

R. Ian Fryer, Rudolph F. Lauer, Eugene J. Trybulski,*
Stephen Vitone, Armin Walsler and Gladys Zenchoff

Research and Development Division, Hoffman-La Roche Inc.,
Nutley, New Jersey 07110
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A facile synthesis of the 4*H*-imidazo[5,1-*c*][1,4]benzothiazine ring system is described. The synthesis utilized the annulation of an imidazole ring onto a 2*H*-1,4-benzothiazin-3(4*H*)-one *via* the addition of the anion of ethyl isocyanoacetate. Methods for the functionalization of the 1-, 3-, 4-, and 5-positions of the ring system are presented.

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In connection with another problem [1] we required a synthesis of the imidazo[5,1-*c*][1,4]benzothiazine ring system which would allow the independent functionalization of the 1-, 3-, 4-, and 5-positions. The only reported preparation of this ring system was that of the tetrahydro-derivative [2] and the synthetic procedure was not amenable to this study. A convenient synthesis of this ring system was devised starting with the construction of the benzothiazine portion of the molecule from aniline using a previously described Hertz reaction [3]. The annulation of the imidazole ring onto the benzothiazine was achieved by means of an isonitrile addition to the corresponding iminophosphate [5] of the amide functionality (Scheme I).

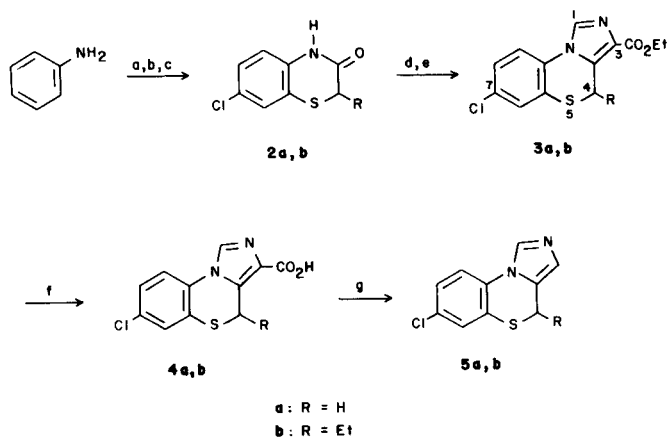
Reaction of aniline hydrochloride **1** with sulfur monochloride produced the chlorinated benzodithiazole which was subsequently treated with sodium hydroxide and either chloroacetic acid or 2-bromobutyric acid to afford in good yields compounds **2a,b**, respectively [3,4]. The iminophosphate derivatives of the benzothiazines **2a,b** were generated *in situ* by the addition of diethylchlorophosphate to a dimethylformamide solution of **2a,b** and potassium *t*-butoxide. Reaction of the iminophosphate with the

anion of ethyl isocyanoacetate [6], formed by the sequential addition of one equivalent of potassium *t*-butoxide and the isonitrile to the reaction mixture, resulted in the annulation of the imidazole ring onto the benzothiazine to give **3a,b**. Saponification of the ester **3a,b** with aqueous sodium hydroxide yielded the carboxylic acid **4a,b** which was heated to reflux in 1,2,4-trichlorobenzene to afford **5a,b**.

The thio group of the imidazobenzothiazine **3a** was oxidized to the sulfoxide **6** and the sulfone **7** by treatment with one and two equivalents of *m*-chloroperbenzoic acid, respectively.

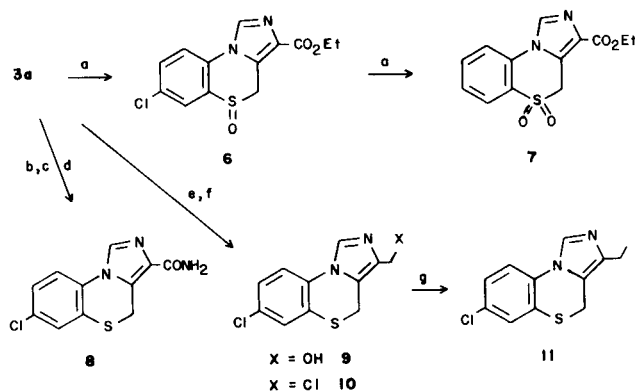
The substitution at the 3-position of the imidazobenzothiazine ring system was varied using the ethyl ester **3a** (Scheme II). The carboxylic acid **4a**, the hydrolysis product of **3a**, was sequentially treated with phosphorous pentachloride and ammonia to give the carboxamide **8**. Conversion of the ester functionality into an ethyl group was conveniently performed in three steps. Reduction of **3a** with lithium aluminum hydride afforded the hydroxymethyl compound **9** which was reacted with thionyl chloride to give the chloro derivative **10**. Treatment of **10** with an excess of lithium dimethyl cuprate (7) gave the ethyl compound **11**.

Scheme I

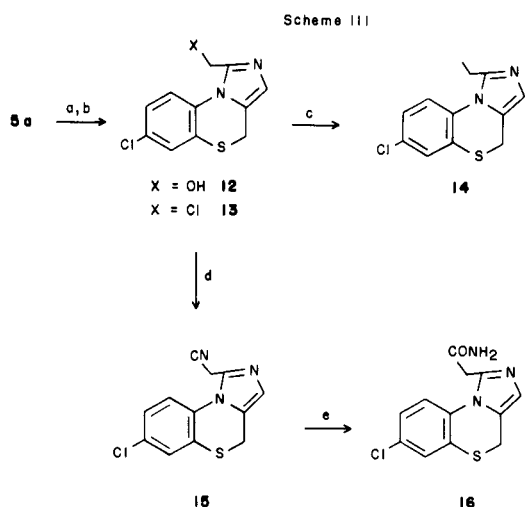


a) S_2Cl_2 / Δ ; b) $NaOH / H_2O$; c) $RCH(X)CO_2H / KOH / EtOH / \Delta$; d) $(EtO)_2POCl / t-BuOK / DMF$; e) $:C=NCH_2CO_2Et / t-BuOK / DMF$; f) $NaOH / THF / MeOH$; g) $C_6H_3Cl_3 / \Delta$.

Scheme II



a) MCPBA / CH_2Cl_2 ; b) KOH / MeOH / THF; c) PCl_5 / CH_2Cl_2 ; d) NH_3 / CH_2Cl_2 ; e) LAH / THF; f) $SOCl_2 / \Delta$; g) $Me_2CuLi / Et_2O / -78^\circ$.



a) 40% aq. CH_2O / Δ ; b) SOCl_2 / Δ ; c) Me_2CuLi / Et_2O / -78° ; d) NaCN / EtOH ; e) H_2SO_4 .

The isolation of **11** from the cuprate addition reaction was facilitated by the introduction of gaseous hydrogen sulfide at the end of the reaction. This procedure precipitated all of the copper salts from the reaction mixture which, if present, coordinated to the benzothiazine and impeded the isolation.

Functionalization of the benzothiazine at the 1-position was accomplished by first hydroxymethylating the imidazole ring (Scheme III). Reaction of **5a** with 40% aqueous formaldehyde at reflux gave **12** in quantitative yield. Treatment of **12** with thionyl chloride afforded the chloro compound **13** which was subsequently converted into the ethyl derivative **14** by treatment with an excess of lithium dimethyl cuprate [7]. Displacement of chloride in **13** by cyanide in aqueous ethanol yielded the nitrile **15** which was hydrated with sulfuric acid to the carboxamide **16**.

In summary, a facile synthesis of the 4*H*-imidazo[5,1-*c*]-[1,4]benzothiazine ring system has been demonstrated which allows the functionalization of the 1-, 3-, 4- and 5-positions of the ring system.

EXPERIMENTAL

Melting points were determined using a Thomas Hoover apparatus and are uncorrected. The nmr spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal TMS standard. Infrared and mass spectra were recorded on Perkin Elmer 137 and CEC-110B instruments respectively. For column chromatography Merck Silica Gel 60, mesh 70-230 was used. Anhydrous sodium sulfate was used for drying of organic solutions.

7-Chloro-2*H*-1,4-benzothiazin-3(4*H*)-one (**2a**).

Compound **2a** was prepared according to the method of Vasiliu *et al.*, [3] mp 201-204°.

7-Chloro-2-ethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**2b**).

Compound **2b** was prepared in the same manner as **2a** except that 2-bromobutyric acid was used in place of chloroacetic acid. The resulting yellow precipitate was dissolved in methylene chloride, dried and concentrated *in vacuo*. The residue was triturated in ether to yield 23.5 g (53%) of the desired product as a colorless solid. Recrystallization from a mixture of methylene chloride and ether gave **2b** as colorless needles, mp 154-156°; ir (potassium bromide): 3200 (NH), 1675 cm^{-1} (C=O); nmr (DMSO- d_6): δ 0.97 (t, J = 6 Hz, 3, CH_3), 1.65 (m, 2, CH_2), 3.40 (m, 1, C_2H), 6.96 (d, J = 8 Hz, 1, C_5H), 7.18 (m, 1, C_6H), 7.35 (d, J = 2 Hz, 1, C_8H), 10.49 (s, 1, NH); ms: m/e 227 (M^+).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{ClNOS}$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.90; H, 4.49; N, 6.19.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid Ethyl Ester (**3a**).

Potassium *t*-butoxide (6.0 g, 53 mmoles) was added to a solution of 10 g (50 mmoles) of **2a** in 150 ml of dry DMF which was cooled to 5° under nitrogen. After 10 minutes 15.5 g (90 mmoles) of diethyl chlorophosphate was added. After an additional 5 minutes, a solution of 8.1 g (71.5 mmoles) of ethyl isocynoacetate [6] in 75 ml of DMF and 8.0 g (70 mmoles) of potassium *t*-butoxide were added sequentially. The mixture was stirred at 5° for 15 minutes, then at room temperature for 15 hours. The reaction was carefully acidified with 10 ml of acetic acid, diluted with 200 ml of water and poured slowly into 1 l of vigorously stirred ice-water. After 0.5 hour, the solid was collected, washed with water and air-dried to give 9.6 g (65%) of crude product. Recrystallization from ethyl acetate gave **3a** as colorless crystals, mp 201-203°; ir (potassium bromide): 1703 (C=O); nmr (DMSO- d_6): δ 1.2 (t, J = 7 Hz, 3, CH_3), 4.20 (q, J = 7 Hz, 2, CH_2), 4.40 (s, 2, C_4H), 7.2-8.4 (m, 4, arom H); ms: m/e 294 (M^+).

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}$: C, 52.97; H, 3.76; N, 9.50. Found: C, 52.87; H, 3.79; N, 9.44.

7-Chloro-4-ethyl-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid Ethyl Ester (**3b**).

The preparation of **3b** was conducted in the same manner as the preparation of **3a** to give **3b** in 28% yield as colorless needles, mp 127-129°; ir (potassium bromide): 1727 cm^{-1} (C=O); nmr (deuteriochloroform): δ 0.98 (t, J = 7 Hz, 3, CH_3), 1.42 (t, J = 7 Hz, 3, CH_3), 1.71 (m, 2, CH_2), 4.42 (q, J = 7 Hz, 2, CH_2), 4.85 (m, 1, C_4H), 7.25 (d, J = 2 Hz, 1, C_6H), 7.46 (s, 1, C_8H), 7.49 (d, J = 2 Hz, 1, C_5H), 7.96 (s, 1, C_1H); ms: m/e 322 (M^+).

Anal. Calcd. for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$: C, 55.81; H, 4.68; N, 8.68. Found: C, 55.76; H, 4.68; N, 8.69.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid (**4a**).

A solution of 5.0 g (17 mmoles) of **3a** in 300 ml of a 1:1 mixture of methanol and tetrahydrofuran was treated with a solution of 0.9 g (22.5 mmoles) of sodium hydroxide in 50 ml of water. The mixture was refluxed for 1 hour. The reaction mixture was neutralized with 3 ml of acetic acid, cooled in an ice bath, and the resulting solid was collected by filtration and dried to afford 4.2 g (93%) of crude **4a**. Recrystallization from a mixture of chloroform, methanol and tetrahydrofuran gave **4a** as pale yellow crystals, mp 287-288°; ir (potassium bromide): 2560-2320 (OH), 1705 cm^{-1} (C=O); nmr (TFA): δ 4.47 (s, 2, C_4H), 7.4-7.8 (m, 4, arom H), 9.36 (s, 1, OH); ms: m/e 266 (M^+).

Anal. Calcd. for $\text{C}_{11}\text{H}_7\text{ClN}_2\text{O}_2\text{S}$: C, 49.54; H, 2.65; N, 10.50. Found: C, 49.46; H, 2.71; N, 10.10.

7-Chloro-4-ethyl-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid (**4b**).

A solution of 8.8 g (27.3 mmoles) of **3b** in 350 ml of methanol was treated with a solution of 1.5 g (37.5 mmoles) of sodium hydroxide in 80 ml of water. The mixture was refluxed for 3 hours. The mixture was neutralized with acetic acid and cooled in an ice-bath. The resulting precipitate was collected by filtration to yield 7.6 g (95%) of **4b** as a yellow solid. Recrystallization from a mixture of methanol and tetrahydrofuran gave **4b** as pale yellow prisms, mp 271-273°; ir (potassium bromide): 2460, 1840 (OH), 1708, 1690 cm^{-1} (C=O); nmr (DMSO- d_6): δ 0.91 (t, J = 7 Hz, 3,

CH₃), 1.66 (m, 2, CH₂), 4.87 (t, J = 7 Hz, 1, C₄H), 7.40 (m, 1, C₆H), 7.56 (d, J = 2 Hz, 1, C₆H), 7.95 (d, J = 8 Hz, 1, C₆H), 8.47 (s, 1, C₁H); ms: m/e 294 (M⁺).

Anal. Calcd. for C₁₃H₁₁ClN₂O₂S: C, 52.97; H, 3.76; N, 9.50. Found: C, 53.23; H, 3.66; N, 9.65.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine (5a).

A mixture of 10.0 g (37.5 mmoles) of **4a** in 500 ml of 1,2,4-trichlorobenzene was refluxed for 1 hour under nitrogen. The reaction was cooled, diluted with hexane and extracted 4 times with 250 ml of 1*N* hydrochloric acid. The combined aqueous extract was basified with concentrated ammonium hydroxide and the resulting colorless solid was extracted with chloroform. The organic layer was dried, filtered and concentrated *in vacuo* to a yellow solid (6.8 g). Crystallization from a mixture of methylene chloride and hexane gave 5.3 g (64%) of **5a** as a pale yellow solid. Recrystallization from a mixture of hexane and ethyl acetate gave **5a** as pale yellow crystals, mp 120-124°; nmr (DMSO-*d*₆): δ 4.20 (s, 2, C₄H), 6.8-8.4 (m, 5, arom H); ms: m/e 222 (M⁺).

Anal. Calcd. for C₁₁H₇ClN₂S: C, 53.93; H, 3.17; N, 12.58. Found: C, 53.90; H, 3.11; N, 12.51.

7-Chloro-4-ethyl-4*H*-imidazo[5,1-*c*][1,4]benzothiazine Hydrochloride (5b).

A solution of 6.0 g (20.3 mmoles) of **4b** in 300 ml of 1,2,4-trichlorobenzene was refluxed for 1 hour. The solution was cooled and treated with 15 ml of 1.4 *M* methanol solution of hydrochloric acid. The resulting precipitate was collected by filtration to give 4.2 g (72%) of **5b** as a

colorless solid. Recrystallization from methanol gave **5b** as colorless needles, mp 275-279°; ir (potassium bromide): 2720, 2530 cm⁻¹ (NH); nmr (DMSO-*d*₆): δ 0.97 (t, J = 7 Hz, 3, CH₃), 1.82 (m, 2, CH₂), 4.51 (t, J = 7 Hz, 1, C₄H), 7.55 (m, 1, C₆H), 7.70 (s, 1, C₆H), 7.73 (d, J = 3 Hz, 1, C₆H), 8.05 (d, J = 9 Hz, 1, C₆H), 9.83 (s, 1, C₁H); ms: m/e 250 (M⁺, -HCl).

Anal. Calcd. for C₁₂H₁₂N₂Cl₂S: C, 50.18; H, 4.21; N, 9.75. Found: C, 50.05; H, 4.45; N, 9.82.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid Ethyl Ester 5-Oxide (6).

A solution of 6.0 g (20 mmoles) of **3a** and 4.6 g (23 mmoles) of 85% *m*-chloroperbenzoic acid in 200 ml of methylene chloride was stirred at room temperature overnight. The methylene chloride solution was washed with dilute aqueous sodium bicarbonate, dried and concentrated *in vacuo*. The residue was triturated with ether to give 5.3 g (85%) of **6** as a colorless solid. Recrystallization from a mixture of methylene chloride and petroleum ether gave **6** as colorless crystals, mp 211-213°; ir (chloroform): 1735, 1705 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 1.41 (t, J = 7 Hz, 3, CH₃), 4.42 (q, J = 7 Hz, 2, CH₂), 4.77 (d, J = 14.5 Hz, 1) and 4.98 (d, J = 14.5 Hz, 1) (AB system, C₄H), 7.6-8.1 (m, 4, arom H).

Anal. Calcd. for C₁₃H₁₁ClN₂O₃S: C, 50.24; H, 3.56; N, 9.01. Found: C, 50.30; H, 3.79; N, 8.84.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxylic Acid Ethyl Ester 5,5-Dioxide (7).

A solution of 0.5 g (1.7 mmoles) of **6** in 20 ml of methylene chloride was treated with 0.6 g (3.0 mmoles) of *m*-chloroperbenzoic acid. After 10 minutes the solvent was removed *in vacuo* and the residue was chromatographed (silica gel; eluent, ethyl acetate) to give 0.2 g (36%) of **7** as a yellow solid. Recrystallization from a mixture of ethyl acetate and hexane gave **7** as yellow crystals, mp 185-188°; ir (potassium bromide): 1722 (C=O) 1332 cm⁻¹ (SO₂); nmr (DMSO-*d*₆): δ 1.35 (t, J = 7 Hz, 3, CH₃), 4.35 (q, J = 7 Hz, 2, CH₂), 5.40 (s, 2, C₄H), 7.4-8.5 (m, 4, arom H); ms: m/e 326 (M⁺).

Anal. Calcd. for C₁₃H₁₁ClN₂O₄S: C, 47.79; H, 3.39; N, 8.57. Found: C, 47.90; H, 3.28; N, 8.45.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-carboxamide (8).

To a solution of 7.2 g (34.6 mmoles) of phosphorous pentachloride in 300 ml of methylene chloride, which was cooled to 5° under nitrogen, was added 6.0 g (22.5 mmoles) of **4a**. After 0.5 hour an additional 2.8 g

(13.5 mmoles) of phosphorous pentachloride was added. After 0.5 hour, excess ammonia was condensed into the reaction, and the mixture was stirred for an additional 1.5 hours. The ammonia was allowed to evaporate, and the mixture was diluted with 800 ml of water. The resulting solid was collected by filtration and air-dried to give 5.6 g (93%) of **8** as a white solid. Recrystallization from acetic acid gave **8** as a colorless solid, mp 317-319°; ir (potassium bromide): 3335, 3300, 3200 (OH), 1698 cm⁻¹ (C=O); nmr (TFA): δ 4.51 (s, 2, C₄H), 7.4-7.8 (m, 3, arom H), 9.32 (s, 1, OH); ms: m/e 265 (M⁺).

Anal. Calcd. for C₁₁H₈ClN₂OS: C, 49.72; H, 3.03; N, 15.81. Found: C, 49.33; H, 3.32; N, 15.73.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-3-methanol (9).

A solution of 8.0 g (27 mmoles) of **3a** in 300 ml of tetrahydrofuran was added dropwise to a solution of 3.0 g (79 mmoles) of lithium aluminum hydride in 300 ml of tetrahydrofuran which was cooled to -78° under argon. When the addition was complete, the reaction mixture was stirred at -78° for 2 hours followed by warming to 0°. The mixture was sequentially treated with 3 ml of water, 3 ml of 3*N* aqueous sodium hydroxide and 9 ml of water. The resulting precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was triturated with ether to give 5.0 g (74%) of **9** as a yellow solid. Recrystallization from methanol gave **9** as off-white needles, mp 187-190°; ir (potassium bromide): 3230-3190 cm⁻¹ (OH); nmr (DMSO-*d*₆): δ 4.18 (s, 2, C₄H), 4.45 (d, J = 5 Hz, 2, CH₂), 4.97 (t, J = 5 Hz, 1, OH), 7.37 (m, 1, arom H), 7.58 (d, J = 2 Hz, 1, arom H), 7.81 (d, J = 9 Hz, 1, arom H), 8.31 (s, 1, C₁H); ms: m/e 252 (M⁺).

Anal. Calcd. for C₁₁H₈ClN₂OS: C, 52.28; H, 3.59; N, 11.08. Found: C, 52.07; H, 3.60; N, 11.08.

7-Chloro-3-(chloromethyl)-4*H*-imidazo[5,1-*c*][1,4]benzothiazine (10).

In one portion, 3.6 g (14.2 mmoles) of **9** was added to 70 ml of thionyl chloride and the solution was refluxed for 1 hour. The mixture was concentrated *in vacuo*. The residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The methylene chloride solution was separated, dried and concentrated *in vacuo* to give 2.7 g (71%) of **10** as a yellow solid. Purification by column chromatography (silica gel, 50 g; eluent 5% methanol in methylene chloride) followed by crystallization from methylene chloride gave **10** as pale yellow needles, mp 180-186° dec; nmr (deuteriochloroform): δ 3.99 (s, 2, C₄H), 4.65 (s, 2, CH₂), 7.2-7.5 (m, 3, arom H), 7.91 (s, 1, C₁H); ms: m/e 270 (M⁺).

Anal. Calcd. for C₁₁H₈Cl₂N₂S: C, 48.72; H, 2.97; N, 10.33. Found: C, 48.53; H, 2.90; N, 10.08.

7-Chloro-3-ethyl-4-imidazo[5,1-*c*][1,4]benzothiazine (11).

An ether solution of methyl lithium (33 ml, 46 mmoles) was added to a mixture of 4.2 g (22 mmoles) of cuprous iodide and 150 ml of tetrahydrofuran, which was cooled to 0° under argon. After stirring for 1 hour, the mixture was reacted with a solution of 3.0 g (11 mmoles) of **10** in 150 ml of tetrahydrofuran. The mixture was diluted with 100 ml of water and hydrogen sulfide gas was added until precipitation ceased. The black precipitate was removed by filtration through celite. The filtrate was washed with water, dried and concentrated *in vacuo* to give 2.1 g (77%) of **11** as a yellow solid. Purification by column chromatography (silica gel, 50 g; eluent, ethyl acetate) gave **11** as pale yellow needles, mp 147-149°; nmr (deuteriochloroform): δ 1.24 (t, J = 7 Hz, 3, CH₃), 2.58 (q, J = 7 Hz, 2, CH₂), 3.88 (s, 2, C₄H), 7.1-7.5 (m, 3, arom H), 7.85 (s, 1, C₁H); ms: m/e 250 (M⁺).

Anal. Calcd. for C₁₂H₁₁ClN₂S: C, 57.48; H, 4.42; N, 11.17. Found: C, 57.50; H, 4.35; N, 11.14.

7-Chloro-4*H*-imidazo[5,1-*c*][1,4]benzothiazine-1-methanol (12).

A mixture of 19.8 g (88.9 mmoles) of **5** in 200 ml of 37% aqueous formaldehyde was refluxed for 18 hours. The mixture was cooled and diluted with water. The resulting solid was collected by filtration and recrystallized from a mixture of methanol and ethyl acetate (charcoal) to give 17.8

g (80%) of **12** as a pale yellow solid, mp 237-240°; ir (potassium bromide): 3150 cm⁻¹ (OH); nmr (DMSO-d₆): δ 4.0 (s, 2, C₄H), 4.45 (d, J = 5 Hz, 2, CH₂), 5.82 (t, J = 5 Hz, 1, OH), 6.75 (s, 1, C₃H), 7.2-8.2 (m, 3, arom H); ms: m/e 252 (M⁺).

Anal. Calcd. for C₁₁H₉ClN₂OS: C, 52.28; H, 3.59; N, 11.08. Found: C, 52.23; H, 3.61; N, 11.19.

7-Chloro-1-(chloromethyl)-4H-imidazo[5,1-c][1,4]benzothiazine (**13**).

A solution of 17.8 g (70.4 mmoles) of **12** in 180 ml of thionyl chloride was heated on a steam bath for 10 minutes. The solution was added dropwise, over a 0.5-hour period, to 1.5 l of rapidly stirred hexane. The resulting precipitate was collected by filtration and washed with ethanol to give 17.8 g (83%) of **13** as a colorless solid. Recrystallization from a mixture of ethyl acetate and ethanol gave **13** as colorless crystals, mp 318-322°; nmr (DMSO-d₆): δ 4.20 (s, 2, CH₂), 5.30 (s, 2, CH₂), 7.4-8.1 (m, 4, arom H).

Anal. Calcd. for C₁₁H₉Cl₂N₂S: C, 42.95; H, 2.95; N, 9.10. Found: C, 42.96; H, 3.02; N, 9.17.

The free base of **13** was prepared by partitioning the hydrochloride salt between ethyl acetate and aqueous ammonium hydroxide solution. The ethyl acetate solution was dried and concentrated *in vacuo* to give the free base of **13** as a pale yellow solid, mp 103-105°; ms: m/e 270 (M⁺).

Anal. Calcd. for C₁₁H₉Cl₂N₂S: C, 48.72; H, 2.97; N, 10.33. Found: C, 48.82; H, 2.89; N, 10.13.

7-Chloro-1-ethyl-4H-imidazo[5,1-c][1,4]benzothiazine (**14**).

An ether solution of methyl lithium (37 ml, 52 mmoles) was added to a mixture of 4.6 g (24 mmoles) of cuprous iodide in 170 ml of tetrahydrofuran, which was cooled to 0° under argon. After stirring for 45 minutes, the mixture was reacted with 3.4 g (12.5 mmoles) of **13** in 170 ml of tetrahydrofuran. The mixture was diluted with 100 ml of water and hydrogen sulfide gas was added until precipitation ceased. The black precipitate was removed by filtration through celite. The filtrate was dried and concentrated *in vacuo* to yield 2.8 g (90%) of **14** as a yellow solid. Purification by column chromatography (silica gel, 50 g; eluent, 50% methylene chloride in ethyl acetate) gave **14** as pale yellow needles, mp 112-113°; nmr (deuteriochloroform): δ 1.39 (t, J = 7 Hz, 3, CH₃), 2.92 (q, J = 7 Hz, 2, CH₂), 3.86 (s, 2, C₄H), 6.82 (s, 1, C₃H), 7.25 (m, 1, C₆H), 7.40 (s, 2, C₅H), 7.49 (m, 1, C₄H); ms: m/e 250 (M⁺).

Anal. Calcd. for C₁₂H₁₁ClN₂S: C, 57.48; H, 4.42; N, 11.17. Found: C, 57.23; H, 4.40; N, 11.02.

7-Chloro-4H-imidazo[5,1-c][1,4]benzothiazine-1-acetonitrile (**15**).

A solution of 16.8 g (54.6 mmoles) of the hydrochloride salt of **13** in 675 ml of ethanol and 75 ml of water was added dropwise to 33.6 g (0.5

mole) of potassium cyanide in 175 ml of water which was cooled to 5°. The mixture was stirred at room temperature overnight followed by solvent removal *in vacuo*. The residue was dissolved in methylene chloride and washed with dilute aqueous sodium bicarbonate and brine. The methylene chloride solution was dried and concentrated *in vacuo* to give after trituration of the residue with ethanol 5.3 g (73%) of **15** as a yellow solid. Recrystallization from a mixture of ethyl acetate and hexane gave **15** as a pale yellow solid, mp 190-192°; ir (potassium bromide): 2265 cm⁻¹ (C≡N); nmr (DMSO-d₆): δ 4.10 (s, 2, C₄H), 4.60 (s, 2, CH₂), 6.90 (s, 1, C₃H), 7.2-7.8 (m, 3, arom H); ms: m/e 261 (M⁺).

Anal. Calcd. for C₁₂H₉ClN₃S: C, 55.07; H, 3.08; N, 16.05. Found: C, 55.24; H, 3.29; N, 15.78.

7-Chloro-4H-imidazo[5,1-c][1,4]benzothiazine-1-acetamide (**16**).

A solution of 3.3 g (12.6 mmoles) of **15** in 25 ml of concentrated sulfuric acid was stirred for 2.5 hours at room temperature. The solution was poured into 330 ml of ice-water, and basified with 10 ml of concentrated ammonium hydroxide. The mixture was extracted twice with 500 ml of ethyl acetate. The ethyl acetate solution was washed with brine, dried and concentrated *in vacuo* to give 3.7 g (100%) of **16** as a yellow solid, mp 191-196°; ir (potassium bromide): 1673 cm⁻¹ (C=O); ms: m/e 279 (M⁺).

Anal. Calcd. for C₁₂H₁₀ClN₃OS: C, 51.52; H, 3.60; N, 15.02. Found: C, 51.45; H, 3.80; N, 15.17.

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REFERENCES AND NOTES

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