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Cyclobutane-Substituted Diacetamido Sulfides and 2,5-Diacylthiophenes

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ABSTRACT: *A general and convenient route for the synthesis of 2,5-di[1-methyl-1-arylcyclobutane-3-yl]-thiophenes* **4a–c** *and bis[1-methyl-1-arylcyclobutane-3-yl]-2-(2-oxyethtylamido)thiazole sulfides* **7a–c** *is reported. The characterization of these compounds was obtained by elemental analyses, IR,* ^{13}C*, and* ^{1}H *NMR techniques.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:26–31, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10207

INTRODUCTION

The formation of substituted cyclobutanes from the reaction of 1-chloro-2,3-epoxy-5-methyl-5-hexene with aromatic hydrocarbons such as benzene, xylene, toluene, naphthalenes, and mesitylene has been reported [1–3]. Aryl-substituted cyclobutanes obtained from this kind of reactions are chlorohydrin derivates as well. It is well known that 3-substituted cyclobutane carboxylic acid derivatives exhibit antiinflammatory and antidepressant activities [4,5] and liquid crystal properties [6]. Various thiazole derivatives show herbicidal [7], antiinflammatory [8,9], antimicrobial [10], or antiparasitic activity [11].

Diketo sulfides of the type $RCOCH_2SCH_2COR$ have two methylene groups activated by both a carbonyl and a sulfide group, and are considered to be suitable for condensation with 1,2-dicarbonyl compounds providing a thiophene nucleus. When R is *O*-alkyl, i.e., thiodiacetic acid ester, the reaction is the well-known Hinsberg thiophene synthesis and has been used extensively to prepare 3,4-disubstituted thiophene derivates [12]. However, the extension of the Hinsberg reaction to diketo sulfides (R = alkly or aryl) has long been unreported in spite of the mention of this possibility by Hinsberg in his first paper [13]. On the other hand, several successful condensations of diketo sulfides with vicinal dialdehydes affording thiepin derivates or the corresponding sulfur-eliminated aromatized products are known [14]. It was expected, therefore, that the condensation of diketo sulfides with glyoxal, the simplest dialdehyde, affording the more stable thiophene ring, might be more facile.

While in the Hinsberg reaction strong bases in high concentrations can and must be used [15], in the reaction of diketo sulfides having very reactive methylenes and keto-carbonyl groups in the same molecule, the use of strong basic conditions brought about extensive self-condensations. The Cannizzaro reaction of glyoxal may also occur, as evidenced by the immediate precipitation of sodium glycolate upon addition of sodium alkoxide to a solution of glyoxal in alcohol. When the reaction was carried out under the following mild conditions, the desired condensations were found to occur efficiently in preference to these side reactions. Thus, when a dilute solution of sodium methoxide was slowly added to a stirred solution of a diketo sulfide and glyoxal in methanol and, if necessary, a cosolvent such as dioxane at approximately room temperature, 2,5-diacylthiophene **4a–c** began to precipitate, generally in just a few minutes. To obtain pure products directly in high yields the base solution must be added very slowly, especially at the beginning of

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the reaction when most of the starting materials are present unreacted.

In the past 15 years much progress has been made in the synthetic chemistry of thiophenes. We have contributed by developing a new thiophene synthesis and by obtaining a thiophene derivative, which involves cyclobutane ring. The results are given in the Experimental section.

RESULTS AND DISCUSSION

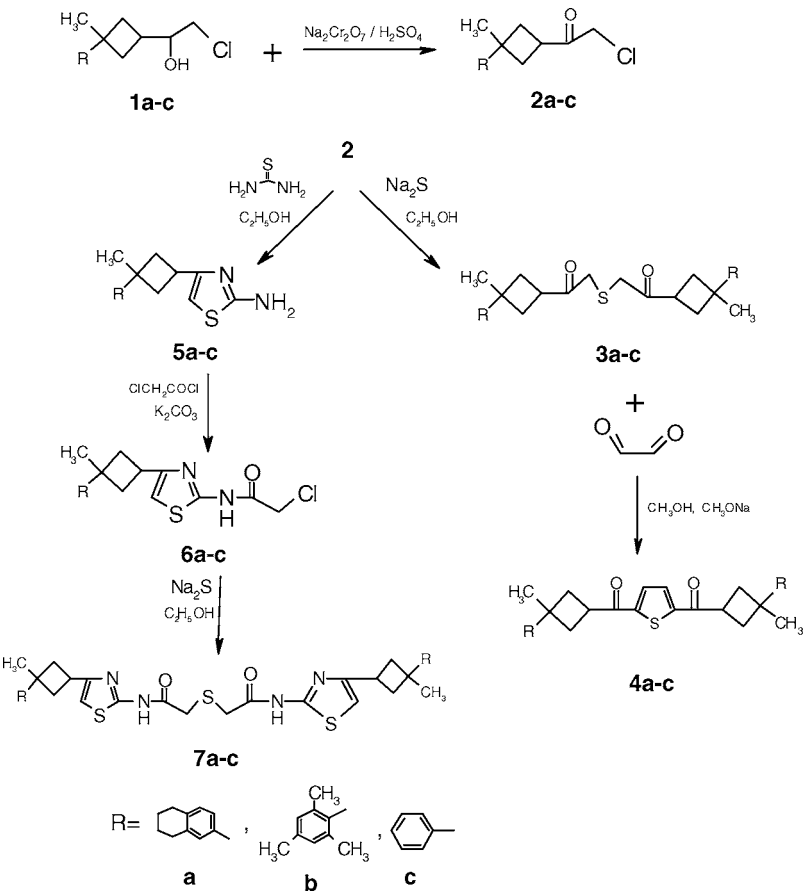
The reactions for the synthesis of **2–7** are shown in Scheme 1. The first step is the synthesis of **2a–c** from the reaction of 1-aryl-1-methyl-3-(2-chloro-1-hydroxyethyl)cyclobutane **1a–c** and $Na_2Cr_2O_7$/H_2SO_4. In the second step we obtain bis[1-methyl-1-arylcyclobutane-3-yl]-3-(1-oxyethyl)sulfide **3a–c** from the reaction of Na_2S and **2**. We obtained cyclobutane-substituted 2,5-diacylthiophenes **4a–c** from the reaction of **3a–c** with glyoxal in methanol. Cyclocondensation of chloroketones **2a–c** with thiourea in ethanol resulted in cyclobutane-2-aminothiazoles **5a–c**.

When chloroacetyl chloride is added to **5a–c** in the presence of potassium carbonate, **6a–c** are obtained. Reaction of **6a–c** with Na_2S in ethanol gives the cyclobutane-substituted diacetamido sulfides **7a–c**.

In the IR spectrum of **5a–c** the most characteristic absorptions are at 3285 and 3310 cm^{-1} $\nu(-NH_2)$, 3275 and 3200 cm^{-1} ν(sec-NH), 1604 cm^{-1} $\nu(C{=}N)$, and 685 cm^{-1} $\nu(C{-}S{-}C)$. Since there are no C—Cl and C=O bands in the IR spectra, these peaks indicate the formation of the expected compound. The data of the all compounds are given in the Experimental section.

EXPERIMENTAL

Tetraline, mesitylene, and benzene were purchased from Merck and used as received. 1-Chloro-5-methyl-2,3-epoxy-5-hexene was synthesized according to the general procedure described earlier [1], starting from the acrolein and dry chlorine and subsequently isobutylene. 1-Chloro-5-methyl-2,3-epoxy-5-hexene was received from an organic chemist in



SCHEME 1

the department of chemistry at the University of Firat and was freshly distilled before use. Melting points were determined on a Thomas Hovver melting point apparatus and are uncorrected, but checked by differential scanning calorimeter. The IR spectra were measured with Mattson 1000 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker WM-400 MHz Varian Gemini 200 MHz and Jeol FX-90Q spectrometers and are reported in ppm (δ) relative to tetramethylsilane as the internal standard and ^{13}C NMR (75.5, 49.5, and 22.4 MHz) are referenced to deuterochloroform ($CDCl_3$). Column chromatography was performed using Merck silica gel, 70–230 mesh. Solvents were dried and purified by known methods [16].

1-Aryl-1-methyl-3-(2-chloro-1-hydroxyethyl)cyclobutanes **1** were prepared according to a method given in the literature [1]. **2c** was synthesized by the method described in the literature [1] and purified through column chromatography prior to use. The yield was about 75%. IR: 1750 (C=O), 735 cm^{-1} (C—Cl; no O—H absorption).

*Synthesis of 1-Tetralino-1-methyl-3-(2-chloro-1-oxoethyl)cyclobutane (**2a**)*

$Na_2Cr_2O_7$ (0.29 mol), 0.52 mol of **1a**, and 50 ml of water were placed in 1000-ml four-necked flask fitted with a condenser, a thermometer, a stirrer, and an addition funnel containing 75 ml of H_2SO_4 (68%, v/v). The sulphuric acid solution was added over about 7–8 h, with the temperature maintained at room temperature. The reaction content was stirred at the same temperature for about 18 h more and then solid particles were filtered off. The filtrate was extracted several times with diethyl ether and dried over anhydrous $CaCl_2$. After removal of diethyl ether, **2a** was distilled off at 186°C (1 mmHg) and filtered through a column filled with silica gel (a 20/1 benzene/ethyl acetate mixture; R_f (retention time) = 0.48). The yield of the ketone was about 75%. IR: 1730 (C=O), 736 cm^{-1} (C—Cl; no OH absorption).

*Synthesis of 1-Mesityl-1-methyl-3-(2-chloro-1-oxoethyl)cyclobutane (**2b**)*

2b was synthesized in the same manner as **2a**, except that the product was crystallized rather than distilled. The melting point was 98°C, and the yield was about 75%. IR: 1728 (C=O), 738 cm^{-1} (C—Cl; no O—H absorption).

General Procedure for the Synthesis of **3**

To a stirred, refluxing solution of **2** (0.03 mol) in 30 ml of ethanol was added dropwise a solution of sodium sulfide nonahydrate (3.6 g; 0.015 mol) in 10 ml of water, over a period of 30 min; the solution was added more slowly toward the end of the addition to prevent orange coloration. After refluxing for an additional 30 min, the solution was allowed to cool slowly. Generally, pure crystals were obtained directly.

*Bis[1-methyl-1-(-2-tetralino)cyclobutane-3-yl)]-3-(1-oxyethyl)sulfide (**3a**).* White solid; yield 74%, mp 201–203°C. IR (KBr) υ: 1699 (C=O), 685 (C—S—C) cm^{-1}. ^1H NMR (DMSO-d_6) δ 6.81–7.38 (m, 6H, Ar—H), 3.29–3.53 (m, 6H, cyclobutane and —CH_2—S—CH_2 protons), 2.65–2.75 (m, 8H, tetraline —CH_2—), 2.29–2.64 (m, 8H, cyclobutane —CH_2—), 1.75–1.83 (m, 8H, tetraline —CH_2—), 1.57 (s, 6H, —CH_3). ^{13}C NMR (DMSO, TMS, δ ppm): 204.65(C_1), 150.16(C_2), 153.01(C_3), 149.02(C_4), 123.21(C_5), 48.98(C_6), 48.89 (C_7), 41.89(C_8), 32.07(C_9), 31.79(C_{10}), 25.51(C_{11}), 25.40(C_{12}), 24.97(C_{13}). Anal calcd for $C_{34}H_{42}O_2S$ (514): C, 79.33; H, 8.22; S, 6.23. Found: C, 78.21; H, 8.19; S, 6.21.

*Bis[1-methyl-1-mesitylcyclobutane-3-yl]-3-(1-oxyethyl)sulfide (**3b**).* White solid; yield 77%, mp 194–195°C. IR (KBr) υ: 1695 (C=O), 690 (C—S—C) cm^{-1}. ^1H NMR (DMSO-d_6) δ 6.71 (s, 4H, Ar—H), 3.31–3.54 (m, 6H, cyclobutane and —CH_2—S—CH_2 protons), 2.22–2.51 (m, 8H, —CH_2— in cyclobutane ring), 2.16 (s, 18H, mesityl —CH_3), 1.49 (s, 6H, —CH_3). ^{13}C NMR (DMSO, TMS, δ ppm): 207.97(C_1), 145.09(C_2), 136.23(C_3), 135.66(C_4), 131.79(C_5), 42.24(C_6), 41.82(C_7), 40.15(C_8), 26.46(C_9), 21.85(C_{10}) Anal calcd for $C_{32}H_{42}O_2S$ (490): C, 78.32; H, 8.63; S, 6.53. Found: C, 78.63; H, 8.21; S, 6.33.

*Bis[1-methyl-1-phenylcyclobutane-3-yl]-3-(1-oxyethyl)sulfide (**3c**).* White solid; yield 72%, mp 188–189°C. IR (KBr) υ: 1700 (C=O), 688 (C—S—C) cm^{-1}. ^1H NMR (DMSO-d_6) δ 6.88–7.44 (m, 10H, Ar—H), 3.26–3.55 (m, 6H, cyclobutane and —CH_2—S—CH_2 protons), 2.25–2.56 (m, 8H, —CH_2— in cyclobutane ring), 1.48 (s, 6H, —CH_3). ^{13}C NMR (DMSO, TMS, δ ppm): 206.93(C_1), 144.09(C_2), 135.23(C_3), 134.66 (C_4), 131.79(C_5), 42.23(C_6), 41.82(C_7), 40.15(C_8), 25.48(C_9), 21.85(C_{10}). Anal calcd for $C_{26}H_{30}O_2S$ (406): C, 76.81; H, 7.44; S, 7.89. Found: C, 76.63; H, 7.21; S, 7.53.

General Procedure for the Synthesis of **4**

A solution of glyoxal was prepared by refluxing a mixture of 168 mg (0.8 mmol, 2.4 mmol as a monomer) of glyoxal trimer dihydrate and (15 ml) of methanol for 1 h with stirring. The diketo sulfide

3 (2.0 mmol) was dissolved in the solution by heating the solution and, if necessary, addition of appropriate amount of a cosolvent such as dioxane (benzene and dichloromethane may also be used) to keep the diketo sulfide in solution. To the still warm (ca. 40–50°C) solution was added a solution of sodium methoxide (50 mg of sodium dissolved in 5 ml of methanol) dropwise via a hypodermic syringe over a period of 5–10 min. In the course of the addition, crystals began to precipitate and rapidly a thick slurry was formed. After stirring for 30 min, the crystals were collected by filtration and washed with methanol. The filtrate was diluted with water and the precipitate was collected and recrystallized.

*2,5-Di[1-methyl-1-(-2-tetralino)cyclobutane-3-yloyl]thiophene (***4a***).* White solid; yield 75%, mp 267–268°C. IR (KBr) υ: 1680 (C=O), 692 (C–S–C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 7.68 (s, 2H, thiophene protons), 6.80–7.37 (m, 6H, Ar–H), 3.87 (quint, 2H, J = 8.98, 2CH, cyclobutane), 2.66–2.78 (m, 8H, tetraline $-CH_2$), 2.29–2.65 (m, 8H, cyclobutane $-CH_2-$), 1.74–1.83 (m, 8H, tetraline $-CH_2$), 1.53 (s, 6H, $-CH_3$). ^{13}C NMR (DMSO, TMS, δ ppm): 195.83(C_1), 149.48(C_2), 145.19(C_3), 136.87(C_4), 133.28(C_5), 132.42 (C_6), 42.78(C_7), 42.49(C_8), 40.54(C_9), 32.06(C_{10}), 31.81(C_{11}), 27.29(C_{12}). Anal calcd for $C_{36}H_{40}O_2S$ (536): C, 80.55; H, 7.51; S, 5.97. Found: C, 79.82; H, 7.21; S, 5.63.

*2,5-Di[1-methyl-1-mesitylcyclobutane-3-yloyl]thiophene (***4b***).* White solid; yield 78%, mp 242–243°C. IR (KBr) υ: 1678 (C=O), 680 (C–S–C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 7.70 (s, 2H, thiophene protons), 6.79 (s, 4H, Ar–H), 3.88 (quint, 2H, J = 9.02, 2CH, cyclobutane), 2.55–2.95 (m, 8H, cyclobutane $-CH_2$), 2.25–2.36 (s, 18H, mesityl $-CH_3-$), 1.69 (s, 6H, $-CH_3$). ^{13}C NMR (DMSO, TMS, δ ppm): 195.82 (C_1), 149.45(C_2), 145.19(C_3), 136.88(C_4), 133.23(C_5), 132.41(C_6), 42.78(C_7), 42.49(C_8), 40.55(C_9), 27.28 (C_{10}), 23.26(C_{11}), 22.36(C_{12}). Anal calcd for $C_{34}H_{40}O_2S$ (512): C, 79.64; H, 7.86; S, 6.25. Found: C, 78.97; H, 7.79; S, 6.11.

*2,5-Di[1-methyl-1-phenylcyclobutane-3-yloyl]thiophene (***4c***).* White solid; yield 68%, mp 217–218°C. IR (KBr) υ: 1670 (C=O), 675 (C–S–C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 7.69 (s, 2H, thiophene protons), 6.90–7.48 (m, 10H, Ar–H), 3.86 (quint, 2H, J = 9.00, 2CH, cyclobutane), 2.46–2.58 (m, 8H, cyclobutane $-CH_2$), 1.53 (s, 6H, $-CH_3$). ^{13}C NMR (DMSO, TMS, δ ppm): 196.82(C_1), 149.41(C_2), 145.23 (C_3), 136.86(C_4), 133.28(C_5), 132.41(C_6), 42.78(C_7), 42.48(C_8), 40.55(C_9), 27.26(C_{10}) Anal calcd for $C_{28}H_{28}O_2S$ (428): C, 78.47; H, 6.58; S, 7.48. Found: C, 77.93; H, 6.38; S, 7.11.

*Synthesis of 4-[1-Methyl-1-(-2-tetralino)-cyclobutane-3-yl]-2-aminothiazole (***5a***)*

The course of the reaction was monitored by IR spectroscopy. To a solution of 0.76 g (10 mmol) of thiourea in 50 ml of absolute ethanol, a solution of 2.76 g (10 mmol) of **2a** in 30 ml of absolute ethanol was added dropwise at 50–60°C with continuous stiring. By monitoring the IR frequency of the carbonyl group of **2a**, the completion of the reaction was easily seen. The solution was then made alkaline with an aqueous solution of NH_3 (5%) to separate the pale white **5a** from the reaction mixture. The precipitate was filtered off, washed with aqueous ammonia solution and water several times, dried in air, and recrystallized from aqueous ethanol (1:3). Yield (74%). White solid; mp 222–223°C. IR (KBr) υ: 3285–3310 ($-NH_2$), 1604 (C=N, 685 (C–S–C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 6.86–7.06 (m, 3H, Ar–H), 5.95 (s, 1H, =CH–S in thiazole ring), 5.48 (s, 2H, $-NH_2$), 3.52 (quint, 1H, J = 8.80, CH, cyclobutane), 2.76–2.80 (m, 4H the alicyclic protons of tetralin as two broad.), 2.33–2.55 (m, 4H, $-CH_2-$ cyclobutane), 1.81–1.84 (m, 4H, the alicyclic protons of tetralin), 1.54 (s, 3H,CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 170.60(C_1), 157.85(C_2), 152.09(C_3), 42.55(C_4), 40.18(C_5), 32.66(C_6), 31.50(C_7), 31.05(C_8), 138.87(C_9), 136.18(C_{10}), 131.04(C_{11}), 127.52(C_{12}), 124.30(C_{13}), 102.27(C_{14}), 25.35(C_{15}), 25.31(C_{16}). Anal calcd for $C_{18}H_{22}N_2S$ (298): C, 72.44; H, 7.43; N, 9.39; S, 10.74. Found: C, 72.10; H, 7.41; N, 8.93; S,10.68.

*Synthesis of 4-[1-Methyl-1-mesitylcyclobutane-3-yl]-2-aminothiazole (***5b***)*

5b was synthesized in the same manner as **5a**, except that the product was crystallized from aqueous methanol (1:4). Yield (65%). White solid; mp 243–244°C. IR (KBr) υ: 3290–3313 ($-NH_2$), 1605 (C=N, 688 (C–S–C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 6.70 (s, 2H, Ar–H), 5.96 (s, =CH– in thiazole ring), 5.44 (s, 2H, $-NH_2$), 3.50 (quint, 1H, J = 9.00, CH cyclobutane), 2.55 (m, 4H, $-CH_2-$ cyclobutane), 2.21 (s, 3H, mesityl $-CH_3$), 2.14 (s, 6H, mesityl $-CH_3$), 1.49 (s, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 170.53(C_1), 157.86(C_2), 130.30(C_3), 127.41(C_4), 126.98(C_5), 126.96 (C_6), 102.56(C_7), 42.43(C_8), 40.62(C_9), 32.73(C_{10}), 32.24(C_{11}), 26.45(C_{12}), 23.38(C_{13}). Anal calcd for $C_{17}H_{22}N_2S$ (286): C, 71.28; H, 7.74; N, 9.78; S, 11.19. Found: C, 71.13; H, 7.51; N, 9.21; S, 10.99.

*Synthesis of 4-[1-Methyl-1-phenylcyclobutane-3-yl]-2-aminothiazole (**5c**)*

5c was synthesized in the same manner as **5a**, except that the product was crystallized from aqueous ethanol (1:4). Yield (70%). Light yellow solid; mp 174–175°C. IR (KBr) υ: 3282–3309 (—NH_2), 1603 (C=N, 687 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 7.14–7.39 (m, 5H, Ar—H), 5.99 (s, 1H, =CH— in thiazole ring), 5.44 (s, 2H, —NH_2), 3.51 (quint, 1H $J = 7$, CH cyclobutane), 2.40 (m, 4H, —CH_2— cyclobutane), 1.53 (s, 3H, —CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 170.53(C_1), 157.83(C_2), 130.30(C_3), 127.41(C_4), 126.97(C_5), 126.94(C_6), 102.51(C_7), 42.41(C_8), 40.59(C_9), 32.74(C_{10}), 32.51(C_{11}). Anal calcd for $C_{14}H_{16}N_2S$ (244): C, 68.82; H, 6.60; N, 11.46; S, 13.12. Found: C, 68.60, H, 6.37; N, 11.09; S, 12.85.

*Synthesis of 4-[1-Methyl-1-(-2-tetralino)cyclobutane-3-yl]-2-(2-chloroacetamido)thiazole (**6a**)*

A sample of 1.35 g (0.012 mol) of chloroacetylchloride was added dropwise with continuous stirring to a mixture of 3.57 g (0.012 mol) of cyclobutanethiazole **5a** and 1.7 g of (0.012 mol) of potassium carbonate in 15 ml benzene. After 4 h, the precipitate of **6a** was filtered off, washed with water, and crystallized from ethanol. White solid; yield 81%, mp 178–179°C. IR (KBr) υ: 3298 (—NH), 1676 (C=O), 1650 (C=N), 706 (C—Cl), 682 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 8.96–9.03 (br, 1H, —NH), 6.83–7.23, (m, 3H, Ar—H), 5.91 (s, 1H, =CH in thiazole ring), 4.09 (s, 2H, CH_2Cl), 3.57 (quint, 1H, $J = 8.80$, CH cyclobutane), 2.60–2.74 (m, 4H, —CH_2— tetraline), 2.18–2.56 (m, 4H, —CH_2— cyclobutane), 1.74–1.80 (m, 4H, CH_2 protons of tetralin), 1.52 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 174.30(C_1), 172.90(C_2), 160.50(C_3), 154.34 (C_4), 149.50(C_5), 138.98(C_6), 136.40(C_7), 131.09(C_8), 127.01(C_9), 79.60(C_{10}), 78.30(C_{11}), 78.10(C_{12}), 44.36 (C_{13}), 41.50(C_{14}), 40.85(C_{15}), 32.10(C_{16}), 31.52(C_{17}), 31.01(C_{18}), 29.93(C_{19}), 25.27(C_{20}). Anal calcd for $C_{20}H_{23}ClN_2OS$ (374): C, 60.70; H, 6.18; N, 7.47; S, 8.55. Found: C, 60.63; H, 6.01; N, 6.98; S, 8.23.

*Synthesis of 4-[1-Methyl-1-mesitylcyclobutane-3-yl]-2-(2-chloroacetamido)thiazole (**6b**)*

This compound was synthesized in the same manner as **6a**. White solid; yield 78%, mp 191–192°C. IR (KBr) υ: 3288 (—NH), 1678 (C=O), 1653 (C=N), 705 (C—Cl), 678 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 8.77–8.79 (br, 1H, —NH), 6.80–7.26 (s, 2H, Ar—H), 6.58 (s, 1H, =CH in thiazole ring), 4.25 (s, 2H, CH_2—Cl), 3.60 (quint, 1H, $J = 8.88$, CH cyclobutane), 2.41–2.70 (m, 4H, —CH_2— cyclobutane), 2.19–2.33 (s, 9H, —CH_3— mesityl), 1.64 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 165.65(C_1), 157.28(C_2), 157.49(C_3), 146.32(C_4), 137.17(C_5), 136.59(C_6), 132.35 (C_7), 109.33(C_8), 45.89(C_9), 43.90(C_{10}), 42.87(C_{11}), 33.30(C_{12}), 23.30(C_{13}), 22.32(C_{14}). Anal calcd for $C_{19}H_{23}ClN_2OS$ (362): C, 62.86; H, 6.39; N, 7.72; S, 8.83. Found: C, 62.56; H, 6.04; N, 7.53; S, 8.78.

*Synthesis of 4-[1-Methyl-1-phenylcyclobutane-3-yl]-2-(2-chloroacetamido)thiazole (**6c**)*

This compound was synthesized in the same manner as **6a**. White solid; yield 76%, mp 138–139°C. IR (KBr) υ: 3295 (—NH), 1673 (C=O), 1655 (C=N), 708 (C—Cl), 690 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 8.84–8.96 (br, 1H, —NH), 7.12–7.33, (m, 5H, Ar—H), 5.89 (s, 1H, =CH in thiazole ring), 3.96 (s, 2H, CH_2Cl), 3.59 (quint, 1H, $J = 9.00$, CH cyclobutane), 2.25–2.75 (m, 4H, —CH_2— cyclobutane), 1.48 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 213.00(C_1), 173.22(C_2), 170.50(C_3), 140.09(C_4), 133.78(C_5), 128.40 (C_6), 127.97(C_7), 124.50(C_8), 99.09(C_9), 63.30(C_{10}), 47.20(C_{11}), 43.10(C_{12}), 39.06(C_{13}), 30.01(C_{14}), 28.90 (C_{15}). Anal calcd for $C_{16}H_{17}ClN_2OS$ (320): C, 59.90; H, 5.34; N, 8.73; S, 9.99. Found: C, 59.43; H, 4.97; N, 8.25; S, 9.89.

*General Procedure for **7***

To a stirred, refluxing solution of **6** (0.02 mol) in 200 ml of ethanol was added dropwise a solution of sodium sulfide nonahydrate (0.01 mol) in 65 ml of water over a period of 25 min; the solution was added more slowly toward the end of the addition to prevent orange coloration. After refluxing for an additional 25 min, the solution was allowed to cool slowly. Generally, pure crystals were obtained directly.

*Bis[1-methyl-1-(-2-tetralino)cyclobutane-2-yl]-2-(2-oxyethylamido)thiazolesulfide (**7a**)*. White solid; yield 64%, mp 200–201°C. IR (KBr) υ: 3289 (—NH), 1665 (C=O), 672 (C—S—C) cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.93–9.01 (br, 2H, —NH), 6.81–7.23, (m, 6H, Ar—H), 5.93 (s, 2H, =CH in thiazole ring), 3.49–3.61 (m, 6H, CH_2—S, and cyclobutane —CH—), 2.61–2.73 (m, 8H, —CH_2 in tetraline ring), 2.18–2.57 (m, 8H, —CH_2— cyclobutane), 1.72–1.81 (m, 8H, CH_2 of tetralin), 1.52 (s, 6H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 171.55 (C_1), 158.28(C_2), 157.49(C_3), 155.79(C_4), 145.53(C_5), 137.09(C_6), 135.69(C_7), 132.33(C_8), 109.31(C_9), 78.35 (C_{10}), 78.15(C_{11}), 45.36(C_{12}), 44.33(C_{13}), 41.49(C_{14}), 40.85(C_{15}), 32.13(C_{16}), 31.54(C_{17}), 31.00(C_{18}), 29.83 (C_{19}), 25.26(C_{20}). Anal calcd for $C_{40}H_{46}N_4O_2S_3$ (710):

C, 67.57; H, 6.52; N, 7.88; S, 13.53. Found: C, 66.93; H, 6.21; N, 7.68; S, 13.02.

*Bis[1-methyl-1-mesitylcyclobutane-2-yl]-2-(2-oxyethylamido)thiazolesulfide (***7b***).* White solid; yield 68%, mp 214–215°C. IR (KBr) υ: 3282 (—NH), 1668 (C=O), 1653 (C=N), 683 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 7.77 (s, 2H, —NH), 6.78 (s, 4H, Ar—H), 6.46 (s, 2H, =CH in thiazole ring), 3.48–3.56 (m, 6H, CH_2—S, and —CH in cyclobutane), 2.55–2.65 (m, 8H, —CH_2— cyclobutane), 2.17–2.25 (s, 18H, —CH_3— mesityl), 1.64 (s, 6H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 170.55(C_1), 159.28(C_2), 158.49(C_3), 156.81 (C_4), 146.63(C_5), 137.17(C_6), 136.59(C_7), 132.35(C_8), 109.33(C_9), 45.89(C_{10}), 42.90(C_{11}), 42.87(C_{12}), 33.20 (C_{13}), 26.72(C_{14}), 23.30(C_{15}), 22.32(C_{16}). Anal calcd for $C_{38}H_{46}N_4O_2S_3$ (686): C, 66.44; H, 6.75; N, 8.16; S, 14.00. Found: C, 65.93; H, 6.22; N, 7.98; S, 13.97.

*Bis[1-methyl-1-phenylcyclobutane-2-yl]-2-(2-oxyethylamido)thiazolesulfide (***7c***).* White solid; yield 69%, mp 156–157°C. IR (KBr) υ: 3284 (—NH), 1663 (C=O), 1652 (C=N), 689 (C—S—C) cm^{-1}. ^1H NMR ($CDCl_3$-d_6) δ 12.13 (s, 2H, —NH), 7.13–7.36, (m, 10H, Ar—H), 6.79 (s, 2H, =CH in thiazole ring), 3.57–3.80 (m, 2H, CH in cyclobutane), 3.51 (s, 4H, —CH_2—S), 2.37–2.58 (m, 8H, —CH_2— cyclobutane), 1.52 (s, 6H, CH_3), ^{13}C NMR ($CDCl_3$, TMS, δ ppm): 211.00(C_1), 172.22(C_2), 171.50(C_3), 141.09(C_4), 136.78(C_5), 129.40 (C_6), 126.97(C_7), 124.50(C_8), 100.09(C_9), 48.11(C_{10}), 46.21(C_{11}), 43.10(C_{12}), 39.08(C_{13}), 31.01(C_{14}), 28.90 (C_{15}). Anal calcd for $C_{32}H_{34}N_4O_2S_3$ (602): C, 63.76; H, 5.68; N, 9.29; S, 15.96. Found: C, 63.82; H, 5.54; N, 8.96; S, 16.01.

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