mixture stirred for 19 h. 4-Phenylbenzaldehyde[15] (9.1 g, 50 mmol) was added and stirring continued for 3 h. PhP_3 (5.2 g, 20 mmol) and CBr_4 (5.0 g, 15 mmol) were added, and the mixture was stirred for 3 h. The CH_2Cl_2 was evaporated and the residue extracted with boiling hexane (4 × 200 mL) and filtered while hot. The filtrates were concentrated to 400 mL when colorless crystals formed of **22** (9.6 g, 56%); mp 105−106 °C; EI-MS *m*/*z* 340 (M + H).

^{n}BuLi in *n*-hexane (6.4 mL, 1.6 M, 10 mmol) was added dropwise to **22** (1.2 g, 6.7 mmol) in THF (15 mL) at −60 °C and the mixture stirred at ambient temperature for 1 h. The mixture was cooled to −60 °C and quinuclidin-3-one (787 mg, 6.3 mmol) in THF (5.0 mL) added dropwise during 10 min. The mixture was stirred for 1 h, and the reaction was quenched by the slow addition of H_2O (1.0 mL). The THF was evaporated to give a residue, which crystallized from MeOH to give, as a colorless solid, **23** (300 mg, 15%): mp 217−218 °C; ^{1}H-NMR (DMSO-d_6) δ 1.2−1.4 (m, 1H), 1.5−1.7 (m, 1H), 1.8−2.02 (m, 3H), 2.6−2.78 (t, 4H, J = 8.3 Hz), 2.8−2.92 (d, 1H, J = 13.3 Hz), 3.02−3.14 (d, 1H, J = 13.3 Hz), 5.61 (s, 1H), 7.32−7.54 (m, 5H), 7.62−7.73 (m, 4H); EI-MS *m*/*z* 304 (M + H). Anal. ($C_{21}H_{21}NO$) C, H, N.

3-[(Biphenyl-4-yl)ethyl]-3-hydroxyquinuclidine Hydrochloride (24). A mixture of **23** (303 mg, 1 mmol), HCO_2NH_4 (800 mg, 12.7 mmol), and 5% Pd/C (50 mg) in MeOH (20 mL) was stirred at 60 °C for 30 min, and further portions of HCO_2NH_4 (100 mg, 1.6 mmol) were added at 20 min intervals over 1 h while maintaining the reaction temperature at 60 °C. The mixture was cooled, filtered through diatomaceous earth, and washed with MeOH. The filtrate was evaporated and the residue dissolved in H_2O, basified with 4 M NaOH, and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried, and an excess of ethereal HCl was added. Et_2O (30 mL) was added to precipitate, as a solid, **24** (280 mg, 90%): mp 224−225 °C; ^{1}H-NMR (DMSO-d_6) δ 1.58−2.1 (m, 5H), 2.15−2.32 (m, 1H), 2.56−2.86 (m, 2H), 2.92−3.3 (m, 7H), 5.16 (s, 1H), 7.28−7.7 (m, 9H); EI-MS *m*/*z* 308 (M + H). Anal. ($C_{21}H_{25}NO$·HCl·0.3H_2O) C, H, N.

3-[[(Biphenyl-4-yl)oxy]methyl]-3-hydroxyquinuclidine (25). A solution[11] of NaOH (9.1 g, 227 mmol) in H_2O (91 mL) was added to a stirred mixture of quinuclidin-3-one (9.5 g, 76 mmol), 4-phenylphenol (13.7 g, 80 mmol), trimethylsulfoxonium iodide (33.4 g, 151 mmol), and tetrabutylammonium hydrogen sulfate (1.2 g, 3.5 mmol) in PhMe (150 mL). The mixture was stirred for 2 days. Saturated brine (220 mL) was added and the mixture extracted with EtOAc (4 × 140 mL). The EtOAc extract was dried and evaporated to give a residue, which was purified by flash column chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (90:10:3). Recrystallization from EtOAc gave, as a colorless solid, **25** (0.8 g, 4%): mp 132−133 °C; ^{1}H-NMR ($CDCl_3$) δ 1.3−1.5 (m, 1H), 1.5−1.7 (m, 2H), 2.0−2.2 (m, 2H), 2.3−2.7 (m, 1H), 2.6−3.1 (m, 6H), 3.9 (d, 1H, J = 8.3 Hz), 4.1 (d, 1H, J = 8.3 Hz), 7.0 (d, 2H, J = 8.3 Hz), 7.2−7.6 (m, 7H); EI-MS *m*/*z* 310 (M + H). Anal. ($C_{20}H_{23}NO_2$·0.2H_2O) C, H, N.

3-[[(Biphenyl-4-yl)thio]methyl]-3-hydroxyquinuclidine (26). The preparation of **26** was identical with that of **25** except that 4-phenylthiophenol was used as starting material. The EtOAc extract was washed with saturated brine (50 mL) and extracted with 2 M HCl (8 × 25 mL). The hydrochloride salt crystallized from the aqueous solution to give, as a colorless solid, **26** (9%): mp 170−175 °C; EI-MS *m*/*z* 326 (M + H).

The aqueous filtrate was cooled in ice, basified with 10 M NaOH (50 mL), and extracted with EtOAc (3 × 130 mL). The EtOAc extract was dried and evaporated to give, as a colorless solid, **26** as free base (4%): mp 145−147 °C; ^{1}H-NMR ($CDCl_3$) δ 1.2−1.4 (m, 1H), 1.5−1.6 (m, 2H), 1.9−2.0 (m, 1H), 2.0−2.2 (m, 1H), 2.5−3.0 (m, 7H), 3.1−3.5 (m, 2H), 7.2−7.6 (m, 9H); EI-MS *m*/*z* 326 (M + H). Anal. ($C_{20}H_{23}NOS$) C, H, N.

3-[[(Biphenyl-4-yl)sulfinyl]methyl]-3-hydroxyquinuclidine (27). $NaIO_4$ (2.5 g, 11.6 mmol) was added to a solution of **26** (1.1 g, 3.3 mmol) in MeOH (10 mL). The mixture was stirred for 5 h and the solvent evaporated. H_2O (15 mL) was added and the ice-cooled mixture made basic with 10 M NaOH. The mixture was extracted with EtOAc (3 × 50 mL), and the extracts were dried and evaporated. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (95:5:3) to give, as a colorless solid, a 2:1 mixture of diastereomers of **27** (0.3 g, 27%): mp 157−162 °C; ^{1}H-NMR ($CDCl_3$) δ 1.3−1.9 (m, 3H), 2.0 (m, <1H, minor diastereomer), 2.1−2.4 (m, 1H), 2.5 (m, <1H, major diastereomer), 2.6−3.1 (m, 7H), 3.0−3.2 (m, 2H), 3.1−3.2 (m, 1H), 4.1−4.6 (m, 1H), 7.35−7.55 (m, 3H), 7.55−7.65 (m, 2H), 7.65−7.8 (m, 4H); EI-MS *m*/*z* 342 (M + H). Anal. ($C_{20}H_{23}NO_2S$) C, H, N.

3-[[(Biphenyl-4-yl)sulfonyl]methyl]-3-hydroxyquinuclidine (28). Oxone (1.85 g, 3 mmol) was added to **26** (1.1 g, 3.3 mmol) in MeOH (20 mL). The mixture was stirred for 4 h and filtered. The residue was washed with MeOH and the filtrate evaporated. The residue was treated with ice-cooled 8 M NaOH (35 mL) and extracted with EtOAc (3 × 50 mL). The extracts were concentrated to 60 mL and the crystals which separated recrystallized twice from MeOH to give, as a colorless solid, **28** (0.3 g, 25%): mp 203−205 °C; ^{1}H-NMR (DMSO-d_6) δ 1.1−1.2 (m, 1H), 1.3−1.7 (m, 2H), 1.8−2.0 (m, 2H), 2.5−2.8 (m, 5H), 3.0 (d, 1H, J = 13.3 Hz), 3.5−3.8 (m, 2H), 4.7 (s, 1H), 7.4−7.6 (s, 3H), 7.6−7.8 (m, 2H), 7.8−8.0 (m, 4H); EI-MS *m*/*z* 358 (M + H). Anal. ($C_{20}H_{23}NO_3S$) C, H, N.

3-[(Biphenyl-4-yl)methyl]quinuclidine Hydrochloride (29). A solution of diethyl [(4-biphenylyl)methyl]phosphonate (2.14 g, 7 mmol) in THF (40 mL) was added to a stirred solution of KO^{t}Bu (790 mg, 7.05 mmol) in THF (40 mL) and the mixture stirred for 10 min. The mixture was cooled to 0 °C and a solution of quinuclidin-3-one (800 mg, 6.4 mmol) in THF (30 mL) added during 10 min while maintaining the reaction temperature at 0 °C. The mixture was stirred for 16 h, during which period the reaction mixture was allowed to warm to ambient temperature. H_2O was added, and the aqueous phases were separated and extracted with Et_2O and CH_2Cl_2. The CH_2Cl_2 and Et_2O extracts were dried and evaporated. The residue (350 mg) was dissolved in MeOH (16 mL), and HCO_2NH_4 (401 mg, 6.36 mmol) was added followed by 10% Pd/C (60 mg). The resulting mixture was stirred at 50−60 °C for 30 min and the catalyst filtered off. The filtrate was evaporated and the residue purified by flash chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (85:10:5) to give a gum. The gum was dissolved in a solution of HCl in EtOH and the EtOH evaporated to a residue which was crystallized from EtOAc to give, as a colorless solid, **29** (290 mg, 82%): mp 283−287 °C; ^{1}H-NMR (DMSO-d_6) δ 1.6−1.9 (m, 4H), 2.0−2.2 (m, 1H), 2.2−2.4 (m, 1H), 2.7−2.9 (m, 3H), 3.0−3.4 (m, 5H), 7.3−7.5 (m, 5H), 7.5−7.7 (m, 4H), 10.2−10.4 (s, 1H); EI-MS *m*/*z* 278 (M + H). Anal. ($C_{20}H_{23}N$·HCl·0.2H_2O) C, H, N.

3-[(Biphenyl-4-yl)thio]quinuclidine (30). NaH (0.2 g, 5 mmol) was added to a stirred solution of 4-phenylthiophenol (0.5 g, 2.66 mmol) in dry DMF (5 mL) and the mixture stirred for 30 min. 3-Chloroquinuclidine hydrochloride (554 mg, 3.05 mmol) was added and the mixture heated under reflux for 16 h. The mixture was evaporated and the residue dissolved in H_2O and extracted with EtOAc. The extract was washed with 1 M $NaHCO_3$ solution, dried, and evaporated. The residue was

purified by flash chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (90:8:2) to give, as a colorless solid, **30** (305 mg, 38%): mp 72−77 °C; ^{1}H-NMR ($CDCl_3$) δ 1.4−1.85 (m, 3H), 1.9−2.0 (m, 1H), 2.0−2.2 (m, 1H), 2.7−3.1 (m, 5H), 7.3−7.6 (m, 9H); EI-MS *m/z* 296 (M + H). Anal. ($C_{19}H_{21}NS$) C, H, N.

3-[(Biphenyl-4-yl)sulfonyl]quinuclidine (31). Oxone (2.41 g, 3.9 mmol) in H_2O (5 mL) was added to **30** (386 mg, 1.3 mmol) in MeOH (5 mL) at 0 °C and the mixture stirred for 2 h. Stirring was continued at ambient temperature and the mixture partitioned between H_2O (10 mL) and EtOAc (50 mL). The EtOAc layer was separated, dried, and evaporated to give an oil which was purified by flash chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (90:8:2) to give, as a colorless solid, **31** (50 mg, 9%): mp 126−127 °C; ^{1}H-NMR for HCL salt (D_2O) δ 2.16 (m, 2H), 2.29 (m, 1H), 2.71 (m, 1H), 2.83 (m, 1H), 3.62 (m, 4H), 3.84 (m, 1H), 4.03 (m, 1H), 4.32 (m, 1H), 7.77 (m, 3H), 7.97 (m, 2H), 8.2 (m, 4H); EI-MS *m/z* 328 (M + H). Anal. ($C_{19}H_{21}NO_2S\cdot0.5H_2O$) C, H, N.

3-[[(Biphenyl-4-yl)hydroxy]methyl]quinuclidines (32 and 33). ^{s}BuLi in cyclohexane (14.87 mL, 1.3 M, 19.3 mmol) was added to 4-bromobiphenyl (4.29 g, 18.4 mmol) in THF (35 mL) at −78 °C and the mixture stirred at −70 °C for 30 min. A solution of freshly prepared 3-formylquinuclidine (2.56 g, 18.5 mmol) in THF (40 mL) was added while maintaining the temperature at −70 °C. The mixture was allowed to warm to ambient temperature and stirred for 16 h. The mixture was evaporated and the residue purified by flash column chromatography on silica gel, eluting with EtOAc−MeOH−0.880 ammonia (90:8:2) to give, after crystallization from EtOAc, the less polar diastereomeric pair as a colorless solid. **32** (184 mg, 2%): mp 182−184 °C; ^{1}H-NMR (DMSO-d_6) δ 1.2−1.7 (m, 3H), 1.75−1.95 (m, 2H), 2.1−2.2 (m, 2H), 2.25−2.45 (m, 1H), 2.55−2.8 (m, 4H), 4.3−4.45 (m, 1H), 5.1−5.2 (m, 1H), 7.3−7.5 (m, 5H), 7.55−7.7 (m, 4H); EI-MS *m/z* 294 (M + H). Anal. ($C_{20}H_{23}NO\cdot0.4H_20$) C, H, N.

Further elution and crystallization from EtOAc gave, as a colorless solid, the more polar diastereomeric pair **33** (170 mg, 2%): mp 213−214 °C; ^{1}H-NMR (DMSO-d_6) δ 1.1−1.5 (m, 4H), 1.65−1.9 (m, 2H), 2.6−2.9 (m, 5H), 2.9−3.1 (m, 1H), 4.4−4.5 (m, 1H), 5.1−5.2 (m, 1H), 7.3−7.5 (m, 5H), 7.55−7.7 (m, 4H); EI-MS *m/z* 294 (M + H). Anal. ($C_{20}H_{23}NO\cdot0.65H_2O$) C, H, N.

3-[4-(Thien-2-yl)phenyl]-3-hydroxyquinuclidine (34). Saturated $NaHCO_3$ solution (10 mL) was added to 3-(4-bromophenyl)-3-hydroxyquinuclidine (490 mg, 1.73 mmol), thiophene-2-boronic acid (320 mg, 2.5 mmol), and $(PPh_3)_4Pd$ (20 mg) in dimethoxyethane (25 mL) and the mixture heated under reflux for 1.5 h. H_2O (100 mL) was added to the cooled mixture and the mixture extracted with EtOAc. The EtOAc layer was extracted with 2 M HCl and the acid extract basified to pH 12 with 8 M NaOH, before extraction with EtOAc. The EtOAc was washed with saturated brine, dried, and evaporated. The residue was recrystallized from EtOAc to give, as a gray solid, **34** (301 mg, 60%): mp 165−168 °C; ^{1}H-NMR (DMSO-d_6) δ 1.20−1.50 (m, 3H), 1.92 (m, 1H), 2.05−2.23 (m, 1H), 2.60−2.97 (m, 5H), 3.32 (d, 1H, J = 13.2 Hz), 5.22 (s, 1H), 7.08−7.15 (m, 1H), 7.42−7.65 (m, 6H); EI-MS *m/z* 286 (M + H). Anal. ($C_{17}H_{19}NOS\cdot0.5H_2O$) C, H, N.

General Procedure B. 3-[4-(Thiazoyl-2-yl)phenyl]-3-hydroxyquinuclidine (35). A solution of ^{s}BuLi in cyclohexane (7.5 mL, 1.3 M, 9.75 mmol) was added dropwise during 10 min to (4-bromophenyl)boronic acid *N*-methyl-*O*,*O*-diethanolamine ester[16] (1.42 g, 5 mmol) in THF (25 mL) at −100 °C. The mixture was stirred for 30 min and a solution of quinuclidin-3-one (0.625 g, 5 mmol) in THF (10 mL) added during 10 min while maintaining the temperature at −100 °C. The mixture was stirred for 1 h at −100 °C, allowed to warm to ambient temperature, and stirred for a further 2 h. An aqueous solution of NH_4Cl (0.55g, 10 mmol) in H_2O (5 mL) was added and the mixture stirred for 30 min. The THF was evaporated, and PhMe (20 mL) and saturated Na_2CO_3 solution (10 mL) were added to the residue. A solution of 2-bromothiazole (870 mg, 5.3 mmol) in absolute EtOH (10 mL) was added to the mixture at 25 °C. $(PPh_3)_4Pd$ (100 mg) was added and the mixture heated under reflux for 4 h. After cooling, ice and 2 M HCl were added, and the mixture was washed with EtOAc. The aqueous phase was basified with 10 M NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with saturated brine solution, dried, and evaporated. The residue was triturated with EtOAc to give, as a solid, **35** (120 mg, 8%): mp 218−219 °C; ^{1}H-NMR (DMSO-d_6) δ 1.20−1.52 (m, 3H), 1.93 (m, 1H), 2.02−2.22 (m, 1H), 2.53−2.9 (m, 3H), 2.93 (d, 1H, J = 13.6 Hz), 3.40 (d, 1H, J = 13.6 Hz), 5.22 (s, 1H), 7.62 (d, 2H, J = 8.4 Hz), 7.75 (d, 1H, J = 3 Hz), 7.90 (m, 3H); EI-MS *m/z* 289 (M + H). Anal. ($C_{16}H_{18}NO_2S\cdot0.5H_2O$) C, H, N.

Biological Assays. SQS inhibition *in vitro* and *in vivo* inhibition of cholesterol biosynthesis were determined as previously reported.[23]

Supporting Information Available: Table of ^{1}H-NMR and mass spectral data for 15 compounds made by the general procedures (2 pages). Ordering information is given on any current masthead page.

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