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1,1,3-TRISUBSTITUTED CYCLOBUTANES CONTAINING THIAZOLE AND THIOUREA FRAGMENTS

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The synthesis of 1-aryl-3-(2-chloro-1-hydroxyethyl)-1-methylcyclobutanes, 1-aryl-3-(2-chloro-1-oxoethyl)-1-methylcyclobutanes, 2-amino-4-(3-aryl-3-methylcyclobutyl)thiazoles, and N-[4-(3-aryl-3-methylcyclobutyl)thiazole-2-yl]-N'-arylthioureas is reported.

Keywords: cyclobutanes, substituted thiazoles, substituted thioureas.

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]. The aryl-substituted cyclobutanes obtained are chlorohydrin derivatives, too.

Thiazole and its derivatives have biological significance, e.g., it is a struc- tural fragment of the vitamin B_1 and of the coenzyme cocarboxylase molecules [4]. The penicillin molecule also contains a thiazolidine ring. 2-Aminothiazoles are known mainly as biologically active compounds with a broad range of activities and as intermediates in the synthesis of antibiotics and dyes [5].

It is well known that 3-substituted cyclobutanecarboxylic acid derivatives exhibit anti-inflammatory and antidepressant activities [6, 7] and liquid crystal properties [8]. Various thiazole derivatives show herbicidal [9], anti-inflammatory [10, 11], antimicrobial [12], or antiparasitic activity [13]. 1,1,3-Tri- substituted cyclobutanes containing thiazole and thiourea functions in their molecules seem to be suitable candidates for further chemical modifications and might be of interest as pharmacologically active compounds and ligands useful in coordination chemistry.

Thiouracil moieties play a vital role in many biological processes and are used as intermediates for the synthesis of drugs [14, 15]. It is well known that derivatives of thiourea compounds exhibit anti-HIV activity [16, 17].

The syntheses of target compounds **1-4** are shown in the Scheme. The first step is the reaction of 1-aryl-3-(2-chloro-1-hydroxyethyl)-1-methylcyclobutanes **1a-c** and $Na_2Cr_2O_7/H_2SO_4$. In the second step cyclocondensation of chloro ketones **2a-c** obtained with thiourea in ethanol resulted in 2-amino-4-cyclobutylthiazoles **3a-c**. The latter undergo reaction with aryl isothiocyanates in dry C_6H_6 to give the corresponding N-substituted thiourea derivatives **4a-o.**

In the IR spectra of **3a-c, 4a-o** the most characteristic absoptions are at 3285 and 3310 cm^{-1} (NH_2), 3275 and 3200 cm^{-1} (*sec*-NH), 1460-1340 cm^{-1} (C=S), 1604 cm^{-1} (C=N), and 685 cm^{-1} (C–S–C). Since there are no C–Cl and C=O bonds in the IR spectra, these peaks indicate the formation of the expected compounds **3a-c**. ^{1}H NMR spectra showed the methine proton at 3.65, which is characteristic of the cyclobutane ring. The NH proton is at 5.99 as a broad singlet and the thiazole proton (1H) at 6.08 as a singlet. The aromatic protons appeared as a multiplet at 7.10-7.35 ppm.

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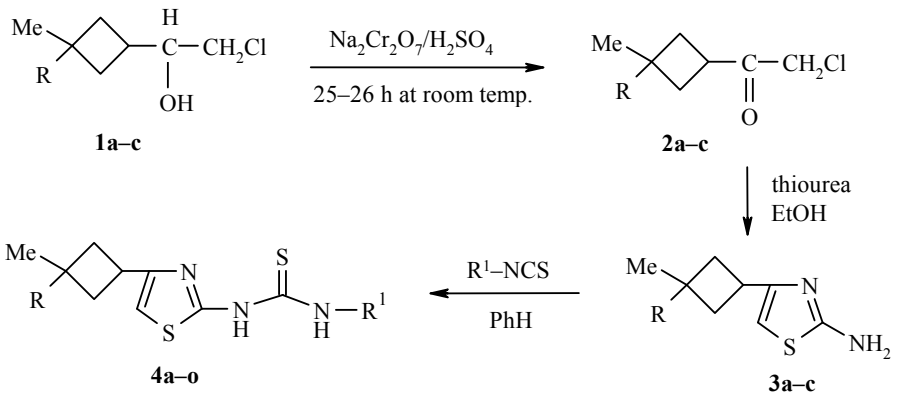

1a-c – 3a-c, **4a-e** R = 5,6,7,8-tetrahydro-2-naphthyl; **4 f-j** R = mesityl, **k-o** R = Ph;
4 a, f, k R^1 = Ph, **b, g, l** R^1 = 4-ClC_6H_4, **c, h, m** R^1 = 4-$NO_2C_6H_4$, **d, i, n** R^1 = 4-MeC_6H_4,
e, j, o R^1 = 4-$MeOC_6H_4$

EXPERIMENTAL

Tetralin, mesitylene, benzene, and aryl isothiocyanates (Merck) were dried over anhydrous $MgSO_4$ before use. Diethyl ether, anyhydrous $CaCl_2$, KOH (Aldrich), anhydrous $AlCl_3$ (Riedel), $Na_2Cr_2O_7$, and H_2SO_4 (Merck) were used as received. Melting points were determined in open capillary tubes on digital Gallenkamp melting point apparatus and are uncorrected. The IR spectra (KBr pellets) were recorded with a Mattson 1000 FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR in $CDCl_3$ spectra were recorded on a FX 90 JEOL (90 MHz) NMR and Varian Gemini 200 MHz (50 MHz for ^{13}C), respectively. Elemental analyses were done on a LECO-CHNS-938.

1-Aryl-3-(2-chloro-1-hydroxyethyl)-1-methylcyclobutanes 1 were prepared according to a method given in the literature [1].

3-(2-Chloro-1-oxoethyl)1-1-methyl-1-(2-tetralyl)cyclobutane (2a). $Na_2Cr_2O_7$ (0.29 mol), compound **1a** (0.52 mol), and water (50 ml) 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 sulfuric 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 mm Hg) and filtered through a column filled with silica gel [20:1 benzene–ethyl acetate mixture; R_f (retention time) 0.48]. The yield of the ketone was about 75%. IR spectrum, ν, cm^{-1}: 1730 (C=O), 736 (C–Cl; no OH absorption).

3-(2-Chloro-1-oxoethyl)-1-mesityl-1-methylcyclobutane (2b) was synthesized similarly, except that the product was crystallized rather than distilled, mp 98°C, and the yield was about 75%. IR spectrum, ν, cm^{-1}: 1728 (C=O), 738 (C–Cl; no O–H absorption).

Compound 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 spectrum, ν, cm^{-1}: 1750 (C=O), 735 (C–Cl; no O–H absorption).

2-Amino-4-[3-methyl-3-(2-tetralyl)cyclobutyl]thiazole (3a). To a solution of thiourea (0.76 g, 10 mmol) in absolute ethanol (50 ml) a solution of compound **2a** (2.76 g, 10 mmol) in absolute ethanol (30 ml) was added dropwise at 50-60°C with continuous stirring. 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 compound **3a**. 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 spectrum, ν, cm^{-1}: 3285-3310 (NH_2), 1604 (C=N), 685 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.86-7.06 (3H, m, Ar–H); 5.95 (1H, s, =CH–S, thiazole); 5.48 (2H, s, NH_2); 3.52 (1H, quint, *J* = 8.80, CH, cyclobutane); 2.76-2.80 (4H, m, the alicyclic protons of tetralin); 2.33-2.55 (4H, m, CH_2, cyclobutane); 1.81-1.84 (4H, m, alicyclic protons of tetralin); 1.54 (3H, s, CH_3). ^{13}C NMR spectrum, 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 ($C_{(16)}$). Found, %: C 72.10; H 7.41; N 8.93; S 10.68. $C_{18}H_{22}N_2S$. Calculated, %: C 72.44; H 7.43; N 9.39; S 10.74.

2-Amino-4-(3-mesityl-3-methylcyclobutyl)thiazole (3b) was synthesized like compound **3a** except that the product was crystallized from aqueous methanol (1:4). Yield 65%. White solid; mp 243-244°C. IR spectrum, ν, cm^{-1}: 3290-3313 (NH_2), 1605 (C=N), 688 (C–S–C). ^1H NMR spectrum, δ, ppm: 6.70 (2H, s, Ar–H); 5.96 (1H, s, =CH, thiazole ring); 5.44 (2H, s, NH_2); 3.50 (1H, quint, *J* = 9.00, CH, cyclobutane); 2.55 (4H, m, CH_2, cyclobutane); 2.21 (3H, s, CH_3, mesityl); 2.14 (6H, s, CH_3, mesityl); 1.49 (3H, s, CH_3). ^{13}C NMR spectrum, 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 ($C_{(13)}$). Found, %: C 71.13; H 7.51; N 9.21; S 10.99. $C_{17}H_{22}N_2S$. Calculated, %: C 71.28; H 7.74; N 9.78; S 11.19.

2-Amino-4-(3-methyl-3-phenylcyclobutyl)thiazole (3c) was synthesized like compound **3a** except that the product was crystallized from aqueous ethanol (1:4). Yield 70%. Light-yellow solid; mp 174-175°C. IR spectrum, ν, cm^{-1}: 3282-3309 (NH_2), 1603 (C=N), 687 (C–S–C). ^1H NMR spectrum, δ, ppm: 7.14-7.39 (5H, m, Ar–H); 5.99 (1H, s, =CH, thiazole ring); 5.44 (2H, s, NH_2); 3.51 (1H, quint, *J* = 7, CH, cyclobutane); 2.40 (4H, m, CH_2, cyclobutane); 1.53 (3H, s, CH_3). ^{13}C NMR spectrum, 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 ($C_{(11)}$). Found, %: C 68.60, H 6.37; N 11.09; S 12.85. $C_{14}H_{16}N_2S$ (244). Calculated, %: C 68.82; H 6.60; N 11.46; S 13.12.

Compounds 4. (General procedure). A mixture of (0.01 mol) of compounds **3a-c** and isothiocyanate (0.01 mol) in dry C_6H_6 was refluxed for 6 h; the solid material obtained on cooling was filtered off and recrystallized from MeOH to give compound **4a-o.**

N-{4-[3-Methyl-3-(2-tetralyl)cyclobutyl]thiazol-2-yl}-N'-phenylthiourea (4a). Yield 60%, mp 299°C. IR spectrum, ν, cm^{-1}: 3280, 3107, 3055, 2980, 1600, 1360, 1159, 655. ^1H NMR spectrum, δ, ppm: 1.51 (3H, s, CH_3); 1.74-1.80 (4H, m, CH_2, tetralin); 2.35-2.57 (4H, m, CH_2, cyclobutane); 2.62-2.76 (4H m, CH_2, tetralin); 3.55-3.74 (1H, m, >CH, cyclobutane); 6.40 (1H, s, =CH, thiazole ring); 6.83-7.43 (8H, m, aromatic protons); 10.00-10.60 (2H, br, NH). ^{13}C NMR spectrum, δ, ppm: 179.30, 163.90, 151.50, 151.40, 138.88, 137.40, 136.09, 131.00, 127.03, 125.50, 123.81, 106.34, 79.60, 78.30, 78.10, 42.36, 40.85, 40.50, 32.10, 31.52, 31.01, 29.93, 22.27. Found, %: C 69.10; H 6.18; N 9.84; S 14.70. $C_{25}H_{27}N_3S_2$. Calculated, %: C 69.25; H 6.28; N 9.69; S 14.79.

N-{4-[3-Methyl-3-(2-tetralyl)cyclobutyl]thiazol-2-yl}-N'-(4-chlorophenyl)thiourea (4b). Yield 68%, mp 219°C. IR spectrum, ν, cm^{-1}: 3288, 3106, 3050, 2980, 1650, 1600, 1360, 1160, 730, 690. ^1H NMR spectrum, δ, ppm: 1.53 (3H s, CH_3); 1.73-1.82 (4H, m, CH_2, tetralin); 2.35-2.55 (4H, m, CH_2, cyclobutane); 2.61-2.75 (4H, m, CH_2, tetralin); 3.56-3.73 (1H, m, >CH–, in cyclobutane ring); 6.41 (1H, s, =CH, thiazole); 6.79-7.46 (7H, m, aromatic protons); 10.01-10.59 (2H, br, NH). ^{13}C NMR spectrum, δ, ppm: 178.30, 164.90, 152.50, 151.50, 139.88, 137.40, 135.09, 131.00, 126.03, 125.56, 123.81, 106.34, 79.60, 79.30, 78.10, 42.36, 40.50, 39.85, 32.20, 31.52, 31.05, 29.83, 23.27. Found, %: C 63.97; H 5.68; N 8.89; S 13.68. $C_{25}H_{26}ClN_3S_2$. Calculated, %: C 64.15; H 5.60; N 8.98; S 13.70.

N-{4-[3-Methyl-3-(2-tetralyl)cyclobutyl]thiazol-2-yl}-N'-(4-nitrophenyl)thiourea (4c). Yield 65%, mp 239°C. IR spectrum, ν, cm^{-1}: 3289, 3105, 3049, 2980, 1650, 1600, 1590, 1560, 1405, 1159, 690. ^1H NMR spectrum, δ, ppm: 1.59 (3H, s, CH_3); 1.74-1.81 (4H, m, CH_2, tetralin); 2.38-2.56 (4H, m, CH_2, cyclobutane);

2.61-2.76 (4H, m, CH_2, tetralin); 3.58-3.72 (1H, m, >CH, cyclobutane); 6.40 (1H, s, =CH, thiazole); 6.76-7.44 (7H, m, aromatic protons); 10.11-10.55 (2H, br, NH). ^{13}C NMR spectrum, δ, ppm: 177.70, 162.90, 157.35, 151.05, 139.08, 137.48, 135.09, 131.00, 126.03, 125.56, 123.82, 106.44, 79.50, 79.30, 78.10, 42.38, 41.50, 39.85, 32.20, 31.52, 31.05, 29.83, 25.27. Found, %: C 62.44; H 5.38; N 11.70; S 13.38. $C_{25}H_{26}N_4O_2S_2$. Calculated, %: C 62.73; H 5.48; N 11.71; S 13.40.

N-{4-[3-Methyl-3-(2-tetralyl)cyclobutyl]thiazol-2-yl}-N'-(4-methylphenyl)thiourea (4d). Yield 75%; mp 209°C: IR spectrum, ν, cm^{-1}: 3260, 3105, 3049, 2981, 1654, 1590, 1305, 1157, 691. ^{1}H NMR spectrum, δ, ppm: 1.53 (3H, s, CH_3); 1.74-1.81 (4H, m, CH_2, tetralin); 2.35 (3H, s, Ar–CH_3); 2.41-2.57 (4H, m, CH_2, cyclobutane); 2.62-2.76 (4H, m, CH_2, tetralin); 3.55-3.74 (1H, m, >CH, cyclobutane); 6.40 (1H, s, =CH, thiazole); 6.82-7.43 (7H, m, aromatic protons); 10.11-10.55 (2H, br, NH). ^{13}C NMR spectrum, δ, ppm: 178.70, 162.92, 157.33, 150.15, 139.08, 137.47, 135.10, 131.10, 126.03, 125.56, 123.81, 106.34, 79.60, 79.30, 78.11, 42.36, 41.51, 39.83, 32.22, 31.52, 31.05, 29.81, 25.22, 22.94. Found, %: C 69.44; H 5.58; N 9.31; S 14.38. $C_{26}H_{29}N_3S_2$. Calculated, %: C 69.76; H 5.53; N 9.39; S 13.32.

N-{4-[3-Methyl-3-(2-tetralyl)cyclobutyl]thiazol-2-yl}-N'-(4-methoxyphenyl)thiourea (4e). Yield 67%; mp 287°C. IR spectrum, ν, cm^{-1}: 3281, 3105, 3050, 2981, 1647, 1598, 1400, 1200, 690. ^{1}H NMR spectrum, δ, ppm: 1.49 (3H, s, CH_3); 1.53-1.85 (4H, m, CH_2, tetralin); 2.41-2.50 (4H, m, CH_2, cyclobutane); 2.56-2.66 (4H, m, CH_2, tetralin); 3.61-3.69 (1H, m, >CH, cyclobutane); 3.82 (3H, s, OCH_3); 6.40 (1H, s, =CH, thiazole); 6.79-7.86 (7H, m, aromatic protons); 10.11-10.55 (2H, br, NH). ^{13}C NMR spectrum, δ, ppm: 178.44, 163.39, 160.35, 151.05, 139.08, 137.48, 135.09, 131.00, 126.03, 125.55, 123.84, 106.31, 79.60, 79.30, 78.10, 57.11, 42.36, 41.50, 39.85, 32.22, 31.52, 31.04, 30.83, 25.26. Found, %: C 67.08; H 6.18; N 8.99; S 13.78. $C_{26}H_{29}N_3OS_2$. Calculated, %: C 67.35; H 6.22; N 9.01; S 13.81.

N-{4-[3-Mesityl-3-methylcyclobutyl]thiazol-2-yl}-N'-phenyl)thiourea (4f). Yield 69%; mp 297°C. IR spectrum, ν, cm^{-1}: 3278, 3107, 3056, 2983, 1600, 1363, 1151, 688. ^{1}H NMR spectrum, δ, ppm: 1.53-1.62 (3H, s, CH_3); 2.11-2.25 (9H, s, CH_3, mesityl); 2.54-2.69 (4H, m, CH_2, cyclobutane); 3.43-3.81 (1H, m, >CH, cyclobutane); 6.59 (1H, s, =CH, thiazole); 7.42-8.22 (9H, m, 2NH– and aromatic protons). Found, %: C 68.14; H 6.39; N 9.99; S 14.98. $C_{24}H_{27}N_3S_2$. Calculated, %: C 68.37; H 6.45; N 9.97; S 15.21.

N-{4-[3-Mesityl-3-methylcyclobutyl]thiazol-2-yl}-N'-(4-chlorophenyl)thiourea (4g). Yield 67%; mp 291°C. IR spectrum, ν, cm^{-1}: 3282, 3102, 3052, 2981, 1605, 1365, 1159, 735, 687. ^{1}H NMR spectrum, δ, ppm: 1.53-1.62 (3H, s, CH_3); 2.13-2.29 (9H, s, CH_3, mesityl); 2.58-2.78 (4H, m, CH_2, cyclobutane); 3.48-3.57 (1H, m, >CH, cyclobutane); 6.42 (1H, s, =CH, thiazole); 6.73-8.12 (8H, m, 2NH– and aromatic protons). ^{13}C NMR spectrum, δ, ppm: 182.91, 163.45, 160.73, 159.77, 146.05, 136.99, 133.46, 132.46, 132.11, 129.36, 128.75, 126.83, 116.81, 106.00, 46.04, 45.64, 42.91, 33.26, 26.70, 26.55, 23.31, 22.38. Found, %: C 62.98; H 5.70; N 9.19; S 14.00. $C_{24}H_{26}ClN_3S_2$. Calculated, %: C 63.21; H 5.75; N 9.21; S 14.06.

N-{4-[3-Mesityl-3-methylcyclobutyl]thiazol-2-yl}-N'-(4-nitrophenyl)thiourea (4h). Yield 65%; mp 300°C. IR spectrum, ν, cm^{-1}: 3278, 3107, 3055, 2984, 1605, 1360, 1290, 1159, 691. ^{1}H NMR spectrum, δ, ppm: 1.53-1.61 (3H, s, CH_3); 2.13-2.28 (9H, s, CH_3, mesityl); 2.58-2.77 (4H, m, CH_2, cyclobutane); 3.48-3.57 (1H, m, >CH, cyclobutane); 6.36-6.42 (1H, s, =CH, thiazole); 6.73-8.13 (8H, m, 2NH– and aromatic protons). ^{13}C NMR spectrum, δ, ppm: 182.93, 163.43, 160.75, 159.77, 146.05, 136.99, 133.46, 132.46, 132.10, 129.35, 128.73, 126.83, 116.80, 106.02, 46.04, 45.64, 42.91, 33.26, 26.71, 26.55, 23.30, 22.38. Found, %: C 61.44; H 5.60; N 11.99; S 13.70. $C_{24}H_{26}N_4O_2S_2$. Calculated, %: C 61.78; H 5.62; N 12.01; S 13.74.

N-{4-[3-Mesityl-3-methylcyclobutyl]thiazol-2-yl}-N'-(4-methylphenyl)thiourea (4i). Yield 70%; mp 280°C. IR spectrum, ν, cm^{-1}: 3288, 3107, 3055, 2980, 1605, 1368, 1292, 1159, 692. ^{1}H NMR spectrum, δ, ppm: 1.53-1.62 (3H, s, CH_3); 2.13-2.29 (9H, s, CH_3, mesityl and 3H, Ar–CH_3); 2.58-2.78 (4H m, CH_2, cyclobutane); 3.48-3.57 (1H, m, >CH, cyclobutane); 6.36-6.42 (1H, s, =CH, thiazole); 6.73-8.11 (8H, m, 2NH– and aromatic protons). ^{13}C NMR spectrum, δ, ppm: 182.91, 163.45, 160.73, 159.77, 146.05, 136.98, 133.48, 132.46, 132.11, 129.36, 128.75, 126.83, 116.81, 106.02, 46.04, 45.64, 42.91, 33.26, 26.70, 26.55, 23.29, 22.38. Found, %: C 68.74; H 6.69; N 9.61; S 14.70. $C_{25}H_{29}N_3S_2$. Calculated, %: C 68.93; H 6.71; N 9.65; S 14.72.

N-{4-[3-Mesityl-3-methylcyclobutyl]thiazole-2-yl}-N'-(4-methoxyphenyl)thiourea (4j). Yield 71%; mp 284°C. IR spectrum, ν, cm^{-1}: 3280, 3101, 3055, 2978, 1605, 1367, 1159, 692. ^{1}H NMR spectrum, δ, ppm: 1.53-162 (3H, s, CH_3); 2.11-2.25 (9H, s, CH_3, mesityl); 2.54-2.69 (4H, m, CH_2, cyclobutane); 3.43-3.56 (1H, m, >CH, cyclobutane); 3.75-3.81 (3H, s, OCH_3); 6.39 (1H, s, =CH, thiazole); 6.72-7.98 (8H, m, 2NH– and aromatic protons). ^{13}C NMR spectrum, δ, ppm: 182.93, 163.48, 160.71, 159.75, 146.05, 136.97, 133.46, 132.44, 132.11, 129.36, 128.76, 126.82, 116.80, 106.01, 57.47, 46.04, 45.64, 42.91, 33.25, 26.72, 26.55, 23.31, 22.38. Found, %: C 65.97; H 6.44; N 9.28; S 14.18. $C_{25}H_{29}N_3OS_2$. Calculated, %: C 66.48; H 6.47; N 9.30; S 14.20.

N-[4-(3-Methyl-3-phenylcyclobutyl)thiazol-2-yl]-N'-phenylthiourea (4k). Yield 63%; mp 274°C. IR spectrum, ν, cm^{-1}: 3285, 3100, 3052, 2978, 1605, 1340, 1150, 670. ^{1}H NMR spectrum, δ, ppm: 1.56 (3H, s, CH_3); 2.46-2.68 (4H, m, CH_2, cyclobutane); 3.60-3.73 (1H, m, >CH, cyclobutane); 6.42 (1H, s, =CH, thiazole); 7.12-7.55 (10H, m, aromatic protons); 10.06-10.46 (2H, br, 2NH). ^{13}C NMR spectrum, δ, ppm: 178.22, 163.11, 157.09, 153.81, 140.79, 131.41, 130.30, 127.84, 126.49, 125.47, 106.56, 42.73, 40.93, 32.61, 32.03. Found, %: C 66.40; H 5.60; N 11.00; S 16.88. $C_{21}H_{21}N_3S_2$. Calculated, %: C 66.46; H 5.58; N 11.07; S 16.90.

N-[4-(3-Methyl-3-phenylcyclobutyl)thiazol-2-yl]-N'-(4-chlorophenyl)thiourea (4l). Yield 75%; mp 264°C. IR spectrum, ν, cm^{-1}: 3280, 3107, 3055, 2980, 1600, 1360, 1158, 733, 691. ^{1}H NMR spectrum, δ, ppm: 1.59 (3H, s, CH_3); 2.46-2.51 (4H, m, CH_2, cyclobutane); 3.18-3.76 (1H, m, >CH, cyclobutane); 6.67 (1H, s, =CH, thiazole); 7.14-7.70 (9H, m, aromatic protons); 10.16-10.40 (2H, br, 2NH). ^{13}C NMR spectrum, δ, ppm: 178.21, 163.11, 157.09, 153.81, 140.79, 131.41, 130.32, 127.84, 126.49, 125.46, 106.56, 42.73, 40.92, 32.61, 32.03. Found, %: C 60.60; H 4.79; N 10.11; S 15.48. $C_{21}H_{20}ClN_3S_2$. Calculated, %: C 60.93; H 4.87; N 10.15; S 15.49.

N-[4-(3-Methyl-3-phenylcyclobutyl)thiazol-2-yl]-N'-(4-nitrophenyl)thiourea (4m). Yield 71%; mp 274°C. IR spectrum, ν, cm^{-1}: 3269, 3101, 3048, 2970, 1600, 1354, 1290, 1158, 691. ^{1}H NMR spectrum, δ, ppm: 1.56 (3H, s, CH_3); 2.46-2.68 (4H, m, CH_2, cyclobutane); 3.60-3.73 (1H, m, >CH, cyclobutane); 6.42 (1H, s, =CH thiazole); 7.12-7.55 (9H, m, aromatic protons); 10.06-10.46 (2H, br, 2NH). ^{13}C NMR spectrum, δ, ppm: 178.22, 163.11, 157.09, 153.83, 140.77, 131.41, 130.32, 127.84, 126.49, 125.47, 106.56, 42.73, 40.93, 32.59, 32.03. Found, %: C 59.10; H 4.69; N 13.13; S 15.00. $C_{21}H_{20}N_4O_2S_2$. Calculated, %: C 59.41; H 4.75; N 13.20; S 15.11.

N-[4-(3-Methyl-3-phenylcyclobutyl)thiazol-2-yl]-N'-(4-methylphenyl)thiourea (4n). Yield 63%; mp 263°C. IR spectrum, ν, cm^{-1}: 3278, 3103, 3055, 2979, 1600, 1372, 1156, 691. ^{1}H NMR spectrum, δ, ppm: 1.56 (3H, s, CH_3); 2.31-2.35 (3H, s, Ar–CH_3); 2.45-2.65 (4H, m, CH_2, cyclobutane); 3.59-3.76 (1H, m, >CH, cyclobutane); 6.41 (1H, s, =CH, thiazole); 7.11-7.40 (9H, m, aromatic protons); 10.40-10.61 (2H, br, 2NH). ^{13}C NMR spectrum, δ, ppm: 178.28, 163.53, 157.16, 157.12, 153.81, 140.79, 131.41, 130.30, 127.84, 126.49, 125.47, 106.56, 42.73, 40.93, 32.59, 32.57, 32.03. Found, %: C 67.00; H 5.72; N 10.59; S 16.61. $C_{22}H_{23}N_3S_2$. Calculated, %: C 67.14; H 5.89; N 10.68; S 16.29.

N-[4-(3-Methyl-3-phenylcyclobutyl)thiazol-2-yl]-N'-(4-methoxyphenyl)thiourea (4o). Yield 64%; mp 273°C. IR spectrum, ν, cm^{-1}: 3279, 3105, 3055, 2979, 1600, 1368, 1156, 691. ^{1}H NMR spectrum, δ, ppm: 1.51 (3H, s, CH_3); 2.45-2.55 (4H, m, CH_2, cyclobutane); 3.31-3.79 (3H, m, OCH_3 and 1H, >CH, cyclobutane); 6.37 (1H, s, =CH, thiazole); 6.81-7.47 (9H, m, aromatic protons); 12.72-13.01 (2H, br, 2NH). ^{13}C NMR spectrum, δ, ppm: 178.28, 163.53, 157.16, 157.12, 153.81, 140.79, 131.41, 130.30, 127.84, 126.49, 125.47, 106.56, 57.14, 42.73, 40.93, 32.59, 32.57, 32.03. Found, %: C 64.20; H 5.56; N 10.14; S 15.35. $C_{22}H_{23}N_3OS_2$. Calculated, %: C 64.52; H 5.66; N 10.26; S 15.66.

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