Novel Heterocycles Derived from Substituted Aroylthioureas: Synthesis of 3,1-Benzothiazin-4-ones, Thieno[3,2-*d*][1,3]thiazin-4-ones and 1,2,4-Thiadiazolo[2,3-*a*][3,1]benzothiazin-5-ones

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Received July 12, 1995

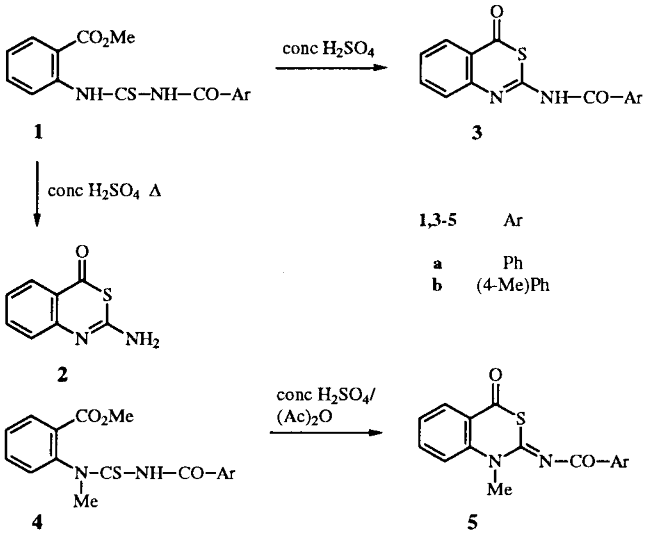
A series of heterocyclic aroylthioureas has been prepared and investigated as starting materials for ring closure reactions. The formation of several new 3,1-benzothiazin-4-ones and thieno[3,2-*d*][1,3]thiazin-4-ones (*via* cyclocondensation reactions) is reported. Oxidative cyclizations were carried out to produce methyl benzothiazole-4-carboxylates (*via* formation of an S-C bond) as well as 1,2,4-thiadiazolo-[2,3-*a*][3,1]benzothiazin-5-ones (*via* formation of an S-N bond).

J. Heterocyclic Chem., **33**, 355 (1996).

Carbo- and heterocyclic thioureas containing a neighboring carboxy, alkoxycarbonyl, or carbonitrile function are versatile starting compounds for the synthesis of heterocyclic compounds. Typically, these thioureas were utilized for cyclocondensation reactions to obtain fused pyrimidines. Under strong acidic conditions, an alternative 1,3-thiazine ring closure can be attained [1]; on treatment of alkyl 2-thioureido-3-thiophenecarboxylates with concentrated sulfuric acid, 2-amino-substituted thieno[2,3-*d*][1,3]thiazin-4-ones were obtained. This method has been successfully applied to the preparation of condensed benzo- [2], indolo- [3], imidazo-, and pyrazolo- [4] 1,3-thiazin-4-ones. Further investigations were directed toward the utilization of 2-thioureido-3-thiophenecarbonitriles [5], as well as alkyl 3-thiophenecarboxylates with 2-diacylthioacetamide- and 2-alkoxythiocarbonylamino residues [6] to prepare thieno[2,3-*d*][1,3]thiazines. Fused 1,3-thiazin-4-ones have gained increasing interest since recent reports have shown serine protease inactivating properties of such compounds [3,7]. In this paper, the synthesis of a series of aroylthioureas and the examination of their synthetic potential is reported.

2-(3-Benzoylthioureido)benzoic acids [8] and corresponding esters, such as **1a** (Scheme 1), are easily available from benzoyl isothiocyanate [9] and anthranilic acid derivatives and therefore attractive precursors for several transformations. In alkaline medium, methyl 2-benzoylthioureidobenzoate **1a** undergoes ring closure followed by debenzoylation to form 2,3-dihydro-2-thioxo-4(1*H*)-quinazolinone [10]. Depending on reaction conditions, treatment of **1a** with concentrated sulfuric acid alternatively affords 2-amino-3,1-benzothiazin-4-one **2** or 2-benzoylamino-3,1-benzothiazin-4-one **3a** [2]. Accordingly, the *p*-toluoylamino derivative **3b** was prepared from **1b** (Scheme 1). The initial approach to introduce a methyl group into the 1-position of the 3,1-benzothiazinone skeleton [11] involved the preparation of the new *N*-methyl-*N'*-aroylthioureas **4**. Indeed, compounds **4** could be converted to the desired 1-methyl-3,1-benzothiazinones **5** in excellent yields. This cyclization was accomplished by the action of a mixture of concentrated sulfuric acid and acetic anhydride [13]. The assigned structures **5a** and **5b** are supported by analytical and spectral data. In particular, the ^{13}C nmr spectra [14] show signals for the C-4 carbon at 183 ppm unequivocally indicating the cyclic thiolester structure of **5**.

Scheme 1

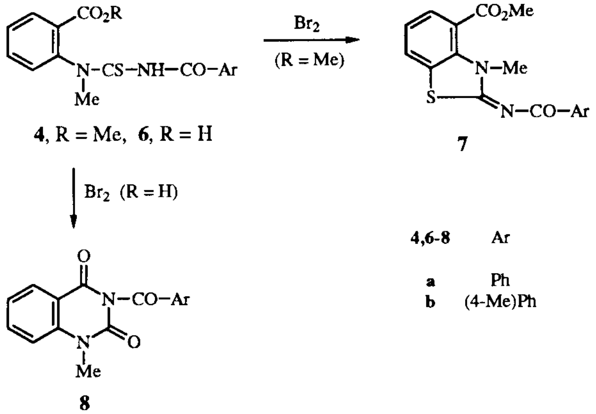


1,3-5	Ar
a	Ph
b	(4-Me)Ph

It was of further interest to investigate the possibility of oxidative cyclization using the aroylthioureidobenzoic acid derivatives as starting materials. A classical route to 2-aminobenzothiazoles involves the oxidation of arylthioureas [15]. However, according to the literature, thioureas derived from alkyl anthranilates or anthranilic acids have not been subjected to conditions for the Hugershoff reaction. The *N*-methyl-*N'*-aroylthioureas **4** were treated at room temperature with an equimolar amount of bromine as dehydrogenative agent in acetic acid. The products formed were established to be methyl 2-aroylimino-3-methyl-2,3-

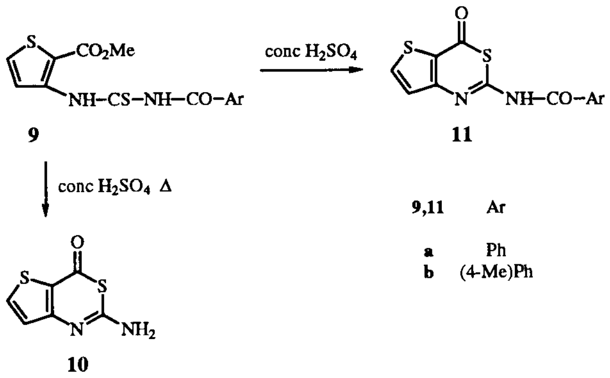
dihydrobenzothiazole-4-carboxylates **7a** and **7b** (Scheme 2). The ^{1}H nmr spectrum of the oxidation product **7a** showed one triplet at 7.44 ppm (J = 7.7 Hz) and two signals at 7.73 and 8.13 ppm (each dd, J = 1.2, 7.7 Hz) for the remaining three protons of the fused benzene ring. A similar pattern appeared in the ^{1}H nmr spectra of **7b**. This cleary demonstrates that cyclization has occured onto the C-3 of the methoxycarbonyl substituted benzene unit and not onto the C-2' of the aroyl substituent. The lower nucleophilicity of the aroyl substituent and the tendency for preferential formation of a five membered ring explains the formation of **7** [17]. Surprisingly, the procedure to obtain **7** was not successful when applied to other related derivatives. The aroylthioureas **1** (Scheme 1) and **9** (Scheme 3) did not yield any dehydrogenated product. When *N*-(2-carboxyphenyl)-*N*-methyl-*N'*-aroylthioureas **6** were treated with bromine in ethyl acetate the quinazolinediones **8** were obtained. Structural assignments for **8a** and **8b** were confirmed by elemental analyses, infrared (three distinct carbonyl stretching frequencies in the range of 1744-1662 cm^{-1}), nmr and mass spectral data. This unexpected conversion to **8** formally involves oxidative desulfurization and cyclocondensation. The mechanism, however, remains somewhat obscure [18].

Scheme 2



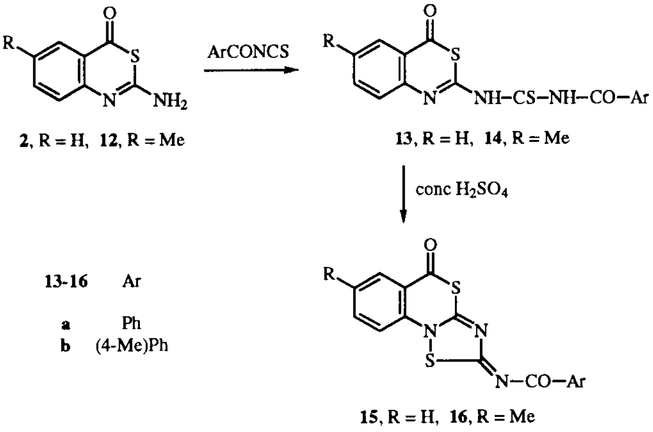
Attempts to replace the benzene skeleton of the 3,1-benzothiazin-4-one structure by a thiophene ring to produce derivatives of the still unknown heterosystem thieno-[3,2-*d*][1,3]thiazine are outlined in Scheme 3. This route involves the preparation of the new methyl 3-aroylthioureido-2-thiophenecarboxylates **9**, which then were subjected to conditions for the 1,3-thiazinone cyclization. The 2-amino-thieno[3,2-*d*][1,3]thiazin-4-one **10** and the aroylamino derivatives **11** were easily obtained in good yields. The structures were established by microanalyses and spectral data. It should be noted that no sulfonated by-products were observed, even when the thiophene **9a** was heated for 4 hours in sulfuric acid to prepare **10**.

Scheme 3



The readily available 3,1-benzothiazin-4-ones **2** and **12** [2] and the thieno[3,2-*d*][1,3]thiazin-4-one **10** were chosen for further transformation to aroylthioureas as potential precursors to tricyclic compounds. While **10** failed to react with benzoylisothiocyanate in boiling acetone, the aminobenzothiazinones **2** and **12** could be converted with aroylisothiocyanates to afford the corresponding heterocyclic substituted aroylthioureas **13** and **14** (Scheme 4). On treatment of **13** and **14** with concentrated sulfuric acid at room temperature compounds **15** and **16** were obtained and established to be derivatives of the new heterosystem 2*H*,5*H*-[1,2,4]thiadiazolo[2,3-*d*][3,1]benzothiazine. Structural elucidation was accomplished on the basis of microanalyses and spectral data. The ^{1}H nmr spectra were recorded in pyridine because of the low solubility of **15** and **16**. From the structural assignment of the products, it became clear that sulfuric acid has acted as an oxidizing agent. The yields of the benzoylimino derivatives **15a** and **16a** could be improved by adding an equimolar amount of *N*-bromosuccinimide [19] to the reaction mixtures. The toluoylthioureas **13b** and **14b**, however, were smoothly oxidized with concentrated sulfuric acid alone, while the addition of *N*-bromosuccinimide yielded brominated by-products. The oxidative cyclization to afford fused

Scheme 4



1,2,4-thiadiazoles from substituted thioureas (*e.g.* from pyridyl- or pyrimidylthioureas with bromine or sulfuryl chloride [20]) is well known. It should be noted that the 4-step route to the tricyclic compounds **15** and **16**, starting from anthranilic acid derivatives involves two nearly identical procedures, each one carried out twofold. Whereas sulfuric acid was used in the second step to accomplish cyclocondensation (accompanied by debenzoylation) to produce **2** or **12**, in the fourth step sulfuric acid promotes an oxidative S-N coupling to form **15** and **16**.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are not corrected. Infrared spectra were recorded on a Perkin Elmer 16PC FTIR. The ^{1}H nmr spectra (300 MHz) and ^{13}C nmr spectra (75 MHz) were recorded on a Varian Gemini 300. Mass spectra (70 eV) were obtained using a Varian MAT CH 6 spectrometer. Analytical tlc was performed on Merck silica gel plates with F-254 indicator. Benzoyl isothiocyanate and 4-methylbenzoyl isothiocyanate were prepared from benzoyl chloride, 4-methylbenzoyl chloride, respectively, and ammonium thiocyanate in dry acetone [9] and directly used for the synthesis of the aroylthioureas.

Methyl 2-[3-(4-Methylbenzoyl)thioureido]benzoate (**1b**).

To methyl anthranilate (4.53 g, 30 mmoles) in dry acetone (6 ml) a solution of 4-methylbenzoyl isothiocyanate in acetone (60 mmoles in 30 ml) was added. The mixture was kept at room temperature for 4 hours. The precipitate was filtered off and washed with cold *n*-hexane to obtain **1b** (9.1 g, 92%), mp 137-138° (methanol); ir (potassium bromide): ν 1712, 1668 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.40 (s, 3H, CH$_3$), 3.84 (s, 3H, OCH$_3$), 7.35 (d, J = 8.2 Hz, 2H, H-3'), 7.36-7.44 (m, 1H, H-5), 7.62-7.69 (m, 1H, H-4), 7.91-7.96 (m, 3H, H-2' and H-3), 8.08 (d, J = 7.8 Hz, 1H, H-6), 11.53 (s, 1H, NH), 13.14 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 61.85; H, 4.66; N, 8.19.

2-(4-Methylbenzoyl)amino-4*H*-3,1-benzothiazin-4-one (**3b**).

Compound **1b** (984 mg, 3 mmoles) was dissolved in concentrated sulfuric acid (3 ml) and kept at room temperature for 2 days. The mixture was poured into ice-water (200 ml). The precipitate was collected by filtration and extensively washed with water to obtain **3b** (710 mg, 80%), mp 205-206° (ethanol); ir (potassium bromide): ν 1676, 1632 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.35 (s, 3H, CH$_3$), 7.30 (d, J = 7.8 Hz, 2H, H-3'), 7.44-7.52 (m, 1H, H-6), 7.64 (d, J = 8.3 Hz, 1 H, H-8), 7.81-7.88 (m, 1H, H-7), 7.95 (d, J = 7.8 Hz, 2H, H-2'), 8.02 (d, J = 8.0 Hz, 1H, H-5), 12.15 (s, 1H, NH); ms: (70 ev) m/z 296 (24%; M^{+}), 119 (100%).

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82. Found: C, 64.89; H, 4.04; N, 9.52; S, 11.08.

Methyl 2-(3-Benzoyl-1-methylthioureido)benzoate (**4a**).

A solution of benzoyl isothiocyanate in acetone (60 mmoles in 30 ml) was prepared and cooled to 0°. Methyl *N*-methylanthranilate (4.95 g, 30 mmoles) dissolved in dry acetone (6 ml) was added. The mixture was kept at room temperature for 3 hours, diluted with diethyl ether (90 ml) and cooled overnight. The precipitate was filtered off (7.1 g, 72%). To prepare an analytical sample, material was dissolved in ethanol at room temperature and treated with water, mp 111-113°; ir (potassium bromide): ν 1719, 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 61.86; H, 4.71; N, 8.42; S, 9.94.

Methyl 2-[3-(4-Methylbenzoyl)-1-methylthioureido]benzoate (**4b**).

This compound was prepared from 4-methylbenzoyl isothiocyanate and methyl *N*-methylanthranilate using the procedure given above. The reaction mixture was diluted with diethyl ether, cooled overnight and evaporated at room temperature. The residue was triturated with *n*-hexane and the solid was collected by filtration (6.9 g, 67%), mp 83-86°; ir (potassium bromide): ν 1714, 1692 cm^{-1} (C=O); ms: (70 ev) m/z 342 (6%, M^{+}), 119 (100%).

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18; S, 9.36. Found: C, 62.88; H, 4.95; N, 8.17; S, 9.74.

2-Benzoylimino-1-methyl-1,2-dihydro-4*H*-3,1-benzothiazin-4-one (**5a**).

Compound **4a** (1.97 g, 6 mmoles) was treated with a cooled mixture prepared from concentrated sulfuric acid (10 ml) and acetic anhydride (5 ml). The reaction mixture was stirred at room temperature until starting material was dissolved (6 hours), kept at room temperature for additional 18 hours, and poured into ice-water. The precipitate was collected by filtration, washed with water and dried *in vacuo* to obtain **5a** (1.7 g, 96%), which was recrystallized from ethyl acetate-cyclohexane with silica gel, mp 199-201°; ir (potassium bromide): ν 1666, 1626 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 4.05 (s, 3H, CH$_3$), 7.42-7.49 (m, 1H, H-6), 7.50-7.56 (m, 2H, H-3'), 7.60-7.68 (m, 1H, H-4'), 7.84 (d, J = 8.7 Hz, 1H, H-8), 7.90-7.96 (m, 1H, H-7), 8.01 (dd, J = 1.8, 7.9 Hz, 1H, H-5), 8.14-8.18 (m, 2H, H-2'); ^{13}C nmr (DMSO-d$_6$): δ 37.4 (CH$_3$), 119.6 (C-8); 120.2 (C-4a), 124.5 (C-6), 125.9 (C-5), 128.5 (C-3'), 129.4 (C-2'), 132.9 (C-4'), 135.4 (C-1'), 136.8 (C-7), 143.0 (C-8a), 159.4 (C-2), 178.8 (CO), 183.0 (C-4); ms: (70 ev) m/z 296 (14%, M^{+}), 105 (100%).

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82. Found: C, 64.49; H, 4.35; N, 9.63; S, 11.07.

1-Methyl-2-(4-methylbenzoyl)imino-1,2-dihydro-4*H*-3,1-benzothiazin-4-one (**5b**).

This compound was prepared from **4b** according to the procedure outlined above in a yield of 94%, mp 200-202° (ethyl acetate-cyclohexane); ir (potassium bromide): ν 1646, 1620 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.39 (s, 3H, CH$_3$), 4.03 (s, 3H, NCH$_3$), 7.33 (d, J = 8.3 Hz, 2H, H-3'), 7.41-7.48 (m, 1H, H-6), 7.82 (d, J = 8.5 Hz, 1H, H-8), 7.88-7.95 (m, 1H, H-7), 8.00 (dd, J = 1.7, 7.8 Hz, 1H, H-5), 8.05 (d, J = 8.3 Hz, 2H, H-2'); ^{13}C nmr (DMSO-d$_6$): δ 21.2 (CH$_3$), 37.3 (NCH$_3$), 119.6 (C-8), 120.1 (C-4a), 124.4 (C-6), 125.9 (C-5), 129.1 (C-3'), 129.5 (C-2'), 132.7 (C-1'), 136.8 (C-7), 143.0 (C-4'), 143.2 (C-8a), 158.9 (C-2), 173.7 (CO), 183.1 (C-4); ms: (70 ev) m/z 310 (14%, M^{+}), 119 (100%).

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.71; H, 4.66; N, 9.02; S, 10.66.

2-(3-Benzoyl-1-methylthioureido)benzoic Acid (**6a**).

A solution of benzoyl isothiocyanate in acetone (60 mmoles in 30 ml) was prepared and cooled to 0°. *N*-Methylanthranilic acid (4.53 g, 30 mmoles) dissolved in dry acetone (90 ml) was added. The mixture was kept at room temperature for 2 hours and cooled overnight. The solution was concentrated *in vacuo* at room temperature to 60 ml and diluted with diethyl ether (60 ml). Next day, the precipitate was filtered off to obtain 5.9 g (63%) of **6a**. To prepare an analytical sample, material was dissolved in ethanol at room temperature and treated with water, mp 121-124; ir (potassium bromide): ν 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 61.55; H, 4.63; N, 9.32; S, 9.88.

2-[3-(4-Methylbenzoyl)-1-methylthioureido]benzoic Acid (**6b**).

This compound was prepared in a yield of 62% from 4-methylbenzoyl isothiocyanate and *N*-methylanthranilic acid using the procedure given above. To prepare an analytical sample, material was dissolved in ethyl acetate at room temperature and treated with petroleum ether, mp 128-130°; ir (potassium bromide): ν 1694 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.08; H, 5.08; N, 8.49; S, 10.10.

Methyl 2-Benzoylimino-3-methyl-2,3-dihydrobenzothiazole-4-carboxylate (**7a**).

Compound **4a** (984 mg, 3 mmoles) in acetic acid (50 ml) was treated dropwise with bromine (480 mg, 3 mmoles) in acetic acid (10 ml) during 10 minutes. The mixture was stirred at room temperature for 30 minutes. The red precipitate was collected by filtration and partionated between ethyl acetate (80 ml) and water (80 ml). The organic layer was dried (sodium sulfate) and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate-petroleum ether to obtain **7a** (411 mg, 42%) as colorless needles, mp 172-173°; ir (potassium bromide): ν 1716, 1608 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 3.90 (s, 3H, NCH$_3$), 3.98 (s, 3H, OCH$_3$), 7.44 (t, J = 7.7 Hz, 1H, H-6), 7.51-7.64 (m, 3H, H-3, and H-4'), 7.73 (dd, J = 1.2, 7.7 Hz, 1H, H-7), 8.13 (dd, J = 1.2, 7.7 Hz, 1H, H-5), 8.27-8.32 (m, 2H, H-2'); ms: (70 ev) m/z 326 (58%, M$^+$), 105 (100%).

Anal. Calcd. for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; N, 8.58; S, 9.82. Found: C, 62.35; H, 4.66; N, 8.39; S, 10.31.

Methyl 3-Methyl-2-(4-methylbenzoyl)imino-2,3-dihydrobenzothiazole-4-carboxylate (**7b**).

This compound was prepared from **4b** according to the procedure outlined above. After 30 minutes, unsoluble material was removed by suction filtration. The solution was kept at room temperature for additional 5 hours. The resulting yellow precipitate was filtered off and recrystallized from methanol to obtain 460 mg (45%) of **7b** as colorless needles; mp 164-165°; ir (potassium bromide): ν 1727, 1607 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.38 (s, 3H, CH$_3$), 3.87 (s, 3H, NCH$_3$), 3.97 (s, 3H, OCH$_3$), 7.32 (d, J = 8.1 Hz, 2H, H-3'), 7.42 (t, J = 7.7 Hz, 1H, H-6), 7.71 (dd, J = 1.3, 7.7 Hz, 1H, H-7), 8.10 (dd, J = 1.3, 7.7 Hz, 1H, H-5), 8.17 (d, J = 8.1 Hz, 2H, H-2'); ms: (FAB) m/z 341 (MH$^+$).

Anal. Calcd. for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.67; H, 4.80; N, 8.35; S, 9.53.

3-Benzoyl-1-methylquinazoline-2,4(1*H*,3*H*)-dione (**8a**).

Compound **6a** (942 mg, 3 mmoles) in ethyl acetate (100 ml) was treated dropwise with bromine (480 mg, 3 mmoles) in ethyl acetate (10 ml) during 10 minutes. The mixture was stirred at room temperature for 40 minutes. Silica gel was added and the mixture was filtrated into petroleum ether. The precipitate formed was collected to obtain pure **8a** (180 mg, 21%), mp > 227° dec; ir (potassium bromide): ν 1740, 1698, 1662 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 3.62 (s, 3H, CH$_3$), 7.28-7.37 (m, 2H, aromatic), 7.46-7.53 (m, 2H, aromatic), 7.62-7.69 (m, 1H, aromatic), 7.74-7.82 (m, 1H, H-7), 7.96-8.01 (m, 2H, H-2'), 8.24 (dd, J = 1.5, 7.8 Hz, 1H, H-5); ^{13}C nmr (deuteriochloroform): δ 30.2 (CH$_3$), 114.1 (C-8), 115.6 (C-4a), 123.6 (C-6), 129.0 (C-5), 129.2 (C-3'), 130.5 (C-2'), 131.8 (C-1'), 135.0 (C-4'), 136.1 (C-7), 141.2 (8a), 149.5 (C-2), 161.2 (CO), 168.8 (C-4); ms: (70 ev) m/z 280 (4%, M$^+$), 105 (100%).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.28; H, 4.65; N, 9.77.

1-Methyl-3-(4-methylbenzoyl)quinazoline-2,4(1*H*,3*H*)-dione (**8b**).

This compound was prepared in a yield of 25% from **6b** using the procedure given above, mp >216 dec; ir (potassium bromide): ν 1744, 1698, 1672 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.41 (s, 3H, CH$_3$), 3.51 (s, 3H, NCH$_3$), 7.34-7.42 (m, 3H, H-6 and H-3'), 7.56 (d, J = 8.5 Hz, 1H, H-8), 7.84-7.91 (m, 1H, H-7), 7.95 (d, J = 8.1 Hz, 2H, H-2'), 8.05 (dd, J = 1.4, 7.7 Hz, 1H, H-5); ms: (70 ev) m/z 294 (8%, M$^+$), 119 (100%).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.16; H, 4.96; N, 9.43.

Methyl 3-(3-Benzoylthioureido)-2-thiophenecarboxylate (**9a**).

Methyl 3-amino-2-thiophenecarboxylate (4.71 g, 30 mmoles) was dissolved in dry acetone (25 ml). A solution of benzoyl isothiocyanate in acetone (60 mmoles in 30 ml) was added. The mixture was refluxed for one hour and kept at 0° overnight. The precipitate was filtered off to obtain **9a** (7.3 g, 76%), mp 144-145° (methanol); ir (potassium bromide): ν 1700, 1682 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 3.89 (s, 3H, CH$_3$), 7.50-7.72 (m, 3H, H-3, and H-4'), 7.93 (d, J = 5.5 Hz, 1H, H-4), 7.99-8.05 (m, 2H, H-2'), 8.58 (d, J = 5.5 Hz, 1H, H-5), 11.70 (s, 1H, NH), 13.73 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{12}N_2O_3S_2$: C, 52.49; H, 3.78; N, 8.74. Found: C, 52.84; H, 4.01; N, 8.79.

Methyl 3-[3-(4-Methylbenzoyl)thioureido]-2-thiophenecarboxylate (**9b**).

This compound was prepared from methyl 3-amino-2-thiophenecarboxylate and 4-methylbenzoyl isothiocyanate in a yield of 66% according to the procedure outlined above, mp 162-163° (methanol); ir (potassium bromide): ν 1690, 1675 cm^{-1} (C=O); ^{1}H nmr (DMSO-d$_6$): δ 2.39 (s, 3H, CH$_3$), 3.87 (s, 3H, OCH$_3$), 7.34 (d, J = 8.3 Hz, 2H, H-3'), 7.91 (d, J = 8.3 Hz, 2H, H-2'), 7.91 (d, J = 5.5 Hz, 1H, H-4), 8.53 (d, J = 5.5 Hz, 1H, H-5), 11.58 (s, 1H, NH), 13.72 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S_2$: C, 53.88; H, 4.22; N, 8.38. Found: C, 53.87; H, 3.99; N, 8.20.

2-Amino-4*H*-thieno[3,2-*d*][1,3]thiazin-4-one (**10**).

A mixture prepared from **9a** (3.2 g, 10 mmoles), 10 drops of water and concentrated sulfuric acid (25 ml) was heated for 4 hours at 100°. It was cooled and poured on a mixture of ice-water and sodium hydrogen carbonate. The precipitate was collected and washed with water to obtain 1.55 g (84%) of **10**, which was recrystallized from ethyl acetate-acetonitrile, mp >285° dec, conversion 245-259°; ir (potassium bromide): ν 1640 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 7.08 (d, J = 5.2 Hz, 1H, H-7), 8.13 (s, 2H, NH_2, exchangeable with deuterium oxide), 8.16 (d, J = 5.2 Hz, 1 H, H-6); ^{13}C nmr (DMSO-d_6): δ 112.6 (C-4a), 126.5 (C-7), 136.1 (C-6), 160.7 (C-7a), 163.2 (C-2), 174.3 (C-4); ms: (70 ev) m/z 184 (100%; M$^+$).

Anal. Calcd. for $C_6H_4N_2OS_2$: C, 39.12; H, 2.19; N, 15.21; S, 34.80. Found C, 39.44; H, 2.29; N, 14.84; S, 35.21.

2-Benzoylamino-4*H*-thieno[3,2-*d*][1,3]thiazin-4-one (**11a**).

This compound was prepared in a yield of 96% from **9a** according to the procedure followed in the preparation of **3b**, mp 230-233° (ethyl acetate); ir (potassium bromide): ν 1686, 1632 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 7.43 (d, J = 5.2 Hz, 1H, H-7), 7.51-7.57 (m, 2H, H-3'), 7.62-7.68 (m, 1H, H-4'), 8.03-8.07 (m, 2H, H-2'), 8.38 (d, J = 5.2 Hz, 1H, H-6), 12.49 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 118.7 (C-4a), 127.2 (C-7), 128.5 (C-2' and C-3'), 131.8 (C-1'), 133.1 (C-4'), 136.7 (C-6), 156.4 (C-7a), 159.4 (C-2), 167.0 (CO), 176.1 (C-4); ms: (70 ev) m/z 288 (23%, M$^+$), 105 (100%).

Anal. Calcd. for $C_{13}H_8N_2O_2S_2$: C, 54.15; H, 2.80; N, 9.72; S, 22.24. Found: C, 54.07; H, 2.76; N, 9.55; S, 22.32.

2-(4-Methylbenzoyl)amino-4*H*-thieno[3,2-*d*][1,3]thiazin-4-one (**11b**).

This compound was synthesized in a yield of 88% from **9b** following the procedure to prepare **3b**, mp 232-234° (ethyl acetate); ir (potassium bromide): ν 1676, 1630 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3); 7.35 (d, J = 8.1 Hz, 2H, H-3'), 7.44 (d, J = 5.3 Hz, 1H, H-7), 7.97 (d, J = 8.1 Hz, 2H, H-2'), 8.39 (d, J = 5.3 Hz, 1H, H-6), 12.41 (s, broad, 1H, NH); ms: (FAB) m/z 303 (MH$^+$).

Anal. Calcd. for $C_{14}H_{10}N_2O_2S_2$: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.76; H, 3.10; N, 9.38; S, 21.10.

2-(3-Benzoylthioureido)-4*H*-3,1-benzothiazin-4-one (**13a**).

2-Amino-4*H*-3,1-benzothiazin-4-one (**2**) [2] (3.56 g, 20 mmoles) was dissolved in dry acetone (150 ml). A solution of benzoyl isothiocyanate in acetone (40 mmoles in 20 ml) was added. The mixture was refluxed for 3 hours and kept at room temperature overnight. The precipitate was collected by filtration, washed with *n*-hexane and dried to obtain 2.10 g (31%) of **13a**, mp 159-161° (ethyl acetate); ir (potassium bromide): ν 1650 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 7.52-7.72 (m, 5H, aromatic), 7.85-7.91 (m, 1H, H-7), 7.96-8.00 (m, 2H, H-2'), 8.04 (d, J = 7.8 Hz, 1H, H-5), 12.33 (s, broad, 1H, NH), 13.44 (s, broad, 1H, NH).

Anal. Calcd. for $C_{16}H_{11}N_3O_2S_2$: C, 56.29; H, 3.25; N, 12.31; S, 18.78. Found: C, 56.22; H, 3.41; N, 12.12; S, 18.35.

2-[3-(4-Methylbenzoyl)thioureido]-4*H*-3,1-benzothiazin-4-one (**13b**).

This compound was prepared in a yield of 44% from **2** and 4-methylbenzoyl isothiocyanate using the procedure given above, mp 189-191° (ethyl acetate-DMF); ir (potassium bromide): ν 1648 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 2.41 (s, 3H, CH_3); 7.38 (d, J = 8.1 Hz, 2H, H-3'), 7.54-7.66 (m, 2H, H-6 and H-8), 7.88-7.94 (m, 3H, H-2' and H-7), 8.06 (d, J = 8.3 Hz, 1H, H-5), 12.22 (s, broad, 1H, NH), 13.53 (s, broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S_2$: C, 57.45; H, 3.69; N, 11.82; S, 18.04. Found: C, 57.67; H, 3.99; N, 11.85; S, 18.17.

2-(3-Benzoylthioureido)-6-methyl-4*H*-3,1-benzothiazin-4-one (**14a**).

2-Amino-6-methyl-4*H*-3,1-benzothiazin-4-one (**12**) [2] (3.84 g, 20 mmoles) was dissolved in dry acetone (180 ml). A solution of benzoyl isothiocyanate in acetone (40 mmoles in 20 ml) was added. The mixture was refluxed for 3 hours. Next day, the precipitate was filtered off, washed with *n*-hexane and dried to obtain **14a** (2.0 g, 28%), mp 181-184° (ethyl acetate-DMF); ir (potassium bromide): ν 1650 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 7.53-7.60 (m, 3H, aromatic), 7.66-7.77 (m, 2H, aromatic), 7.87 (s, 1H, H-5), 7.96-8.00 (m, 2H, H-2'), 12.15 (s, broad, 1H, NH), 13.50 (s, broad, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}N_3O_2S_2$: C, 57.45; H, 3.69; N, 11.82; S, 18.04. Found: C, 57.83; H, 4.10; N, 12.12; S, 17.80.

6-Methyl-2-[3-(4-methylbenzoyl)thioureido]-4*H*-3,1-benzothiazin-4-one (**14b**).

This compound was prepared from **12** and 4-methylbenzoyl isothiocyanate in a yield of 31% according to the procedure outlined above, mp 179-180° (ethyl acetate-DMF); ir (potassium bromide): ν 1654 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 2.41 (s, 3H, 4'-CH_3), 2.44 (s, 3H, 6-CH_3), 7.37 (d, J = 8.1 Hz, 2H, H-3'), 7.55 (d, J = 8.3 Hz, 1H, H-8), 7.71-7.75 (m, 1H, H-7), 7.86 (s, 1H, H-5), 7.90 (d, J = 8.1 Hz, 2H, H-2'), 12.16 (s, broad, 1H, NH), 13.36 (s, broad, 1H, NH).

Anal. Calcd. for $C_{18}H_{15}N_3O_2S_2$: C, 58.52; H, 4.09; N, 11.37; S, 17.36. Found: C, 58.68; H, 4.14; N, 11.45; S, 17.51.

2-Benzoylimino-2*H*,5*H*-[1,2,4]thiadiazolo[2,3-*a*][3,1]benzothiazin-5-one (**15a**).

A mixture of **13a** (1.71 g, 5 mmoles), *N*-bromosuccinimide (890 mg, 5 mmoles), and concentrated sulfuric acid (12 ml) was kept at room temperature for 3 days. The mixture was poured into ice-water (150 ml). The precipitate was collected by filtration, washed with water, sodium hydrogen carbonate solution and again with water, and dried. The crude product was recrystallized from ethyl acetate-2-methoxyethanol to obtain **15a** (1.18 g, 70%) as colorless crystals, mp 233-237°; ir (potassium bromide): ν 1666, 1596 cm^{-1} (C=O); ^{1}H nmr (pyridine-d_5): δ 7.41-7.55 (m, 4H, aromatic), 7.79-7.86 (m, 1H, H-8), 7.99 (d, J = 8.2 Hz, 1H, H-9), 8.19 (dd, J = 1.6, 8.0 Hz, 1H, H-6), 8.59-8.64 (m, 2H, H-2'); ms: (70 ev) m/z 339 (3%, M$^+$), 105 (100%).

Anal. Calcd. for $C_{16}H_9N_3O_2S_2$: C, 56.62; H, 2.67; N, 12.38; S, 18.89. Found: C, 56.83; H, 3.04; N, 12.43; S, 18.56.

2-(4-Methylbenzoyl)imino-2*H*,5*H*-[1,2,4]thiadiazolo[2,3-*a*]-[3,1]benzothiazin-5-one (**15b**).

This compound was prepared from **13b** and concentrated sulfuric acid according to the procedure given above, but no *N*-bromosuccinimide was used. Recrystallization from ethyl acetate-DMF gave **15b** in a yield of 78%, mp 282-283°; ir (potassium bromide): ν 1666, 1596 cm^{-1} (C=O); ^{1}H nmr (pyridine-d_5): δ 2.27 (s, 3H, CH_3), 7.31 (d, J = 8.1 Hz, 2H, H-3'), 7.40-7.47 (m, 1H, H-7), 7.78-7.85 (m, 1H, H-8), 7.99 (d, J = 8.5 Hz, 1H, H-9), 8.19 (dd, J = 1.4, 8.1 Hz, 1H, H-6), 8.54 (d, J = 8.1 Hz, 2H, H-2'); ms: (70 ev) m/z 353 (36%, M$^+$), 119 (100%).

Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.78; H, 3.14; N, 11.89; S, 18.14. Found: C, 57.75; H, 3.49; N, 12.19; S, 18.59.

2-Benzoylimino-7-methyl-2*H*,5*H*-[1,2,4]thiadiazolo[2,3-*a*]-[3,1]benzothiazin-5-one (**16a**).

This compound was prepared from **14a** according to the procedure followed in the preparation of **15a**. Recrystallization from ethyl acetate-2-methoxyethanol gave **16a** in a yield of 71%, mp 259-261°; ir (potassium bromide): ν 1664, 1608 cm^{-1} (C=O); ^{1}H nmr (pyridine-d$_5$): δ 2.29 (s, 3H, CH$_3$), 7.46-7.55 (m, 3H, H-3' and H-4'), 7.63-7.68 (m, 1H, H-8), 7.93 (d, J = 8.4 Hz, 1H, H-9), 8.00 (s, 1H, H-6), 8.61-8.66 (m, 2H, H-2'); ms: (70 ev) m/z 353 (21%, M$^+$), 105 (100%).

Anal. Calcd. for $C_{17}H_{11}N_3O_2S_2$: C, 57.78; H, 3.14; N, 11.89; S, 18.14. Found: C, 57.32; H, 3.18; N, 11.84; S, 17.70.

7-Methyl-2-(4-methylbenzoyl)imino-2*H*,5*H*-[1,2,4]thiadiazolo[2,3-*a*][3,1]benzothiazin-5-one (**16b**).

This compound was synthesized from **14b** and concentrated sulfuric acid according to the procedure followed in the preparation of **15a**, but no *N*-bromosuccinimide was used. Recrystallization from ethyl acetate-DMF gave **16b** in a yield of 72%, mp 254-257°; ir (potassium bromide): ν 1668, 1605 cm^{-1} (C=O); ^{1}H nmr (pyridine-d$_5$): δ 2.27 (s, 3H, CH$_3$), 2.28 (s, 3H, CH$_3$), 7.30 (d, J = 8.1 Hz, 2H, H-3'), 7.62-7.67 (m, 1H, H-8), 7.91 (d, J = 8.2 Hz, 1H, H-9), 7.98 (s, 1H, H-6), 8.54 (d, J = 8.1 Hz, 2H, H-2'); ms: (70 ev) m/z 367 (35%, M$^+$), 119 (100%).

Anal. Calcd. for $C_{18}H_{13}N_3O_2S_2$: C, 58.84; H, 3.57; N, 11.44; S, 17.45. Found: C, 58.78; H, 3.73; H, 11.19; S, 17.03.

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