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EFFICIENT SYNTHESIS OF SOME NEW 1,3,4-THIADIAZOLE AND THIAZOLE DERIVATIVES VIA THIOSEMICARBAZONE DERIVATIVES

Mohamed Abdelmonem Raslan

Chemistry Department, Faculty of Science, Aswan University, Aswan, 81528, Aswan, Egypt; E-mail: raslanma47@yahoo.com.

Abstract – We reported here reactions of hydrazinecarbodithioate and hydrazinecarbothioamide derivatives with hydrazonoyl chloride derivatives to afford 1,3,4-thiadiazole and thiazole derivatives, respectively. Also, reactions of hydrazinecarbothioamide derivatives with α -halo esters derivatives, diethyl acetylenedicarboxylate and chloroacetonitrile afforded thiazole derivatives. The structures of the newly synthesized compounds were established based on its elemental analyses and spectral data.

1,3,4-Thiadiazole is a prevalent and important five-membered heterocyclic system containing two nitrogen atoms and a sulfur atom. 1,3,4-Thiadiazole derivatives are applied widely in pharmaceutical, agricultural, and materials chemistry. In particular, the 1,3,4-thiadiazoles displaying a broad spectrum of biological activities such as antimicrobial, antituberculosis, antioxidant, etc. have been document.¹⁻¹⁴

Thiazole derivatives are of special importance because of their versatile biological and pharmacological activities, hence antiparkinsonian, anti-inflammatory, antibiotic, antibacterial, etc. have been document.¹⁵⁻³⁴ Also, we know that thiazoles are essential class of heterocyclic compounds, found in many effecting biologically active drugs such as Sulfathiazol, Ritonavir, Abafungin and Tiazofurin.³⁵ Furthermore, compounds containing thiazolyl moiety have been reported to exhibit enzyme inhibition^{36,37} and play an vital role in regulating humans and biological metabolism process.^{38,39}

On the other hand, some synthetic thiosemicarbazone derivatives exhibit a wide range of biological activities, such as antitumor, anti-inflammatory, anti-bacterial, etc.⁴⁰⁻⁵² and also exhibit some industrially roles such as anticorrosion and antifouling effects⁵³ and plant growth promoting.⁵⁴

In view of the above and in continuation of our previous reports in synthesis of thiazole and 1,3,4-thiadiazole derivatives,⁵⁵⁻⁶² we are herein interested in synthesis of some new thiazole and

1,3,4-thiadiazole derivatives using *N*-(5-acetyl-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide **1** as versatile building blocks for the title compounds.

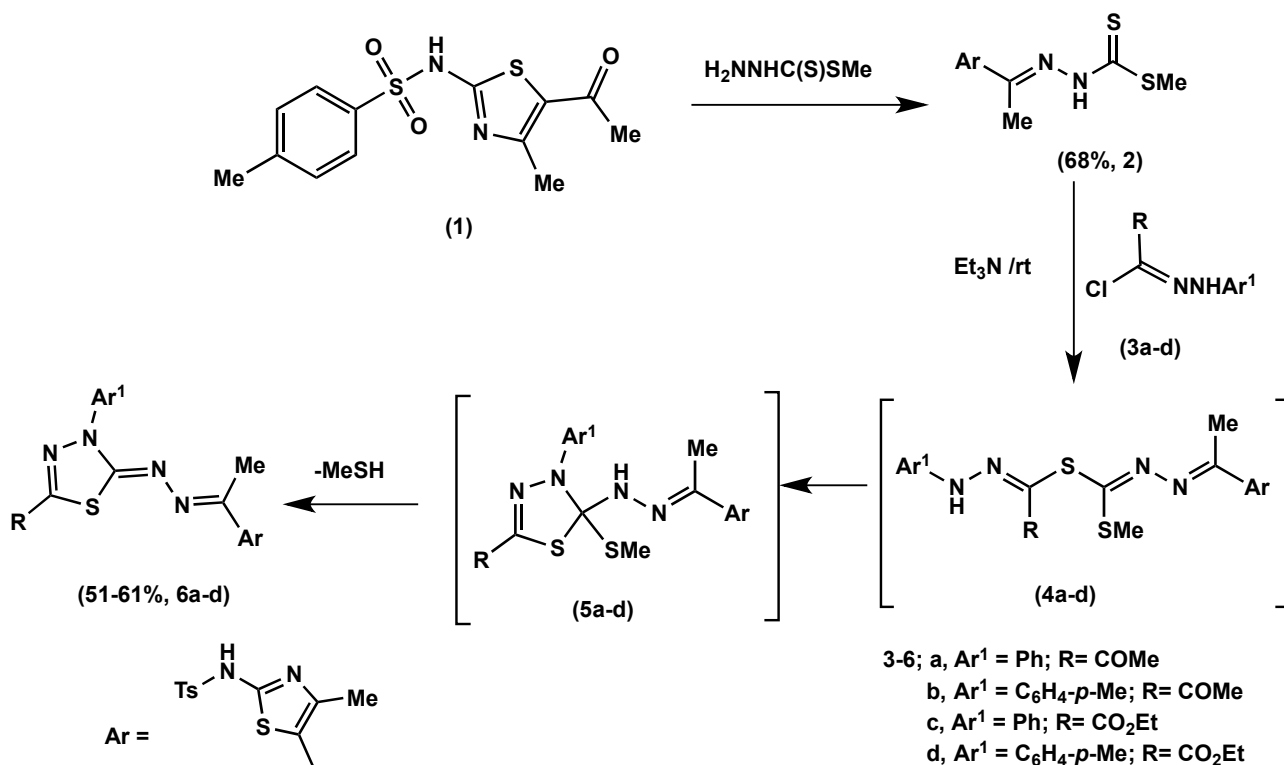
The presence of S and N donor ligands have attracted attention as a versatile intermediates for synthesis of various heterocyclic derivatives such as thiazoles.⁶³ Thus, treatment of *N*-(5-acetyl-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide **1** with methyl hydrazinecarbodithioate in ethanol at room temperature afforded methyl 2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinecarbodithioate **2**. The structure of the isolated hydrazinecarbodithioate derivative **2** was established on the basis of its elemental analyses and spectral data. Its IR spectrum revealed absorption bands at 3331, 3185 and 1621 cm^{-1} due to 2NH and C=N function, respectively. Its ^1H NMR spectrum revealed six singlet signals at δ 2.36, 2.43, 2.51, 2.65, 11.35 and 12.78 ppm due to four methyl and 2NH protons, respectively. Its mass spectrum showed a molecular ion peak at m/z 414 (M^+ , 59) corresponding to a molecular formula $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_4$ (**Scheme 1**).

We investigated the reactivity of hydrazinecarbodithioate derivative **2** towards highly versatile active reagents hydrazonoyl halide derivatives that consider as a key for the synthesis of thiazole and thiadiazole derivatives. Thus, treatment of compound **2** with *C*-acetyl-*N*-arylhydrazonoyl chloride derivatives (**3a,b**) in refluxing ethanol containing catalytic amount of TEA afforded 1,3,4-thiadiazole derivatives (**6a,b**). The formation of the latter compounds proceeds via the intermediate thiohydrazonate (**4a,b**), which undergoes intramolecular cyclization as soon as it is formed to afford the intermediate (**5a,b**) which undergoes elimination of MeSH as soon as it is formed to afford 1,3,4-thiadiazole derivatives (**6a,b**).

The structures of the 1,3,4-thiadiazole derivatives (**6a,b**) were established on the basis of its elemental analyses and spectral data. For example, IR spectrum of *N*-(5-(1-((5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (**6a**) revealed absorption bands at 3189, 1667 and 1615 cm^{-1} due to NH, CO and C=N function, respectively. Its ^1H NMR revealed five singlet signals at δ 2.32, 2.39, 2.47, 2.62 and 12.35 ppm due to four methyl and NH protons, respectively, in addition to an aromatic multiplet in the region of 7.16-7.79 ppm. Its mass spectrum showed a molecular ion peak at m/z 526 (M^+ , 51) corresponding to a molecular formula $\text{C}_{23}\text{H}_{22}\text{N}_6\text{O}_3\text{S}_3$ (**Scheme 1**).

In a similar manner, treatment of compound **2** with *C*-ethoxycarbonyl-*N*-arylhydrazonoyl chloride derivatives (**3c,d**) under the same conditions furnished the corresponding 1,3,4-thiadiazole derivatives (**6c,d**). The structures of (**6c,d**) were established on the basis of its elemental analyses and spectral data. For example, IR spectrum of ethyl-5-((1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**6c**) revealed absorption bands at 3180, 1719 and 1613 cm^{-1} due to NH, C=O and C=N functions, respectively. Its ^1H NMR revealed both triplet and quartet signals at δ 1.29-1.31 and 4.31-4.35 ppm due to ethyl

carboxylate protons. Its mass spectrum showed a molecular ion peak at m/z 556 (M^+ , 68) corresponding to a molecular formula $C_{24}H_{24}N_6O_4S_3$ (**Scheme 1**).



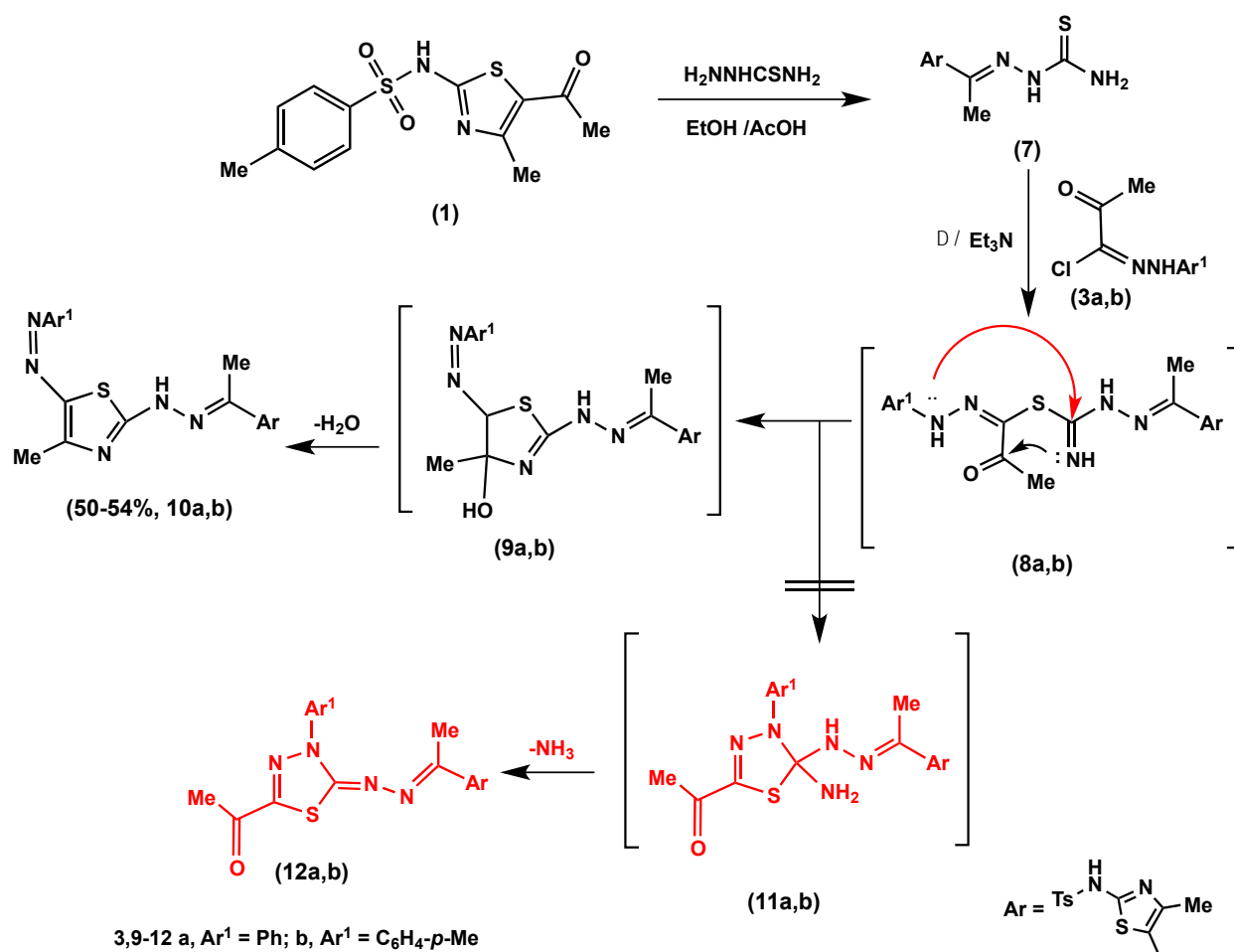
Scheme 1

The precursor 2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinecarbothioamide **7** was synthesized in good yield by reaction of compound **1** with thiosemicarbazide in refluxing ethanol containing catalytic amount of glacial acetic acid. The structure of the isolated thiosemicarbazone derivative **7** was established on the basis of its elemental analysis and spectral data. Its ¹H NMR spectrum revealed six singlet signals at δ 2.33, 2.41, 2.71, 8.16, 11.42 and 12.73 ppm due to three methyl, NH₂ and 2NH protons, respectively. Its mass spectrum showed a molecular ion peak at m/z 383 (M^+ , 62) corresponding to a molecular formula $C_{14}H_{17}N_5O_2S_3$ (**Scheme 2**).

Thiosemicarbazones have a special considerable potential as a key for the synthesis of highly biologically active ingredients and are considered as good precursors for the synthesis of thiazole derivatives. Thus, we reported here the synthesis of thiazole derivatives (**10a,b**) through the behaviors of the C-acetyl-*N*-arylhydrazonoyl chloride derivatives (**3a,b**) towards thiosemicarbazone **7**. For example, treatment of thiosemicarbazone **7** with 2-oxo-*N'*-phenylpropanehydrazonoyl chloride (**3a**) in refluxing ethanol containing catalytic amount of TEA afforded a single product that was identified as 4-methyl-*N*-(4-methyl-5-(1-(2-(5-methyl-4-(phenyldiazenyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-

yl)benzenesulfonamide (**10a**). The other possible structure (**12a**) was ruled out on the basis of the spectral data of the isolated product. The IR spectrum of **10a** revealed absence of absorption band due to carbonyl function.

The reaction proceeded through the alkylation of thiol group in thiourea moiety to give the non-isolable intermediates (**8a**) which underwent intramolecular cyclization as soon as it is formed to afford the intermediate (**9a**) which underwent elimination of water as soon as it is formed to afford the desired 1,3,4-thiadiazole derivative (**10a**) (Scheme 2).

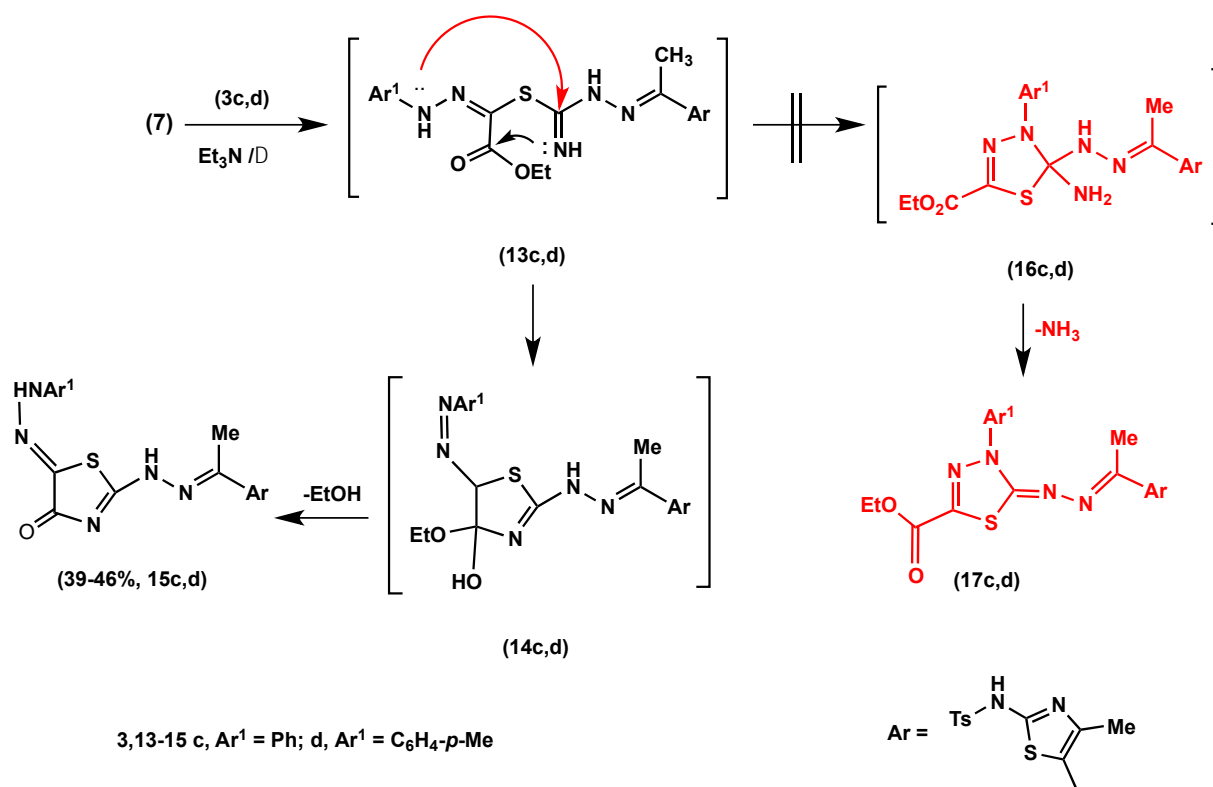


Scheme 2

In a similar manner, treatment of compound **7** with 2-oxo-*N'*-(*p*-tolyl)propanehydrazono)yl chloride (**3b**) under the same conditions furnished the corresponding 4-methyl-*N*-(4-methyl-5-(1-(2-(5-methyl-4-(*p*-tolyl)diazenyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (**10b**). Similarly, thiosemicarbazone derivative **7** reacted with *C*-acetyl-*N*-arylhydrazono)yl chloride derivatives (**3c,d**). For example, treatment of thiosemicarbazone **7** with ethyl 2-chloro-2-(2-phenylhydrazono)acetate (**3c**) in refluxing ethanol containing catalytic amount of TEA afforded a single product that was identified as

4-methyl-*N*-(4-methyl-5-(1-(2-(5-oxo-4-(2-phenylhydrazono)-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)-thiazol-2-yl)benzenesulfonamide (**15c**). The other possible structure (**17c**) was ruled out on the basis of the spectral data of the isolated product. The ^1H NMR spectrum agreed with compound (**15c**), and it revealed absence of signals due to ethyl carboxylate protons and appearance of three singlet signals at δ 10.54, 11.89 and 12.82 ppm due to three NH protons, in addition to an aromatic multiplet in the region 7.17-7.85 ppm. Its mass spectrum showed a molecular ion peak at m/z 527 (M^+ , 31) corresponding to a molecular formula $\text{C}_{22}\text{H}_{21}\text{N}_7\text{O}_3\text{S}_3$.

In a similar manner, treatment of **7** with ethyl 2-chloro-2-(2-(*p*-tolyl)hydrazono)acetate (**3d**) under the same conditions furnished the corresponding 4-methyl-*N*-(4-methyl-5-(1-(2-(5-oxo-4-(2-(*p*-tolyl)-hydrazono)-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (**15d**) (Scheme 3).



Scheme 3

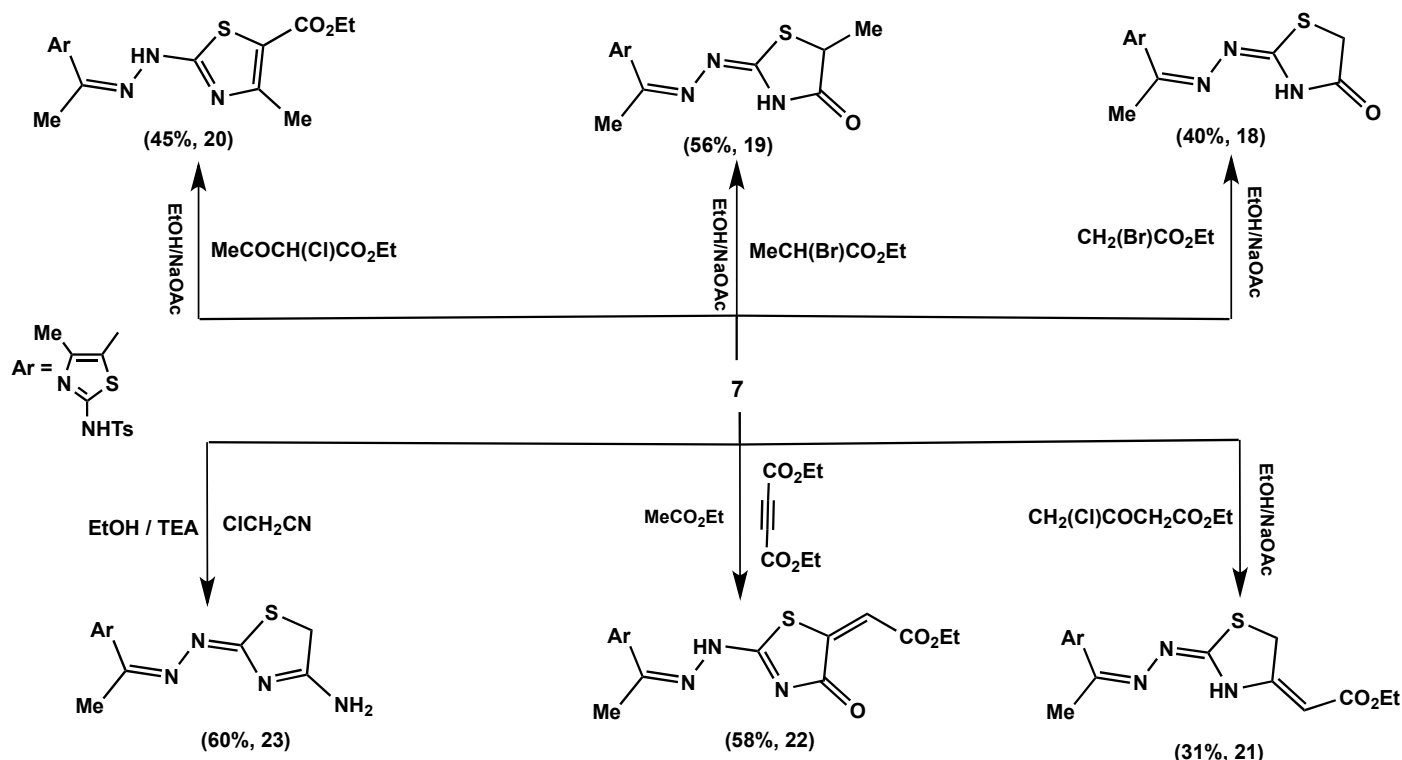
Next, the reactivity of the key intermediates thiosemicarbazone derivative (**7**) towards α -halo esters was evaluated. For example, thiosemicarbazone derivative (**7**) reacted with ethyl 2-bromoacetate in ethanol containing sodium acetate to yield a single product that was identified as 4-methyl-*N*-(4-methyl-5-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (**18**). The structure of the isolated thiazolidinone derivative (**18**) was established on the basis of its elemental analysis and spectral data. Its IR spectrum showed band due to C=O at 1717 cm^{-1} . The ^1H NMR spectra

revealed the presence of methylene group signal at δ 4.04 ppm. The formation of thiazolidinone derivative (**18**) is assumed to proceed through initial alkylation and intramolecular cyclisation via elimination of ethanol (**Scheme 4**).

Also, treatment of **7** with ethyl 2-bromopropanoate, ethyl 2-chloro-3-oxobutanoate, and ethyl 4-chloro-3-oxobutanoate in ethanol containing equivalent amount of sodium acetate yielded the corresponding substituted thiazole derivatives (**19-21**), respectively. The structure of compounds (**19-21**) were confirmed by elemental analyses and spectral data.

On the other hand, reaction of compound **7** with diethyl acetylenedicarboxylate (*DEAD*) in ethyl acetate at room temperature afforded ethyl 2-(2-(2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)-ethylidene)hydrazinyl)-4-oxothiazol-5(4*H*)-ylidene)acetate (**22**). The structure of compound (**22**) was confirmed by elemental analysis and spectral data. For example, its IR spectrum revealed absorption bands at 3256, 3218, 1721, 1685 and 1625 cm^{-1} due to 2NH, 2CO and C=N, respectively. The low frequency of the carbonyl ester stretching absorption is probably the result of the conjugation of the C=C bond. Its ^1H NMR spectrum showed sharp singlet signal readily recognized as arising from =CHCO₂Et at δ 6.68 ppm, in addition to a triplet signal at δ 1.23-1.26 ppm and a quartet at δ 4.20-4.24 ppm corresponding to the presence of the CH₃ and CH₂ protons of the ethyl group, respectively. Its mass spectrum showed a molecular ion peak at m/z 507 (M^+ , 42) corresponding to a molecular formula C₂₀H₂₁N₅O₅S₃ (**Scheme 4**).

In addition, the reaction of **7** with chloroacetonitrile in refluxing ethanol containing catalytic amount of TEA afforded a single product that was identified as *N*-(5-(1-((4-aminothiazol-2(5*H*)-ylidene)-hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (**23**). The structure of compound (**23**) was confirmed by elemental analysis and spectral data. For example, its IR spectrum revealed absorption bands at 3310, 3235, 3208 and 1616 cm^{-1} due to NH₂, NH and C=N, respectively. Its ^1H NMR spectrum showed singlet signals readily recognized as arising from CH₂ and NH₂ at δ 4.11 and 8.49 ppm, respectively. Its mass spectrum showed a molecular ion peak at m/z 422 (M^+ , 62) corresponding to a molecular formula C₁₆H₁₈N₆O₂S₃ (**Scheme 4**).



Scheme 4

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded using KBr pellets and a Perkin-Elmer 2000 FT-IR instrument at Aswan University. ¹H and ¹³C NMR spectra were recorded on a Bruker spectrometer (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR). Chemical shifts (δ) were expressed in parts per million and internally referenced (2.49 ppm for DMSO-*d*₆ for ¹H NMR and 39.5 ppm for DMSO-*d*₆ for ¹³C NMR). Mass spectra were measured using VG Autospec MS 9 (AEI) spectrometer, with the EI (70 eV) model. The microanalysis was performed at Microanalytical Center, Cairo University Egypt.

Methyl 2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinecarbodithioate (2).

To a solution of compound **1**⁶² (10 mmol) in EtOH (20 mL), methyl hydrazinecarbodithioate (10 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. (TLC control). The solid product was collected by filtration and finally recrystallized from DMF/EtOH to give pale yellow solid; mp 221-223 °C; yield 68%; IR: (ν_{max} /cm⁻¹): 3331, 3185 (NH), 1621 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.36 (s, 3H), 2.43 (s, 3H), 2.51 (s, 3H), 2.65 (s, 3H), 7.13-7.84 (m, 4H), 11.35 (s, 1H, D₂O-exchangable), and 12.78 (s, 1H, D₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 17.34, 18.46, 19.93, 21.49, 128.84, 129.89, 133.11, 136.68, 137.72, 155.46, 157.13, 166.73, 199.76 ppm; MS, *m/z* (%) 414 (M⁺, 59), (Anal. Calcd for C₁₅H₁₈N₄O₂S₄: C, 43.46; H, 4.38; N, 13.51; S, 30.94. Found: C, 43.39; H, 4.35; N, 13.47; S, 30.91%).

General procedures for the synthesis of *N*-(5-(1-((5-acetyl-3-aryl-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (6a-d).

To a mixture of carbodithioate derivative **2** (5 mmol) and the appropriate hydrazoneyl halides (**3a-d**) (5 mmol) in EtOH (50 mL), Et₃N (1 mL) was added, and the mixture was stirred at room temperature for 8-12 h. (TLC control). The solid product was collected by filtration and finally recrystallized from DMF to give the corresponding 1,3,4-thiadiazole (**6a-c**).

***N*-(5-(1-((5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (6a)**. Yellow solid; mp 267-277 °C; yield 59%; IR: (ν_{\max} /cm⁻¹): 3189 (NH), 1667 (C=O), 1615 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.32 (s, 3H), 2.39 (s, 3H), 2.47 (s, 3H), 2.62 (s, 3H), 7.16-7.79 (m, 9H) and 12.35 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 17.31, 20.87, 21.54, 25.12, 123, 124.19, 128.71, 129, 129.51, 132.77, 136.64, 137.56, 138.91, 148.65, 156.46, 158.81, 165, 166.37, 194.66 ppm; MS, *m/z* (%) 526 (M⁺, 51), (Anal. Calcd for C₂₃H₂₂N₆O₃S₃: C, 52.45; H, 4.21; N, 15.96; S, 18.27. Found: C, 52.41; H, 4.18; N, 15.95; S, 18.21%).

***N*-(5-(1-((5-Acetyl-3-(*p*-tolyl)-1,3,4-thiadiazol-2(3*H*)-ylidene)hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (6b)**. Yellow solid; mp 292-293 °C; yield 61%; IR: (ν_{\max} /cm⁻¹): 3194 (NH), 1670 (C=O), 1618 (C=N), ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.35 (s, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 2.65 (s, 3H), 7.18-7.89 (m, 11H) and 12.12 (s, 1H, *D*₂O-exchangable) ppm; MS, *m/z* (%) 540 (M⁺, 38), (Anal. Calcd for C₂₄H₂₄N₆O₃S₃: C, 53.31; H, 4.47; N, 15.54; S, 17.79. Found: C, 53.25; H, 4.41; N, 15.52; S, 17.73%).

Ethyl 5-((1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (6c). Yellow solid; mp 208-209 °C; yield 51%; IR: (ν_{\max} /cm⁻¹): 3180 (NH), 1719 (C=O), 1613 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 1.29-1.31 (t, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 2.69 (s, 3H), 4.31-4.35 (q, 2H), 7.15-7.72 (m, 9H) and 11.97 (s, 1H, *D*₂O-exchangable) ppm; MS, *m/z* (%) 556 (M⁺, 68), (Anal. Calcd for C₂₄H₂₄N₆O₄S₃: C, 51.78; H, 4.35; N, 15.10; S, 17.28. Found: C, 51.72; H, 4.32; N, 15.08; S, 17.23%).

Ethyl 5-((1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazono)-4-(*p*-tolyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (6d). Yellow solid; mp 202-203 °C; yield 52%; IR: (ν_{\max} /cm⁻¹): 3193 (NH), 1717 (C=O), 1616 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 1.28-1.30 (t, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 2.50 (s, 3H), 2.67 (s, 3H), 4.32-4.35 (q, 2H), 7.16-7.99 (m, 9H) and 11.95 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 14.12, 17.35, 20.58, 21.35, 21.53, 61.23, 122.13, 128.49, 129.47, 130, 131.37, 132.85, 135.64, 137, 137.89, 148.45, 156.74, 158.67, 162.55, 165.01, 166.47 ppm; MS, *m/z* (%) 570 (M⁺, 49), (Anal. Calcd for C₂₅H₂₆N₆O₄S₃: C, 52.61; H, 4.59; N, 14.73; S, 16.86. Found: C, 52.57; H, 4.56; N, 14.68; S, 16.83%).

2-(1-(4-Methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinecarbothioamide (7).

To a solution of compound **1** (10 mmol) in EtOH (50 mL) and thiosemicarbazide (10 mmol), few drops of glacial AcOH was added. The reaction mixture was stirred with reflux for 4-6 h. (TLC control). The solid product that formed while heating was collected by filtration and finally recrystallized from dioxane to give yellowish white solid; mp 281-283 °C; yield 74%; IR: (ν_{\max} /cm⁻¹): 3420, 3250, 3189 (NH₂ and NH), 1621 (C=N), 1293 (C=S); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.33 (s, 3H), 2.41 (s, 3H), 2.71 (s, 3H), 7.12-7.79 (m, 4H), 8.16 (brs, 2H, *D*₂O-exchangable), 11.42 (s, 1H, *D*₂O-exchangable) and 12.73 (s, 1H, *D*₂O-exchangable) ppm; MS, *m/z* (%) 383 (M⁺, 62), (Anal. Calcd for C₁₄H₁₇N₅O₂S₃: C, 43.84; H, 4.47; N, 18.26; S, 25.08. Found: C, 43.81; H, 4.41; N, 18.25; S, 25.03%).

General procedures for the synthesis of *N*-(5-(1-(2-(4-(aryldiazenyl)-5-methylthiazol-2-yl)hydrazono)ethyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (10a,b) and 4-methyl-*N*-(4-methyl-5-(1-(2-(5-oxo-4-(2-arylhydrazinyl)-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (15c,d).

To a mixture of thiosemicarbazone derivative **7** (5 mmol) and the appropriate hydrazonoyl halides (**3a-d**) (5 mmol) in EtOH (50 mL), Et₃N (1 mL) was added. The reaction mixture was refluxed for 4-6 h (TLC control). After evaporation of the solvent, the remaining was treated with acidic ice/water, then leave it overnight and the solid was collected by filtration and finally recrystallized from DMF to give the corresponding thiazole (**10a,b**) and (**15c,d**), respectively.

4-Methyl-*N*-(4-methyl-5-(1-(2-(5-methyl-4-(phenyldiazenyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (10a). Pale red solid; mp 223-224 °C; yield 50%, IR: (ν_{\max} /cm⁻¹): 3395, 3203 (NH), 1604 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.35 (s, 3H), 2.43 (s, 3H), 2.74 (s, 3H), 7.19-7.82 (m, 12H), 10.82 (s, 1H, *D*₂O-exchangable) and 12.19 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 11.12, 17.31, 20.33, 21.30, 128.41, 128.79, 129.12, 130.10, 132.79, 132.95, 136.85, 137.23, 137.58, 155.96, 156.65, 167.33, 170.21 ppm ; MS, *m/z* (%) 525 (M⁺, 39), (Anal. Calcd for C₂₃H₂₃N₇O₂S₃: C, 52.55; H, 4.41; N, 18.65; S, 18.30. Found: C, 52.51; H, 4.37; N, 18.63; S, 18.24%).

4-Methyl-*N*-(4-methyl-5-(1-(2-(5-methyl-4-(*p*-tolyl diazenyl)thiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (10b). Red solid; mp 241-243 °C; yield 54%; IR: (ν_{\max} /cm⁻¹): 3375, 3199 (NH), 1610 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.37 (s, 3H), 2.39 (s, 3H), 2.44 (s, 3H), 2.71 (s, 3H), 7.18-7.89 (m, 11H), 10.88 (s, 1H, *D*₂O-exchangable) and 12.27 (s, 1H, *D*₂O-exchangable) ppm; MS, *m/z* (%) 539 (M⁺, 33), (Anal. Calcd for C₂₄H₂₅N₇O₂S₃: C, 53.41; H, 4.67; N, 18.17; S, 17.82. Found: C, 53.36; H, 4.62; N, 18.15; S, 17.79%).

4-Methyl-*N*-(4-methyl-5-(1-(2-(5-oxo-4-(2-phenylhydrazono)-4,5-dihydrothiazol-2-yl)hydrazono)-ethyl)thiazol-2-yl)benzenesulfonamide (15c). Red solid; mp 251-253 °C; yield 46%; IR: (ν_{\max} /cm⁻¹): 3295, 3203, 3117 (NH), 1715 (C=O), 1608 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆), δ 2.37 (s, 3H), 2.45

(s, 3H), 2.75 (s, 3H), 7.17-7.85 (m, 9H), 10.54 (s, 1H, *D*₂O-exchangable), 11.89 (s, 1H, *D*₂O-exchangable) and 12.82 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 17.35, 20.23, 21.36, 114.89, 122.67, 128.47, 129.06, 130.11, 132.57, 136.79, 137.63, 144.13, 151.32, 155.86, 156.80, 159, 167.22, 192.24 ppm; MS, *m/z* (%) 527 (M⁺, 31), (Anal. Calcd for C₂₂H₂₁N₇O₃S₃: C, 50.08; H, 4.01; N, 18.58; S, 18.23. Found: C, 50.02; H, 3.97; N, 18.53; S, 18.21%).

4-Methyl-N-(4-methyl-5-(1-(2-(5-oxo-4-(2-(*p*-tolyl)hydrazono)-4,5-dihydrothiazol-2-yl)hydrazono)-ethyl)thiazol-2-yl)benzenesulfonamide (15d). Pale red solid, mp 262-263 °C; yield 39%; IR: (ν_{\max} /cm⁻¹): 3276, 3199, 3122 (NH), 1719 (C=O), 1619 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.39 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 2.79 (s, 3H), 7.16-7.81 (m, 8H), 10.45 (s, 1H, *D*₂O-exchangable), 11.25 (s, 1H, *D*₂O-exchangable) and 12.32 (s, 1H, *D*₂O-exchangable) ppm; MS, *m/z* (%) 541 (M⁺, 47), (Anal. Calcd for C₂₃H₂₃N₇O₃S₃: C, 51.00; H, 4.28; N, 18.10; S, 17.76. Found: C, 50.95; H, 4.23; N, 18.18; S, 17.73%).

General procedures for the synthesis of rhodanine analogues (18-21).

A mixture of the thiosemicarbazones **7** (10 mmol) and the appropriate α -halo compounds including ethyl 2-bromoacetate, ethyl 2-chloro-3-oxobutanoate, ethyl 2-bromopropanoate and ethyl 4-chloro-3-oxobutanoate in ethanolic solution of anhydrous sodium acetate (10 mmol) was refluxed for 2–8 h (TLC control). After cooling, the mixtures were washed with ice cold water several times. The formed solids were filtered off and dried then crystallized from DMF/EtOH to afford the corresponding rhodanine analogues, (**18-21**), respectively.

4-Methyl-N-(4-methyl-5-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (18). Pale yellow solid; mp 276-277 °C; yield 40%; IR: (ν_{\max} /cm⁻¹): 3285, 3219, (NH), 1717 (C=O) and 1611 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.37 (s, 3H), 2.40 (s, 3H), 2.48 (s, 3H), 4.04 (s, 2H), 7.14-7.76 (m, 4H), 11.65 (s, 1H, *D*₂O-exchangable) and 12.12 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 17.31, 20.41, 21.38, 33.12, 128.45, 129.76, 132.64, 136.74, 137.69, 156.93, 159.12, 165.14, 167.32, 174.11 ppm; *m/z* (%) 423 (M⁺, 32), (Anal. Calcd for C₁₆H₁₇N₅O₃S₃: C, 45.37; H, 4.05; N, 16.54; S, 22.71. Found: C, 45.31; H, 4.01; N, 16.50; S, 22.66%).

4-Methyl-N-(4-methyl-5-(1-((5-methyl-4-oxothiazolidin-2-ylidene)hydrazono)ethyl)thiazol-2-yl)benzenesulfonamide (19). Pale gray solid; mp 298-299 °C; 56% yield; IR: (ν_{\max} /cm⁻¹): 3356, 3227 (NH), 1728 (C=O), 1617 (C=N); ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.64-1.66 (d, 3H), 2.39 (s, 3H), 2.48 (s, 3H), 2.46 (s, 3H), 4.12-4.14 (q, 1H), 7.19-7.72 (m, 4H), 10.45 (s, 1H, *D*₂O-exchangable) and 12.22 (s, 1H, *D*₂O-exchangable) ppm; ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 17.32, 20.43, 21.36, 21.11, 46.20, 128.43, 129.66, 132.68, 136.71, 137.76, 156.43, 159.18, 165.34, 167.43, 179.41 ppm; MS, *m/z* (%) 437 (M⁺, 38), (Anal. Calcd for C₁₇H₁₉N₅O₃S₃: C, 46.66; H, 4.38; N, 16.01; S, 21.98. Found: C, 46.61; H, 4.33; N, 16.0; S, 21.95%).

Ethyl 4-methyl-2-(2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinyl)thiazole-5-carboxylate (20). Yellow crystals, mp 334-335 °C; yield 45%; IR: (ν_{\max} / cm^{-1}): 3176, 3219, (NH), 1719 (C=O), 1613 (C=N); ^1H NMR (400 MHz, DMSO- d_6), δ 1.23-1.26 (t, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 4.23-4.28 (q, 2H), 7.22-7.82 (m, 4H), 8.89 (s, 1H, D_2O -exchangable) and 12.19 (s, 1H, D_2O -exchangable) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ : 14.42, 16.85, 17.39, 20.54, 21.35, 62.12, 117.32, 128.64, 129.56, 132.86, 137.10, 137.82, 155.74, 157.12, 162.75, 167.15, 171.32 ppm; MS, m/z (%) 493 (M^+ , 36), (Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_4\text{S}_3$: C, 48.66; H, 4.70; N, 14.19; S, 19.49. Found: C, 48.62; H, 4.66; N, 14.13; S, 19.45%).

Ethyl 2-(2-(2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinyl)thiazol-4(5H)-ylidene)acetate (21). Yellow crystals, mp 217-219 °C; yield 31%; IR: (ν_{\max} / cm^{-1}): 3168, 3227, (NH), 1729 (C=O), 1615 (C=N); ^1H NMR (400 MHz, DMSO- d_6), δ 1.24-1.28 (t, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.55 (s, 3H), 3.75 (s, 2H), 4.15-4.21 (q, 2H), 7.25-7.81 (m, 5H), 10.19 (s, 1H, D_2O -exchangable) and 12.33 (s, 1H, D_2O -exchangable) ppm; MS, m/z (%) 493 (M^+ , 25), (Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_4\text{S}_3$: C, 48.66; H, 4.70; N, 14.19; S, 19.49. Found: C, 48.64; H, 4.64; N, 14.15; S, 19.47%).

Ethyl 2-(2-(2-(1-(4-methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazinyl)-4-oxothiazol-5(4H)ylidene)acetate (22).

To a solution of thiosemicarbazone **7** (10 mmol) in dry EtOH (30 mL) was added diethyl acetylenedicarboxylate (10.1 mmol). The solution was refluxed for 6 h., the precipitated product after cooling was filtered, washed with methanol, and recrystallized from DMF to yield yellow solid; mp >360 °C; yield 58%; IR: (ν_{\max} / cm^{-1}): 3256, 3218, (NH), 1721, 1685 (C=O), 1625 (C=N); ^1H NMR (400 MHz, DMSO- d_6), δ 1.23-1.26 (t, 3H), 2.38 (s, 3H), 2.43 (s, 3H), 2.54 (s, 3H), 4.20-4.24 (q, 2H), 6.68 (s, 1H), 7.32-7.76 (m, 4H), 11.09 (s, 1H, D_2O -exchangable) and 12.24 (s, 1H, D_2O -exchangable) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ : 14.45, 17.35, 20.32, 21.39, 62.32, 128.61, 129.52, 132.74, 136.97, 137.85, 147.55, 151.71, 155.76, 156.96, 158.91, 166.27, 167.11, 168.12 ppm; MS, m/z (%) 507 (M^+ , 42), (Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_5\text{S}_3$: C, 47.32; H, 4.17; N, 13.80; S, 18.95. Found: C, 47.28; H, 4.12; N, 13.76; S, 18.91%).

2-(2-((1-(4-Methyl-2-(4-methylphenylsulfonamido)thiazol-5-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl)acetamide (23).

To a solution of thiosemicarbazone **7** (10 mmol) in EtOH (30 mL) was added Et_3N as basic catalyst (0.5 mL) and the mixture was stirred for 30 min at ambient temperature. To the resulting clear solution was added chloroacetonitrile (10 mmol) dropwise whilst the reaction mixture was stirred. After complete addition, the reaction mixture was refluxed for 3–5 h (TLC control). The solid that precipitated was filtered off, washed with water several times, dried and finally recrystallized from DMF to yield pale brown solid; mp 327-329 °C; yield 60%; IR: (ν_{\max} / cm^{-1}): 3310, 3235, 3208 (NH₂ and NH), 1616 (C=N),

^1H NMR (400 MHz, DMSO- d_6), δ 2.36 (s, 3H), 2.47 (s, 3H), 2.64 (s, 3H), 4.11 (s, 2H), 7.19-7.84 (m, 4H), 8.49 (brs, 2H, D_2O -exchangeable) and 12.31 (s, 1H, D_2O -exchangeable) ppm; MS, m/z (%) 422 (M^+ , 62), (Anal. Calcd for $C_{16}H_{18}N_6O_2S_3$: C, 45.48; H, 4.29; N, 19.89; S, 22.77. Found: C, 45.43; H, 4.24; N, 19.83; S, 22.74%).

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