

Synthesis of (*Z*)-hetarylmethylene and (*Z*)-substituted benzylidene derivatives of 4*H*-benzo[1,4]thiazine-3-thiones and their subsequent conversion to benzothiopyrano-[3,2-*b*][1,4]benzothiazines

Sukanta Kamila, Benjamin Koh, Hongming Zhang, and Edward R. Biehl*

Department of Chemistry, Southern Methodist University, Dallas, Texas-75275, USA

E-mail: ebiehl@smu.edu

Abstract

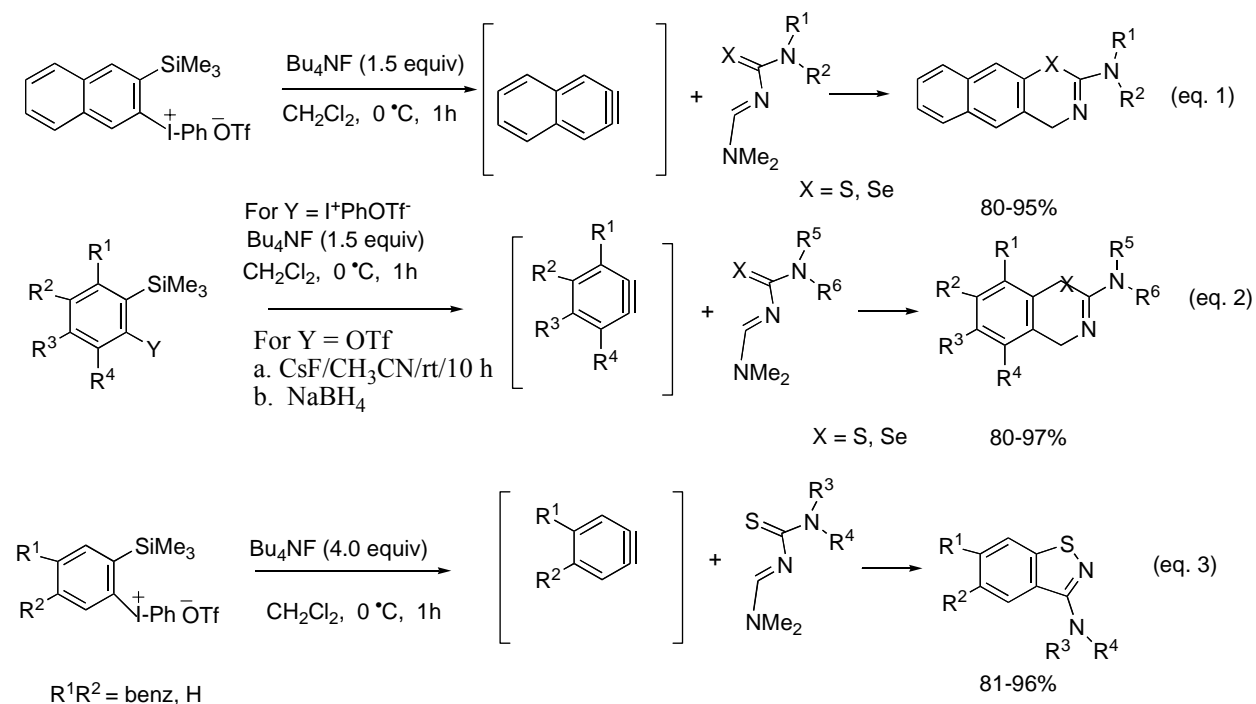
(*Z*)-Hetarylmethylene and (*Z*)-substituted benzylidene derivatives of 4*H*-benzo[1,4]thiazine-3-thiones were prepared by the reaction of 4*H*-benzo[1,4]thiazine-3-thiones with various aldehydes. Subsequent treatment of the thiazine-3-thiones with dimethyl acetylenedicarboxylate and various arynes gave the corresponding dimethyl-4-aryl-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylates and 12-aryl-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazines, respectively.

Keywords: 3,4-Dimethoxybenzyne, cycloaddition, Diels-Alder, benzothiopyrano[3,2-*b*][1,4]benzothiazines, (*Z*)-(hetarylmethylene-2-yl)-4*H*-benzo[1,4]-thiazine-3-thiones, dimethyl acetylenedicarboxylate

Introduction

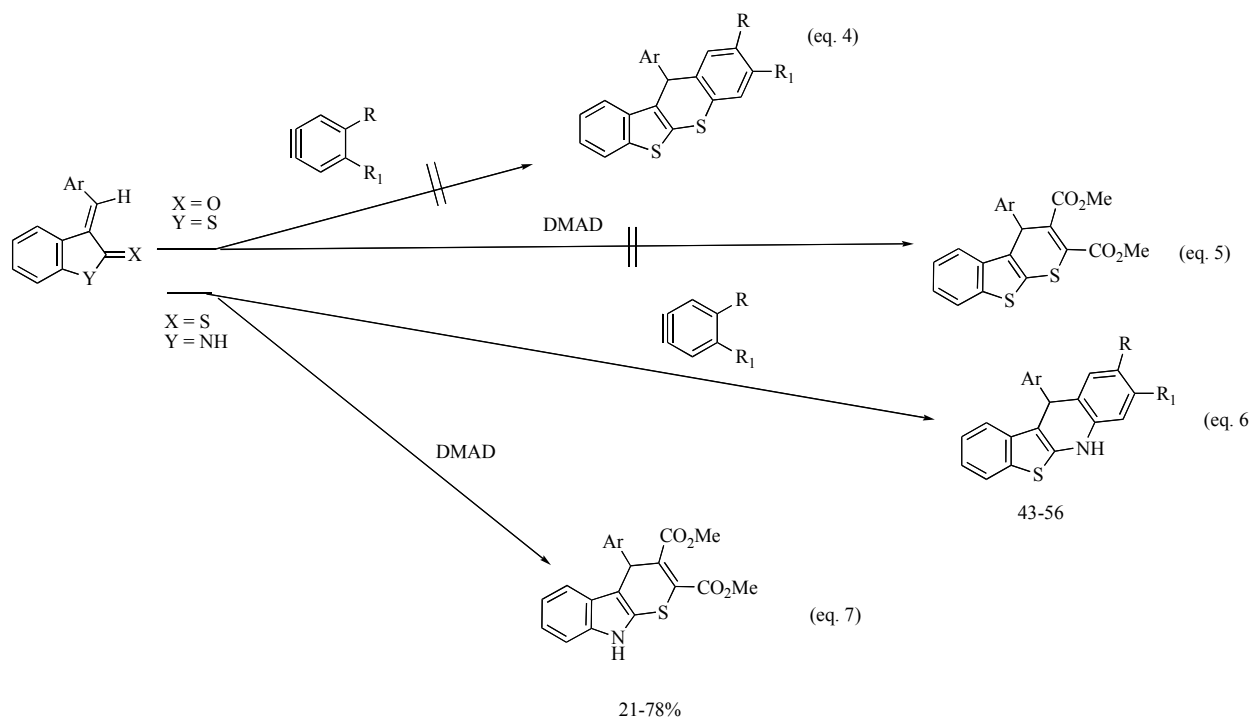
During the course of our study of the use of arynes in preparing biologically important N/S heterocycles,¹ we have developed a facile two-step process for preparing heterocycles that contain two or more ring heteroatoms (generally N and S and/or Se). The first step involves the synthesis of acyclic dienes possessing two heteroatoms (*e.g.*, thiaazadienes and selenazadienes) or the synthesis of dienes that are part of or attached to a heterocyclic ring (*e.g.*, substituted benzylidene derivatives of thiazine-3-thiones). The second step involves a [4+2] cycloaddition reaction between those heterocyclic dienes with arynes and occasionally with dimethyl acetylenedicarboxylate [DMAD]. A brief summary of the results of this research is shown in Scheme 1. Thus, as shown in Scheme 1, 2,3-didehydronaphthalenes react with thiaazadienes and selenazadienes (eq. 1) to give 4*H*-naphtho[2,3-*b*]-1,3-thiazines² and 4*H*-naphtho[2,3-*b*]-1,3-selenazines³ in yields ranging from 85–94%, respectively. In addition, various arynes react with thiaazadienes and 4*H*-1,3-benzoselenazines⁴ in yields ranging from 80–95% and 81–97%,

respectively. In most cases, the aryne intermediates were generated at 0 °C by the reaction of (phenyl)[(trimethylsilyl)aryl]-iodonium triflates with 1.5 equiv of Bu₄NF.⁵ In the other cases, 2-trimethylsilyltriflates were treated with CsF/MeCN at room temperature.⁶ Interestingly, when arynes and 2,3-didehydronaphthalene were generated from the appropriate iodonium triflate with 4.0 equiv of Bu₄NF, benzoisothiazoles and naphtho-isothiazoles (eq. 3) were obtained in yields ranging from 85–94% and 81–96%, respectively.³ A possible mechanism for this interesting rearrangement involving the trapping of an aryne intermediate with a nitrile sulfide generated *in situ* by the reaction of dialkylaminothiazadine, fluoride ion, and trimethylsilyl fluoride has been proposed.³



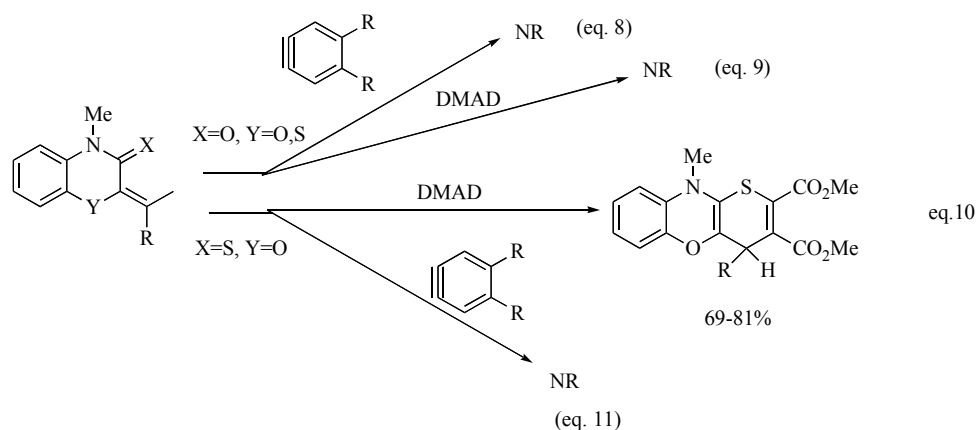
Scheme 1

We next turned our attention to studying dienes in which one of the double bonds of the diene was part of or attached to a heterocyclic ring. Dienes that were part of a five-membered heterocycle were first studied. As shown in Scheme 2, substituted benzylidene derivatives of benzo[*b*]thiophene-2-ones failed to react with arynes (eq. 4) and DMAD (eq. 5). However, by replacing the O and S of the ring and thiocarbonyl group with S and NH, respectively, the resulting benzo[*b*]pyrrole-2-thiones reacted with arynes and DMAD, albeit at higher temperatures than those given in Scheme 1, to give benzothiopyrano[2,3-*b*]indoles (43–56%) (eq. 6) and the 2,5-dihydro-9-substituted thiopyrano[2,3-*b*]indole-2,3-dicarboxylic acid dimethyl esters (21–78%) (eq. 7).⁷



Scheme 2

We next sought heterocyclic dienes that would deliver a 1,4-benzoxazine or 1,4-benzothiazine moiety *via* [4+2] cycloaddition reactions with arynes and DMAD. This basic ring structure is found in several molecules that exhibit a wide range of biological activity. As shown in Scheme 3, the 1,4-benzoxazine-3-(4*H*)-ones and 1,4-benzothiazin-3-(4*H*)-ones did not react with arynes (eq. 8) and DMAD (eq. 9). However, 1,4-benzothiazin-3-(4*H*)-thiones, which possess a thio-carbonyl group, did react with DMAD (eq. 10) to give thiopyrano[3,2-*b*]benzoxazine-2,3-dicarboxylic acid dimethyl esters in 69–81% yields.⁸ However, they did not react with benzyne even at high temperatures (eq. 11).⁸

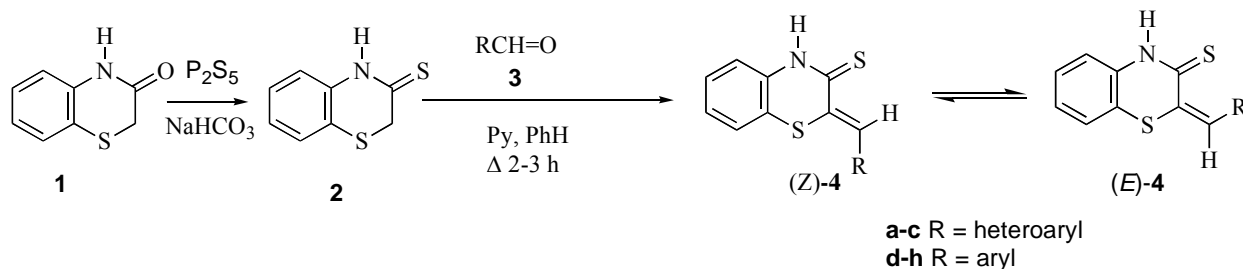


Scheme 3

We have now synthesized several six-membered heterodienes, *viz.* hetarylmethylenes and substituted benzylidenes of 4*H*-benzo[1,4]thiazine-3-thiones, which reacts with both arynes and DMAD to give the title compounds, and report the results herein.

Results and Discussion

As shown in Scheme 4, the 2-hetarylmethylene **4a-c** and substituted 2-benzylidene-4*H*-benzo[1,4]thiazine-3-thiones **4d-h** were prepared by the reaction of 4*H*-benzo[1,4]thiazine-3-thione **2** with the appropriate aldehyde (**3**). 4*H*-Benzo[1,4]thiazine-3-thione **2** was prepared from 4*H*-benzo[1,4]-thiazine-3-one **1** by the reaction with P₂S₅ in presence of NaHCO₃. All of the products were solids and thus were recrystallized from ethyl acetate-hexane mixtures. The yields of **4a-h**, which are listed in Table 1, ranged from 80-95%. None of the (*E*)-**4** diastereomers was detected.



Scheme 4

As shown in Scheme 4, the thiazine-3-thiones **4** may exist as *Z* and *E* diastereomers. The *Z*-diastereomers are thermodynamically more stable than the *E*-diastereoisomers⁹ and in several previous studies it was assumed that 2-hetarylmethylene- and arylmethylene-4*H*-benzo[1,4]-thiazine-3-thiones with undetermined stereochemistry were probably *Z*-diastereomers.^{10,11} The unstable *E*-diastereomers can be prepared by irradiation of the *Z*-form with sunlight¹² or UV/VIS light.^{10,12,13} However, upon removal of the irradiation, the *Z*-diastereomers reformed. We confirmed the *Z* configuration in two ways. First, the structure of **4b** was confirmed by X-Ray crystallography. An ORTEP drawing of **4b** is shown in Figure 1. To our knowledge this is the first x-ray study reported on thiones of this type. Furthermore, the NMR data of our compounds **4a-h** have the vinyl proton with chemical shifts in the range of 8.36-8.49 ppm. This range is slightly higher than that reported for 3-oxo analogs (~8.0-8.30) ppm but significantly higher for those reported for *E*-diastereomers (~7.34 ppm).^{14,15}

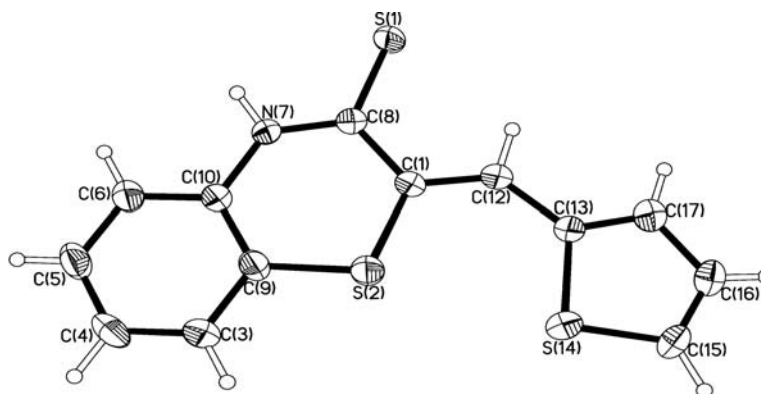
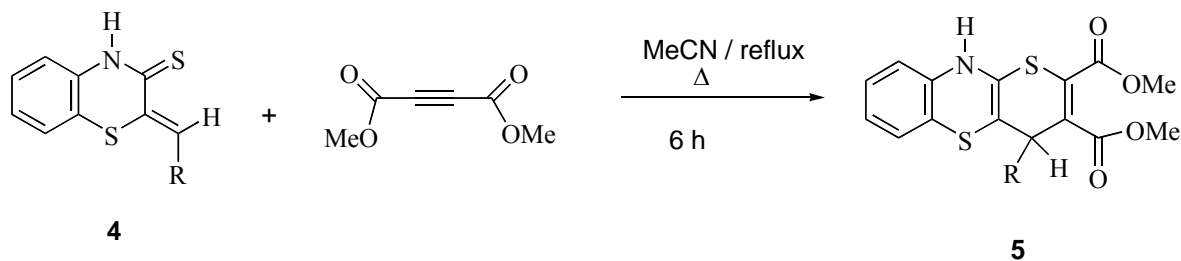


Figure 1. ORTEP of **4b**.

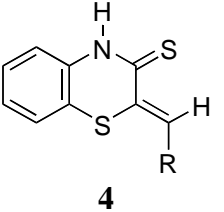
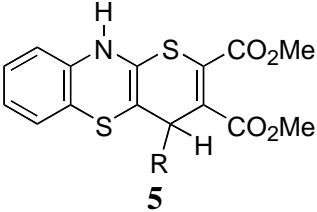
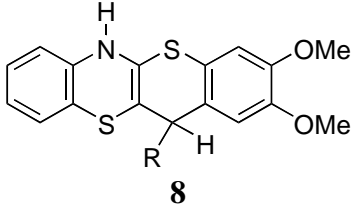
The thiazine-3-thiones **4a-h** were then treated with several dienophiles. Of the non-aryne dienophiles studied, the reaction of DMAD give the best yields (77-88%) of dimethyl-4-aryl-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylates (**5a-h**) when treated with **4** in refluxing MeCN for 6 h (see Scheme 5 and Table 1). Interestingly, when **4** was treated with non-arynic dienophiles such as acrolein and acrylonitrile, complex mixtures of inextractable tars were obtained.



Scheme 5

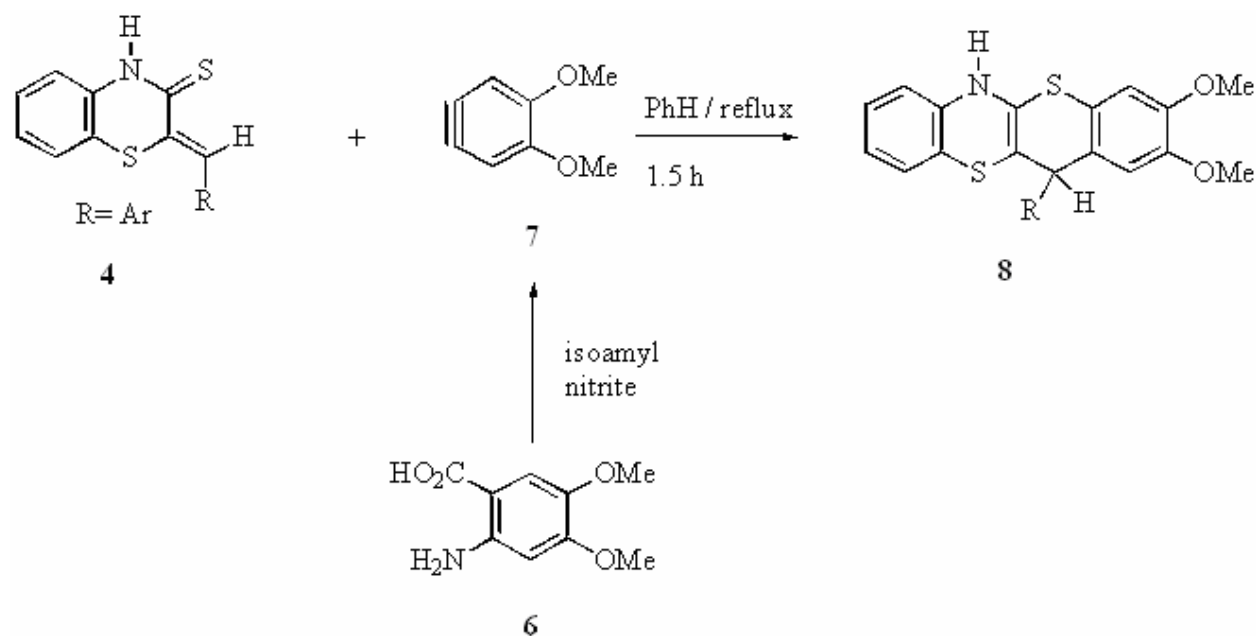
We next explored the [4+2] cycloaddition reaction of **4** with arynes. We first generated arynes from arylodonium triflates and trimethylsilyltriflates in the presence of **4**. Unfortunately, these reactions did not yield Diels-Alder adducts, but gave a complex mixture of products none of which was the desired heterocycle. However, as shown in Scheme 6, 4,5-dimethoxyanthranilic acid (**6**) was converted to 4,5-dimethoxybenzyne (**7**) by the method of Hart¹⁶ which involves the addition of a benzene solution of isoamyl nitrite to a refluxing benzene solution of **6**.

Table 1. Product yields of compounds **4**, **5** and **8**

				
	R	Yield, %	Yield, %	Yield, %
a	2-furanyl	90	78	68
b	2-thienyl	89	80	62
c	2-pyrrolyl	93	87	56
d	4-dimethylamino	95	88	58
e	4-methoxyphenyl	80	78	88
f	3,4,5-trimethoxyphenyl	88	86	67
g	4-chlorophenyl	89	88	59
h	2,5-dimethoxyphenyl	86	85	60

Aryne (**7**) was subsequently trapped by **4a-h** to give the desired products **8a-h** in yields (listed in Table 1) in the range of 56–88%. The structures of **8a-h** were determined by ^1H NMR, ^{13}C NMR, and elemental analysis. That the 3-thiones **4** underwent [4+2] cycloaddition reactions indicates that they, like 1,4-benzothiazin-3-(4*H*)-thiones which also was found previously to react with arynes,⁷ are behaving as α,β -unsaturated moieties.

In summary, we have developed a new method for the synthesis of benzothiopyrano[3,2-*b*][1,4]benzothiazines by the [4+2] cycloaddition of hetarylmethylene and substituted benzylidenes derivatives of 4*H*-benzo[1,4]thiazine-3-thiones with arynes and DMAD. The convenient synthesis provides ready access to polynuclear S/N-heterocycles which contain the basic ring structure found in molecules that exhibits, for example, antihypertensive drugs,¹⁷ calcium antagonists,¹⁸ and highly potent inhibitors of LDL oxidation.¹⁹



Scheme 6

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Elemental analysis were obtained from SMU Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific.

Synthesis of 4H-benzo[1,4]thiazine-3-thione (2). To a well-stirred solution of 4H-benzo[1,4]thiazine-3-one (1) (5 g, 33.1 mmol) in 50 mL of dry THF was added P_2S_5 (14.7 g, 33.1 mmol), and the resulting mixture was stirred at rt for 45 min. After NaHCO_3 (9.2 g, 109.5 mmol) was added in three portions, the mixture was stirred an additional 3h at rt during which time a precipitate formed. The precipitate was collected by vacuum filtration and the mother liquor was concentrated to dryness. The resulting residue was treated with 100 mL of ice water, extracted with CHCl_3 (3 X 60 mL), and purified by column chromatography on SiO_2 using ethyl acetate-hexane as eluent to give 3-thione (2) (5.3 g, 89%) as a light yellow solid, mp: 126-128 °C (lit.,²⁰ 128 °C). ^1H NMR δ 3.88 (s, 2H, $-\text{CH}_2-$), 7.02 (d, $J = 8.0$ Hz, 1H, aromatic), 7.10 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.20 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.34 (d, $J = 7.8$ Hz, 1H, aromatic), 10.40 (br s, 1H, NH). ^{13}C NMR δ 37.5 (t), 117.9 (d), 122.9 (d), 125.7 (d), 127.5 (d), 128.4 (s), 136.1 (s), 192.5 (s).

General procedure for the synthesis of (Z)-2-hetarylmethylene-4H-benzo[1,4]thiazine-3-thiones (4a-c) and (Z)-substituted benzylidene-4H-benzo[1,4]thiazine-3-thiones (4d-g). A reaction mixture containing **2** (0.5 g, 2.7 mol), an appropriate aldehyde (3.3 mol) and piperidine (one drop) in dry benzene (10 mL) was stirred at 90 °C for 4 h, then cooled to rt. The crude product, which precipitated during cooling, was collected by vacuum filtration, washed with benzene, dried and purified by column chromatography on SiO₂ using ethyl acetate-hexane (1:4, v/v). The physical and spectral properties the thiones (**4a-h**) are given below.

(Z)-2-(Furan-2-ylmethylene)-4H-benzo[1,4]thiazine-3-thione (4a). This compound was isolated as an orange red fluffy solid (ethyl acetate-hexane), mp: 208–209 °C. ¹H NMR (acetone-*d*₆) δ 6.74 (d, *J* = 8.0 Hz, 1H, aromatic), 7.12 (s, 1H, aromatic), 7.17 (d, *J* = 7.5 Hz, 1H, aromatic), 7.27 (dd, *J* = 7.5, 8.0 Hz, 1H, aromatic), 7.37–7.39 (m, 2H, aromatic), 7.85 (s, 1H, aromatic), 8.36 (s, 1H, vinyl proton), 11.55 (br s, 1H, NH). ¹³C NMR (acetone-*d*₆) δ 117.7 (d), 125.4 (d), 126.3 (d), 127.8 (d), 128.1 (d), 130.5 (s), 131.2 (s), 134.2 (s), 138.9 (s), 188.5 (s). *Anal.* Calcd for C₁₃H₉NOS₂: C, 60.20; H, 3.50; N, 5.40. Found: C, 60.31; H, 3.57; N, 5.48.

(Z)-2-(Thiophene-2-ylmethylene)-4H-benzo[1,4]thiazine-3-thione (4b). This compound was isolated as an orange solid (ethyl acetate-hexane), mp: 207–208 °C. ¹H NMR (acetone-*d*₆) δ 6.89 (d, *J* = 8.0 Hz, 1H, aromatic), 7.12 (d, *J* = 7.5 Hz, 1H, aromatic), 7.18–7.21 (m, 2H, aromatic), 7.32 (d, *J* = 7.5 Hz, 1H, aromatic), 7.63 (d, *J* = 4.2 Hz, 1H, aromatic), 8.40 (s, 1H, vinyl proton), 11.41 (br s, 1H, NH). ¹³C NMR (acetone-*d*₆) δ 113.3 (d), 116.0 (d), 117.7 (d), 121.8 (s), 123.2 (d), 125.4 (d), 125.9 (d), 127.6 (d), 145.6 (s), 151.7 (s), 155.1 (s), 188.9 (s). *Anal.* Calcd for C₁₃H₉NS₃: C, 56.59; H, 3.29; N, 5.09. Found: C, 56.72; H, 3.32; N, 5.16.

(Z)-2-(1H-Pyrrol-2-ylmethylene)-4H-benzo[1,4]thiazine-3-thione (4c). This compound was isolated as an orange reddish powdered solid (ethyl acetate-hexane), mp: 191–193 °C. ¹H NMR (acetone-*d*₆) δ 6.40 (s, 1H, aromatic), 7.01 (s, 1H, aromatic), 7.13 (dd, *J* = 7.5, 8.0 Hz, 1H, aromatic), 7.19 (s, H, aromatic), 7.22–7.25 (m, 2H, aromatic), 7.32–7.37 (m, 2H, aromatic), 8.40 (s, 1H, vinyl proton), 10.87 (br s, 1H, NH), 11.21 (br s, 1H, NH). ¹³C NMR (acetone-*d*₆) δ 111.4, 115.5, 116.8, 117.4, 119.5, 123.4, 125.1, 126.0, 127.4, 127.9, 129.3, 133.5, 188.9. *Anal.* Calcd for C₁₃H₁₀NO₂S₂: C, 60.43; H, 3.90; N, 10.84. Found: C, 60.53; H, 3.96; N, 10.74.

(Z)-2-(4-Dimethylaminobenzylidene)-4H-benzo[1,4]thiazine-3-thione (4d). This compound was isolated as a reddish brown powdered solid (ethyl acetate-hexane), mp: 227–228 °C. ¹H NMR (acetone-*d*₆) δ 3.07 (s, 6H, -NMe₂), 6.76 (d, *J* = 8.0 Hz, 2H, aromatic), 6.86 (d, *J* = 8.0 Hz, 1H, aromatic), 7.05 (dd, *J* = 7.5, 8.0 Hz, 1H, aromatic), 7.13 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.19 (d, *J* = 7.8 Hz, 1H, aromatic), 7.69 (d, *J* = 8.0 Hz, 2H, aromatic), 8.49 (s, 1H, vinyl proton), 11.3 (br s, 1H, NH). ¹³C NMR (acetone-*d*₆) δ 40.4 (t X 2), 111.7 (d), 116.7 (d), 120.7 (d), 123.4 (s), 125.4 (d), 126.2 (d), 127.2 (s), 133.1 (d), 133.4 (s), 141.2 (s), 151.2 (s), 188.3 (s). *Anal.* Calcd for C₁₇H₁₆N₂S₂: C, 65.35; H, 5.16; N, 8.97. Found: C, 65.39; H, 5.10; N, 8.91.

(Z)-2-(4-Methoxybenzylidene)-4H-benzo[1,4]thiazine-3-thione (4e). This compound was isolated as a yellow, fluffy solid (ethyl acetate-hexane), mp: 194–196 °C. ¹H NMR (acetone *d*₆) δ 3.89 (s, 3H, -OMe), 7.08 (d, *J* = 8.0 Hz, 2H, aromatic), 7.14 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.25 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.31–7.35 (m, 2H, aromatic), 7.72 (d, *J* = 8.0

Hz, 2H, aromatic), 8.46 (s, 1H, vinyl proton), 11.5 (br s, 1H, NH). ^{13}C NMR (acetone- d_6) δ 55.1 (q), 113.4 (d), 117.5 (d), 120.9 (d), 125.1 (d), 125.4 (d), 126.0 (d), 126.4 (d), 127.3 (s), 132.0 (s), 140.3 (s), 144.1 (s), 160.6 (s), 189.5 (s). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NOS}_2$: C, 64.18; H, 4.38; N, 4.68. Found: C, 64.28; H, 4.31; N, 4.76.

(Z)-2-(3,4,5-Trimethoxybenzylidene)-4H-benzo[1,4]thiazine-3-thione (4f). This compound was isolated as a yellow fluffy flakes (ethyl acetate-hexane), mp: 196–198 °C. ^1H NMR (acetone- d_6) δ 3.81 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 3.93 (s, 3H, -OMe), 7.05 (s, 2H, aromatic), 7.14 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.24 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.35–7.38 (m, 2H, aromatic), 8.49 (s, 1H, vinyl proton), 11.5 (br s, 1H, NH). ^{13}C NMR (acetone- d_6) δ 55.6 (q), 56.1 (q), 56.3 (q), 108.5 (d), 117.5 (d), 119.3 (d), 124.4 (d), 125.3 (d), 126.1 (d), 127.6 (d), 130.7 (s), 133.5 (d), 138.5 (s), 139.7 (s), 144.3 (s), 154.6 (s), 155.6 (s), 160.6 (s), 189.4 (s). *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3\text{S}_2$: C, 60.14; H, 4.77; N, 3.90. Found: C, 60.25; H, 4.71; N, 3.93.

(Z)-2-(4-Chlorobenzylidene)-4H-benzo[1,4]thiazine-3-thione (4g). This compound was isolated as a light orange fluffy solid (ethyl acetate-hexane), mp: 224–226 °C. ^1H NMR (acetone- d_6) δ 7.16 (d, $J = 7.8$ Hz, 2H, aromatic), 7.28–7.36 (m, 2H, aromatic), 7.49–7.55 (m, 2H, aromatic), 7.71 (d, $J = 7.8$ Hz, 2H, aromatic), 8.41 (s, 1H, vinyl proton), 11.57 (br s, 1H, NH). ^{13}C NMR (acetone- d_6) δ 117.7 (d), 125.5 (d), 126.1 (d), 127.7 (d), 128.9 (s), 131.6 (d), 132.1 (d), 133.5 (s), 134.2 (d), 136.4 (d), 136.7 (s), 138 (s), 144.3 (s), 188.8 (s). *Anal.* Calcd for $\text{C}_{15}\text{H}_{10}\text{NClS}_2$: C, 59.30; H, 3.32; N, 4.61. Found: 59.37; H, 3.30; N, 4.54.

2-(4,5-Dimethoxybenzylidene)-4H-benzo[1,4]thiazine-3-thione (4h). This compound was isolated as an orange solid (ethyl acetate-hexane), mp: 205–207 °C. ^1H NMR (acetone- d_6) δ 3.76 (s, 3H, -OMe), 3.84 (s, 3H, -OMe), 7.02 (s, 1H, aromatic), 7.12 (d, $J = 7.6$ Hz, 2H, aromatic), 7.25 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.30 (d, $J = 7.8$ Hz, 1H, aromatic), 7.35 (d, $J = 8.0$ Hz, 1H, aromatic), 8.60 (s, 1H, vinyl proton). ^{13}C NMR (acetone- d_6) δ 55.6 (q), 55.9 (q), 112.0 (d), 115.4 (d), 116.0 (d), 117.9 (d), 124.1 (d), 125.0 (d), 125.9 (s), 127.5 (s), 135.8 (d), 136.3 (s), 144.3 (s), 152.6 (s), 153.3 (s), 189.7 (s). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{S}_2$: C, 61.98; H, 4.59; N, 4.25. Found: C, 62.05; H, 4.49; N, 4.18.

General procedure for the [4+2]Diels-Alder reaction yielding compounds (5a–h). To a well-stirred solution of compound (4) (0.7 mmol) in dry MeCN (5 mL) contained in a round-bottom flask fitted with a reflux condenser under argon atmosphere, was added a solution of dimethyl acetylenedicarboxylate (0.56 g, 3.8 mmol) in MeCN (1 mL) *via* a needle syringe system. The mixture was heated to reflux for 6 h and then cooled. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography using silica gel and ethyl acetate-hexane (1:4, v/v) as eluent. The physical and spectral properties of 6a–h are given below.

Dimethyl 4-(furan-2-yl)-4,10-dihydrothiopyrano[3,2-*b*] benzothiazine-2,3-dicarboxylate (5a). Reddish gummy liquid. ^1H NMR (CDCl_3) δ 3.82 (s, 3H, -OMe), 3.89 (s, 3H, -OMe), 4.81 (s, 1H, Ha), 6.27 (s, 1H, aromatic), 6.50 (d, $J = 8.0$ Hz, 1H, aromatic), 6.94–7.01 (m, 3H, aromatic), 7.25 (s, 1H, aromatic), 7.34 (s, 1H, aromatic), 11.35 (br s, 1H, NH). ^{13}C NMR (CDCl_3) δ 42.8 (d), 52.9 (q), 53.9 (q), 102.9 (d), 107.9 (d), 110.7 (s), 117.7 (s), 125.3 (s), 127.4

(d), 127.7 (d), 128.8(d), 132.1(d), 136.4(d), 139.6(d), 141.8(s), 143.1(s), 147.1 (s), 150.5 (s), 164.7(s), 164.9 (s). *Anal.* Calcd for C₁₉H₁₅NO₅S₂: C, 56.84; H, 3.77; N, 3.49. Found: C, 56.94; H, 3.73; N, 3.42.

Dimethyl 4-(thiophen-2-yl)-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylate (5b). Yellowish gummy liquid. ¹H NMR (CDCl₃) δ 3.86 (s, 3H, -OMe), 3.89 (s, 3H, -OMe), 4.94 (s, 1H, Ha), 6.51 (d, *J* = 8.0 Hz, 1H, aromatic), 6.91 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 6.98–7.00 (m, 2H, aromatic), 7.04 (s, 1H, aromatic), 7.16 (d, *J* = 4.2 Hz, 1H, aromatic), 7.27 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 11.41 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ 43.9(d), 53.2(q), 53.9(q), 105.4(d), 110.1 (s), 117.7 (s), 125.3 (d), 125.5 (d), 125.8 (s), 127.1 (s), 127.4 (d), 127.6 (d), 128.4 (d), 132.2 (d), 139.5 (s), 141.1 (d), 141.8 (s), 147.5 (s), 164.6 (s), 164.8 (s). *Anal.* Calcd for C₁₉H₁₅NO₄S₃: C, 54.66; H, 3.62; N, 3.35. Found: C, 54.61; H, 3.65; N, 3.30.

Dimethyl 4-(1*H*-pyrrol-2-yl)-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylate (5c). Reddish gummy liquid. ¹H NMR (CDCl₃) δ 3.89 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 4.60 (s, 1H, Ha), 6.10 (s, 1H, aromatic), 6.49 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 6.74 (s, 1H, aromatic), 6.98–7.00 (m, 3H, aromatic), 7.25 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 10.91 (br s, 1H, NH), 11.41 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ 42.8 (d), 53.3(q), 53.9 (q), 103.2 (d), 107.7 (d), 108.7 (s), 117.4 (d), 118.8 (d), 124.6 (d), 125.4 (s), 127.0 (s), 127.7 (d), 128.2 (d), 128.9 (d), 131.6 (s), 136.1 (s), 139.6 (s), 141.7 (s), 163.9 (s). *Anal.* Calcd for C₁₉H₁₆N₂O₄S₂: C, 56.98; H, 4.03; N, 7.00. Found: C, 56.90; H, 4.09; N, 7.05.

Dimethyl 4-(4-*N,N*-dimethylaminophenyl)-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylate (5d). Reddish brown gummy liquid. ¹H NMR (CDCl₃) δ 2.91 (s, 6H, -NMe₂), 3.70 (s, 3H, -OMe), 3.89 (s, 3H, -OMe), 4.51 (s, 1H, Ha), 6.48 (d, *J* = 8.0 Hz, 1H, aromatic), 6.65 (d, *J* = 8.0 Hz, 2H, aromatic), 6.88 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 6.92–6.96 (m, 1H, aromatic), 7.27–7.31 (m, 3H, aromatic), 11.41 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ 40.8 (qX2), 48.4 (d), 53.0 (q), 53.9 (q), 106.7 (d), 113.0 (s), 117.6 (s), 125.1 (d), 126.1 (d), 126.7 (d), 127.4 (s), 129.0 (d), 130.7 (d), 131.8 (d), 132.1 (d), 137.3 (s), 139.6 (s), 141.8 (s), 150.5 (s), 165.8 (s), 166.1 (s). *Anal.* Calcd for C₂₃H₂₂N₂O₄S₂: C, 60.77; H, 4.88; N, 6.16. Found: C, 60.78; H, 4.93; N, 6.2.

Dimethyl 4-(4-methoxyphenyl)-4,10-dihydrothiopyrano[3,2-*b*] benzothiazine-2,3-dicarboxylate (5e). Yellowish solid, mp: 206–208 °C. ¹H NMR (CDCl₃) δ 3.87 (s, 3H, -OMe), 3.81 (s, 3H, -OMe), 3.86 (s, 3H, -OMe), 3.94 (s, 1H, Ha), 6.95 (d, *J* = 7.8 Hz, 2H, aromatic), 7.07–7.14 (m, 2H, aromatic), 7.19 (dd, *J* = 7.8, 8.0 Hz, 1H, aromatic), 7.37 (d, *J* = 8.0 Hz, 1H, aromatic), 7.61 (d, *J* = 7.8 Hz, 2H, aromatic), 11.39 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ 43.7(d), 53.0 (q), 53.9 (q), 108.1(d), 114.1 (s), 116.9 (d), 118.4 (s), 121.1 (d), 124.9 (d), 126.4 (s), 127.1 (d), 129.4 (s), 131.7 (d), 133.1 (d), 137.8 (s), 139.0 (s), 141.6 (d), 145.5 (d), 156.7 (s), 167.0 (s), 167.1 (s). *Anal.* Calcd for C₂₂H₁₉NO₅S₂: C, 59.85; H, 4.34; N, 3.17. Found: C, 59.78; H, 4.39; N, 3.22.

Dimethyl 4-(3,4,5-trimethoxyphenyl)-4,10-dihydrothiopyrano[3,2-*b*]benzothiazine-2,3-dicarboxylate (5f). Reddish gummy liquid. ¹H NMR (CDCl₃) δ 3.75 (s, 3H, -OMe), 3.76 (s, 3H, -OMe), 3.77 (s, 3H, -OMe), 3.82 (s, 6H, -OMe X2), 4.64 (s, 1H, Ha), 6.51 (d, *J* = 7.8 Hz, 1H,

aromatic), 6.69 (s, 2H, aromatic), 6.96-7.00 (m, 2H, aromatic), 7.27 (d, $J = 7.8$ Hz, 1H, aromatic), 11.39 (br s, 1H, NH). ^{13}C NMR (CDCl_3) δ 48.8 (d), 52.8 (q), 53.6 (q), 56.2 (q), 61.1 (q), 104.5 (d), 105.0 (d), 117.4 (s), 125.0 (d), 125.4 (d), 127.4 (s), 127.6 (d), 128.7 (d), 130.0 (s), 132.3 (s), 133.8 (d), 137.8 (s), 139.4 (s), 141.9 (s), 153.6 (s), 164.8(s), 165.9(s). *Anal.* Calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_7\text{S}_2$: C, 57.47; H, 4.62; N, 2.79. Found: C, 57.36; H, 4.52; N, 2.89.

Dimethyl 4-(4-chlorophenyl)-4,10-dihydrothiopyrano[3,2-*b*] benzothiazine-2,3-dicarboxylate (5g). Reddish crystal, mp: 174–176 $^\circ\text{C}$. ^1H NMR (CDCl_3) δ 3.81 (s, 3H, -OMe), 3.84 (s, 3H, -OMe), 3.93 (s, 1H, Ha), 6.36-6.49 (m, 2H, aromatic), 6.71 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.10–7.16 (m, 2H, aromatic), 7.21–7.28 (m, 3H, aromatic), 11.41 (br s, 1H, -NH). ^{13}C NMR (CDCl_3) δ 43.7 (d), 54.0 (q), 56.2 (q), 116.9 (s), 119.3 (s), 120.6 (d), 121.3 (d), 124.9 (d), 125.0 (d), 127.3 (s), 128.0 (d), 128.9 (d), 129.7 (s), 131.2 (d), 133.5 (s), 134.5 (s), 140.2 (s), 147.6 (s), 166.9 (s), 167.0 (s). *Anal.* Calcd for $\text{C}_{21}\text{H}_{16}\text{NO}_4\text{ClS}_2$: C, 56.56; H, 3.62; N, 3.14. Found: C, 56.50; H, 3.68; N, 3.18.

Dimethyl 4-(2,5-dimethoxyphenyl)-4,10-dihydrothiopyrano[3,2-*b*] benzothiazine-2,3-dicarboxylate (5h). Reddish brown gummy liquid. ^1H NMR (CDCl_3) δ 3.78 (s, 3H, -OMe), 3.80 (s, 3H, -OMe), 3.84 (s, 6H, -OMe X2), 4.51 (s, 1H, Ha), 6.59 (d, $J = 2.5$ Hz, 1H, aromatic), 6.89 (d, $J = 7.8$ Hz, 1H, aromatic), 6.91 (dd, $J = 2.5, 7.8$ Hz, 1H, aromatic), 6.98 (d, $J = 8.0$ Hz, 1H, aromatic), 7.00–7.13 (m, 3H, aromatic), 11.38 (br s, 1H, NH). ^{13}C NMR (CDCl_3) δ 43.8 (d), 52.7 (q), 53.5 (q), 56.2 (q), 56.9 (q), 101.4 (d), 115.1 (s), 116.8 (d), 123.0 (d), 124.1 (d), 125.0 (s), 127.4 (s), 128.3 (d), 128.6 (d), 129.9 (d), 134.5 (d), 136.5 (s), 141.1 (s), 151.0 (s), 154.4 (s), 158.5 (s), 161.7 (s), 166.3 (s). *Anal.* Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_6\text{S}_2$: C, 58.58; H, 4.49; N, 2.97. Found: C, 58.44; H, 4.56; N, 3.04.

General procedure for benzyne reactions yielding products (8a-h). A well stirred solution containing **4a** (0.52 g, 0.18 mmol) and a one drop of trichloroacetic acid in dry benzene (10 mL) was heated under reflux in a three-neck flask fitted with a reflux condenser and two addition funnels under argon atmosphere. At this point the dropwise addition of solutions of 4,5-dimethoxyanthranilic acid (1.4 g, 6.9 mmol) and isoamyl nitrite (0.96 g, 6.9 mmol) in dry benzene (5 mL) from the addition funnel was started. The addition was stopped when the starting materials were no longer detected in the reaction mixture by TLC (~1.5 h). The resulting solution was cooled to rt and evaporated to dryness. The residue was dissolved in CH_2Cl_2 , washed with 5% HCl solution, 5% NaOH, and water and dried over Na_2SO_4 . Evaporation of the solvent under reduced pressure afforded the crude product which was purified by column chromatography using SiO_2 with ethyl acetate-hexane (1:4, v/v] as eluent. The physical and spectral data are given below for compounds (**8a-h**).

12-(Furan-2-yl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazine (8a). Brownish gummy liquid. ^1H NMR (CDCl_3) δ 3.95 (s, 3H, -OMe), 3.99 (s, 3H, -OMe), 4.27 (s, 1H, Ha), 6.50 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 6.92 (s, 1H, aromatic), 6.95 (s, 1H, aromatic), 7.36 (s, 1H, aromatic), 7.40–7.45 (m, 2H, aromatic), 7.77 (d, $J = 7.8$ Hz, 2H, aromatic), 11.30 (br s, 1H, NH). ^{13}C NMR (CDCl_3) δ 41.0 (d), 56.3 (q), 56. (q), 101.3 (s), 115.1 (d), 115.6 (d), 116.1(d), 118.5 (d), 119.3 (d), 123.1 (s), 125.3 (d), 126.5 (d), 126.7 (s), 127.0 (d),

130.3 (s), 130.8 (d), 131.7 (s), 139.9 (s), 148.5 (s), 149.9 (s). *Anal.* Calcd for $C_{21}H_{17}NO_3S_2$: C, 63.77; H, 4.33; N, 3.54. Found; C, 63.87; H, 4.25; N, 3.61.

12-(Thiophen-2-yl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazine (8b). Yellowish liquid. 1H NMR ($CDCl_3$) δ 3.91 (s, 3H, -OMe), 3.96 (s, 3H, -OMe), 4.76 (s, 1H, Ha), 6.81 (s, 1H, aromatic), 7.08–7.11 (m, 3H, aromatic), 7.19–7.23 (m, 3H, aromatic), 7.41 (s, 1H, aromatic), 7.54 (d, $J = 4.5$ Hz, 1H, aromatic), 11.23 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 39.1 (d), 56.3 (q), 56.5 (q), 101.1 (s), 111.6 (d), 119.0 (s), 120.6 (d), 121.3 (d), 122.1 (d), 125.4 (d), 127.1 (d), 127.8 (s), 128.9 (d), 129.3 (s), 131.1 (d), 131.6 (s), 138.9 (s), 139.7 (s), 148.4 (s), 149.3 (s). *Anal.* Calcd for $C_{21}H_{17}NO_2S_3$: C, 61.29; H, 4.16; N, 3.40. Found: C, 61.33; H, 4.23; N, 3.27.

12-(1*H*-Pyrrol-2-yl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazine (8c). Reddish gummy liquid. 1H NMR ($CDCl_3$) δ 3.97 (s, 3H, -OMe), 3.99 (s, 3H, -OMe), 4.60 (s, 1H, Ha), 6.41 (s, 1H, aromatic), 6.50 (s, 1H, aromatic), 6.82 (s, 1H, aromatic), 7.02 (s, 1H, aromatic), 7.14 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.19 (s, 1H, aromatic), 7.25–7.38 (m, 3H, aromatic), 10.81 (br s, 1H, -NH), 11.23 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 39.0 (d), 56.3 (q), 56.5 (q), 101.3 (s), 107.9 (d), 108.3 (d), 115.4 (d), 115.6 (d), 116.3 (d), 117.5 (d), 118.8 (d), 119.9 (s), 126.3 (s), 130.0 (s), 130.9 (s), 131.0 (s), 131.6 (d), 144.3 (s), 144.9 (s), 148.1 (s). *Anal.* Calcd for $C_{21}H_{18}N_2O_2S_2$: C, 63.93; H, 4.60; N, 7.10. Found: C, 64.13; H, 4.51; N, 7.17.

12-(4-*N,N*-Dimethylphenyl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]-benzothiazine (8d). Reddish brown gummy liquid. 1H NMR ($CDCl_3$) δ 2.89 (s, 6H, -NMe₂), 3.95 (s, 3H, -OMe), 3.98 (s, 3H, -OMe), 4.65 (s, 1H, Ha), 6.50 (s, 1H, aromatic), 6.75 (d, $J = 8.0$ Hz, 2H, aromatic), 6.81 (s, 1H, aromatic), 6.86 (d, $J = 8.0$ Hz, 1H, aromatic), 7.01 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.15 (dd, $J = 7.5, 7.8$ Hz, 1H, aromatic), 7.20 (d, $J = 7.8$ Hz, 1H, aromatic), 7.68 (d, $J = 7.8$ Hz, 2H, aromatic), 11.23 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 38.5 (d), 43.5 (q x 2), 56.3 (q), 56.5 (q), 101.5 (s), 113.5 (d), 113.6 (d), 115.3 (d), 115.5 (d), 116.6 (d), 118.5 (d), 119.3 (s), 125.7 (s), 126.5 (d), 129.3 (d), 130.1 (s), 130.5 (d), 135.1 (s), 137.5 (s), 144.3 (s), 145.9 (s), 147.9 (s), 148.5 (s). *Anal.* Calcd for $C_{25}H_{24}N_2O_2S_2$: C, 66.93; H, 5.39; N, 6.24. Found: C, 66.73; H, 5.44; N, 6.29.

12-(4-Methoxyphenyl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazine (8e). Yellowish gummy liquid. 1H NMR ($CDCl_3$) δ 3.83 (s, 3H, -OMe), 3.92 (s, 3H, -OMe), 3.97 (s, 3H, -OMe), 4.60 (s, 1H, Ha), 6.50 (s, 1H, aromatic), 6.68 (d, $J = 8.0$ Hz, 2H, aromatic), 6.82 (s, 1H, aromatic), 6.86 (d, $J = 8.0$ Hz, 1H, aromatic), 6.98 (d, $J = 8.0$ Hz, 2H, aromatic), 7.05 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.13 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.19 (d, $J = 7.8$ Hz, 1H, aromatic), 11.23 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 37.8 (d), 56.5 (q), 56.6 (q), 101.5 (s), 113.5 (d), 113.6 (d), 115.3 (d), 115.6 (d), 116.3 (d), 118.3 (d), 119.3 (s), 125.6 (s), 126.1 (d), 129.1 (d), 129.2 (d), 130.1 (s), 135.1 (s), 137.6 (s), 144.9 (s), 145.8 (s), 147.4 (s), 159.1 (s). *Anal.* Calcd for $C_{24}H_{21}NO_3S_2$: C, 66.18; H, 4.86; N, 3.22. Found: C, 66.12; H, 4.50; N, 3.29.

12-(3,4,5-Trimethoxyphenyl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]-benzothiazine (8f). Colorless gummy liquid. 1H NMR ($CDCl_3$) δ 3.89 (s, 3H, -OMe), 3.91 (s,

6H, -OMe x 2), 3.98 (s, 6H, -OMe x 2), 4.60 (s, 1H, Ha), 6.09 (s, 2H, aromatic), 6.29 (s, 1H, aromatic), 6.52 (s, 1H, aromatic), 6.56-6.64 (m, 2H, aromatic), 7.06 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.13 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 11.39 (br s, 1H, NH). ^{13}C NMR (CDCl_3) δ 40.1 (d), 55.9 (q), 56.3 (q x 2), 56.6 (q x 2), 101.3 (s), 107.3 (d), 107.4 (d), 115.4 (d), 115.5 (d), 116.4 (d), 118.5 (d), 119.7 (s), 125.3 (s), 126.7 (d), 131.1 (s), 131.5 (d), 138.5 (s), 138.9 (d), 148.3 (s), 150.1 (s), 150.5 (s), 150.9 (s), 151.1 (s). *Anal.* Calcd for $\text{C}_{26}\text{H}_{25}\text{NO}_5\text{S}_2$: C, 63.01; H, 5.08; N, 2.83. Found: C, 63.11; H, 5.12; N, 2.80.

12-(4-Chlorophenyl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]benzothiazine (8g). Brownish gummy liquid. ^1H NMR (CDCl_3) δ 3.78 (s, 3H, -OMe), 3.81 (s, 3H, -OMe), 4.74 (s, 1H, Ha), 6.41 (s, 1H, aromatic), 6.51 (s, 1H, aromatic), 6.51-6.59 (m, 2H, aromatic), 7.05 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 7.09 (d, $J = 8.0$ Hz, 2H, aromatic), 7.19 (d, $J = 8.0$ Hz, 2H, aromatic), 7.21 (dd, $J = 7.5, 8.0$ Hz, 1H, aromatic), 11.19 (br s, 1H, -NH). ^{13}C NMR (CDCl_3) δ 38.9 (d), 55.9 (q), 56.1 (q), 101.3 (s), 115.1 (d), 115.4 (d), 116.3 (d), 118.3 (d), 119.3 (s), 125.3 (s), 126.8 (d), 129.1 (d), 129.5 (d), 129.9 (d), 130.1 (s), 130.8 (d), 131.1 (s), 131.5 (d), 137.9 (s), 141.3 (s), 148.5 (s), 149.9 (s), 150 (s). *Anal.* Calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_2\text{ClS}_2$: C, 62.79; H, 4.12; N, 3.18. Found: C, 62.88; H, 4.19; N, 3.28.

12-(2,5-Dimethoxyphenyl)-6,12-dihydro-2,3-dimethoxy[1]benzothiopyrano[3,2-*b*][1,4]-benzothiazine (8h). Low melting yellowish solid. ^1H NMR (CDCl_3) δ 3.78 (s, 3H, -OMe), 3.81 (s, 6H, -OMe X 2), 3.89 (s, 3H, -OMe), 4.71 (s, 1H, Ha), 6.45-6.49 (m, 5H, aromatic), 6.50 (s, 1H, aromatic), 6.54 (d, $J = 7.8$ Hz, 1H, aromatic), 7.04 (dd, $J = 7.8, 8.0$ Hz, 1H, aromatic), 7.19 (d, $J = 7.8$ Hz, 1H, aromatic), 11.31 (br s, 1H, -NH). ^{13}C NMR (CDCl_3) δ 30.1 (d), 55.9 (q), 56.3 (q), 56.5 (q), 56.6 (q), 101.3 (s), 111.9 (d), 115.3 (d), 115.5 (d), 115.9 (d), 116.0 (d), 118.1(d), 119.3 (s), 125.3 (s), 126.1 (d), 129.3 (s), 130.1 (s), 131.1 (d), 137.8 (s), 147.4 (s), 151.0 (s), 151.9 (s), 152.6 (s), 153.2 (s). *Anal.* Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_4\text{S}_2$: C, 64.49; H, 4.98; N, 3.01. Found: 64.51; H, 4.93; N, 3.03.

Acknowledgements

This work was supported by a grant from the Robert Welch Foundation, Houston, TX, USA.

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