Inhibition of 5-Lipoxygenase by Substituted 3,4-Dihydro-2*H*-1,4-thiazines

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Abstract □ A series of substituted 3,4-dihydro-2*H*-1,4-thiazines inhibit 5-lipoxygenase from rat leukocytes and exhibit submicromolar IC_{50} values. A novel synthesis of these compounds was developed based on the formation of hydroxymethyleneamine **13** and its cyclization to the title compounds. The dihydrothiazines have low oxidation potentials, typically $E_{1/2}$ is near 0.3 V, and a representative compound reduces Fe(III)(phen)$_3$, with $k = 10^5$ $M^{-1}s^{-1}$. We propose that these lipophilic compounds bind to 5-lipoxygenase and reduce the iron in the active site, thus inactivating the enzyme.

5-Lipoxygenase (5-LO) is the first enzyme involved in the conversion of arachidonic acid to the biologically important leukotrienes (LT). For example, the diol LTB_4 is a potent chemotaxin for neutrophils[1] and the peptidoleukotrienes LTC_4, LTD_4, and LTE_4 comprise the slow-reacting substance of anaphylaxis.[2,3] Attention has focused on the role of leukotrienes in the development of certain physiological disorders such as allergic asthma and inflammation.[4] The potential for treating these diseases by the inhibition of 5-LO is an attractive goal.[5-7]

Lipoxygenases are thought to contain an iron atom which is necessary to catalyze the oxidation of a double bond in arachidonic acid.[8-11] A "horseshoe" conformation for arachidonic acid in the active site of the enzyme has been postulated.[12] This conformation is shown in Figure 1, where the dotted lines emphasize its similarity to fused or 1,1′-linked unsaturated ring systems. One approach to lipoxygenase inhibitors is to contrive a compound that can mimic this conformation and that contains an electron-rich group that would provide interactions with the electrophilic iron atom.[13] With this in mind, we evaluated 6-phenyl-3,4-dihydro-2*H*-1,4-thiazines[14] as potential inhibitors of 5-LO. In particular, these compounds feature a phenyl ring in 1,1′-linkage to an electron-rich dihydrothiazine ring. Two dihydrothiazines have already been reported to inhibit 5-LO. The benzo-1,4-thiazine **2** was shown to be a potent inhibitor with an IC_{50} value of 2.7 μM[15] and the benzoyl-substituted dihydrothiazine **1** was recently claimed[16] to have LO-inhibiting activity, though our results indicate that it is at best a weak 5-LO inhibitor ($IC_{50} > 100$ μM). We, therefore, synthesized a series

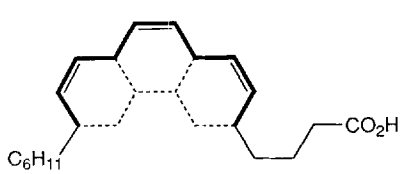
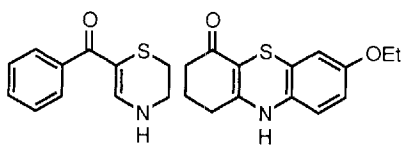


Figure 1—Horseshoe conformation of arachidonic acid. The dotted lines represent a fused aromatic ring system overlayed on the arachidonic acid.



1 **2**

of substituted dihydrothiazines (Table I) and tested them as inhibitors of 5-LO.

Results and Discussion

Chemistry—We recently reported that cyclization of urethane **3** gave lactam **5** which, upon reduction with lithium aluminum hydride (LAH), gave dihydrothiazine **6m** as the major product along with minor amounts of tetrahydrothiazine **7**[14] (Scheme I). Synthesis of **6a**, **6b**, **6c**, **6d**, and **6h** required alkylation of secondary lactam **4** with an appropriate alkyl halide, followed by reduction of the resulting tertiary amide with lithium aluminum hydride.

Alternatively, a more direct route was developed which involved the conversion of the amine **11** (R = Ph, R_2 = H) to the dihydrothiazine **6e** (R = CH_2CH_2Ph, R_2 = H; Scheme II). The reactions of β-mercaptoethylamines with α-haloketones represent an important synthetic entrance to dihydrothiazines.[17] We felt if we could prepare the aldehyde **12** it would readily cyclize to the desired dihydrothiazine. We were encouraged by a recent patent of Renfroe[16] and a report by Chiba et al.[18] who prepared dihydrothiazines by a similar method. A dianion generated from amine **11** and lithium diisopropylamide was reacted with one equivalent of ethyl formate to generate the dianion of hydroxymethylene amine **13**. Quenching the reaction with ammonium chloride directly provided dihydrothiazine **6e**.

Biology—Compounds were tested for inhibition of partially purified 5-LO from rat neutrophils by incubation of the inhibitor with the enzyme for 10 min followed by addition of the substrate to initiate a 10-min assay. Enzyme concentrations in control reactions were chosen to give 70–80% conversion of the substrate, and IC_{50} values represent the inhibitor concentration necessary to limit substrate conversion to half that of the control. The results are collected in Table I. Under these conditions we were able to confirm that the previously described dihydrothiazine **2** was indeed a potent inhibitor of 5-LO (IC_{50} = 0.5 μM). The inhibitory potency of a representative dihydrothiazine (**6a**) is compared in Table II with those of standard 5-LO inhibitors under these assay conditions.

All the compounds in this study in which a phenyl group was directly attached to the dihydrothiazine were good inhibitors of 5-LO. The inhibitory potency was found to be

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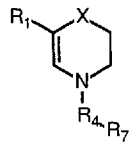
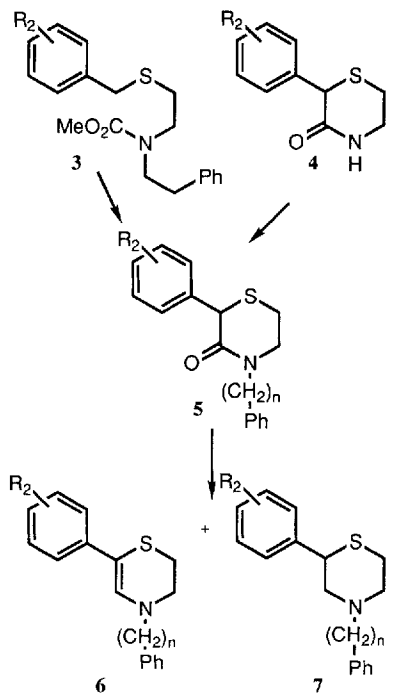
Table I—6-Phenyl-3,4-dihydro-2*H*-1,4-thiazine Inhibitors of 5-Lipoxygenase

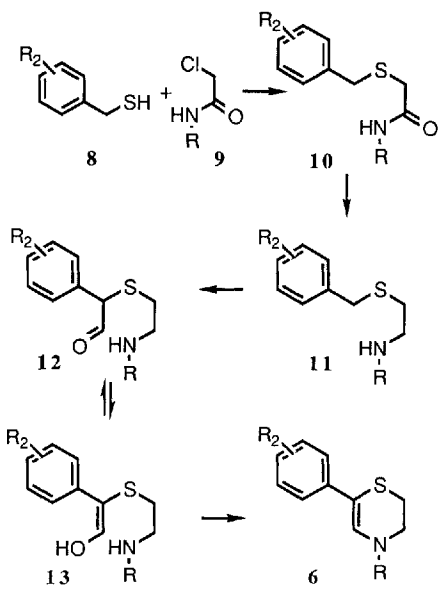


Compound	X	R_1	R_4	R_7	IC_{50}, μM[a]	$E_{1/2}$[b]
6a	S	Ph	$(CH_2)_4$	Ph	0.4	0.23
6b	S	Ph	$(CH_2)_3$	Ph	0.4	0.23
6c	S	Ph	CH_2CH_2	Ph[c]	0.5	0.27
6d	S	Ph	CH_2	Ph	0.4	0.29
6e	S	Ph	—	Ph	1.5	0.44
6f	S	3-MeOPh	$CH(Me)CH_2$	Ph	0.8	0.24
6g	S	Ph	CH_2CH_2	Me	4	
6h	S	Ph	CH_2CH_2	OH[c]	6	0.25
6i	S	H[d]	CH_2CH_2	Me	10	0.27
6j	S	1-$C_{10}H_7$	CH_2CH_2	Ph	0.6	0.26
6k	S	4-ClPh	CH_2CH_2	Ph	0.2	0.28
6l	S	4-MeOPh	CH_2CH_2	Ph	0.3	0.16
6m	S	3-MeOPh	CH_2CH_2	Ph	2	0.24
7m	S	3-MeOPh[e]	CH_2CH_2	Ph[c]	90	0.99
5m	S	3-MeOPh[f]	CH_2CH_2	Ph[c]	100	>1.4
6n	O	Ph	CH_2	Ph	0.8	0.18
6o	S	PhCO	CH_2CH_2	Ph	>100	0.77
6p	S	3-MeOPh[e]	$COCH_2$	Ph	20	>1.4
6q	S	3,4-$(MeO)_2$Ph	CH_2CH_2	3,4-$(MeO)_2$Ph[c]	6	0.15

[a] IC_{50} values, measured as described in the text, are reproducible to one significant figure (±30%). [b] Average of reversible oxidation and reduction potentials measured by cyclic voltammetry in acetonitrile containing 0.2 M LiClO4, V versus Ag:AgCl. [c] See ref 14. [d] 5-Phenyl. [e] 3,4,5,6-Tetrahydro. [f] 3,4,5,6-tetrahydro-5-oxo.



Scheme I



Scheme II

relatively insensitive to variations in the substituent on the nitrogen. A majority of the compounds in this study has a phenyl group attached to the nitrogen via an alkyl spacer; variation in the length or branching of this spacer had little effect on the activity (**6a–6f**). Furthermore, while replacement of this phenyl ring with methyl (**6g**) or hydroxyl (**6h**) groups resulted in the loss of approximately an order of magnitude in potency, such large effects on the lipophilic character of the molecule could have been expected to have a more dramatic effect.

Similarly, there was little effect of varying the 6-phenyl substituent. A 6-naphthyl group (**6j**) was equipotent to **6c**, as were 3- and 4-substituted derivatives (**6f** and **6k–6m**), although extensive substitution as in the bis-dimethoxy analogue (**6q**) resulted in reduced activity. Moving the phenyl group from C-6 to C-5 (**6i**) was not deleterious, nor was substituting an oxygen atom for the sulfur (**6n**). The IC_{50} values were, however, sensitive to reduction of the double bond of the dihydrothiazine ring (**7** and **5**).

Table II—Comparison of 6-Phenyl-3,4-dihydro-2*H*-1,4-thiazine with Standard Inhibitors of 5-Lipoxygenase

Compound	IC_{50}, μM[a]	$E_{1/2}$[a]
6a	0.4	0.23
ETYA[b]	2	—
Diphenyl disulfide	0.08	—
Phenidone[c]	90	0.05[e]
BW 755C[d]	80	0.24[e]

[a] Determined as for Table I. [b] 5,8,11,14-Eicosatetraynoic acid. [c] 2-Phenyl-1*H*-indene-1,3(2*H*)-dione. [d] 4,5-Dihydro-1-[3-(trifluoromethyl)-phenyl]-1*H*-pyrazol-3-amine hydrochloride. [e] Redox potentials measured in aqueous solution.

Since enzyme inhibition by this series of compounds is insensitive to structural changes on the ring, it is likely that factors in addition to conformational effects are important. The dihydrothiazines have low oxidation potentials, in marked contrast to the tetrahydrothiazines. Reduction of the 5,6-double bond (**5m**, **6p**, and **7m**) also has a large, negative effect on enzyme inhibition. It seems likely, then, that oxidation of the dihydrothiazines plays a role in the mechanism of action.

There is evidence that 5-LO requires lipid peroxide for activity,[19] and the inhibitory effect of the dihydrothiazines could result from reduction of these lipid hydroperoxides. However, a representative dihydrothiazine, **6c**, did not detectably reduce 15-hydroperoxyeicosatetraenoic acid acid under the conditions of the enzyme assay.

The role of lipid hydroperoxides is proposed to be involved in maintaining the iron of the enzyme in the oxidized Fe(III) state.[8–11] Our inhibitors might act by directly reducing the iron in the active site of the enzyme. In a model experiment, we were able to demonstrate that **6m** was capable of reducing $Fe^{III}(phen)_3$ with a rate constant $>10^5\ M^{-1}s^{-1}$. It is probable, therefore, that the dihydrothiazines studied here are acting by maintaining 5-LO in the reduced state. The lack of inhibitory activity of **6o**, a 6-benzoyl dihydrothiazine of higher oxidation potential, can be rationalized by its inability to affect iron reduction.

The inhibitory potency of 5-LO inhibitors is clearly not solely a function of reduction potential, however. Despite the modest dependence on structure for this series of dihydrothiazines, known inhibitors with a different redox-activity functional group, phenidone and BW 755C (Table II), have markedly lower reduction potentials but are poorer 5-LO inhibitors. In addition, the following compounds were tested as inhibitors of soybean lipoxygenase, which presumably has a similar reaction mechanism: **6a–d**, **6h**, **6m**, **6n**, **6p**, **6q**, **5m**, and **7m**. None of these inhibited the soybean enzyme (<5% inhibition at 40 μM). There is, therefore, some structural specificity in the inhibition of 5-LO by this series of dihydrothiazines.

Three of the compounds, **6f**, **6k**, and **6n**, were evaluated to determine if they would inhibit LTB_4 production in calcium ionophore (A23187)-stimulated rat whole blood. The compounds were ~100-fold less potent in this test system compared with the isolated enzyme system. In addition, **6f** was evaluated at dose levels of 100 and 400 mg/kg ip in rats. Blood drawn 1 h after compound administration showed no evidence of 5-LO inhibition.

Conclusions

A synthetic method for preparing a variety of 6-aryl-3,4-dihydro-2*H*-1,4-thiazine analogues has been presented. Compounds containing the dihydrothiazine ring and a phenyl group on the nitrogen tether provide the most potent inhibitors. These compounds probably act by reducing the iron in the enzyme.

Experimental Section

General—The NMR spectra were obtained with a Varian FT80-A or a Varian VXR300 magnetic resonance spectrophotometer in $CDCl_3$ with Me_4Si as an internal standard. Infrared (IR) spectra were obtained with a Perkin-Elmer 521 grating spectrophotometer or a Perkin-Elmer 1800 FT spectrophotometer as neat smears. The ultraviolet (UV) spectra were recorded with a Perkin-Elmer 350 spectrophotometer in ethanol. The standard drying agent was $MgSO_4$ and the solvents were removed under reduced pressure on a rotary evaporator. Distillations were done on an Aldrich brand Kugelrohr bulb-to-bulb apparatus. All chromatography was done using flash chromatography[20] with E. Merck 230–400 mesh silica gel 60. Cyclic voltametry was performed with a glassy carbon electrode at a scan rate of 20 mV/s.

Evaluation of Compounds—5-Lipoxygenase (5-LO) was prepared from rat neutrophils and assayed as previously described.[21] Compounds were tested for inhibition of 5-LO by incubating with enzyme in the presence of 2 mM Ca^{2+} and 2 mM ATP for 10 min. [^{14}C]Arachidonic acid (0.8 μM) was then added to initiate the assay, which was continued for 10 min further. Inhibition of soybean lipoxygenase (Sigma Chemical) was tested in 0.1 M sodium borate, pH 9.5, at 26 °C using 0.1 mM linoleic acid (Sigma Chemical) as substrate. Enzyme activity was determined from the maximum rate of absorbance change at 235 nm. Reaction of selected compounds with Fe(III) was monitored as an increase in absorbance at 506 nm when the compounds (6.7 μM) were incubated at 25 °C in acetonitrile with 5 μM $Fe^{III}(phen)_3(ClO_4)_3$.[22] Reaction of selected compounds with organic peroxides was measured in 0.1 HEPES buffer containing 1 nM EDTA and 20% ethanol by incubating the compounds (50 μM) with 20 μM 15-hydroperoxyeicosa tetraenoic acid for 20 min. Any unreduced hydroperoxide was then measured by reaction with glutathione (10 μM) in the presence of glutathione peroxidase (2 μM/mL) for 20 min. Unreacted glutathione was in turn measured with 1 mM 5,5′-dithiobis(2-nitrobenzoic acid) as the change in absorbance at 408 nm ($\Delta\epsilon$ = 13.6 $mM^{-1}cm^{-1}$).

To test 5-LO inhibition in whole blood, the generation of LTB_4 was measured. The test compound was added to the blood and the samples were incubated for another 30 min at 37 °F. The samples were then stimulated with 30 mM A23187 and incubated for another 30 min. Enzymatic activity was stopped by the addition of ice cold saline, and the cells were removed by centrifugation (28,000 *g*-min). Protein was precipitated with aqueous methanol (2:1) and then adjusted to 15% methanol with the addition of water prior to solid-phase C_{18} extraction. Samples were washed on the columns with 15% methanol and eluted with 100% methanol. The methanolic extracts were diluted to 75% methanol with water and LTB_4 is quantitated by reversed-phase HPLC (C_{18} column; 75% methanol: 25% water: 0.01% TFA).

Scheme I Procedure—*2-Phenyl-3-thiomorpholinone (4, R_2 = H)*—A stirred, cooled mixture of α-chlorophenylacetyl chloride (50.37 g, 0.266 mol) and 2-thiolethanamine *S*-acetate hydrochloride[23,24] (*S*-acetyl cysteamine, 39.02 g, 0.251 mol) in dichloromethane (CH_2Cl_2, 700 mL) was treated in a dropwise manner with triethylamine (55.8 g, 0.551 mol) in CH_2Cl_2 (70 mL). After 3 h, the mixture was washed with 10% HCl, followed by saturated $NaHCO_3$, then dried, treated with charcoal, filtered, and concentrated. The residue was treated with a solution of sodium methylate [from sodium (7.0 g, 0.304 mol) and methanol (500 mL)]. After 18 h, the solvent was removed and the residue was partitioned between dilute HCl and CH_2Cl_2. The organic layer was dried, treated with charcoal, filtered, and concentrated to a solid which was crystallized from acetone to give 4 (R_2 = H, 25.16 g, 52.4%), mp 158–159 °C; ^{1}H NMR (DMSO-D_6): δ 2.65–2.95 (2H, m), 3.28–3.63 (2H, m), 4.72 (1H, s), 7.33 (5H, s), and 7.93 ppm (1H, v br s); IR (KBr): ν 3440, 3200, 1650 cm^{-1}.

Anal.—Calc. for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.36; H, 5.75; N, 7.16; S, 16.70.

General Procedure—*2-Phenyl-4-(phenylalkyl)-3-thiomorpholinone (5)*—A stirred suspension of 50% sodium hydride (25.9 mmol) in toluene (100 mL) under an argon atmosphere was treated with lactam 4 (R_2 = H, 25.8 mmol) and warmed briefly until hydrogen evolution ceased. The warm solution was treated with an appropriate halide (28.9 mmol) and heated to boiling for 18 h. The cooled mixture was acidified with acetic acid (5 mL), diluted with CH_2Cl_2 (30 mL), and extracted with water (100 mL). The separated organic layer was dried and concentrated. The residue was purified by chromatography (toluene:ethyl acetate).

2-Phenyl-4-(4-phenylbutyl)-3-thiomorpholinone (5, R = H, n = 4)—Yield of 21.4%, mp 83–86 °C; ^{1}H NMR: δ 1.46–1.75 (4H, m), 2.47–2.69 + 2.78 (4H, m + t), 3.31–3.61 (4H, m), 4.59 (1H, s), and 7.03–7.44 ppm (10H, m); IR ($CHCl_3$): ν 1650, 1640 cm^{-1}.

Anal.—Calc. for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30; S, 9.85. Found: C, 73.82; H, 7.15; N, 4.07; S, 9.78.

2-Phenyl-4-(3-phenylpropyl)-3-thiomorpholinone (5, R = H, n = 3)—Yield of 31.0%, mp 90–92 °C; ^{1}H NMR: δ 1.88 (2H, quint), 2.62–2.78 (4H, pr t), 3.30–3.59 (4H, m), 4.58 (1H, s), and 7.06–7.41 ppm (10H, m); IR ($CHCl_3$): ν 1650, 1640, cm^{-1}.

Anal.—Calc. for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50; S, 10.30. Found: C, 73.05; H, 6.81; N, 4.22; S, 10.15.

2-Phenyl-4-(2-phenylethyl)-3-thiomorpholinone (5, R = H, n = 2)—Yield of 43.9%, mp 56–57 °C (ether): ^{1}H NMR: δ 2.56–3.00 (4H, m), 3.28–4.00 (4H, m), 4.59 (1H, s), and 7.20 + 7.28 ppm (10H, pr s); IR (KBr): ν 1650sh, 1640, cm^{-1}.

Anal.—Calc. for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.68; H, 6.53; N, 4.56; S, 10.81.

2-Phenyl-4-(phenylmethyl)-3-thiomorpholinone (5, R = H, n = 1)—As a liquid (69.7%); ^{1}H NMR: δ 2.73 (2H, t) 3.50 (2H, m), 4.65 + 4.70 (3H, pr s), and 7.28 ppm (10H, s); IR ($CHCl_3$): ν 1650sh, 1640 cm^{-1}.

Anal.—Calc. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94; S, 11.31. Found: C, 72.16; H, 6.08; N, 4.89; S, 11.14.

General Procedure—*6-Phenyl-4-(phenylalkyl)-3,4-dihydro-2H-1,4-thiazine (6a–d, 6h)*—A stirred suspension of lithium aluminum hydride (26.3 mol) in tetrahydrofuran (THF, 150 mL) was treated in a dropwise manner with a solution of **5** (16.6 mol) in THF (30 mL). After 24 h, the excess reagent was decomposed by cautious, dropwise addition of water and dilute KOH, $MgSO_4$ was added, and the inorganic salts were filtered and washed with THF. The combined filtrate and wash was concentrated. The residue was purified by chromatography (toluene:hexane) to an oil.

3,4-Dihydro-6-phenyl-4-(4-phenylbutyl)-2H-1,4-thiazine (6a)—Yield of 35.2%; ^{1}H NMR: δ 1.47–1.78 (m, 4H), 2.88–3.19 (m, 2H), 3.34–3.56 (m, 2H), 6.56 (s, 1H), and 7.00–7.44 ppm (m, 10H); IR: ν 1610, 1590, 745, 690 cm^{-1}.

Anal.—Calc. for $C_{20}H_{23}NS$: C, 77.62; H, 7.49; N, 4.53; S, 10.36. Found: C, 77.30; H, 7.49; N, 4.45; S, 10.37.

[The tetrahydrothiazine was obtained in 6.9% yield; IR: ν 740, 690 cm^{-1}. (*Anal.*—Calc. for $C_{20}H_{25}NS$: C, 77.12; H, 8.09; N, 4.50. Found: C, 75.87; H, 7.98; N, 4.22).]

3,4-Dihydro-6-phenyl-4-(3-phenylpropyl)-2H-1,4-thiazine (6b)—Yield of 46.4%; ^{1}H NMR: δ 1.85 (quint, 2H), 2.62 (t, 2H), 2.83–3.14 (m, 4H), 3.31–3.52 (m, 2H), 6.56 (s, 1H), and 7.00–7.4 ppm (m, 10H); IR: ν 1610, 1585, 1160, 745, 690 cm^{-1}.

Anal.—Calc. for $C_{19}H_{21}NS$: C, 77.24; H, 7.16; N, 4.74; S, 10.85. Found: C, 76.78; H, 7.50; N, 4.66; S, 10.47.

[The tetrahydrothiazine results were as follows: ^{1}H NMR: δ 1.78 (quint, 2H), 2.31–2.78 (m, 7H), 2.88–3.31 (m, 3H), 4.05 (dd, 1H), and 7.02 ppm (m 10H); IR: ν 745, 690 cm^{-1}; (*Anal.*—Calc. for $C_{19}H_{23}NS$: C, 76.72; H, 7.79; N, 4.71; S, 10.78. Found: C, 75.92; H, 7.84; N, 4.38; S, 10.04).]

3,4-Dihydro-6-phenyl-4-(2-phenylethyl)-2H-1,4-thiazine (6c)[14]—Yield of 22.6%; ^{1}H NMR: δ 2.70–2.84 (dt, 4H), 3.40 (dq, 2H), 3.64 (dt, 2H), 3.83 (s, 3H), 4.59 (s, 1H), and 6.69–7.38 ppm (m, 9H); IR: ν 1610, 1590, 1360, 1160, 750, 690 cm^{-1}.

Anal.—Calc. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.46; H, 6.49; N, 4.06; S, 9.54.

[The tetrahydrothiazine yield was 3 g (48.4%).]

3,4-Dihydro-6-phenyl-4-phenylmethyl-2H-1,4-thiazine (6d)—Yield of 51.9%; ^{1}H NMR: δ 2.78–3.00 (m, 2H), 3.28–3.45 (m, 2H), 4.17 (s, 2H), 6.76 (s, 1H), and 7.03–7.47 ppm (m, 10H); IR: ν 1610, 1590, 1360, 950 cm^{-1}.

Anal.—Calc. for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24; S, 11.99. Found: C, 76.11; H, 6.55; N, 5.16; S, 11.79.

[The tetrahydrothiazine[25] was found in a yield of 0.9 g (20.1%); ^{1}H NMR: δ 2.31–2.75 (m, 3H), 2.84–3.25 (m, 3H), 3.56 (s, 2H), 4.05 (dd, 1H), and 7.28 ppm (s, 10H); IR: ν 735, 690 cm^{-1}. (*Anal.*—Calc. for $C_{17}H_{19}NS$: C, 75.79; H, 7.11; N, 5.20; S, 11.90. Found: C, 75.57; H, 6.94; N, 4.98; S, 11.42).]

3,4-Dihydro-6-phenyl-4-(2-hydroxyethyl)-2H-1,4-thiazine (6h)—From 2-[3,4-dihydro-6 phenyl-2*H*-1,4-thiazin-4-yl]acetic acid (47%): ^{1}H NMR: δ 2.10 (br s, 1H, exchangeable), 2.84–3.22 (m, 2H), 3.31–3.81 (m, 4H), 6.67 (s, 1H), and 6.91–7.47 ppm (m, 5H); IR: ν 3400, 1610, 1585 cm^{-1}.

Anal.—Calc. for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 64.33; H, 6.74; N, 6.11; S, 14.04.

Ethyl 2-[3,4-dihydro-6-phenyl-2*H*-1,4-thiazin-4-yl] acetate—Lactam 4 (R_2 = H, 15.67 g, 81 mmol) was alkylated as above and purified by preparative HPLC (hexane:40% ethyl acetate) to give the ester (9.6 g, 42.4%), mp 58–62 °C; ^{1}H NMR: δ 1.32 (t, 3H), 2.68–3.02 (m, 2H), 3.65 (t, 2H), 4.03 + 4.20 + 4.28 (s + q + s, 4H), 4.68 (s, 1H), and 7.20–7.62 ppm (m, 5H); IR ($CHCl_3$): ν 1735, 1640 cm^{-1}; UV: λ 253 nm (ε 736).

Anal.—Calc. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 59.98; H, 6.14; N, 4.93; S, 11.45.

2-[3,4-Dihydro-6-phenyl-2*H*-1,4-thiazin-4-yl] acetic acid—A solution of the above ester (4.3 g, 16.2 mmol) in methanol (40 mL) was treated with a solution of lithium hydroxide (0.75 g, 17.9 mmol) in water (15 mL) and stirred for 2.5 h. The solution was concentrated and the residue dissolved in water and acidified with 10% HCl. The resulting solid was filtered off, washed with water, dried, and crystallized from aqueous acetone to give the acid (2.54 g, 62.4%), mp 149–150 °C, which was used above to prepare **6h**; ^{1}H NMR: δ 2.88 (t, 2H), 3.73 (t, 2H), 4.10 (d, 2H), 4.87 (s, 1H), and 4.72 ppm (s, 5H); IR (KBr): ν 4320, 1745, 1610 cm^{-1}.

Anal.—Calc. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.17; H, 5.31; N, 5.70; S, 12.76.

2-(3-Methoxyphenyl)-4-(2-phenylethyl)-3-thiomorpholinone (5m), 3,4-Dihydro-6-(3-methoxyphenyl)-4-(2-phenylethyl)-2*H*-1,4-thiazine (6m), and 3,4,5,6-Tetrahydro-6-(3-methoxyphenyl)-4-(2-phenylethyl)-2H-1,4-thiazinc (7m)—A solution of KOH (26.3 g, 0.399 mol) in 95% ethanol (350 mL) was treated consequently with 2-thiolethanamine HCl (41.33 g, 0.399 mol) and with 3-methoxybenzyl chloride (56.2 g, 0.399 mol), and then stirred overnight at room temperature. Most of the solvent was removed and the residue was diluted with water (500 mL) and extracted with ether (400 mL). The aqueous layer was separated and extracted with ether (400 mL). The combined ether extract was dried and concentrated to a liquid which was distilled to give 2-[[(3-methoxyphenyl)methyl]thio]ethanamine (46.1 g, 58.6%), bp 116–120 °C/0.25 T; ^{1}H NMR: δ 1.30 (s, 2H), 2.52 (t, 2H), 2.82 (t, 2H), 3.67 (s, 2H), 3.80 (s, 3H), 6.70–686m, 1H), 6.91–6.97 (m, 2H), and 7.27 ppm (t, 1H); IR: ν 3480–3380, 1610, 1590, 1495, 1270 cm^{-1}.

Anal.—Calc. for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.07; H, 7.66; N, 7.37; S, 17.21.

A stirred solution of 2-[[(3-methoxyphenyl)methyl]thio]ethanamine (33.6 g, 0.17 mol), triethylamine (25.8 g, 0.255 mol), and ether (1 L) was treated in a dropwise manner with a solution of phenylacetyl chloride (26.3 g, 0.17 mol) in ether (75 mL). After 2 h, the mixture was extracted with water (500 mL) and saturated $NaHCO_3$ (250 mL), dried, and concentrated to a liquid which was distilled to give *N*-[2-[[(3-methoxyphenyl)methyl]thio]ethyl]phenylacetamide (40.2 g, 74.9%), bp 222–226 °C/0.25 T.

A stirred solution of *N*-[2-[[(3-methoxyphenyl)methyl]thio]ethyl]phenylacetamide (40.2 g, 0.127 mol) in THF (370 mL) was treated in a dropwise manner with borane:dimethyl sulfide (32 mL, 0.32 mol) and stirred overnight. Methanol (65 mL) was added in a dropwise manner with caution, and the solution was stirred overnight. The solvent was removed, and the residue was treated with more methanol and concentrated. The residue was treated with methanol (100 mL) and 20% HCl (300 mL) and heated on a steam bath for 30 min. The cooled solution was made basic with conc. NH_4OH (200 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined extract was dried and concentrated to a liquid which was distilled to give *N*-[[2-[(3-methoxyphenyl)methyl]thio]ethyl]benzeneethanamine (32.2 g, 83.8%), bp 190–195 °C/0.25 T; ^{1}H NMR: δ 1.44 (s, 1H), 2.58 (t, 2H), 2.74–2.88 (m, 6H), 3.66 (s, 2H), 3.80 (s, 3H), 6.74–6.79 (m, 1H), 6.83–6.87 (m, 2H), and 7.15–7.32 ppm (m, 6H); IR: ν 3310, 1605, 1500, 1460 1285, 700 cm^{-1}.

Anal.—Calc. for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69; N, 4.65; S, 10.64. Found: C, 71.20; H, 7.52; N, 4.56; S, 10.84.

A stirred solution of the above amine (16.5 g, 54.7 mmol), triethylamine (11.1 g, 109.4 mmol), and ether (500 mL) was cooled in an ice water bath and treated in a dropwise manner with methyl chloroformate (5.17 g, 54.7 mmol) in ether (100 mL). After 1 h, the reaction mixture was extracted with water (2 × 500 mL), and 5% HCl (1 × 500 mL), and then dried, filtered, and concentrated to a liquid which was purified by chromatography (toluene:25% hexane, toluene, toluene:30% ethyl acetate) to give [2-[[(3-methoxyphenyl)methyl]-thio]ethyl][2-phenylethyl]carbamic acid methyl ester (3, R_2 =

3-MeO, 17.9 g, 90.9%) as a liquid; ^{1}H NMR: δ 2.31–2.91 (4H, m), 3.09–3.53 (4H, m), 3.66 (5H, s), 3.78 (3H, s), 6.66–6.94 (3H, m), and 7.03–7.34 ppm (6H, m); IR: ν 1700, 1600, 1580 cm^{-1}.

Anal.—Calc. for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 67.04; H, 7.13; N, 3.94; S, 8.84.

A solution of the above carbamate (17.9 g, 49.8 mmol) in THF (1 L) under an argon atmosphere was cooled to −78 °C and treated with a solution of 1.87 M lithium diisopropylamide[26] (53.3 mL, 99.6 mmol) after which it was stirred at room temperature for 2.5 h. Saturated NH_4Cl (400 mL) and water (100 mL) were added. The organic layer was separated, dried, and concentrated to a liquid which was purified by chromatography (toluene:15% ethyl acetate) to give **5m** (12.3 g, 75.5%) as a liquid; ^{1}H NMR: δ 2.70–2.84 (4H, dt + pr d), 3.40 (2H, dq), 3.64 (2H, dt), 3.83 (3H, s), 4.59 (1H, s), and 6.69–7.38 ppm (9H, m); IR: ν 1700(w), 1660, 1630, 1580, 1480 cm^{-1}.

Anal.—Calc. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; S, 9.79. Found: C, 69.46; H, 6.49; N, 4.06; S, 9.54.

Lactam **5m** (3.05 g, 9.31 mmol) was reduced as above to give **6m** (0.8 g, 27.6%); ^{1}H NMR: δ 1.46 (1H, s), 2.69–3.03 (4H, m), 3.14–3.59 (4H, m), 4.70 (3H, s), 6.52 (1H, s), and 6.59–7.34 ppm (9H, m); IR: ν 1615, 1590, 1150 cm^{-1}.

Anal.—Calc. for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50; S, 10.30. Found: C, 73.38; H, 7.02; N, 4.29; S, 9.76.

[The tetrahydrothiazine **7m** was obtained as a liquid (1.0 g, 34.5%); ^{1}H NMR: δ 2.25–2.94 (8H, m), 3.00–3.34 (2H, m), 3.75 (3H, s), 3.98 (1H, dd), and 6.62–7.34 ppm (9H, m); IR: ν 1600, 1580, 1270 cm^{-1}. (*Anal.*—Calc. for $C_{19}H_{23}NOS$: C, 72.80; H, 7.40; N, 4.47; S, 10.23. Found: C, 72.87; H, 7.42; N, 4.38; S, 9.94).]

Using Scheme II—Synthesis of [(aryl)methyl]-*N*-(substituted)-acetamides.

*(Phenylmethyl)thioacetanilide (**10**, R = Ph, R_2 = H)*—A mixture of the chloroacetanilide **9** (R = Ph, 24.4 g, 0.144 mol), benzyl mercaptan (17.9 g, 0.144 mol), K_2CO_3 (19.2 g, 0.158 mol), Adogen 464 (60 mg), and toluene (150 mL) was vigorously stirred for 20 h.[27] Water (500 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 300 mL). The combined extract was dried and concentrated to a solid which was purified by chromatography (toluene:ethyl acetate) to give **10** (R = Ph, R_2 = H); ^{1}H NMR: δ 3.14 (s, 2H), 3.68 (s, 2H), 6.93–7.57 (m, 10H), and 8.50 ppm (br s, 1H).

General Procedure—A solution of KOH (0.173 mol) in 95% ethanol (250 mL) was treated with the thiol (0.147 mol) and then with *N*-(2-phenylethyl)chloroacetamide (0.147 mol) and stirred for 3 h. Most of the solvent was removed and the residue was diluted with water (500 mL) and extracted with CH_2Cl_2 (2 × 300 mL). The organic layer was dried and concentrated to a solid which was crystallized.

*2-[1-Naphthaleneylmethyl)thio]-N-(2-phenylethyl)acetamide (**10**, R = $PhCH_2CH_2$, R_2 = 1-$C_{10}H_7$)*—Yield of 78.9%, mp 89–90 °C (acetone:hexane); ^{1}H NMR: δ 2.51 (t, 2H), 3.09 (s, 2H), 3.22 (q, 2H), 4.02 (s, 2H), 6.55 (unres t, 1H), and 7.03–8.03 ppm (m, 8H); IR (KBr): ν 3440–3320, 1660, 780 cm^{-1}.

Anal.—Calc. for $C_{21}H_{21}NOS$: C, 75.19; H, 6.31; N, 4.18; S, 9.56. Found: C, 75.20; H, 6.43; N, 4.00; S, 9.52.

*2-[[(4-Chlorophenyl)methyl]thio]-N-(2-phenylethyl)acetamide (**10**, R = $PhCH_2CH_2$, R_2 = 4-Cl)*—Yield of 93.7%, bp 195–200 °C/0.1 T, solidified on standing; ^{1}H NMR: δ 2.81 (t, 2H), 305 (s, 2H), 3.49 + 3.50 (q + s, 2H) 6.63 (br s, 1H), 7.08–7.14 (m, 2H), and 7.19–7.38 ppm (m, 8H); IR (KBr): ν 3300, 1650, 1560, 1495 cm^{-1}.

Anal.—Calc. for $C_{17}H_{18}ClNOS$: C, 63.84; H, 5.67; N, 4.38; S, 10.02. Found: C, 63.88; H, 5.71; N, 4.31; S, 10.00.

*2-[[(4-Methoxyphenyl)methyl]thio]-N-(2-Phenylethyl)acetamide (**10**, R = $PhCH_2CH_2$, R_2 = 4-MeO)*—Yield of 62.8%, mp 64–65 °C; ^{1}H NMR: δ 2.78 (t, 2H), 3.05 (s, 2H), 3.47 + 3.50 (q + s, 4H), 3.76 (s, 3H), 6.73 (br s, 1H), 6.78–6.85 (m, 2H), 7.05–7.11 (m, 2H), and 7.18–7.38 ppm (m, 5H); IR (KBr): ν 3400, 1650, 1610, 1510, 1250 cm^{-1}.

Anal.—Calc. for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; S, 10.16. Found: C, 68.50; H, 6.83; N, 4.37; S, 10.18.

*Synthesis of N-[2-[(Arylmethyl)thio]ethyl]-substituted Amines (**11**)—N-[2-[(phenylmethyl)thio]ethyl]benzeneethanamine (**11**, R = Ph, R_2 = H)*—A suspension of lithium aluminum hydride (2.98 g) in THF (400 mL) was treated in a dropwise manner with a solution of **10** (R = Ph, R_2 = H, 9.0 g, 35 mmol) in ether:THF (1:1, 300 mL) and stirred overnight at room temperature. The excess hydride was decomposed by cautious addition of water and dilute NaOH, $MgSO_4$ was added, and then the solids were filtered and washed with ether. The combined filtrate and wash was concentrated to a liquid which was distilled to give **11** (R = Ph, R_2 = H, 6.99 g, 82.1%), bp 155–160 °C/0.025 T; ^{1}H NMR: δ 1.54 (s, 1H, exchangeable), 2.68 (t, 2H), 3.20–3.30 (m, 2H), 3.72 (s, 2H), 3.97 (br s, 1H), 6.59 (d, 2H), 6.73 (t, 1H), 7.18 (t, 2H), and 7.22–7.37 ppm (m, 6H); IR: ν 3380, 1600, 1505, 745, 680 cm^{-1}.

Anal.—Calc. for $C_{15}H_{17}NS$: C, 74.03; H, 7.04; N, 5.76; S, 13.17. Found: C, 73.38; H, 6.84; N, 5.17; S, 13.50.

General Procedure—A stirred solution of amide **10** (0.115 mol) in THF (350 mL) was treated in a dropwise manner with borane:dimethyl sulfide (29 mL, 0.29 mol) and stirred overnight. Methanol (60 mL) was added in a dropwise manner with caution and the solution stirred overnight. The solvent was removed, and the residue treated with more methanol and then concentrated. The residue was treated with methanol (100 mL) and 20% HCl (275 mL) and heated on a steam bath for 45 min. The cooled solution was made basic with conc. NH_4OH (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined extract was dried and concentrated to a liquid which was distilled.

*N-[2-[(1-Naphthalenylmethyl)thio]ethyl]benzeneethanamine (**11**, R = $PhCH_2CH_2$, R_2 = 1-$C_{10}H_7$)*—Yield of 62.6%, bp 220–228 °C/0.75 T; ^{1}H NMR: δ 1.38 (s, 1H), 2.59 (t, 2H), 2.66–2.82 (m, 6H), 4.13 (s, 2H), 7.13–7.37 (m, 7H), 7.42–7.54 (m, 2H), 7.70–7.77 (m, 1H), 7.80 (d, 1H), and 8.10 ppm (d, 1H); IR: ν 3320, 1575, 1460, 780, 700 cm^{-1}.

Anal.—Calc. for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36; S, 9.47. Found: C, 78.40; H, 7.17; N, 4.43; S, 9.94.

*N-[2-[[(4-Chlorophenyl)methyl]thio]ethyl]benzeneethanamine (**11**, R = $PhCH_2CH_2$, R_2 = 4-Cl)*—Yield of 74.9%, bp 187–189 °C/0.3 T; ^{1}H NMR: δ 1.42 (s, 1H), 2.53 (t, 2H), 2.73–2.91 (m, 6H), 3.61 (s, 2H), and 7.18–7.36 ppm (m, 9H); IR: ν 3310, 1495, 1095, 795 cm^{-1}.

Anal.—Calc. for $C_{17}H_{20}ClNS$: C, 66.76; H, 6.59; N, 4.58; S, 10.48. Found: C, 66.71; H, 6.54; N, 4.55; S, 10.25.

*N-[2-[[(4-Methoxyphenyl)methyl]thio]ethyl]benzeneethanamine (**11**, R = $PhCH_2CH_2$, R_2 = 4-MeO)*—Yield of 93.4%, bp 191–195 °C/0.3 T; ^{1}H NMR: δ 1.48 (s, 1H), 2.55 (t, 2H), 2.73–2.87 (m, 6H), 3.55 (s, 2H), 3.77 (s, 3H), 6.81 (d, 2H), and 7.14–7.31 ppm (m, 7H); IR: ν 3320, 1615, 1510, 1250 cm^{-1}.

Anal.—Calc. for $C_{18}H_{23}NO_2S$: C, 72.72; H, 7.69; N, 4.65; S, 10.64. Found: C, 71.76; H, 7.70; N, 4.69; S, 10.68.

*2-[[(3-Methoxyphenyl)methyl]thio]ethanamine[28] (**11**, R = H, R_2 = 3-MeO)*—A stirred solution of KOH (26.3 g, 0.40 mol) in 95% ethanol (350 mL) was treated with 2-thiolethanamine hydrochloride (41.3 g, 0.40 mol) and then in a dropwise manner with benzyl chloride (56.2 g, 0.40 mol). Most of the solvent was removed. The residue was dissolved in water (500 mL), made acidic with 10% HCl (250 mL), and washed with ether (2 × 250 mL). The aqueous layer was made basic with conc. NH_4OH and extracted with ether (2 × 250 mL). The combined ether extract was dried, filtered, and concentrated to a liquid which was distilled to give **11** (R = H, R_2 = 3-MeO, 46.1 g, 58.6%), bp 108–112 °C/0.01 T; ^{1}H NMR: δ 1.30 (2H, s), 2.52 (2H, t), 2.82 (2H, t), 3.67 (2H, s), 3.80 (3H, s), 6.70–6.86 (1H, m), 6.91 (2H, m), and 7.27 ppm (1H, t); IR: ν 3480–3380, 1610, 1590, 1495, 1279 cm^{-1}.

Anal.—Calc. for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10; S, 16.25. Found: C, 60.07; H, 7.66; N, 7.37; S, 17.21.

*N-[[2-[(3-methoxyphenyl)methyl]thio]ethyl](2-phenyl)propanamine (**11**, R = Ph, R_2 = H)*—A solution of **11** (R = H, R_2 = 3-MeO, 18.7 g, 94.8 mmol), phenylpropan-2-one (12.7 g, 94.8 mmol), 4-toluenesulfonic acid (0.5 g), and benzene (500 mL) was heated to boiling under a Dean-Stark water separator for 4 h. The cooled solution was extracted with saturated $NaHCO_3$ (100 mL), dried over K_2CO_3:$MgSO_4$, filtered, and concentrated to a liquid which was dissolved in anhydrous ethanol (500 mL) and treated in a portionwise manner with $NaBH_4$ (3.6 g, 94.7 mmol) while cooling in a water bath. After 3 h, acetone (100 mL) was added. After 40 min more, the reaction was concentrated. The residue was diluted with water (600 mL) and acidified with conc. HCl (100 mL). The mixture was washed with CH_2Cl_2 (2 × 200 mL), made basic with conc. NH_4OH, and extracted with CH_2Cl_2 (2 × 300 mL). The combined extract was dried and concentrated to a liquid which was purified by flash chromatography (toluene:0.5% triethylamine:ethyl acetate) to give **11** (R = CH[Me]CH_2Ph, R_2 = 3-MeO, 19.1 g, 63.9%); ^{1}H NMR: δ 1.01 (m, 3H), 1.53 (br, 1H), 2.41–2.88 (m, 7H), 3.53 (s, 2H), 3.71 (s, 3H), 6.64–6.91 (m, 3H), and 7.05–7.30 ppm (m, 6H); IR: ν 3300, 1600, 1265, 1150 cm^{-1}.

Anal.—Calc. for $C_{19}H_{25}NOS$: C, 72.34; H, 7.99; N, 4.44; S, 10.16. Found: C, 72.59; H, 8.02; N, 4.39; S, 9.84.

General Procedure—*6-Phenyl-4-(phenylalkyl)-3,4-dihydro-2H-1,4-thiazine (**6e, f, j, k, l**)*—A stirred solution of diisopropylamine

(0.20 mol) in THF (550 mL) under argon atmosphere was cooled to −78 °C and treated with 2.3M butyl lithium (0.20 mol). After 10 min, the reaction was treated with a benzeneethanamine **11** (66.8 mmol) in THF (30 mL). The reaction was warmed to 0 °C for 1 h, then treated with ethyl formate (66.8 mmol). After 3.75 h, the reaction was cooled back to −78 °C and quenched with saturated NH_4OH (400 mL). The aqueous layer was separated and extracted with ether (150 mL). The combined organic layer and ether extract was dried and concentrated to a liquid which was purified by chromatography (toluene:50% hexane).

*3,4-Dihydro-4,6-diphenyl-2H-1,4-thiazine (**6e**)*—Yield of 42.2%; ^1H NMR: δ 3.12–3.19 (m, 2H), 3.82–3.88 (m, 2H), 6.94–7.00 (m, 3H), 7.06 (s, 1H), 7.14–7.22 (m, 1H), 7.25–7.33 (m, 4H), and 7.42–7.47 ppm (m, 2H); IR: ν 1615, 1590 cm^{-1}; UV: λ 225 (ε 11,610), 271 (6,870), 342 nm (21,580).

Anal.—Calc. for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.86; H, 6.04; N, 5.30; S, 12.87.

*3,4-Dihydro-6-(1-naphthyl)-4-(2-phenylethyl)-2H-1,4-thiazine (**6j**)*—Yield of 26.6%; ^1H NMR: δ 2.82 (t, 2H), 3.07 (t, 2H), 3.23 (t, 2H), 3.53 (br s, 2H), 6.19 (s, 1H), 7.33–7.68 (m, 9H), 7.71–7.91 (d, 1H), 7.96–8.03 (m, 1H), and 8.38–846 ppm (m, 1H); IR: ν 1620 cm^{-1}; UV: λ 224 (ε 64,030), 273 (11,440), 373 nm (4,160).

Anal.—Calc. for $C_{22}H_{21}NS$: C, 79.72; H, 6.39; N, 4.23; S, 9.67. Found: C, 79.72; H, 6.48; N, 4.19; S, 9.76.

*3,4-Dihydro-6-(4-chlorophenyl)-4-(2-phenylethyl)-2H-1,4-thiazine (**6k**)*—Yield of 58.9%; ^1H NMR: δ 2.84 (t, 2H), 2.93–2.98 (m, 2H), 3.30 (t, 2H), 3.44–3.49 (m, 2H), 6.48 (s, 1H), and 7.12–7.33 ppm (m, 10H); IR: ν 1615, 1165 cm^{-1}; UV: λ 224 (ε 12,530), 250sh (9,670), 339 nm (14,980).

Anal.—Calc. for $C_{18}H_{18}ClNS$: C, 68.45; H, 5.74; N, 4.43; S, 10.15. Found: C, 68.65; H, 5.69; N, 4.24; S, 10.21.

*3,4-Dihydro-6-(4-methoxyphenyl)-4-(2-phenylethyl)-2H-1,4-thiazine (**6l**)*—Yield of 29.2%; ^1H NMR: δ 2.78 (t, 2H), 2.95 (t, 2H), 3.23 (t, 2H), 3.42 (t, 2H), 3.78 (s, 3H), 6.39 (s, 1H), 6.81 (d, 2H), and 7.15–7.36 ppm (m, 7H); IR: ν 1620, 1510, 1245, 820 cm^{-1}; MS (CI): *m/z* 311 (100%, P^+); MS (EI): *m/z* 311 (65%, P^+), 220 (100%, P-$PhCH_2$), 192 (45%).

Anal.—Calc. for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50; S, 10.30. Found: C, 73.45; H, 6.94; N, 4.54; S, 10.10.

*3,4-Dihydro-6-phenyl-4-(1-phenyl-2-propyl)-2H-1,4-thiazine (**6f**)*—Yield of 30.0%; ^1H NMR: δ 1.20 (3H, d), 2.69 (1H, dd), 2.80–2.90 (3H, m), 3.33–3.46 (3H, m), 3.78 (3H, s), 6.59–6.66 (2H, s + m), 6.84–6.94 (2H, m), and 7.12–7.32 ppm (6H, m); IR: ν 1610, 1590 cm^{-1}; MS (CI): *m/z* 325 (65%, P + 1), 234 (100%, P − 91); UV: λ 254 (ε 6,900), 339 nm (11,100).

Anal.—Calc. for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30; S, 9.85. Found: C, 74.08; H, 7.22; N, 4.11; S, 9.80.

*3,4-Dihydro-5-phenyl-4-(1-propyl)-2H-1,4-thiazine (**6i**)*—A solution of KOH (13.18 g, 0.20 mol) in 95% ethanol (1 L) under nitrogen atmosphere was treated with *N*-(2-mercaptoethyl)propionamide (26.64 g, 0.20 mol) and then immediately with α-bromoacetophenone (39.81 g, 0.20 mol). After stirring overnight at room temperature, the solvent was removed and the residue was diluted with water and extracted with ether (2 × 500 mL). The ether extract was dried and concentrated, and the residue was chromatographed (toluene:ethyl acetate) to give a solid. The latter was crystallized from ether:hexane to give a keto-amide (21.4 g, 42.6%), mp 44–48 °C; ^1H NMR: δ 1.16 (t, 3H), 2.22 (q, 2H), 2.74 (t, 2H), 2.92–2.98(m, 2H), 3.47 (q, 2H), 3.89 (s, 2H), 6.14 (br s, 1H), 7.47–7.55 (m, 2H), and 7.59–7.66 ppm (m, 1H); IR (KBr): ν 3500–3300, 1675, 1660, 1640, 1550, 1540, 1280 cm^{-1}.

Anal.—Calc. for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.81; N, 5.57; S, 12.76. Found: C, 62.04; H, 6.88; N, 5.49; S, 12.97.

A vigorously stirred mixture of above keto-amide (21.16 g, 84.2 mmol), ethylene glycol (40 mL), 4-toluenesulfonic acid (0.5 g), and benzene (400 mL) was heated to boiling under a Dean-Stark water separator for 4 h. The cooled mixture was extracted with saturated $NaHCO_3$ (200 mL), and the separated aqueous layer was extracted with ether (100 mL). The combined organic layer was dried over K_2CO_3:$MgSO_4$ and concentrated to a liquid which was chromatographed (toluene and toluene:25% ethyl acetate) to give an amido-ketal (16.1 g, 64.8%); ^1H NMR: δ 1.11 (t, 3H), 2.18 (q, 2H), 2.64 (t, 2H), 2.96 (s, 2H), 3.38 (q, 2H), 3.76–3.88 (m, 2H), 4.04–4.16 (m, 2H), 6.08 (br s, 1H), 7.24–7.36 (m, 3H), and 7.41–7.47 ppm (m, 2H); IR: ν 3320, 1655, 1540, 1220, 1040 cm^{-1}.

Anal.—Calc. for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.74; S, 10.85. Found: C, 61.11; H, 7.32; N, 4.72; S, 10.83.

A stirred suspension of lithium aluminum hydride (1.2 g) in ether (100 mL) was treated in a dropwise manner with a solution of the above amido-ketal (4.8 g, 16.2 mmol) in ether (30 mL). The excess hydride was decomposed by cautious, dropwise addition of water, $MgSO_4$ was then added, and the salts were filtered off and washed with ether. The combined filtrate and wash was concentrated to a liquid which was distilled to give an amino-ketal (3.7 g, 81.0%), bp 155–158 °C/0.05 T; ^1H NMR: δ 0.91 (t, 2H), 1.48 (hex, 2H), 2.53 (t, 2H), 2.62–2.77 (m, 4H), 3.00 (s, 2H), 3.76–3.86 (m, 2H), 4.04–4.16 (m, 2H), 7.24–7.36 (m, 3H), and 7.43–7.50 ppm (m, 2H); IR: ν 1450, 1045, 695 cm^{-1}.

Anal.—Calc. for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 63.72; H, 8.34; N, 4.97; S, 11.48.

A solution of the above amino-ketal (3.5 g, 12.4 mmol) in acetone (50 mL) was treated with 10% HCl (20 mL) and stirred at room temperature for 3 h. The reaction was made basic with K_2CO_3, diluted with water, extracted with ether (100 mL) and ethyl acetate (100 mL). The combined organic extract was washed with water, dried, and concentrated to a solid which was chromatographed (toluene:ethyl acetate) to give **6i** (0.3 g, 11%); ^1H NMR: δ 0.78 (t, 2H), 1.49 (hex, 2H), 2.52–2.58 (m, 2H), 2.81–2.86 (m, 2H), 3.37–3.44 (m, 2H), 5.37 (s, 1H), and 7.23–7.44 ppm (m, 5H); IR: ν 750, 695 cm^{-1}; UV: λ 230 (ε 11,320), 306 nm (7,730).

Anal.—Calc. for $C_{13}H_{17}NS$: C, 71.18; H, 7.81; N, 6.39; S, 14.62. Found: C, 71.42; H, 7.71; N, 6.10; S, 14.39.

*3,4-Dihydro-6-phenyl-4-(phenylmethyl)-2H-1,4-oxazine (**6n**)*—A solution of 6-hydroxy-3,4-tetrahydro-6-phenyl-4-(phenylmethyl)-2*H*-1,4-oxazine[29,30] (19.1 g, 70.9 mmol) and 4-toluenesulfonic acid (14.8 g, 77.8 mmol) in benzene (500 mL) was heated at reflux using a Dean-Stark water separator for 2 h during which time a solid material formed. The mixture was cooled to room temperature and the crystals were filtered off, washed with benzene and then with ether, and dried to give **6n**·4-toluenesulfonic acid salt (22.2 g, 74.0%); ^1H NMR: δ 2.30 (2, 3H), 3.41–3.66 (m, 2H), 4.28–4.56 (m, 4H), 5.78 (s, 1H), 7.00–7.60 (m, 14H), and 7.77 ppm (d, 3H, 1 exchangeable proton); IR (KBr): ν 3440, 2400–2600, 1665(w), 1225, 1155 cm^{-1}.

Anal.—Calc. for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31; S, 7.57. Found: C, 67.86; H, 5.90; N, 3.24; S, 7.60.

The above salt (12.0 g) was suspended in CH_2Cl_2 (500 mL) and extracted with saturated $NaHCO_3$ (2 × 250 mL). The organic layer was dried over K_2CO_3:$MgSO_4$, filtered, and concentrated to a yellow liquid which was purified by chromatography (hexane:ethyl acetate) to give **6n** (5.9 g); ^1H NMR: δ 3.08 (t, 2H), 4.03 (s, 2H), 4.13 (t, 2H), 6.48 (s, 1H), and 7.24–7.47 ppm (m, 10H); IR: ν 1725(w), 1680, 1650, 1600 cm^{-1}.

Anal.—Calc. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 79.60; H, 6.74; N, 5.55.

*6-Benzoyl-3,4-dihydro-4-(2-phenylethyl)-2H-1,4-thiazine (**6o**)*—A magnetically stirred suspension of 60% sodium hydride:mineral oil (0.33 g, 8.12 mol) in DMF (35 mL) was treated with 6-benzoyl-3,4-dihydro-2*H*-1,4-thiazine[16] (1.15 g, 5.6 mmol). After 30 min the solution was treated with phenylethyl bromide (1.04 g, 5.6 mmol) and stirred at room temperature for 3 h. The reaction was quenched with 5% HCl (5 mL), diluted with saturated $NaHCO_3$ (150 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with water (3 × 75 mL), dried, filtered, and concentrated to a yellow mixture. Ether was added and the solid was filtered off, washed with ether, and dried to give the starting amine (0.56 g, 48.7%). The filtrate was concentrated and residue purified by chromatography (toluene and toluene:25% ethyl acetate) to give **6o** (0.3 g, 50.8% based on recovered amine), mp 144–145 °C (CH_2Cl_2:MeOH); ^1H NMR: δ 1.60 (s, 2H), 2.85 (t, 2H), 2.92–2.97 (m, 2H), 3.42 (t, 2H), 3.56–3.64 (m, 2H), 6.94 (s, 1H), 7.18–7.28 (m, 4H), and 7.32–7.49 ppm (m, 6H); IR (KBr): ν 1655, 1585, 1565–1550, 1350, 735 cm^{-1}.

Anal.—Calc. for $C_{19}H_{19}NOS$: C, 73.75; H, 6.19; N, 4.53; S, 10.36. Found: C, 73.71; H, 6.18; N, 4.60; S, 10.41.

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Acknowledgments

We wish to thank Mr. William Magner of the Merrell Dow Analytical Department for carrying out the cyclic voltammetry experiments.