ARTICLE

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Novel 3-phenylprop-2-ynylamines as inhibitors of mammalian squalene epoxidase †

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The synthesis of a novel series of 3-phenylprop-2-ynylamines as selective mammalian squalene epoxidase inhibitors is described. Structure–activity relationship studies led to the discovery of compound **19**, 1-[3-(3,5-dichlorophenyl)-prop-2-ynyl]-3-methylpiperidine hydrochloride with an IC_{50} of 2.8 ± 0.6 μM against rat liver squalene epoxidase. Against 23 strains of fungal squalene epoxidase compound **19** was found to be inactive.

Introduction

The link between elevated plasma cholesterol levels and coronary atherosclerosis is now well established.[1] Studies have shown that lowering plasma cholesterol levels produces a higher incidence of lesion regression and reduces formation of new lesions.[2] The cholesterol biosynthesis pathway can be interrupted at a number of different sites. Triparanol, for example, inhibits Δ^{24}-reductase an enzyme near the end of the biosynthesis pathway. Inhibition of this enzyme allows accumulation of desmosterol with induction of myotonia, a serious side effect.[3] Compactin inhibits HMG-CoA reductase,[4] an enzyme at the beginning of the biosynthesis pathway. Inhibition of HMG-CoA reductase can affect the production of important substances that are derived from mevalonate,[5] for example, ubiquinones, dolichols, isopentenyl t-RNA and isoprenylated proteins. Folkers *et al.*[6] have reported decreased levels of Coenzyme Q10 in humans administered lovastatin. Our approach was to inhibit an enzyme at an intermediate stage of the cholesterol biosynthesis pathway. The epoxidation of squalene, catalyzed by squalene epoxidase to give 2,3-oxidosqualene, has been reported to be the first step in the late stages of cholesterol biosynthesis.[7] Since it had been reported that high intake of squalene does not appear to be associated with a high risk of atherosclerosis[8,9] and in man does not increase serum cholesterol levels consistently,[10] we felt that inhibition of squalene epoxidase (EC 1.14.99.7) with the resulting accumulation of squalene might not be deleterious.

We were interested in finding squalene epoxidase inhibitors specific to the mammalian enzyme. Several classes of compounds have been reported to be inhibitors of mammalian squalene epoxidase[11,12] (Fig. 1). Screening of a diverse set of compounds led to the discovery that compound **33**, (3*R**,5*S**)-3,5-dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride [*cis*], inhibited squalene epoxidase with an IC_{50} of 34 μM. This paper describes our initial efforts in the synthesis and squalene epoxidase inhibitory activity of a novel series of 3-phenylprop-2-ynylamines. The 3-phenylprop-2-ynylamines are selective inhibitors of the rat squalene epoxidase enzyme. The most potent analog is compound **19** shown in Fig. 2.

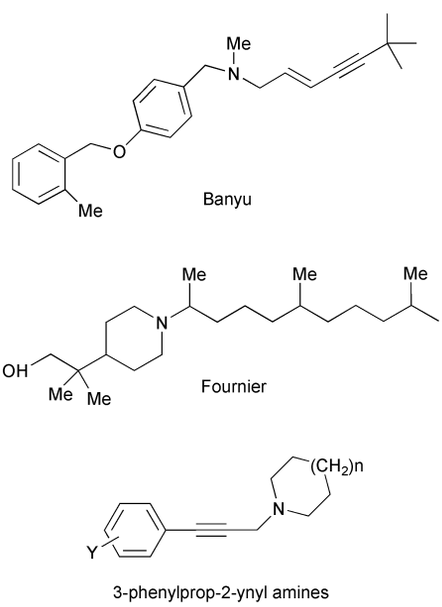
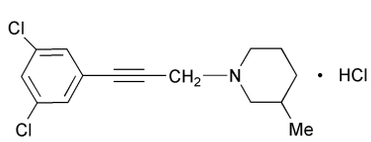


Fig. 1



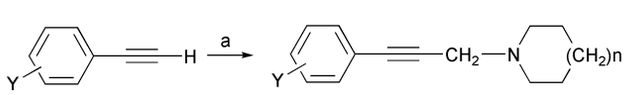
19

Fig. 2

Results and discussion

Chemistry

The 3-phenylprop-2-ynylamines (**1**–**54**) shown in Tables 1–3 were prepared from the phenylacetylenes and the desired amine under Mannich[13] reaction conditions as shown in Scheme 1.



Scheme 1 a) paraformaldehyde CuCl, HN (CH2)n dioxane, Δ.

† Electronic supplementary information (ESI) available: Proton NMR spectra for the intermediate piperidines **56**–**60** and acetylenes **63-81** and **85**,**86**. See http://www.rsc.org/suppdata/ob/b2/b209165h/

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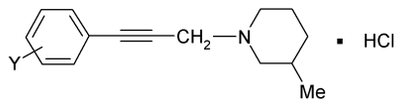
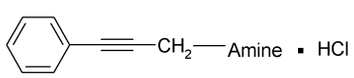
Table 1 Effect of aryl substituents



Comp. No.	Y	Squalene epoxidase inhibition, IC_{50} (μM), rat	Mp/ °C	Yield (%)	Formula [a]
Banyu Compd Fig. 1		13.1			
1	H [b]	54 ± 16	161.5–163.5	46	$C_{15}H_{20}ClN$
2	4-Cl	20	203–205	14	$C_{15}H_{19}Cl_2N$
3	4-F	34 ± 3	168–170	13	$C_{15}H_{19}ClFN$
4	4-CF_3	27 ± 8	209–211	8	$C_{16}H_{19}ClF_3N$
5	4-Me	117	154–158	34	$C_{16}H_{22}ClN$
6	4-SO_2NH_2	666 ± 483	212–214	30	$C_{15}H_{21}ClN_2O_2S$
7	4-CN	29 ± 1	186–188	48	$C_{16}H_{19}ClN_2$
8	3-Cl	22 ± 3	165–167	46	$C_{15}H_{19}Cl_2N$
9	3-Me	139 ± 18	132–134	6	$C_{16}H_{22}ClN{\cdot}0.13H_2O$ [c]
10	3-OMe	74 ± 21	127–130	25	$C_{16}H_{22}ClNO$
11	3-CN	51 ± 9	212–214	38	$C_{16}H_{19}ClN_2$
12	2-Cl	400 ± 267	178–180	29	$C_{15}H_{19}Cl_2N$
13	2,3-Cl_2	18 ± 4	183.5–186	30	$C_{15}H_{18}Cl_3N$
14	2,4-Cl_2	29 ± 10	183–185	40	$C_{15}H_{18}Cl_3N$
15	2,5-Cl_2	43 ± 16	218–219	45	$C_{15}H_{18}Cl_3N$
16	2,6-Cl_2	35 ± 6	246–247	47	$C_{15}H_{18}Cl_3N$
17	3-CF3, 4-Cl	8 ± 4	211–213	31	$C_{16}H_{18}Cl_2F_3N$
18	3,4-Cl_2	14 ± 5	206–208	26	$C_{15}H_{18}Cl_3N$
19	3,5-Cl_2	2.8 ± 0.6	220–221	42	$C_{15}H_{18}Cl_3N$
20	3-Cl, 5-OMe	33 ± 12	183–185	54	$C_{16}H_{21}Cl_2NO$
21	3,5-F_2	61 ± 21	201–203	15	$C_{15}H_{18}ClF_2N$

[a] Elemental analyses on all compounds were within 0.4% of the theoretical values. [b] Ref. 24. [c] 0.13 H_2O; Calcd: 0.85; Found: 0.74.

Table 2 Effect of amine moiety

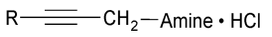


Comp. No.	Amine	Squalene epoxidase inhibition, IC_{50} μM, rat	Mp/ °C	Yield (%)	Formula [a]
22	2-Methylpiperidine [b]	91	164–165	65	$C_{15}H_{20}ClN$
23	4-Methylpiperidine [b]	~95	184–185	49	$C_{15}H_{20}ClN$
24	3-Ethylpiperidine	55 ± 8	142–144	45	$C_{16}H_{22}ClN$
25	2-Ethylpiperidine	132 ± 17	128–129	42	$C_{16}H_{22}ClN$
26	2-Propylpiperidine	32 ± 3	107–109	64	$C_{17}H_{24}ClN$
27	2-Methylpyrrolidine	114	144–146	55	$C_{14}H_{18}ClN$
28	*cis*-2,3-Dimethylpiperidine	111 ± 10	143–145	55 [c]	$C_{16}H_{22}ClN$
29	*trans*-2,3-Dimethylpiperidine	>400	162–164	7 [c]	$C_{16}H_{22}ClN$
30	*cis*-2,5-Dimethylpiperidine	259 ± 122	173–175	37 [c]	$C_{16}H_{22}ClN$
31	*trans*-2,5-Dimethylpiperidine	295 ± 63	167–169	24 [c]	$C_{16}H_{22}ClN$
32	*cis*-2,6-Dimethylpiperidine	Inactive	144–146	41	$C_{16}H_{22}ClN$
33	*cis*-3,5-Dimethylpiperidine	34	189–191	25 [c]	$C_{16}H_{22}ClN$
34	*trans*-3,5-Dimethylpiperidine	42	159.5–161.5	7 [c]	$C_{16}H_{22}ClN$
35	*cis*-2,6-Dimethylmorpholine	Inactive	220–222	44 [c]	$C_{15}H_{20}ClNO$
36	*trans*-2,6-Dimethylmorpholine	60	133–135	10 [c]	$C_{15}H_{20}ClNO$
37	*cis*-Decahydroisoquinoline	Inactive	194–196	24 [c]	$C_{18}H_{24}ClN$
38	*trans*-Decahydroisoquinoline	Inactive	180–182	10 [c]	$C_{18}H_{24}ClN$
39	1,2,3,4-Tetrahydroisoquinoline	Inactive	oil	22	$C_{18}H_{17}N$
40	*trans*-Decahydroquinoline	Inactive	206–209	19	$C_{18}H_{24}ClN$
41	3,3,5-Trimethylhexahydroazepine	Inactive	154–155	42	$C_{18}H_{26}ClN$
42	1-Indoline	Inactive	33–35 [d]	11	$C_{17}H_{15}N$
43	2,*N*,*N*-Trimethylpropyldiamine	150	202–204 [e]	32	$C_{15}H_{24}Cl_2N_2$

[a] Elemental analyses on all compounds were within 0.4% of the theoretical values. [b] See footnote *b*, Table 1. [c] Isolated from the same reaction using flash chromatography on silica gel. [d] Free base not HCl salt! [e] Dihydrochloride salt!

The 3-phenyl, 3-butyl, 2-propyl, 3-ethyl, 2,3-dimethyl, and 2,5-dimethyl piperidines (**55**–**60**) were prepared from the appropriately substituted pyridines by catalytic hydrogenation [14] with platinum oxide in glacial acetic acid. The piperidines were used as racemates in the synthesis of **1**–**54**. The pyridines were commercially available. Examples in Table 2 where a mixture of *cis* and *trans* disubstituted amines was used, the diastereomeric isomers of the final products were separated by chromatography on silica gel using ethyl acetate–hexanes mixtures as the eluent. ^1H and ^{13}C NMR confirmed the isomer identification. The phenylacetylenes (**63**–**81**, **84**–**86**) that were not commercially available were prepared from the corresponding bromobenzenes or aryltriflates by reaction with trimethylsilylacetylene under Sonogashira reaction conditions. The catalyst for

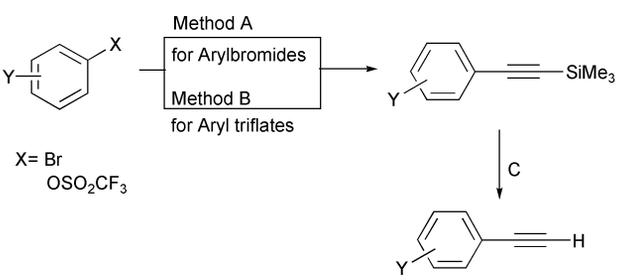
Table 3 Miscellaneous analogues



Comp. No.	R	Amine	Squalene epoxidase inhibition, IC_{50} (μM), rat	Mp/ °C	Yield (%)	Formula[a]
44	3,4-Cl_2–C_6H_3	3-Ethylpiperidine	19 ± 3	196–197	11	$C_{16}H_{20}Cl_3N$
45	3,4-Cl_2–C_6H_3	3-Butylpiperidine	Inactive	196–198	17	$C_{18}H_{24}Cl_3N$
46	3,4-Cl_2–C_6H_3	3-Phenylpiperidine	Inactive	212–213	17	$C_{20}H_{20}Cl_3N$
47	3,5-Cl_2–C_6H_3	3-Benzylpiperidine	Inactive	172–174	17	$C_{21}H_{22}Cl_3N$
48	3,5-Cl_2–C_6H_3	Pyrrolidine	87 ± 18	228–230	43	$C_{13}H_{14}Cl_3N$
49	5-$C_4N_2H_3$	3-Methylpiperidine	Inactive	216–218	12	$C_{13}H_{18}ClN_3$
50	Phenethyl	3-Methylpiperidine	31	122–124	23	$C_{17}H_{24}ClN$
51	3-Pyridyl	3-Methylpiperidine	Inactive	195–197	12	$C_{14}H_{20}Cl_2N_2$[b]
52	3-Thienyl	3-Methylpiperidine	69 ± 22	198–200	46	$C_{13}H_{18}ClNS$
53	Cyclohexen-1-yl	3-Methylpiperidine	Inactive	172–174	19	$C_{15}H_{24}ClN$
54	2-Naphthyl	3-Methylpiperidine	29	206–208	22	$C_{19}H_{22}ClN$

[a] Elemental analyses on all compounds were within 0.4% of the theoretical values. [b] Isolated as the dihydrochloride salt!

reaction with bromobenzenes was tetrakis(triphenyphosphine)-palladium[15] (Method A) and for the triflates, bis(triphenyl-phosphine)palladium(II) chloride[16] (Method B) was used. The resulting trimethylsilylphenylacetylenes were deprotected to the corresponding phenylacetylenes by reaction with potassium carbonate in methanol[17] (Scheme 2).



Scheme 2 Method A) $(Ph_3P)_4Pd$, CuI, Et_3N, trimethylsilylacetylene. Method B) $(Ph_3P)_2PdCl_2$, Et_3N, DMF, trimethylsilylacetylene. C) K_2CO_3, MeOH.

Structure–activity relationship discussion

Screening of a diverse set of chemical structures, we discovered the squalene epoxidase inhibitory activity of **33**. Our screen measured squalene epoxidase activity as described by Popjak *et al.*[18] for cell-free biosynthesis of sterols. Recently recombinant rat squalene epoxidase that appears to have similar properties to rat microsomal squalene epoxidase has been reported.[19] The IC_{50}s reported in Tables 1–3 are generally an average of at least three determinations. For compounds that showed some activity at 100 μM, an IC_{50} was determined. Compounds with no activity at 100 μM were reported as inactive. The Banyu[11] compound shown in Fig. 1 was screened in our assay and is included in Table 1 for comparison. The Topliss Tree[20] approach to analogue selection was then employed to explore the effect substitution on the aryl ring had on the inhibition of rat liver squalene epoxidase activity (Table 1). We initially used 3-methylpiperidine as the amine moiety. The unsubstituted derivative **1** had an IC_{50} of 54 ± 16 μM. Substitution at the four position of the aryl ring with a chlorine **2** increased the potency by a factor of two. The potency was slightly increased, as compared to **2**, by addition of a second chlorine at the three position to give the 3,4-dichloro analogue **18** with an IC_{50} of 14 ± 5 μM. The Topliss Tree requires examination of the 3-CF_3, 4-Cl analogue **17**. This compound was essentially equipotent with **18** having an IC_{50} of 8 ± 4 μM. Since the 3,4-Cl_2 analogue was more potent than the parent compound we decided to examine other dichloro substituted analogues. We found that the 2,4-Cl_2 **14**; 2,5-Cl_2 **15** and the 2,6-Cl_2 **16** analogues were all less potent than **18**. However, the 2,3-Cl_2 **13** analogue was essentially equipotent with **18** and the 3,5-Cl_2 analog **19** was the most potent analogue in the series with an IC_{50} of 2.8 ± 0.6 μM. Compound **19** is approximately five times more potent than the Banyu compound in our assay.

The second stage of the structure–activity relationship (SAR) study probed the effect of different amines on the inhibition activity as shown in Table 2. Substituting the 2-methyl **22** or 4-methylpiperidine **23** for the 3-methylpiperidine in **1** resulted in approximately a 1.7 fold loss of activity. The 3-ethylpiperidine **24** and *trans*-2,6-dimethylmorpholine **36** derivatives are equipotent with **1**. Of the amines studied in Table 2 only the *cis*- and *trans*-3,5-dimethylpiperidine analogues **33** [IC_{50} = 34 μM] and **34** [IC_{50} = 42 μM] respectively were more potent than **1**. Using compound **18**, the 3,4-Cl_2 analog, for comparison we found that increasing the length of the alkyl group on the piperidine moiety to an ethyl group **44** resulted in retention of inhibitory activity as shown in Table 3. Larger groups such as 3-butyl **45**, 3-phenyl **46** and 3-benzyl **47** caused a complete loss of activity. Incorporation of the nitrogen into a five membered ring such as the pyrrolidine **48** analogue gave a six-fold loss in activity.

The final stage of the SAR considered the substitution of the aryl ring with other groups. As compared to **1**, the bioisosteric thienyl derivative **52** [IC_{50} = 69 ± 22 μM] retained activity while increased potency was found with the phenethyl **50** and 2-naphthyl **54** derivatives having IC_{50}s of 31 μM and 29 μM, respectively. Heterocycles and non-aromatic substituents resulted in loss of inhibitory activity.

Finally, screening of the most potent analogue **19**, against 23 different strains of fungal squalene epoxidase showed MIC's ≥ 100 μg mL^{-1}.

Conclusion

Compound **19** represents a new class of potent and selective inhibitors of mammalian squalene epoxidase with an IC_{50} of 2.8 ± 0.6 μM against the rat liver enzyme. This compound lacks the typical ene-yne moiety of the allylamines or the extended saturated/ unsaturated carbon chain of substrate analogs reported in the literature.[21,22] As this work is preliminary, further evaluation of **19** in HepG2 cells is necessary. To examine the effect of chirality on inhibition of squalene epoxidase, the piperidines should be resolved and the corresponding optically active analogs of **19** evaluated as inhibitors.

Experimental

Chemistry

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR data were recorded on a Varian XL-200 instrument. Proton

chemical shifts are recorded as parts per million (δ) relative to tetramethylsilane (0.0 ppm). All compounds gave NMR spectra consistent with the reported structure. Microanalysis were performed by Atlantic Microlab Inc. (Norcross, GA) and agree within 0.4% of the calculated values. All column chromatography was performed on silica gel using modified sintered glass funnels as columns. The eluent was pulled through the silica gel *via* vacuum.

The following procedure illustrates the typical preparation of the substituted piperidines from the commercially available pyridines.

3-Ethylpiperidine (55)

A mixture of 3-ethylpyridine (10.0 g, 0.09 mol) and platinum oxide hydrate (0.5 g) in glacial acetic acid (200 mL) was hydrogenated at room temperature and 30–60 psi hydrogen pressure. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in water and the mixture was made basic with 40% aqueous sodium hydroxide solution. The mixture was extracted with diethyl ether. The extracts were dried (potassium carbonate) and concentrated on a steam bath at atmospheric pressure to give 9.2 g (92%) of **55** as a colorless oil. ^{1}NMR ($CDCl_3$) δ 0.87 (t, 3H), 0.99–1.49 (m, 6H), 1.61 (m, 1H), 1.79 (br d, 1H), 2.19 (dd, 1H), 2.50 (t, 0.5H), 2.51 (t, 0.5H), 3.00 (br t, 2H).

The 3-ethylpiperidine was used without further purification.

The following alkyl/arylpiperidines were prepared as described above for **55**.

2-Propylpiperidine (56)

3-Butylpiperidine (57)

3-Phenylpiperidine (58)

2,3-Dimethylpiperidine (59)

2,5-Dimethylpiperidine (60)

Preparation of the substituted phenylacetylenes

Method A. The following procedure illustrates the typical preparation of the appropriately substituted phenylacetylenes from the corresponding aryl halide. Phenylacetylene, 4-ethynyltoluene, 1-ethynylcyclohexene and 4-phenylbut-1-yne were commercially available. In general the crude trimethylsilylacetylenes and arylacetylenes were used without further purification in subsequent reactions.

4-[2-(Trimethylsilyl)ethynyl]benzonitrile (61)

A mixture of 4-bromobenzonitrile (10.0 g, 0.06 mol), trimethylsilylacetylene (8.8 g, 0.09 mol), tetrakis(triphenylphosphine)palladium (1.0 g, 0.009 mol) and copper iodide (0.44 g, 0.002 mol) in triethylamine (150 mL) was heated to 80 °C under a nitrogen atmosphere for 7.5 h. The mixture was concentrated *in vacuo* and diethyl ether (300 mL) was added to the residue. The mixture was filtered and concentrated *in vacuo* to give 12.4 g of crude **61** as a brown solid. The crude product was purified by column chromatography on silica gel using hexanes–ethyl acetate (35 : 1) as eluent to give 10.8 g of an orange solid. Recrystallization from hexanes gave 9.5 g (79%) of **61** as a white solid: mp 97–98 °C. ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H, Si[CH_3]$_3$), 7.27–7.61 (m, 4H, aromatic Hs). *Anal:* Calcd. for $C_{12}H_{13}NSi$ (mw 199.31): C, 72.31; H, 6.57; N, 7.02. Found: C, 72.27; H, 6.57; N, 7.00%.

4-Ethynylbenzonitrile (62)

A mixture of **61** (8.9 g, 0.05 mol) and potassium carbonate (1.0 g, 0.007 mol) in methanol (50 mL) was stirred at ambient temperature under a nitrogen atmosphere for 18 h. The mixture was concentrated *in vacuo* and partitioned between 5% aqueous sodium bicarbonate and dichloromethane. The dichloromethane solution was dried (Na_2SO_4) and concentrated *in vacuo* to give 5.7 g of crude **62**. A sample (0.75 g) was recrystallized from hexanes–dichloromethane (8 : 1) mixture to give 0.37 g of analytically pure **62** as a white solid: mp 158–159 °C. ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 1H, CH), 7.54–7.64 (m, 4H, aromatic Hs). *Anal:* Calcd. for C_9H_5N (mw 127.14): C, 85.02; H, 3.96; N, 11.02. Found: C, 84.92; H, 3.98; N, 11.00%.

The following phenylacetylenes were prepared as described above for **62**.

3-Ethynylbenzonitrile (63)

4-Chlorophenylacetylene (64)

3-Chlorophenylacetylene (65)

2-Chlorophenylacetylene (66)

2,3-Dichlorophenylacetylene (67)

2,6-Dichlorophenylacetylene (68)

3,4-Dichlorophenylacetylene (69)

3,5-Dichlorophenylacetylene (70)

4-Chloro-3-trifluoromethylphenylacetylene (71)

4-Fluorophenylacetylene (72)

3,5-Difluorophenylacetylene (73)

4-Trifluoromethylphenylacetylene (74)

3-Methylphenylacetylene (75)

3-Methoxyphenylacetylene (76)

4-Ethynylbenzenesulfonamide (77)

3-Ethynylthiophene (78)

2-Naphthylacetylene (79)

3-Ethynylpyridine (80)

5-Ethynylpyrimidine (81)

Method B. The following procedure illustrates the typical preparation of the appropriately substituted phenylacetylenes from the corresponding phenols.

2,5-Dichlorophenyl trifluoromethanesulfonate (82)

To a mixture of 20.0 g (0.07 mol) of trifluoromethanesulfonic anhydride in dichloromethane (60 ml) at ice bath temperature was added dropwise a mixture of 10.0 g (0.06 mol) of 2,5-dichlorophenol and 4.8 g (0.06 mol) of pyridine in dichloromethane (60 ml). After stirring at room temperature overnight, the reaction mixture was washed several times with water. The dichloromethane phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give 16.3 g of an orange oil. Chromatography on silica gel with hexane as eluent gave 13.8 g (77%) of a colorless oil. A sample was place in a vacuum desiccator at room temperature overnight to give analytically pure **82**. ^{1}H NMR ($CDCl_3$) δ 7.25–7.49 (m, 3H, aromatic Hs). *Anal*: Calcd. for $C_7H_3Cl_2F_3O_3S$ (mw 295.07): C, 28.49; H, 1.03. Found: C, 28.71; H, 1.04%.

2-(2,5-Dichlorophenyl)trimethylsilylacetylene (83)

A mixture of 13.7 g (0.05 mol) of **82**, 6.4 g (0.07 mol) of trimethylsilylacetylene, 0.7 g (0.001 mol) of bis(triphenylphosphine)palladium(II) chloride, and triethylamine (25 ml) in dimethylformamide (130 ml) under a nitrogen atmosphere was heated at 70 °C for 18 h. The reaction mixture was diluted with water (900 ml) and extracted with diethyl ether. The diethyl ether phase was washed repeatedly with water and dried (Na_2SO_4). Evaporation *in vacuo* gave 10.8 g of a dark orange

oil. Chromatography on silica gel with hexane as the eluent gave 6.3 g (56%) of a yellow oil. A second fraction amounting to 2.5 g containing minor impurities (by NMR) was obtained. A sample of the first fraction was placed in a vacuum desiccator at room temperature overnight to give analytically pure **83**. ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H, Si[CH_3]$_3$), 7.19–7.48 (m, 3H, aromatic Hs). *Anal*: Calcd. for $C_{11}H_{12}Cl_2Si$ (mw 243.21): C, 54.32; H, 4.98. Found: C, 54.46; H, 4.99%.

2,5-Dichlorophenylacetylene (84)

A mixture of 8.7 g (0.04 mol) of **83** and 1.0 g (0.007 mol) of K_2CO_3 in MeOH (50 ml) was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and 5% aqueous sodium bicarbonate solution. The dichloromethane phase was dried (Na_2SO_4), and concentrated on a steam bath to give 6.9 g of an orange oil which solidified on cooling. A sample was recrystallized from ethanol–water mixtures to give analytically pure **84**. Mp 41–43 °C. ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 1H, CH), 7.24–7.51 (m, 3H, aromatic Hs). *Anal*: Calcd for $C_8H_4Cl_2$ (mw 171.02): C, 56.18; H, 2.36. Found: C, 56.03, H, 2.38%.

The following acetylenes were prepared as described above for **84**.

2,4-Dichlorophenylacetylene (85)

3-Chloro-5-methoxyphenylacetylene (86)

The following procedure illustrates the preparation of the appropriately substituted 3-phenylprop-2-ynylamine from the appropriately substituted phenylacetylene.

1-[3-(3,5-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (19)

A mixture of **70** (7.5 g, 0.04 mol), 3-methylpiperidine (4.4 g, 0.04 mol), paraformaldehyde (1.6 g. 0.04 mol) and copper chloride (0.5 g, 0.005 mol) in dioxane (75 mL) were refluxed for 4.5 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using hexanes–ethyl acetate (2 : 1) as eluent to give 6.6 g of an orange oil. The oil was dissolved in diethyl ether and treated with diethyl ether–hydrogen chloride. The resulting solid was filtered and recrystallized from ethanol–diethyl ether mixtures to give 5.9 g (52%) of **19** as a white solid: mp 220–221 °C. ^{1}H NMR ($CDCl_3$) δ 0.97 (d, 3H, CH_3), 1.11 (m, 1H, CH), 1.90 (br d, 2H, CH_2), 2.40 (m, 3H, CH_2's), 2.89 (br t, 1H, CH_2), 3.38 (br dd, 2H, CH_2), 4.09 (s, 2H, CH_2), 7.34–7.39 (m, 3H, aromatic Hs). *Anal* : Calcd. for $C_{15}H_{18}Cl_3N$ (mw 282.21) C, 56.53; H, 5.69; N, 4.40. Found: C, 56.65; H, 5.72; N, 4.34%.

The 3-phenylprop-2-ynyl amines, **1**–**18** and **20**–**54**, were prepared as described above for **19**. The proton NMR spectra for **1**–**18** and **20**–**54** are given below. The corresponding melting points and overall percent yields are given in Tables 1–3.

1-[3-(4-Chlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (2)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.07 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 2.0 (br m, 1H, CH_2), 2.61 (br t, 1H, CH_2), 2.86 (br m, 1H, CH_2), 3.45 (br m, 2H, CH_2's), 4.26 (s, 2H, CH_2), 7.47–7.59 (dd, 4H, aromatic Hs).

1-[3-(4-Fluorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (3)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.77 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.55 (br t, 1H, CH_2), 2.87 (br m, 1H, CH_2), 3.47 (br m, 2H, CH_2's), 4.25 (s, 2H, CH_2), 7.27 (t, 2H, aromatic Hs), 7.61 (dd, 2H, aromatic Hs), 11.02 (br, 1H, HCl).

1-[3-(4-Trifluoromethylphenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (4)

^{1}H NMR (DMSO-d_6) δ 0.97 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.90 (br d, 2H, CH_2's), 2.34 (br m, 2H, CH_2), 2.60 (br t, 1H, CH_2), 2.92 (br t, 1H, CH_2), 3.33 (br d, 1H, CH_2's), 3.46 (br d, 1H, CH_2's), 4.11 (s, 2H, CH_2), 7.59 (s, 4H, aromatic Hs), 12.90 (br, 1H, HCl).

1-[3-(4-Methylphenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (5)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.82 (br m 3H, CH_2's), 1.98 (br m, 1H, CH_2), 2.13 (s, 3H, CH_3), 2.60 (br t, 1H, CH_2), 2.86 (m, 1H, CH_2), 3.44 (br m, 2H, CH_2's), 4.24 (s, 2H, CH_2), 7.22 (d, 2H, aromatic Hs), 7.42 (d, 2H, aromatic Hs), 11.24 (br, 1H, HCl).

4-[3-(3-Methylpiperidin-1-yl)prop-1-ynyl]benzenesulfonamide hydrochloride (6)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.07 (m, 1H, CH), 1.81 (br m, 3H, CH_2's), 1.96 (br m, 1H, CH_2), 2.61 (br m, 1H, CH_2), 2.90 (br m, 1H, CH_2), 3.44 (br m, 2H, CH_2's), 4.31 (s, 2H, CH_2), 7.50 (s, 2H, NH_2), 7.73 (d, 2H, aromatic Hs), 7.85 (d, 2H, aromatic Hs), 11.13 (br, 1H, HCl).

1-[3-(4-Cyanophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (7)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.67 (br t, 1H, CH_2), 2.87 (br m, 1H, CH_2), 3.44 (br m, 2H, CH_2's), 4.31 (s, 2H, CH_2), 7.74 (d, 2H, aromatic Hs), 7.91 (d, 2H, aromatic Hs), 11.06 (br, 1H, HCl).

1-[3-(3-Chlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (8)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.97 (br m, 1H, CH_2), 2.62 (br t, 1H, CH_2), 2.88 (br m, 1H, CH_2), 3.48 (br m, 2H, CH_2's), 4.27 (s, 2H, CH_2), 7.48 (m, 3H, aromatic Hs), 7.66 (s, 1H, aromatic H), 11.25 (br, 1H, HCl).

1-[3-(3-Methylphenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (9)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.11 (m, 1H, CH), 1.81 (br m, 3H, CH_2's), 1.98 (m, 1H, CH), 2.30 (s, 3H, CH_3), 2.63 (br m, 1H, CH), 2.88 (m, 1H, CH), 3.45 (br m, 2H, CH_2), 4.25 (s, 2H, CH_2), 7.30 (m, 4H, aromatic Hs).

1-[3-(3-Methoxyphenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (10)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.08 (m, 1H, CH), 1.81 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.62 (br t, 1H, CH_2), 2.88 (br m, 1H, CH_2), 3.48 (br m, 2H, CH_2's), 3.76 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 7.07 (m, 3H, aromatic Hs), 7.33 (t, 1H, aromatic H), 11.1 (br, 1H, HCl).

1-[3-(3-Cyanophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (11)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.08 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.63 (br t, 1H, CH_2), 2.90 (br m, 1H, CH_2), 3.48 (br m, 2H, CH_2's), 4.30 (s, 2H, CH_2), 7.64 (t, 1H, aromatic H), 7.90 (m, 2H, aromatic Hs), 8.10 (s, 1H, aromatic H), 11.0 (br, 1H, HCl).

1-[3-(2-Chlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (12)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.79 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.65 (br t, 1H,

CH_2), 2.91 (br m, 1H, CH_2), 3.47 (br m, 2H, CH_2's), 4.35 (s, 2H, CH_2), 7.44 (m, 2H, aromatic Hs), 7.63 (m, 2H, aromatic Hs), 11.27 (br, 1H, HCl).

1-[3-(2,3-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (13)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.04 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.99 (br m, 1H, CH_2), 2.66 (br t, 1H, CH_2), 2.91 (br m, 1H, CH_2), 3.47 (br m, 2H, CH_2's), 4.38 (s, 2H, CH_2), 7.42 (t, 1H, aromatic H), 7.71 (m, 2H, aromatic Hs), 11.20 (br, 1H, HCl).

1-[3-(2,4-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (14)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.80 (br m, 3H, CH_2's), 1.99 (br m, 1H, CH_2), 2.62 (br t, 1H, CH_2), 2.87 (br m, 1H, CH_2), 3.46 (br m, 2H, CH_2's), 4.28 (s, 2H, CH_2), 7.53 (dd, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.89 (d, 1H, aromatic H), 11.16 (br, 1H, HCl).

1-[3-(2,5-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (15)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.65 (br t, 1H, CH_2), 2.91 (br m, 1H, CH_2), 3.46 (br m, 2H, CH_2's), 4.37 (s, 2H, CH_2), 7.59 (m, 2H, aromatic Hs), 7.84 (d, 1H, aromatic H), 11.16 (br, 1H, HCl).

1-[3-(2,6-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (16)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.01 (m, 1H, CH), 1.80 (br m, 3H, CH_2's), 1.98 (br m, 1H, CH_2), 2.66 (br t, 1H, CH_2), 2.93 (br m, 1H, CH_2), 3.48 (br m, 2H, CH_2's), 4.45 (s, 2H, CH_2), 7.48 (dd, 1H, aromatic H), 7.60 (s, 1H, aromatic H), 7.64 (d, 1H, aromatic H), 11.22 (br, 1H, HCl).

1-[3-(4-Chloro-3-trifluoromethylphenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (17)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.08 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.96 (br m, 1H, CH_2), 2.63 (br t, 1H, CH_2), 2.89 (br m, 1H, CH_2), 3.46 (br m, 2H, CH_2's), 4.30 (s, 2H, CH_2), 7.84 (m, 2H, aromatic Hs), 8.01 (s, 1H, aromatic H).

1-[3-(3,4-Dichlorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (18)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.62 (br t, 1H, CH_2), 2.86 (br m, 1H, CH_2), 3.46 (br m, 2H, CH_2's), 4.27 (s, 2H, CH_2), 7.53 (dd, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H).

1-[3-(3-Chloro-5-methoxy)prop-2-ynyl]-3-methylpiperidine hydrochloride (20)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 1.99 (br m, 1H, CH_2), 2.61 (br t, 1H, CH_2), 2.86 (br m, 1H, CH_2), 3.47 (br m, 2H, CH_2's), 3.79 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 7.07 (m, 1H, aromatic H), 7.14 (m, 1H, aromatic H), 7.21 (m, 1H, aromatic H), 11.21 (br, 1H, HCl).

1-[3-(3,5-Difluorophenyl)prop-2-ynyl]-3-methylpiperidine hydrochloride (21)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.05 (m, 1H, CH), 1.76 (br m, 3H, CH_2's), 1.97 (br m, 1H, CH_2), 2.62 (br t, 1H, CH_2), 2.89 (br m, 1H, CH_2), 3.53 (br m, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.39 (m, 3H, aromatic Hs), 11.11 (br, 1H, HCl).

3-Ethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (24)

^{1}H NMR (DMSO-d_6) δ 0.86 (t, 3H, CH_3), 1.08 (m, 1H, CH), 1.27 (m, 2H, CH_2), 1.80 (br m, 4H, CH_2), 2.65 (br t, 1H, CH_2), 2.91 (br m, 1H, CH_2), 3.44 (br m, 2H, CH_2), 4.27 (s, 2H, CH_2), 7.45 (m, 3H, aromatic Hs), 7.54 (m, 2H, aromatic H), 11.50 (br, 1H, HCl).

2-Ethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (25)

^{1}H NMR (DMSO-d_6) δ 0.92 (t, 3H, CH_3), 1.71 (m, 8H, CH_2's), 3.16 (m, 2H, CH_2), 3.50 (br m, 1H, CH), 4.31 (m, 2H, CH_2), 7.43 (m, 3H, aromatic Hs), 7.54 (m, 2H, aromatic H).

2-Propyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (26)

^{1}H NMR (DMSO-d_6) δ 0.89 (t, 3H, CH_3), 1.63 (m, 10H, CH_2's), 3.18 (m, 2H, CH_2), 3.50 (br m, 1H, CH), 4.35 (m, 2H, CH_2), 7.44 (m, 3H, aromatic Hs), 7.53 (m, 2H, aromatic H).

2-Methyl-1-(3-phenylprop-2-ynyl)pyrrolidine hydrochloride (27)

^{1}H NMR (DMSO-d_6) δ 1.41 (d, 3H, CH_3), 1.67 (m, 1H, CH), 1.97 (m, 2H, CH_2), 2.21 (m, 1H, CH), 3.26 (m, 1H, CH), 3.56 (m, 2H, CH_2), 4.36 (br q, 2H, CH_2), 7.44 (m, 3H, aromatic Hs), 7.53 (m, 2H, aromatic H).

(2*R,3*R**)-2,3-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (28) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 0.89 (d, 2H, CH_3), 0.99 (d, 1H, CH_3), 1.13 (d, 2H, CH_3), 1.29 (d, 1H, CH_3), 1.43 (m, 1H, CH_2), 1.76 (m, 2H, CH_2), 2.20 (br, 1H, CH), 3.15 (m, 3H, CH_2), 3.63 (m, 1H, CH), 4.25 (m, 1.5H, CH_2), 4.37 (d, 0.5H, CH_2), 7.44 (m, 3H, aromatic Hs), 7.53 (m, 2H, aromatic Hs).

(2*R,3*S**)-2,3-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (29) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 0.95 (d, 3H, CH_3), 1.25 (m, 1H, CH), 1.36 (d, 3H, CH_3), 1.81 (m, 4H, CH_2), 3.09 (m, 2H, CH_2), 3.52 (br d, 1H, CH), 4.37 (br s, 2H, CH_2), 7.43 (m, 3H, aromatic Hs), 7.55 (m, 2H, aromatic Hs), 11.16 (br, 1H, HCl).

(2*R,5*S**)-2,5-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (30) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 2H, CH_3), 1.06 (d, 1H, CH_3), 1.26 (d, 2H, CH_3), 1.39 (d, 1H, CH_3), 1.62 (m, 2H, CH_2), 2.07 (m, 2H, CH_2), 2.72 (br q, 1H, CH), 3.18 (m, 1.5H, CH_2), 3.47 (m, 0.5H, CH_2), 3.85 (br s, 1H, CH), 4.21 (m, 1.5H, CH_2), 4.42 (d, 0.5H, CH_2), 7.43 (m, 3H, aromatic Hs), 7.52 (m, 2H, aromatic Hs).

(2*R,5*R**)-2,5-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (31) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.23 (m, 1H, CH), 1.34 (d, 3H, CH_3), 1.79 (m, 3H, CH_2), 2.05 (m, 1H, CH), 2.74 (br q, 1H, CH), 3.22 (br, 1H, CH), 3.44 (m, 1H, CH_2), 4.34 (br s, 2H, CH_2), 7.44 (m, 3H, aromatic Hs), 7.55 (m, 2H, aromatic Hs).

(2*R*i*,6*S)-2,6-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (32) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 1.38 (d, 6H, CH_3), 1.67 (m, 6H, CH_2's), 3.37 (m, 2H, CH_2), 4.38 (s, 2H, CH_2), 7.43 (m, 3H, aromatic H), 7.56 (m, 2H, aromatic H), 11.04 (br, 1H, HCl).

(3*R,5*S**)-3,5-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (33) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 6H, CH_3's), 1.75 (br d, 1H, CH), 2.02 (br, 2H, CH_2), 2.55 (br, 2H, CH_2), 3.42 (m, 3H, CH_2),

4.27 (s, 2H, CH_2), 7.43 (m, 3H, aromatic H), 7.55 (m, 2H, aromatic H), 11.45 (br, 1H, HCl).

(3*R,5*R**)-3,5-Dimethyl-1-(3-phenylprop-2-ynyl)piperidine hydrochloride (34) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 0.93 (d, 3H, CH_3), 1.05 (d, 3H, CH_3), 1.30 (m, 1H, CH), 1.43 (br d, 1H, CH), 2.08 (br, 1H, CH_2), 2.29 (br, 1H, CH_2), 2.61 (q, 1H, CH), 3.40 (s, 2H, CH_2), 3.12 (m, 1H, CH), 4.32 (d, 2H, CH_2), 7.44 (m, 3H, aromatic H), 7.58 (m, 2H, aromatic H), 10.13 (br, 1H, HCl).

(2*R,6*S**)-2,6-Dimethyl-4-(3-phenylprop-2-ynyl)morpholine hydrochloride (35) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 1.15 (d, 6H, CH_3), 2.70 (br t, 2H, CH_2), 3.46 (br d, 2H, CH_2), 4.00 (m, 2H, CH_2), 4.29 (s, 2H, CH_2), 7.43 (m, 3H, aromatic H), 7.55 (m, 2H, aromatic H).

(2*R,6*R**)-2,6-Dimethyl-4-(3-phenylprop-2-ynyl)morpholine hydrochloride (36) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 1.15 (br s, 3H, CH_3), 1.47 (br s, 3H, CH_3), 1.31 (m, 1H, CH), 2.75 (br, 1H, CH_2), 3.20 (br, 2H, CH_2), 4.13 (br, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.443 (m, 3H, aromatic H), 7.56 (m, 2H, aromatic H), 11.65 (br, 1H, HCl).

(4a*R,8a*R**)-2-(3-Phenylprop-2-ynyl)decahydroisoquinoline hydrochloride (37) [*cis*]**

^{1}H NMR (DMSO-d_6) δ 1.10–2.20 (m, 9H, CH_2s), 2.30 (m, 1H, CH), 2.95–3.40 (m, 6H, CH_2s), 4.31 (s, 2H, CH_2), 7.44 (m, 3H, aromatic Hs), 7.55 (m, 2H, aromatic Hs), 10.65 (br, ½H, HCl), 11.20 (br, ½H, HCl). COSY NMR was used to confirm that the methines of the fused ring were *cis*.

(4a*S,8a*R**)-2-(3-Phenylprop-2-ynyl)decahydroisoquinoline hydrochloride (38) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 0.97 (m, 2H, CH_2), 1.21 (m, 2H, CH_2), 1.64 (m, 6H, CH_2s), 2.74 (br t, 1H, CH), 3.04 (br t, 1H, CH), 3.36 (m, 3H, CH_2), 3.53 (br d, 1H, CH), 4.27 (s, 2H, CH_2), 7.45 (m, 3H, aromatic Hs), 7.56 (m, 2H, aromatic Hs), 11.40 (br s, 1H, HCl).

COSY NMR was used to determine that the methines of the fused ring were diaxial confirming the *trans* fused system.

2-(3-Phenylprop-2-ynyl)-1,2,3,4-tetrahydroisoquinoline (39)

^{1}H NMR (DMSO-d_6) δ 2.94 (m, 4H, CH_2's), 3.73 (s, 2H, CH_2), 3.85 (s, 2H, CH_2), 7.10 (m, 4H, aromatic Hs), 7.28 (m, 3H, aromatic Hs), 7.43 (m, 2H, aromatic Hs).

(4a*S,8a*R**)-1-(3-Phenylprop-2-ynyl)decahydroquinoline hydrochloride (40) [*trans*]**

^{1}H NMR (DMSO-d_6) δ 1.27 (m, 5H, CH_2), 1.69 (br t, 4H, CH_2), 1.87 (m, 3H, CH_2s), 2.21 (br d, 1H, CH), 2.90 (br m, 1H, CH), 3.15 (br m, 1H, CH_2), 3.54 (br d, 1H, CH), 4.36 (s, 2H, CH_2), 7.45 (m, 3H, aromatic Hs), 7.56 (m, 2H, aromatic Hs), 11.16 (br s, 1H, HCl). COSY NMR was used to determine that the methines of the fused ring were diaxial confirming the *trans* fused system.

3,3,5-Trimethyl-1-(3-phenylprop-2-ynyl)azepine (41)

^{1}H NMR (DMSO-d_6) δ 0.89 (s, 6H, CH_3's), 0.92 (d, 3H, CH_3), 1.39 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.10 (m, 1H, CH), 2.85 (m, 1H, CH_2), 3.31 (m, 3H, CH_2's), 4.29 (br s, 2H, CH_2), 7.45 (m, 3H, aromatic Hs), 7.54 (m, 2H, aromatic Hs).

1-(3-Phenylprop-2-ynyl)indoline (42)

^{1}H NMR (DMSO-d_6) δ 2.99 (t, 2H, CH_2), 3.49 (t, 2H, CH_2), 4.14 (s, 2H, CH_2), 6.71 (m, 2H, aromatic Hs), 7.11 (m, 2H, aromatic Hs), 7.28 (m, 3H, aromatic Hs), 7.37 (m, 2H, aromatic Hs).

***N*^{1},*N*^{1},2-Trimethyl-*N*^{2}-(3-phenylprop-2-ynyl)propane-1,2-diamine (43)**

^{1}H NMR (DMSO-d_6) δ 1.56 (s, 6H, CH_3's), 2.89 (s, 6H, CH_3's), 3.62 (s, 2H, CH_2), 4.19 (s, 2H, CH_2), 7.45 (m, 5H, aromatic Hs), 10.39 (br, 2H, HCl/NH), 10.98 (br, 1H, HCl/NH).

1-[3-(3,4-Dichlorophenyl)prop-2-ynyl]-3-ethylpiperidine hydrochloride (44)

^{1}H NMR (DMSO-d_6) δ 0.86 (t, 3H, CH_3), 1.08 (m, 1H, CH), 1.26 (q, 2H, CH_2), 1.81 (br m, 4H, CH_2's), 2.65 (br t, 1H, CH_2), 2.92 (br m, 1H, CH_2), 3.47 (br t, 2H, CH_2's), 4.28 (s, 2H, CH_2), 7.53 (dd, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H).

1-[3-(3,4-Dichlorophenyl)prop-2-ynyl]-3-butylpiperidine hydrochloride (45)

^{1}H NMR (DMSO-d_6) δ 0.86 (d, 3H, CH_3), 1.07 (m, 1H, CH), 1.24 (br s, 6H, CH_2s), 1.76 (br m, 4H, CH_2's), 2.64 (br t, 1H, CH_2), 2.91 (br m, 1H, CH_2), 3.45 (br t, 2H, CH_2's), 4.28 (s, 2H, CH_2) 7.53 (dd, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H).

1-[3-(3,4-Dichlorophenyl)prop-2-ynyl]-3-phenylpiperidine hydrochloride (46)

^{1}H NMR (DMSO-d_6) δ 1.73 (m, 1H, CH), 1.93 (br m, 3H, CH_2), 3.16 (br m, 3H, CH_2), 3.51 (br m, 2H, CH_2), 4.34 (s, 2H, CH_2), 7.32 (m, 5H, aromatic Hs), 7.53 (dd, 1H, aromatic H), 7.70 (d, 1H, aromatic H), 7.88 (d, 1H, aromatic H).

1-[3-(3,5-Dichlorophenyl)prop-2-ynyl]-3-benzylpiperidine hydrochloride (47)

^{1}H NMR (DMSO-d_6) δ 1.15 (m, 1H, CH), 1.75 (br m, 4H, CH_2), 2.15 (br, 1H, CH_2), 2.58 (d, 2H, CH_2), 2.72 (br, t, 1H, CH), 2.93 (br m, 1H, CH), 3.50 (m, 1H, CH), 4.29 (s, 2H, CH_2), 7.26 (m, 6H, aromatic H), 7.59 (d, 1H, aromatic H), 7.75 (t, 1H, aromatic H), 11.02 (br, 1H, HCl).

1-[3-(3,5-Dichlorophenyl)prop-2-ynyl]pyrrolidine hydrochloride (48)

^{1}H NMR (DMSO-d_6) δ 1.96 (br s, 4H, CH_2s), 3.31 (br s, 4H, CH_2s), 4.37 (s, 2H, CH_2), 7.63 (d, 2H, aromatic Hs), 7.73 (t, 1H, aromatic H), 11.60 (br, 1H, HCl).

5-[3-Methylpiperidin-1-yl)prop-1-ynyl]pyrimidine hydrochloride (49)

^{1}H NMR (DMSO-d_6) δ 0.91 (d, 3H, CH_3), 1.07 (m, 1H, CH), 1.82 (br m, 3H, CH_2's), 2.00 (br m, 1H, CH_2), 2.65 (br t, 1H, CH_2), 2.82 (br m, 1H, CH_2), 3.42 (br m, 2H, CH_2's), 4.34 (s, 2H, CH_2), 9.03 (s, 2H, aromatic Hs), 9.23 (2, 1H, aromatic H), 11.29 (br, 1H, HCl).

3-Methyl-1-(5-phenylpent-2-ynyl)piperidine hydrochloride (50)

^{1}H NMR (DMSO-d_6) δ 0.83 (d, 3H, CH_3), 0.92 (m, 1H, CH), 1.68 (br m, 3H, CH_2's), 1.90 (br m, 1H, CH_2), 2.30 (br t, 1H, CH_2), 2.57 (br m, 3H, CH_2's), 2.78 (t, 2H, CH_2), 3.19 (br t, 2H, CH_2), 3.89 (s, 2H, CH_2), 7.25 (m, 5H, aromatic Hs), 10.95 (br, 1H, HCl).

3-[3-(3-Methylpiperidin-1-yl)prop-1-ynyl]pyridine dihydrochloride (51)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.80 (br m, 3H, CH_2's), 2.01 (br m, 1H, CH_2), 2.65 (br q, 1H,

Table 4 Elemental Analysis

Compd. No.		Elemental analysis					
		Calculated			Found		
		% C	% H	% N	% C	% H	% N
1	$C_{15}H_{20}ClN$	72.13	8.07	5.61	72.21	8.12	5.63
2	$C_{15}H_{19}Cl_2N$	63.38	6.74	4.93	63.09	6.80	4.87
3	$C_{15}H_{19}ClFN$	67.28	7.15	5.23	67.24	7.20	5.21
4	$C_{16}H_{19}ClF_3N$	60.47	6.03	4.41	60.30	6.06	4.38
5	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.72	8.43	5.32
6	$C_{15}H_{21}ClN_2O_2S$	54.78	6.44	8.52	54.73	6.45	8.48
7	$C_{16}H_{19}ClN_2$	69.93	6.97	10.20	69.96	7.00	10.20
8	$C_{15}H_{19}Cl_2N$	63.38	6.74	4.93	63.43	6.75	4.96
9	$C_{16}H_{22}ClN.0.13H_2O$ [a]	72.23	8.43	5.27	71.97	8.43	5.24
10	$C_{16}H_{22}ClNO$	68.68	7.93	5.01	68.53	7.98	4.96
11	$C_{16}H_{19}ClN_2$	69.93	6.79	10.20	69.85	6.99	10.19
12	$C_{15}H_{19}Cl_2N$	63.38	6.74	4.93	63.38	6.77	4.98
13	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.44	5.70	4.38
14	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.37	5.71	4.34
15	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.59	5.72	4.39
16	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.60	5.71	4.35
17	$C_{16}H_{18}Cl_2F_3N$	54.56	5.15	3.98	54.48	5.15	3.99
18	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.68	5.76	4.41
19	$C_{15}H_{18}Cl_3N$	56.53	5.69	4.40	56.65	5.72	4.34
20	$C_{16}H_{21}Cl_2NO$	61.15	6.74	4.46	61.07	6.76	4.44
21	$C_{15}H_{18}ClF_2N$	63.04	6.35	4.90	62.96	6.38	4.92
22	$C_{15}H_{20}ClN$	72.13	8.07	5.61	72.19	8.12	5.65
23	$C_{15}H_{20}ClN$	72.13	8.07	5.61	72.34	8.11	5.69
24	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.61	8.39	5.26
25	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.92	8.44	5.35
26	$C_{17}H_{24}ClN$	73.49	8.71	5.04	73.57	8.72	5.03
27	$C_{14}H_{18}ClN$	71.32	7.70	5.94	71.22	7.74	5.91
28	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.93	8.42	5.29
29	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.78	8.45	5.31
30	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.80	8.43	5.28
31	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.81	8.41	5.27
32	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.91	8.44	5.27
33	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.76	8.44	5.24
34	$C_{16}H_{22}ClN$	72.84	8.41	5.31	72.74	8.46	5.36
35	$C_{15}H_{20}ClNO$	67.78	7.58	5.27	67.71	7.59	5.24
36	$C_{15}H_{20}ClNO$	67.78	7.58	5.27	67.62	7.60	5.23
37	$C_{18}H_{24}ClN$	74.59	8.35	4.83	74.58	8.37	4.83
38	$C_{18}H_{24}ClN$	74.59	8.35	4.83	74.50	8.38	4.82
39	$C_{18}H_{17}N$	87.41	6.93	5.66	87.33	6.93	5.62
40	$C_{18}H_{24}ClN$	74.59	8.35	4.83	74.5	8.36	4.84
41	$C_{18}H_{26}ClN$	74.04	8.98	4.80	73.97	9.01	4.77
42	$C_{17}H_{15}N$ [b]	87.51	6.48	6.00	87.49	6.53	5.97
43	$C_{15}H_{24}Cl_2N_2$ [c]	59.40	7.98	9.24	59.38	7.90	9.33
44	$C_{16}H_{20}Cl_3N$	57.76	6.06	4.21	57.84	6.10	4.21
45	$C_{18}H_{24}Cl_3N$	59.93	6.71	3.88	59.99	6.74	3.86
46	$C_{20}H_{20}Cl_3N$	63.09	5.29	3.68	63.01	5.30	3.65
47	$C_{21}H_{22}Cl_3N$	63.89	5.62	3.55	63.96	5.66	3.51
48	$C_{13}H_{14}Cl_3N$	53.72	4.86	4.82	53.64	4.86	4.80
49	$C_{13}H_{18}ClN_3$	62.02	7.21	16.69	61.75	7.22	16.61
50	$C_{17}H_{24}ClN$	73.49	8.71	5.04	73.36	8.77	5.04
51	$C_{14}H_{20}Cl_2N_2$ [c]	58.54	7.02	9.75	58.45	7.06	9.82
52	$C_{13}H_{18}ClNS$	61.03	7.09	5.48	61.07	7.15	5.42
53	$C_{15}H_{24}ClN$	70.98	9.53	5.52	70.80	9.58	5.50
54	$C_{19}H_{22}ClN$	76.11	7.40	4.67	76.03	7.42	4.65

[a] H_2O Calcd: 0.85; found: 0.74. [b] Free base; not HCl salt! [c] Isolated as dihydrochloride salt.

CH_2), 2.93 (br m, 1H, CH_2), 3.46 (br t, 2H, CH_2), 4.32 (d, 2H, CH_2), 7.50 (br, 1H, HCl), 7.62 (m, 1H, aromatic H), 8.16 (dt, 1H, aromatic H), 8.70 (dd, 1H, aromatic H), 8.87 (d, 1H, aromatic H), 11.47 (br, 1H, HCl).

3-Methyl-1-[3-(3-thienylprop-2-ynyl]piperidine hydrochloride (52)

^{1}H NMR (DMSO-d_6) δ 0.90 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.80 (br m, 3H, CH_2's), 1.95 (br m, 1H, CH_2), 2.60 (br t, 1H, CH_2), 2.86 (br m, 1H, CH_2), 3.43 (br m, 2H, CH_2), 4.24 (s, 2H, CH_2), 7.23 (dd, 1H, aromatic H), 7.65 (dd, 1H, aromatic H), 7.94 (d, 1H, aromatic H), 11.04 (br, 1H, HCl).

1-(3-Cyclohex-1-en-1-ylprop-2-ynyl)-3-methylpiperidine hydrochloride (53)

^{1}H NMR (DMSO-d_6) δ 0.88 (d, 3H, CH_3), 1.03 (m, 1H, CH), 1.54 (br d, 4H, CH_2's), 1.70 (br m, 4H, CH_2), 1.94 (br m, 1H, CH_2), 2.07 (br m, 4H, CH_2), 2.52 (br m, 1H, CH_2), 2.76 (br m, 1H, CH_2), 3.31 (br m, 2H, CH_2's), 4.10 (s, 1H, CH_2), 6.20 (s, 1H, C=C H), 11.17 (br, 1H, HCl).

3-Methyl-1-[3-(2-naphthyl)prop-2-ynyl]piperidine hydrochloride (54)

^{1}H NMR (DMSO-d_6) δ 0.92 (d, 3H, CH_3), 1.06 (m, 1H, CH), 1.81 (br m, 3H, CH_2's), 2.00 (br m, 1H, CH_2), 2.65 (br t, 1H,

CH_2), 2.83 (br m, 1H, CH_2), 3.48 (br m, 2H, CH_2's), 4.32 (s, 2H, CH_2), 7.57 (m, 3H, aromatic Hs), 7.94 (m, 3H, aromatic Hs), 8.17 (s, 1H, aromatic H), 11.19 (br, 1H, HCl).

Biology

Methods and Materials. [2-^{14}C] Mevalonolactone (MVL) (50 mCi per mmol), [4-^{14}C]cholesterol (55 mCi per mmol), and [4,8,12,13,17,21-^{3}H]squalene (26 Ci per mmol) were purchased from New England Nuclear (Boston, MA). Solvents for high performance liquid chromatography (HPLC) analysis of reaction products were obtained from EM Sciences (Gibbstown, NJ). Reversed phase 4.6 × 25 cm OD5 Octadecyl columns were obtained from Burdick and Jackson Co. (Muskegon, MI). Authentic (racemic) squalene epoxide and squalene diepoxide were provided by Dr T. A. Spencer, Department of Chemistry, Dartmouth College, Hanover, NH. The chromatographic equipment was composed of a model 710B autosampler and 720 system controller (Waters Associates Inc., Milford, MA), a model 773 Spectroflow ultraviolet detector (Kractos Instruments, Ramsey, NJ), and a model Flo-One Betq radiochemical detector (Radiomatic Instruments and Chemical Co., Tampa, FL). Scintverse E scintillation fluid was purchased from Fisher Scientific (Fair Lawn, NJ). Other reagents of high purity were obtained from Sigma Chemical Co., (St. Louis, MO).

Procedure. Female Sprague Dawley CD rats weighing 250 grams were obtained from Charles River Breeding Laboratories, Raleigh, NC. Animals were housed in temperature- and humidity-controlled quarters under a 12 hour light–dark cycle. Postmitochondrial supernatant fraction (PMSF) from rat livers was used as a source of squalene epoxidase activity. Rat livers were homogenized at 0–4 °C in 0.1 M potassium phosphate buffer containing 30 μM nicotinamide and 1 μM EDTA at pH 7.4. The PMSF was obtained by differential centrifugation and stored at −70 °C until used in the assay. Protein determinations were performed by the Lowry method.[23]

Squalene epoxidase activity was determined as described by Popjak *et al.*[18] for cell-free biosynthesis of sterols. The epoxidase assay was performed in two steps: (1) generation of squalene from MVL and (2) the epoxidation reaction.

In the preincubation step, the vessels contained 6–8 mg of PMSF, 0.1 M potassium phosphate buffer containing 30 μM nicotinamide at pH 7.4, 10 μM magnesium sulfate, 10 μM ATP, and 1 mM (0.1 mCi) [^{14}C] MVL. The preincubation reaction (step 1) generating squalene from MVL was conducted for 20 min at 37 °C. The epoxidase reaction (step 2) was performed on the preincubated reaction samples in the presence of 1 μM NADPH and 40 μM FAD and incubated for 30 min at 37 °C. The reaction was stopped by addition of 0.1 mL of 5 M potassium hydroxide, and the products were extracted with chloroform–methanol–methyl *tert*-butyl ether (2 : 1 : 1). Extraction solvents were evaporated under nitrogen at 40 °C, and the products were quantitated by reversed phase HPLC analysis and radiometric detection.

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